ANKARA UNIVERSITY
FACULTY OF PHARMACY

ISOPS 13th International SYMPOSIUM ON PHARMACEUTICAL SCIENCES

Book of Abstracts

JUNE 22-25, 2021
ANKARA, TURKEY

Ankara University Faculty of Pharmacy Publication No:129

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Ankara University Faculty of Pharmacy Publication No:129
June 2021 Ankara, Turkey
ISBN: 978-605-136-537-4

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Dear Participants and Guests,

I would like to express my sincere appreciation for the valuable contributions of all the participants of 13th International Symposium on Pharmaceutical Sciences (ISOPS). As we all know, the COVID-19 pandemic is still ongoing and the vaccination programmes are proceeding throughout the world. However, during 2021 we continue to face travel bans, governmental and contract restrictions in many countries. Therefore, the symposium was organized as a virtual event for the first time in its history.

ISOPS, initiated in 1989, has successfully brought international scientists, researchers, students together from pharmaceutical sciences and related areas. This symposium was organized biannually until 1997 and then every three years.

Ankara University, Faculty of Pharmacy is the first faculty of pharmacy in Turkey and was established in nineteen sixty (1960). Since the establishment, the institution rapidly progressed and now has very advanced scientific and physical infrastructure. Pharmaceutical science refers to a category of scientific fields and has followed important development processes, mainly in line with the developments in Biotechnology, Nanotechnology and Health Technologies, which are among the priority of the technology fields of today. While realizing the modern requirements, our Faculty has a 5-year undergraduate education programme since 2005 and besides Turkish; it provides an instruction programme in English language since 2015. Our faculty has 6689 graduates since its establishment and the current number of students is 1267. Present educational and scientific resources allow a total of 138 faculty members, 45 professors, 22 associate professors, 5 assistant professors, 51 research assistants in our faculty. Moreover, 66 administrative staff members and other personnel are working at different offices.

The mission of 13th International Symposium of Pharmaceutical Sciences was to perform a broad scientific perspective by the invitation of distinguished scientists having national / international reputation in their areas, so most recent advances were discussed interactively, and to empower the knowledge-based drug research development and multidisciplinary collaborations. It was our intention to make this symposium a memorable event.

This year, scientists from 24 countries registered to ISOPS-13. Our programme consisted of 40 plenary lectures, 212 oral and 200 poster presentations. Excellent research works were presented in different sessions. The speakers in the programme were uniquely placed in accordance to their area of expertise.

I would like to refer also to other initiatives that took place in our symposium. A workshop on “Employability of the Graduates of the Faculty of Pharmacy in Europe” was held with the contribution of Prof. Luciano Saso, Prof. Claire Anderson, Prof. Lilian M. Azzopardi, Prof. Sibel Süzen, Prof. İlkay Erdogan Orhan and Pharm. Nilhan Uzman. This workshop was interesting in terms of discussing the priorities and developments on this topic from local, regional and international respects.

On June 25, our panel on “University-industry-public sector cooperation in drug and vaccine development processes” was carried out by Prof. Dr. Asuman BOZKIR. The heads and *senior representatives of relevant institutions* including; Prof. Hasan Mandal, Assoc. Prof. Tolga Karakan, Pharm. Dr. Nihan Burul Bozkurt, Prof. Erhan Akdoğan, Assoc. Prof. Rabia Çakır Koç, Prof. Mayda Gürsel, Prof. Rana Sanyal, Prof. Hülya Ayar Kayalı, Dr. Süha Taşpolatoğlu, Dr. Hasan Ersin Zeytin, and Pharm. Dr. Ferhat Farşi were with us. This event has been a great platform to discuss the existing practices and requirements, and to propose solutions.

On behalf of the Organizing Committee, I would like to mention my gratitude to the President of Ankara University who gave full support for the Symposium Organization. ISOPS-13 was organized successfully, without any professional support, with the contribution of all our faculty members, especially our symposium secretary Assoc. Prof. Zerrin Sezgin-Bayındır. I congratulate the organizing committee and all the other committees with all my heart, as well as all academic and managing personnel because of their extensive work.

Prof. Dr. Asuman BOZKIR

Chair of ISOPS-13

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PLENARY LECTURES

PL1: DUAL BENEFITS OF MELATONIN ANALOGUES AS AROMATASE INHIBITORS AND OXIDATIVE STRESS MODULATORS IN BREAST CANCER

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Introduction: Aromatase is involved in the final stage of the biosynthesis of estrogen, in the conversion of androgens to estrogen. Under the conditions of breast cancer, aromatase expression is enhanced leading to local overproduction of estrogen that promotes breast cancer. Among the non-steroidal inhibitors, the most studied compounds are indole derivatives such as melatonin.

Materials and Methods: New indole-based compounds were synthesized with the modifications we have made on the melatonin molecule. Aromatase inhibiting potential of the new compounds are investigated, and compared with melatonin, with direct measurement via cell-free assay and direct measurement via cell-based assay where cell proliferation was determined in ER + human breast cancer cells in the absence of estrogen and the presence of testosterone. Also Docking studies of active compounds into the aromatase active site was employed to detect interaction with enzyme.

Results: In the direct measurement of aromatase activity. Almost all 2-methyl indole hydrazone derivatives showed moderate to high inhibitory activity at 100 µM concentration. Five most active compounds of direct aromatase activity measurement were also tested at their various concentrations to evaluate their aromatase inhibitory effect in indirect measurement assay. The interaction of this molecule with the enzyme was investigated using molecular docking. The most active derivative is settled properly to the active site of the enzyme.

Conclusions: It can be said that 5 out of 19 compounds showed rather strong inhibitory activities towards CYP19A as indicated by IC50 values lower than 20 µM. Those five compounds are shown to be stronger aromatase inhibitors than melatonin. However they have approximately 10 times less activity than a well-known aromatase inhibitor, ketoconazole. Compounds, especially m- and p-chlorinated 2-methyl indole hydrazone derivatives seem to be promising candidates for prevention and treatment of ER + breast cancer because of their dual benefits as aromatase inhibitors and oxidative stress modulators.

Acknowledgements

This study was supported by a grant of TUBITAK (112S375 and109S099) and Ege University Research Fund (13BIL009 and 13ECZ008).

PL2: MACHINE LEARNING MODELS FOR PREDICTING DRUG SYNERGY AND SIDE EFFECTS

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In this talk, I will present two algorithms: DeepSide and MatchMaker. DeepSide is a deep learning based framework that predicts drug side effects using drug chemical structure and drug-perturbed gene expression signatures. We show that a convolutional neural network-based model that uses only SMILES string representation of the drugs achieves the best results and provides 13% macro-AUC and 3.1% micro-AUC improvements over the state-of-the-art. The second algorithm, MatchMaker is also deep learner which predicts drug combination effects. For the first time, our model utilizes the largest known drug combination dataset to date, DrugComb. We compare the performance of MatchMaker with the state-of-the-art models and observe up to ∼15% correlation and ∼33% mean squared error improvements over the next best method.

PL3- THE ERA OF MRNA VACCINES

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PL4: CYCLODEXTRIN POLYMER COATINGS FOR DRUG DELIVERY: FROM NANOPARTICLES TO HYDROGELS

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Introduction: Cyclodextrin polymers offer the possibility to tailor macromolecular assemblies in aqueous solutions due to their ability to form inclusion complexes with apolar guests. Indeed, the specific recognition between β-cyclodextrin units (β-CD) and hydrophobic derivatives such as adamantyl groups has been used to build three-dimensional structures spontaneously forming in aqueous solution. A guest polymer containing several β-cyclodextrin units (P β-CD) is mixed in water to a host polymer containing several lipophilic groups (hydrophobically modified dextran). The resulting multivalent interactions between the CD cavities and the lipophilic groups constitute the temporary crosslinks of a network of connected chains.

Results: The interplay between macromolecular design and structure and interactions in the nanoassemblies has been utilized to tailor different kinds of hierarchical nanostructures, such as host-guest self-assembled nanoparticles, core-shell nanoparticles constituted of a PLA or a solid lipid nanoparticle core and a lbl P β-CD shell or core-shell PNIPAM microgels stabilized by a P β-CD and a dextran-adamantyl-PEG bilayer.[1-3] Hierarchically structured hydrogels could be obtained from host-guest connected hydrogels, paving the way to the design of injectable hydrogels.[4]

Conclusion: These systems are of great interest for drug delivery applications as they combine the low toxicity of the hydrophilic compounds, the easiness of preparation, the specific affinity for apolar drugs due to the presence of β-CD units and the ability to control the drug release.[1]

Acknowledgements

This work was in part supported by the NanoS3 – 290251 ITN project of the European Commission, which is gratefully acknowledged.

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PL5: MESOPOROUS SILICA FOR ADVANCED DRUG DELIVERY APPLICATIONS

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Introduction: Mesoporous silica (MSNs for nanoparticles) has since the beginning of the 2000's found an established role as a versatile nanomedicine development platform, due to its controllable properties on many levels. Associated traits are their design modularity combined with the vast surface functionalization approaches adoptable for silica. Here, the chemical, structural, and textural robustness of the architecture of this inorganic material platform can be readily fine-tuned with the aid of responsive, biocompatible and flexible organic modifications to form multifunctional hybrid materials. Silica is also the most widely used coating for other inorganic nanoparticles, since it is biocompatible and hydrophilic, allows for easy further functionalization, and efficiently protects the core material from the surroundings. Upon coating wtih mesoporous silica, the porous shell can also be utilized for loading of active molecules such as drugs or molecular imaging agents - a popular approach for creating nanotheranostic agents.[1]

Results: Multifunctional designs comprising mesoporous silica constructs (hybrid materials, core@shell structures) have demonstrated a wide variety of applicabilities to date. While enhanced dissolution of poorly soluble drugs have already been clinically verfied [2], hybrid materials can meet the demands of delivering water-soluble drugs or biomolecules. Our recent discovery further point to intrinsic cancer stem cell-killing activity of hybrid MSNs [3], while core@shell nanocomposites have been constructed to successfully function as nanozymes [4] and nanoantibiotics. The robust MSN platform further enables easy further formulation of these nanocarriers into dosage forms [5], while protecting the incorporated active agents.

Conclusion

This Plenary Lecture will outline design aspects that emphasize the utilization of MSNs as a versatile platform for nanomedicine development, covering materials design and formulation aspects with different types of active agents as well as application examples.

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PL6: NOVEL DRUG TARGETING FOR LOCALIZED-DIRECT TREATMENT OF LUNG DISEASES

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Several lung diseases are present all over the world and millions of people die annually due to chronic lung diseases such as asthma, COPD, cystic fibrosis, idiopathic-pulmonary fibrosis, and pneumonia. The use of conventional drugs requires high doses for lung targeting, which leads to undesirable adverse effects. For this reason, it is necessary to develop inhaled dosage forms that can be applied locally to the lungs in order to obtain a more effective treatment.
In addition to this situation, the inadequacy of locally applied drugs makes it necessary to investigate the use of repurposed drugs as inhaled, as well as the discovery of new active substances. There are studies conducted with these drugs for their uses in various treatments. For example, Amodiaquine is an antimalarial drug, but the local application to the lungs has been studied for its anticancer effect. Similarly, several studies are underway for other drug groups such as antibiotics and antivirals. Some have even made it to the market and is currently being prescribed. To date, our study group has focused on the local treatment of lung diseases and targeted macromolecules through heparin, mRNA and GapmeRs. The findings show that the pulmonary administration of nebulized heparin in the form of controlled release micro particles proves to be more effective as inhibitory treatment for airway hyperresponsiveness (AHR) as opposed to administration of an equivalent dose of heparin solution by the same frequency. Also, we optimized the production of NCMPs of miR-146a-containing PGA-co-PDL NPs for dry powder inhalation in terms of size, morphology, aerosol performance, moisture content and miRNA functionality. These past 18 months, our latest study topic has focused on COVID-19. We have achieved promising results on our conducted preclinical and clinical studies for some repurposed drugs. The findings showed that these locally applied drugs can provide effective treatments at much lower doses for Covid-19. In addition, patient compliance was observed to increase as opposed to the adverse side effects seen with high doses of oral application. All these studies justify our enthusiasm for the development of new local treatments for the lungs.

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PL7: MODULATION OF OXIDATIVE STRESS AS A PHARMACOLOGICAL STRATEGY

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Oxidative stress (OS) plays an important role in neoplastic diseases and inhibitors of nuclear factor erythroid 2-related factor 2 (Nrf2), the master regulator of endogenous antioxidant enzymes, could be useful in their treatment. However, novel approaches to redox therapies are necessary and the development of reliable biomarkers capable to predict the clinical responses is crucial.

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PL8: MODULATION OF BETA ADRENERGIC SYSTEM FOR EXACERBATED INFLAMMATION

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PL9- DRUG DESIGN AND BIOLOGICAL ACTIVITY OF COMPOUNDS TARGETING HUMAN AND/OR PATHOGENIC PROTEASES

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Introdution: Infectious diseases and malignancies are among the pathological conditions with the highest rate of mortality. Therefore, most of the drug discovery efforts are focused on the identification of specific molecular targets that play essential roles in the progress of such conditions. In this context, our current interest is mainly pointed towards the target-based drug design and synthesis of novel protease inhibitors to tackle viral infections, as well as novel inhibitors of proteins involved in the tumor pathogenesis (*i.e.* proteasome and HDACs).

Materials and Methods: To validate our results, the following materials and methods were employed. *i*) Molecular docking (AutoDock 4.2.6 software implemented in YASARA) and MD simulations (target-ligand interactions); *ii*) CPE-based assay (inhibition of the replication of coronaviruses); *iii*) MTT-MT4 (anti-HIV activity); *iv*) QPCR analysis (anti-HIV mechamism of action); *v*) resazurin assay and MTS assay (cytotoxic effects); *vi*) fluorimetric assays (anti-20S proteasome and anti-HDAC activity) by means of an Infinite 200 PRO microplate reader (Tecan) and IC_{50} values were calculated with the program GraFit® using the two-parameter equation. Synthetic strategies to obtain the compounds include the nucleophilic halomethylation, peptide coupling reactions and Schiff condensation.

Results: Our studies led to the identification of compounds endowed with notable (micromolar range) antiviral activity in vitro in cell-based assays with low cytotoxicity profile,[1,2] and compounds with remarkable (submicromolar range) antiproliferative properties towards different tumor cell lines.[3-5]

Conclusions:

The above results indicate that the target-based drug design represent one of most valuable strategy to efficaciously counter with infectious diseases and malignant tumors.

Acknowledgements

This research activity was supported by grants of MIUR.

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PL10: DESENSITIZATION OF β_3-ADRENOCEPTORS: COMPARISON OF cAMP AND BIASED SIGNALING

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Introduction: β_3-Adrenoceptors (B3AR) couple to G_s proteins to stimulate adenylyl cyclase and generate cAMP in all cell types, but additional signal pathways such as extracellular signal-regulated kinase (ERK) can be activated in some cells types. Some B3AR ligands are biased agonists, i.e. antagonists or weak agonists for cAMP formation but strong agonists for other patways such as ERK. B3AR are less sensitive than other BAR subtypes regarding agonist-induced desensitization, but this has only been tested for cAMP formation until now (1). Therefore, we have compared desensitization of cAMP formation and ERK phosphorylation by multiple ligands in CHO cells.

Materials and Methods: Stably transfected CHO cells were exposed to various ligands for 24 h, followed by washout and stimulation with fresh ligand solutions to assess cAMP formation and ERK phosphorlyation (pERK).

Results: B3AR ligands (10 µM each) stimulated cAMP accumulation with a rank order of isoprenaline ≈ L755,507 ≥ CL316,243 > L748,337 ≈ SR59,230. Pre-treatment with pertussis toxin (PTX) did not affect the cAMP response to any ligand. Pre-treatment (10 µM for 24 h) with isoprenaline desensitized the concentration-response curves for the freshly added ligand whereas pre-treatment with L748,337 had little effect. Ligands increased pERK with a rank order of L755,507 ≈ CL316,243 ≈ isoprenaline ≥ SR59,230 ≥ L748,337. PTX markedly lowered

basal pERK and enhanced all agonist responses relative to this lowered basal. Pretreatment with isoprenaline lowered basal, reduced potency by 0.8 log units and increased E_{max} relative to the lowered basal. In contrast, L748,337 did not change basal pERK or pEC_{50} but reduced E_{max}. Neither changed total ERK.

Conclusions: We conclude that full, partial and biased agonists exhibit different patterns of desensitization of the cAMP and ERK pathway.

Acknowledgements

This study was supported by a grant from Velicept Pharmaceuticals.

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PL11: GRK2 INHIBITION FOR HEART FAILURE - NEARING TRANSLATION

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Introduction: Over the last several years, my laboratory has been investigating the role of cardiovascular G protein-coupled receptor (GPCR) kinases (GRKs) in several in vivo model systems.

Materials and Methods: Original studies were done in transgenic mice where GRK-based transgenes were targeted specifically to the heart.

Results: We have found that one GRK, GRK2, plays a significant role in the development of pathological cardiovascular conditions including heart failure (HF). GRK2 has been found to be elevated in the heart when it has compromised contractile function and these changes appear to be maladaptive and pathological and targeted inhibition of GRK2 is therapeutic in certain cardiovascular disorders. Indeed, cardiac expression of a GRK2 inhibitor, known as the bARKct, has rescued several animal models of HF including most recently in porcine post-MI failure. More recently, we have found GRK2 to be a pro-death kinase during acute ischemic injury in the heart due to its localization to the mitochondria and alos due to its negatie influence on insulin signaling in the heart. Thus, we have identified GRK2 as critical regulator of cardiovascular signaling, metabolism, survival and function, which have wide implications for future research in order to elucidate novel roles for these GRKs in physiology and pathology. In addition to using the bARKct, we are developing small molecule inhibitors of GRK2 and the latest data with these will be presented.

Conclusions: Overall, we have found GRK2 up-regulation in the stress and injured heart to be pathological and its inhibition for the treatment of heart failure is nearing translation

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These studies were supported by multip NIH grants since 1998

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PL12: NANOBIOSENSORS FOR POINT-OF-CARE DIAGNOSTICS APPLICATIONS

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There is a high demand to develop innovative and cost effective devices with interest for health care beside environment diagnostics, safety and security applications. The development of such devices is strongly related to new materials and technologies being nanomaterials and nanotechnology of special role. We study how new nanomaterials such as nanoparticles, graphene, nano/micromotors can be integrated in simple sensors thanks to their advantageous properties. Beside plastic platforms physical, chemical and mechanical properties of cellulose in both micro and nanofiber-based networks combined with their abundance in nature or easy to prepare and control procedures are making these materials of great interest while looking for cost-efficient and green alternatives for device production technologies. These devices should be REASSURED: Real-time connectivity, Ease of specimen collection, Affordable, Sensitive, Specific, User-friendly, Rapid, Robust, Equipment-free, Delivered to those who need it. How to design simple paper-based biosensor architectures? How to tune their analytical performance upon demand? How one can couple nanomaterials with paper and what is the benefit? Which are the perspectives to link these simple platforms and detection technologies with mobile communication? I will try to give responses to these questions through various interesting applications related to protein, DNA and even contaminants detection all of extreme importance for diagnostics, nanotheranostics, environment control, safety and security.

PL13: BUILDING NEW ANALYTICAL PLATFORMS BASED ON CARBON NANOMATERIALS FOR BIOMARKERS BIOSENSING

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The development of nanomaterials-based biosensing platforms that allow an improved electroanalytical performance in terms of sensitivity and selectivity, is receiving enormous attention. In this sense, carbon nanostructures have demonstrated to be extremely useful materials to build innovative electrochemical biosensors due to their unique properties.

This presentation will describe general aspects about the functionalization of carbon nanotubes and graphenaceous materials with polymers and biomolecules. Special attention will be given to the discussion of new alternatives to build biosensing nanoarchitectures based on innovative carbon nanostructures-functionalization schemes using agents that allow not only the successful exfoliation of the nanostructures but also the efficient site-specific anchoring of biorecognition molecules. Different supramolecular architectures will be described, based on graphene oxide or chemically reduced graphene oxide modified with chitosan as platform to support the biorecognition layer and improve the transduction of the bioaffinity event. The advantages of these new avenues for plasmonic or electrochemical biosensing of microRNA 21, DNA copy of SARS-CoV-2 RNA, glucose and hydrogen peroxide will be also discussed. In summary, we will demonstrate that the rational selection of the strategy to functionalize the carbon nanostructures and the transduction scheme are critical aspects for the development of competitive biosensors.

The authors acknowledge to CONICET, SECyT-UNC, ANPCyT and MINCyT-ECOS for the financial support.

PL14- VACCINE DESIGN AND INNATE IMMUNE NETWORK

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Introduction: Macrophages are among the cellular components of the innate immune system and play key roles in elimination of infectious agents, inflammation, wound healing, angiogenesis and the maintenance of homeostasis. The spectrum of capabilities chiefly rely on activation states of these cells. Driven by the microenvironment, macrophages are known to polarize into classical (M1 – proinflammatory) and alternative (M2 – regulatory) gene expression signatures. Vast amount of multi-omic (mostly transcriptomic) data has been generated in attempt to expose the underlying genetic regulation of these different activated forms. However, gene expression data promises only indirect evidences concerning stochastic decision making process of macrophage polarization, unless, obtained from single cells.

Here, I introduce a novel data analysis pipeline and a customizable knowledge graph database to gain insights on potential stochastically expressed genes in immune cells.

Materials and Methods: A custom data analysis pipeline has been developed, in order to process gene expression data, generated either by using sequencing or hybridization based techniques, in order to project stochastically expressed genes.

A novel multi-model database was developed for the functional analysis of the gene sets. ArangoDB was chosen as the database engine. Either restricted or bulk UniProt, IntAct; ChEBI were downloaded from EBI servers. Ontologies were downloaded forn The OBO Foundry and converted into JSON graphs. A BLAST atlas of the included protein sequences were generated. Post translational modifications were downloaded from PtmDB These datasets were converted and organized into key-value or graph database entries.

Results: Stochastically expressed gene sets were projected from various macrophage related gene expression datasets. Metabolic pathway terms, small chemicals, structures, protein – protein interactions related to gene sets were discovered by using the multi-model database.

Conclusions: Metabolism of the innate immune cells is of key importance in mounting appropriate responses to pathogens. Specifically, macrophages occur as an highly heterogeneous population of cells. Thus, distinct M1 and M2 polarization states might be an oversimplification of the whole picture, which overlooks the stochastic nature of the polarization decision process. Discovering the components of this stochasticity might aid minimizing immunization failures and side effects.

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PL15: TARGETED NANOPARTICLES FOR BRAIN DELIVERY OF DRUGS

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Introduction: The selection of targeting molecules is a key step in the design of nanoparticles developed for brain delivery. Molecules interacting with receptors on the luminal surface of brain endothelial cells have been the most investigated specific targeting vectors. Ligands of other transporters of the blood-brain barrier (BBB), including solute carriers (SLCs), are less examined for nanoparticle targeting. We found high mRNA expression levels for SLCs carrying hexoses, amino acids, and vitamins in isolated brain microvessels, and culture models of the BBB (Veszelka et al. 2018). Our hypothesis was, that (i) molecules that bind to nutrient transporters of brain endothelial cells increase the transfer of nanoparticles across the BBB and (ii) combination of targeting vectors (dual labeling) can elevate BBB transfer as compared to labeling with a single targeting molecule.

Results: We demonstrated that biotin as a targeting ligand of SMVT/SLC5A6 elevated the uptake and permeability of solid nanoparticles in cultured human brain endothelial cells as compared to non-targeted ones (Veszelka et al. 2017). Glucopyranose and alanine as ligands of SLC-transporters and glutathione as a reference BBB targeting molecule were tested in our next study. Dual labeling, functionalization of vesicular nanoparticles with two different types of ligands, increased the cellular uptake and permeability of albumin cargo, which has a very low BBB penetration in both in vitro and in vivo experiments (Mészáros et al. 2018). The transfer of the targeted nanoparticles was an active process, and both membrane fusion and endocytosis contributed to it. Partial removal of the negative luminal charge of brain endothelial cells increased the cellular uptake of the nanoparticle cargo (Mészáros et al. 2018). This finding indicates an important role for the negative surface charge at the BBB as a regulator of transport (Walter et al. 2021). Wealso showed that alanine & glutathione dual-targeting of niosomes enhanced the delivery of a large protein cargo into cultured cells of the neurovascular unit, namely brain endothelial cells, pericytes, astrocytes and neurons (Porkoláb et al. 2020).

Conclusions:

Dual-labeling of nanoparticles with ligands of multiple SLC transporters can potentially be exploited to deliver drugs, even biopharmacons, across the BBB and into multiple cell types in the brain.

Acknowledgements

This study was supported by grants from the National Research, Development and Innovation Office, Hungary (NNE-129617-M-ERA.NET2 nanoPD and GINOP-2.3.2-15-2016-00060).

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PL16: USE OF MAGNETIC-INDUCED HYPERTHERMIA FOR CANCER TREATMENT

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PL17- PROGRESS AND TRENDS IN POTENTIAL UTILIZATION OF NATURAL COMPOUNDS AS DRUGS PRENYLATED PHENOLICS

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Introduction: Natural substances often have a pleiotropic effect and can affect several cellular processes in parallel. They can have parallel anti-inflammatory and antibacterial effects, together with the current antiviral effect. Their mechanism of action is complex. However, the problem of natural substances is often their limited solubility and consequently also problematic bioavailability (1).

Materials and Methods: Series of prenylated phenols were isolated from Paulowniaceae, Moraceae, and Euphorbiaceae plants (2-5).

Results: As part of the lecture, we will introduce the isolation and identification of prenylated phenols with potential antiviral and anti-inflammatory effects, we will describe their bioactivity, their formulations to increase solubility, and will describe the possibilities of their further development.

Conclusions: We described the effects of phenolics *in vitro* in cellular or biochemical systems on the production and release of inflammation-related cytokines; their effects on the inhibition of cyclooxygenases and lipoxygenases, and also some *in vivo* experiments confirming activity. At the end, an improvement of solubility by incorporating of tested substances into liposomes was presented.

Acknowledgements

The work was supported by the Ministry of Education, Youth and Sports of the Czech Republic under the project "FIT" CZ.02.1.01/0.0/0.0/15_003/0000495, and Czech Ministry of Agriculture grant no. RO0518.

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PL18: THE ROLE OF CHITOSAN-COLLAGEN BINDING IN DRUG TARGETING TO FIBROTIC DISEASES

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Increased collagen deposition is observed in a number of diseases, including fibrosis of liver, kidney and lung, cancer and atherosclerosis among others (1-3). Nanocarriers decorated with collagen binding peptides (CBPs) have in fact been therefore utilized in targeting of the aforementioned diseases (3, 4). However, CBPs usually come at an elevated cost, are sensitive and care has to be taken in the process of nanoparticle (NP) decoration so as not to jeopardize their collagen binding abilities. We have demonstrated that chitosan, a cheap biodegradable polymer and a common pharmaceutical excipient shows intrinsic collagen binding properties and have exploited such abilities in drug targeting in liver fibrosis(3).
Chitosan NPs were formulated via the ionotropic gelation method and either used as such or when modified with different densities of CBP (CCQDSETRTFY), directly or via PEG spaces. *In-vitro* experiments using bovine collagen demonstrated the ability of unmodified chitosan NPs to bind to collagen in a similar extent as CBP modified NPs at all densities (3). Additionally, in fibrotic mouse models, unmodified chitosan NPs showed an ability to accumulate in fibrotic livers following intravenous administration (5). The same was not observed in healthy livers in which collagen is available in lower amounts. However, while this collagen binding assists in the accumulation of the NPs in the collagen rich diseased site, it hinders the interaction of the NPs with their target cell (5). For such reason the co-administration of collagenase-loaded chitosan NPs could help deliver collagenase to the diseases site, enabling collagen digestion and liberation of bound NPs allowing them to deliver drugs into their target cell. In fact, with the aim of the reversal of liver fibrosis, the deactivation of activated hepatic stellate cells (aHSCs) was achieved using a combination tumor growth factor- beta (TGFβ) siRNA loaded NPs that were modified with platelet derived growth factor receptor-beta (PDGFR-β) binding peptides in combination with collagenase loaded chitosan NPs(5). Upon intravenous administration both NPs accumulate in fibrotic livers, where the released collagenase liberated the siRNA loaded NPs that have been entrapped within the collagen rich net enabling its uptake by the HSCs using receptor mediated endocytosis and the successful intracellular delivery of TGFβ siRNA and the consequent deactivation of aHSCs. In conclusion, chitosan NPs offer an interesting platform for drug delivery to collagen rich diseases. In case the NP intracellular delivery is required, the co-administration of collagenase loaded NPs may enable NP interaction with target cell

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PL19: IN VITRO TOPICAL TOXICITY TESTING OF MEDICAL DEVICES IN LINE WITH THE NEW ISO 10993-23

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PL20: PLANT CHEMOPHENETIC STUDIES FROM ASTERACEAE TO ZOSTERACEAE

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Plant chemosystematic or chemotaxonomic studies of small molecules have become obsolete as tools to study phylogenetic relationships of higher plants due to the advent of the much more powerful (macro-) molecular techniques and new methods of data analyses established in parallel to these techniques. Thus, studies aimed at the elucidation of the characteristic array of specialized natural products of plant taxa should nowadays better be called plant chemophenetics studies (1). I will introduce the new term, taking the Cichorieae tribe of the Asteraceae (2) and the seagrass *Zostera marina* L. (Zosteraceae) as examples (3-5). The Cichorieae tribe is morphologically very homogeneous and thus particularly poor in differential morphological characters. Chemophenetic characters are thus in addition to the classic anatomic, morphologic, and karyologic characters well suited to describe organisms and to characterize clades found with the help of modern molecular methods.
Seagrasses are the only higher plants living in marine environments; they play a significant role in coastal ecosystems. While polar compounds from *Zostera marina* have been studied quite extensively, we have recently started to study for the first time its array of apolar compounds. So far, seven mostly formerly undescribed cyclic diarylheptanoids have been found, including three dimers.

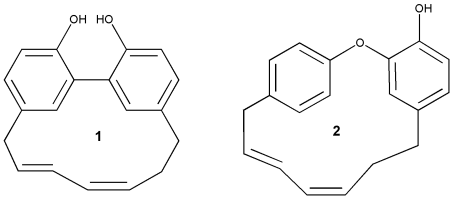

Figure 1. Cyclic diarylheptanoids from *Zostera marina*: deoxycymodienol **1** and isotedarene A **2**.

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PL21: THE IMPORTANCE OF BIOMONITORING OF GENOTOXICITY BIOMARKERS IN OCCUPATIONAL SETTINGS

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People in various occupational settings have the potential to be exposed to hazardous substances, which are known to be genotoxic and can lead to genetic alterations. The measurement of molecular or cellular biomarkers as the indicators of exposure or preventive factors has many applications in occupational toxicology. An increased level of DNA damage represents a relevant event in the pathway leading to a chronic disease and eventually to death. There have been many reports over the years of elevated DNA damage levels (strand breaks and/or oxidized bases) associated with a wide range of clinical conditions such as coronary artery disease, diabetes, kidney disease, chronic obstructive pulmonary disease, multiple sclerosis, and Alzheimer's diseas. Genotoxicity tests that assess the potential risks and adverse effects of chemicals are becoming increasingly important as humans are constantly exposed to a large number of chemical and physical agents in their environment especially in occupational settings. DNA damage and DNA repair are important elements in the etiology of cancer and in its treatment. Micronucleus assay, chromosome aberration test and comet assay are widely used genotoxicity tests in biomonitoring of DNA damage in workers. Measurement of DNA damage and DNA repair using Comet assay is a reliable biomarker of genotoxic exposure and cancer risk. The most important advantage provided by the Comet assay for assessing the genotoxicity in vivo is that DNA damage can be measured in cells of

any organ, regardless of the extent of mitotic activity.

Acknowledgements

This study was supported by a grant of TUBITAK (SBAG-115S564)

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PL22: TOWARD MULTIOMICS BIOELECTROANALYTICAL PROFILING FOR PERSONALIZED MEDICINE

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Introduction: Since human diseases evolution involves a highly dynamic and interactive system of multiple layers of molecular markers (e.g. genetics, epigenetics, mRNA transcripts, proteins and metabolites), it is fully accepted that the simultaneous analysis of biomarkers of different molecular level aids early detection and prognosis of diseases. In this sense, features such as versatility to profile multiomics biomarkers, simplicity, affordable cost and remarkably shorter analysis time and sample quantity for the analyses compared to latest generation omics technologies make electrochemical bioplatforms suitable alternatives to address this challenge [1].

Materials and Methods: The developed methodologies exploit the smart use and coupling of novel bioreceptors and chemistries, functionalized magnetic microcarriers, attractive bioassays formats and amperometric individual or multiplexed transduction at disposable devices.

Results: This plenary lecture will discuss the most remarkable attributes of selected bioelectroanalytical tools developed last year in our research group, potentially transferable to the clinic due to their simplicity, cost, testing time and decentralized character, which have shown pioneering applications to decisively assist in personalized diagnosis by targeting deregulated miRNAs, methylation events in nucleic acids and autoantibodies. Particular attention will be paid to their demonstrated potential to: i) perform the accurate determination of miRNAs in a small amount of total RNA extracted from tissues or directly in serum samples without genetic material extraction or amplification; ii) discriminate the aggressiveness of cancer cells and tumor from healthy tissues by multiplexing four methylations events at global level in nucleic acids of different nature (5-mC, 5-hmC, 6mA in DNA and m6A in RNA), using small amounts of extracted genomic DNA or raw total unfragmented RNA and without enriching or adopting other amplification strategies than conventional enzymatic labeling; and iii) to assist the early and minimally invasive diagnosis of a particular neoplasia by targeting specific serum autoantibody signatures against circulating tumor associated antigens or those identified in exosomes released by cancer cells or tumor tissues.

Conclusions: This research proves that current bioelectroanalytical tools provide unique opportunities for the clinical validation and determination of candidate diagnostic, prognostic, or predictive biomarkers discovered by high-throughput omics technologies at a multilayer level, in a simple, versatile and affordable way. These amazing advances make us dream that we are getting closer and closer to the desired precision medicine and the benefits it is expected to bring in terms of improving both outcomes and quality of life of patients and alleviating the financial burden on healthcare systems.

Acknowledgements

PID2019-103899RB-I00 Research Project (Spanish Ministerio de Ciencia e Innovación), PI17CIII/00045 and PI20CIII/00019 grants from the AES-ISCIII program and S2018/NMT-4349 grant from the Comunidad de Madrid.

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PL23: PRE-CONCENTRATION AND SELECTIVE ADSORPTION OF PLANT SECONDARY METABOLITES BY SOLID SORBENTS

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Introduction: Solid-phase extraction (SPE) is nowadays one of the most common and well validated technique employed for the pre-concentration and extraction of analytes from matrices of different origin. The most favourable features of SPE are represented by high recoveries and enrichment factors, low cost, rapid phase separations, and the combination with different detection techniques. In this context, the choice of the sorbent is a key factor influencing analytical

parameters of pivotal importance like selectivity, affinity, and capacity. Activated carbon, silica (normal- and C-18 reverse phases), activated alumina, molecularly imprinted polymers, and different resins are used as sorbents in SPE (1) However, the search for novel, more efficient, and more versatile materials to accomplish SPE-based processes is a field of current and growing interest.

Materials and Methods: Solid sorbents have found limited interest until now in the phytochemical practice. In this lecture we wish to report the investigation about the performance of hydrotalcites and other solid supports like magnesium oxide and hydroxide, another lamellar structure like zirconium phosphate, and finally the phyllosilicates talc and bentonite for the selective concentration of different categories of secondary metabolites from raw solid extracts of different plant matrices. Quantification have been accomplished using HPLC coupled to Uv/Vis detection. Anthraquinones, diarylheptanoids, polyphenols, purine alkaloids, capsaicinoids, and oxyprenylated coumarins have been used as substrates.

Results: Several solid sorbents displayed very good and selective adsorption capacities towards the listed categories of plant secondary metabolites. In particular the hydrotalcite zinc aluminum oleate and magnesium aluminum azelate and MgO were largely the most effective allowing to easily recover anthraquinones, MgO and $Mg(OH)_2$ for curcumin, bentonite fo polyphenols and caffeine, and finally the hydrotalcite magnesium aluminium azelate and bentonite for capsaicinoids and oxyprenylated coumarins.

Conclusions: Results outlined herein enforce and further validate the versatility of some solid sorbents as agents to selectively adsorb and concentrate naturally occurring biologically active compounds from raw plant extracts. The methodology depicted herein represent valid alternatives to the already existing methodologies and materials.

Acknowledgements

This study was supported by a grant issued by the University “G. d’Annunzio” of Chieti-Pescara (FONDI FAR 2020)

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PL24: HYDROGEN SULFIDE PATHWAY ROLE IN CARDIOVASCULAR SYSTEM: A POTENTIAL THERAPEUTIC TARGET

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Gaseous transmitters, nitric oxide (NO), carbon monoxide and more recently hydrogen sulfide (H_2S) are recognized to be involved in the cardiovascular system playing a main role in the regulation of vascular homeostasis. In particular, H_2S is synthesized by cystathionine β-synthase (CBS), cystathionine γ-lyase (CSE), and the sequential action of cysteine aminotransferase and 3-mercaptopyruvate sulfurtransferase. All H_2S-producing enzymes are expressed in the vasculature but CSE seems to be the more relevant in the cardiovascular system (1) where its down-regulation is observed during hypoxia, hypertension and myocardial infarction. H_2S can react with various proteins, polysulfides, and oxygen compounds to form a sulfide storage compound termed sulfane sulfur. Thus H_2S can signal through a specific protein modification, termed sulfhydration, where by a sulfhydryl(-SH) group is post-translationally added to cysteine residue. This sulfhydration alters function and has been shown to upregulate protective signaling pathways. Several targets have been proposed for the H_2S vasculoprotective effects such as a direct stimulation of plasma membrane KATP channels; the inhibition of L-type Ca2 channels and the stimulation of charybdotoxin/apamin-sensitive K channels in vascular endothelium and in cardiomocites. An increase in nucleotides leves by activates adenylate cylcase and inhibition of phosphodiesterases have been proposed (2). On the other hand at low concentration H_2S causes a vasoconstriction and recently we proposed a mechanism of action implying a disruption in nucleotide levels (3). In rodents, CBS or CSE deficiency induced by genetic deletion or chronic treatment with PAG results in a severe hypertension and severe loss of endothelial function (4). Interestingly, spontaneously hypertensive rats have lowered H_2S concentrations than rats from other species (i.e. WKY, Wistar, Sprague-Dawley). CBS deficiency leads to hyperhomocysteinemia, increased blood pressure and endothelial dysfunction (5). Although CBS is not considered to be the main vascular source of H_2S, tissue deficiencies in CBS are thought to manifest in the vasculature as a consequence of homocysteine accumulation. Recently, we have suggested a role of CBS in vasculature. As known, CBS converts L-cysteine into L-serine and H_2S. L-serine is also involved in the de novo sphingolipid biosynthesis. We demonstrated that L-serine contributes to the

vasodilator action of L-cysteine. The L-serine effect involves both NO and sphyngosine 1phosphate. This mechanism could be involved in the marked dysregulation of vascular tone in hyperhomocysteinemic patients (CBS deficiency) and may represent a feasible therapeutic target (6). Thus, H_2S acts as a protective factor in the cardiovascular system, therefore H_2S based therapy are needed in the future to treat various human disease associated to a dysfunction of H_2S pathway.

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PL25: ENANTIOSELECTIVE LIQUID CHROMATOGRAPHY IN A TRANSLATIONAL CHEMISTRY PERSPECTIVE

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Introduction: Many life processes take place in asymmetric environments and involve molecules of defined chirality. Chirality is now a top-class subject for academic research as well as for pharmaceutical development in industry. Chiral compounds are also intimately linked to specific diseases with significant diagnostic potential as putative biomarkers. Furthermore, chiral analysis in the food field are performed, *inter alia*, for the control and monitoring of microbiological activity. With increasing evidence of problems related to stereoselectivity, enantioselective analysis by chromatographic methods, in particular HPLC, has become the focus of intensive research of separation scientists.

Materials and Methods: Selected studies with the most relevant chiral selectors and CSPs (that is, those based on glycopeptides, proteins, polysaccharides, *Cinchona* alkaloids, and amino acids) will be presented. Applications in the principal elution modes (RP and NP, as well as PO and PI) will be discussed. Focus will be also given to the spectroscopic- and *in silico*-based methods aimed at determining the absolute configuration of enantiomers, in the absence of pure reference standards.

Results: The development and application of HPLC methods aimed at appraising the quality of enantioselective synthesis protocols of pharmaceutically relevant compounds will be shown. Furthermore, the potential of the principal commercially available CSPs towards the laboratory-scale HPLC-based enantioresolution of pharmaceutically relevant compounds belonging to different chemical classes, will be described. The utility of 2D-HPLC achiral-chiral chromatographic methods to assess the impact of natural or artificial interventions on the product quality will be highlighted. Still in the context of food analysis, the importance of chiral analysis for the identification of enantiomeric impurities or adulterations that can occur during the storage or the preparation of foods or food supplements will be discussed. Finally, the enantioseparation of the disease-related biomarkers will be presented.

Conclusions: This presentation aims at describing the multi-purpose importance of enantioselective liquid chromatography, spanning from the control of asymmetric synthesis protocols to the study of food and biological matrices.

PL26: CANNABINOIDS AGAINST CISPLATIN NEUROTOXICITY

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Introduction: Cisplatin (CIS), an effective antineoplastic agent with broad spectrum causes peripheral neuropathy which is a major dose-limiting side-effect. Cannabinoids are known to have a potential analgesic effect. The antinociceptive and neuroprotective effects of anandamide (AN), a cannabinoid receptor agonist were investigated against CIS-induced neuropathy and the role of nitric oxide (NO) in this effect.

Materials and Methods: Primary DRG cultures were prepared from one day old rats for *in vitro* investigations. DRG cells were incubated with CIS (100-300 mM), and AN (10, 50, 100 and 500 µM) was administered with the submaximal concentration of CIS. Male Wistar rats were divided into four groups: Control, CIS, CIS+AN, CIS+AN+ L-NG-nitro arginine methyl ester (L-NAME). CIS was administered 3 mg/kg ip once weekly for five weeks. Saline (2 ml) was also given to prevent

nephrotoxicity. AN (1 mg/kg ip) or in combination with 10 mg/kg ip L-NAME was administrated 30 min before every CIS injection. Mechanical allodynia, thermal hyperalgesia and tail clip tests were performed on the 6th day of each drug injections and hind paw, tail withdrawal latencies were recorded. Cannabinoid tetrad also was evaluated. At the end of the drug administration, rats were fixed by intracardiac perfusion. Right sciatic nerves (SN) and associated dorsal root ganglia (DRG) were isolated were investigated histologically. Data were analyzed with one way and two way ANOVA. Significance level was accepted as $p<0.05$.

Results: CIS caused concentration-dependent neurotoxicity in vitro and decreased hind paw withdrawal latency in mechanical allodynia test, but did not alter this latency in thermal hyperalgesia and tail clip tests. AN decreased concentration-dependently CIS-induced neurotoxicity and increased hind paw withdrawal latency in mechanical allodynia. Cannabinoid tetrad was maintained partly as the locomotor activity and catalepsy. In the assessment of SN, the ratio of degenerate/normal (Deg/Nor) axons significantly increased in CIS group, AN decreased while L-NAME reversed this effect. In CIS+AN group, soma area of DRG neurons in the range of 801-1000 μm^2 significantly were higher than those of CIS group.

Conclusion: Our results indicate that AN treatment attenuated CIS-induced neurotoxicity and neuropathy. It seems that NO may have a role in these effects. These findings indicate that AN may be a therapeutic alternative for CIS-induced peripheral neuropathy however its central adverse effects must be considered.

PL27: MICROSAMPLING IN BIOANALYSIS: NEW CHALLENGES AND PERSPECTIVES

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Introduction: There is a growing interest in the implementation of miniaturised approaches for the determination of therapeutic drugs, drugs of abuse, metabolites and biomarkers in biological samples involved in a wide range of applications. This interest is due to the advantages of sampling minute amounts of biomatrices, particularly for those studies performed in delicate populations. Moreover, these technologies facilitate sampling in locations usually difficult to be reached. Finally, they enable feasible, straight-forward and time- and cost-effective analytical protocols (1).

Materials and Methods: This lecture gives a comprehensive insight about the optimisation of advanced strategies in bioanalytical method development and validation, providing recommendations for best practice in a wide range of applications. A panel of novel, miniaturised protocols have been designed for the determination of classical drugs of abuse (eg. cannabinoids, cocaine and methadone), new psychoactive substances (NPS), doping agents (both small molecules to doping-relevant peptides), as well as prescription drugs.

Results: The developed microsampling approaches include capillary volumetric blood microsampling, volumetric absorptive technologies and microfluidic strategies. These allow to collect microvolumes of biological matrices in an accurate manner regardless of density and to guarantee sample integrity, subject compliance, a solid chain of custody and feasible, yet effective analytical protocols (2). For sample pretreatment, miniaturised solid phase extraction optimised to be applied to a broad range of microsamples and is herein represented by microextraction by packed sorbent, disposable pipette extraction and stop-and-go extraction.

Conclusion: All the factors and conditions involved in the sample collection, extraction and clean-up steps have been extensively evaluated in order to produce solid and robust protocols. This allowed to obtain a comparative evaluation of procedures and techniques offering peculiarities, advantages and challenges that could guide bioanalytical scientists towards the best miniaturisation choice in relation to the different application scenarios.

Acknowledgements

This research work was financially supported by the World Anti-Doping Agency (WADA) within the 2019 Research grants [Project 19A08LM].

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PL28: TOWARD PHARMACOLOGICAL MODULATION OF SERCA FUNCTION: WHY AND HOW

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SERCA is the Ca^{2+}-pump (ATPase) responsible for Ca^{2+} clearance from the cytosol and its accumulation in the sarcoplasmic reticulum of cardiac muscle.

SERCA dysfunction is among the main features of heart failure and contributes to many of the derangements peculiar of the condition.
Selective enhancement of SERCA function may represent a novel ino-lusitropic strategy in the treatment of heart failure.
The presentation will discuss the rationale for therapeutic SERCA modulation and how it can be achieved. Data on new small-molecule compounds, recently developed for the purpose, will be presented

Acknowledgement

The research presented has been supported by grants from CVie Therapeutics (Taiwan) and Windtree Therapeutics (USA)

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PL29: THE IN VITRO ANTIMICROBIAL-ACTIVITY APPROACH AGAINST MDR BACTERIA USING METAL/METAL-OXIDE NANOPARTICLES

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The use of nanoparticles (NPs) and research on antimicrobial activity is increasing. The use of NPs in catheters, on medical textiles and other surfaces in the healthcare settings is still a challenge because the non-specific nature of the antibacterial effect is different from known antimicrobial agents and biocides. An interdisciplinary approach aiming to develop the antibacterial coatings as a medical product is crucial to evaluate their antibacterial activity. The critical part of translational research is to determine the antimicrobial activities of NPs *in vitro*. The various *in vitro* approaches aim to elucidate the activity in time with different colloidal NPs in contact with bacterial cells with an endpoint such as cell viability, membrane plasticity in the cell wall and inhibition of biofilm formation. The use of traditional assays such as MIC (minimum inhibitory concentration) and MBIC (minimum biofilm inhibitory concentration) determination is compromised because NPs were inhibited by microbiological media compounds. The large surface area of NPs also aggregates in media and causes overall false negative results in antimicrobial based *in vitro* assays with their inhibition by proteins. On the other hand, impregnation of medical textiles with NPs coatings is challenging due to the lack of precise and accurate evaluation of antimicrobial activity of coatings. However, these drawbacks are leading to a rethinking of the *in vitro* antimicrobial approach to certain issues raised by the use of "classical" assays. However, some NPs, particularly those with slow oxidation, are leading to the concept of depot - as preserved antimicrobial activity in time, which represents major advantages over antimicrobials and biocides. The talk will present current *in vitro* approaches to antimicrobial activity of various colloidal NPs against MDR bacteria, challenges, and potential solutions.

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PL30: STRATEGIES FOR RE-DISCOVERY OF CNS DRUGS FROM AFRICAN PLANTS

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It is well known that many currently used drugs originated from natural sources, especially plants. Based on chemical structures, these drugs are as simple as aspirin to as complex as morphine. They may be used as isolated or may need to undergo chemical modifications to yield the drugs, followed by appropriate formulations. These drugs are used for the treatment of various diseases, including CNS disorders, from pain to neurodegenerative disorders. Importantly, two of the four drugs that are USA FDA approved for the treatment of Alzheimer's disease, a neurodegenerative disorder are plant alkaloids. The possible fifth drug (aducanumab) is generating a lot of controversy at this time. The two drugs are alkaloids galantamine and rivastigmine. In the latter case, the natural product is physostigmine. Chemical modifications of it to optimize activity and increase CNS bioavailability led to rivastigmine. Chemical modifications to decrease CNS bioavailability led to neostigmine which is used for urinary retention, myasthenia gravis, and Ogilvie Syndrome. The natural product itself, physostigmine, is used for the treatment of glaucoma. All the three compounds achieve their pharmacological actions, at least in part, as acetylcholine esterase inhibitors. Physostigmine was isolated from the Calabar bean which is native to Nigeria. Given the emergence of new technologies such as combinatorial chemistry, high throughput screening, better abilities to evaluate synergies, and better pharmacological assays, the question becomes whether it is worth re-examining African plants for CNS drug leads? The question is more pertinent now given the very high failure rate in clinical trials for drugs in this class and the increasing need. This talk will focus on possibilities in neurodegenerative disorders treatments.

PL31: INHIBITION OF NUCLEOSIDE DIPHOSPHATE KINASES AS A NOVEL THERAPEUTIC OPTION IN THE TREATMENT OF CARDIOVASCULAR DISEASES

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Nucleoside diphosphate kinases (NDPKs) are important housekeeping enzymes in nucleotide triphosphate homeostasis. Early reports during the 1990s already indicated a close association of NDPKs with heterotrimeric G proteins to replenish GTP required for their activation. We meanwhile identified oligomers of the NDPK isoform B and C to form a complex with heterotrimeric G proteins[1]. Apparently, NDPK C is essential for a complex formation with the G protein βγ dimer. As proven by knockdown experiments in zebrafish embryos the interaction formation of NDPK B and C with Gβγ is required for the contractility of the heart[1,2]. Intriguingly, besides its classical enzymatic activity, its ability to function as protein histidine kinase also contributes to its specific interaction with Gβγ. Within the complex a specific is histidine residue is phosphorylated in Gβ[3]. If this His is mutated to Ala, the isoprenaline-induced cAMP formation and single cell contractility in cardiomyocytes is significantly impaired[4]. Interestingly, NDPK C is upregulated in human heart failure and is preferentially found in complexes with the inhibitory G protein of the adenylyl cyclase, G_i. In contrast, in non-failing hearts, NDPK is preferentially bound to the stimulatory G protein G_s[1]. Therefore, NDPK C likely contributes to well-known chronic inhibition of cAMP formation in failing heart muscle.

A second target, which is regulated in its activation by NDPKs, is the intermediated conductance potassium channel SK4. We could show that the phosphorylation of the channel on a C-terminal histidine residue by NDPK B is required for vascular smooth muscle cell proliferation and neointima formation after vessel injury[5]. It is apparently also involved in arrhythmogenesis in patients with arrhythmogenic right ventricular cardiomyopathy[6].

Therefore, small molecule inhibitors targeting specifically NDPKs might be relevant for new therapeutic strategies in cardiovascular disease. Out of a library of several hundred potential candidates, we identified several substances, of which one, SanWie3, showed a preference for NDPK C whilst a second one preferentially inhibited NDPK B. Both inhibited the enzymatic activity of NDPKs in an allosteric manner. Interestingly, when applied in adult cardiomyocytes, SanWie3 increased the isoprenaline (ISO)-induced cAMP formation exclusively in the SERCA subdomain. In accordance, it also increased the ISO-induced phosphorylation of phospholamban, caused an enhancement of the SR Ca^{2+} load, the systolic Ca^{2+} amplitude and increased the ISO-induced contractility of left ventricular strips. It is therefore an interesting candidate to be structurally optimized and further tested for the potential use as novel therapeutic option.

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PL32: BACTERIOPHAGE THERAPY: PAST, PRESENT, FUTURE

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Introduction: Bacteriophages (phages) bacterial viruses were discovered 100 years ago by Felix d'Herelle, who proposed to use them for treatment and prophylaxis of bacterial infections. Uncontrolled use of antibiotics led to development and broad spread of multiply resistant bacterial pathogens, which became practically untreatable. Nowadays phages are considered as alternatives to antibiotics. Novel technologies facilitated progress in understanding of phage biology and genetics, which opened new areas for their exploitation for the benefit of human health. The aim of this presentation is to introduce the audience with the history of phage discovery, further development of phage therapy, new achievements, approaches to tackle regulatory hurdles, methods for advancing manufacturing process and future perspectives.

Materials and Methods: The information provided to audience is based on the previously unknown old publications, so called "grey" literature. The presentation will focus on the results of the recently performed clinical trials for treatment of UTI infections among patients undergoing transurethral resection of prostate (TURP).

Results: The randomised, placebo supported, double blind clinical trials accomplished for treatment confirmed that the phages are safe. Phages and placebo were administered via catheterization, while an antibiotic was administered orally. No adverse events typical for antibiotic therapy have been observed. However, the outcome in the placebo and phage group appeared to be similar. These results are contrusting with the the same obtained during personalized treatment.

Conclusions: Phage therapy has important advantages in comparison with antibiotics, such as an action specifically targeting the cause of infection without disturbing human microflora, effectiveness against drug resistant pathogens, safety, etc. However, use of bacteriophages may have some limitations, therefore it is necessary to perform more clinical trials and advance the mode of administration (e.g. elaborate phage-based intravenous solutions). To avoid adverse events synthetic phages can be developed.

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PL33: DRUG-INDUCED HYPERSENSITIVITY: OPPORTUNITIES TO EXPAND NON-ANIMAL MODEL FOR THE IDENTIFICATION OF SENSITIZATION TO DRUGS

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Starting from the assumption that allergenic drugs share with chemical allergens common mechanisms of cell activation, it is possible to speculate for drugs the possibility of tracking human drug allergens from the identification of peptide-binding, dendritic cell (DC) activation and chemical-specific naive human T-cell priming as currently done for chemical allergens. It may be also possible by choosing different markers (e.g. type 1 and type 2 cytokines) to discriminate different types of hypersensitivity by the intrinsic capacities of allergens to polarize DC towards DC1 and DC2, irrespective of local factors such as those determined by cutaneous or mucosal epithelial microenvironments. While without any doubt, additional efforts and extensive resources are necessary to improve preclinical testing methodologies, including optimization of the experimental design and interpretation of data, the possibility of using currently in vitro methods for the hazard identification of the allergenic potential of chemicals for drugs will be presented and discussed.

PL34: POSITIVE OR NEGATIVE EFFECTS OF RECREATIONAL SCUBA DIVING - CAN WE ADAPT TO A CHALLENGING ENVIRONMENT?

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PL35: DEVELOPING, IMPLEMENTING AND EVALUATING ADVANCED PHARMACY SERVICES WORKING WITH PRACTITIONERS AND POLICY MAKERS

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This talk will first describe the community pharmacy contract and services in England. Two major advanced services will be described in detail, influenza and COVID-19 vaccination and the new Community Pharmacy Consultation Service. The Community Pharmacy Consultation Service is a service whereby patients are referred to pharmacies from general practitioners (primary care) and from the national telephone triage service (NHS111). The talk will demonstrate how it is important to use evidence to develop new services, to train the pharmacists and their staff as well as the importance of ongoing evaluation and dialogue with the profession and policy makers.

PL36: POTENTIAL MECHANISMS UNDERLYING THE PROTECTIVE EFFECTS OF ANTHOCYANINS IN METABOLIC SYNDROME AND RELATED DISORDERS

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Metabolic syndrome (MetS) is a set of risk factors which severely increases the risk of type II diabetes and cardiovascular diseases. Over the last decades, epidemiological studies underlined the role of dietary bioactive compounds in features of MetS. Due to their multiple properties, anthocyanins (ACN), a class of polyphenolic compounds widely found in various vegetables and fruits, have demonstrated to provide positive effects in metabolic-related diseases (1). In particular ACN have reported health benefits contributing to vascular homeostasis, reducing hypertension, inflammation and platelet aggregation, and also improving insulin resistance and dyslipidaemia. In addition, ACN decrease fat accumulation in adipose tissue reducing local oxidative stress and inflammation and attenuating adipocytokine dysregulation (2). Many in vitro and in vivo studies revealed an array of mechanisms through which ACN could prevent or reverse metabolic-related disease including promotion of antioxidant and anti-inflammatory activities.
ACN, like several plant antioxidants, exhibit hormetic properties, by acting as 'low-dose stressors' that may prepare cells to resist more severe stress. In fact, the discovery of specific genes (HO-1, NQO1, g-GCS) and pathways (redox sensitive Nrf2, NF-kB regulated signaling) affected by antioxidants, led to the hypothesis that anthocyanins may act as modulators of gene regulatory and signal transduction pathways (3). Furthermore, ACN positively regulate glucose transporters density and function in endothelium and adipose tissues via the insulin signaling pathway and induce switching of the cells from an anabolic to a catabolic state through the upregulation of AMPK signaling (3).
The ACN-mediated protection against obesity, T2DM and vascular dysfunction will be discussed focusing on the underlying molecular mechanisms.

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PL37: ROLE OF CENTELLA ASIATICA, AEROBIC EXERCISE AND ITS COMBINATION IN WOMEN WITH MILD COGNITIVE IMPAIRMENT

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Introduction: Mild Cognitive Impairment is characterized by a decrease in mild cognitive function and is still able to carry out daily activities (1). Women are also known to experience brain atrophy faster than men because of differences in sex hormones, behavior towards life, and estradiol deflation (2). Centella asiatica (CA) is one of the traditional plants that is known to have neuroprotective effects, strengthening memory and intelligence because of its active compounds asiaticosides and madecosides (3). Several studies have shown the benefits of aerobic exercise (AE) for preventing cognitive impairment, stimulating the brain, and increasing BDNF. The purpose of this study was to analyze the efficacy of Centella asiatica, aerobic exercise, and their

combination on brain-derived neurotrophic factor (BDNF), estradiol, apolipoprotein E, and tumor necrosis factor-α (TNF-α) plasma, cognitive function, physical fitness, and quality of life in women with MCI (Mild Cognitive Impairment).

Materials and Methods: The study design was a 12-week single-blind randomized controlled trial. The research subjects were consisted of 64 MCI women aged 53.25 ± 4.82 years and divided into four groups. Physical fitness assessment included hand muscle strength with the handgrip test and lower extremity strength with the 30 seconds chair stand test, while the balance was assessed with the one-leg standing test. Quality of life was measured by WHO-QoL questionnaire, and cognitive function is measured by MoCA-Ina, Verbal Fluency, Digit Span, Visual Memory, and Trail Making Test.

Results: The results showed that *Centella asiatica*, aerobic exercise, and their combination were effective in increasing plasma BDNF, estradiol, cognitive function, physical fitness, and quality of life as well as decreasing APOE and TNF-α plasma in Mild Cognitive Impairment (MCI) women. CA showed the highest increase in semantic fluency (∆=4,44; p=0,002), forward digit span (∆=0,63; p=0,001), and backward digit span (∆=2,75; p<0,001). Furthemore, AE showed the highest increase in BDNF plasma (∆=331,13; p=0,001) and one leg balance with open-eyes (∆=34,06; p=0,007). Meanwhile, the CA-AE combination led to the highest increase in TNF-α plasma (∆= -10,48; p=0,007), MoCA-Ina (∆=4,63; p<0,001), phonemic fluency (∆=1,75; p=0,003), visual recall (∆=6,88; p<0,001), TMT-B (∆=-21,38; p=0,007), righthand strength (∆=4,09; p<0,001), lefthand strength (∆=3,44; p=0,002), and lower extremity strength (∆=6,88; p<0,001). Assessment on quality of life showed the CA had significant increases in physical (p=0.028) and environmental (p=0.016) domains, while the AE and the CA-AE combination had significantly increased values in all domains of physical, psychological, social relations, and the environment.

Conclusions: Taken together, the results of the present investigation indicate that *Centella asiatica*, aerobic exercise, and their combination are effective in ameliorating plasma levels of BDNF, estradiol, APOE, TNF-α, cognitive function, physical fitness, and quality of life in women with mild cognitive impairment. For further research, clinical trials can be conducted with a larger number of respondents, both women and men.

Acknowledgements

This study was supported by a grant of Indonesian Collaborative Research Program, The Ministry of Research and Technology.

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PL38: MEDICATION DYSPHAGIA: FOCUS GROUP PILOT STUDY ON PHARMACISTS' KNOWLEDGE, ATTITUDES & PRACTICES MEDICATION DYSPHAGIA: FOCUS GROUP PILOT STUDY ON PHARMACISTS' KNOWLEDGE, ATTITUDES & PRACTICES

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Introduction: Solid oral dosage forms (SODFs) are commonly used due to their convenience and ease of accurate dosing [1]. Therapeutic efficacy depends on the patient's ability to swallow SODFs. However, 10-40% of patients reportedly experienced medication dysphagia (MD) [2] – the subjective sensation of difficulty swallowing oral medications. Among patients with MD, 9.8% and 83.7% experienced MD with each medication and with every dose taken, respectively [3]. One of the strategies for our holistic, concerted, sustained and multi-pronged approach to the prevalent but often overlooked problem of MD is to investigate health professionals' knowledge, attitudes, and practices (KAP) in caring for patients with MD.

Materials and Methods: An inductive qualitative study design via the asynchronous online focus group (AOFG) was adopted to elicit responses through participant interactions. The research protocol received ethics approval (PHA-DERC-14) on 15-02-2021. Prior literature review of MD guided the development of AOFG discussion guide. Questions were reviewed by 4 pharmacists for face and content validity. The AOFG was pilot tested in a convenience sample of another 7 pharmacists. Inclusion criteria included current involvement in direct patient care and possession of a device with internet access. Participants' consent and contact details for dissemination of invitation links and reminders were collected via email replies. Thematic analysis was conducted using Braun and Clarke's 6-phase framework, taking semantic and latent level approaches and open coding to

facilitate the inductive identification of themes [4,5]. Themes were reviewed for refinement and identification of subthemes and relationships, then named and defined by discussion and consensus.

Results: Thematic analysis of transcripts revealed 5 interrelated themes as summarised in the following table.

Themes	Findings
1. Knowledge about MD	Room for improvement regarding prevalence and assumptions about affected demographics
2. Management of MD	Modifying medications and switching formulations as preferred strategies; Assisted by references and hindered by time constraints
3. Expectations of patient proactivity	Limited screening for MD despite recognizing opportunities for earlier identification
4. Desire for objectivity	Emphasis on objective factors accounting for the seemingly lower perceived importance of MD; Overlooking of subjective factors and the corresponding management strategies
5. Professional roles	Distinct but complementary functions for each profession in MD management; Provision of administration instructions as the minimum standards to safeguard healthcare professionals from liability

Conclusions: The insight into pharmacists' KAP and methodological considerations may be incorporated into a full-scale study involving all healthcare professions. Future work may also include studies on MD's prevalence across care settings and development of MD management plans.

Acknowledgements
This study was supported by a grant (R-148-000-311-114) of the Singapore Ministry of Education Academic Research Fund Tier 1.

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PL39: PROMISING INHIBITORS TARGETING MPRO: SELENIUM BASED COMPOUNDS WITH ANTI-SARS-COV-2 ACTIVITY

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Introduction: In 2020, a global pandemic caused by the SARS-CoV-2 spread all around the world, producing more than 3,4 millions of deaths. Even if vaccination is the method of choice for its containment, after 6 months from the beginning of the prophylaxis campaign less than 5% of the global population is currently fully vaccinated, and the disease will remain a cause of severe infections, fatal cases with an increased risk of escape variants. For these reasons the development of new small molecules able to block virus replication is highly demanded.

Materials and Methods: The Main protease of SARS-Cov-2 is considered an ideal therapeutic target Starting from the seminal work of Haitao (1) we developed the synthesis of a new library of Ebselen that were tested in the M^{pro} inhibition as well as in the inhibition of the viral replication in infected cells. NMR investigations were designed to investigate the redox mechanism that is at the base of the activity by the covalent interaction with Cys-145. Similarly, considering that the same enzymatic portion can be non-covalently targeted by quercetin (2), we investigated the in vitro and in vivo activity of a series of quercetin derivatives unprecedently functionalized at C-8 with organoselenium functional groups.

Results and Conclusion: We report here new insights into the mechanism of interaction between Ebselen, its derivatives and the corresponding diselenides with naturally occurring thiols and reactive cysteines proving the anti-SARS-Cov-2 activity of some newly synthetized compounds. Furthermore we also discovered that the C-8 functionalization of quercetin with a p-tolylselenenyl group iproduce a 24-fold improvement of the antiviral activity in cell.

Acknowledgements

This study is part of the activities of the international Scientific Network SeSRedCat and has been realized thanks to a collaboration with : UFPel (*Peotas Brazil*): S. F. Fonseca, L. Abenante, E.J. Lenardão, D. Alves; University of Torun (Poland): J. Scianowski, A. Pacula, M. Obieziurska; Jagellonian Uiversity Cracow (Poland): A. Kula-Pacurar, K. Pyrc, A. Dabrowska, P. Botwina; Shangai Tech University (China):

Haitao Yang, Ying Lei, Juan Kong, Yao Zhao; University of Zaragoza (Spain): A. Velazquez-Campoy, D. Ortega-Alarcon; A. Jimenez-Alesanco, L. Ceballos-Laita, O. Abian; CNR-NANOTEC (Rende, Italy): B. Rizzuti; University of Pisa (Italy): G. Ciancaleoni

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PL40- INNOVATIVE DIHYDROOROTATE DEHYDROGENASE (HDHODH) CLINICAL READY INHIBITORS AS PAN-CORONAVIRUS (SARS-COV-2) ANTIVIRALS: TARGETING THE UNEXPECTED WITH INNOVATION

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Introduction: The devastating effects of the new **CO**rona**VI**rus **D**isease (COVID-19) have taught the world the weakness and general unpreparedness in tackling such a viral pandemic. SARS and MERS outbreaks indeed indicate that SARS-CoV-2 is not the first zoonotic *coronavirus* (CoVs) that humanity has to face, and it would likely not be the last. Already at the beginning of a novel CoVs emergence, effective antivirals should be available to slow down the spread of infection, saving life, and gaining time while waiting for the specific CoV vaccine development. Thus, ***pan-***CoVs ***antivirals*** effective for the management of SARS-CoV-2 infection that can be rapidly deployed against future emerging CoVs are urgently needed.

Materials and Methods: To contribute to this preparedness, a *hit-to-lead* optimization process have been applied for the discovery of a class of potent *human dihydroorotate dehydrogenase* (*h*DHODH) inhibitors based on the hydroxypyrazole[1,5-*a*]pyridine scaffold[1] to be investigated as *Host-Targeting Antivirals* (HTAs).

Results: Among—this class of molecules, **MEDS433** has been shown to be a potent HTA and it is being developed until preclinical level. By affecting the host *de novo* pyrimidine biosynthesis, MEDS433 in fact inhibits the *in vitro* replication of several hCoVs, such as SARS-CoV-2,[2] hCoV-OC43 and hCoV-229E, as well as a large virus panel[3] with EC_{50}s always in the low nM range and an incredibly effective *Safety Index* (SI). In order to pave its future entrance in clinical trials for COVID-19, drug combination strategies to enhance MEDS433's antiviral effectiveness are also being explored.

Conclusions: Due to the favorable PK and toxicity in mice, MEDS433 is proposed as dual acting pan-CoVs HTA, effective against SARS-CoV-2 and other CoVs infections by directly inhibiting virus replication through pyrimidine depletion and by stimulating the antiviral innate immune responses.

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ORAL PRESENTATIONS

OP001: DEVELOPMENT AND OPTIMIZATION OF SULPHAMETHOXAZOLE NANOSUSPENSION FORMULATIONS

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Introduction: Sulfamethoxazole (SMX) is a sulfonamide-derived antimicrobial agent listed in BCS Class II (1,2). Nanosuspensions (NS) can be defined as nano-sized colloidal dispersions of drug particles that are stabilized with surfactants and/or polymers (3). In this study, preliminary studies were carried out for the preparation of NS to increase the solubility and antimicrobial activity of SMX, and the effect of some process variables on NSs was evaluated.

Materials and Methods: SMX-NS were prepared with media milling technique. Firstly, SMX was added to surfactant (Pluronic F127) and polymer (PVP-K30) solution, and pre-mixed was applied first with Ultra-Turrax (15000 rpm, 10 min) and then with ultrasonic probe (55% power, 1 min). Zirconium oxide beads with a diameter of 0.3-0.4 mm were added to the suspension obtained after pre-mixing, and comminution was carried out on a magnetic stirrer. A three-factor, three-level Box-Behnken design was employed to evaluate the effect of polymer and surfactant concentration and stirring time on the critical quality attributes of NS (particle size, PDI, and zeta potential). Type of polymer and surfactant, milling media, SMX concentration, and stirring rate were kept same for all the experiments.

Results: The stirring time was determined as 15 hours, the surfactant concentration was 2%, and the polymer concentration was 1.4% for optimum formulation. Particle size, PDI, and zeta potential values of the optimum formulation were found 196.4±7.98 nm, 0.493±0.021, and -8.17±1.09 mV, respectively.

Conclusions: This study demonstrated the effect of polymer and surfactants concentration, and stirring time on the SMX-NS using Box Behnken design. Also, the NS might be useful for improvement of antimicrobial activity and solubility of SMX.

Acknowledgements

This study was supported by Atatürk University Scientific Research Foundation (Project No: THD-2020-8265)

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OP002: STABILITY ENHANCEMENT OF S-ADENOSY-L-METHIONINE THROUGH NANOFORMULATION APPROACH

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Introduction: S-adenosyl-L-methionine (SAMe) is a universal methyl donor naturally present in all cells. SAMe is involved in many chemical reactions especially methylation. Although SAMe has a high potential for the treatment of different diseases, it has stability problems such as high chemical instability, diastereoisomerism, alkali sensitivity, oxidation and thermal degradation (1). In this study, SAMe was encapsulated in inulin and pectin nanoparticles to prevent its stability problems and characterization studies were conducted. These formulations were subjected to different conditions to evaluate the stability of SAMe.

Materials and Methods: S-Adenosylmethionine 1,4 butanedisulphonate (Carbosynth NA), Pectin (55-70% esterified potassium salt, Sigma Aldrich) and inulin (Sigma Aldrich) were used for all experiments. For encapsulation of SAMe, pectin and inulin nanoparticle formulations were prepared. Pectin nanoparticles were prepared using ionic gelation method. Inulin nanoparticles were prepared using desolvation method with ion pairing. In order to estimate the formulation stability, two different storage conditions were chosen: 5±3˚C and 25±2˚C. After certain incubation periods, (initial, 1st, 3rd and 6th months) samples were removed and characterized in terms of particle size, polydispersity index (PDI), zeta potential (ZP), drug loading (DL %) and encapsulation efficiency (EE %).

Results: According to results, drug content was highly stabilized via inulin nanoparticles compared to pectin nanoparticles. On the other hand, temperature was found to be very effective on the stability of SAMe.

Conclusions: Among the prepared formulations, inulin nanoparticles were found to be the ideal formulation to maintain the stability of SAMe. Under these circumstances the temperature of 5±3˚C is suggested as an appropriate storage condition for SAMe loaded inulin nanoparticles.

Acknowledgements

This study is supported by the Turkish Scientific and Technological Research Council (TÜBİTAK grant number 115S339).

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OP003: MESOPOROUS SILICA-BASED NANOCARRIER FOR TARGETED CANCER THERAPY

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Introduction: An important aim in cancer therapy is the development of drug carriers to successfully carry chemotherapeutics to tumor cells while reducing chemotherapy induced severe side effects. Mesoporous silica nanoparticles (MSN) represent ideal nanodevices for localized drug delivery thanks to their peculiar structural properties and biocompatibility. MSNs with their large surface areas and easy surface functionalization allow to encapsulate diverse therapeutic agents and to bind ligands for targeting biomarkers overexpressed on cancer cells (1). In this study, a MSN-based nanocarrier (FOL-MSN-BTZ) loaded with the antineoplastic drug bortezomib (BTZ) and bearing folic acid (FOL) as targeting function has been designed and developed.

Materials and Methods: MSNs were synthesized by an interfacial synthesis procedure using Triton X-100 as structure-directing agent and tetraethylorthosilicate as silica source. Boron content of FOL-MSN-BTZ was measured by Atomic Absorption Spectroscopy.

Results: FOL-MSN-BTZ (2,3) consists of MSU-type silica nanoparticles functionalized with folic acid on the external surface and containing inside the pores the antitumor drug Bortezomib, drug of choice for the treatment of multiple myeloma (MM). A 1,2-diol group is grafted inside MSNs pores to anchor BTZ through the formation of a pH-sensitive boronate ester. The system is designed to be recognized by MM cells overexpressing folate receptors (FR+) and subsequently internalized into the cells where the drug is released at slightly acid pHs. FOL-MSN-BTZ prototype was tested on FR positive (FR+) cancer cells and FR negative (FR-) normal cells. These experiments showed that FOL-MSN-BTZ provokes death predominantly in FR+ MM cells while free BTZ resulted toxic for both cell lines. Remarkably, the vehicle alone (MSN-FOL) showed no evident toxicity on both cells.

Conclusions: FOL-MSN-BTZ represents a great system for the targeted therapy of MM. Ongoing in vivo studies to assess the biocompatibility and efficacy of FOL-MSN-BTZ in mouse xenograft models are also highly promising.

Acknowledgements

This study was supported by POR Calabria FESR–FSE 2014-2020 Action1.2.2 (NANOCAL-CUP J28C17000200006), and European Union and MIUR, European Social Fund-PON R&I 2014-2020.

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OP004: DEVELOPMENT AND *IN VIVO* EVALUATION OF A PULSATILE-RELEASE CAFFEINE FORMULATION

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Introduction: Sleep inertia is a disabling state of reduced physical and mental drive following wakening, which typically lasts for less than 30 minutes, but symptoms may persist for several hours in susceptible individuals (1-4). An adenosine receptor antagonist, caffeine, is widely used to reduce sleep inertia symptoms, yet the initial, most severe impairments are hardly alleviated by post-awakening caffeine intake. To ameliorate this disabling state more potently, we aimed to develop a pulsatile-release caffeine formulation, which is administered before the sleep, releases only insignificant amounts of caffeine during sleep and provides adequate caffeine blood plasma levels before the planned awakening time.

Materials and Methods: The pulsatile-release caffeine formulation was manufactured using a fluid bed coater with a Wurster tube. The formulation was developed using an inert microcrystalline cellulose core, a drug layer comprising caffeine and a release-controlling layer comprising a polymeric system that is based on methacrylic acid copolymers, which controls the release of caffeine both pH-dependently and pH-

independently. For simulating gastrointestinal tract conditions, the *in vitro* release studies were carried out in the media with a pH transition from 1.2 to 7.2 in a 10-hour period. The *in vivo* caffeine release profile was determined in 10 male individuals. After oral intake at 22:30, the study participants were allowed to sleep from 23:00 - 07:00, while their blood was continuously sampled for a total of 17.5 hours after the administration of the study formulation. The blood samples were analysed using a validated LC-MS/MS method after a suitable sample preparation procedure.

Results: The pulsatile-release caffeine formulation exhibited an *in vitro* release profile, where not more than 10% of caffeine is released during the first 5 hours and not less than 90% of caffeine is released until the 9th hour. The blood plasma concentration of caffeine reached 5 µM after 4 hours following the administration and the C_{max} was observed at about 10.5 hours following the administration of the developed pulsatile-release caffeine formulation to the human subjects.

Conclusions: The study results showed that the developed formulation exhibited an appropriate pulsatile-release profile, where the *in vivo* caffeine release during sleep was below the clinically significant threshold, which is followed by the rapid release of caffeine with a lag time around 8 hours after the administration of the study formulation. It was observed that the *in vivo* release of caffeine was well correlated with the *in vitro* release results of the developed formulation. Based on the *in vitro* and *in vivo* results, it was concluded that a pulsatile-release caffeine formulation was successfully developed. Further clinical efficacy and safety studies are planned to understand the relation of the pharmacokinetics and pharmacodynamics of the developed formulation for the facilitation of the sleep-to-wake transition in sleep-restricted healthy adults.

Acknowledgements

We thank Dr. Dario Dornbierer from the Institute of Pharmacology and Toxicology, University of Zurich, Zurich, Switzerland for conducting the *in vivo* experiments of this study.

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OP005: CELLULAR UPTAKE OF POLYMERIC TUBULAR NANOCARRIERS

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Introduction: Nanocarriers play a major role for the effective cellular delivery of drugs, due to their small size which facilitates them to extend drug half-life in blood circulation (1). Recent studies demonstrate that, the shape of nanocarrier is a critical parameter affecting circulation time and tumor accumulation and also cylindrical nanocarriers circulate longer giving them more time to reach target tissue (2). Template-assisted synthesis is one of the most promising ways of fabrication polymer tubular nanostructures. Anodized aluminum oxide (AAO) membrane is one of the most popular templates for nanorod/nanotube fabrication by template wetting method (3). Due to effective chemotherapy depends on prolonged exposure of cancer cells to cytotoxic agents, the cellular uptake of drug loaded nanocarriers is an important parameter (4). The aim of this study is to fabricate fluorescent Coumarin-6 (C6) loaded PLGA tubular nanocarriers and evaluate them for cellular uptake into A549 cells.

Materials and Methods: AAO membrane (Anodisc 47, Whatman™) with pore diameter of 200 nm. PLGA and Tween 80 were purchased from Sigma-Aldrich. A549 cells were seeded on Millicell® EZ Slides in DMEM containing high concentration glucose, 2 mM L-glutamine, 10% fetal bovine serum and 1% penicillin/streptomycin. Cells were incubated for 24 h in a 5% CO_2 incubator (37°C). On the second day after seeding, the growth medium was replaced with fluorescent C6 loaded nanocarrier suspension, incubated for 2h and 4h at 37°C, and the cell monolayers were fixed with 4% paraformaldehyde. The uptake of nanostructures into cancer cells was visualized using a confocal microscope (Zeiss LSM 510).

Results: Throughout these studies tubular nanocarriers seemed capable of cellular internalization into A549 cells.

Conclusions: C6 loaded PLGA tubular nanocarriers were successfully fabricated and evaluated for cellular uptake into A549 cells. Nanocarriers were found promising for the delivery of antineoplastic agents.

Acknowledgements

This study was supported by a grant of TUBITAK (SBAG-113S201).

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OP006: PREPARATION AND CHARACTERIZATION OF FAST-DISSOLVING DESLORATADINE ORAL FILM FOR GERIATRIC USE

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Introduction: Special needs of the pediatric and geriatric patients led to the introduction of new oral dosage forms that have been expected to enhance therapeutic effects and improve patient compliance or develop currently available ones. Oral strip technology (OST) has been developed as an alternative to oral disintegrating tablets and to overcome their disadvantages. (1). Desloratadine (DSL) is one of the better-known second-generation antihistamines that has been studied for being effective in relieving the allergic nasal and skin symptoms (2). The aim of this study was to develop DSL orodispersible film (ODF) with fast disintegration time and suitable mechanical strength to treat allergic symptoms in geriatrics to increase patient compliance and convenience.

Materials and Methods: DSL (gifted by Berko İlaç, Turkey), Hydroxypropyl methyl cellulose (Sigma, USA). All other chemicals were in analytical grade. Solvent casting method has been used including different polymers and plasticizers with different ratios (3). A modified HPLC method was used for the determination of DSL (4). The resultant films were evaluated for disintegration time, folding endurance, surface pH, weight variation, thickness, surface morphology, drug content, content uniformity, moisture loss, moisture uptake, drug-excipient compatibility using differential scanning calorimetry and fourier transform infrared spectroscopy, and dissolution.

Results: Compsition of the formulations and characterization studies of the resultant films are summerized in Table 1. Resultent transparent film (Fig 1.), Drug release profile (Fig. 2)

Table 1. Compositions and characterizationsof ODF (Mean ± SE, n=3)

Code	DSL (mg)	HPMC (mg)	PEG 400 (mg)	Gly (mg)	Water+ ethanol (mL)	Thickness (µm)	pH	Folding Endurance	Disintigration time (sec.)	DSL (%)
C1	88	300	90	-	10	50.66 ± 2.03	6.42± 0.02	62.25 ± 4.03	11.25 ± 0.5	98.30 ± 3.55
C2	88	300	-	90	10	51.33 ± 2.01	6.59± 0.01	103.75 ± 5.05	13.25 ± 0.5	104.46 ± 11.13
D1	88	300	120	-	10	53.33 ± 1.93	6.48± 0.01	96.25 ± 2.98	8.50 ± 0.7	102.49 ± 3.75
D2	88	300	-	120	10	52.66 ± 1.96	6.60± 0.02	311.25 ± 11.08	8.75 ± 0.9	101.82 ± 2.56

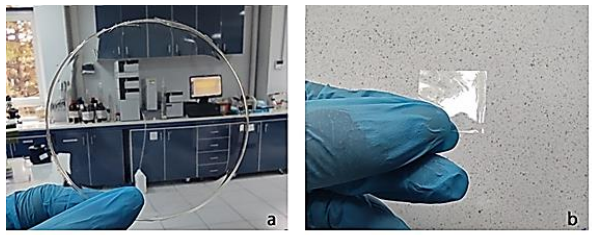

Figure 1. a: *Non-sticky transparent film separated from petri dish,* b: *Film of desired size (2x2 cm)*

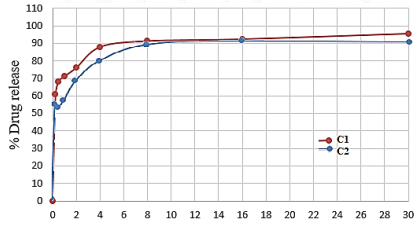

Figure 2. *% Drug release profile of C1 and C2 films*

Conclusions: Approximately 5 mg of DSL was obtained in most of our formulations with a pH within the range of normal pH of the oral cavity and this indicates the suitability of this dosage form and the successful of solvent casting method in preparing 5 mg DSL films for oral consumption as an alternative to conventional dosage forms with higher patient compliance and convenience to treat allergic symptoms in geriatric patients.

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OP007: PREPARATION AND CHARACTERIZATION OF BERBERINE LOADED CHITOSAN MICROPARTICLES

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Introduction: Chitosan (CS) based polymeric drug delivery systems have received great attention in the recent times (1). CS microparticles (CMPs) can be prepared by different methods (2). Berberine (BER) is a quaternary benzylisoquinoline alkaloid that can be obtained from many different plants. In recent years many therapeutics effects of BER have been studied by various researchers. There has been a need to develop a drug delivery system to increase the oral bioavailability of BER. The objective of the study is to develop new CMPs which can be used as potential delivery systems for BER oral usage.

Materials and Methods: BER loaded CMPs were prepared using ionotropic gelation method. Several process parameters were examined to achieve a suitable size of CMP such as CSS concentration, CS:BER ratio, TPPS concentration, CSS pH and homogenization. Low molecular weight CS was dissolved in 2%v/v acetic acid and TPP in distilled water and adjusted to pH 6. CSS adjusted to pH 4.7. BER was dissolved in methanol and added to CSS than mixed 1 hour. TPPS was added to CSS at droplet size on a magnetic stirrer. The solution was stirred for 30 min (3). The resulting CMPs were purified by centrifugation and encapsulation efficiency (EE %) was calculated by indirect method using HPLC. The particle size (PS), zeta potential (ZP), polydispersity index (PDI) of CMPs were measured by using Zetasizer (NanoSeries, Nano-ZS, Malvern Instruments, UK).

Results: According to the PS, ZP, PDI and EE % results the ideal formulations (412.6±25.2 nm, 41.6±0.838 mV, 0.549±0.105 and 26.1±1.23 %) was obtained with 1.5 % CSS concentration, 10:1 CS:BER ratio, 0.5 % TPPS concentration and CSS pH at 4.7. It has been observed that homogenization while preparing the formulation significantly reduces the ZP. The homogenization process also slightly decreased the EE% and increased the PS.

Conclusions: In our experiments, the effects of varying production parameters on CMP properties were studied. It has been observed that the concentration of the TPPS is an effective parameter in the formulation characteristics. The objective of the this study of formulation and characterization of BER loaded CMPs has been achieved with success.

Acknowledgements

This study was supported by Ankara University Scientific Research Projects Commission (Project Number: 19L0237002).

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OP008: THE EFFECT OF GEL PROPERTIES OF CYCLODEXTIN BASED NANOGEL ON THE RELEASE AND STABILITY STUDIES

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Introduction: Nanogels can be defined as three-dimensional hydrogels in the nanoscale size range formed by crosslinked swellable polymer networks (1). Cyclodextrins (CD) are cyclic oligosaccharides having hydrophobic inner space and hydrophilic outer surface, thus they increase the water solubility of hydrophobic molecules such as flurbiprofen (FB) (2). CD-based nanogels combine the advantages of CD and nanogels and the specific properties such as pH, viscosity, rheological properties affect the final performance of gels (3). The main objective of this study was to investigate the effect of pH values, mechanical rheological behaviors and flow properties on the stability and release profile of different nanogels.

Materials and Methods: FB-loaded CD-based nanogels were prepared with the emulsification-solvent evaporation method by using 3^3 full factorial design and incorporated in HPMC gel. The visual examination, pH, rotational and oscillatory measurements, drug content analysis were performed on these gels. The oscillation analysis was evaluated by determining the storage modulus (G′), loss modulus (G″), tangent alpha, complex viscosity at 25±0.1°C and 37±0.1°C. The effect of permeation enhancer (Transcutol®) on the release profile was evaluated by using dialysis membrane at Franz diffusion cells. Stability studies of optimum gel were performed at 4 °C, 25 °C and 40 °C for 12 months.

Results: Nanogels were successfully prepared and characterization studies were completed. While the pH values of the FB-loaded nanogel were 10.6±0.1; the nanogels in the HPMC gel were close to neutral pH (7.5±0.1). While the lowest viscosity values were found in the HPMC gel containing FB-free nanogels, the highest viscosity was observed in the FB-loaded nanogels. G′ and tangent alpha values of HPMC gel containing FB-loaded nanogel were higher than the FB-loaded nanogel at 25°C and 37 °C. The released amount of FB from nanogels prepared in HPMC gel reached 100% at the end of 48 hours and the

addition of Transcutol® did not have a positive effect on the release profile. The optimum formulation was found physically and chemically stable during 12 months.

Conclusions: By means of CD-based nanogels, more effective nanoformulations may be improved especially for hydrophobic molecules. The pH values, viscosity and other mechanical rheological behaviors of CD-based nanogels affect their applicability, compatibility, stability and release profile.

Acknowledgements

This study was supported by a grant of TUBITAK (117S149).

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OP009: BSA LOADED POLY(ISOBUTYL-METHYL GLYCOLIDE) NANOPARTICLES FOR DRUG DELIVERY SYSTEMS

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Introduction: Non-functional poly(alkyl-substituted glycolide)s, which are alternative structures to biodegradable and biocompatible polymers such as polylactide (PLA), polyglycolide (PGA) and poly(lactide-*co*-glycolide) (PLGA) are of great interest (1). The ability of these polymers to be used in biomedical applications is closely linked to the non-toxicity of catalysts for polymer syntheses. Metal-based catalysts are often preferred in ring-opening polymerization (ROP), however metal residues must be completely removed from the synthesized polymers for use in biological applications. The final product should be subjected to strict controls in the presence of metal. Therefore, instead of using metal-based catalysts for ROP, metal-free catalysts (organocatalysts) have attracted considerable attention in recent years. For these reasons, the aim of our study is to prepare BSA loaded nanoparticles after performing the metal-free ROP of asymmetric isobutyl-methyl glycolide (IBMG) monomer with the bifunctional *trans*-1,2-diaminocyclohexane (*trans*-1,2-DACH) derivative Rawal squaramide organocatalyst (2).

Materials and Methods: The synthesis of IBMG monomer was performed in two steps: *i-* the formation of brominated carboxylic acid intermediate from the reaction of L-2-hydroxy-4-methylpentanoic acid with 2-bromopropionyl bromide and *ii-* cyclization reaction of intermediate with $NaHCO_3$ in DMF (3). Poly(isobutyl-methyl glycolide) (PIBMG) were obtained by ROP using Rawal catalyst (2) and $Sn(Oct)_2$ (for comparison) in presence of benzyl alcohol as an initiator. BSA loaded/unloaded nanoparticles were prepared by double emulsion-solvent evaporation method ($w_1/o/w_2$) (4). PLA homopolymers were also synthesized with both catalysts in order to compare the results of PIBMG.

Results: Characterizations of both monomer and homopolymers were verified by ATR-FTIR and NMR techniques. Molecular weights and polydispersities (PDI) of polymers were determined by GPC. Size and PDI of the nanoparticles were characterized by DLS. After the loading of BSA into nanoparticles was confirmed by ATR-FTIR, encapsulation efficiency % was found by UV.

Conclusions: PIBMG was synthesized using both Rawal catalyst in DCM solvent and metallic $Sn(Oct)_2$ (for comparison) in bulk medium. Homopolymers were obtained with Rawal catalyst at ambient temperature in very narrow PDI values and high conversions. The BSA loaded nanoparticles fabricated by $w_1/o/w_2$ showed uniform size distribution without aggregation.

Acknowledgements

This study was supported by a grant of TUBITAK (119Z067)

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OP010: MICROFLUIDIC APPROACH FOR SURFACE MODIFICATION OF MESOPOROUS SILICA NANOPARTICLES

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Introduction: Microfluidic systems are one of the cutting-edge technologies to design complex and controllable in vitro environments where the microchannel design can be adjusted to the desired properties. Formulation optimization is time-consuming and therefore requires the development of a suitable platform for reproducible and rapid production of a wide range of nanoparticles. Microfluidics are an ideal approach for the rapid preparation and evaluation of nanoparticles in different compositions (1, 2). In this study, mesoporous silica nanoparticles (MSNs) for providing high encapsulation of protein were developed. The protein-loaded MSNs were then modified with a pH-responsive cationic polymer by the designed microfluidic device.

Materials and Methods: MSNs were synthesized by the surfactant-micelle-templating method. Microfluidic parameters such as flow rates, flow rate ratios and polymer concentration and MSN concentration have been varied throughout the experimentation to reach the optimum parameters that achieves the best modification results. Particle size determination, zeta potential measurements and TEM analyses were done before and after modification. The in vitro release of loaded protein was also performed to evaluate the effect of surface modification on the release profile.

Results: MSNs were synthesized with a size around 120 nm and net surface charge (zeta potential) under neutral pH conditions was -21 mV. TEM images of the MSNs clearly showed that they were highly uniform in size, well dispersed and the center-radial dendritic mesopore channels could be observed. After surface modification, particle size was slightly increased and the formulation was positively charged according to zeta potential results. Loaded protein was released in pH 7.4 phosphate buffer in a sustained manner for up to 24 hours.

Conclusions: Results show that the microfluidic systems might be a promising approach for the modification of nanoparticles for protein delivery.

Acknowledgements

This work was supported by the Scientific and Technological Research Council of Turkey (TUBITAK) under Grant 2219.

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OP011: POLYELECTROLYTE COMPLEX NANOPARTICLES-FILLED ENTERIC-COATED CAPSULES FOR ORAL INSULIN DELIVERY

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Introduction: Although the subcutaneous route is the most commonly used method in insulin therapy, it sometimes causes poor patient compliance. For this reason, alternative routes of administration for insulin such as oral, buccal, rectal, ocular, transdermal, intravaginal, pulmonary, and nasal routes of administration have been evaluated by researchers (1, 2). In this study, insulin-loaded polyelectrolyte complex (PEC) nanoparticles loaded into enteric-coated hard gelatin capsules were prepared for oral administration of insulin.

Materials and Methods: Recombinant human insulin was obtained from SAFC (Switzerland). Sodium alginate (Low viscosity) and protamine sulfate (Sigma, Germany) were from Sigma (Germany).

PEC nanoparticles were prepared using the ionic cross-linking method (3). Optimum nanoparticle formulation determined by Taguchi experimental design are placed in enteric-coated hard gelatin capsules to target them to the intestine and their in vivo effectiveness were also tested on the diabetic rats.

Results: The results obtained from in-vivo studies showed that, enteric-coated capsules containing insulin-loaded PEC nanoparticles significantly decreased the blood glucose level of rats at the 8th hour compared to oral insulin solution.

Conclusions: It was concluded that PEC nanoparticles loaded into enteric-coated hard gelatin capsules provide a promising delivery system for oral administration of insulin.

Acknowledgements

This study was supported by a grant of TUBITAK (SBAG- 117S586).

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OP012: FORMULATION AND CHARACTERIZATION OF RESVERATROL LOADED SELF-MICROEMULSIFYING DRUG DELIVERY SYSTEMS (SMEDDS) FOR TOPICAL DRUG DELIVERY

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Introduction: Resveratrol is a natural polyphenolic, which has high antioxidant activity and can reduce skin aging (1). Polyphenolic compounds such as resveratrol, penetration of the skin restricted due to the low solubility (**2**). Microemulsions are considered suitable drug delivery systems since their easy formulation, thermodynamically stable properties, and facilitating the delivery of both lipophilic and hydrophilic active ingredients (2,3). To overcome the drawback of stability problems and low skin bioavailability of resveratrol, self microemulsifying drug delivery systems could be a suitable delivery system. The aim of this investigation was to prepare an optimal formulation of microemulsion (ME) and evaluate them according to characterization tests.

Materials and Methods: Oil-in-water MEs were prepared using tween 80, olive oil, and distilled water as a surfactant, oily phase, and aqueous phase respectively. A triangle phase diagram was obtained to determine the amounts of ME components. Points studies were used to determine ME region on the triangle phase diagram. Some component ratios were selected within the ME region to evaluate their stability and other characteristics. Chosen formulations were exposed to stability stress tests such as centrifuge and thermal stress. Characterization studies such as droplet size, size distribution, zeta potential, viscosity, pH measurement were performed.

Results: In terms of the characterization test results, there wasn't a significant difference observed between ME8 and ME9 coded formulations that contained surfactant, oily phase, and aqueous phase at rates 20,4: 1,6: 77,9, and 20,8: 1,6: 77,6, respectively.

Conclusion: ME9 coded microemulsion formulation was considered as most suitable formulation according to droplet size (12,27 ± 0,086) and PDI values (0,146 ± 0,007). In addition, the zeta potential of the ME9 coded formulation was found to be more suitable compared to ME8 in terms of stability.

Acknowledgements

This study was supported by Scientific Research Projects Unit of Istanbul University (Project code: TDK-2020-35272).

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OP013: DEVELOPMENT OF A PRINTABLE COATING FILAMENT FOR 3D COLON-TARGETING TABLETS

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Introduction: The use of three-dimentional printing (3DP) technologies in the pharmaceutical field is promising in the treatment of diseases where the dose varies from person to person or according to the severity of the disease. Fused-deposition-modeling (FDM) technology is the most researched 3DP method for pharmaceutical applications. In colon-specific diseases, in whose treatment antineoplastic agents and corticosteroids are generally used, individual dosing is required to increase the efficiency of treatment (1). Eudragit-S100 is the most commonly used pH-dependent coating polymer for colon targeting tablets (2). However, it is difficult to produce a formulation including Eudragit-S100 by FDM-3DP due to its degradation at the glass transition temperature There is no study in the literature in which Eudragit-S100 is printed below its degradation temperature. The aim of this study is to develop a Eudragit-S100 coating filament that can be printed below its degradation temperature by FDM-3DP to be a model for colon-specific tablets.

Materials and Methods: Citric acid monohydrate, magnesium stearate were donated by Drogsan. Eudragit S100 and triacetin were gifted from Evonik and BASF, respectively. For the preparation of the filaments, a single screw extruder (Noztek, UK) was used. The diameter of filaments was measured by a caliper. The brittleness and flexibility of filaments were evaluated manually and the morphological characteristics were determined visually. The

printability of filaments was demonstrated by fabricating model tablets using an FDM 3D Printer (Craftboat-3, Hungary).

Results: The filament was extruded at 110ºC. The diameter of the filament was 1.74±0.03 mm, and the mechanical properties were suitable. Tablets was successfully printed at 165ºC which was lower than the degradation temperature (173ºC) of the polymer.

Conclusion: In this study, Eudragit-S100 was printed below its degradation temperature for the first time. This printable filament formulation can be used as a coating layer for a wide range of 3D colon-targeted drugs. The filament formulation developed in this study can be combined with core filaments containing various active ingredients and turned into a finished product in future studies.

Acknowledgements

This study was supported by a grant of TUBITAK (219S197)

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OP014: NICLOSAMIDE LOADED NIOSOME FOR TOPICAL APPLICATIONS: DEVELOPMENT AND IN VITRO CHARACTERIZATION

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Introduction: Atopic dermatitis is a chronic inflammatory skin disease (1). In 2018, phase II trials of niclosamide (NIC) for the treatment of impetigo and atopic dermatitis were completed (2). The objective of the investigation was to design a vesicular formulation of NIC and evaluate its ability to topical permeability and improve the therapeutic efficacy of the drug.

Materials and Methods: Niosomes containing NIC was prepared by ethanol injection method (3). NIC, surfactant and cholesterol in different ratios were dissolved in ethanol. The resulting solution was slowly injected using syringe into distilled water under a magnetic stirrer at different rpm and 60°C. To determine entrapment efficiency (EE), the unentrapped drug was separated from drug-loaded niosomes via centrifugation. The absorbance of the NIC in the supernatant measured using a UV-Vis spectrophotometer at 291 nm. The particle size (PS), zeta potential (ZP), and polydispersity index (PdI) of the niosomes were investigated utilizing the Malvern Zetasizer Nano-ZS. In vitro release of NIC from niosomes was conducted by dialysis bag method (4).

Results: Ten formulations were prepared to examine the stirring rate, active substance ratio, charge inducer and nonionic surfactant type effect. Low PS (445.033±6.189 nm) and PdI (0.643±0.104), and highest ZP (-21.833±0.125 mV) value were obtained with S3 formulation, whereas lowest PS (186.067±1.855 nm) and PdI (0.156±0.015) were obtained with S7 formulation. All formulations showed high encapsulation efficiency between 94.425% and 99.969%. In in vitro release study, it was observed that NIC suspension released approximately 60% of the drug within 4 h, while vesicle formulations S3 and S7 showed 40% and 65% drug release, respectively.

Conclusions: When all studies were evaluated, it was observed that the best results were obtained with S7. For topical administration, the resulting formulation can be loaded into the hydrogel and thus the release time of the drug can be extended.

Acknowledgements

This research did not receive any specific grant from funding agencies.

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OP015: PRECLINICAL DEVELOPMENT OF AN INJECTABLE MULTIPURPOSE PREVENTION TECHNOLOGY (MPT) FORMULATION

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Introduction: There is growing interest in the development of MPT products for women that combine hormonal contraception with HIV prevention. Since long-acting injectable (LAI) contraceptive products are already widely used by women in countries where HIV infection is highest, and efforts are ongoing to develop injectable antiretroviral formulations, there is a strong rationale for combining a progestin and antiretroviral drug in a single injectable product. Here, we report preclincial development of a LAI aqueous suspension product containing the antiretroviral rilpivirine (RPV) and the progestin medroxyprogesterone acetate (MPA).

Materials and Methods: RPV was milled to produce an aqueous nanosuspension, and then reformulated with commercial micronised Depo-Provera® to produce the MPT test product (~90mg/mL RPV; ~45mg/mL MPA). Suspension formulations were characterized for particle size, charge, pH, osmolality, drug concentration, and by thermal analysis. The lead candidate MPT formulation and controls (Depo-Provera® and RPV-only nanosuspension) were sterilised and then administered intramuscularly in cynomolgus monkeys for 90-day pharmacokinetic evaluation, with quantification of MPA/RPV in vaginal fluid/blood plasma by UPLC-MS/MS.

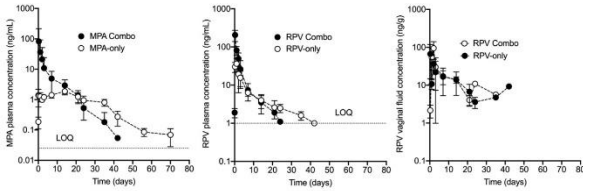

Figure 1. Plasma and vaginal fluid concentration vs. time plots for medroxyprogesterone acetate (MPA) and rilpivirine (RPV) following intramuscular injection of Depo-Provera® (MPA-only), a RPV nanosuspension formulation (RPV-only) and a combination formulation (RPV-Combo).

Results: All test formulations were confirmed sterile and stable over three months, and showed a bimodal particle size distribution (Dv(50) values – RPV ~114 nm; MPA ~ 9.6 µm). Plasma concentrations of RPV and MPA in macaques decreased from ~100 ng/mL to ~0.1 ng/mL, and over time periods ranging from 25–70 days depending upon the formulation (Figure 1). RPV vaginal fluid concentrations decreased from ~100 ng/g to ~2 ng/g over up to 40 days.

Conclusions: This study demonstrates the potential for reformulating Depo-Provera® with an antiretrovral drug as a LAI MPT strategy for contraception and HIV prevention. Further work is needed to maintain drug concentrations over longer periods of time.

Acknowledgements

The authors thank the World Health Organization (WHO) for funding.

OP016: HOW USEFUL ARE MICROSCOPIC TECHNIQUES TO PREDICT DRUG RELEASE PROFILE FROM THE LIPID MICROPARTICLES

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Introduction: Solid lipid microparticles (SLM) as biocompatible and multi-compartment carrier of drug substances are considered as a dosage form for both local and systemic administration. The main advantage of SLM is the relatively simple technology and ability to provide sustained release and action of the active substance. Only effective and permanent incorporation of the drug substance into the lipid matrix of the particles provides the SLM carrier with the aforementioned properties. At the same time, it is a main problem, even in the case of highly lipid soluble substances (1).

The aim of the conducted research was to indicate the most advantageous microscopic techniques for the assessment of SLM structure with the potential to detect changes occurring during the release study.

Materials and Methods: Tested formulations were obtained both in the form of liquid dispersion (produced by the hot emulsification method) and fine powder (obtained in the process of spray drying). Characterization of SLM was performed by optical microscopy, scanning electron microscopy (SEM), Raman spectroscopy and atomic force microscopy (AFM) (2). The release of model drug substances (cyclosporine, indomethacin) from SLM was investigated in the membrane-free system.

Results: SEM as a high-resolution technique allowed for an in-depth analysis not only of the shape of the obtained microspheres, but above all of their surface structure. Meanwhile, the AFM microscope was used to compare the viscoelastic properties of *placebo* and drug loaded SLM surface by measuring the adhesion of the probe tip to the tested surface [2]. Since the fraction of the drug substance responsible for the initiating dose in the release study is located on the surface of the lipid particles, microscopic techniques allowed to observe the differences in the tested formulations and their correlation with the results of the release studies.

Conclusions: All of the used microscopical methods could be considered complementary and providing valuable information, however SEM and AFM techniques were recognized as the most valuable. Regardless of microscopic methods and other instrumental techniques, the results of the dissolution studies provide irreplaceable knowledge about the properties of the dosage form

and allow the detection of even subtle changes in the distribution and behavior of the drug substance.

Acknowledgements

This study was supported by a grant of the National Science Centre, Poland, 2017/01/X/NZ7/01717.

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OP017: PICKERING EMULSIONS STABILIZED BY CYCLODEXTRIN DERIVATIVES FOR TREATMENT OF ATOPIC DERMATITIS: OPTIMIZATION AND *IN VITRO* CHARACTERIZATION

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Introduction: The use of stabilizers in the emulsions is crucial to formulate them and to provide their long-term stability due to being thermodynamically unstable systems. The synthetic surfactants have mostly been used as stabilizers in the emulsion formulations. However, most of surfactants may cause irritation and/or allergic responses in the skin. In order to overcome this problem, Pickering emulsions have emerged for drug delivery in the recent years, which are stabilized by adsorption of biopolymers or solid particles having emulsifier and non-irritant features (1). Atopic dermatitis is a chronic inflammatory disease characterized by itching, erythema, and eczematous lacerations. The dry skin, irritants, allergies, infection, and so on trigger atopic dermatitis (2). Hence, we aimed to develop surfactant-free topical formulations exhibiting no irritation/allergic responses in the treatment of atopic dermatitis.

Materials and Methods: The cyclodextrins (α-CD, β-CD, γ-CD) were obtained as gift samples from Wacker Chemie (Germany). Tacrolimus monohydrate was kindly donated by Bilim Pharmaceuticals (Turkey). Rotor-stator homogenizator method was used to prepare Pickering emulsions. Olive oil and cyclodextrin derivatives (in the ratios of 1:7, 1:3, 1:1, 3:1 and 7:1, w/w) were weighed, and stirred before adding ultrapure water. Emulsification was conducted using Ultraturrax (IKA, Germany). Tacrolimus monohydrate (0.03 % w/w) was added concurrently with cyclodextrins. After emulsification, phase diagrams of oil/CD/water systems were constructed by observing the presence of phase separation to determine concentration ranges of components for stable Pickering emulsions. Then, the emulsions were characterized in terms of pH, electrical conductivity, homogeneity and rheological behaviours.

Results: pH values of optimized Pickering emulsions were about 4.5 and 5.5, indicating their feasibility for skin delivery. The electrical conductivity values revealed that type of the emulsions was oil in water (O/W). The bright-field microscopy images depicted that the emulsions composed of spherical droplets with high homogeneity, especially ones stabilized by γ-CD. The emulsions stabilized by α-CD exhibited the highest viscosity values. Moreover, elasticity of the emulsions was found greater than that of viscous modulus for optimized formulations with all types of cyclodextrins.

Conclusions: Overall the results indicate that optimized Pickering emulsions could be promising alternative dosage forms for tacrolimus used in the treatment of atopic dermatitis.

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OP018: DEVELOPMENT AND IN-VITRO IN-VIVO EVALUATION OF HYDROPHILIC GEL FORMULATIONS FOR TREATMENT OF KERATOCONUS BY NON-INVASIVE TECHNIQUE

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Introduction: Keratoconus is a ectatic progressive disease which characterized by thinned and conical cornea (1). In order to treat keratoconus and halt its progression, riboflavin-5-phosphate sodium solutions are dropped into the eye and UV-A light is applied to create cross-links between stromal collagens (2). The aim of this study was to develop the gel formulations of Riboflavin and riboflavin-5-phosphate sodium, to reduce the frequency of instillation and to prevent the removal of the epithelial layer in the standard procedure.

Materials and Methods: Thermosensitive hydrogels were prepared using Pluronic F-127. Four different formulations were prepared according to their active substance and whether they contain permeation enhancing agent or not

(Table 1). Gelation temperature, viscosity graphs and drug release studies were carried out within the scope of the characterization studies of gels. The efficacy of the formulations was compared with marketed products by in vivo biomechanical studies.

Table 1. Hydrophilic gel formulations

Code	Riboflavin (%)	Riboflavin-5-phosphate sodium (%)	Pluronic F-127 (%)	NaCl (%)	Benzalkonium chloride (%)	Transcutol P (%)	Water (mL)
BHJ	0.1	-	18	0.7	0.01	-	25
BHJ-TP	0.1	-	18	0.7	0.01	0.1	25
THJ	-	0.1	18	0.7	0.01	-	25
THJ-TP	-	0.1	18	0.7	0.01	0.1	25

Results: All formulations and marketed products showed higher stress values than the UV-only control group in all tension percentages. Also, as the tension percentage increased, the stress values also increased as expected. Only THJ-TP formulation was found statistically better than marketed Epi-On product. However, other hydrogel formulations showed a similar effect to the marketed Epi-On product, despite the lower frequency of instillation (Figure 1).

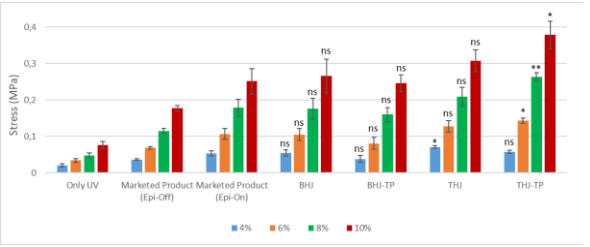

Figure 1. Obtained resistance data was expressed in Stress (mPA) shown as mean±SEM for n=3. Statistical significance shown between marketed product (epi-on) as *=P<0.05, **=P<0.01 and ns=not significant.

Conclusions: The hydrogel formulation containing riboflavin-5-phosphate sodium and transcutol p (THJ-TP) was found to be more effective than the marketed product developed for epi-on administration with less dropping frequency.

Acknowledgements

This study was supported by a grant of TUBITAK (SBAG-215S685)

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OP019: PREPARATION AND CHARACTERIZATION OF BIGEL SYSTEMS CONTAINING CICLOPIROX AND UREA

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Introduction: Onychomycosis is a fungal infection of the nail bed and nail plate caused by dermatophytes, non-dermatophyte molds and yeasts (1). It affects approximately 20% of individuals worldwide and accounts for approximately 50% of all nail infections (2). The treatment is performed by using oral and topical antifungal agents alone or in combination. The aim of study is to investigate efficacy of bijels as carriers for dermal delivery of ciclopirox, a broad spectrum antifungal drug. The urea contained in hydrogel, which is outer phase, will increase effectiveness of ciclopirox by contributing to expansion of pores in nail and skin. Bigels are prepared by mixing organogel and hydrogel at certain temperature and ratio at high speed. They are semi-solid systems in which inner phase is dispersed as droplets in outer phase. Bijels are considered that increase penetration of lipophilic active substances in the inner phase by expanding pores in skin and nails when applied topically, since outer phase is water.

Materials and Methods: Organogel consists of MCT-oil glyceryl monostearate (GMS), span 80 and ciclopirox, while hydrogel consists of distilled water, urea, Carbopol 974P, tween 80, propylene glycol (PG). After organogel and hydrogel are heated to 70˚C, they are mixed at 6000 rpm. Bigel systems were prepared with 2^3 full factorial designs using different ratios of Carbopol 974P, GMS and MCT-oil. Optimum formulations were selected according to viscosity, size of oil droplets in internal phase and centrifuge results of formulations prepared. Oil droplets in outer phase were observed using fluorescent microscope.

Results: As internal phase ratio increased, viscosity increased. As oil droplets in outer phase grew, phase separation was observed in centrifuge performed as an accelerated endurance study. In addition, increase percentage of GMS in organogel increased durability of system. As viscosity increases, structure of bigel changes from shear thinning to shear thickening. The droplet size of bigels varied between 413.6-2287.0 nm.

Conclusions: In vitro results have shown that the bigel system is a suitable delivery system for ciclopirox and urea. After this, in-vitro release study and ex-vivo permeation study of ciclopirox and urea will be performed.

Acknowledgements

This study was supported by a grant of GAZİ-BAP (02/2020-22)

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OP020: STABILITY STUDIES ON MEDICAL DEVICE PREPARED BY VANCOMYCIN-LOADED BONE CEMENT

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Introduction: In this study, it is aimed to conduct stability studies by simulating the antibiotic loaded bone cements used in local treatment, the preparation stages of the loaded antibiotics and the in vivo environments that the bone cement will encounter when placed into the body after hardening in order to reduce the incidence of infection. The test methods and results to be determined in the stability studies will be beneficial in re-evaluating, updating and expanding the existing guidelines (1).

Materials and Methods: Within the scope of the stability studies, first, temperature monitoring was carried out during the preparation phase. Quantification was determined in order to measure the effect of the temperature on the polymerization reaction of the loaded vancomycin at the preparation of bone cement. Release studies of bone cement have been carried out and release amounts / profile and release rates have been determined. In addition, the structural changes of the prepared bone cement were examined, mechanical strength was also detected. Antimicrobial activity test was performed to measure the effectiveness of the antibiotic released over time from bone cement.

Results: It was found that the heat generated during the hardening of the bone cement had a minimal effect on the stability for vancomycin, degradation products occurred, but it was stable in terms of strength and antibacterial efficacy.

Conclusions: Stability evaluations of medical device bone cements loaded with antibiotics will guide future studies with our study. It will also be able to contribute to the work to be done to develop standards such as the relevant ISO (2).

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This study was supported by a grant of University of Health Sciences of Turkey-BAP- 2021/

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OP021: PREPARATION AND IN VITRO EVALUATION OF APO-E MODIFIED SOLID LIPID NANOPARTICLES FOR DELIVERY OF HUMANIN PEPTIDE

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Introduction: Alzheimer's disease is the most common type of dementia. Current treatments are symptomatic, so new cures are needed to prevent disease (1). Humanin protects the cells against cytotoxicity due to Aβ42(2), so we planned to prepare Humanin-SLNs to across the blood-brain-barrier (BBB) easily and the bonding of Apo-E to the SLNs is aimed for targetting.

Materials and Methods: Humanin was obtained from Proteogenix and Apo-E from Peprotech. Humanin-loaded solid lipid nanoparticles (SLNs) were prepared by homogenization/ultrasonication method and the effects of various parameters on SLNs were investigated. Optimum SLNs were modified by using Apo-E and cyctotoxicicity and uptake studies on SH-SHY5Y cells were carried out.

Results: Humanin SLNs showed spherical shapes with particle sizes around 104-186nm. Encapsulation efficiency for optimum formulation 98,99% and burst effect for 1h and continuously release for 24h was observed during release studies. Apo-E modified SLNs showed 124,9 nm particle size and after 2 hour incubation Apo-E SLNs didn't show toxic effect on SH-SY5Y cells and, the functionalization of the SLNs resulted a significantly better uptake.

Conclusions: We achieved to obtain SLNs with a particle size of less than 200 nm which can cross BBB easier and high encapsulation efficiency. SLNs modified with Apo-E successfully and Apo-E SLNs increased the uptake in neurons according to non-modified SLNs. These results may contribute to develop more efficient drug delivery systems for the nervous system.

Acknowledgements

This study was supported by TUBITAK (SBAG-119S124; BİDEB-2214/2211 Scholarship Programs).

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OP022: DESIGN, FABRICATION AND CHARACTERIZATION OF SURFACE MODIFIED HALLOYSITE/POLYMER NANOCOMPOSITE AND ITS 5-FLUOROURACIL CONJUGATES

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Introduction: In recent years, polymeric drug conjugates, nanoparticles, nanocapsules, liposomes, micelles, dendrimers and nanogels have been gaining great attention. Also, nano-sized nanocomposite (NC) materials have attracted attention in polymeric drug delivery systems (1). In this study synthesis and characterization of poly (maleic anhydride-*alt*-acrylic acid) (Poly (MA-*alt*-AA)) *via in situ* charge transfer complex (CTC) copolymerization to be aimed (2, 3). For better compatibility of halloysite nanotubes (HNT) with monomers, surface modification was performed with 3-aminopropyltriethoxysilane (APTS) (4-5). Polymer/modified HNT was used the synthesis of nanocomposites. For polymer-drug conjugate was prepared by 5-fluorouracil (5-FU).

Materials and Methods: Poly(MA-*alt*-AA), was prepared by complex-radical polymerization technique *via* charge transfer complex (*CTC*) (50/50 in p-dioxane, at 70 ºC, benzoyl peroxide (BPO), under a nitrogen atmosphere). Surface modification of halloysite nanotubes (HNT) with 3-aminopropyltriethoxysilane (APTS) was performed to obtain organic functionalized halloysite. The obtained poly (MA-*alt*-AA)/halloysite and poly (MA-*alt*-AA)/modified halloysite nanotubes were synthesis in the same route and the chemical conjugation was performed with 5-fluorouracil (5-FU). Characterization studies carried out using spectroscopic methods (XRD, ATR-FTIR, HR-Raman and XPS), thermal analysis (TGA), dynamic mechanical properties (DMA) and morphology with Transmission Electron Microscopy (TEM).

Results: It can be briefly concluded that surface modification of HNT, synthesis of copolymer/HNT nanocomposites and its 5-FU drug conjugates preparation and characterization successfully achieved.

Conclusions: According to the results obtained; it is thought that uniquely designed, synthesized and characterized halloysite-copolymer drug conjugates are obtained with potential materials to be used in cancer treatment.

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OP023: CHEMOSENSITIVE EVALUATION OF METHOTREXATE LOADED NIOSOMES ON BURKITT LYMPHOMA CELLS

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Introduction: Burkitt lymphoma is defined as an extremely aggressive B-cell Non-Hodgkin's Lymphomas originating from B lymphocytes (1). Methotrexate (MTX), a folate antimetabolite, is one of the widely used therapeutic agents in high doses to treat many solid tumors including Burkitt lymphoma. However, higher doses of MTX lead to decreased bioavailability. Nanotechnology have great interest in recent years to improve therapeutic efficacy (2). In this study, we aimed to investigate *in vitro* anticancer activities of methotrexate loaded niosomes to contribute remarkable progress in the therapeutic scenario.

Materials and Methods: Methotrexate loaded niosomes were produced through the thin film method combined with sonication. In hydration step, alkaline solution (A), phosphate buffer solution (P) or urea solution (U) was used. All produced niosomes were characterized in terms of particle size and distribution, zeta potential and entrapment efficiency. The chemosensitive evaluation of pure MTX solution and MTX loaded niosomes on Burkitt's Lymphoma cell line Raji cells was performed by colorimetric XTT cell viability

test. Raji cells were seeded in a 96-well plate in an amount of 10,000 cells/well and treated alone with increasing concentrations of MTX ranging from 125 nM to 3.9 nM (dilution factor:2) for 24 hours. The cells were also exposed to MTX loaded niosomes following the same treatment protocol.

Results: All niosome formulations were successfully produced in small particle size (under 400 nm), with relatively high entrapment efficiency. IC50 value of MTX was 85 nM, while IC50 values of niosomes were 57 nM, 72 nM, and 82.5 nM for A, P, and U, respectively. As a result, it was observed that the use of niosomes significantly increased the cytotoxic activity of the anticancer agent on the Burkitt Lymphoma cell line. Moreover, alkaline solution boosted their chemosensitivity. This might be caused by the acidic microenvironment of the tumor cells.

Conclusions: Developed niosomal formulations were found more effective than free-MTX on cell death. These promising results might be ideal drug to treat aggressive Burkitt lymphoma.

Acknowledgements

This research did not receive any specific grant from funding agencies.

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OP024: DESIGN AND EVALUATION OF SEMI-SOLID LIPID NANOPARTICLES AS NOVEL NANOCOSMECEUTICALS

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Introduction: Nanotechnology is the curcial factor to design and produce next-generation cosmetics. While nanotechnology provides a solution for the active ingredients, it also increases the effectiveness and performance of the product. Nano-cosmeceuticals, which are the hybrid formulations between pharmaceuticals and cosmetics, are produced by transferring nano-drug carrier systems to cosmetics (1). When the cosmetic application of nanomaterials are considered, semi-solid lipid nanoparticles (Semi-solid LNs) are fairly new systems and they exhibit many advantages over other nano-carriers. The single-step production methods of semi-solid LNs allow obtaining low costs products in a short time and the product can be applied directly to the skin without any further process. Viscoelastic semi-solid structure can be obtained as well as colloidal size can be protected (2). The purpose of this study is to design active anti-aging molecule and vegetable oil encapsulated semi-solid LNs to obtain skin positive effect and to characterize the novel nanotechnology-based cosmeceutical formulation.

Materials and Methods: Semi-solid LNs were prepared by hot homogenization method. Solid lipid - vegetable oil mixture was used to form the lipid nanoparticles and semi-solid structure as well. The particle characteristics, including average particle size, size distribution, and zeta potential; textural, rheological, and occlusive properties of semi-solid LNs were investigated. Thermal behaviour of the formulations and morphological characteristics were also examined.

Results: Semi-solid LN formulations with an average particle size of less than 300 nm with highly negative zeta potential have been successfully produced. The morphological evaluation results showed that spherical lipid nanoparticles with no aggregation were obtained. According to DSC results, the loss of the melting peak of active molecule and vegetable oil may also be evidence that they are included in the lipid matrix structure. It has been observed that the presence of vegetable oils contributes to the occlusive character of the system.

Conclusions: Herein, the advantages of lipid nanoparticles and vegetable oils were successfully combined in the semi-solid LN structure to achieve a synergistic effect on skin hydration and the anti-aging effect. As a result, a novel semi-solid lipid nanoparticle formulation was developed as a promising candidate of nano-cosmeceuticals.

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OP025: ROBUST FORMULATION DESIGN USING COMPACTION SIMULATOR AND QBD APPROACH

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Introduction: Application of Quality by Design (QbD) approach was used to obtain an optimum formulation and design space. This approach allows formulators to optimize formulations and enhance the product development with built in product quality. The aim was to design optimum compact formulation for Nimesulid using compaction simulator and a QbD approach.

Materials and Methods: Preformulation studies, solubility study, powder consolidation properties were carried out to charactarize powders used in the formulation. Compressibility parameters were evaluated by compaction simulator Styl'cam 200R (Medelpharm). Binder and disintegrants were selected as key components for poorly soluble Nimesulide. Formulations were produced by direct compression method using 11.28 mm punch. Quality control test results were used as inputs for QbD analysis using MODDE software to obtain a design space.

Results: Tensile strength values give insight into powder compressiblity which assists in production of a robust formulation. Addition of superdisintegrant (Figure1) affects tensile strength values, hence has limitations during tablet formulation and design.

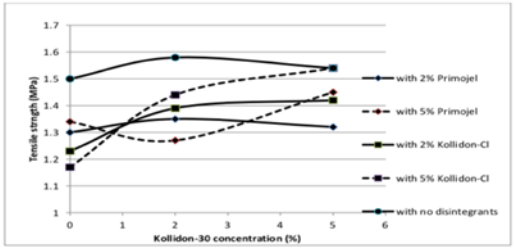

Figure 1. Effect of key excipients on tensile strength at 10kN force.

Figure 2 shows results of QbD analysis, a design space was obtained for all parameters and excipients using QbD analysis. The green zone shows area containing the most robust formulations.

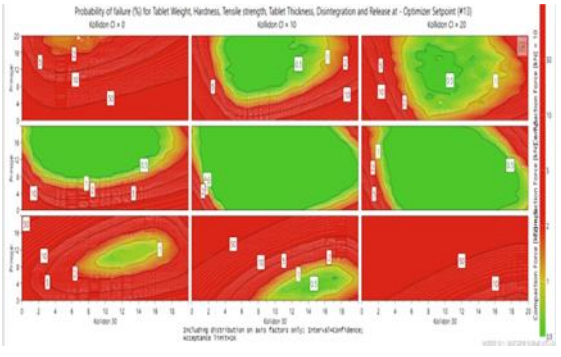

Figure 2. Design space for combination formulations

Conclusions: Compaction simulators are benificial to test the functionality and performance of excipients as well as characterise tabletting properties of powders. They assist in development of robust formulations for industrial production by evaluation of compaction properties. It can be concluded that, characterizing excipients behaviour in the formulation was critical for robust formulation development. Less number of formulation will be use for the quality control tests to optimize the final formulation. QbD can be used to obtain a design space by optimizing excipients and process parameters in order to obtain a robust formulation.

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OP026: LIPOSOMAL ANTIAGING FORMULATION STUDIES CONTAINING SOME PROBIOTIC COMBINATION

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Introduction: Liposomes are special carrier systems that have both water and oil-soluble properties, a hydrophilic head and a lipophilic tail, which take the name phytosome when they entrap plant actives (1, 2). In our research study, a probiotic combination included in the optimized liposomal anti-aging formulation and conventional anti-aging formulation were evaluated in *in vitro* conditions.

Materials and Methods: Liposome dispersions (LIPOSFACE) were prepared by film technique. The dried film was then hydrated over a water bath with phosphate buffer (pH 5.5). Microorganism content representing skin microbiota was created for *in vitro* efficacy studies. *Streptococcus pyogenes, Streptococcus salivarius, Peptostreptococcus prevotii, Micrococcus luteus, Corinebacterium spp, Propionibacterium acnes, Staphylococcus aureus, Staphylococcus epidermidis, Lactobacillus acidophilus, Candida albicans* microorganisms were used in these content. 100 cm^2 each 5 control groups and 5 study groups were formed. Approx.$5*10^4$ cfu / cm^2

intraoral microbiota elements were applied on 100 cm^2.
It was left to dry for 2 hours at 25 ^oC in an anaerobic / aerobic environment. After drying, 1 g of live probiotic liposomal and conventional anti-aging formulations were applied to the surface. 2 hours at 25 ^oC, it was allowed to dry in an anaerobic environment. After drying, a sample was taken from the area with the swab technique. The count was made by homogenising in 1/10 dilution liquid.

Results: The optimum formulation was selected as liposome (LIPOSFACE and ATABIOTIC) cream formulation with Probiotics (A1). Because, A1 probiotic bacteria in the skin microbiota significant positive change was observed in the number of beneficial bacteria found after the application of anti-aging cream with liposomes. It seems that number of pathogen has been significantly decreased in liposome cream formulation with Probiotics. However, number of beneficial microorganisms has been increased after this application (*Lactobacillus acidophillus* and so on). A2 Formulation (Conventional probiotic (ATABIOTIC) cream) showed that effective results in artificial skin microbiota. However, the results showed that A2 formulation microbiota activity less than A1 formulation because of liposomal encapsulation.

Conclusions: As a concluded of this effects, due to the increase of beneficial probiotics, A1 formulation protects the skin barrier strongly. It has been evaluated in the direction and concluded that liposomal probiotic antiaging formulation (A1) contains positive results according to individual figures.

Acknowledgements

The author wish to thank M Sc Biologist Leyla Tarhan and SFA R&D Laboratories (İstanbul, Turkey) for their great technical support (Liposomes and probiotics supply).

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OP027: PRODUCTION AND CHARACTERIZATION OF OMEPRAZOLE LOADED NA ALGINATE/POLYVINYLPYRROLIDONE FILMS BY ELECTROSPINNING AND SOLVENT CASTING TECHNIQUES

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Introduction: The fast dissolving oral film (FDOF) is a sort of thin, flexible and non-friable polymeric film containing one or more dispersed active pharmaceutical ingredients (API).Various strategies have been proposed to produce the FDOF, whereas solvent casting and electrospinning are the most common ones. In addition, nanofibers produced by electrospinning have high surface area and highly porous structure that enhance fast-wetting surface properties and increase the release rate of drugs or bioactive compounds (1). The efficiency of this method has been evaluated by placing high doses of drugs in the fibers and facilitating the solubility of some insoluble drugs (2). Omeprazole (OP) is a proton pump inhibitor used to treat infections like peptic ulcers, gastro esophageal disorders and Zollinger Ellison syndrome. It comes under BCS class II drug with low solubility and high permeability having half-life of 0.5-1hrs (3). The objectives of the present study were to fabricate the OP-PVP-Na Alginate based FDOF by electrospinning and solvent casting techniques and compare in terms of their credibility for orodispersible delivery of OP through a variety of *in vitro* and *ex-vivo* investigations.

Materials and Methods: Na Alginate/ Polyvinylpyrrolidone (PVP) FDOF containing OP were produced using the electrospinning and solvent casting techniques. Assessments were carried out using scanning electron microscopy (SEM), Fourier transform infrared (FTIR) spectroscopy, and differential scanning calorimetry (DSC). Ex-vivo, dissolution tests and disintegration time were also carried out.

Results: The results showed that prepared FDOF with OP significantly increase the dissolution rate of OP. In comparison films which was prepared in different technologies the 90% of OP could be diffuse into the dissolution medium within 1 min and 5 min, respectively, demonstrating that the nanofiber improved the drug release rate in comparison to the solvent cast films.

Conclusions: The Na Alginate/PVP based nanofibrous oral films might be employed as promising fast dissolving drug delivery systems to increase the convenience and therapeutic efficacy of the OP for gastrointestinal diseases treatment.

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OP028: DETECTION OF REACTIVE OXYGEN SPECIES IN SKIN WITH MICRONEEDLES

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Introduction: Inflammatory skin diseases arise in various forms, from occasional rashes accompanied by skin itching and redness, to chronic conditions such as eczema, seborrheic dermatitis, rosacea and psoriasis (1). Under physiological conditions, the production and detoxification of reactive oxygen species (ROS) are quite balanced, when a greater imbalance occurs in favor of the ROS, oxidative stress ensues (2). Fluorescent ROS sensors, such as dihydrorhodamine 123 (DHR), are widely used to detect inflammation processes. Microneedles (MN) are composed of arrays of micron-size needles, which are able to bypass the stratum corneum without stimulating dermal nerves when applied to skin. The aim of this research was to develop and characterize polymeric dissolving microneedles loaded with DHR, as a simple and rapid tool for *in vivo* dermal ROS sensing.

Materials and Methods: Dissolving microneedle patches were prepared by using solvent casting method (3). Hyaluronic acid (HA) and dextran (DEX) were selected for the polymer matrix material. Microneedles were characterized in terms of morphology, mechanical strength and *in-vitro*/*ex-vivo* ROS sensing capacities.

Results: Images of DHR loaded HA/DEX MNs showed that, MNs tips were formed properly and completely dissolved in the skin after application. The compression force of MNs reached 24.36 ± 5.99 N at 400 µm displacement and was consistent with literature. Sensing capacity of DHR loaded HA/DEX MNs was evaluated after dissloving patches in Fenton's reagent (oxidizing agent) or water as control and found that DHR was still capable of sensing ROS. Fenton's reagent (1mM/10mM) treated skin presented increasing fluorescent intensity with time and reached 5 fold increase at the end of 1 hour. On the other hand, lower concentration Fenton's reagent (0.5mM/5mM), treated skin also demonstrated increasing pattern with time and reached 2.5 fold increase at the end of 1 hour.

Conclusions: Dissolvable polymeric MNs were successfully prepared using a mixture of HA and DEX, and were characterized in terms of morphology and mechanical properties. The sensing capacities of the MNs were confirmed in both *in vitro* and *ex vivo* situations.

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This study was supported by a grant of TUBITAK (2219- 1059B191600267).

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OP029: PREPARATION OF SILK FIBROIN NANOPARTICLES FROM BOMBYX MORI COCOONS BY DOE APPROACH

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Introduction: Silk fibroin (SF) is a natural, protein-based biopolymer. In this study, silk fibroin was extracted, and nanoparticles were produced by the nanoprecipitation method.

Materials and Methods: Silk fibroin was obtained with the Ajisawa method (1) from bombyx mori cocoons, characterized and quantified with the Bradford method (2). Kollidon VA64, Poloxamer 188, and Tween 80 were used as stabilizing agents in the nanoprecipitation step at various concentrations.

Results: According to the results (Table 1), Tween 80 was selected as the stabilizing agent and the effect of the SF and Tween 80 concentration on the particle size and polydispersity index (PDI) was evaluated by experimental design. Results of the experimental design were given in Figure 1. According to the experimental design results, it was observed that as the concentration of polymer and stabilizing agent decreased, the PDI and particle size decreased.

Table 1. Effect of stabilizer type and concentration on the particle size and PDI

Stabilizing agent	Kollidon VA64				Poloxamer 188			Tween 80	
Concentration	7,5%	10%	16%	7,5%	10%	16%	7,5%	10%	16%
Particle size (nm)	1655±209	434±42	698±24	1290±321	287±36	1493±912	966±121	300±15	620±107
PDI	0,730±0,137	0,328±0,043	0,217±0,035	0,602±0,155	0,321±0,092	0,525±0,260	0,841±0,095	0,152±0,067	0,344±0,103

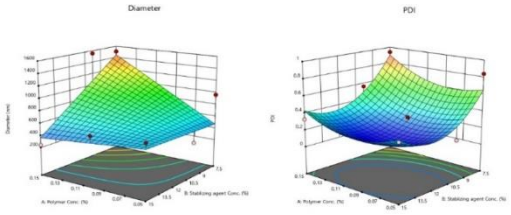

Figure 1. Changes of PDI and diameter of particles with changing Tween 80 and SF concentration

Conclusion: SF nanoparticles were successfully prepared with the nanoprecipitation method using Tween 80 as the stabilizing agent.

Acknowledgement

Ayşegül YILDIZ was supported by a scholarship from The Scientific and Technological Research Council of Turkey (TUBITAK) 2211-C National PhD Scholarship Program in the Priority Fields in Science and Technology.

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OP030: *IN VITRO* INCORPORATION STUDIES OF ^{99m}Tc-IBANDRONATE SODIUM ON BONE CANCER CELL LINE

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Introduction: Detection of bone cancer in the early stages plays an important role in controlling symptoms, reducing pain and improving quality of life. The development of new radiopharmaceuticals with higher efficiency and stability for bone cancer diagnosis is still significant (1). In this study, we aimed to develop a new radiopharmaceutical, using ibandronate sodium (IBD) as a model drug, that can be used for bone cancer diagnosis.

Materials and Methods: IBD was labeled with technetium-99m (^{99m}Tc) and quality control studies of the newly developed radiopharmaceutical were performed using radioactive thin layer chromatography (2). After, the hydroxyapatite (HA) binding assay and lipophilicity study of [^{99m}Tc]Tc-IBD were performed. Then, incorporation of [^{99m}Tc]Tc-IBD to cancer line was evaluated in human bone osteosarcoma cell line (U_2OS) (3).

Results: The radiochemical purity of [^{99m}Tc]Tc-IBD was found over 95% at room temperature up to 6 h which conditions were 20 µg stannous chloride and 37 MBq TcO_4^- at pH 5,5. The percentage of binding of IBD to HA was found to be 83,70±3,67 and the logP of [^{99m}Tc]Tc-IBD were found to be -1.0104. According to cell culture studies, [^{99m}Tc]Tc-IBD was higher incorporated than Reduced/Hydrolized ^{99m}Tc to U_2OS cells (Figure 1).

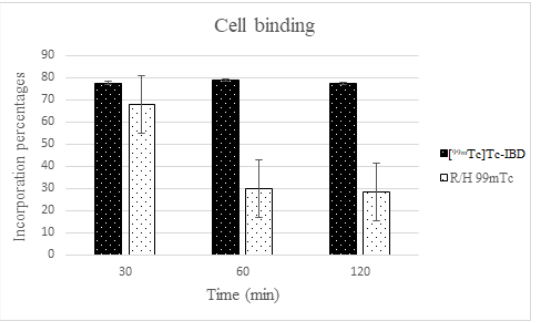

Figure 1. Incorporation percentage of [^{99m}Tc]Tc-IBD and R/H ^{99m}Tc to the U_2OS cell lines for 30, 60 and 120 min.

Conclusions: Consequently, these promising radiolabeling, HA binding and cell culture data show that [^{99m}Tc]Tc-IBD will be a step for further studies for bone cancer diagnosis in nuclear medicine patients.

Acknowledgements

The authors thank to Ege University Nuclear Medicine Department for obtaining ^{99m}Tc and to Dr. Petek Ballar-Kirmizibayrak for providing cell line.

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OP031: DEVELOPMENT OF THE MICELLAR BASED OCULAR *IN SITU* GELLING SYSTEMS OF POSACONAZOLE WITH QUALITY BY DESIGN (QbD) APPROACH

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Introduction: Ocular fungal infections cause serious results, although they have low incidence. Thiazole agents are first choice of antifungal therapy but there isn't any ocular forms. There are some successful case reports results indicating the potential efficacy of oral suspension of a thiazole agent, Posaconazole (PSC), despite of being a non-suitable for ocular administration. Conventional ocular drugs have also some disadvantages namely low bioavailability, high dose frequency, low patient compliance. Because of these limitations, highly lipophilic drugs can not be used efficiently in ocular diseases. Thus, drug

delivery systems are more suitable than conventional dosage forms in the treatment of ocular diseases. We optimized PSC-loaded micelles to increase the aqueous solubility of PSC in our previous study. In this study, the effect of *in situ* gels of PSC loaded micelles on ocular permeation and reduction of elimination by nasolacrimal drainage was evaluated using the QBD approach.

Materials and Methods: PSC-loaded micelles were used to develop the micellar-based in-situ gelling systems. *In-situ* gels were prepared with different concentrations of Polaxamers (407/188) or HPMC (50M/60M). A detailed analysis of the rheological behaviors (*continuous shear, oscillatory, interaction parameter, and transition temperature-Tsol/gel*) of *in-situ* gels were done. *In vitro* drug releases and drug loading efficiency were also performed. Minitab 18 program was used to create the design space and evaluate the statistical coefficients of the factors.

Results: The loading efficiency of micellar *in-situ* gels was found to be very high (*at least* 85%). Rheological properties and of micelles improved *via* an *in-situ* gelling system. The drug release performance of *in-situ* gels is better than PSC micelles and suspension include same dose of drug.

Conclusions: Studies have shown that PSC-loaded micelles whose efficiency was shown previously are suitable for developmet of the *in-situ* gel formulations. The improvement in rheological properties and drug releases of micelles *via* in-situ gelling systems indicate that these gels seem to be a promising ocular drug delivery system pf PSC.

Acknowledgements

This study was supported by a grant of the Research Fund of Istanbul University (TAB-2020-36873).

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OP032: ^{99m}Tc-LABELED, COLISTIN ENCAPSULATED, THERANOSTIC LIPOSOMES

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Introduction: The early detection and effective treatment of infection plays an important role to avoid the progression of disease and development of drug resistance (1). To that end, in our study, cationic and neutral, colistin encapsulated, liposomes were prepared, characterized, and radiolabelled with ^{99m}Tc to develop more specific and effective theranostic (therapeutic and diagnostic) agent for infection.

Materials and Methods: All reagents were of analytical or higher grade and obtained from commercial sources except colistin. Liposomes were prepared by the film-hydration method, and colistin was entrapped to the aqueous core of liposomes (2). In characterization studies, the mean particle size, polydispersity index, zeta potential, and encapsulation efficiency were determined, and the release behaviour of colistin from liposomes was studied by dialysis method. Liposomes were radiolabelled with ^{99m}Tc by tin-reduction method, and the different amounts of $SnCl_2$ were tested to detect of the optimum radiolabelling conditions (3). The radiochemical purity of radiolabelled liposome formulations was assessed by thin-layer chromatography at different time intervals for 6 h.

Results: All liposome formulations showed proper characterization with encapsulation efficiency of about 73%, mean particle size of around 180 nm, and zeta potential of around -4 and +1 mV for neutral and cationic liposomes, respectively. Colistin was released from cationic and neutral liposomes at the end of 8 and 10 h, respectively. The liposomal formulations were labelled with high efficiency and the radiochemical purities of formulations were detected higher than 80% at different time intervals.

Conclusions: By the result of characterization, in vitro drug release, and radiolabelling studies, nanosized, colistin encapsulated liposome formulation was found to be a promising carrier system for the imaging and treatment of infection.

Acknowledgements

The authors would like to thank Polifarma for the generous gift of Colistin, and this study was supported by the grant of Izmir Katip Celebi University Scientific Research Projects Coordination Unit, Project No: 2019-GAP-ECZF-0005.

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OP033: DEVELOPMENT OF PLGA NANOPARTICLES TO PROMOTE ALVEOLAR BONE REGENERATION

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Introduction: Regenerative treatment usually requires bone grafting. However, grafts are associated with the risk of numerous complications that limit their clinical applications, such as donor site complications, infection, and immune problems (1). For this purpose, it is recommended to modulate the host response with the use of antimicrobials or anti-inflammatories in treatments with regenerative growth factors (2).

The aim of this study is to prepare and *in vitro - in vivo* evaluation of bone morphogenetic protein (BMP) and clindamycin phosphate (CDP) loaded polymeric nanoparticles to accelerate hard tissue regeneration during the regenerative process.

Materials and Methods: PLGA nanoparticles (100 mg PLGA, (50:50) (M_W:24-38 k Da)) loaded only BMP (F1) (BSA used as model drug for *in vitro* drug release experiments (F1-BSA)) (4 µg) or combined with CDP (F2 and F2-BSA) (20 mg) were prepared by emulsifying and solvent evaporation technique. Nanoparticles were characterized by particle size, zeta potential (ZP), encapsulation efficiency (EE) and *in vitro* drug release profiles. Regeneration of the bone was evaluated *in vivo* at defected mandibular ramus of Wistar albino rats and analyzed visually and quantitatively by micro-computed tomography (micro-CT). Also, the micro-CT data were compared with histopathological results at mandibular bone tissue.

Results: The mean particle sizes were between 449.6 ± 19.23 nm and 790.9 ± 24.84 nm. In addition, size distribution was acceptable for all the formulations (PDI<0.7). The ZP values were between -18.87 ± 0.87 mV and -28.07 ± 0.25 mV. It was observed that the EE % values of BMP (F1: 64.15 ± 5.49 and F2: 68.37 ± 8.06) and BSA (F1-BSA: 60.17 ± 11.47 and F2-BSA: 68.23 ± 13.98) were significantly higher than that of CDP (F2: 42.48 ± 0.57 and F2-BSA: 44.78 ± 0.94). Histopathological evaluations were found to be consistent with the results obtained by micro-CT, and it was determined that significant ossification was obtained even after 2 weeks with the F1 and F2 formulations compared to the control group.

Conclusions: Through *in vitro* assays, controlled release was achieved for more than two months and following *in vivo* experiments, conducted micro-CT and histopathological analysis indicated that the BMP-CDP combination (F2) at a single drug delivery system advanced bone regeneration therapy further than that of only BMP loaded F1 formulation.

Acknowledgements

This study was supported by Ankara University, Coordinator of Scientific Research Projects (Grant number: 17A0234001)

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OP034: A NEW ORODISPERSIBLE TABLET FORMULATION OF AN ANTIHYPERTENSIVE DRUG

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Introduction: Fosinopril sodium is an angiotensin converting enzyme inhibitor and is mainly used for hypertension and congestive heart failure treatment. The hydrophobic interactions between fosinopril sodium molecules results in micellar aggregates which in turn could cause solubility decrease in the presence of metal ions and low absorption in clinical trials (1). In this study it was aimed to prepare cyclodextrin fosinopril sodium complexes to increase fosinopril sodium solubility and to develop and evaluate oro-dispersible tablets (ODTs) with this complex.

Materials and Methods: Fosinopril sodium cyclodextrin complex was prepared with kneading method. Tablets were prepared with direct compression method. Croscarmellose sodium,

crospovidone, magnesium stearate, aspartame, microcrystalline cellulose and raspberry flavor was used as excipients. Quality control tests such as weight uniformity, hardness, friability, wetting time, content uniformity, disintegration time and dissolution studies were carried out. Dissolution studies were performed at 37 ° C and in 900 mL pH 6.8 phosphate buffer using the pedal method at 50 rpm.

Results: Quality control studies revealed that tablets were acceptable in terms of weight uniformity, hardness, friability and content uniformity. The disintegration time of the tablets was 18 sec and the wetting time was 33.5 ± 1.8 sec. In dissolution studies, 77.7 % of fosinopril sodium was released within 1 min and 88.6 % within 9 min for ODT formulation while only 35.2 % of fosinopril sodium was released within 9 min for marketed conventional tablets.

Conclusions: Fosinopril beta cyclodextrin complex was successfully implemented for preparing fast disintegrating oro-dispersible tablets with a rapid drug release profile.

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OP035: DEVELOPMENT AND CHARACTERIZATION OF ERLOTINIB-RANDOMLY METHYLATED-β-CYCLODEXTRIN COMPLEX FOR THE TREATMENT OF NON-SMALL LUNG CANCER

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Introduction: Erlotinib (ERL) is used clinically as a tyrosine kinase inhibitor for the treatment in non-small cell lung cancer (1). ERL, a BCS class II drug, shows low bioavailability and patient variability leading to therapeutic failure due to poor aqueous solubility (2). Thus, there is need to develop a novel formulation of ERL which can overcome these drawbacks. The purpose of this study was to evaluate the orally tablets containing an erlotinib-randomly methylated-β-cyclodextrin (RAMEB) complex on drug solubility and permeability.

Materials and Methods: Erlotinib Hydrochloride (ERL, MW: 429.9 g/mol, Hetero labs, India) was a kind gift from Nobel İlaç, Turkey. Randomly methylated-β-cyclodextrin (RAMEB, MW:1291.8 g/mol) was as kind gifts of Cyclolab, Hungary. Phase-solubility study was carried out as reported Higuchi and Connors. The inclusion complexes were prepared by two methods (kneading and liyophilization) and characterized by different techniques including fourier transform infrared spectroscopy (FT-IR), differential scanning calorimetry (DSC), scanning electron microscopy (SEM) and X-ray diffractometry (XRD). The dissolution profiles of drug-cyclodextrin inclusion complex were evaluated. Cytotoxicity of inclusion complex was determined in L929 and A549 cells with MTT assay. In vitro permeability study was done across Caco-2 cells and analysed with HPLC. Tablet formulation was prepared with optimum inclusion complex using direct compression method. The quality control tests like hardness, diameter, thickness, friability, weight variability, disintegration and dissolution were done for tablet formulation of erlotinib with RAMEB-CD.

Results: Phase solubility study demonstrated erlotinib showed maximum solubility in RAMEB-CD solution. The optimum formulation was obtained with ERL-RAMEB in 1:1 molar ratio using lyophilization method. Characterization studies confirmed the inclusion complex formation. In vitro dissolution study confirmed ERL-RAMEB increase drug dissolution with 1.5 fold than ERL solution at one hour. The in vitro cytotoxicity results indicated that ERL-RAMEB inclusion complex reduced cell viability than free erlotinib. The in vitro permeability study resulted in 5-fold higher uptake of ERL-RAMEB inclusion complex than the drug solution in Caco-2 cells. Tablet formulation using ERL-RAMEB inclusion complex (drug dose equivalent to 25 mg) was prepared using direct compression. The thickness, diameter and hardness values were 3.92±0.05 mm, 11.3±0.06 mm and 81.38±2.27 N, respectively. The average weight was 404.57 ± 1.6 mg, with less than 5% deviation for 20 tablets. Friability value was 0.27%. The disintegration time was less than 15 minutes. Dissolution study showed that 99% drug was released from tablet formulation at one hour.

Conclusions: Complexation of Erlotinib with RAMEB lead a more efficient tablet formulation with improved dissolution and intestinal permeability of erlotinib.

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OP036: DESIGN OF DEXPANTHENOL LOADED ORALLY DISINTEGRATING FILMS

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Introduction: Dexpanthenol (DEX) is a topical agent, which has 100 mg commercial pastille dosage form and has been investigated against sore throat in post-intubation. However, an orally disintegrating film (ODF) of DEX has not studied yet. ODFs are alternative dosage forms that shows the advantages of fast dissolution, ease of application and accurate dosing (1). In this study, 50 mg DEX loaded ODFs were produced using hydroxypropyl methylcellulose (HPMC LV 100), kollicoat IR (KIR) and maltodextrine (MD) polymers, to achieve a suitable disintegration time and good physicochemical properties for local treatment.

Materials and Methods: Films was prepared by solvent casting method by HPMC-MD or HPMC-KIR-MD mixture in 5% glycerine solution with or without addition of DEX. Mixing was achieved by stir-pak and films were dried in the oven at 37ºC for 18 hr. Prior to film casting, viscosity, adhesion, pH controls were performed on gels. Films were evaluated for thickness, disintegration and dissolution properties, adhesive properties, tensile strength (TS; MPa) and elongation (E; %) (Stable Texture Analyzer) (2). Content uniformity was done by HPLC.

Results: Viscosity of gels was found between 2400-3200 cP at 50 rpm. As shown in Figure 1, due to the plasticizing effect of DEX, drug-loaded films with a thickness of 175-260 µm were found to be soft and tough due to their lower TS and higher E %. All films disintegrated in less than 13 min and dissolution completed within 90 min in PBS 6.75 buffer. Due to swelling and surface erosion properties of HPMC, films casted from HPMC-MD polymers provided slower disintegration. On the contrary, addition of KIR affected the films by increasing dispersibility.

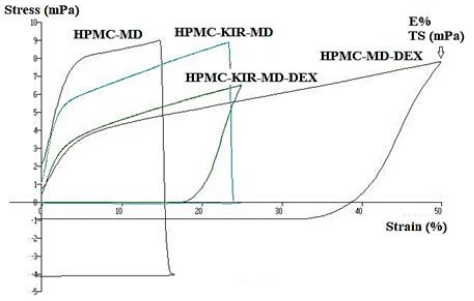

Figure 1. Texture properties of films

Conclusions: Even both films showed adequate mechanical and adhesive properties, due to faster disintegration, HPMC-KIR-MD-DEX film was found promising for further studies.

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OP037: EVALUATION AND COMPARISON OF β-CYCLODEXTRIN DERIVATIVES ON AQUEOUS SOLUBILITY OF DESLORATADINE

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Introduction: Low aqueous solubility of active pharmaceutical ingredients is one of the most challenging aspect for formulation development. Cyclodextrins are mainly used as complexing agents to increase the solubility of active substances poorly soluble in water in order to increase their bioavailability, to become applicable to patient and also to improve stability. In this context we initiated this research to investigate solubility enhancement and affinity of Hydroxypropyl-β-cyclodextrin (HP-β-CD) and Sulfobutylether-β-cyclodextrins (SBE-β-CD) with poorly water soluble drug, Desloratadine.

Materials and Methods: Desloratadine was donated from Nobel İlaç. HP-β-CD (Cavasol W7 HP Pharma) and SBE-β-CD were kindly supplied Ashland and Captisol, respectively. Phase-solubility studies were performed according to the method described by Higuchi and Connors (1, 2). Excess amount of Desloratadine was added 10 mL of distilled water containing various concentrations of Cyclodextrins in stoppered glass vial. Suspensions were mixed in a magnetic mixer at 25 ℃ for 3 days in water bath. Aliquots were filtered through a 0.45 µm PTFE filter and after dilution drug content assayed spectrophotometrically at

280 nm. The complexation efficiency and stability constant of Desloratadine-CD complexes were determined from the slope of phase solubility diagrams[3].

Results: The phase solubility diagram of Desloratadine with both SBE-β-CD and HP-β-CD exhibited A_L type profile. The aqueous solubility of Desloratadine was increased linearly as a function of HP-β-CD/SBE-β-CD concentration and the slope was less than unity confirming the formation 1:1 M complexes. Calculated stability constant were found 2931 M^{-1} and 1682 M^{-1} for HP-β-CD and SBE-β-CD, respectively. These findings indicate that obtained complexes are reasonably stable.

Conclusions: The results of this study show that aqueous solubility of Desloratadine was significantly enhanced by complex formation of both β-CD derivatives. This work has revealed that, especially using HP-β-CD, new Desloratadine containing formulations and dosage forms could be developed.

Acknowledgements

This study is supported by Gazi University Scientific Research Projects (BAP), Project number:02/2018-02

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OP038: OPTIMIZATION OF LIDOCAINE BASE NANOSUSPENSIONS WITH EXPERIMENTAL DESIGN

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Introduction: Lidocaine base (LID) is one of the local anesthetic drugs which is practically insoluble in water so it has low dermal permeability (1, 2). Nanosuspensions have a positive effect on the permeation of dermally administered drugs by better penetration into the skin (3). The aim of this study was to develop LID nanosuspensions using an experimental design (DoE) approach. Effect of critical formulation attributes (CFAs), critical process parameters (CPPs) and their interactions were determined.

Materials and Methods: LID nanosuspensions were prepared using wet milling method (RETCH® PM100, Germany). As the first step of the process, drug and stabilizer solution were stirred with Ultraturrax (Heidolph®–Silent Crusher M) at 15.000 rpm-10 min. After the complete wetting of coarse LID particles, wet milling process were applied. The process parameters were selected as 0,5-1mm bead size, 20 mL volume of milling beads,1-2 hours milling time and a milling rate of 200-300 rpm for polyvinyl alcohol (PVA) and 300-400 rpm for poloxamer 407 (POL). After these processes, as dependent variables the particle size (PS), polydispersity index (PDI), zeta potential (ZP) values of nanosuspension were measured using a Malvern Zeta Sizer (Malvern Instruments). 2^3 factorial design was used with Design-Expert software to optimize process independent parameters. Stability and characterization studies of the prepared nanosuspensions were carried out.

Results: The optimum formulation and process parameters were found as 4:1 LID:POL ratio, 0.5 mm bead size (A), 2 hours milling time (B), 300rpm milling rate (C). The PS, PDI and ZP were found 170.033±3.523 nm, 0.279±0,036 and -32.56±0.907 mV respectively. As a result of the short-term stability test, it was observed that POL nanosuspension was more stable than PVA nanosuspension at 4ºC and 25ºC.

Conclusions: This study demonstrated the usefulness of QbD approach using DoE to understand the optimum process parameters of LID nanosuspensions.

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OP039: DEVELOPMENT AND IN VITRO CHARACTERIZATION OF PREGABALIN LOADED NANOPARTICULAR SYSTEM

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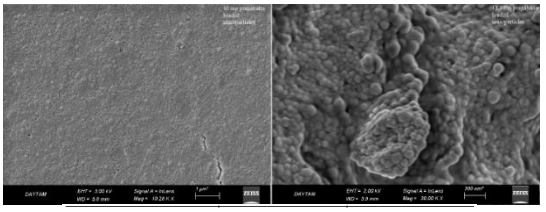
Introduction: The main target in the design of nanoparticles as drug delivery systems is to control the particle size, surface properties, and the release of active pharmaceutical agents to ensure that the drug acts at the therapeutically optimum dose and speed (1). Pregabalin (PG) resembles gamma-aminobutyric acid (GABA), which is the neurotransmitter of mammals with both structural and pharmacological properties. Its primary effect is anticonvulsant, and it is used in epilepsy. However, it also has analgesic, antidiabetic, and

anti-inflammatory effects (2, 3). PG has many advantages compared to other antiepileptics as it does not have pharmacokinetic interactions with other drugs or is induced by enzymes (4). PG is recommended in conventional therapy (as capsules) in the treatment of neuropathic pain at the usual dose of 75 mg twice a day or 50 mg three times a day (5). The aim of this study is to prepare and characterize PG-loaded PLGA nanoparticles as an alternative to capsules in order to achieve maximum efficiency with low side effects and reduce dosing.

Materials and Methods: PG was a gift from İlko İlaç (Turkey) and PLGA was purchased from Lactel (USA). In the preparation of PG-loaded (10 mg and 12.5 mg) nanoparticles, the nanoprecipitation method was used. Morphology, encapsulation efficiencies (EE), loading capacity (LC) and yields (Y), particle size, zeta potential, DSC thermograms, FT-IR spectra of nanoparticles prepared within the scope of characterization studies were examined.

Results: SEM image of PG (10 mg and 12.5 mg) loaded nanoparticles and EE, LC, Y values are given below. In addition, the particle size and zeta potential values of nanoparticles containing 10 mg of PG are 135.7±0.48 nm and -18.8±0.35 mV.



Pregabalin Amount in Nanoparticles (mg)	10	12.5
% EE±SD*	17.26±1.47	14.97±2.14
% LC±SD*	25.23±1.17	24.11±2.47
% Y±SD*	68.41±5.47	69.58±3.45

*SD: Standard deviation

Conclusions: PG-loaded PLGA nanoparticles have been successfully prepared and characterized. However, the amount of PG loaded on the spherical nanoparticles was low due to the hydrophilic nature of PG. Better results can be obtained with additional studies in the future and can be used as an alternative to conventional treatment.

Acknowledgements

This study was supported by a grant of Atatürk University Scientific Research Projects Coordination Unit (BAP-THD-2018-6547).

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OP040: EVALUATION OF IN VITRO PERMEABILITY OF AN ANTIVIRAL DRUG, FAVIPIRAVIR, FOR BCS CLASSIFICATION

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Introduction: Favipiravir (6-fluoro-3-hydroxy-2-pyrazinecarboxamide) is a pyrazine carboxamide derivative, which is one of the antiviral agents used in the treatment of influenza (1). Since the recent outbreak caused by 2019-novel coronavirus (nCoV), there has been a seek for effective antiviral agents for the treatment of coronavirus disease 2019 (COVID-19), and Favipiravir has been one of the emerging options. Herein, in vitro permeability characteristics of Favipiravir was determined for BCS classification using Caco-2 cell line.

Materials and Methods: Permeability studies were performed with Caco-2 cell line (ATCC® HTB-37™, passage number between 10 to 15). Caco-2 cells were seeded into the inserts (ThinCert™, 12 wells, 1 µM pore diameter, transparent) at a concentration of $12x10^4$ cells/mL and studies were performed after 21 days when the cell monolayer reached confluency. Favipiravir solutions with three different concentrations (0.8 mg/ml, 0.4 mg/ml and 2 mg/ml) and metoprolol tartrate (0.4 mg/ml) were applied to the apical compartment in transport medium. Verapamil HCl (50 µM) was used to determine the effect of P-gp efflux on the transport mechanism. After 2 hours of incubation, the medium in the basolateral compartment was collected and stored at −20 °C for HPLC analysis and the apparent permeability coefficients (P_{app}) were calculated (2).

Results: The apparent permeability of Metoprolol tartrate, reference permeability standard, was found to be $0.856x10^{-5}$±$0.0428x10^{-5}$ cm/s, and the permeability ratio of Favipiravir was between 1.27 to 1.62 for three concentrations with or without P-gp inhibitor. The in vitro permeability of Favipiravir was found to be between 1.08–$1.38x10^{-5}$ cm/s, depending on concentration. A significant difference was observed in permeability between the doses of 0.8 and 0.4 mg/ml, 0.8 and 0.2 mg/ml as well as between 0.4 and 0.2 mg/ml ($p=0.0002$, $p<0.0001$ and $p=0.0308$, respectively). The

difference was also statistically significant for the groups treated with Verapamil (p=0.0108, p<0.0001 and p=0.0147, respectively).

Conclusions: Favipiravir could be considered as a representative of high permeability class.

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OP041: ACE2 LOADED CATIONIC LIPOSOMES FOR COVID-19 TREATMENT

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Introduction: SARS-CoV-2 infects human cells by entering through ACE2 receptors which are located on the membran of cells (1). After administration of rhACE2 to the body, the virus could be able to bind to rhACE2, instead of binding to ACE2 receptors of body cells (2). In this study, it was aimed to develop ACE2 loaded decoy liposomes produced with dialkyl cationic lipids such as 1,2-dioleoyl-3-trimethylammonium-propane (DOTAP) and/or 1,2-dioleoyl-sn-glycero-3-phosphoethanolamine (DOPE) and cholesterol for treatment of Covid-19.

Materials and Methods: rhACE2 and cholesterol was purchased from Sigma-Aldrich. DOTAP and DOPE was products of Avanti Lipids. Cationic liposomes are prepared in DOTAP/DOPE (1:1 molar ratio, S1), DOTAP / DOPE / Chol (cholesterol) (2:1: 1 molar ratio, S2), DOTAP / Chol (1:1 molar ratio, S3). Lipid solutions were dried under pressure in a rotavapor at 80 rpm and 37°C for 15 minutes. Thin lipid film was observed on the inner walls of the flask. The thin lipid film was diluted with 1.6 mL of PBS 7.4. Formulations were incubated in 2µg/0.8 mL ACE2 PBS 7.4 solution at room temperature for 1.5 hours or 24 hours. After the incubation period, formulations were first extruded using 3 µm and then 0.1 µm polycarbonate filters at 50°C for 10 times. Particle size(nm), PDI and zeta potential(mV) were measured with Malvern NANOZS (n=3).

Results: Effect of formulation and process variables on size, PDI, and ZP was determined. While S1 had only the DOTAP/DOPE combination, cholesterol was added to S2 and S3 formulations by keeping the total lipid concentration constant. It was observed that particle size was increased with cholesterol addition (Table 1). Studies have shown that increasing the incubation time with the protein and liposome, increases the loading efficiency. In our study, increasing incubation time decreased the stability of the formulation. Also, extrusion was an effective method for the size reduction of liposomes.

Table 1. In vitro characteristics of liposome formulations obtained after 1.5 hour of incubation with ACE2 (n=3).

Formulation	Particle Size (nm)	PDI	Zeta potential (mV)
S1	326,5±20,96	0,56± 0,425	25,5±5,57
S2	690,3±60,96	0,690±0,125	20,6±3,28
S3	815,2±12,5	0,796±0,256	29,6±5,62

Conclusions: Decoy liposomes carry the binding receptors of viruses and prevent viral infection by allowing viruses to bind to these systems instead of receptors on the cell membranes. In this study, a new treatment option for covid-19 was developed. Also, different formulation and process variables were discussed to achieve better development technology.

Acknowledgements

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OP042: IMMUNOLOGICAL EFFECTS OF A NEW DEVELOPED CYCLOSPORINE A NANOSUSPENSION IN RATS FOR ORAL ADMINISTRATION

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Introduction: Cyclosporine A (CsA) is a polypeptide drug with low water solubility, which is used as an immunosuppressive after organ transplantation (1). CsA plays an important role in

the release of many cytokines, especially T cells, which play an important role in the immune system. Nanosuspensions are nano-sized colloidal dispersions prepared using stabilizers and consist of 100% drug molecules. Nanosuspensions are preferred because they can increase the solubility, dissolution, and bioavailability of drugs with low water solubility (2). The aim of this study was to evaluate the immunological effect of developed CsA nanosuspension prepared by wet media milling (WM) method compared to CsA coarse powder, physical mixture, and commercial product (Sandimmune Neoral®).

Materials and Methods: CsA nanosuspension was prepared by WM method after 1 hour milling with 600 rpm milling speed. Hydroxypropyl methylcellulose (HPMC) and sodium dodecyl sulfate (SDS) were used for stabilizers and developed nanosuspension was characterized (3). *In vivo* immunological study was performed on Wistar albino rats. Coarse powder, physical mixture, CsA nanosuspension, and commercial product were administered orally at 10 mg/kg of CsA once a day for 21 days. Blood samples were collected at 7, 14, and 21 days. The plasma levels of IL-2 and IFN-γ were detected with Multiplex immunoassay by RAT CytokinePlex Panel kit using the Luminex-200TM. The analyses of IL-22 and TGF-β1 levels from plasma were performed with the standard ELISA method.

Results: As shown in Figure 1, the highest IL-22 level was found in the commercial product administered group on the 7th, 14th, and 21st days. IL-22 level decreased from the 7th day to 21st day in all groups. When the plasma concentrations of TGF-β1 and IFN-γ (Figure 2) values after 21 days of administration were examined; it was found that there was no statistical difference both between all groups and between all days ($p>0.05$). The lower IL-2 level was obtained with CsA nanosuspension and these results indicated that the immunosuppressive effect is maintained a longer and higher immunosuppression.

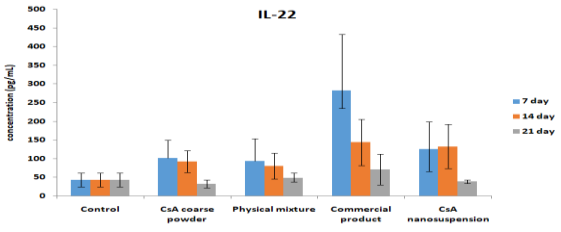

Figure 1. IL-22 levels of all groups

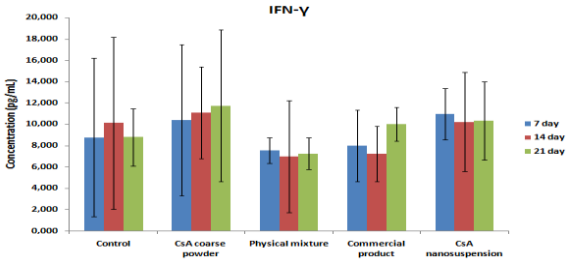

Figure 2. IFN-γ levels of all groups

Conclusions: In conclusion, the immune response obtained with CsA nanosuspension was found to be acceptable after immunological evaluation.

Acknowledgments

This study was supported by a grant of Gazi University Scientific Research Project Foundation (Project No: 02/2017-14).

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OP043: ORGANOTYPIC BRAIN SLICE CULTURES

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Introduction: In-vivo studies are complex experiments, may cause secondary complications. They are ethically painful, stressful, time-consuming, and far from the 3R. In-vitro cell cultures do not imitate the nature of organism due to no interaction with other cells and tissue organization. 3D cultures such as organotypic brain slice cultures act as bridges and fill the gap between in-vitro and in-vivo. The aim of this study is to evaluate the advantages, disadvantages of organotypic brain slice cultures and show the effect of NGF, memantine and quinidine on cholinergic neurons.

Materials and Methods: Organotypic brain slice culture techniques are classified as roller tubes, membrane cultures, culture dishes and co-cultures. In the study, membrane cultures were prepared. The brain slices are placed on a semi-permeable membrane with a small amount of medium and fixed on the membrane. The membrane allows the diffusion of substances in the culture medium necessary for the survival of the slice. This method is suitable for the application of drug and gene silencing, biochemical studies or

overexpression (1). Organotypic brain slices of were incubated with 100 ng/mL NGF, 10 µM memantine, 10 µM quinidine and combinations of these treatments for 2 weeks.

Results: Immunohistochemistry results obtained from organotypic brain slice cultures demonstrated that memantine improves the survival of cholinergic neurons of nBM (223±28; n=6) in organotypic brain slices compared to control group (106±9; n=7). Though, memantine and NGF do not show an additive survival effect on cholinergic neurons (210±27; n=6). Contrary to expectations, quinidine alone does not have a negative effect on the survival of cholinergic neurons of nBM. However, quinidine inhibits the protective effects of both memantine and NGF on cholinergic neurons. Western blotting results implied that NGF treated samples had significantly higher optical density compared to control group at 35 kDa band and memantine treated samples had slightly higher optical density for 35 kDa band compared to control group, but this difference was not found statistically significant ($p>0.05$).

Conclusions: There are many possible experimental models to choose from to study the complexity of the brain functionally and pathologically. Depending on the research question, it is possible to choose the appropriate brain slice model.

Acknowledgement
The author would like to thank Prof. Selma Sahin, Prof. Christian Humpel and Buket Ucar.

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OP044: DEVELOPMENT OF AN *IN VIVO* TEST METHOD FOR THE NASAL DELIVERY OF LYOSPHERES®

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Introduction: Nasal route is a promising delivery route especially for peptide drugs as the epithelial barrier permits a significant transport of such compounds (1). A solid fast-dissolving powder formulation can provide an increased stability to peptides compared to the liquid alternatives, while dissolving rapidly in the mucus and having a substantial absorption. Spray freeze-dried particles (lyospheres®) offer increased stability, ease of application due to its low density and superior flow properties, and instant dissolution due to its highly porous structure (2). The aim of this study is to develop an *in vivo* test method to test the nasal administration of the lyospheres® and the systemic bioavailability of the model drug carried by them.

Materials and Methods: Insulin was used as a model peptide, as its relatively small size allows observing the penetration through the nasal mucosa evidently and its bioavailability can be tracked simply by measuring the blood glucose level. A commercial nasal powder spray device and a custom-made device were tested for the nasal administration of the Insulin loaded lyospheres® to the Sprague Dawley albino rats. Emission rates were determined for lyospheres® of different particles sizes. Blood sugar level measurement might be influenced by several factors. Therefore, influence of the factors like fasting and Streptozotocin-induced diabetes were tested. Healthy and diabetic rats with/without fasting prior to the experiment were tested and the blood glucose profiles were obtained for each condition.

Results: Both devices were found to have a high emission rate, however custom-made device was found to have more flexibility for testing on rats. Although the commercial device is very promising for human use, the rat adaptor seemed to be occluded during nasal administration. The blood glucose levels were found to be rather unstable, and the variability was higher among the diabetic rats and the rats which were fasting for long hours. It was more stable for healthy animals and it remained within the measurement range of the glucometer.

Conclusions: An *in vivo* test method was developed successfully for the nasal administration of the lyospheres® and various factors impacting the test method were evaluated. The findings will cast light onto the future studies on lyospheres®.

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OP045: CURCUMIN LOADED SEMISOLID SLN DISPERSIONS: FORMULATION OPTIMIZATION AND IN VIVO EVALUATION

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Introduction: Solid lipid nanoparticles (SLNs) are extensively used as dermal drug delivery systems since they have several advantages. Semisolid SLN dispersions have a gel-like structure and they retain the colloidal particle size despite their high lipid content and semisolid consistency (1). Curcumin is a polyphenolic compound with important anti-inflammatory and antioxidant activities. However, the poor aqueous solubility of curcumin limits its skin penetration (2). The aim of this study was to develop and optimize the semisolid SLN formulations to achieve increased anti-inflammatory activity of curcumin.

Materials and Methods: Semisolid SLN formulations were prepared by high shear homogenization and ultrasonication method. Formulation optimization was performed using artificial neural network (ANN) (3). Different Tristearin:Compritol 888 ATO ratios and total lipid contents were evaluated as critical material attributes (CMA). Particle size and drug release (%) at 24th hour were determined as critical quality attributes (CQA). Optimum semisolid SLN formulation was prepared using same method. *In vitro* characterization and stability tests were performed. In vivo anti-inflammatory activity of the optimum formulation was evaluated by paw edema test on rats (Local Animal Ethics Committee of Ankara University 2018-19-126).

Results: The particle size of the optimum formulation was found as 204,7nm±1,47 and it was significantly smaller than the particle sizes of semisolid SLN formulations previously prepared. The drug release (%) at 24th hour of optimum formulation was also found as 38.34 % ± 3.48. It was determined that optimum semisolid SLN formulation showed significantly higher anti-inflammatory activity compared with the conventional gel formulation of curcumin. The optimum formulation effectively reduced the inflammation in rats right from the 1st hour.

Conclusions: Semisolid SLN dispersions were developed as a novel dermal delivery system for curcumin and formulation optimization was successfully realized by ANN. The anti-inflammatory activity of curcumin was increased by the optimum formulation developed.

Acknowledgements

This study was supported by the Management of Scientific Research Projects (BAP) of Ankara University (19B0237002)

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OP046: DEVELOPMENT OF THYMOQUINONE LOADED NANO-FORMULATIONS VIA CENTRAL COMPOSITE DESIGN

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Introduction: In the field of drug delivery, advances in nanomaterials and nanotechnology have mostly centered on the use of nano-scale lipid or polymer-based particles. Various advantages, such as controlled drug release features, improved pharmacokinetic profile, and increased cell permeability were acquired as a result of the use of these nanotherapeutics to overcome the drawbacks of traditional treatments. In this research, we engineered and formulated Thymoquinone (TQ) encapsulated biocompatible polymer-based nanoparticle (NP) formulations. The Central Composite Design (CCD) methodology (1) was used to refine the nano formulation.

Materials and Methods: TQ encapsulating NPs were fabricated using emulsion-solvent evaporation method. The critical NP formulation parameters including TQ/polymer ratio, sonication duration and stabilizer concentration have been optimized by CCD methodology to obtain NP formulation having smaller particles with uniform distribution along with higher TQ encapsulation efficiency. The hydrodynamic diameter of the NPs, polydispersity index, zeta potential, encapsulation efficiency, and TQ release profile of the nano-formulations were revealed and the morphology of the particles were imaged via transmission electron microscopy. Additionally, the optimized nano-formulation was validated experimentally by refabricating at defined optimized variable levels.

Results: Nano-formulations encapsulating TQ were fabricated with an average particle size of 200 nm – 300 nm and polydispersity (PDI) values of 0.10 – 0.30. The transmission electron microscopy images of the nano-formulations validated these particle size observations and also imaged the spherical forms of the nanoparticles. The zeta potentials ranged from -10 to -20 millivolts. Furthermore, reverse phase HPLC measurements were used to determine the quantities of encapsulated TQ in nano-formulations, with encapsulation efficiency values ranging from 30% to 90%. The □100% of the encapsulated TQ was released within 96 hours, resulting in a modified release profile.

Conclusions: To summarize, the nano-formulations proposed in this research have the

ability to provide modified TQ delivery and can be used to create novel treatment approaches.

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OP047: HUMAN SERUM ALBUMIN NANOPARTICLES FOR TARGETED CANCER THERAPY

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Introduction: Gefitinib is an EGFR tyrosine kinase inhibitor, has activity in cancer treatment with tumors with EGFR mutation. This study aimed to produce gefitinib-containing HSA nanoparticles and optimize the production method, in order to overcome the challenges of gefitinib with low solubility, variable absorption, low oral bioavailability, side effects, and drug resistance (1).

Materials and Methods: Gefitinib was kindly provided by Nobel İlaç (Istanbul, TR). Human Albumin Grifols® 20% (Each mL contains 0.2 g HSA, sodium caprylate, sodium N-acetyltryptophanate and water for injection) was used as HSA source. Dipalmitoylphosphatidylcholine (DPPC) was purchased from Sigma (St. Louis, MO, USA). All other chemicals were of analytical grade. Before producing gefitinib-HSA nanoparticles, the fluorescence spectroscopy method was used to demonstrate the binding of the drug to HSA. Gefitinib binding to HSA in the presence and absence of DPPC, keeping the HSA concentration constant, was demonstrated with Stern-Volmer plots. Nanoparticles were prepared by modifying the Nab™ technology (2). For this purpose, gefitinib was dissolved in the organic phase and injected into the aqueous solution of HSA using Ultraturrax. The crude emulsion was homogenized in a high-pressure homogenizer. The organic solvent was evaporated using a rotavapor. The particle size distribution was measured before and after the resulting nanoparticle suspension was filtered through a 0.22 µm filter. In order to optimize the method, the effects of critical production parameters such as organic:aqueous phase, drug:HSA, DPPC concentration, homogenization cycle on particle size distribution were evaluated using the Box-Behnken design.

Results: The Stern Volmer plot obtained by fluorescence spectroscopy showed that the rate of HSA binding of gefitinib utilized in the presence of DPPC. Uniform nanoparticles with a PDI value of less than 0.3 and a particle size of less than 200 nm were produced with the optimized preparation method.

Conclusions: As a result, this method, optimized based on Nab™ technology, proved promising for preparing targeted HSA nanoparticles containing gefitinib to obtain higher treatment efficacy with lower side effects.

Acknowledgements

This study was supported by a grant of TUBITAK (SBAG-120S895).

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OP048: ELECTROSPUN NANOFIBERS AS ORAL FAST-DISSOLVING DELIVERY SYSTEM OF RISPERIDONE

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Introduction: Many patients, particularly children and the elderly population find it inconvenient to ingest conventional solid dosage forms such as tablets and capsules due to an impaired ability to swallow (1). This issue can be addressed through the development of orally disintegrating dosage forms that disperse or dissolve in the saliva and are swallowed without water. Besides improving the acceptability and compliance of patients, orally disintegrating dosage forms have been investigated for their potential to increase the bioavailability through the enhancement of the dissolution rate.

Materials and Methods: Fast-dissolving oral drug delivery systems were prepared by electrospinning method using polyethylenoxide (PEO) with different molecular weight (100,000, 200,000, 600,000 g/mol). By using equal amount of Xylitol or Kollidon VA-64 with the polymer (PEO), it was aimed to disintegrate the nanofibers faster. Scanning electron microscopy (SEM), Fourier-transform infrared (FTIR) and differential scanning calorimetry (DSC) analysis were applied to investigate the physicochemical properties of electrospun nanofibers. Disintegration test was performed in a petri dish with a diameter of 10 cm using 2-layer filter paper and simulated oral saliva. The USP Apparatus 1 was used for in vitro dissolution tests. Dissolution rate of nanofiber formulations compared with the commercially available product. Distilled water was used as the dissolution medium since the risperidon is already highly soluble in acidic medium.

Results: The SEM images showed that nanofibers prepared with electrospinning PEO/VA-64/Risperidon polymer mixture solutions possessed an ultrafine morphology with an average diameter in the range of 500-1000 nm.

Nanofibers obtained with XYL had a rough structure and as the molecular weight of the PEO increased, the nanofiber structure became smoother. All nanofiber formulations disintegrated within 30 seconds. In the dissolution studies, 100% drug release was reached within 15 minutes in the most of the formulations. The release studies indicated that drug can be released in a burst manner (risperidon to an extent of 100% within 15 min) from the PEO nanofibrous matrices.

Conclusion: The data reported herein clearly demonstrate that electrospun PEO/XYL and PEO/VA-64 fibers comprise excellent candidates for oral fast-dissolving films, which could be particularly useful for children and patients with swallowing difficulties.

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OP049: PREPARATION AND CHARACTERIZATION OF TENOFOVIR DISOPROXIL FUMARATE LOADED NANOFIBER FOR VAGINAL DELIVERY

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Introduction: Human immunodeficiency virus (HIV) which causes the acquired immunodeficiency syndrome (AIDS) is a virus that can be transmitted in many ways (1). The purpose of this study is to develop mucoadhesive nanofibers using by electro-spinning method for vaginal application of Tenofovir Disoproxil Fumarate (TDF). TDF is an antiretroviral drug used to treat HIV.

Materials and Methods: Nanofiber formulations were prepared using PVP (polyvinyl pyrrolidone, K90) in three different concentrations (10%, 12.5%, 15%). For the nanofibers (blank nanofibers as T1, T2 and T3 and %0,5 TDF loaded nanofibers as T4, T5 and T6) prepared by the electrospinning method, the process parameters of our previous study were used (2). The polymer solutions were characterized. The contact angle, tensile strength, elongation at break, average fiber diameter, mucoadhesive properties, in vitro release and release kinetics of the formulations were calculated for nanofiber formulations. The ex-vivo permeation of TDF nanofiber formulations were also evaluated.

Results: The viscosity, conductivity and surface tension of the polymer solutions were found to be suitable for producing nanofibers, especially for T6 formulation. Based on the in vitro diffusion results of the T4, T5 and T6 formulations, approximately 80% of the total drug spread after 8 hours and 100% within 24 hours. The flux and permeability coefficient parameters are given Table 1. The flux of the TDF through the cow vagina after 24 h for T6 formulation was significantly higher than that of T4. When all results were evaluated, it was seen that mucoadhesive properties, in vitro diffusion, permeation and flux values increased as the concentration of polymers increase.

Table 1. Characterization and ex-vivo permeation results of nanofiber formulations

	T1	T2	T3	T4	T5	T6
Average fiber diameter (nm)	677± 131	1031± 202	1564± 270	877± 129	1340± 210	1550± 195
Tensile strength (MPa)	3.07± 0.33	3.94± 0.73	5.87± 0.25	4.04± 0.51	5.18± 0.87	6.11± 0.11
Elongation at break values (%)	63.87± 9.81	28.46± 7.24	15.90± 4.93	64.09± 8.85	52.89±9 .06	44.43± 5.85
Contact Angle (°)	0	0	0	0	0	0
Work of mucoadhesion ($mJ.cm^{-2}$)	0,173± 0,030	0,182± 0,021	0,212± 0,012	0,234± 0,014	0,328±0 ,039	0,332± 0,012
Flux ($\mu g.cm^{-2}.h^{-1}$)	-	-	-	115±1	130±2	131±2
Permeability coefficient ($cm.h^{-1}$)	-	-	-	0.05±0. 00	0.0543± 0.004	0.055± 0.001

Conclusions: PVP concentration directly affected nanofiber diameter, mechanical, and mucoadhesion properties of nanofibers. It was concluded that nanofiber containing T6 formulation was more suitable for vaginal application.

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OP050: LABEL-FREE DETECTION of miRNA-34a by CARBON NANOFIBER ENRICHED SCREEN-PRINTED ELECTRODES

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Introduction: Recent studies have identified that, circulating miRNA levels are related to cancer, immunological diseases, cardiovascular diseases, neurological diseases (1). Therefore, there has been a growing interest for fast, reliable, and ultrasensitive biosensors for detection of trace amounts of miRNAs. Carbon nanofibers (CNFs) are great nanomaterials for development of novel sensor surfaces, as they provide such properties as high surface area, non-toxicity, acceptable biocompatibility (2). The aim of this work is the development of a label-free voltammetric biosensor for detection of miRNA-34a by carbon nanofiber enriched disposable screen-printed electrodes (CNF-SPEs) (3).

Materials and Methods: The amino linked miRNA-34a DNA probe and complementary miRNA-34a or miRNA-15a/miRNA-660 were purchased (as lyophilized powder) TIB Molbiol (Germany). AUTOLAB-PGSTAT with GPES 4.9007 software (Eco Chemie, The Netherlands) was used for electrochemical measurements. CNF-SPEs were purchased from DropSens (Spain). The voltammetric detection of miRNA-34a was performed in three steps (3): (*i*) immobilization of DNA probe onto CNF-SPEs, (*ii*) solid state hybridization of DNA probe and miRNA-34a target and (*iii*) voltammetric measurements.

Results: 18-folds enhanced guanine signal in a better reproducibility was obtained by CNF-SPEs in comparison to the SPE. After optimization of experimental conditions, such as DNA probe concentration, the detection limit (DL) of miRNA-34a was found to be 10.98 µg/mL (54 pmol in 35 µL sample) according to the Miller and Miller method (4). The selectivity of the electrochemical miRNA-34a biosensor was also examined in the presence of other miRNA sequences; miRNA-15a and miRNA-660 by resulting with a good selectivity (3).

Conclusions: A novel, label-free, miRNA biosensing assay was successfully developed by incorporation of inosine substituted DNA probe and CNF-SPEs in our study (3). CNF-SPEs can be used as a practical and reliable platform for monitoring of nucleic acid hybridization. This assay principle presents a great promise for development of low-cost and sensitive sensing protocol for healthcare monitoring.

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OP051: POLYETHYLENEIMINE FUNCTIONALIZED CRYOGEL MEMBRANES AS A CONTROLLED RELEASE SYSTEM

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Introduction: Controlled release systems have some advantages such as utilizing less drug dose, extending the dosing interval, and reducing side effects (1, 2). Because implant systems can deliver high amounts of drugs around the tumor site, the therapeutic effectiveness of chemotherapy may increase while the side effects of the drug decrease (3). The objective of the study is to design polyethyleneimine (PEI) functionalized cryogel membranes which can be used as a potential delivery system.

Materials and Methods: The membranes based on 2-hydroxyethyl methacrylate and glycidyl methacrylate, were synthesized via cryopolymerization using ethylene glycol dimethacrylate as a crosslinking agent. After the polymerization step and washing process, PEI was immobilized on the cryogel membranes through the reactive glycidyl groups of the cryogels. Then, Cu (II) ions were chelated on the cryogel membranes through NH_2 groups of PEI. 5-fluorouracil (5-FU) was loaded in the PEI-functionalized cryogel membranes. *In vitro* release experiments were performed to investigate the effects of pH, crosslinker ratio, and amount of 5-FU on the release rate of 5-FU from modified cryogel membranes in buffer medium.

Results: Surface area, macroporosity, and swelling ratios of the cryogel membranes were found out as 16.2 m^2/g cryogel, 76.7% and 5.76 g H_2O/g cryogel, respectively. According to results of *in vitro* cumulative release studies, cryogel membranes exhibited a burst effect and then slower release rates. An increment in release rate was observed in the cryogels having less crosslinker ratio. Release rates of 5-FU from the cryogel membranes were increased by decreasing the medium pH.

Conclusions: PEI-functionalized cryogel membranes showed a pH-responsive behavior as well as higher drug release at lower pH. It can be concluded that modified cryogel membranes could be promising candidates for implantable drug delivery systems.

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OP052: MULTIPLE-TARGETING LIGANDS AGAINST PROSTATE CANCER: EFFECT ON BOTH AKR1C3 ENZYME AND ANDROGEN RECEPTOR

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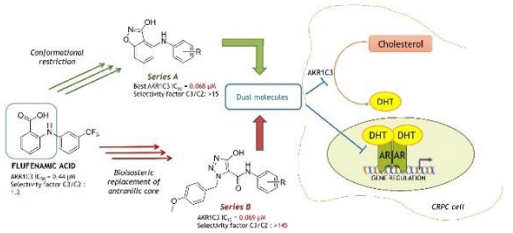
Introduction: The steroidogenic enzyme AKR1C3 and Androgen Receptor (AR) have synergistic action in development of Castration Resistant Prostate Cancer (CRPC). The two targets are compatible in terms of ligand accommodation as they are both able to interact with DHT as product and ligand respectively. Starting from potent and selective AKR1C3 inhibitors previously developed (1, 2), we here present multiple ligands for both AKR1C3 and AR to target prostate cancer.

Materials and Methods: *In silico* design, synthesis and biological activity on AKR1C3 enzyme of new compounds, as well as their capability to address AR, are here described.

Results: Bioisosteric replacement of flufenamic acid antranilic core gave rise to two series of hydroxylated compounds, benzoisoxazoles and triazoles. Both series show potent AKR1C3 inhibition and AR antagonism activity; their potency and dual action are translated into citotoxicity against CRPC cellular models.

Conclusions: Starting from AKR1C3 inhibitors and identifing structural elements required for activity on the complementary target AR, we here present two series of compounds useful for treatment of CRPC. Among these new derivatives, some compounds act on the two targets, and represent a starting point for multiple-targeting ligand development applied to CRPC.



Acknowledgements

This study was supported by a grant of Fondazione CRT (Prog. NACTUS) and TUBITAK (The Scieniıfic and Technologıcal Research Council of Turkey)-2219 program.

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OP053: FUNCTIONALIZED NANOPARTICLES AS POTENTIAL ANTIBIOFILM AGENTS

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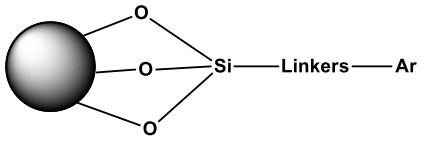
Introduction: Although some bacterial biofilms could be beneficial to human health (e.g. human microbiome), it is known that they are also recognized as one of the main pathogenesis factors in the development of chronic infectious processes. Their growth can be prevented through surface modification by hindering bacterial adhesion or by inhibiting the development of bacterial microcolonies, using antibiofilm agents (passive or active coating). The aim of our research was the covalent functionalization of nanoparticles with natural derivatives that, previously used to obtain new materials (1), have shown interesting antibiofilm properties (2), limiting the problems related to existing coatings.

Materials and Methods: Ludox HS-40 colloidal silica was selected for the functionalization, considering its potential to be used as coating on different types of surfaces. The compounds used to functionalize Ludox HS-40, through suitable linkers (differing for nature and length), were salicylic and cinnamic acids derivatives (Figure 1). The obtained nanoparticles were characterized by means of qualitative analyses (FT-IR and Raman)

to verify the functionalization of the new nanoparticles and quantitative analyses (TGA, XPS) to assess the degree of nanoparticles functionalization.



Ar = SA and CA derivatives

Figure 1. Schematic representation of novel functionalized Ludox HS-40 nanoparticles

Results: The analytical data confirmed that the functionalization procedures occurred correctly both in the final derivatives and in the various intermediates.

Conclusions: These novel nanoparticles could provide long-term protection from biofilm growth and reduce the risk of developing resistant strains.

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OP054: SYNTHESIS OF NOVEL 1-BENZYL-2-SUBSTITUTED-BENZIMIDAZOLE-5-SULFONAMIDE DERIVATIVES AND INVESTIGATION OF THEIR EFFECTS ON CHOLINESTERASES AND CARBONIC ANHYDRASE ENZYMES

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Introduction: Benzimidazole derivative drugs are used in the treatment of various diseases such as anti-Alzheimer's, anticancer, antimicrobial. These compounds can be easily synthesized according to literature methods, and their structures are proving with spectral and instrumental methods. Investigating the cholinesterases and carbonic anhydrase enzymes inhibitor effects of new benzimidazole derivatives (1a,1b,1c,1d,1e,1f,1g,1h,1ı,1j), which are synthesized and characterized, evaluating the research results, and thus determining the pharmacophore group and pioneer compound that will shed light on future studies are the basic requirements of this study.

Materials and Methods: In this study, 4-Chloro-3-nitrobenzenesulfonyl chloride, substituted benzaldehydes, and piperazine derivatives were used frequently in research to synthesize benzimidazole derivatives bearing aminosulfonyl group. The synthesis of a new derivative was taken place in 2 steps: In the first step, salt was formed after waiting in the mixer for 24 hours. In the second stage, the new product was obtained with 3-amino-4-(benzylamino) benzenesulfonamide after leaving it in the refluxing cooler at a temperature of 130 ^{o}C and a speed of 390 ppm, with a minimum waiting time of 4 hours.

Results: The structures were illuminated by taking IR, NMR and HRMS spectra of the synthesized compounds. The inhibitory effects of these derivatives were investigated *in vitro* against cholinesterases and carbonic anhydrase (*h*CA) I and II isoenzymes. It has been determined that the synthesized compounds effectively inhibited both *h*CA isoenzymes.

Conclusions: According to the findings, these derivatives may be considered interesting lead compounds against the *h*CA enzyme.

Acknowledgements

This study was supported by the Research Fund of Erzincan Binali Yıldırım University (grant number: TSA-2020-691).

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OP055: NEXT GENERATION MONOCLONAL ANTIBODIES: NOVEL APPROACH TO ATTAIN DIAGNOSTIC AND THERAPEUTIC IMMUNOCONJUGATES

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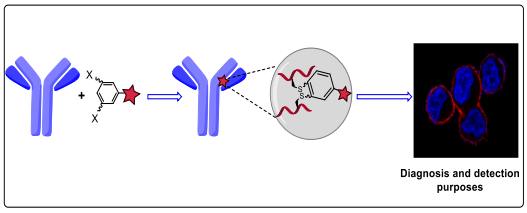
Introduction: Monoclonal antibodies (mAbs) and mAbs-based bio-therapeutics have attained considerable attention as a targeted anticancer treatment. Antibody-drug conjugates (ADCs) are a new wave of therapeutics that employ mAbs to carry the cytotoxic payload toward cancer tissue (1). The construction of mAbs conjugates is usually achieved through using conventional chemistries with a wide range of limitations (2). The primary focus of our research is to develop affordable chemistries to label mAbs whilst maintaining the structural integrity, hence, tackling the limitations of the currently employed conjugation methods.

Materials and Methods: A range of rebridging linkers were synthesized and characterized using NMR and HRMS. Antibodies were Kindly provided from Qualasept ltd. Reduction and rebridging the mAbs with the synthesized linkers were subsequently performed. The conjugates were characterized using protein MS and SDS-PAGE. Then, the fluorescent conjugates were employed to label HER-2 cell-lines and imaging was done using a confocal microscope.

Results: The rebridging of mAbs using our novel aryl-based linkers results in well-defined and stable rebridged conjugates. The developed linkers have been applied to 'Click' reaction to attain fluorescently-labelled immunoconjugates which have been gratifyingly used in the labeling of HER-2 +ve cell-lines (see below). Next, the construction of therapeutic conjugates is underway.



Conclusions: The widespread advantages of the developed platforms could facilitate the construction of ground-breaking therapeutics, such as ADCs and bispecific antibodies.

Acknowledgments

This study was supported by the PhD studentship and research grant number 28/4/2020 from the Deanship of Scientific Research and Graduate Studies, the University of Petra.

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OP056: NEW INHIBITORS OF THE INDUCIBLE NITRIC OXIDE SYNTHASE AS ANTICANCER AND ANTIINFLAMMATORY AGENTS

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Introduction: Nitric Oxide (NO) is a free radical signalling molecule, involved in different biological processes and produced by nitric oxide synthases (NOS). There are two constitutive NOS (the endothelial and neuronal ones) and an inducible NOS (iNOS). This last is highly involved in the innate immunity, and has a role in inflammatory diseases. Moreover, in tumour biology, correlation between iNOS expression and clinical outcome associated to worse prognosis, was evaluated in different types of tumours. Therefore, inhibition of iNOS has been proposed as a targeted therapy in several cancers, including breast cancer, prostate cancer and gliomas (1-3).

Materials and Methods: Different compounds were synthesised with the aim to obtain more potent and selective iNOS inhibitors, and different chemical scaffolds were explored with ameliorated pharmacokinetics. Compounds were assayed both on the iNOS and the costitutive NOS, and the most promising compounds were subjected to a deep biological evaluation on glioma and breast cancer cell lines. Moreover, some compounds were also evaluated on LPS-stimulated monocites and BV2 microglia cells to ascertain their potential antiinflammatory activity.

Results: Selected acetamidine-based iNOS inhibitors showed encouraging antiglioma activity, moreover they were able to modulate the inflammatory response in monocytes and BV2 microglia cells. Selected azole-based iNOS inhibitors showed antiproliferative activity against MCF-7 breast cancer cell line.

Conclusions: iNOS inhibitors demonstrated to be promising compounds to counteract cancer progression and inflammation. The piridine-based compounds revealed to be very potent iNOS inhibitors and further investigation on these compounds could give further insights into the nitric oxide-dependent tumor progression.

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OP057: NEUROMODULATORY ACTIVITY ON THE CANNABINOIDERGIC SYSTEM BY NEW PYRAZOLE STYRYLQUINAZOLINONES

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Introduction: Pharmacological compounds acting on endocannabinoid receptors type 1 and 2 are able to regulate different neuronal processes. Emerging evidence indicates that hyperactivity or dysfunction in the endocannabinoid system might be implicated in disturbance or abnormality of neural processes, pointing at it as a key component of several pathologies. This research study was undertaken to determine if a new structural analogue of rimonabant, (E)-6-chloro-3-(3-methyl-1-phenyl-1H-pyrazol-5-yl)-2-styrylquinazolin-4(3H)-one (compound 1), was able to counteract the behavioral signs of the activation of the endocannabinoidergic system induced by the administration of the agonist CP 55,940.

Materials and Methods: The analogue of rimonabant was obtained in laboratory through synthesis procedures obtaining a compound a quinazolinones structure bearing a heterocyclic pyrazole nucleus. Behavioral assessment on rats was carried out using the tetrad task and the novel object recognition test, to evaluate cannabinoid effects on declarative memory. The endocannabinidergic system was activated by the administration of the cannabinoid agonist CP 55,940, (0.1 mg/kg i.p.) and 30 min after rats were tested in the tetrad task. Declarative memory was assessed in the novel object recognition test.

Results: Our study showed that compound 1 at the dose of 10 mg/kg, 30 min before CP 55,940 administration, was able to counteract the effects exerted by CP 55,940, as shown by an increase in body temperature, in total distance travelled, in latency to fall down and a decrease in tail flick latency. Furthermore, compound 1 was able to prevent the memory impairment induced by the cannabinoid agonist, showing that (E)-6-chloro-3-(3-methyl-1-phenyl-1H-pyrazol-5-yl)-2-styrylquinazolin-4(3H)-one is able to counteract the cannabinoid activation induced by the agonist CP 55, 940.

Conclusions: This study shows that compound 1 is able to counteract the cannabinoid activation induced by the agonist CP 55.940. Further investigations are in progress to evaluate its pharmacological profile and in order to consider the obtained compound as a potential candidate for clinical studies and to employ it as pharmacological agent in managing different pathological conditions such as motor incoordination, obesity and brain related disorders.

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OP058: SYNTHESIS OF NEW PYRAZOLINE DERIVATIVES AND THEIR ANTICANCER ACTIVITIES

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Introduction: Pyrazolines, an important class of heterocyclic compounds, display numerous biological and pharmaceutical properties such as antimicrobial, analgesic, antioxidant, anticancer, antidepressant effects (1). In this study, we aimed that a novel series of pyrazoline derivatives bearing benzodioxole ring system were synthesized. The potential anticancer effects of all synthesized compounds were investigated by the MTT test.

Materials and Methods: Pyrazolines were synthesized in two steps. Firstly, the Claisen-Schmidt reaction was carried out with a ketone bearing benzodioxole ring and aromatic aldehydes in the absence of ethanolic sodium hydroxide. Then, pyrazoline derivatives from chalcones were obtained with phenylhydrazine hydrochloride or substituted aromatic semicarbazide (Figure 1)(2). The novel pyrazoline derivatives were assayed for their *in vitro* anticancer activity on HeLa, MCF-7 cancer cells and NIH-3T3 normal cells by the MTT test (3).

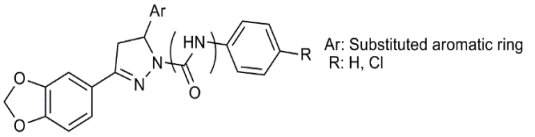

Figure 1. The general structure of the synthesized compounds.

Results: All synthesized compounds were confirmed by IR, ^{1}H-NMR and elemental analysis. In the Infrared spectrum, the C=N stretching bands belonging to pyrazolines were observed 1591-1635 cm^{-1}. In the ^{1}H-NMR spectrum, the synthesis of pyrazoline rings was proved by the absence of

three doublets of doublet peaks belonging to pyrazoline rings at 2.92–3.28 ppm, 3.70–3.96 ppm and 5.33–5.75 ppm, respectively. Pyrazolines bearing nitro, bromo and trifluoromethyl substituent on aromatic ring exhibited high cytotoxicity on Hela and MCF-7 cells. Especially, the compound carrying pyridine ring as an aromatic aldehyde group was found to show high cytotoxicity against HeLa and MCF-7, but lower toxicity to NIH-3T3 normal cells.

Conclusions: In the present work, new pyrazoline derivatives containing a benzodioxole ring were synthesized and characterized. Their anticancer activities on HeLa, MCF-7 and NIH-3T3 were evaluated by the MTT test. Among these, compound carrying pyridine ring exhibited high cytotoxic effects against both HeLa and MCF-7 with high selectivity index. This molecule can be a lead compound for further anticancer investigations.

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OP059: SYNTHESIS AND STRUCTURE ELUCIDATION OF NEW FENAMATE THIOSEMICARBAZIDE

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Introduction: Thiosemicarbazide compounds have been reported to have diverse biological activities including anticonvulsant, antiviral, anti-inflammatory, antibacterial, antimycobacterial, antifungal, antioxidant and anticancer (1). Therefore, the studies about thiosemicarbazide compounds have recently gained importance.

Materials and Methods: In this study, the ester and the hydrazide derivatives of mefenamic acid are prepared (2). The thiosemicarbazide structure was obtained according to previously reported method (3). Compounds' structure were elucidated by FT-IR and NMR (^{1}H, ^{13}C, DEPT, HMBC) spectroscopic methods and their purity were proven by TLC and elemental analysis.

Results: The intermediate hydrazide compound was synthesized by a newly developed microwave synthesis method. For thiosemicarbazide structure; C-6; C=S and C=O carbons are not detected in ^{13}C-NMR however, the DEPT and HMBC results proved the formation of thiocarbonile. The correlation between aromatic protons and C-6, C=S and C=O carbons are also determined.

Conclusions: The diverse biological activities of thiosemicarbazide compounds is a key point in designing and developing new drug canditate molecules carrying thiosemicarbazide functionality. Here in this study, the formation of thiosemicarbazide function starting from a non-steroidal anti-inflammatory drug is shown. Following the synthesis of other derivatives, the further biological activity studies will be performed for the novel drug candidate compounds.

Acknowledgement:

This study was supported by a grant of CUBAP (Cumhuriyet University Scientific Research Unit) (ECZ039)

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OP060: INVESTIGATION OF THE ANTIBACTERIAL EFFECTS OF SOME SCHIFF BASES COMPOUNDS CONTAINING NAPHTHALENE AND INDOLE RINGS

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Introduction: Increasing of drug-resistant pathogens has been become as serious problems in clinical microbiology (1). Thus, researching for effective agents against multidrug-resistant microbial infections and finding more effective compounds have become the main focus of researchers. Recently some studies demonstrate that indole and naphthalen derivatives which substituted with Schiff bases exhibited biological activities such as anti-tuberculosis, antiviral, antibacterial and antifungal (2, 3). In this presentation, the antimicrobial effects of some hydrazine derivatives were investigated against standard drugs and antibacterial efficacy evaluations were done (4).

Materials and Methods: The effectiveness of compounds were evaluated using 2-fold serial dilutions against Staphylococcus aureus, Methicillin-Resistant-Staphylococcus aureus (MRSA), Enterococcus faecalis, Pseudomonas

aeruginosa, Escherichia coli, and Candida albicans.

Results: Minimum inhibitory concentration (MIC) was determined for test compounds and for the reference standards ciprofloxacin, ampicillin and miconazole.

Conclusions: In this presentation, antibacterial effects of two different hydrazine group compounds which containing naphthalene and indole rings were examined and compared. According to the results that we obtained in this study the Indole-hydrazine derivatives exhibited potent antibacterial activity than the naphthalene hydrazine derivatives. In addition, while the tested naphthalene derivatives did not show antifungal effects, indole derivatives demonstrated acceptable antifungal activities. It is believed the pyrrole ring in the indole structure might be one of the main reasons for the antifungal effect of indole derivatives.

Acknowledgements

This study was supported by Scientific Research Council of Erzincan Binali Yildirim University under the Project No of SAG-A-240215-0120.

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OP061: SYNTHESIS OF NOVEL HYDRAZONE DERIVATIVES AND EVALUATION OF THEIR INHIBITORY ACTIVITIES AGAINST MONOAMINE OXIDASES AND β-SECRETASE

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Introduction: Alzheimer's disease (AD) is one of the most common causes of dementia and is related to the loss of cognitive functions. For treatment of AD, cholinesterases, monoamine oxidases (MAOs) and β-secretase have been considered a promising target (1,2). Hydrazones constitute an important class of compounds and are target molecules for various biological activities (3). The aim of this study was to synthesize 19 (18 new) tosylated hydrazone derivatives (**3a-t**) from ethyl paraben and investigate their cholinesterase, MAO, and β-secretase inhibition potential.

Materials and Methods:

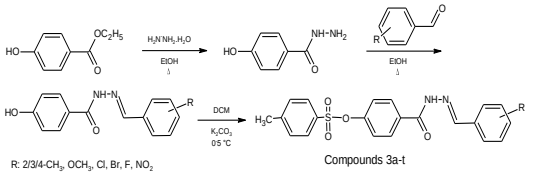

Fig. 1. Synthesis of compounds (**3a-t**).

Results: Compound **3o** was the most potent inhibitor of MAO-A, with an IC_{50} value of 1.54 µM, followed by **3a** and **3p** (IC_{50} = 3.35 and 4.77 µM, respectively). Compound **3s** was the most potent inhibitor of MAO-B, with an IC_{50} value of 3.64 µM, followed by **3t** and **3a** (IC_{50} = 5.69 and 7.69 µM, respectively). **3e**, **3g**, and **3n** inhibited BACE-1 with IC_{50} values of 8.63, 9.92, and 8.47 µM, **respectively, which were lower than the IC_{50} of the quercetin reference.**

Conclusions: In this study, 19 novel *N*'-(4-/3-/2-substitued benzylidene)-4-[(4-methylphenyl)sulfonyloxy]benzohydrazide derivatives (**3a-t**) were synthesized. It is concluded that **3o** and **3s** are effective reversible and competitive MAO-A and MAO-B inhibitors, respectively, and **3e**, **3g**, and **3n** are strong BACE-1 inhibitors. These results suggest that these compounds can be considered potential agents for the treatment of AD.

Acknowledgements

This study was supported by the National Research Foundation of Korea (NRF) grant funded by the Korean government (NRF-2019R1A2C1088967), Republic of Korea, Taif University Researchers Supporting Project (No. TURSP-2020/68 to A. Khames), Saudi Arabia and Scientific Research Projects Coordination Unit of Karadeniz Technical University (Project Number: FLO-2019-7883), Turkey.

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OP062: LIPASE INHIBITOR ACTIVITY AND MOLECULAR MODELLING STUDIES OF NEW PYRIDAZINONE DERIVATIVES

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Introduction: Lipids play diverse and important biological roles. Altering the levels of specific lipid species through activating or inactivating their biosynthetic or degradative pathways has been shown to provide either therapeutic benefit or cause disease. Lipases play critical roles in human health and disease (1). The conserved biochemistry across this enzyme class, coupled with certain chemical scaffolds that target serine hydrolases, have enabled the development of inhibitors against many lipases. Pyridazinone derivatives have been claimed to possess such interesting bioactivity (2). In this study, five pyridazinone derivative (compounds **1-5)** were synthesized and their lipase inhibitory effects were determined. Binding modes of the synthesized compounds to lipase enzyme as well as the key interactions in their active sites were determined via molecular docking simulations. Structure-activity relationships were established upon comparison of the results from the in vitro enzyme inhibition and molecular docking studies.

Materials and Methods: All compounds were synthesized according to literature methods (3). Compounds was shown in Figure 1. The synthesized compounds were evaluated for lipase inhibitory effects modified method by using porcine pancreatic lipase type II (PLL) (EC 3.1.1.3) inhibitory assay and for molecular docking studies used *p*-nitrophenyl butyrate (CAS: 2635-84-9) as a substrate (4).

Results: Three of compounds **2, 3** and **5** show moderate lipase inhibitor activity. Compound **1** and **4** did not show inhibitor activity (Table 1).

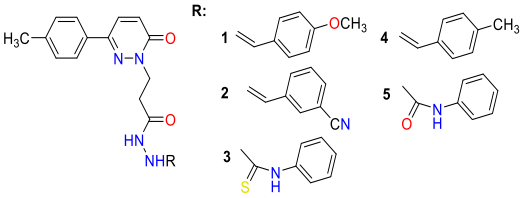

Figure 1. Structure of synthesized compounds

Table 1. PLL inhibition of synthesized compounds **1-5**

Compounds	PLL Inhibition* (IC_{50} (*µg*/ml) ± SD**)
1	93,15±4,2592
2	52,06±3,7526
3	32,66±2,8265
4	92,70±3,2231
5	60,59±4,3285
Orlistat	13,49±1,2262

*Porcrine pancreatic lipase **Standard deviation

Conclusions: PLL inhibition of synthesized compounds was evaluated against orlistat, is an inhibitor of pancreatic and other lipases. Compound **3** (**1-(3-(6-oxo-3-*p*-tolylpyridazin-1(6*H*)-yl)propanoyl)-4-phenylthiosemicarbazide)** was found as most active compound by inhibiting at 32.66±2.8265 µg/ml dose. While semicarbazide (compound **5**) coming after thiosemicarbazide (compound **3**) in the activity ranking shows the importance of sulfur in activity; the nitrile, methyl and methoxy sequences (compounds **2,4,1**) of the substituents in *N*-benzilidenhydrazide derivatives show that electron withdrawing groups are important for activity. Docking scores and activity results are in harmony. Orlistat has been shown to have similar interactions with the most active compound **5**.

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OP063: SYNTHESIS AND HUMAN CARBONIC ANHYDRASE INHIBITION STUDIES OF SOME 1,3,4-THIADIAZOLES

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Introduction: Human carbonic anhydrases (hCAs) belong to carbonic anhydrases (CAs; EC 4.2.1.1), a ubiquitous family of zinc-included metalloenzyme which catalyzes the reversible conversion of carbon dioxide to bicarbonate and a proton. hCAs are members of the α-subfamily of CAs and divided into 15 different isoforms (hCA I-XV). Cytosolic isoforms hCA I and II are widespread in the human body while transmembrane isoforms hCA IX and XII are located especially in hypoxic tumour cells, hence also called tumour-related hCA isoforms. Studies for discovering of hCA XI/XII targeted and hCA I/II off-targeted new molecules as a selective carbonic anhydrase inhibitors (CAIs) presents a new approach for anticancer chemotherapy (1-2). To this aim, thirteen new sulfonamido-indole linked 1,3,4-thiadiazole derivatives were prepared and tested with enzyme inhibition assays for their inhibitory activity against four hCA isoforms (hCA I/II and hCA IX/XII).

Materials and Methods: After the synthesis of the thiosemicarbazide derivatives of 3-phenyl-5-sulfonamido-1*H*-indole-2-carbohydrazide with suitable isothiocyanates, new 1,3,4-thiadiazoles were obtained by cyclization in an acidic medium. Crude products were purified with crystallization with ethanol and characterized with spectral and analytical methods (IR, ^{1}H-NMR, ^{13}C-NMR, and

elemental analyses). For enzyme inhibition studies a stopped-flow CO_2 hydrase assay was used (3).

Results: Cyclization of thiosemicarbazide derivatives was proven by spectral and analytical analyses. Enzyme inhibition assays revealed that all new compounds showed excellent selectivity against off-targeted isoforms hCA I/II and very good inhibitory activity against tumour-releated hCA IX/XII at nanomolar level.

Conclusions: Three of thirteen successfully synthesized and characterized compounds showed ***K***i values lower than 30 nM against hCA IX or XII with high selectivity ratios up to ~50- fold over hCA I/II. This study may lead to further development of new thiadiazole derivatives as potent CAIs.

Acknowledgements

This study was supported by IU Scientific Research Projects Department (TDK-2018-32263).

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OP064: SYNTHESIS AND ANTIPROLIFERATIVE ACTIVITY OF SELENIUM CONTAINING COMPOUNDS

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Introduction: Diselenides and benzisoselenazolones are important classes of organoselenium compounds because of their biological properties, and synthetic utility. İn anticancer research field, ethaselen is of worth mentioning, as one of the novel antitumor agent, that reached phase I clinical trials for the treatment of TrxRd-overexpressing non-small cell lung cancers[1] In this communication, we aim to report our efforts toward the identification of antiproliferative organoselenium compounds.

Materials and Methods: a small series of benzisoselenazolones and aryl diselenides were prepared exploiting known chemistry with the aim of evaluating their antiproliferative properties. Their cytotoxic profile against a series of cellular model of cancer and the synergistic effects with cisplatin will be discussed.

Results: Based on the studies we conducted, most of the compounds displayed a noteworthy antiproliferative activity with benzylamine derived diselenide that was found to show inhibitory effects on Glutathione S Transferase enzyme with a potency that well correlates with the cytotoxicity observed in MCF7 cells.

Conclusions: Glutathione *S* Transferase enzyme could be responsible for the antiproliferative activity of diselenides and benzisoselenazolones.

Acknowledgements

This project has received funding from the European Union's Horizon 2020 research and innovation programme under Marie Skłodowska-Curie grant agreement No. 665778, Polish National Science Centre UMO-2016/21/P/ST5/03512 POLONEZ 2 (granted to LS)

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OP065: INSIGHT INTO REDOX PROPERTIES OF SOME SELENIDES AND DISELENIDES

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Introduction: In nature, Selenium, is pivotal as part of selenium-containing proteins, in regulating critical redox mechanisms, such as in glutathione peroxidase (GPx). In fact, GPx is one of the enzymes deputed to protect sensible structures, as lipid membranes and other oxidable cellular components, against the reactive oxygen species (ROS). The redox catalytic center of the enzyme is constituted by a residue of Sec (selenocysteine) in which the selenol moiety catalyzes the reduction of peroxides at the expense of a thiol co-factor, generally glutathione. Inspired by the relevance of the selenium-enzyme function, great efforts of several research groups have been involved in the synthesis of new organodiselenides and organoselenides as potential antioxidants based on their ability to function as GPx mimetic (1-3).

Materials and Methods: We propose ^{77}Se-NMR spectroscopy as a simple, reliable, and efficient tool to gain new insight into the selenium redox character of antioxidant selenium derivatives.

Results: Here we report our investigation on some selenides and diselenides redox properties in both

the oxidation and reduction step of the GPx-like catalytic cycle. The discussion will highlight the advantages and limits of ^{77}Se-NMR spectroscopy assay as well as the main differences in the two classes of investigated compounds (selenides and diselenides).

Conclusions: Our studies evidenced a superior ability of selenides with respect to diselenides to act as catalysts. Furthermore, the low sensitivity of the selenium nucleus results in a limitation while using ^{77}Se-NMR assay, which not always allow the detection of transient species.

Acknowledgements

This work has been undertaken under the umbrella of the International Network Selenium, Sulfur, Redox and Catalysis (SeSRedCat).

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OP066: SYHTHESIS, ANTINEOPLASTIC ACTIVITY AND MOLECULAR DOCKING STUDIES OF NOVEL INDOLE-THIAZOLIDINEDIONE DERIVATIVES

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Introduction: Cyclin-dependent kinase 6 (CDK6) became a valid target for breast cancer therapy over the past decades. Binding of this enzyme to E2F transcription factors eventually controls cell division. Therefore, inhibition of this enzyme becomes vital in apoptosis of the breast cancer cells. Besides, indole-thiazolidinediones prove to be a valuable asset in breast cancer therapy. The wide range of findings in this study area has encouraged us to design and synthesize novel indole-thiazolidinedione derivatives (**9-24**) (1, 2).

Materials and Methods: For the synthesis of the derivatives **9-24,** mixture of appropriate indole-3-carboxaldehyde, phenacyl-methyl-thiazolidine-2,4-dione and diethanolamine in MeOH was refluxed until starting materials were consumed (determined by TLC, purified with cc). After synthesizing these derivatives, their anticancer activity was probed on MCF-7 cell lines and their gene suppressing profiles were elucidated. For the thorough evaluation of their mechanism of action involving CDK6 pathway, docking of these compounds and standard Palbociclib was made with corresponding enzyme using AutoDock Vina (3). Moreover, druglikeness of indole-thiazolidinedione derivatives were calculated with SwissADME (4) and compared to the commercial anticancer drugs.

Results: According to biological activity assays; compounds **10**, **15**, and **18** were found to possess favorable cytotoxicity on MCF-7 cells. Comparing to other genes, these compounds inhibited gene expression of CDK6 remarkably. Regarding docking analysis, **15** and **18** possessed higher affinity with better binding interactions relative to that of compound **10**.

Conclusions: With higher gene suppression characteristics, and low IC50 values, compounds **15** and **18** were highlighted as possible candidates for the upcoming design studies of CDK6 inhibitors. These compounds also have had better interaction profiles with the related enzyme.

Acknowledgements

The work was supported by Ankara University Research Grant under grant number: 19B0237003.

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OP067: THIOUREA-BASED INHIBITORS OF *MYCOBACTERIUM TUBERCULOSIS* GROWTH AND ENOYL ACYL CARRIER PROTEIN REDUCTASE

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Introduction: Tuberculosis, caused by *Mycobacterium tuberculosis*, remains the most deadly infectious disease due to the emergence of drug-resistant strains (1). In this study, we carried out rational molecular modifications on the chemical structure of the urea-based co-crystallized ligand of enoyl acyl carrier protein reductase (InhA) with the PDB code:5OIL (2) to reach effective antitubercular agents.

Materials and Methods: We synthesized thiourea-based derivatives by one-pot reaction of the amines with corresponding isothiocyanates. The obtained compounds were evaluated for their abilities to inhibit *M. tuberculosis* H37Rv using Microplate Alamar Blue Assay (MABA) method. Moreover, the most active compounds were tested against latent as well as dormant forms of the bacteria. Enzyme inhibition assay was carried out against enoyl-acyl carrier protein reductase and molecular docking studies were performed using LigandScout.

Results: The results revealed that some compounds exhibited promising antitubercular activity combined with low cytotoxicity. Enzyme inhibition assay against enoyl-acyl carrier protein reductase identified InhA as the important target of some compounds (Figure 1).

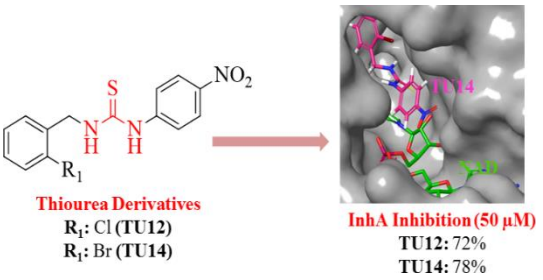

Figure 1. Chemical structures and docking pose of the most active InhA inhibitors

Conclusions: We identified effective *Mycobacterium tuberculosis* growth inhibitors that are also capable of acting on dormant or latent forms of the bacteria. Moreover, we demonstrated that some compounds exhibit their antimycobacterial activities by inhibiting InhA enzyme.

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OP068: MANDELIC ACID-BASED NOVEL SPIROTHIAZOLIDINONES: SYNTHESIS, ANTIMYCOBACTERIAL ACTIVITY AND MOLECULAR MODELLING STUDIES

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Introduction: Tuberculosis (TB), an airborne infectious disease caused by *Mycobacterium Tuberculosis*, is one of the leading death-causing diseases (1). Together with the rapid development of resistance in *M. Tuberculosis*, the long duration of antitubercular regimen has born the necessity to develop new drugs with a shorter duration of therapy to effectively treat tuberculosis and counteract resistance (2). Enoyl-[acyl-carrier-protein]-reductase (*Mt*InhA), a target of activated isoniazid, is an NADPH-dependent enzyme lacking in humans and catalyses the essential step of fatty acid elongation in the biosynthesis of mycolic acid responsible for the virulence of *M. Tuberculosis* (3). 1,3-thiazolidin-4-one is an intriguing heterocyclic scaffold that affords a wide range of biological activities including antimycobacterial activity (4). This study is focused on the synthesis and biological assessment of novel mandelic acid-based spirothiazolidinone derivates against *M. Tuberculosis,* and the docking studies followed by 50 ns molecular dynamic simulations of the most potent compound to determine whether it exerts its antimycobacterial activity by inhibiting the *Mt*InhA enzyme.

Materials and Methods: The compounds were prepared from a one-pot sequential reaction of mandelhydrazide, a cyclic ketone and thioglycolic acid/thiolactic acid. The compounds were characterized by spectral analyses. The antimycobacterial activity was conducted using MABA and BACTEC 460 radiometric systems. Molecular modelling studies were carried out with MOE LeadIT and Schrödinger software packages.

Results: One of the compounds showed growth inhibition of 98% at 6.25 µg/mL and molecular modelling studies of this compound suggested that it may bind to the apo form of *Mt*InhA enzyme.

Conclusions: The desired compounds were successfully prepared using a two-step one-pot reaction. The modelling results indicate that the active compounds may bind to the apo form of *Mt*InhA which is a validated target for antimycobacterial drugs.

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OP069: NOVEL 1,2,4-TRIAZOLES FROM IBUPROFEN AS POTENTIAL mPGES-1 INHIBITORS: SYNTHESIS, *IN VITRO* AND *IN SILICO* STUDIES

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Introduction: Today, many studies have shown that tumor growth can be inhibited by the selective inhibition of mPGES-1 enzyme which has become one of the important targets in cancer treatment (1). However there is no FDA-approved selective mPGES-1 inhibitor yet, and the number of mPGES-1 inhibitors with proven efficacy is quite limited. In this study, our aim synthesis of potential mPGES-1 inhibitors and evaluation of their antiproliferative effect.

Materials and Methods: In this study, we synthesized several new 1,2,4-triazoles containing thioether side chain starting from ibuprofen, a well-known NSAID (2). During the docking studies, 5K0I protein was used as the mPGES-1 crystal structure. The structures of target compounds were prepared by using Biovia Discovery Studio. Docking studies of all target compounds were done with AutoDock. Antiproliferative effects of the synthesized thioether derivatives were determined against breast cancer (MCF-7) and lung cancer (A549) cells at 10 µM dose, by using the MTT method (3).

Results: The docking studies showed that C=O and NH groups in thioacetamide chains of synthesized compounds increase the hydrogen bond interactions with the active site. Also in the presence of hydrogen bond acceptors such as sulphamoyl or acetyl function, affinity of related compounds against active site are increased because of interaction with Arg126, Ser127 amino acids etc. Substitution of fourth position of triazole core with methyl, ethyl or propyl brought along the pi-alkyl interaction with Tyr130 aminoacid in the active site. As a results of biological studies, compound 9 has antiproliferative effect on both cancer cells, with 65% inhibition value against MCF-7 cells. Additionally it was determined that few compunds had an inhibition above 30% against MCF-7 cells.

Conclusions: According to the docking studies, potential mPGES-1 inhibitors were synthesized and it was observed that these compounds have a higher antiproliferative effect against the MCF-7 cells in comparison to A549 cells.

Acknowledgements

This study was supported by Scientific and Technological Research Council of Turkey (TÜBİTAK)(Project code: 1001, Project number: 218S549).

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OP070: DESIGN SYNTHESIS AND IN VITRO BIOLOGICAL ACTIVITIES OF NEW 6,8,9-TRISUBSTITUTED PURINE DERIVATIVES AS PROMISING HSPs INHIBITORS

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Introduction: The purine ring forms the basic structure of vital importance biological compounds such as nucleic acids. The use of purine derivatives, precursors of nucleic acids, as antimetabolite chemotherapeutic agents in cancer treatment begins with the idea that nucleic acids have significant roles of cellular proliferation. Instead of treatment with non-selective compounds that show cytotoxic activity by inhibiting the growth of healthy cells as well as cancer cells, treatment with specific inhibition of the targeted molecules known to be associated with cancer disease is preferred (1). Targeting Hsps is an exciting mechanism due to their overexpression in cancer cells and their part on carcinogenesis through proliferation, differentiation, migration and metastasis (2-3). The aim of this work is to synthesize new 6,8,9-trisubstituted purine analogues, elucidate their biological activities on selected cancer cell lines and perform molecular

docking studies on Hsp70 and Hsp90 to find out predicted binding conformation.

Materials and Methods: The 6,9-(4-subsituted diphenyl)-8-[5-(4-chlorophenyl)-1,2-oxazole/4-substituted phenyl] purine derivatives were readily obtained from commercially available 4,6-dichloro-5-nitro pyrimidine in four steps. The cytotoxicity of this newly synthesized compounds were screened by the XTT cell viability test on breast (MCF7), liver (HepG2), prostate (PC3) and leukemia (K562) cell lines *in vitro*. Molecular docking studies were carried out using PyRx.

Results: Among the synthesized compounds, **10** and **13** showed 89% cell viability on MCF7 cell line. Molecular docking results showed that all compounds bind to Hsp70 ATP binding pocket between -8.5 and -10.8 kcal/mol; Hsp70 substrate binding site between -6.5 and -7.6 kcal/mol; Hsp90α between -7.6 and -8.7 kcal/mol; Hsp90β between -8.6 and -9.8 kcal/mol binding energies. Particularly, compound **12** binds to Hsp70 ATP binding site and compound **13** binds to Hsp90 α and 90β with high affinity and good binding energies.

Conclusions: New purines were prepared and their cytotoxic activities identified. Considering the binding attitudes of the synthesized derivatives in the selected proteins and their binding energies, it is thought that the common skeleton of the compounds can be determined and potential main structure for anticancer drugs in our further studies.

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OP071: IDENTIFICATION OF A POTENT INDOLE *N*-OXIDE DERIVATIVE HIF PHD2 INHIBITOR THROUGH HYBRIT VIRTUAL SCREENING

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Introduction: Cellular response to hypoxia by enlisting survival pathways is controlled by activation of hypoxia induced factors (HIFs), which upregulates a set of genes. Inhibition of HIF prolyl 4-hydroxylase domain-containing proteins (PHDs) has been applied as a strategy against hypoxia-related diseases such as anemia with clinical success (1). We identified a sub-micromolar HIF PHD2 inhibitor through virtual screening of a commercial compound library.

Materials and Methods: InterBioScreen (IBS) library was prepared and molecular descriptors were calculated using QikProp (2020-4, Schrödinger, LLC). Shape similarity screening was performed by Maestro and molecular docking by Glide (2020-4, Schrödinger, LLC) (2). HIF-PHD2 inhibition tests were performed using solid phase extraction-mass spectroscopy (3).

Results: 68,373 compounds from the IBS library were filtered using a set of molecular descriptors related to druglikeness. Remaining compounds were screened for 3D similar to known HIF PHD2 inhibitors. Selected compounds were docked to human HIF-PHD2 structure and 11 compounds were identified for *in vitro* tests, which gave the hit compound, a sub-micromolar inhibitor in indole *N*-oxide structure (Figure 1).

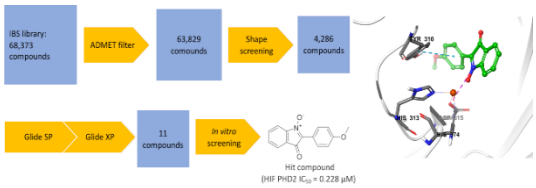

Figure 1. The virtual screening process, the hit compound, and its interactions with HIF PHD2

Conclusions: A virtual screening campaign combining the benefits of ligand- and structure-based methods yielded highly potent HIF PHD2 inhibitor with a scaffold not reported before.

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OP072: A NOVEL GREEN SYNTESIS OF NANO/MICRO PARTICLES DIRECTLY FROM *CITRUS SINENSIS L.* PEEL EXTRACTS AND THEIR USE IN BIOMEDICAL APPLICATIONS

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Introduction: In the last 10 years, nano / micro particles as biocompatible, soft and flexible materials used in biomedical and pharmaceutical applications have attracted great attention (1). Although it is possible to prepare these particles with solid state methods, the drawbacks of excessive chemical use and the inability to prepare

specialized structures for each desired material have led to the search for more effective ways. Hydro/solvothermal method is defined as the synthesis of substances dissolved in closed and heated water or organic solvent at suitable temperature (100-1000 °C) and pressure (1-100 MPa) by chemical reactions (2). There are no studies in the literature on the preparation of nano/micro particles directly from plant extracts using hydro/solvothermal technique. In this study, we aimed to prepare nano/microparticles and reveal their usability in the biomedical field by using only the peel, which is the waste product of oranges grown in our country.

Materials and Methods: *Citrus sinensis L. (Rutaceae)* peel was dried at room temperature and ground in coarse powder. Water and 96% ethanol extracts were prepared from orange peels. The extracts that reached room temperature were centrifuged at 5000xg for 10 minutes and the supernatant was taken. From these extracts, nano and micro sized particles were prepared by hydro/solvothermal synthesis for 180 ℃, 24 hours in a certain volume. In order to obtain particles with different sizes, these extracts were mixed in certain proportions before thermal processing and the mixture was subjected to hydro/solvothermal treatment again. New groups were added to the structure with post modification. For characterization, SEM, TEM, TGA, FTIR, Fluorescence / confocal analyzes were used and the antimicrobial, antioxidant activity and cytotoxic effects of the particles were determined.

Results: Particles close to monodispersed between 70 nm and 5 µm were prepared from *Citrus sinensis L.* water and ethanol extracts. It has been found that the particle size can be controlled by the extract concentration and the water/ethanol ratio. The particles synthesized show autofluorescent properties. A new functional group could be added to the structure with the modification. In addition to its antioxidant and antimicrobial effects, its effects on cancer cell lines and its IC_{50} value are shown.

Conclusions: According to the results, the particles can be used as a carrier system (drug, DNA, protein, etc.) due to their autofluorescent properties. We believe that it has a high application potential in the biomedical field due to its antioxidant, antibacterial effect and even its cytotoxicity can be adjusted with the controlled modification of the particles.

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OP073: DESIGN, SYNTHESIS, ADME AND MOLECULAR DOCKING STUDIES OF NOVEL UREA AND SULFONAMIDE DERIVATIVES OF ISATINE AS POTENTIAL ANTICANCER AGENTS

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Introduction: In this study, we have reported the studies to novel design of new urea and sulfonamide derivatives of isatin Schiff bases similar to the structures like **sorafenib** and **sunitinib** by taking urea and sulfonamide linkers, respectively (1).

Materials and Methods: 16 novel urea and sulfonamide derivatives of isatin Schiff bases were synthesized and tested for their potentials to inhibit metabolic activity of cancerous and non-cancerous cell lines. Potential activities and drug-likenesses of compounds as anti-cancer agents were also determined by ADME predictions and molecular docking studies.

Results: Compounds **7a**, **7b**, **7c**, **7d**, **7h**, **8a** and **8f** exhibited potent inhibitions of cellular proliferation activity against HepG2 cells with average IC_{50} values of 31.97, 42.13, 31.50, 47.98, 32,59, 43.44 and 37.81 µM respectively. Moreover, the docking studies of the most active compound **7c** showed good binding properties with receptor binding site of NS5B polymerase comparison to other active compounds (Figure 1-A). ADME prediction studies of compounds revealed that all compounds presented drug-like properties. The most of interactions were observed with the active site amino acids SER365 (7.50-10.00%) and MET414 (6.25%) for urea compounds (**7a-h**) and with SER365, SER368, ASN316, LEU204, ARG200 (20.00%) and TYR415, ASN316 (18.75%) amino acids for sulfonamide compounds (**8a-h**), (Figure 1-B).

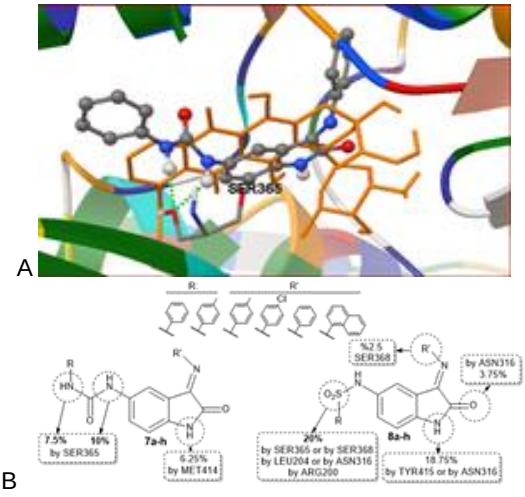

Figure 1. (A) 3D structural interaction of the most active compound **7c** comparison with doxorubicin (orange color) in the binding site of NS5B polymerase (PDB ID: 3FQK) and (B) hydrogen bonding percentages of marked functional groups in a total of 80 conformation of eight compounds for each series.

Conclusions: In vitro experiments and in silico studies established evidence that novel urea and sulfonamide derivatives of isatin Schiff bases showed the potential activity compared to reference compound doxorubicin.

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OP074: DEVELOPMENT OF NON-STEROIDAL AMINOTHIAZOLE ANALOGS ACTIVE ON MCF7 CELL LINE AND AROMATASE ENZYME

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Introduction: Breast cancer is one of the most common cancer types. Majority of breast cancers are ER+, thus suppressing estrogen biosynthesis is an important approach for drug design. Aromatase plays a key role in estrogen biosynthesis, its steroidal and non-steroidal inhibitors have their own binding mode. Non-steroidal inhibitors usually contain an azole ring, which is important to coordinate with the active site Fe^{+2}. Based on published works of our group, in this study, we synthesized a series of 9 pyridyl-aminothiazole derivatives for follow-up. Compounds were tested on MCF7 cell line for cytotoxic activities. Induced-fit docking studies were performed on human placental aromatase cytochrome P450 in complex with androstenedione (3EQM) crystal structure for evaluating the binding modes of the most active compound (1). Furthermore, most active compound also evaluated for its intrinsic activity on CYP2C9, 2D6, 3A4 enzymes compared to anastrozole by using induced-fit docking and in silico techniques.

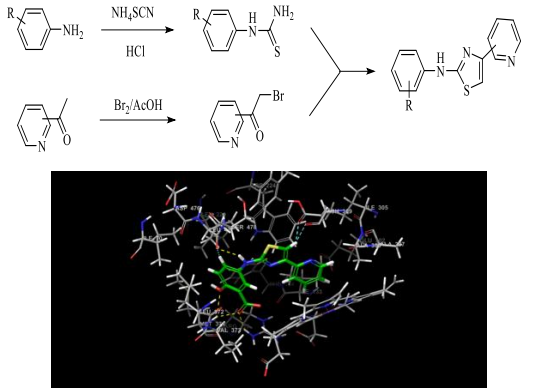

Figure 1. General synthetic method and the docking pose of compound 7

Materials and Methods: Final compounds were synthesized by usual Hantzsch thiazole synthesis (Figure 1). Structure elucidation were successfully realized by IR, NMR and Mass spectrometry. MTT test was applied for antitumor activity. In silico binding and intrinsic activity studies were visualized and processed with Schrödinger Maestro software.

Results: Compounds yields were between 60%-80%. IR, NMR and MS results were consistent. Docking results were consistent with Caporuscio et al. lead study (2). Antitumor activity was found 21 μM for compound 7 (2-hydroxy-5-((4-(pyridin-2-yl)thiazol-2-yl)amino)benzoic acid). Other compounds also showed activity between 32-55 μM (IC_{50}) on MCF7 cell line.

Conclusions: Compounds binding pose gave a functional hydrogen bond donor site following previous studies. Ongoing work will be done to evaluate enzyme binding and developing novel compounds.

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OP75: THE EFFECT OF SACUBITRIL/VALSARTAN ON PROTEIN EXPRESSION OF DIASTOLIC COMPONENTS IN HFD/STZ INDUCED DIABETIC RAT HEART

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Introduction: Cardiovascular complications are the major cause of diabetes-related morbidity and mortality (1). Sacubitril/valsartan combination was shown to have beneficial effects on the diabetic heart, however underlying mechanisms remain unclear. We aimed to evaluate possible effect of sacubitril/valsartan on the diabetic heart in terms of expression of SERCA2a (is an indicator of cardiac diastolic function) and phospholamban (PLN) (has an inhibitory effect on SERCA2a function) protein levels compared to valsartan alone.

Materials and Methods: Western Blot experiment was performed on frozen left ventricle tissues as previously described with minor changes (2). Blots were exposed to film. Films were scanned and protein bands were analyzed by using Image J. Data are expressed as mean ± SD. One-way ANOVA, followed by post-hoc Bonferroni test was used for multiple comparisons. p-values < 0.05 was considered as statistically significant.

Results: The expression of SERCA2a was significantly decreased in diabetic and sacubitril/valsartan treated diabetic group. Although there was a decrease in valsartan treated diabetic group compared to control, it was not found statistically significant. The expression of PLN was found comparable amoung the groups. On the other hand, the p-PLN/PLN ratio was significantly decreased in diabetic animals and did not reach to control level with both treatment approaches. SERCA2a/PLN ratio was not found different among the groups.

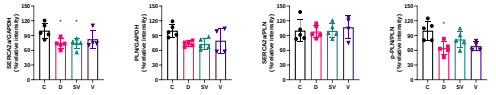

Figure 1. Protein expression levels. (C: Control, D: Diabetic, SV: Sacubitril/valsartan treated diabetic, V: Valsartan treated diabetic)

Conclusions: Decreased expression of SERCA2a and reduced p-PLN/PLN ratio in the diabetic group, which are indicators of impaired diastolic function in diabetes, were not improved after the treatment approches. We conclude that sacubitril/valsartan combination may exert its beneficial effect on the diabetic heart through other mechanisms rather than the improvement of diastolic function components.

Acknowledgements

This study was supported by a grant of TUBITAK (SBAG-117S936) and Ankara University Scientific Research Projects Coordination Unit (19H0237004)

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OP076: THE SYNERGIC EFFECTS OF AGOMELATINE ON THE ANTICANCER POTENTIAL OF DOXORUBICIN IN MCF-7 BREAST CANCER CELLS

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Introduction: Treatment of breast cancer using doxorubicin (DOX), a potent antitumoral drug, is broadly considered one of the most common treatment modalities. However, the cytotoxic effects of the DOX significantly restrict its use, and also the development of resistance to DOX is frequently seen. Therefore, the combination therapies of DOX with different compounds and molecules to overcome drug resistance and minimize cytotoxic effect appears to be more promising in cancer cells (1). Melatonin (MEL) is a hormone secreted from the pineal gland and has an anti-proliferative effect on various tumor types (2). While many cancer studies on MEL are used as an adjuvant with chemotherapeutic drugs, no research in this direction has been found regarding agomelatine (AGO), which is MT1/MT2 melatonin receptor agonist. With the aim of developing a new adjuvant therapy, the present study tested the effects of AGO alone or combined with DOX on breast cancer.

Materials and Methods: The effects of DOX, MEL, AGO, and their combinations (DOX+MEL and DOX+AGO) were investigated on the proliferation in the MCF-7 cells. The MCF-7 cells were separated into the following six groups: Control, DOX, MEL, AGO, DOX+MEL and DOX+AGO. Cell viability was determined by the 3-(4,5-dimethylthiazol- 2-yl)-2,5-diphenyl-tetrazolium bromide (MTT) assay. The cells were exposed to appropriate nontoxic concentrations and incubation times for AGO by assessing cell viability in cell culture. Then cells were incubated with DOX, MEL, and AGO for 24 h.

Results: Our study showed that the treatment with MEL, AGO, and DOX alone significantly decreased

viability on MCF-7 cells. Median inhibitory concentrations (IC50) of DOX, MEL, and AGO were found to be 0.23 µg/ml, 0.016 µg/ml, and 117.9 µg/ml, respectively. Interestingly, when combined with DOX, both MEL and AGO in some concentrations intensified the anticancer potential of DOX alone in the MCF-7 cells.

Conclusions: The combined use of AGO and DOX on MCF-7 cells increases the treatment efficacy of DOX and alleviates its unwanted side effects. These promising results may lead to further inquiry.

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OP077: THE ROLE OF NEBIVOLOL ON ERECTILE DYSFUNCTION IN RATS WITH HEART FAILURE

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Introduction: Beta-blockers are widely prescribed to reduce mortality in heart failure (HF) however, they are associated with a greater risk for erectile dysfunction (ED) (1). Nebivolol is a third-generation beta-blocker with also having a Nitric oxide (NO) releasing effect. NO plays a key role in penile erection (2). The aim of this study was to investigate the NO-mediated effects of Nebivolol on erectile dysfunction in HF.

Materials and Methods: Rats were divided into sham-operated control (SC), HF induced control (HFC) and nebivolol treated (HFNEB). HF was induced by the ligation of the left anterior descending coronary artery (3). Eight weeks after ligation, NO-mediated effects of nebivolol were assessed by functional, hemodynamic, biologic, and histologic studies.

Results: HF rats displayed erectile dysfunction represented by decreased intracavernosal/mean arterial pressure ratio (ICP/MAP). Increased nitrosative damage/decreased antioxidant capacity was consistent with decreased eNOS and increased iNOS and nNOS immunoreactivity in this group. Nebivolol treated animals were characterized by improved functional capacity, increased antioxidant, and decreased oxidant capacity. Prevention of eNOS and an increase in nNOS immunoreactivity was also significant in this group.

Conclusions: Our study showed the positive effects of nebivolol on erectile dysfunction in HF. NO-mediated mechanisms behind this effect can be summarized as eNOS mediated dilation of the cavernous body and nNOS mediated smooth muscle relaxation. To the best of our knowledge, this study is the first in the literature to explain the NO-mediated effects of nebivolol on erectile function at the molecular level by discussing all three NOS isoforms.

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OP078: INVESTIGATION OF DRUG-DRUG INTERACTION OF FAVIPIRAVIR WITH ALLOPURINOL AND VERAPAMIL USING PHARMACOKINETIC PARAMETERS

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Introduction: The New Coronavirus Disease (COVID-19) is a global epidemic. Favipiravir is an antiviral used effectively in the treatment of COVID-19. Favipiravir is metabolized by aldehyde oxidase (AO) and xanthine oxidase (XO) (1). This study aims to investigate drug-drug interactions between Favipiravir and allopurinol, verapamil which affect the AO and XO enzyme activity with pharmacokinetic parameters.

Materials and Methods: 25 Spraque Dawley female rats, 250-300 g, were randomly divided into 5 equal groups (n = 5). Groups; 1. Favipiravir group, 2. Verapamil group, 3. Favipiravir+Verapamil group, 4. Allopurinol group, 5. Favipiravir+Allopurinol group. Blood samples were taken from the jugular vein at the end of 0., 15., 30., 45. min and 1., 2., 4., 6., 8. h after the drugs were administered. Drug-blood concentration was determined on the HPLC-UV device using plasma and standard solutions. Pharmacokinetic parameters were calculated by the PKSolver Non-Compartmental Analysis pharmacokinetics software program.

Results: Favipiravir decreased the maximum serum concentration (C_{max}), time taken to reach Cmax (T_{max}), elimination half-life ($T_{1/2}$), area under the curve (AUC), mean residence time (MRT) values of allopurinol, increased clearance (Cl) time and apparent volume of distribution (V_d). Allopurinol prolonged the Favipiravir T_{max} and decreased C_{max}, AUC, MRT, Cl, V_d values. Verapamil did not affect the pharmacokinetic parameters of Favipiravir. However, favipiravir reduced the absorption of verapamil and slowed its elimination. Verapamil C_{max}, T_{max}, AUC, Cl, values decreased. $T_{1/2}$, MRT, and V_d increased.

Conclusions: As a result, the use of favipiravir with other drugs that affect the AO and/or XO enzyme activities may cause the pharmacokinetic profiles of the drugs to change. Time and dose adjustments are required to maintain drug efficacy.

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OP079: ROLE OF TOLL- LIKE RECEPTOR2 SIGNALING IN RAT MODEL OF CAVERNOUS NERVE INJURY-INDUCED ERECTILE DYSFUNCTION

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Introduction: Erectile dysfunction (ED) is a highly prevalent complication in men who have undergone radical prostatectomy (RP) and it is strongly linked to a neurogenic basis due to mechanical damage of cavernous nerves (CN) during surgery. However, current understanding of underlying molecular mechanism(s) and treatment of neurogenic ED are limited (1). Toll-like receptors (TLRs) are known to have key roles in immune response, neuroinflammation, and also in peripheral neuropathies including traumatic nerve damage (2,3,4). The aim of this study was to investigate the role of TLR2 signaling in a rat model of CN injury-induced ED.

Materials and Methods: To investigate the functional role of TLR2 signaling in ED, we evaluated *in vivo* erectile function (EF) by electrical stimulation of CN in male Spraque-Dawley rats (275-400 g) (5) treated with a single dose Pam3CSK4 (TLR2 agonist, 1mg/kg, i.p) and in rats treated with CuCPT22 (TLR2 antagonist, 3mg/kg/day, i.p) for 3 days after bilateral CN-injury (n=5/group). EF was evaluated as maximal intracavernosal pressure (ICP) and total ICP (ICP area under the curve) normalized to mean arterial pressure. To determine the role of TLR2 signaling pathway, the protein expressions of TLR2 and MyD88 (downstream adaptor molecule of TLR) in penile tissue and major pelvic ganglia (MPG) were analyzed with western blotting.

Results: EF was lower in bilateral CN-injury group compared with sham group at 3-days post-injury ($p<0.001$, $p<0.05$) whereas EF was preserved in CN-injury group treated with CuCPT22. Administration of Pam3CSK4 alone, did not cause a significant decline in EF. The protein expressions of TLR2 or MyD88 in penile tissue and MPG did not alter after CN injury or with any treatment.

Conclusions: Preservation of EF in rats treated with a selective TLR2 antagonist indicated a role of increased TLR2 signaling after CN-injury. However, EF was not impaired by activation of TLR2 with administration of an agonist, suggesting that TLR2 pathway was not involved in baseline regulation of EF. The increased TLR2 signaling after CN-injury appear to be via MyD88 independent pathway both in penile tissue and MPG. To better understanding the exact mechanism, the role of inflammatory, fibrotic and apoptotic processes associated with the other TLR pathways will be further examined.

Acknowledgements

This study was supported by a grant of TUBITAK (SBAG-217S434)

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OP080: A DROSOPHILA APPROACH TO STUDY THE EFFECTS OF ATYPICAL ANTIPSYCHOTIC DRUGS

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Introduction: Genetic variations in the DTNBP gene encoding dysbindin-1 can alter D2 receptor availability and are associated with cognitive response to antipsychotic drug treatment (1). The mechanisms underlying the efficacy and adverse effects induced by these drugs are, to date, not sufficiently explained (2). In Drosophila, dysbindin (Dysb) regulates glutamatergic and dopaminergic transmission at neuronal and glial levels, respectively (3). To investigate the role od Dysb in the mechanism of action of atypical antipsychotic drugs (AAPs), we used Drosophila loss of function models of dysb to analyse the effects of olanzepine, risperidone and ziprasidone at molecular, cellular and behavioral levels.

Materials and Methods: *Drosophila* RNAi and mutant strains ($Dysb^{1}$) of *dysb* were used for loss of function studies; ubiquitous, astrocyte, neuron and glia driver lines were employed to selectively reduce dysb in *Drosophila*. Confocal microscopy was used to identify endo-lysosomal defects in neuronal and glial cells; qRT-PCR to measure the relative expression changes of the receptor transcripts (D1,D2, 5-HT(2A), β1, β2 and β3) and glia transcription factors; climbing and activity tests to investigate behavioral differences. Ziprasidone, risperidone and olanzepine were chronically administrated at 30 uM in the food.

Results: $Dysb^{1}$ flies showed increased locomotor activity (as reported previously), increased expression of D2 receptors (up to 10-fold), 5-HT(2A) (1.8-fold) and β3 (1.5-fold), a partial loss of glia cells with a concomitant reduction of astrocyte-specific transcription factors expression. A selective downregulation of dysb in astrocytes lead to a defective endolysosomal pathway and the increased of D2 expression (6 fold). Of note, climbing activity of Dysb1 was increased, whereas the astrocytes selective reduction of dysb caused a decrease in locomotor activity that was associated to a striking hyperexcitability behavior in adult flies. All the tested AAPs drugs restored receptor expressions in a dose dependend manner. However, while risperidone and ziprasidone ameliorated cellular astrocytic defects, olanzepine had the greatest effects at behavioral level.

Conclusions: Our data demonstrate that dysb regulates astrocytes specific intracellular recycling, with a consequent modulation of dopaminergic function and thus of the dopamine-related behavioral phenotypes. Importantly, these dysb-dependent mechanisms are differently affected by AAPs including olanzepine, risperidone and ziprasidone.

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This study was supported by the Young Investigator grant GR, Ministery of Italy

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OP081: A DROSOPHILA BASED APPROACH TO DEVELOP SPECIES-SELECTIVE VERTEBRATE DRUGS

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Introduction: Here we propose an alternative approach to replace vertebrate models in preclinical research. We are developing fruit-fly models to test Norbormide (NRB) target and its species selective toxicity. NRB is a *Rattus*-specific toxicant relatively harmless to other species. NRB's lethal effect is due to its vasoactive properties. Since its development in the 1960s the mechanism of NRB remains unknown, nevertheless some hypotheses have been postulated. Based on previous data a possible target was proposed to be the KATP channel composed by the SUR2b/Kir6.1 subunits (1, 2). New NRB derivatives were synthetized and tested for vasoconstriction properties and localization in *ex vivo* and *in vitro* tests. We thought to develop *Drosophila* transgenic animals expressing the rat and mouse KATP channels and to characterize NRB derivatives properties.

Materials and Methods: Rat and mouse cDNAs, with epitope tags, of the subunits of Kir6.1 and SUR2B were cloned in PUAST-ATTB vector for transgenesis in *Drosophila.* Ubiquitous driver lines were used to express the subunits, separately. Immunohistochemistry was used to visualize subunits expression in *Drosophila* tissues. Fluorescent derivatives of NRB were used in live imaging experiments to visualize the subcellular localization in control, downregulated *Drosophila* homologues of SUR2 and Kir and KATP expressing animals. Toxicity tests were done to evaluate the effects of NRB derivatives on *Drosophila* wild type and KATP models.

Results: Here we present preliminary data on rat KATP channel expression in *Drosophila*. Our data shows that the inividual expression of KATP channel subunits colocalize with endoplasmic reticulum membrane, as previuolsy shown *in vitro* for these subunits. NRB derivative with NBD or BODIPY groups showed the same localization observed in rat cell lines, with a ER localization for compounds of group 1 of and plasma membrane for group 2. NRB derivatives (with and without fluorophores) were atoxic when administrated to wild type *Drosophilae*. Analysis of flies coexpressig

the two subunits (to reconstitute the channel) are ongoing.

Conclusions: *Drosophila* models expressing species-selctive receptors can be used to replace vertebrate models during preliminary preclinical experimentations allowing the selection of the most promising compounds for future studies.

Acknowledgements

This project was supported by the New Zealand MBIE Endeavor Fund C09X1710 (BH, SB, and) and by the University of Padua, project no. 148125/14 (GO, SB).

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OP082: GENDER DIFFERENCES IN ß3-ADRENOCEPTOR-MEDIATED CARDIAC REMODELING

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Introduction: β-adrenoceptors (AR) are the critical regulators of cardiac function. However their chronic activation leads to receptor desensitization and thus loss of inotropy. Interestingly, the third isoform, β3-ARs are resistant desensitization and are upregulated under persistent sympathethic activation. β3-ARs have been shown to improve cardiac functioning, metabolism and remodeling. On the other hand, it has recently shown that β3-ARs are among sex-dominated genes (1). Thus, we aimed to investigate the gender differences in β3-AR-mediated cardiac remodeling.

Materials and Methods: Cardiac remodeling was induced by transverse aortic constriction (TAC) as previously described (2). Wild type C57BL/6 (WT) and β3-AR knockout (β3-KO) male and female mice at 8-10 weeks of age were used. After 4 weeks post TAC, echocardiography was performed to evaluate global cardiac function. Parasternal short-axis echocardiographic views and (M)-mode measurements were used to calculate ejection fraction (EF) (%), fractional shortening (FS) (%), stroke volume (SV), cardiac output (CO), systolic and diastolic left ventricular posterior wall thicknesses (LVPW) and left ventricular anterior wall thicknesses (LVAW).

Results: Mice subjected to TAC had impaired EF and FS, whereas increased SV and CO parameters. This hypertrophic response was more prominent in β3-KO male mice compared to WT male mice. Moreover, the increase in LVPW was apparent only in male β3-KO mice. However, there was no difference in cardiac parameters between female WT and β3-KO mice.

Conclusions: Our results indicate that there are gender-dependent differences in β3-AR-mediated cardiac remodeling. In the literature, there are contradictory studies regarding to the role of β3-ARs in cardiac dysfunctions. Our findings may be an explanation of this inconsistency. Nevertheless, further studies should be performed for a better understanding which ultimately may lead to the development of gender-based treatment strategies.

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OP083: THE CONTRIBUTION OF ADRENERGIC AND SEROTONERGIC RECEPTORS IN THE ANALGESIC EFFECT OF QUERCETIN

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Introduction: Quercetin is a sugar-free aglycon known to have antioxidant, analgesic, anti-inflammatory and anti-cancer effects. It is stated that the GABAergic, serotonergic and nitrergic system may play a role in the analgesic effect of quercetin (1, 2). We aimed to investigate and compare the role of adrenergic and serotonergic receptors in the analgesic effect of quercetin.

Materials and Methods: Quercetin was administered intraperitoneally at doses of 15, 30, 60 and 120 mg/kg in mice. 60 mg/kg quercetin was chosen to investigate the mechanism of antinociceptive effect. Therefore, ketanserin (5-HT2 receptor antagonist), ondansetron (5-HT3 receptor antagonist) (both; 1 mg/kg, ip) and prazosin (α-1 adrenoceptor antagonist), yohimbine (α-2 adrenoceptor antagonist) (both; 1 mg/kg, i.p.) were administered in hot plate and tail immersion tests (3,4,5).

Results: Quercetin showed significantly antinociceptive effect in experimental pain models. In the hot plate test, ondansetron and yohimbine reversed antinociceptive effect of quercetin; in tail immersion test, ketanserin, ondansetron and yohimbine reversed antinociceptive effect of quercetin. It was determined that in the analgesic effect of quercetin, 5-HT2 receptors were involved only in the spinal level and 5-HT3 serotonergic and α-2 adrenergic receptors were involved in the supraspinal and spinal level.

Conclusions: The elucidation of the effect and mechanisms of actions of quercetin will contribute to new therapeutic approaches and provide guidance for new analgesic drug development studies.

Acknowledgements

This study was supported by a grant of Anadolu University (BAP- 1804S083)

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OP084: INVESTIGATION OF EFFECT OF INACTIVE PARAPOXVIRUS IMMUNOMODULATOR ON LEUKOCYTE PROLIFERATION

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Introduction: İnactivated P. ovis shows strong immunomodulatory activity in several species and is used in immunostimulatory biological agent for the prevention and/or treatment of infectious diseases (1). Parapoxvirus ovis activity is based on the activation of innate cells and consequent cytokine production, stimulates and regulates the secretion of cytokines by leukocytes (2).

Materials and Methods: In this study, 12 calves older than 6 months of age were used to measure specific immune factor. These calves were divided into 3 groups wıth each containing 4 calves. The first group assigned as the control group, inactivated Parapoxvirus and IBR vaccine were applied to the 2nd group, and only the IBR vaccine was applied to the 3rd group. After administration, blood samples were collected using heparinized vacuum tubes on the day of vaccination and on the 21th and 36th days of vaccination. Total leukocyte count in collected blood samples, Isolation of polymorph nuclear leukocytes, Serum Neutralization tests for leukocytes were conducted.

Results: According to the evaluation of the Serum Neutralization Test, the titers of the control group were found 0 on the vaccination day, the 21st day and the 36th day. Average of titers of IBR vaccinated group were measured 0 on the vaccination day, 5.29 on the 21st day, 6.10 the 36th day. Finally in IBR Vaccine + Parapoxvirus immunomodulator applied group, the average titers were measured 0 on the vaccination day, 5.98 on the 21st day, and 6.72 on the 36th day. According to the test results, the antibody titers of the animals in the group with immunmodulator and IBR vaccine were found to be 12% higher than the other 2 groups. Meanwhile in a healthy cattle the leukocyte count is between 6,000-10,000 µ / l. As a result of our Total leukocyte counts, it was seen that the leukocyte count was the highest in the immunostimulant group.

Conclusions: Based on our study results, we concluded that immunmodulators play a key role in supporting leukocytes which are the important part of immunity system. Therefore, we aim to test the inactive parapoxvirus immunomodulator on different animal species and to look at different immunity elements.

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This study was supported by a grant of Dollvet A.Ş

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OP085: THE EFFECT OF METHYLENE BLUE TREATMENT ON COGNITIVE FUNCTIONS IN THE D-GALACTOSE-INDUCED AGE RELATED DEMENTIA MOUSE MODEL

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Introduction: Dementia is one of the most devastating geriatric disorders and characterized by a deterioration of intellectual functions such as cognition, memory and judgement (1). Chronic administration of D-galactose has been reported to cause deterioration of cognitive and motor skills that are similar to symptoms of aging (2). Methylene blue has been used clinically for about a century to treat numerous diseases and is arousing interest for neurodegenerative diseases recently (3). The aim of our study to investigate the potential therapeutic effect of methylene blue on cognitive functions in a mouse model of dementia.

Materials and Methods: Eighteen female (16-24 weeks) Balb/c mice were randomly divided into three groups (n=6 mice/group, Hacettepe University Animal Experimentations Local Ethical Board No: 2020/02-04). In the D-galactose and

methylene blue treatment groups, mice were injected with D-galactose (50 mg/kg) subcutaneously for 60-days. In the control group, mice were injected subcutaneously with saline. In the methylene blue treatment group, mice were treated with methylene blue (2 mg/kg, oral) for last 14-days of experiments. Morris water maze (MWM) test was used to assess the spatial learning and memory of mice in the end of the treatment. Mice were given 4 trials per day for 4 consecutive days to assess spatial learning. 24-hours after the last acquisition session, a probe trial was used to assess the spatial memory. Statistical analysis were carried out using one-way analysis of variance followed by Newman-Keuls test.

Results: MWM test indicated that chronic administration of D-galactose impaired the spatial learning and memory which was significantly ameliorated by chronic methylene blue treatment. In the learning curve, D-galactose group showed longer average escape latency compared to control group in every acquisition day. Methylene blue treatment decreased average escape latency compared to D-galactose group ($p<0.05$). In the probe test, the percentages of time spent in the target quadrant indicating memory consolidation were 44.2±2.6, 29.8±2.8 and 43.4±5.7 for control, D-galactose and methylene blue treatment groups respectively. Methylene blue treatment increased the time spent in the target quadrant significantly compared to D-galactose group ($p<0.05$).

Conclusions: Methylene blue has been investigated as a promising agent in various neurodegenerative diseases. Although the mechanism of action needs to be investigated in future studies, our findings implicate that methylene blue is beneficial for cognitive impairments and can be a potential drug candidate for neurodegenerative diseases.

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OP086: THE EFFECT OF 4-PHENYLBUTYRIC ACID ON HYPERTENSION-INDUCED CARDIAC IMPAIRMENTS

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Introduction: Hypertension is one of the most common cardiovascular diseases and it is also causes structural and functional changes in the heart (1). Different stressors lead to the accumulation of unfolded/misfolded proteins, resulting in endoplasmic reticulum (ER) dysfunction called ER stress (ERS). ERS is recognized as a therapeutic target for cardiovascular diseases (2). In this study, the effects of ERS inhibitor 4-phenylbutyric acid (4-PBA) on hypertension-induced cardiac dysfunction were examined.

Materials and Methods: Hypertension was induced by unilateral nephrectomy followed by deoxycorticosterone acetate-salt administration in male Wistar rats for 12 weeks. Blood pressure was measured weekly. ERS inhibitor 4-PBA (150mg/kg/day) was given intraperitoneally last four weeks. At the end of treatment, right atrium (RA) and left papillary muscle (LPM) were isolated and rhythmic activity and contractions of tissues were recorded.

Results: 4-PBA treatment significantly decreased systolic blood pressure in hypertensive group, but it did not affect body weight of rats. In Ca^{2+}-free medium, resting tension of RA were higher in hypertensive rats, this response were significantly lower in 4-PBA treated-hypertensive group. In Ca^{2+}-free medium, noradrenalin-stimulated and additional Ca^{2+}-induced contractions and rhythmic activity of cardiac tissues were similar in all groups. High ryanodine concentrations-induced contractions of RA (developed tension) were smaller in 4-PBA treated-hypertensive group than hypertensive group. Also, high ryanodine concentrations-induced contractions of LPM were greater in hypertensive rats but this response were not changed by 4-PBA treatment.

Conclusions: These findings suggest that ERS inhibition by 4-PBA improves blood pressure and may have a beneficial effect on impaired cardiac function in hypertension.

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OP087: CONTRIBUTION OF CANNABINOID SYSTEM TO THE ANTIHYPERALGESIC EFFECTS OF ANTIEPILEPTIC DRUGS

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Introduction: Alterations in TRP channel activity results in mechanical and thermal hypersensitivity and they are possible targets of cannabinoid system mediated analgesia, especially in inflammatory conditions (1, 2). Antiepileptic drugs have been shown to exhibit analgesic activity in inflammatory pain models and vanilloid receptor 1 (TRPV1) channels are shown to contribute to their antihyperalgesic action (3, 4). In this study it was aimed to investigate the involvement of cannabinoid system to antihyperalgesic action mechanism of antiepileptic drugs in a rat model of TRPV1 agonist capsaicin-induced mechanical hyperalgesia.

Materials and Methods: Pre-treatment with AM251, CB1 receptor antagonist, was followed by pregabalin (50 mg/kg, *i.pl.*), gabapentin (600 µg/paw *i.pl.*), oxcarbazepine (500 µg/paw *i.pl.*), carbamazepine (140 µg/paw *i.pl.*) administrations. Electronic von-Frey apparatus was used to evaluate mechanical hyperalgesia and pain thresholds were recorded at 15, 30, 60, 90, 120, 150 and 180 minutes following the drug injections.

Results: Gabapentin, pregabalin, carbamazepine and oxcarbazepine time-dependently reversed the development of mechanical hyperalgesia. AM251 antagonized the antihyperalgesic effects of antiepileptics in a varying rate.

Conclusions: The results of this study demonstrate that the mechanisms of action of gabapentin, pregabalin, carbamazepine and oxcarbazepine are associated with TRPV1-cannabinoid pathway. TRPV1 channels are considered to be ionotropic cannabinoid receptors and may be modulated by endocannabinoids. Therefore, these drugs may contribute to the desensitization of TRPV1 channels by altering the endocannabinoid levels.

Acknowledgements

This study was supported by a grant of Anadolu University (BAP – 1905S073).

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OP088: THE EFFECTS OF HYDROGEN SULFIDE DONORS ON ERK AND WNT SIGNALING PATHWAYS IN AN *IN VITRO* LIPOPOLYSACCHARIDE-INDUCED AIRWAY INFLAMMATION MODEL IN MICE

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Introduction: Hydrogen sulfide (H_2S) involves various pathophysiological processes in the respiratory system. ERK, a mitogen-activated protein kinase, and WNT/β-catenin signaling pathways are closely related to inflammatory and fibrotic processes in airway diseases (1, 2). In this study we aimed to investigate the effects of H_2S donors on ERK and WNT/β-catenin signaling pathways in isolated mice tracheas in an *in vitro* chronic airway inflammation model in tissue culture.

Materials and Methods: 20-25 g male BALB/c mice were sacrificed by cervical dislocation and their tracheas were isolated. Tracheas were placed into culture media and incubated with lipopolysaccharide (LPS, 10 µg/ml) at 37 ̊C in 5% CO^2 for four days to induce inflammation. The subgroups were incubated with either rapid-releasing (NaHS, 1000µM) or slow-releasing (GYY4137, 100µM; AP39, 30nM) H_2S donors concomitantly with LPS in tissue culture. After the culture period, tracheas were homogenised in Tris-HCl lysis buffer. Samples were separated with SDS-PAGE electrophoresis and transferred to polyvinylidene fluoride membrane. After blocking with 5% milk powder, membranes were incubated with primary antibodies for β-catenin, phospho-ERK1/2, ERK1/2 and beta-tubulin, and then incubated with horseradish peroxidase-conjugated seconder antibodies. Signals were detected with CCD camera and analyzed with Image J.

Results: Incubation of tracheas with LPS in tissue culture significantly enhanced the expression levels of β-catenin ($P<0.05$) (Fig.1A). GYY4137 and AP39 application prevented the increase of β-catenin expression induced by LPS ($P<0.05$), whereas NaHS did not alter β-catenin levels when

compared to that of LPS group (P>0.05) (Fig1A). There was no significant difference between the groups in ERK1/2 protein expression (P>0.05) (Fig1B). Although it was not statistically different, there was a tendency to increase in pERK1/2 protein expression and the pERK1/2/ERK1/2 ratio with LPS incubation, and all of the studied H_2S donors reversed this pattern (P>0.05) (Fig1B).

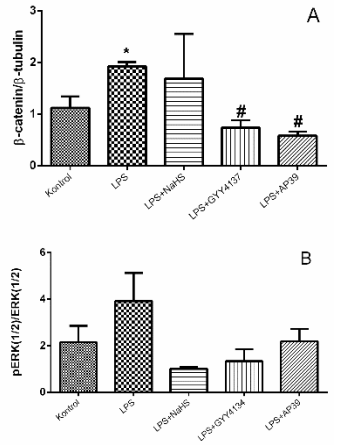

Fig.1. β-catenin (A) and pERK1/2/ERK1/2 (B) expression levels in mice trachea homogenates from control (n=4), LPS (n=4), LPS+NaHS (n=3) and LPS+GYY4137 (n=3) and LPS+AP39 (n=4) groups. *P=0.01 versus control; #P<0.01 versus LPS. Data were presented as mean±s.e.m.

Conclusions: Our results indicate that H_2S donors may ameliorate the changes induced by LPS in inflammatory and fibrotic signalling pathways like ERK and WNT. This data is compatible with our previous results that H_2S donors prevented LPS-induced increase in inflammatory cytokine levels in lung tissues and abolished inflammation-induced hyperreactivity of isolated mice tracheas in an *in vitro* airway inflammation model at the same concentrations (3). It can be concluded that ERK and WNT/β-catenin signaling pathways are contributed to anti-inflammatory effects of H_2S donors.

Acknowledgements
This study was supported by a grant of TUBITAK (SBAG-315S289).

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OP089: EFFECT OF FLUVOXAMINE ON THE PHARMACOKINETICS OF PARACETAMOL IN MICE

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Introduction: Paracetamol is one of the most widely used non-steroidal anti-inflammatory drugs in the world due to its analgesic and antipyretic effects. Fluvoxamine is a selective serotonin reuptake inhibitor drug used in the treatment of depression. Fluvoxamine and paracetamol can be used simultaneously in treatment. In the combined use of drugs, there may be drug-drug interactions at the point of absorption, distribution, metabolism and excretion. As a result of drug-drug interaction, a decrease in the effectiveness of drugs or toxic effects may be observed. No study was found on the pharmacokinetics of paracetamol after concomitant use with fluvoxamine in mice. The aim of this study was to determine the effect of low and high dose fluvoxamine administration on the pharmacokinetics of paracetamol in mice.

Materials and Methods: In this study, 96 male mice of Swiss Albino race (8-12 weeks old) were used. After the control group (n = 6) was separated, the mice were divided into three groups in equal numbers (n = 30). Paracetamol (700 mg / kg) was administered to the first group, paracetamol + low dose (30 mg / kg) fluvoxamine to the second group, and paracetamol + high dose (150 mg / kg) fluvoxamine to the third group. Plasma concentrations of paracetamol were assayed using the high-performance liquid chromatography (HPLC)-UV, and pharmacokinetic parameters were calculated by noncompartmental analysis.

Results: After a single administration of paracetamol, the elimination half-life ($t_{1/2\lambda z}$), area under the concentration-time curve ($AUC_{0-\infty}$) and peak plasma concentration (C_{max}) were 2.99 h, 880.72 h*µg/mL, and 486.74 µg/mL, respectively. Low and high dose fluvoxamine administration resulted in an increase in $AUC_{0-\infty}$ 32% and 61%, and C_{max} 15% and 27% of paracetamol, respectively.

Conclusions: As a result, low and high dose fluvoxamine administration increased the plasma concentration of paracetamol in mice. This increase in the concentration of paracetamol, the effect of which is dose dependent, may lead to an

increase in the therapeutic effect. However, further research is needed to determine the safety and mechanism of interaction following the concomitant use of paracetamol and fluvoxamine.

Acknowledgements

This study was supported by The Coordination of Scientific Research Projects, University of Erzincan Binali Yıldırım, Turkey (Project No. TYL-2021-755).

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OP090: EVALUATION OF PARENTAL KNOWLEDGE, ATTITUDES AND PRACTICES REGARDING ANTIBIOTIC USE IN ACUTE UPPER RESPIRATORY TRACT INFECTIONS IN CHILDREN IN A TERTIARY CARE HOSPITAL IN TURKEY

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Introduction: The problem of unnecessary and inappropriate antibiotic use among children is a concern for antibiotic resistance in low- and middle-income countries (1). This study aims to evaluate parents knowledge of antibiotics in upper respiratory tract infections, their attitudes towards their use and the behaviors of applying antibiotics to their children.

Materials and Methods: Our study was carried out between December 14, 2021 and April 1, 2021 for parents older than 18 with a child under the age of 18 who applied to the general pediatrics outpatient clinics of Gazi University Faculty of Medicine Hospital Department of Pediatrics. The survey consists of 30 questions including demographic information, antibiotic knowledge, attitude and practices of the participants.

Results: A total of 554 parents were included, of those 34,5 (191) were male and 60% of the participants were between the ages of 30-44. Parents 13.5% strongly disagree, 15% disagree, 34.5% uncertain, 33.9% agree, 3.1% strongly agree with the statement that antibiotics can cure respiratory infections caused by viruses. Parents 80.9% never, 10.6% rarely, 6% sometimes, 1.6% frequently, 0.9% always with the statement that I reuse the remaining antibiotics when similar symptoms of an upper respiratory tract infection are present. Participants stated that they learned their knowledge about antibiotics from a doctor (73.1%), pharmacist (15.3%) and internet (8.7%). Female gender, higher education level and high income has been associated with better antibiotic knowledge and attitude ($p<0,05$).

Conclusions: Although there are some deficiencies in the antibiotic knowledge of the parents, their attitudes and practices seem appropriate. The national rational drug use action plan was found to be useful. Parents should continue to be informed about antibiotics.

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This study was not supported by any grant.

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OP091: OPINIONS OF CANCER PATIENTS TOWARDS THE COVID-19 VACCINE

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Introduction: It is known that cancer patients receiving chemotherapy are at higher risk of infection, including COVID-19 which can be more severe in these group of patients (1). The COVID-19 vaccinations have been carried out in Turkey since the beginning of 2021 and the priority has been given to the healthcare providers and patients at high risk (such as patients aged over 65 years, have chronic conditions and/or being immunosuppressed). Several international guidelines have been developed to assist healthcare professionals about the timing of COVID-19 vaccine and systemic chemotherapy in cancer patients (2). The aim of this study is to determine the current vaccination status of cancer patients and to evaluate the patients' attitudes towards the COVID-19 vaccine.

Materials and Methods: This was a point prevalence study conducted prospectively at the outpatient clinics of Hacettepe University Oncology Hospitals between 28th-30th April 2021. The patients older than 18 years and attended the clinics during the study period were included. Participated patients were asked to complete a questionnaire that includes 16-questions regarding the COVID-19 vaccine.

Results: A total of 72 (54.2% male) patients were included and the mean (± standard deviation) age was 58.4 (±13.3) years. Among the patients, 66 (92%) were diagnosed with solid cancers, 37 (51.3%) had no chronic diseases, but 39 (54.2%) were ex-smoker. Only 12 patients (16.7%) had history of COVID-19 infection and 1 patient indicated to use vitamin D as a supplement against COVID-19. In terms of COVID-19 vaccination, 62% of the patients stated that they had consulted with their oncologists about vaccination and 55% were vaccinated (of those n=23 received 2nd doses of the vaccine). When the type of the vaccine is examined; 80% of the vaccinated patients (n = 40) have received the attenuated vaccine and 25% of patients stated that they experienced side effects from the COVID-19 vaccine. Among the patients who were not vaccinated (n=32), 50% did not think of being vaccinated, 40% worried that vaccination affects the existing cancer treatments. The opinions of patients were diverse; the patients stated that the vaccine is protective (50%), safe (50%), have no concern about its effectiveness (50%) but have concerns about the side effects (47.2%) of the vaccines.

Conclusions: This study showed that the desired rate of COVID-19 vaccination has not been achieved yet in cancer patients. Although the patients have concerns about side effects of the vaccine, the most appropriate timing for vaccination should be determined and cancer patients should be informed about the COVID-19 vaccine.

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The authors would like to thank all participating patients and hospital staff at the clinics.

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OP092: EVALUATION OF THE PSYCOLOGICAL BUDERN OF COVID-19 PANDEMIC ON YOUNG ADULT POPULATION

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Introduction: Coronavirus Disease is an ongoing global pandemic which affected the world since December 2019, caused by SARS-CoV-2 (1, 4). In Turkey, the first COVID-19 case was seen in March 2020. Pandemic had a sound effect on humans' life, especially psychological effects that interfere with daily routine activities. Lack of social life, time spent following COVID-19 news and being anxious about the future are inevitable reasons for the psychological changes (2, 3). The aim of this study is to determine the psychological effect of the pandemic on the young adult Turkish population.

Materials and Methods: A survey was performed using Google Forms and included validated questionnaires such as the Patient Health Questionnaire (PHQ-9) for depression, Generalized Anxiety Disorder (GAD-7) for anxiety, and the Insomnia Severity Index (ISI) for sleeping issues. Age, gender, current or previous diagnosis, and drug use were all inquired. The survey was shared on social media and has a 5-day completion deadline. The statistical analyses for the PHQ-9, GAD-7, and ISI were performed using SPSS 26 (Statistical Package for the Social Sciences).

Results: 170 participants mainly University students completed the survey, 73,5% were females, the age of (92.9%, n=170) of the participants were between 18-35 years old. 5.3% of the participants had no depression, 17.6% had mild depression, 33.5% had moderate depression, 18.2%had fairly extreme depression, and 25.3% had severe depression. The results revealed that 14.1% of the participants had a low level of anxiety, 37% had a mild level of anxiety, 23.5%had a moderate level of anxiety, and 25.3% had an extreme level of anxiety. Insomnia levels specified as 36.4% minimal, 38.8% of subthreshold Insomnia, 20.6% moderate, and 4.1% of the participants were classified under the severe insomnia level. Age had a negative association with depression and anxiety ($r:-0,31$, $p<0,05$), ($r: -0,270$, $p<0,05$), respectively.

Conclusions: The young population, especially students, are suffering from a variety of psychological disorders that may have been triggered or exacerbated by the COVID 19 Pandemic, necessitating the creation of online support programs to assist in reducing anxiety and treating depression symptoms.

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OP093: ASSESSMENT OF THE PROPER INHALER TECHNIQUE IN ASTHMA AND COPD PATIENTS

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Introduction: Medication nonadherence (MNA) is a main problem in patients with asthma and chronic obstructive pulmonary disease (COPD). Improper inhaler technique is an unintentional component of MNA (1). In this study, we aimed to examine patients' inhaler medication usage skills.

Materials and Methods: This cross-sectional study was conducted for two months in a university hospital chest diseases outpatient clinic. The study was approved by the ethics committee of the university. All the included patients' inhaler technique were assessed by clinical pharmacists. IBM SPSS 25.0 was used as a software program for statistical analysis.

Results: Thirty-two asthma and 38 COPD patients were included in the study. Only 32,9% of the patients included in the study were using their inhalers properly. There were only 10 (13,3%) patients who had all steps correct. Age, comorbidity and inhaler type were not found to be associated with the proper inhaler technique. Only educational status have approached statistical significance in affecting the proper inhaler technique (*p*:0,072). Whilst the rate of proper use of inhalers was 50% for high school and university graduates, it was 26,9% for illiterate and primary or secondary school graduates. In addition it was found that the inhalation skills scores of different education level groups were different (*p*:0,037).

Conclusions: In previous studies, rates of inappropriate technique have varying from 4% to 97% depending on patient sample and inhaler device types (2,3). The present study concludes that most COPD and asthma patients use their inhalers improperly. More attention should be paid to inhaler use skills training, especially in the low education level group.

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OP094: THE EFFECTS OF CARVACROL AND EPIGALLOCATECHIN GALLATE ON DRUG RESISTANCE IN NEUROBLASTOMA CELL LINE

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Introduction: Topotecan (TOP) is a topoisomerase 1 inhibitor antineoplastic agent showing its cytotoxic effect by preventing the separation of DNA + topoisomerase 1 complex. Carvacrol (CVC) and epigallocatechin gallate (ECGC) are plant-derived antioxidant and anticancer compounds. In our study, the effect of CVC and ECGC on the development of drug resistance was evaluated in the N1E-115 neuroblastoma cell line due to TOP application. MRP1 (multi drug resistant associated protein 1) and p-glycoprotein, which are members of the ATP binding cassette transporter transport protein family, are membrane proteins that play a role in the development of multidrug resistance (1).

Materials and Methods: In our study, MRP1 and P-glycoprotein mRNA expressions were determined by qRT-PCR method after the application of IC50 dose to N1E-115 mouse neuroblastoma cell line for 24 hours. TOP 20.66 µM, CVC 2.09 µM, ECGC 3.44 µM, TOP + CVC 4.18 µM, TOP + ECGC 6.27 µM IC50 doses were used in our study.

Results: MRP1 and p-glycoprotein expression levels decreased in the CVC group compared to the TOP group. While MRP1 did not change in the ECGC group, p-glycoprotein expression was decreased. In the TOP + CVC group, MRP1 decreased while p-glycoprotein increased. While MRP1 decreased in the TOP + ECGC group, p-glycoprotein did not change.

Conclusions: A positive result can be evaluated against the development of multi-drug resistance in neuroblastoma cell line of CVC's MRP1 expression and p-glycoprotein expression level of ECGC. However, the decrease in MRP1 expression in both of our combined groups compared to the TOP group is seen as a positive result against multi-drug resistance.

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This study was partially supported by a grant of TUBAP (2018-176)

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OP095: THE ANTIANGIOGENIC ACTIVITY OF METFORMIN IN HT29-HUVEC CO-CULTURE: INVOLVEMENT OF miR-21 EXPRESSION

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Introduction: Colon adenocarcinoma is a major cause of cancer mortality worldwide (1). Type 2 diabetic people show up to have rising risk of developing colorectal cancer compared with nondiabetic people. Metformin is the first-line treatment for type 2 diabetic mellitus and it has a regulatory effect on the process of angiogenesis (2,3). Our aim to identify microRNA21 expression associated with angiogenesis in colon adenocarcinoma, and investigate the metformin therapeutic outcome.

Materials and Methods: Human colorectal adenocarcinoma *cell* (HT-29) and Human Umbilical Vein Endothelial (HUVEC) co-cultures were used to simulate the human enviroment. The cells were treated with increasing concentrations of Metformin (20-160 µg/ml) and incubated for 24 h (5% CO_2; 37 °C). We investigated the cytotoxic effects of metformin on HT29-HUVEC coculture cells using the MTT [3-(4,5 dimethylthiazoyl-2-yl)-2,5- diphenyltetrazolium bromide] assay for cell viability. PTEN,IP3 and miR-21 expressions were measured by Real time polymerase chain reaction. The statistical analysis was done by one-way analysis of variance (ANOVA) and Tukey's HSD test.

Results: Data obtained from the analyses with coculture cells revealed a dose response with regard to the cytotoxicity of metformin. With the increasing concentrations of metformin, cell death increased. According to Real time PCR analysis results, 80 and 160 µg/ml metformin groups PTEN expression and all of the groups PIP3 and miR-21 expressions were found to statistically significant increased,

Conclusions: Increased PTEN signaling in endothelial cells prevent angiogenesis through an reduced cell proliferation and migration. Although there was not statistically significant, an inverse correlation was found between PTEN and miR-21 levels. miR-21/PTEN/Akt signaling pathway may serve a crucial role in the molecular mechanism of metformin's effect.

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OP096: COMPARATIVE *CYSTEINE S-CONJUGATE β-LYASE* ACTIVITIES OF DIFFERENT ORGANS TOWARDS PARACETAMOL IN MICE

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Introduction: Paracetamol (acetaminophen; PAR) toxicity is a common cause of acute liver failure and it also induces acute kidney injury (1, 2). Even though studies on its toxicity have concentrated upon the mechanism of liver injury, it is increasingly paying attention to other possible adverse effects such as pulmonary, developmental, and neurological toxicity. Experimental, clinical, and epidemiological studies on these toxic effects were critically evaluated in a recently reported article (3). One of the possible mechanisms for these adverse reactions is *cysteine S-conjugate β-lyase*-mediated activation of PAR-cysteine (PAR-Cys), a breakdown metabolite of PAR-glutathione conjugate in mercapturic acid pathway. The objective of the present study is to provide data whether mitochondrial and cytosolic *β-lyase* activities towards PAR-Cys are significantly different relative to each other and whether PAR-Cys is activated to reactive intermediates by these organs.

Materials and Methods: PAR-Cys was synthesized in house as described by Stern et al., (4) and all other chemicals and reagents were obtained from local suppliers. Cytosolic and mitochondrial fractions were prepared by differential centrifugation. Activity of *β-lyase* was measured by monitoring pyruvic acid formation with an HPLC method with fluorescence detection (ex/em = 336/420 nm). Formation of reactive intermediates was screened by *N*-benzylpyridine trapping (5).

Results: The present study demonstrated that PAR-Cys serves as substrate for cytosolic and mitochondrial *cysteine S-conjugate β-lyases* in different organs. In addition, findings suggested that PAR-Cys is activated to reactive intermediates to different extents in each organ.

Conclusions: Extrahepatic toxic effects of PAR may be originated from *β-lyase*-catalysed

activation to reactive intermediates especially in kidney, where proximal tubular cells express the highest level of the enzyme and several halogenated cysteine conjugates proved to be nephrotoxic via this pathway. Finding *β-lyase* activity towards PAR suggested an explanatory mechanism for the suspected chronic adverse effects of the drug in other organs such as lungs.

Acknowledgements: This study was supported by a grant from Aliye Üster Foundation-Turkey. IBG-Vivarium Rodent Facility is acknowledged for providing animal tissues.

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OP097: SMOKING BEHAVIORS IN COVID 19: AN ONLINE SURVEY AMONG 749 UNIVERSITY STUDENTS

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Introduction: The COVID-19 pandemic has a massive impact on human health, causing sudden lifestyle changes (1). As it affects health, determining the lifestyles of university students related to smoking has gained importance. This study aims to provide evidence of change in smoking behavior among university students in Turkey during the on-going Covid-19 pandemic (2).

Materials and Methods: This cross-sectional survey study was conducted via an electronic questionnaire between 10 November and 10 December 2020 among university students in Turkey. The study comprised a structured questionnaire that inquired demographic information; and the Fagerström Test for Nicotine Dependence. The questionnaire was distributed randomly to university students; it required 6 minutes to complete.

Results: A total of 749 respondents have been included in the study, aged between 19 and 30 years (54,8% females). Of 749 participants, a total of 571 health science students (medicine, pharmacy dentist, etc) completed the survey. The pre-pandemic and Covid-19 pandemic mean nicotine dependence scores were 3,03 and 2,97, respectively. A difference was seen pre-pandemic (p=0.002) and during pandemic (p=0.005) for those studying in health departments and other departments. Students who have middle socio-economical status had significantly higher nicotine dependence scores pre-covid-19, compared to during the pandemic. (p=0.027). Compared to pre and during the pandemic, the mean score of dependence was significantly lower in students whose parents were non-smokers during the pandemic. (p=0.017). For students who had to be in quarantine due to their relatives or family members, their dependency level was significantly higher compared to pre-pandemic. (p=0.011).

Conclusions: In this study, we have provided the first data on the Turkish university student's nicotine dependence changes during the COVID 19 lockdown. The nicotine dependence level may change based on various factors including behavioral changes. Crucial times like pandemic can affect individuals, thus smoking addiction can increase. Behavioral support for quitting smoking such as digital platforms, internet, and television programs should also assist to support smokers quitting successfully during this supreme time.

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OP098: EFFECTS OF PERIOSTIN, TENASCIN-C, YKL-40, TETRAHYDROBIOPTERIN ON THE LIVER CANCER CELL LINE

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Introduction: Periostin is a matricellular protein that is secreted by cancer-associated fibroblasts (CAFs), and that promotes cancer deviation, initiation and progression (1). Tenascin-C (TNC) is an extracellular matrix (ECM) glycoprotein with anti-adhesive properties, and is expressed in human malignant neoplasms (2). YKL-40 (a chitinase-like protein) is an inflammatory biomarker produced at the disease site by various cells, including cancer cells and cancer-associated macrophages, and is associated with the pathogenesis of lung lesions (3). Tetrahydrobiopterin (BH-4) is a cofactor of the three aromatic amino acid hydroxylase enzymes, used in the degradation of amino acid phenylalanine and in the biosynthesis of the neurotransmitters (4). However, the effects of biomarkers on cancer cell lines are not yet clearly known. The aim of this study is to investigate the effects of these biomarkers on cell viability and cell proliferation in HEP3B (liver cancer cell line) cells compared to L929 (healthy fibroblast cell lines).

Materials and Methods: Cells were added in 96-well plates at $5x10^3$ cells per well. Serial dilutions for periostin; 1, 2.5, 5, 7.5, 10 ng/ml, for TNC 1, 5, 10, 20, 40 ng/, for YKL-40 and for BH-4 1, 5, 10, 20, 40 ng/ml were added respectively. All cell lines were incubated with for 24 and 48 hours. The cytotoxic activity of biomarkers on cancer and healthy cell lines was determined in vitro by the MTS (3-(4,5-dimethylthiazol-2-yl)-5-(3-carboxymethoxyphenyl)-2-(4-sulphophenyl)-2H-tetrazolium) cell viability test. Cell viability was measured at 450 nm spectrophotometrically in ELISA at the end of the 24th and 48th hours.

Results: After 48 hours, the changes in the cells were examined. Periostin exhibited a 15% cytotoxic effect on HEP3B cells at a concentration of 7.5 ng / ml and a 20% cytotoxic effect to L929 cells at all doses. TNC increased cell proliferation at all concentrations. However, it showed a 20% cytotoxic effect on the L929 cell line. YKL-40 showed a 50% cytotoxic effect on HEP3B at a concentration of 10 ng / ml compared to healthy cells. While BH-4 showed a cytotoxic effect in the L929 cell line, it increased proliferation in the HEP3B cell line.

Conclusion: As a result of this study, the effects of periostin, TNC, YKL-40, BH-4 biomarkers on the HEP3B cell line were demonstrated. Available biomarkers were first tested on cancer cell lines with our in vitro study. We found that YKL-40 significantly reduced the viability of HEP3B cells compared to L929 cells.

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OP099: EVALUATION OF ANTIOXIDANT, ANALGESIC, ANTI-INFLAMMATORY AND ANTISPASMODIC ACTIVITY AND GENOTOXIC EFFECT OF *MICROMERIA FRUTICOSA SUBSP BRACHYCALYX IN VITRO* AND *IN VIVO*

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Introduction: Today, antioxidants have been using diversely in various medical conditions. Therefore, there are growing interest for discovering and developing more effective and safer antioxidants derived from natural sources. Certain *Micromeria* species were identified as a rich source of antioxidant agents (1). This study aimed to investigate possible antioxidant, analgesic, anti-inflammatory and antispasmodic activity and genotoxicity of *Micromeria fruticosa subsp brachycalyx* in methanol extract both *in vitro* and *in vivo*.

Materials and Methods: *In vitro* antioxidant activity of the plant extract was evaluated by DPPH, ABTS, FRAP and CUPRAC assays. *In vivo* analgesic, anti-inflammatory and antispasmodic analyses performed on Balb/c mice by Formalin Test, Croton Oil Induced Ear Edema Test and Intestinal Motility Test (Marmara University Experimental Animals Research and Implementation Centre Approval Date: 05.08.2019, Number: 45.2019.mar). Myeloperoxidase levels were analyzed in mice tissues as *in vivo* oxidative stress indicator. Genotoxic effect was determined in mice blood with Comet Technique. The 8-hydroxy-2'-deoxyguanosine was analyzed in mice liver and kidney tissues with commercial ELISA kit. The statistical analyses were performed by GraphPad Prism version 8.0.0 for Windows, GraphPad Software, San Diego, California USA.

Results: The results showed that plant extract showed strong CUPRAC value, however, lower ABTS and FRAP values and DPPH radical scavenging activity versus to standards. In Formalin Test and Croton Oil Induced Ear Edema Test, the plant extract showed analgesic and anti-inflammatory activity as indomethacin. It was found that the plant extract showed its analgesic and anti-inflammatory activity by COX-1 pathway. In Intestinal Motility Test, the plant extract exerted potent antispasmodic activity as atropin. The chronic use of the plant extract showed no significant difference in MPO levels in tissue samples. The chronic use of the plant extract also showed no genotoxic effect.

Conclusions: Our study showed that *Micromeria fruticosa subsp brachycalyx* has a potential antioxidant, analgesic, anti-inflammatory and antispasmodic activity. It has also been contributed

to raise awareness to this species in terms of its safety with the obtained results. Therefore, the usage of this species as natural source is promising for new drug candidates.

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OP100: EVALUATION OF THE IN-VITRO CYTOTOXIC ACTIVITY OF SUNSET YELLOW IN ACUTE AND CHRONIC DOSING SCENARIOS

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Introduction: A synthetic anionic azo dye, sunset yellow (SY) is widely used as colorant and food additives worldwide since its ability to give different shades of orange (1). However, genotoxicity and teratogenic activities of SY, as well as developmental toxic activities and potentials of causing oxidative damage are frequently reported (2-4). In this study, it was aimed to evaluate the *in vitro* toxicological activity of SY under acute and chronic dose scenarios.

Material and Methods: For this purpose, the human TK6 and AHH1 lymphoblastoid cell lines were employed. The relative population doubling (RPD%) test was used for the determination of cytotoxic effects of SY in different dose concentrations. In the calculation of RPD% (5), cells were seed in the 6-well plate as 1 x 10^5 /mL, after counting by Neubauer hemacytometer with a reversed-phase microscope. Although the acute dosing study was performed by applying the total dose to the cells in a single time within 24 hours, chronic dosing was performed by applying the same total dose divided into fractions to the cells on 5 days. SY concentrations were optimized to 380, 760, 1140, 1520, and 1900 µg/mL in the study.

Results: In the acute study, it was clearly observed that the cytotoxic activity of SY was dose-dependent at the applied 5 dose concentrations for both cell lines. The RPD% values observed at the concentrations given above in the acute study were 87.75%, 76.48%, 74.09%, 71%, and 66.06%, respectively in the TK6 cell line. RPD% values of chronic dosing were 97.11%, 86.90%, 87.23%, 92.61% and 92.10%. In the AHH1 cell line, same concentrations' RPD% values were found as 89.12%, 76.42%, 74.04%, 72.97%, 65.66%. RPD% values of chronic dosing were 93.68%, 91.47%, 92.91%, 95.29%, 93.65%. For these concentration RPD% values, it was observed that the acute study caused an increase in cytotoxicity by 1.11, 1.14, 1.18, 1.30, and 1.40 times, respectively, compared to chronic application in TK6. As the same, the comparing of cytotoxicity acute to chronic dosing were observed as 1.00, 1.05, 1.13, 1.31, 1.51 in the AHH1 cell line.

Conclusions: The study performed in-vitro on TK6 and AHH1 cells showed that SY's cytotoxicity was dose-dependent, and it was steadily decreased with a fold change of 1.09 to 1.51 with 5 days of chronic dosing. Our laboratory studies for determining the further toxic effects of SY are still progressing.

Acknowledgements

This work was supported by The Scientific and Technological Research Council of Turkey (TUBITAK) under The Science Fellowships and Grand Programme [1919B012001095].

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OP101: THE IMPACT OF THE CYTOCHROME P450 3A4 (*CYP3A4*22*) POLYMORPHISM ON TACROLIMUS DOSE REQUIREMENTS AND EXPOSURE DURING EARLY PERIOD FOLLOWING KIDNEY TRANSPLANTATION

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Introduction: Tacrolimus (Tac) is an effective immunosuppressant used in renal transplantation (1). The clinical use of Tac is complicated by the high interindividual variability and narrow therapeutic index, which makes therapeutic drug monitoring (TDM) compulsory. However, in some cases despite TDM, patients may expose sub or supratherapeutic Tac levels and consequently experience adverse effects or graft loss (2, 3). Effective management of Tac treatment is extremely important to avoid these undesirable adverse effects. Since the CYP3A4 enzyme has an essential role in the metabolism of Tac, this study

aimed to investigate the impact of the *CYP3A4*22* rs35599367 genetic difference on Tac dose requirements and Tac blood levels of renal transplant recipients in the early period following transplantation.

Materials and Methods: A total of 302 renal transplant recipients were enrolled, blood levels of Tac were obtained by cloned enzyme donor immunoassay. Genomic DNA was isolated from whole blood by high salt method, genomic analysis performed with the use of Polymerase Chain Reaction followed by Restriction Fragment Length Polymorphism. SPSS Statistics26 was used for all statistical analyses.

Results: In the group of patients receiving similar doses of Tac (p=0.769), *CYP3A4*22* allele carriers had significantly higher (13.73%) Tac blood levels compared with *CYP3A4*1/*1* genotype patients at day 3 (p=0.014). On days 10 and 30 following transplantation, required doses of the Tac between the groups become different regarding their *CYP3A4* status, patients with *CY3A4*1/*1* genotype required 33.3% and 50% higher doses respectively to obtain target levels. The difference between genotype groups in terms of the Tac trough levels disappeared on days 10 and 30.

Conclusions: The results indicate that *CYP3A4*22* polymorphism is associated with lower Tac dose requirements and exposure to higher levels of Tac compared to *CYP3A4*1/*1* genotype patients in the early period following transplantation. *CYP3A4* genotype might be a useful pharmacogenetic indicator in explaining the interindividual differences, in the early post-transplant period. CYP3A4 genotype-based dosing strategies could be helpful for the individualization of the treatment by preventing adverse effects and organ rejection.

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OP102: A PRELIMINARY STUDY; IN VITRO ANTICANCER ACTIVITY OF PATULIN ON HEP3B AND A549 CELLS

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Introduction: Patulin (PAT) is a secondary metabolite produced by various fungi, mainly *Penicillium* and *Aspergillus*. It is generally found in apple and apple derived products (1, 2). Limited data are available on the anticancer activity of PAT in different cell lines. However, some studies have found that patulin causes apoptosis on cancer cells (3, 4). This study aims to determine the cytotoxic activity of PAT on A549 (human non-small cell lung cancer cell line) and HEP3B (human hepatoma cell lines) compared to L929 (healthy fibroblast) cells by the MTS method.

Materials and Methods: After 24 hours of incubation, increasing doses of 1, 2.5, 5, 10, 25, 50 and 100 µM of PAT were added to the cells. All cell lines were incubated with PAT for 24 and 48 hours. Cytotoxic activity of PAT on cancer and healthy cell lines was demonstrated in vitro by MTS (3- (4,5-dimethylthiazol-2-yl) -5- (3-carboxymethoxyphenyl) -2- (4-sulphophenyl) -2H tetrazolium) was determined.

Results: After 48 hours, PAT caused 74% cytotoxic activity at a concentration of 50 µM and 91% at a concentration of 100 µm in the A549 cell line. The PAT showed a 25% cytotoxic effect at a concentration of 5-10 µM and an 80% cytotoxic effect at a concentration of 50 µm in the HEP3B cell line compared to the L929 healthy cell line. However, it showed 100% cytotoxic activity at a concentration of 100 µm on both cancer cell lines. Additionally, at concentrations ranging from 1-100 µM, PAT did not show cytotoxic effects on normal fibroblast cells.

Conclusions: As a result of this study, we found that patulin significantly reduced cell growth in HEP3B and A549 cell lines. It is also an important finding that it does not show cytotoxic activity on healthy cells at the concentrations studied. Our study will be important in elucidating other cellular mechanisms.

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OP103: DIRECT PEPTIDE REACTIVITY ASSAY (DPRA) FOR MEASURING SKIN SENSITIZATION POTENTIALS OF COSMETIC INGREDIENTS

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Introduction: A testing ban of using animal tests on cosmetic ingredients has been in force in the EU since 2004, while in 2013 a marketing ban came

into force for all kinds of animal toxicity tests including skin sensitization test (1). Direct Peptide Reactivity Assay (DPRA) - an *in chemico* method - have been developed and validated for skin sensitization test and provides information on the assessment of the skin sensitization potential of chemicals (2). In our study, we aimed to set up the DPRA acording to the guideline by applying the sensitization potency known chemicals.

Materials and Methods: The standard concentrations of peptides, positive control and cosmetic ingredients (paraphenylendiamine (PPD), isoeugenol, geraniol and sodium dodecyl sulphate (SDS)) were analysed according to the OECD guideline by HPLC (Agilent 1100 on a Zorbax SB-C18 column (2.1 mm x100 mm x 3.5 micron)) with UV detection at 220 nm. Mean percent peptide depletion gives the skin sensitization potency of the chemicals regarding the haptenization activity of the chemical leads to more peptide depletion.

Results: The calibration curve was drawn according to seven different concentrations of cysteine and lysine standards. The r^2 value of standard curve was found to be 0.9977 and 0.9972 for lysine and cysteine respectively. The percent lysine and cysteine depletion was calculated by using peak areas of chemicals and found to be 90.58, 6.08, 96.2, 6.59, 99.15 and 91.16, 32.71, 99.11, 93.63, 14.16 for positive control, geraniol, PPD, isoeugenol, and SDS, the chemicals were classified acording to mean depletion as high, low, high, high and high reactivity respectively.

Conclusions: The results of our DPRA studies for sensitivity classification of cosmetic ingredients were compatible with previous *in vivo* and *ex vivo* studies' results except the irritant chemical SDS(3-5). The lysine depletion gave a false positive result. According to our results it can be suggested that cysteine depletion results are more reliable in this method whereas lysine combination model or only cysteine prediction model was also suggested acording to guideline. We conducted the DPRA according to our scope of the study and set up a validated method in our laboratory for investigating the sensitization potency of chemicals.

Acknowledgements

This study was supported by a grant of Ankara University, BAP (Project No: 19L0237003)

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OP104: THE EFFECTS OF DIFFERENT BISPHENOL DERIVATIVES ON OXIDATIVE STRESS, DNA DAMAGE AND DNA REPAIR IN RWPE-1 CELLS: A COMPARATIVE STUDY

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Introduction: Bisphenol A (BPA) is a well-known endocrine disruptor and it is widely used mainly in the plastics industry. Due to recent reports on its possible impact on health (particularly on the male reproductive system), bisphenol F (BPF) and bisphenol S (BPS) are now being used as alternatives (1). These alternative compounds have replaced on the market without proper toxicological evaluation. This may lead to inevitable human exposure to such chemicals. Considering the toxicity potentials of BPF and BPS and their high presence in the environment, the present study aimed to compare the cytotoxic, genotoxic and oxidative stress-causing potentials of these BPF and BPS chemicals to BPA in prostate cell lines (RWPE-1). Moreover, the effects of bisphenol derivatives were assessed on DNA repair proteins, particularly responsible for the Base Excision Repair (BER) pathway.

Materials and Methods: The RWPE-1 cell line was exposed to 0 to 600 µM bisphenols for 24 hours. Cell viability was determined by MTT assay. The IC20 values for each bisphenol derivative were used in the enzymatic and nonenzymatic antioxidants, namely superoxide dismutase (SOD), catalase (CAT), glutathione peroxidase (GPx) and glutathione reductase (GR), levels of glutathione (GSH) and total antioxidant levels (TAOC). Comet assay were performed to assess the genotoxicity. The BER gene expressions (Polβ, OGG-1, Ape-1, MyH) and P53 were evaluated by quantitative real-time PCR.

Results: The cytotoxicity potentials were ranged as BPA> BPF> BPS in RWPE-1 cells. All cell groups exposed to bisphenol derivatives also showed alterations in the activities of SOD, CAT, GPx and GR, as well as levels of GSH and TAOC. Lipid peroxidation levels were not changed. In the Comet analysis, all bisphenol derivatives caused significantly increases of DNA damage compared to control groups. All the bisphenol-exposed groups showed decreases in BER pathway-related proteins, p53 protein levels as well as in DNA repair proteins (OGG1, Ape-1 and MyH). All these datas suggest that BPA derivatives can also have both cytotoxic and genotoxic properties. They also alter the expression of DNA repair enzymes.

Conclusions: The results suggest that BPF and BPS, which are used as alternatives, cause adverse effects at least as much as BPA. Although 'BPA-free products' are now available, these products contain either BPS or BPF, the toxicities of which should be carefully determined before they are considered as 'safer alternatives'. This study contributes significantly to the toxicological profiles of this alternative that needs to be evaluated.

Acknowledgements

Ozge Kose is a recipient of French Government and CEA (Grenoble, France) grants and completed this work in CEA/INAC/LAN, Grenoble, France

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OP105: BIOCOMPATIBILITY OF PULP CAPPING MATERIALS ON L929 MOUSE FIBROBLAST CELLS

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Introduction: Dental care practices are now extensive throughout the world. Despite that, teeth loss is still taking place due to cavities. Teeth loss can cause psychological and speech problems as well as nutritional disorders which are a result of chewing problems. As a result of this, dental care practices are required to safeguard the oral tissues (1). To determine the biocompatibility of pulp capping materials *in vivo* and *in vitro* tests are performed. Toxicity levels of materials differ with time, most materials are toxic when they are fresh and the toxicity levels decrease with time (2). Therefore biocompatibility of capping materials is of high priority. This study evaluated the *in vitro* cytotoxic and genotoxic effects of Bio-MTA+, TheraCal, and Dermabond (2-octyl cyanoacrylate) on L929 mouse fibroblast cells.

Materials and Methods: The materials were prepared according to the manufacturer's instructions. Cells were seeded in 96 well plates with $5x10^3$ cells/100 µL media per well for MTT assay, 6 well plates with $2x10^5$ cells /2 mL media per well for comet assay,12-well plates with $2x10^5$cells/well for apoptosis assay and cells were exposed to the material eluates. The cell viability, genotoxicity and apoptotic status were evaluated by MTT, Comet and Apoptosis assays respectively at three different times (24h, 1w and 2w). Flow cytometry was used to determine the apoptotic status of L929 cells exposed to material eluates.

Results: There was no statistically significant difference ($p>0.05$) between Bio MTA+ and Dermabond at 24 h, 1w and 2w exposures. However, TheraCal LC significantly reduced the cell viability at 1w exposure 66.70% ($p<0.05$). TheraCal caused DNA damage at all exposures and there was a statistically significant difference ($p<0.05$). According to flow cytometry results, TheraCal at 24-hour and 1-week showed significantly higher cytotoxic effects compared to Bio MTA and Dermabond. No significant differences were detected between Bio MTA and Dermabond.

Conclusion: As observed from the current study it can be concluded that Bio MTA and Dermabond are biocompatible capping materials in vital endodontic treatments. Since TheraCal exhibited cytotoxic and genotoxic effects caution should be exercised when it is being used.

Acknowledgements

This study was fully supported by Ankara University Research Fund, Ankara, Turkey; Project Number: 19B0237001.

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OP106: EVALUATION OF IN VITRO CYTOTOXIC ACTIVITY OF HYDROXYCHLOROQUINE

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Introduction: Hydroxychloroquine (HCQ) is an anti-malarial medication that has been utilized as treatment for a variety of autoimmune diseases, such as rheumatoid arthritis, systemic lupus erythematosus, and other inflammatory and dermatologic conditions (1). It is also reported to be used for the treatment of the COVID-19 pandemic (2). However, hydroxychloroquine has been reported to have very serious toxic effects, especially on the cardiovascular system (3). In this study, it is aimed to conduct an *in vitro*-based research in order to determine the cytotoxic activity of hydroxychloroquine with different dosing methods.

Material and Methods: In this study, a human TK6 lymphoblastoid cell line was used. The relative population doubling (RPD%) test was used to determine the cytotoxic effects of HCQ at different dose concentrations. In the calculation of RPD%, OECD's guideline numbered 487 was used (4). Cell were cultured at 5% CO_2 and 100 % humudity in the 6-well plate. The cell counting operations was carried out by a neaubeaur style heamocytometer with a reversed phase mycroscope. Acute and chronic dosing applications were carried out in 3 replicate experiments for each dose concentration of HCQ. Although the acute dosing study was performed by applying the total dose to the cells in a single time within 24 hours, chronic dosing was performed by applying the same total dose divided into fractions to the cells on 5 days. After the preliminary tests to determine the correct dose concentrations to be used in the experiment, 20, 40, 60, 80, and 100 µM HCQ concentrations were used in the study.

Results: First of all, both in acute and chronic study, it was clearly observed that the cytotoxic activity of HCQ was dose-dependent at the applied 5 dose concentrations. The RPD% values observed at the concentrations given above in the acute study were 98.84%, 75.22%, 71.52%, 38.20% and 25.47% respectively. Chronic dosing RPD% results were observed as 96.36, 89.65, 77.62, 28.18, and -24.39. At these concentration values, it was observed that the acute study caused increasing cytotoxicity by 8.97%, 13.71%, 17.81%, 26.92%, and 40.28%, respectively, compared to chronic application.

Conclusions: The study performed *in-vitro* on TK6 cells showed that HCQ was cytotoxic in a dose-dependent and and 5 days of chronic dosing resulted in a very clear increase in toxicity relative to acute dosing. Our laboratory studies are still ongoing to elucidate the mechanism behind this unexpected toxic activity of HCQ.

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This work was supported by The Scientific and Technological Research Council of Turkey - (TUBITAK) under The Science Fellowships and Grand Programme [1919B012001095].

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OP107: GENISTEIN AND 5-FLUOROURACIL ENHANCES TRAIL MEDIATED APOPTOSIS VIA INHIBITION OF XIAP AND DCR1 IN SW480 CELLS

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Introduction: Cancer causes more deaths than heart diseases and colorectal cancer is one of the most common cancers (1). However, surgical intervention and chemotherapy provide limited benefit in the recovery and survival of patients. The most important factors in not seeing the expected treatment efficacy are the drug resistance of patients and the need for targeted treatment that can reduce side effects. In order to increase the efficacy of colorectal cancer treatment, it was investigated that the exposure effects of SW480 colon adenocarcinoma cells to genistein with known anticancer effects, 5-fluorouracil, which is the basis of chemotherapy, and Tumor Necrosis Factor (TNF) - Related Apoptosis Inducing Ligand (TRAIL) which is the mediator of apoptosis

Materials and Methods: The cytotoxic effects of these compounds were determined by MTT assay, comet assay were used for genotoxic effects and apoptotic effects were evaluated by RT-PCR assay, also using assay kits of Annexin V FITC, mitochondrial membrane potential, caspase 3, 8 and 9 activity and reactive oxygen species.

Results: According to our results, genistein, 5-fluorouracil and TRAIL had synergistic apoptotic effects via DR5 upregulation. Also, their double and triple combinations caused ROS production and DNA damage mediated increased caspase 3,

8 and 9 activity and decreased mitochondrial membrane potential.

Conclusions: The combination of genistein, 5-fluorouracil and TRAIL had synergistic apoptotic effects in SW480 cells. However, further studies are needed to incorporate the project materials into colorectal cancer treatment.

Acknowledgements

This study was supported by a grant of The Scientific and Technological Research Council of Turkey (Grant number: 219S200) and Hacettepe University Scientific Research Projects Coordination Unit (Project Number: TDK-2019-18077).

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OP108: POSSIBLE EFFECT OF CHELATION TREATMENT ON METABOLOMIC AND LIPIDOMIC ANALYSIS IN LEAD EXPOSURE

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Introduction: Lead is a widely preferred heavy metal in the industry due to its useful physicochemical properties and it has important toxic effects in biological systems such as hematopoietic, renal, reproductive, and central nervous systems (1,2). The present study was designed to investigate the possible influence of chelation treatment on metabolomic and lipidomic profile.

Materials and Methods: Heparinized blood and urine samples were collected from occupationally lead exposed workers (age 36±7.6 years, n=42) before and after chelation therapy. Consent was obtained from 42 individuals diagnosed with lead poisoning and two different blood samples and urine were collected before and after chelation therapy. Oxysterol derivatives formed by autoxidation 7-ketocholesterol (7-KC), 3β, 5α, 6β trihydroxy cholestane (triol) and S1P levels were analyzed by LC-MS/MS. Metabolomic analyzes were performed with GC-MS/MS.

Results: 7-KC and triol levels before chelation were measured as 37.35 ± 2.53 ng/ml and 41.81 ± 2.54 ng/ml while after chelation they were 22.91 ± 4.49 ng/ml and 17.64 ± 3.42 ng / ml, respectively ($p < 0.001$). S1P levels were measured as 60.76 ± 15.03 ng/ml before chelation and 48.79 ± 10.75 ng/ml for afterwards. In addition, pathway analysis was made using the metabolites determined in the metabolomic studies. The results showed that important pathways such as aspartate, glutamate, homocysteine metabolisms, mitochondrial electron transport chain, as well as sphingolipid metabolism and linolenic and linoleic acid metabolism pathways were affected.

Conclusions: In the experiments, it was determined that the chelation treatment reversed the increased cholesterol auto-oxidation when compared before and after chelation treatment, and S1P levels decreased with chelation treatment. The metabolomics data obtained also revealed changes in many metabolite profiles with which lipid pathways are related, and it was concluded that it is necessary to carry out large-scale lipidomic studies by increasing the number of patients in the future. This is also the first pilot study related to lead toxicity was evaluated with all its parameters.

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OP109: MALE REPRODUCTIVE SYSTEM TOXICITY OF DI (2-ETHYLHEXYL) PHTHALATE: A COMPARISON IN TERMS OF EXPOSURE TIME AND ROUTE

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Introduction: Di(2-ethylhexyl) phthalate (DEHP) is a common used plasticizer having endocrine disruptor properties and also known as toxic to male reproductive system. It is possible to be exposed in all periods of life through many routes.

Recent studies indicate that toxicity due to exposure during fetal period, lactation, childhood and puberty may be enhanced when compared to adulthood. Moreover, these toxic effects may be permanent and cause lifelong outcomes. Therefore, we aimed to compare the results of our two different studies related to DEHP toxicity (Study A and Study B) from the perspective of "the timing makes the poison".

Materials and Methods: In Study A, Sprague-Dawley pregnant rats were exposed 30 mg/kg/day DEHP during pregnancy and lactational period. Male offspring from each mother were euthanized by cardiac exsanguination under deep anesthesia. In Study B, male Sprague-Dawley rats were exposed to same dose of DEHP from postnatal 21-23. day (after weaning) until the end of puberty (37 days) and euthanized in the postnatal 10. week. In both studies; body, testis and epididimis weight, sperm count, motility and morphology, tissue histopathology, apoptosis, the levels of total glutathione (GSH) and lipid peroxidation (MDA) were measured and compared to control groups of each study.

Results: In both study, histopathological examination showed that, 30 mg/kg DEHP causes testicular tissue damage. The comparison of other parameters in both studies is shown in Table 1.

Table1. Comparison of the results in both study.

	STUDY A *(Prenatal and Lactational Exposure)*	***STUDY B*** *(Prepubertal and Pubertal Exposure)*
Body weight	↑*	↔
Testicular weight	↑*	↔
Relative epididimis weight	↑*	↓*
Sperm count	↓*	↔
Sperm motility	↓*	↔
Abnormal sperm (%)	↑*	↑*
Apoptotic testicular cell count	↑*	↑*
GSH level	↔	↔
MDA level	↑*	↑*

* Indicates statistically significant difference compared to the control ($p < 0.05$).

Conclusions: Our results suggested that the toxicity of DEHP on male reproductive system may differ according to the route and the time of exposure and the effects of prenatal exposure to DEPH can be more pronounced.

Acknowledgements

These studies were supported by the Academic Member Training Program (OYP) of The Council of Higher Education (YOK) of Turkey, Hacettepe Research Fund (Project No: THD-2017-12150), Lokman Hekim University Scientific Research Projects Coordination Unit (Project No: 20K00301) and the Scientific and Technological Research Council of Turkey (TUBITAK) under 2214-A program.

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OP110: HEPATOPROTECTIVE EFFECTS OF *VACCINIUM MYRTILLUS* AGAINST APAP-INDUCED LIVER INJURY IN HEPG2 CELLS

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Introduction: Paracetamol (APAP) is one of the most popular medications used for the relieving mild and moderate pain. It is considered as a clinically safe in therapeutic doses. However, overdose of APAP can cause hepatotoxicity (1). *Vaccinium myrtillus* are a rich dietary source of different phytonutrients, including anthocyanins, which contribute significantly to their antioxidant capacity and have a wide range of biological activities. These include protection against oxidative stress, inflammatory responses and several degenerative diseases (2).

Materials and Methods: 2,2-diphenyl-1-picrylhydrazyl (DPPH) free radical scavenging and cupric reducing antioxidant capacity (CUPRAC) were used to determine antioxidant activity of *Vaccinium myrtillus* extracts. The *in vitro* hepatotoxicity of APAP and the hepatoprotective effect of the extracts were evaluated by measuring cell viability and oxidative stress parameters such as glutathione (GSH), and malondialdehyde (MDA) levels.

Results: The IC50 values for DPPH radicals with fruit and leaf extract of the *Vaccinium myrtillus* were found to be, 0.72 ± 0.02% and 0.41 ± 0.03%, respectively. 1 mg/mL of fruit extract (152.95 ± 1.56 µg/mL) and leaf extract (67.18 ± 1.69 µg/mL) showed the strong activity in the CUPRAC assay. The MTT assay results showed a significant recovery in cell viability (approximately 41%) with *V. myrtillus* pretreatments compared to 15 mM APAP treated cells. In addition, *V. myrtillus* pre-treatment exerted significant increase in the GSH level and decrease in MDA level.

Conclusions: Our results suggest that *V. myrtillus* may be a potential therapeutic agent to attenuate APAP-induced liver damage and its associated diseases. In future studies, the hepatoprotective properties of *V. myrtillus* against APAP will be investigated by measuring the AST, ALT, SOD and

CAT activity. Additionally, HPTLC analysis of the *V. myrtillus* extracts will be performed.

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OP111: TAMOXYFEN AND SODIUM THIOSULPHATE THERAPEUTIC EFFECT IN RATS WITH LIVER DAMAGE CAUSED BY EXPERIMENTAL *Xanthium strumarium* POISONING

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Introduction: *Xanthium strumarium* causes severe liver damage in humans and many animal species. The toxic compound atractyloside (ATR) in tissues causes cell death by preventing oxidative phosphorylation in tissues, creating an energy crisis, causing oxidative damage and mitochondrial dysfunction (mPTP opening). Sodium thiosulfate is a liver booster as a sulfur source and tamoxifen is a mPTP blocker. The aim of this study is to determine the possible protective effects of sodium thiosulfate and tamoxifen in rats with liver damage by *X. strumarium*.

Materials and Methods: Classical histopathology was performed on the tissue samples taken at the end of the study. Biochemically, AST, ALT, ALP, LDH, CK, BUN, creatinine and glucose levels were measured in the blood. MDA, GSH and SOD analyzes were performed on tissue samples. The Ca^{+2} level and the opening rate of the mPTP channels in the mitochondria isolated from the tissues were determined.

Results: The application of plant extract increases blood biochemistry parameters, decreases glucose level; increases MDA levels in tissues; on the other hand, it was determined that it decreased GSH levels and SOD activities. It increases mitochondrial $Ca+^{2}$ level and mPTP opening rate; ın histopathological examinations, it was determined that it caused the death of necrotic cells. All treatment group also brought blood biochemistry parameters closer to normal values with oxidative stress. It was observed that ATR+TAM and ATR+TAM+STS treatment groups had a curative effect on mitochondrial Ca^{+2} increase and mPTP opening, but the ATR+STV group did not. It was determined that all three treatment groups were effective in preventing pathological damage, especially the ATR+TAM+STS.

Conclusions: The study aimed to develop an antidote to be used in poisoning due to *X. strumarium*, and as a result, strong findings were obtained confirming that TAM and STS can be used as effective antidotes in ATR toxicity.

Acknowledgements

This study was conducted with an individual budget.

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OP112: DETERMINATION OF THE ELECTROCHEMICAL BEHAVIOUR OF AN ANTICANCER DRUG IN PHARMACEUTICAL AND BIOLOGICAL SAMPLES

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Introduction: Axitinib (AXT), a second-generation targeted drug, is a potent and selective inhibitor of VEGFR tyrosine kinase. AXT, also used in combination therapies, is an approved drug molecule used in the treatment of advanced kidney cell cancer (1). The present study aims to develop fast, selective, and sensitive methods for determination of AXT at low concentrations, in pharmaceutical dosage forms, human serum, and urine samples, and to investigate the electrochemical behavior of AXT on GCE surfaces using cyclic (CV) and adsorptive stripping differential pulse voltammetry (AdSDPV) methods.

Materials and Methods: All materials used in the experiment were used directly without much processing. The stock solution of 1.0 mM AXT was prepared in methanol. Standard solutions used in calibration curves were prepared by diluting from the stock solution with the selected supporting electrolyte containing 20% methanol. For electrochemical measurements, different buffers such as sulfuric acid (pH 0.3-1.0), phosphate buffer (pH 1.5-8.0), acetate buffer (pH 3.7-5.7), and Britton-Robinson (BR) buffer (pH 2.0-8.0) were

employed and prepared with double distilled water. Electrolyte solutions, standard and stock solutions of all other compounds were kept in a 4 °C refrigerator.

Results: AXT provided an irreversible oxidation peak at a potential of 0.976 V versus Ag/AgCl electrode in pH 2.0 BR buffer. Under optimal experimental conditions, AdSDPV was used for the determination of AXT. AdSDPV methodology was proposed for the sensitive determination of AXT in a linear concentration range from 80 nM to 2.0 µM, with a detection limit of 1.11 nM and a good repeatability (RSD of 0.815 %). The developed methods were applied to analysis of the human urine, synthetic serum samples and tablet dosage form with the recoveries 100.02%, 99.68%, and 103.67%, respectively. Interfering agents were considered using the calibration equation of bulk form that gave a relative error of less than ±12% except for ascorbic acid, dopamine, uric acid.

Conclusions: The proposed sensors were utilized for quantification of AXT in pharmaceutical dosage forms and biological samples with excellent recovery and precision results. The response time for sensing, environmentally friendly, simplicity of sample pre-treatment is the advantage of developed methods.

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OP113: VOLTAMMETRIC DETERMINATION OF EPIRUBICIN BY A MODIFIED GLASSY CARBON ELECTRODE

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Introduction: Cancer, one of the most serious health problems, is a group of heterogeneous diseases that can affect almost any part of the body. According to World Health Organization, cancer is the second leading cause of death globally. Epirubicin (EPI) is an anti-cancer drug belong to the anthracyclines, one of the most effective anti-cancer agents. In this work, fabrication of a Fe_3O_4-$CuBi_2O_4$-MoS_2 based electrochemical sensor and development of a voltammetric method, using the Fe_3O_4-$CuBi_2O_4$-MoS_2 based sensor as a working electrode, for EPI determination was aimed.

Materials and Methods: The electrochemical characterization of the sensor was carried out by cyclic voltammetry (CV). The electrochemical behavior of EPI was investigated by DPV.

Results: Electrochemical behavior of EPI was investigated by CV and well-defined oxidation and reduction peaks were observed at 578.6 mV and 341.8 mV, respectively. Modification of the glassy carbon electrode surface caused an increment at the anodic peak current. The pH of the supporting electrolyte was optimized as 5. It was observed that the occurring reaction at the electrode surface is controlled by adsorption besides diffusion. The accumulation potential and accumulation time were optimized as -0.2 V and 30 s, respectively. Under the optimized condition, the linear working range was defined between 0.1 µM and 2.5 µM. The related regression equation is I_{pa} = 0.9615 C_{EPI} – 0.067 (R^2 = 0.9907) with LOD values of 0.029 µM. The repeatability and reproducibility of the sensor were investigated by recording DPVs of EPI 10 times with the same electrode and with 6 different electrodes, respectively, and the RSDs were found as 2.03% and 2.47%, respectively. The selectivity of the sensor towards EPI was investigated in the presence of 100-fold excess of different interferents and the maximum change at the signal was 5.24%.

Conclusions: Herein, an electrochemical sensor based on Fe_3O_4-$CuBi_2O_4$-MoS_2 was fabricated and a sensitive and selective electroanalytical method was developed for the determination of EPI. The electrochemical characterization of the sensor and optimization of the method was carried out with satisfactory results. Based on the obtained data, it can be said that the developed sensor and method are very promising for EPI analysis.

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OP114: IN VITRO DNA AND BSA INTERACTION OF ANTIVIRAL DRUG TENOFOVIR BY SPECTRAL METHODS

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Introduction: Tenofovir, (TEN), [(2R)-1-(6-aminopurin-9-yl) propan-2-yl]oxymethylphosphonic acid) is an adenine analog with antiviral activity against the human immunodeficiency virus (HIV) and hepatitis B (1). DNA plays a vital role in cellular progression such as transcription, translation, and replication and thus, is the most significant target for pharmaceuticals. Binding of small molecules to the DNA may cause inhibit or change the DNA function. Similarly, many drugs and bioactive small molecules bind reversibly to albumin. Binding of drugs to plasma protein assumes great importance

since it influences their pharmacokinetic and pharmacodynamics properties. Therefore, the investigation of drug-DNA/BSA interaction is needed for a better understanding of the mechanism of drug action and pharmacokinetic behavior. The main aims of this study were to explore the mechanism of TEN-DNA/BSA interactions using UV–VIS and fluorescence spectroscopic techniques.

Materials and Methods: Stock solutions of TEN, DNA, BSA, and phosphate buffer (0.01 M, pH 7.4) were prepared in deionized water and kept in the refrigerator. A Varian Cary Eclipse spectrofluorimeter and Specord 50 Plus spectrophotometer with a 10 × 10 mm quartz cuvette was used for the fluorescence and absorption measurements.

Results: It was observed that the absorption of DNA and BSA increased upon the addition of TEN. The maximum peak positions of TEN-DNA/BSA were shifted slightly towards lower wavelength. The fluorescence of BSA regularly decreased and slightly blue shift was observed with the increasing concentration of TEN, indicating that TEN interacted with BSA and quenched its intrinsic fluorescence. The binding constant of TEN to DNA and BSA were 1×10^4 M^{-1} and 3×10^4 M^{-1}, respectively, and number of binding site to BSA was approximately equal to 1.

Conclusions: The binding of TEN to ds-DNA and BSA resulted in significant changes in spectral characteristics. The fluorescence emission of BSA was efficiently quenched, which indicated that TEN could interact directly with BSA.

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OP115: A SIMPLE AND SENSITIVE ELECTROANALYSIS OF NILOTINIB IN BIOLOGICAL SAMPLES IN THE PRESENCE OF SODIUM LAURYL SULPHATE

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Introduction: Nilotinib (NLT), is a selective inhibitor of tyrosine kinase breakpoint cluster region-Abelson murine leukemia (Bcr-Abl). Therapeutic drug monitoring of NLT is a significant tool for the administration of chronic myelogenous leukemia patients; thereby its sensitive determination in human serum is of paramount importance. Sodium lauryl sulfate (SLS), is an anionic surfactant that is a synthetic organic compound of amphiphilic structure composed of an anionic organosulfate attached to a sulfate group. In this study, the adsorptive stripping square wave (AdSSW) voltammetric method developed for the sensitive determination of NLT in the presence of SLS on a glassy carbon electrode. The electrochemical sensor applied to the quantification of NLT in human serum and urine.

Materials and Methods: Electrochemical measurements were performed using a PalmSens equipment with software PSTrace 5.7. The stock solutions of 1.0×10^{-3}M NLT were prepared in methanol. The different supporting electrolytes; 0.1 M sulphuric acid, acetate buffer (pH 3.6–5.6), phosphate buffer (pH 2.0, 3.0 and pH 6.0–8.0) and Britton-Robinson buffer (BR, 0.4 M, pH 2.0-10.0) used for the effect of different pH values.

Results: The effect of SLS concentration, pH, scan rate, deposition potential and time, SWV parameters on NLT signals were performed, The cyclic voltammograms proved that electrochemical behavior of NLT showed irreversible and diffusion-adsorption controlled oxidation processes in 0.1M H_2SO_4. The concentration effect of surfactant on the first and second peaks of NLT was examined. Depending on whether the surfactants are monomer or monolayer hemimicelle structure, they can be attracted to amine moieties at related points in NLT structure through the electrostatic interaction. The sensitivity of the method was markedly enhanced in the presence of SLS. Under optimum conditions, NLT can be determined in the concentration range of $2.0x10^{-8}$ and $2.0x10^{-6}$M for human serum, $4.0x10^{-8}$ and $2.0x10^{-6}$M for human urine by AdSSWV in 0.1M H_2SO_4 containing 2.0 x 10^{-7} M SLS.

Conclusions: A simple, highly sensitive, precise and accurate voltammetric method was described for quantification of NLT in human serum and urine samples that does not require any pre-processing include sample pre-treatment, time-consuming extraction and evaporation steps.

OP116: DEVELOPMENT OF A NEW HPLC METHOD FOR THE DETERMINATION OF MESALAZINE IN HUMAN PLASMA AND APPLICATION TO A PHARMACOKINETIC STUDY

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Introduction: Mesalazine (5-Aminosalicylic acid, 5-ASA) is the most commonly used drug for the treatment of inflammatory bowel disease. In order to avoid the toxic effects of sulphasalazine, the actual tendency is to use formulations of olsalazine or 5-ASA. Although 5-ASA is considered relatively safe and effective drug, a number of renal side effects have been reported (1-3).

Materials and Methods: In this study, a new, fast and sensitive HPLC-FL method for the determination of mesalazine in human plasma was developed, validated and applied to a pharmacokinetic study. The sample preparation stage consists of the liquid-liquid extraction of plasma samples. Mesalazine was precolumn derivatized with NBD-Cl (7-chloro-4-nitrobenzofurazan), and the fluorescent derivate was separeted on C18 (150 × 4.6 mm × 2.6 µ) analytical column with 0.1 % o-phosphoric acid in water and acetonitrile as mobile phase with isocratic elution with flow rate of 1 mL min^{-1}. The method was based on the measurement of the derivative using fluorescence detection (λ_{ex}= 280 nm / λ_{em}= 325 nm).

Results: The calibration curve was linear over the range of 0.25-1.5 µg/mL with correlation coefficient is more than 0.9997. LOD and LOQ were found to be 0.075 and 0.25 µg mL^{-1}, respectively. Intraday and interday RSD values were less than 5.92%. The developed method was validated according to ICH guideline and the validate method applied to a prototype pharmacokinetic assay by ethical committee approval (4). The plasma concentration-time profile and pharmacokinetic parameters such as AUC_{0-t}, $AUC_{0-\infty}$, C_{max}, t_{max}, $t_{1/2}$, were calculated according to the proposed method.

Conclusions: The presented HPLC-FL method is sensitive, cost effective and reproducible. The retantion time of the drug substance is about 3.08 min, which shows the duration of the analyse is very short. The presented method can certainly be used for bioequivalence and bioavailability investigations and routine analysis of the drug in plasma.

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OP117: COMPARATIVE HPLC-PDA AND LC-MS/MS APPROACHES OSBs LEVELS OF SIMULATED ARTIFICIAL BODY FLUIDS AND SIGNIFICANCE OF RAW DATA FOR CHEMOMETRIC DISCRIMINATION OF OSBs

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Introduction: Oxidative stress (OS) may be quantified accurately by measuring levels of DNA/RNA damage, lipid peroxidation, and protein oxidation/nitration, through oxidative stress biomarkers (OSBs) rather than targetting reactive oxygen species with pretty short half-life (1). Our aim was to develop and validate two liquid chromatographic methods for simultaneous determination of a group of OSBs in a group of simulated artificial body fluids, while performing principle component analysis (PCA) of raw MS/MS data for discrimination of OSBs.

Materials and Methods: 2'-deoxyadenosine (2dA), 2'-deoxycytidine (2dC), 2'-deoxyuridine (2dU), 3-nitro-L-tyrosine (3NLT), 5-hydroxymethyl uracil (5HMU) and 8-hydroxy-2'-deoxyguanosine (8OHdG) were model OSBs. Liquid chromatographic measurements were proformed with Thermo Dionex Ultimate 3000 series HPLC-PDA and Thermo Scientific TSQ Quantum Access Max series LC-MS/MS system. Chemometric analysis were done by Minitab 20.2 software.

Results: HPLC-PDA and LC-MS/MS methods were linear for $1.0x10^{-6}$ – $1.0x10^{-4}$M and $1.0x10^{-8}$ – $1.0x10^{-6}$M concentration ranges, respectively. Methods were validated according to ICH Q2(R1) guideline. Specificity, linearity, range, accuracy, precision, reproducibility, LOD, LOQ and recovery parameters were achieved.

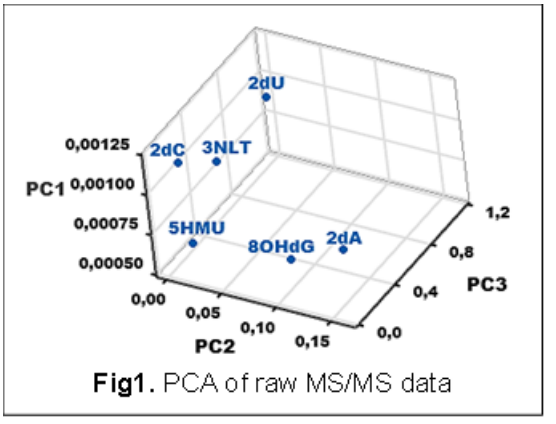

Fig1. PCA of raw MS/MS data

Conclusions: To our best knowledge there is no paper on the simultaneous determination of the very same OSBs in various simulated body fluids

with two different methods and performing PCA analysis of raw data for discrimination of OSBs. Thus the findings will make a contribution to literature. Furthermore these methods may be applicable to clinical studies to examine OS patterns in various pathophysiological phenomena.

Acknowledgements

This study was supported by a grant of Ege University Department of Scientific Research Projects (BAP, Project numbers: 2014-TIP-086 and 16/ECZ/022).

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OP118: DESIGN OF A NOVEL NANOSENSOR FOR THE DETERMINATION OF CARDIAC INOTROPE DRUG MILRINONE

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Introduction: Milrinone (MIL) is cardiac inotrope drug widely used in congestive heart failure. Several chromatographic methods have been reported for determination of milrinone since 2005 (1). Electrochemical sensors have some extraordinary features such as rapidty, easy preparation, suitability to miniature chip technology. Furthermore, working electrodes can be modified with various nanomaterials thanks to major advancements in nanotechnology. The aim of this study is electrochemical detection of milrinone using flower-like zinc oxide (ZnO) modified nanodiamond decorated carbon paste electrode (ZnO/nD@CPE) in pharmaceutics and biological samples.

Materials and Methods: In order to modify CPE, graphite powder and diamond nanoparticles were mixed well to get a uniform mixture. Then, mineral oil was added, and the mixture was mixed with mortar and pestle to get a soft paste. ZnO/nD@CPE was prepared by dropping an optimized amount of ZnO suspension onto the nD@CPE surface and drying. Electrochemical measurements were performed with differential pulse voltammetry (DPV). The general morphologies of the modified electrode surfaces were characterized by SEM and IR spectroscopy. Electrochemical characterization of ZnO/nD@CPE was performed cyclic voltammetry (CV) and electrochemical impedance spectroscopy (EIS) techniques.

Results: The effect of key parameters such as modifying agent amount, dropping volume, pH of buffer solution, and scan rate was studied and optimized to achieve the best response for the electrochemical behavior of the MIL. ZnO/nD@CPE increases MIL electrochemical oxidation signals ~5 fold compared to CPE. Therefore, ZnO /nD@CPE has been chosen as the most suitable surface for MIL detection. In the linear range from 6 x 10^{-7} to 1 x 10^{-5} M, the limit of detection (LOD) was found as 1.42 x 10^{-7} M using ZnO/nD@CPE. Furthermore, the developed ZnO /nD@CPE exhibited excellent linearity from 6 x 10^{-7} to 1 x 10^{-5} M in the serum and from 8 x 10^{-7} to 1 x 10^{-5} M in the urine. LODs were found as 1.23 x 10^{-7} M and 2.86 x 10^{-7} M, in the serum and urine samples, respectively.

Conclusions: A novel nanosensor was developed for the determination of MIL in pharmaceutics and serum samples. Sensitive detection of the MIL was performed for the first time using an electrochemical method. Electrode conductivity for sensing was substantially changed by modifying ZnO with flower structure to nD@CPE surface. The determination of MIL in bulk, ampoule, human serum, and urine samples was successfully performed by the DPV method.

Acknowledgements

The authors would like to thank VEM İlaç San. ve Tic. A.Ş, (Istanbul, Turkey) for chemical substances and their pharmaceutical dosage form support.

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OP119: ASSESSMENT OF ANTIOXIDANT AND ANTICANCER ACTIVITIES OF *ACHILLEA PHRYGIA* EXTRACT LOADED CHITOSAN NANOPARTICLES

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Introduction: The aim of this research was to prepare a chloroform extract of *Achillea phrygia* and test its antioxidant and cytotoxic properties. Then, on the most effective extracts, nanoparticles (NPs) were synthesized, and the biological activities of the free forms of the extracts were compared to the NPs forms.

Materials and Methods: Antioxidant, and cytotoxic activities of eight fractions (from A to H) obtained using column chromatography from *A. phrygia* chloroform extract, which was found to have a stronger effect than methanol extract in MCF-7 cell line, were evaluated. Antioxidant capacities of the extracts were found by FRAP, DPPH and CUPRAC methods. The cytotoxic activities of all fractions were evaluated on MCF-7 and HT-29 cell lines using the XTT cell viability assay (1). Then, NPs were prepared with most active fraction by combining with chitosan using the ionic gelation method (2).

Results: The results showed that the B fraction exhibited the strongest antioxidant activity with significantly higher ($p < 0.05$) DPPH radical scavenging activity (IC_{50} 0.399±0.091 mg/mL), CUPRAC (1.713±0.065 mMTE/mg analyte) and FRAP results (40.984±0.201 mM$FeSO_4$/mg analyte) than the other fractions. In cells treated with B extract, the cell viability of HT29 and MCF7 cells were found as 56.338 ± 1.220 and 64.764 ± 1.368, respectively.

Conclusions: When looking at both antioxidant and cytotoxic activity results, B extract showed more effect than the others. While the antioxidant activity of chitosan NPs was close to the unencapsulated extracts, the anticancer activity gave better results. This finding shows that NPs made from chloroform extract may be useful in preclinical and clinical cancer research.

Acknowledgement

This study was supported by a grant of TUBITAK (SBAG-116S509)

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OP120: ELECTROCHEMICAL ANALYSIS OF DAPAGLIFLOZIN USING BORON-DOPED DIAMOND ELECTRODE

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Introduction: Diabetes is a disease with a high level of glucose in the blood. Sodium Glucose Transporter İnhibitors 2 (SGLT2), glyphosins, are used to treat Type 2 Diabetes (T2D). Dapagliflozin (DPG) is a glyphosins and using as an antidiabetic drug by acting on the sodium inhibitor of glucose co-transporter (1). The present study aims to develop fast, selective, and sensitive electroanalytical methods for the determination of DPG at low concentrations, in pharmaceutical dosage forms, human serum, and urine samples, and to investigate the electrochemical behavior of DPG on the boron-doped diamond electrode (BDDE) surfaces using cyclic (CV) and differential pulse voltammetry (DPV) methods.

Materials and Methods: All materials used in the experiment were used directly without much processing. The stock solution of 1.0 mM DPG was prepared in methanol. Standard solutions used in calibration curves were prepared by diluting from the stock solution with the supporting electrolyte containing 20% methanol. For electrochemical measurements, different buffers such as sulfuric acid (0.1 and 0.5 M), phosphate buffer (pH 1.5-8.0), acetate buffer (pH 3.7-5.7), and Britton-Robinson (BR) buffer (pH 2.0-8.0) were used. All buffers and solutions were prepared with double-distilled water.

Results: DPG provided an irreversible oxidation peak at a potential of 1.18 V versus Ag/AgCl electrode in 0.1 M H_2SO_4. Under optimal experimental conditions, DPV was used for the determination of DPG. DPV methodology was proposed for the sensitive determination of DPG in a linear concentration range from 0.6 µM to 80.0 µM, with a detection limit of 0.0147 µM and good repeatability (RSD of 1.36 %). The developed method was applied to the analysis of the human urine, synthetic serum samples, and tablet dosage form with the recoveries 102.63%, 102.68%, and 99.21%, respectively. The impact of common interfering compounds (ascorbic acid, dopamine, paracetamol, glucose, etc.) on the electrochemical response of DPG was investigated for selectivity of the method.

Conclusions: The proposed sensors with BDDE were utilized for the quantification of DPG in pharmaceutical dosage forms and biological samples with excellent recovery and precision. The method does not need any sample treatment process or an expensive analytical instrument.

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OP121: A NOVEL DESIGN OF GRAPHENE-BASED ELECTROCHEMICAL NANOSENSOR FOR THE DETECTION OF ANTIMETABOLITE ANTICANCER AGENTS

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Introduction: Anticancer drugs show a high cytotoxicity on both healthy and cancerous cells due to their low selectivity during the chemotherapy, and this situation leads to the crucial side effects in human body. To control the side effect level in the body, an amount of the anticancer drug in biological samples should be periodically analyzed. Herein, electrochemical approaches using novel nanomaterials have attracted great attention to detect the drug molecules in clinical or pharmaceutical samples (1, 2). Graphene, a two-dimensional (2D) carbon allotrope, is a strong candidate to construct a sensitive electrochemical sensor due to its excellent electronic, chemical and physical property (3, 4). The aim of this study is to develop a sensitive and selective electrochemical sensor using graphene for the detection of antimetabolite anticancer agents in clinical samples.

Materials and Methods: Graphene nanosheets (GNs) in a bulk form were synthesized from graphite by a novel chemical approach. The synthesized GNs was modified onto the screen-printed electrode (SPE) to fabricate the portable sensing platform (GNs/SPE).

Results: In this study, we developed a graphene-based electrochemical sensing platform for the detection of antimetabolite anticancer agents in human serum samples. The synthesized GNs were characterized by Raman spectroscopy, x-ray photoelectron spectroscopy and transmission electron spectroscopy. The electrocatalytic activity of GNs/SPE was tested by cyclic voltammetry in a redox probe solution. The fabricated GNs/SPE showed a good electrochemical performance with a low detection limit towards the antimetabolite anticancer agent under optimal conditions.

Conclusions: As a conclusion, the developed GNs/SPE could be alternative analytical approach for the detection of electroactive antimetabolite anticancer agents in clinical samples.

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OP122: POLY (HPBAs) FOR VOLTAMMETRIC DETERMINATION OF FLUORIDE IN DENTAL FORMULATIONS (DFs); PCA APPROACH

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Introduction: Hydroxyphenylboronic acids (HPBAs) form stable complexes with fluorides (F^-) (1). Aim of this work is to investigate hydrolytic stability of HPBAs on the related substitutions and focus on electropolymerization of HPBAs for the selective voltammetric determination of F^-, and perform principle component analysis (PCA) of DFs. F^- detection is based on the cathodic shift of the anodic redox peak potentials of HPBAs upon increasing F^- concentration.

Materials and Methods: TGA, DSC, FTIR measurements were done with Perkin Elmer TGA4000 Thermogravimetric Analyzer, DSC6000 Differential Scanning Calorimeter and Spectrum100 FTIR Spectrometer, respectively. Voltammetry was performed with Bioanalytical Systems BAS100B/W potentiostat. OriginPro 2020 software was used for pKa prediction calculations. Chemometric analysis were done by Minitab 20.2 software.

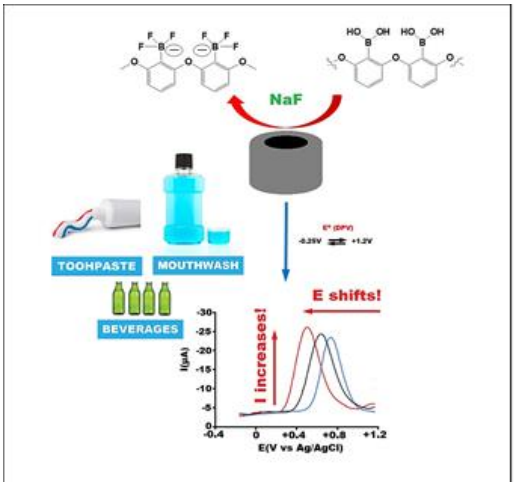

Fig1. Overall scheme of F^- determination

Results: pKa of 2-, 3- and 4-HPBAs are determined by spectrophotometric and potentiometric methods. Dehydratation (boroxine formation) reactions are proposed based on thermal stabilities of HPBAs investigated by DSC, TGA and FTIR. Entire DPV data on the quantification of F^- in commercial samples are summarized as Tables with the use of calibration plots based on the anodic peak potential shift.

Conclusions: In conclusion, poly(HPBAs) modified electrodes were used in F^- determination and PCA of Dfs.

Acknowledgements

This study was supported by a grant of National Boron Research Institute (BOREN, Project number: BOREN-2008-Ç0138) The authors would also like to thank FABAL (Pharmaceutical Sciences Research Laboratory of Faculty of Pharmacy of University of Ege, Izmir, Türkiye - https://www.fabal.ege.edu.tr) where DSC, TGA and FTIR measurements were performed.

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OP123: ELECTROCHEMICAL DETERMINATION OF ANTINEOPLASTIC DRUG IN HUMAN PLASMA BY MODIFIED GLASSY CARBON ELECTRODE

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Introduction: Topotecan (TPT) is semisynthetic unoriginal of the herb alkaloid camptothecin and is used as an anti-tumor and inhibitor of topoisomerase I in more than 70 countries as a second treatment for ovarian cancer and more than 30 countries for the treatment of lung cancer (1-3). The principal purpose of this work is to complete the straight oxidation of TPT and then to enhance a new electrochemical method for the sensitive and fast detection of TPT.

Materials and Methods: TiO2 NPs and 2DMoS2 NFs were ultrasonicated for 20 min in separately 2.0 mL of DI water to prepare the TiO2 and 2D-MoS2 dispersions. Then, 7.0 µL of various concentrations of 2D-MoS2 was dropped on the GCE and permitted to dry at room temperature then 7.0 µL of diverse concentration of TiO2 solution was reformed onto GCE and permitted to dry up at room temperature.

Results: DPV method was used to verify the electroanalytical capacity of 2D-MoS2/TiO2 to detect TPT. The anodic signal increased linearly with the rising of TPT concentration in the one ranges of 0.01–18.44µM with the following regression equation: I_p (µA) = 0.0702 C_x (µM) + 0.1199 (R^2 =0.9931).

Conclusions: The results of proposed this voltammetric study shows that the reaction is an irreversible, and diffusion-controlled process. The proposed 2D-MoS_2/TiO_2/GCE system offers excellent features, including low-cost, simple, rapid, good stability, and sensitivity response to TPT with applicability to real sample analysis.

Acknowledgements

This work was supported by the Scientific Research Projects Commission of Ankara University (Project Number: 19L0237001 and 19L0237004)

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OP124: AN ELECTROCHEMICAL PLATFORM BASED ON MAGNETIC/CHITOSAN NANOMATERIALS FOR DETERMINATION OF THE DAPAGLIFLOZIN IN DIFFERENT MATRICES

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Introduction: Dapagliflozin (DPG), managing diabetes mellitus type 2, is a sodium-glucose co-transporter 2 inhibitor. DPG, also used in combination with diet and exercise in adults, helps to improve glycemic control by inhibiting glucose resorption in the proximal tubule of the nephron and causing glycosuria (1). The present study aims to develop fast, selective, and sensitive

methods for the determination of DPG at low concentrations, in pharmaceutical dosage forms, human serum, and urine samples, and to investigate the electrochemical behavior of DPG on Fe_3O_4/Chit/ GCE surfaces using cyclic (CV) and adsorptive stripping differential pulse voltammetry (AdSDPV) methods.

Materials and Methods: All materials in the experiment were used directly without much processing. The stock solution of 1.0 mM DPG was prepared in methanol. Standard solutions used in calibration curves were prepared by diluting from the stock solution with the selected supporting electrolyte containing 20% methanol. For electrochemical measurements, different buffers such as sulfuric acid (0.1 and 0.5 M), phosphate buffer (pH 1.4-5.6), acetate buffer (pH 3.2-5.4), and Britton-Robinson (BR) buffer (pH 2.0-8.0) were employed and prepared with double distilled water.

Results: DPG provided an irreversible oxidation peak at a potential of 1.18 V versus Ag/AgCl/KCl electrode in pH 0.1 M H_2SO_4 buffer. Under optimal experimental conditions, AdSDPV was used for the determination of DPG. AdSDPV methodology was proposed for the sensitive determination of DPG in a linear concentration range from 0.1 µM to 8.0 µM, with a detection limit of 2.09 nM and good repeatability (RSD of 0.60 %). The developed methods were applied to the analysis of the human urine, synthetic serum samples, and tablet dosage form with the recoveries 99.31%, 99.36%, and 97.25%, respectively. The effect of interfering compounds such as ascorbic acid, dopamine, paracetamol, glucose, several ions on the current response of DPG was explored in detail.

Conclusions: The proposed sensors were utilized for the quantification of DPG in pharmaceutical dosage forms and biological samples. It was proved that without any sample pre-treatment, and utilizing a simple measurement device, the sensor can constitute an alternative method for analysis of pharmaceutical products and clinical samples.

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OP125: A SENSITIVE ELECTROCHEMICAL NON-ENZYMATIC HYDROGEN PEROXIDE SENSOR USING AuNPs-ERGO/POLY(INDOLE-5-CARBOXYLIC ACID) NANOCOMPOSITE

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Introduction: Hydrogen peroxide (H_2O_2) is an essential product of biochemical reactions catalyzed by several oxidase enzymes in living organisms (1). The high levels of H_2O_2 can cause a pathophysiological case called oxidative stress (2). Thus, it is necessary to develop a sensitive and selective method for measuring H_2O_2. Various composites based on several conjugated polymers have recently been used as modifiers because of their specific functional groups (3). In this study, poly-(indole-5-carboxylic acid) (P(In-5-COOH)), AuNPs, and rGO have been selected to modify the GCE surface due to its high stability, homogenous coating, and good conductivity.

Materials and Methods: All electrochemical measurements were carried out using an AUTOLAB-PGSTAT 302N electrochemical analyzer connected with a three-electrode cell stand. The electropolymerization of In-5-COOH on GCE was carried out by using the CV technique. 1.0 mM $HAuCl_4$ and 2 mg/mL GO solution was prepared and sonicated for 2 hours. Then, AuNPs-rGO was electrodeposited at a potential of +0.6 V and –1.5 V at a scan rate of 0.025 mV s^{-1} for 10 cycles in 0.1 M PBS (0.1 M KCl, pH 7.0). After that GCE/AuNPs-rGO electrode was placed in 0.1 M TBAP containing 1.0 mM In-5-COOH. Then, the electrode was scanned by 10 cycles in the potential range from –0.2 V to +1.1 V at 50 mV/s. The prepared GCE/AuNPs-rGO/P(In-5-COOH) electrode was washed with ultra-pure water.

Results: The proposed electrode was characterized by SEM, EIS, and CV techniques. The electrochemical behavior of H_2O_2 was investigated using the CV method. Several parameters such as pH, applied potential, and scan number for electrodeposition of AuNPs-ERGO were optimized. The peak current showed a linear dependence with a concentration in the range of 1.0-167.0 µM for chronoamperometry. The developed non-enzymatic H_2O_2 sensor was employed for the detection of H_2O_2 in urine and serum samples with high recovery values.

Conclusions: The electrochemical reduction of H_2O_2 at GCE/AuNPs-rGO/P(In-5-COOH) was studied with a low LOD. The analysis showed satisfactory results with good sensitivity and a wide linear range for electrochemical determination of H_2O_2 compared to the methods in the literature.

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OP126: FABRIC PHASE SORPTIVE EXTRACTION FOLLOWED BY HPLC-PDA DETECTION FOR THE MONITORING OF PIRIMICARB AND FENITROTHION PESTICIDE RESIDUES

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Introduction: Increasing food shortage and deteriorating food quality have emerged as a global concern in recent years, and a large amount of agrochemicals are used globally to protect and increase the yields of agricultural production. Pesticides are known as toxic chemical compounds (1, 2) and are well known for their harmful impact to human health and the environment (3).

Materials and Methods: A sensitive and readily deployable analytical method has been reported for the simultaneous analysis of pirimicarb (PRM) and fenitrothion (FEN) pesticide residues in environmental water samples using fabric phase sorptive extraction (FPSE) followed by high-performance liquid chromatography combined with photodiode array (HPLC-PDA) detector.

Results: The quantitative data for PRM and FEN were obtained at their maximum wavelengths of 310 nm and 268 nm, respectively. The calibration plots were linear in the range 10.00–750.00 ng mL−1 and 10.00–900.00 ng mL−1 with correlation coefficient of 0.9984 and 0.9992 for PRM and FEN, respectively. Major FPSE experimental variables were investigated in detail, such as contact time with the FPSE membrane, pH and electrolyte concentration, and the volume and type of desorption solvent. Under the optimized conditions, the developed method showed satisfactory reproducibility with relative standard deviations less than 2.5% and low limits of detection of 2.98 and 3.02 ng mL−1 for PRM and FEN, respectively.

Conclusions: The combined procedure allows for enhancement factors ranging from 88 to 113, with pre-concentration values of 125 for both analytes. The chromatographic resolutions were approx. 12 for FEN (retention factor of 3.52) and PRM (retention factor of 6.09), respectively, with a selectivity factor of 1.73. Finally, the validated method was successfully applied to real environmental water samples for the determination of these pesticides

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OP127: A NOVEL METHOD FOR ANALYTICAL DETERMINATION OF COVID-19 DRUG, FAVIPIRAVIR, IN TABLETS

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Introduction: Favipiravir (FAV) is an antiviral drug that inhibits the RNA-dependent RNA polymerase of RNA viruses, thus preventing the viral reproduction[1]. It has been used in the treatment of COVID-19 throughout the world[2]. Currently there are only a few publications in literature for the determination of FAV in tablets, all of which rely on liquid chromatography. Here we present, for the first time in literature, a facile and sensitive stability-indicating spectroscopic method at micro molar scale. In this paper a simple, precise and rapid high-performance liquid chromatography method with UV detection has been developed for the determination of saxagliptin and metformin in bulk. An Agilent, Zorbax CN (250 × 4.6 mm I.D., 5 µm) column was used with a mobile phase mixture of methanol-50 mM phosphate buffer (pH 2.7) in a gradient elution mode at a flow rate of 1.0 ml min^{-1}. The analytes were detected at 225 nm and total run time for the method was 7 min. The calibration graphs were linear in the range of 5.00-125.00 µg ml^{-1} for saxagliptin and 2.50-62.50 µg ml^{-1} for metformin. For stability indicating study, saxagliptin was subjected to acid, neutral and alkali hydrolysis, oxidation and heat stress. The developed method could be used for quality control assay for SAX in tablets and for stability studies as the method separates SAX from its degradation products and tablet excipients.

Materials and Methods: Amongst all solvents tried, water was selected as the solvent due to its high absorbance response and environmentally friendly nature. Forced degradation study was conducted in terms of acidic, basic, oxidative degradation at room temperature as well as 60^0C and thermal degradation. Full method validation was performed in accordance with ICH guideline.

Results: 359 nm and 230 nm were determined as maximum absorbance wavelengths and linearity studies were performed in both wavelengths. The

linearity range was determined between 5-30 µg/mL with correlation coefficient > 0.999. LOD and LOQ values were calculated as 1.2 and 3.7 µg/mL, respectively. Recovery results were found to be 99.6-100.88 % within satisfactory precision values.

Conclusions: A novel, sensitive and rapid stability indicating UV spectrophotometric method was developed, validated and successfully applied to commercially available tablets for the first time.

Acknowledgements

The authors are very grateful to Biophore India Pharmaceuticals Private Limited, India for providing favipiravir drug substance to carry out the study.

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OP128: SIMULTANEOUS DETERMINATION OF FEBUXOSTAT AND MONTELUKAST IN HUMAN PLASMA BY USING FABRIC PHASE SORPTIVE EXTRACTION AND HIGH PERFORMANCE LIQUID CHROMATOGRAPHY

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Introduction: Febuxostat (FBX) is a widely used drug substance for treatment of gout by decreasing high uric acid levels in serum (1). It is mostly preferred in case allopurinol is not adequate for his treatment. Montelukast (MON) is a leukotriene modifier which is used in a bronchoconstriction and asthma (2). In pharmacological treatments with FBX with different drug combinations safety becomes more critical. Because of the frequent administration of these drugs and their safety evaluation, this study aimed to develop a novel and sensitive HPLC method with fluorimetric detection was developed for the determination of FBX and MON in human plasma and applied to a pharmacokinetic study.

Materials and Methods: The analytes were extracted from plasma by using fabric phase absorption extraction technique. FBX and MON was separated on an RP-C18 column using a mobile phase composed of acetonitrile: water including 0.032% glacial acetic acid (60:40 v/v), by gradient elution with changing flow rate from 0.5 to 1.5 mL min^{-1}. The method was based on the measurement of the emission at 380 and 400 nm for FBX and MON, with excitation at 320 and 450 nm FBX and MON respectively.

Results: The calibration curve was linear over the range of 0.1-10 $ngmL^{-1}$ and 5-100 $ngmL^{-1}$ for FBX and MON respectively. The absolute recovery of FBX and MON from plasma was examined by extraction of spiked plasma samples and comparison with peak areas obtained after derivatization of the same amounts of aqueous unextracted solutions of the drugs. The mean absolute recovery of FBX and MON were of 89.17 and 92.32% respectively. LOD and LOQ were found to be 0.03 and 0.1 $ngmL^{-1}$ for FBX and 1.5 and 5 $ngmL^{-1}$ for MON, respectively. Intraday and interday RSD% values were less than 5.79 %.

Conclusions: The advantages of the methods mainly depend on the pretreatment procedure which was carried out by sorbent fabric phase sorptive extraction technique. The sorbent synthesized according to the chemical structure of the analyte drugs in order to provide high affinity and efficient extraction recovery. After this simple pretreatment the reverse phase chromatographic process and fluorimetric detection provided sensivity and selective assay in plasma samples. By the protype study it is clear to understand that the presented method is feasible for plasma analysis in patients. The method maintains to quantitate FBX and MON in $ngmL^{-1}$ level in their pharmacokinetic concentration range.

Acknowledgements

This study is financially supported by the Scientific Research Projects Committee of Bezmialem Vakif University (Project number: 20210204E) and the study protocol was approved by the Clinical Trials Ethics Commitee of Bezmialem Vakif University (Approval, No. 15/10).

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OP129: SYNTHESIS OF COBALT OXIDE NANOPARTICLES FROM PLANT EXTRACT OF DURANTA RIPENS FOR THE SENSITIVE ELECTROCHEMICAL DETERMINATION OF TRAMADOL IN PHARMACEUTICAL FORMULATION

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Introduction: Nanomaterials are chemical based substances or materials that are manufactured and used at a very small scale. There are two types of Nanomaterials which are organic and inorganic nanomaterials (1). Metal oxide nanoparticles, as cobalt oxide, can exhibit unique physical and chemical properties due to their limited size and high density surface sites and they have been used in several applications (2). Duranta Repens is traditionally be used as homeopathic drug for treatment of malaria and intestinal worms. The aim of this study is synthesize cobalt oxide nanoparticles using this plant extract in accordance with gren chemistry protocols and using this methods in determination of tramadol from pharmaceutical preparations.

Materials and Methods: The experimental procedure in this study consists of the following steps: Biosynthesis procedure and characterization of Co_3O_4 nanoparticles, Modification of glassy carbon electrode, Electrochemical characterization of modified electrode, Application to real samples.

Results: Various characterization techniques confirm the formation of pure magnetic Co_3O_4 nanoparticles with the average size of 24 nm and cubic crystalline phase structure. The modified glassy carbon electrode with Co_3O_4 nanoparticles show excellent electro-catalytic activity toward oxidation of tramadol under the optimized experimental conditions. The highly sensitive determination of tramadol was achieved with detection limit of 0.001 µM and limit of quantification was found to be 0.0003 µM.

Conclusions: In this study, a bio and eco-friendly protocol for the synthesis of Co_3O_4 nanoparticles were developed. A glassy carbon electrode were modified with these nanoparticles for sensitive determination of tramadol in pharmaceutical preparations.

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OP130: BIOINSPIRED DESIGN OF POROUS MOLECULARLY IMPRINTED NANOFILM FOR SELECTIVE AND SENSITIVE SENSING OF AN ANTICANCER DRUG RUXOLITINIB

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Introduction: Ruxolitinib (RUX), is an inhibitor of Janus kinases (JAKs), is the first drug approved by FDA to the specifically treat patients with myelofibrosis which also has shown efficacy in vitiligo treatment (1). The present study aims to develop fast, selective, and sensitive methods for the determination of RUX at low concentrations, in pharmaceutical dosage forms, human serum, and to investigate the electrochemical behavior of RUX on GCE surfaces using cyclic (CV) and differential pulse voltammetry (DPV) methods.

Materials and Methods: In this study highly selective and specific recognition was established for the analyte through incorporating nucleotide-based polymerizable functional monomer. RUX-imprinted poly-(2-hydroxyethyl methacrylate-thymine methacrylate- (PHEMA-ThyM) nanofilm was synthesized on a glassy carbon electrode surface in the presence of polyvinyl alcohol (PVA) via the molecular imprinting polymers (MIP) technique.

Results: The practical utility of the developed GCE/MIP@PHEMA-ThyM sensor for RUX was assessed using calibration curves with DPV. A linear response is seen over a wide concentration range of $1.0x10^{-14}$ M to $1.0x10^{-13}$ M. LOD of $1.93x10^{-15}$ M and LOQ of $6.44x10^{-15}$ M was obtained based on 3s/m and 10s/m, respectively. The abbreviation of s is the standard deviation of intercept of calibration curve and m is the slope of the related calibration curve. The developed methods were applied to the analysis of the synthetic serum samples and tablet dosage form with the recoveries 102.23% and 97.16%, respectively. Interfering agents were considered using the calibration equation of bulk form that gave a relative error of less than ±2%.

Conclusions: This work draws special attention to the development of a selective MIP for RUX detection by synthesizing a homogeneous thin polymer film on GCE using the photopolymerization technique. The proposed system represents the high sensitivity and

selectivity, and also excellent enforceability for the measurement of RUX level in the pharmaceutical dosage form and synthetic human serum samples.

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OP131: QUANTITATIVE PYRROLIDONYL ARYLAMIDASE ASSAY FOR GROUP A *STREPTOCOCCUS PYOGENES* DETECTION WITH IMAGE ANALYSIS

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Introduction: Rapid antigen tests is the most preferred method in Group A *Streptococcus pyogenes* (GAS) detection, reason of pharyngitis, however he results must be confirmed with plate counting method, which is a gold standard in this field (1). GAS colonies forms after 24-48 hours and definition should also be done with biochemical tests, such as pyrrolidonyl arylamidase (PYR) activity test (2). In this work, PYR test was transformed to a quantitative assay instead of defining a GAS colony.

Materials and Methods: The capture of GAS with cotton swabs and the related steps were applied in our previous study (3). 400 µL of GAS-nanoparticle complex was added to 500 µL of PYR-broth and incubated 38°C for 4 hours. Then, 25 µL of DMACA reagent was added and red color formation was the sign of GAS presence. The color difference between sample and blank was evaluated with image analysis, proposing a formula for Δgray, since gray value is a brightness calculation with RGB channels of the image. In addition, PYR amount in broth, incubation time, effect of ambient light was optimized and practical sample was evaluated.

Results: The linear correlation was found between the log of bacteria count and mean gray of RGB image with R^2 of 0.9685. The limit of detection and limit of quantification were calculated as 3.3×10^2 and 4.2×10^2 CFU/mL of GAS, respectively. In addition, in the presene of *Enterococcus faecalis* and the proposed assay worked selectively, obtaining Δgray values for GAS bigger than 50. It was also critical that a regular ambient light and a white background should be existed for image analysis. The measurement of blank was improved accuracy of the assay. Furthermore, 4 hours incubation was efficient enough to obtain red color, positive result for GAS.

Conclusions: Here, selective and sensitive assay for GAS detection was performed with PYR using image analysis. This was the first study for PYR using as a probe for quantifying GAS without the back-up of the gold standard.

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OP132: MICROSAMPLING AND HRMS FOR THE ANALYSIS OF TRYPTOPHAN-DERIVED BIOMARKERS IN A MURINE MODEL OF AMYOTROPHIC LATERAL SCLEROSIS

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Introduction: Amyotrophic lateral sclerosis (ALS) is a neurodegenerative neuromuscular disease causing paralysis and early death, and currently there is no cure nor effective treatments for ALS. Pathogenetic mechanisms for ALS have been proposed, including central nervous system (CNS) neuroinflammation driven by immunoregulatory responses, while it has been shown how Trp metabolites are involved in neurological disorders (1).

Materials and Methods: The purpose of this study is the design and development of an analytical approach based on miniaturised sampling and pretreatment for the assessment of several Trp metabolites in advanced biological samples, obtained from both ALS-bearing and wild type mice. The availability of limited sample volumes and the reduction of solvents and reagents in the framework of sustainable protocols, make advanced microsampling and miniaturised pretreatment technologies particularly attractive and promising (2).

Results: An original miniaturised sample collection workflow has been developed based on dried matrix spots and on volumetric absorptive microsampling. The developed and finely tuned microsampling strategy has been coupled to an original LC-MS/MS for reliable quantitative evaluations, while high resolution mass spectrometry (HRMS) was exploited to further confirm target analyte identity in the considered microsamples. This approach has been fully validated on a wide set of TRP metabolites,

obtaining promising results in terms of sensitivity, extraction yields, precision and accuracy

Conclusions: The developed analytical platform represents a promising and versatile tool allowing the evaluation of a broad panel of Trp-related compounds in miniaturised biosamples. The methodology is being applied for the analysis of miniaturised samples and will allow to evaluate specific TRP metabolites that could potentially have a role in the onset and progression of ALS.

Acknowledgements

This research was financially supported by the Research Projects of National Relevance (PRIN) 2017 funds (Italian Ministry of Education, University and Research, 20173EAZ2Z).

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OP133: FABRICATION OF 2D-G-C_3N_4/SDS/GNPS AS AN ELECTROCHEMICAL SENSOR FOR BIOMEDICAL APPLICATION

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Introduction: Doxorubicin is a famous anticancer drug with many side effects that make it crucial to determine it in an actual sample. Doxorubicin (DOX) is commonly used to treat childhood solid tumours, lymphoma, ovarian, lung, and bladder cancer (1). It is significant because cancers cause many deaths each year worldwide. Most cancers are treated with antineoplastic drugs such as doxorubicin and 4′-epidoxorubicin(Epirubicin), which have many side effects. Therefore, monitoring these drugs in real biological samples has great importance in clinical diagnosis.

Materials and Methods: Doxorubicin, melamine ($C_3H_6N_6$), graphene nanoplatelets (GNPs), sodium dodecyl sulfate (SDS) were purchased from Sigma Aldrich company, and screen printed electrodes (SPE) were purchased from Metrohm DropSens. All of these substances are analytical grade, and water di-ionized were utilized. Britton-Robinson buffer (B-R) was used in all steps. Firstly, 2D-g-C_3N_4/SDS/GNPs as a novel sensor was synthesized and characterized. Then, The SPE electrode was modified with a certain concentration of nanocomposite. The electrochemical properties of the developed were observed by several methods such as differential pulse voltammetry (DPV), cyclic voltammetry (CV), and chronoamperometry (CA) under optimal conditions.

Results: The 2D-g-C_3N_4/SDS/GNPs was characterized by XRD, SEM, TEM, EDX and FT-IR, and 2D-nanostructure confirmed. The developed sensor exhibited excellent electrochemical performance, such as a wide dynamic range from 0.08-1.1 and 1.1-12.8µM, a low limit of detection (LOD) of 0.06 µM, and good reproducibility and repeatability. The modified electrode was utilized to detect DOX in biological samples and showed appropriate recovery and RSD.

Conclusions: The 2D-g-C_3N_4/SDS/GNPs/SPE were found to be excellent for the determination of DOX. The principal advantage of the 2D-g-C_3N_4/SDS/GNPs/SPE is sensitivity and selectivity in the presence of interfering agents. An enhanced oxidation current was observed in the case of 2D-g-C_3N_4/SDS/GNPs/SPE. The possibility of monitoring the DOX in human plasma makes the voltammetric method useful for biological purposes.

Acknowledgements

Ankara University's Scientific Research Projects Commission funded this research. (Project Number: 21B0237005 and 19L0237004). M.O. thanks the Turkish Academy of Sciences (TUBA) for partial support.

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OP134: QSRR-ANN MODELLING IN β-CD-MODIFIED RP-HPLC

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Introduction: Cyclodextrin (CD) added to RP-HPLC mobile phase interacts with analytes, solvent components and stationary phase surface. Therefore, the retention is influenced by the analyte's distribution between CD dissolved in the mobile phase, free CD and formed inclusion complex adsorbed onto the stationary phase, and stationary phase itself (1, 2). The research goal was to reveal the structural characteristics affecting the inclusion complexation and retention in these kinds of chromatographic systems by employing QSRR-ANN models.

Materials and Methods: Mixed QSRR model included large pool of molecular descriptors, complex association constants and experimental parameters towards the retention factor of risperidone, olanzapine and structurally related impurities. The experimental space was adequately covered with central composite design, while experiments were conducted on Dionex Ultimate 3000 (U) HPLC. QSRR-ANN modelling was performed in STATISTICA Neural Networks.

Results: To evaluate the individual influence of each of the descriptors, the difference in the highest and lowest retention factor value across the investigated range of the descriptor's values was calculated. The highest ratios were associated with the following descriptors RDF075m, UE, Mor04v and CATS2D_08_PL, making them the most contributing towards the selected output. RDF075m descriptor shows the three-dimensional mass distribution calculated at a distance of 7.5 Å from the geometrical centre of the molecule and it refers to steric factors at the same distance. Groups approximately 7.5 Å distant from the geometrical centre of risperidone, olanzapine and related compounds in their optimized conformations were determined. These groups were the same ones involved in the complexation process according to previously performed NMR study. Identified groups and their steric factors are the most important for the formation of inclusion complexes, and, in this way, the value of RDF075m contributes to the retention of the selected compounds. The importance of Mor04v confirms the influence of molecular size and shape in retention in these kinds of chromatographic systems, while CATS2D_08_PL accounts for lipophilicity.

Conclusions: The current study resulted in development of QSRR-ANN with remarkable performances, which enabled the elucidation of the molecular features significantly influencing the retention in β-CD-modified RP-HPLC. The pronounced effect of molecular structure on retention was best described through RDF075m, followed by UE, Mor04v and CATS2D_08_PL. Retention behaviour is also highly affected by molecular size and shape, as well as lipophilicity of the investigated compounds. Moreover, the size and polarity of the chosen CD should not be neglected, due to the consequent structural fit.

Acknowledgements

This study was supported by the Ministry of Education, Science and Technological Development of the Republic of Serbia (Project no. 451-03-9/2021-14/200161).

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OP135: ELECTROCHEMICAL INVESTIGATION OF SURFACTANT EFFECT ON THE ETODOLAC AND THIOCOLCHICOSIDE SIGNALS

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Introduction: Etodolac (ETO) and Thiocolchicoside (TCC) are used in combined form in order to provide a rapid analgesic effect on especially serious pain cases such as vertebral colon syndrome, severe trauma, and surgery operations. The combined form does not change the pharmacokinetic properties of both drugs. It has also a synergetic effect on the analgesic feature. Therefore, it is very important to determine the concentration of each drug found in pharmaceutical preparations for quality control studies (1). The main purpose of the present study is to demonstrate a novel approach based on electrochemical oxidation of ETO and TCC at modification-free glassy carbon electrode (GCE) in the presence of sodium dodecyl sulphate (SDS). This study is the first electrochemical method which is used for the simultaneous determination of ETO and TCC.

Materials and Methods: A conventional three-electrode cell was connected to PalmSens EmStat 3 potentiostat (DropSens, Metrohm, Turkey) with PSTrace 5.5 software for electrochemical measurements. For voltammetric measurements, the required concentration of ETO and TCC were taken and diluted with Britton-Robinson (BR) buffer (pH 6.0 including 20% methanol and 70 µM SDS). Recovery studies have been carried out to examine the accuracy of the proposed method and to check interference of common excipients using Etotio® tablets (each film-coated tablet containing 400 mg ETO and 8 mg TCC). The standard addition method was used for the recovery studies.

Results: In this study, the voltammetric response of TCC was improved almost 2-fold when SDS was present in the electrolyte solution at pH 6.0. Moreover, the oxidation signals at around +0.63 V for ETO and +1.37 V for TCC allowed simultaneous determination of ETO and TCC with differential pulse voltammetry (DPV). The calibration curves were linear for both drugs over concentration ranges of 1–80 µM, with detection limits of 0.11 µM for ETO and 0.20 µM for TCC. In order to test the precision of the developed method, the relative standard deviation values of peak currents were

calculated as less than 1.08%, which suggest that GCE produces sufficiently reproducible results in ETO and TCC determination. Furthermore, the recovery studies showed that the recovery %(≥99.2) and Bias % (≤0.79) were all in acceptable ranges.

Conclusions: SDS added to the electrolyte medium increased the signal of TCC, contributing the applicability of the method to the tablet. Finally, the proposed DPV method provided lower detection limits, and relatively wider linear ranges compared with reported methods (2–4).

Acknowledgements

The authors would like to thank Nobel Drug Company (Istanbul, Turkey) for chemical substances.

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OP136: USE OF NOVEL BIOCHAR-DERIVATIZED MAGNETIC NANOCOMPOSITE AS MAGNETIC SOLID-PHASE EXTRACTION ADSORBENT FOR PRECONCENTRATION AND DETERMINATION OF SDZ BY HIGH-PERFORMANCE LIQUID CHROMATOGRAPHY

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Introduction: Sulfonamides are widely used in human and veterinary pharmaceuticals to prevent and treat diseases. Sulfonamides and other antibacterial residues in animal by-product has low limits of detection (1, 2). Therefore, pre-concentration techniques are mandatory before determination with analytical method (3). In this study, magnetic solid phase method was developed and optimized before the determination of sulfadiazine (SDZ) which is one of the sulfonamide group antibiotics, which is used prophylactically in various water and milk samples, by high performance liquid chromatography-ultraviolet detection (HPLC-UV).

Materials and Methods: In present study, the magnetic biochar nanocomposite (Fe_3O_4-BCPN) was synthesized by using the chemical co-precipitation method of pine needle biochar (BCPN) and iron oxide nanoparticles (Fe_3O_4). The characteristics of Fe_3O_4-BCPN were evaluated by scanning electron microscopy (SEM), energy dispersive X-ray spectrometry (EDX), X-ray diffraction (XRD), vibrating sample magnetometer (VSM) and Brunauer–Emmett–Teller (BET) surface area. The prepared Fe_3O_4-BCPN was employed in pre-concentration and separation in magnetic solid phase extraction (MSPE) for sulfadiazine (SDZ). Some of the important parameters in MSPE such as pH, sample solution volume, amount of adsorbent and eluent type were investigated and optimized. After pre-concentration, the Fe_3O_4-BCPN was conveniently separated from the aqueous samples by an external powerful magnet, and the SDZ desorbed from Fe_3O_4-BCPN was determined HPLC-UV.

Results: The scanning electron microscopy and energy dispersive X-ray spectroscopy analysis showed that magnetic particles were successfully loaded on the surface of biochar materials. Its saturation magnetization value was measured as 17,95 emu/g. Fe_3O_4-BCPN particle sizes using Debye-Scherrer formula 11.8 nm has been calculated. Under the magnetic solid phase extraction optimized conditions: sample solution volume was 40 mL; initial pH:7, amounts of Fe_3O_4-BCPN: 150 mg; desorption solvent (% 5 NH_3 in methanol) volume, 1 mL; adsorption and desorption time; 10 min. In these extraction conditions, the proposed procedure pre-concentration factors between 40; detection 10.7 µg /L. Relative standard deviations obtained for the SDZ were less than 4.2% and 7.7 % for intra-day and inter-day precisions, respectively.

Conclusions: The suggested MSPE method based on the synthesized the Fe_3O_4-BCPN was showed to be an efficient strategy for the pre-concentration of SDZ. Besides the proposed method can be used for the extraction and determination of trace amounts other sulfonamides in animal by-products.

Acknowledgements

This work is supported by the Scientific Research Project Fund of Cumhuriyet University under the project number ECZ-081

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OP137: NEW SCHIFF BASE LIGAND-COMPLEXES AS CARBONIC ANHYDRASE AND CHOLINESTERASE ENZYME INHIBITORS: SYNTHESIS, CHARACTERIZATION AND *IN VITRO* / *IN SILICO* EVALUATION

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Introduction: Schiff bases and their metal complexes are increasingly used in various branches such as medicine and pharmacy, preparing certain drugs, biological systems, cosmetics, the production of dyestuffs, the production of polymers, and many industries. Schiff bases are highly studied compounds because of their biological and structural importance. Also, Schiff bases and some of their metal complexes have antitumor, anticancer, antimicrobial, antifungal, and antibacterial properties (1, 2).

Materials and Methods: In this study, we have conducted an investigation that involved the synthesis, characterization and biological activity of a series of metal complexes to discover novel carbonic anhydrase (*h*CA) and cholinesterase (ChE) inhibitors (3, 4). Hence, the ligand of 5-florosalicylidene-4-chloro-o-aminophenol was synthesized by the reaction of 5-florosalicylaldehyde, and 4-chloro-o-aminophenol in the absolute ethanol at 50˚C by the catalyzed of p-toluenesulfonic acid. Later, the complexes of this ligand were prepared with Co(II), Ni(II), Cu(II), Zn(II), Cd(II), Mn(II), Pb(II), and Fe(II) in acetate forms at pure EtOH. Compounds were characterized by spectroscopic techniques (2). Furthermore, molecular docking studies were carried out to assess those complexes inhibition mechanisms against the aforementioned targets.

Results: All of the Schiff base complexes were found to be bidentate ligands involving the imino nitrogen and phenolic oxygen atoms in the complexes. The structures of ligand and complexes were identified using FT-IR, ^{1}H-NMR, ^{13}C-NMR, UV-Vis as techniques. And then, *in vitro* and *in silico* studies, novel metal complexes of 5-florosalicylidene-4-chloro-o-aminophenol were determined to be potent inhibitors of *h*CA and ChE (4).

Conclusions: One Schiff base ligand and eight metal complexes were synthesized and the structures of ligands and complexes were characterized by various techniques and ensured the formation of compounds. According to the findings, the synthesized complexes may represent interesting lead agents and might maintain further structural guidance to explore and design more potent *h*CA and ChE inhibitors.

Acknowledgements

This study was supported by a grant of EÜBAP TSA-2021-756

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OP138: SPECTROPHOTOMETRIC and HPLC DETERMINATION OF NAFTIFINE HCL

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Introduction: In this study, it was aimed to analyze the antifungal active ingredient of Naftifine hydrochloride, which is used for treatment of dermatophytic infections (1), both by UV-VIS spectrophotometric and reverse phase HPLC quantition methods. The optimum conditions for the analysis were evaluated, qualitatively and quantitatively.

Materials and Methods: A double beam, Agilent Cary 60 UV-VIS spectrophotometer with fixed slit with (2nm) connected to an IBM-PC computer was used. The UV spectra of standard and test solutions were recorded in 1cm quartz cells. Absorption spectra of Naftifine HCL in methanol were determined by zero-order spectrophotometry of this drug in cream dosage forms. For determination of Naftifine HCl, measurement of peak-zero amplitude in the zero-order spectra at 255 nm was used. Optimum HPLC conditions were as follows; Agilent 1100 HPLC, Supelco C18 (5 µm, 15 cmx 4.6 mm) column and 10 µL injection volume, 1.5 mL/min flow rate with 254 nm. Mixed mobil phase was consisting acetonitrile:water:triethylamine (800:200:0.2 v/v/v). System compatibility tests were performed.

Results: The maximum absorbance was measured at 255 nm wavelength by UV-VIS

spectrophotometry scanning at 230 - 350 nm. The developed spectrophotometry method has been validated by examining linearity and range linear between 6.476-32.38 µg/mL concentration range with the determination coefficient of 0.999 and for 1.307 µg/mL LOD, 3.959 µg/mL LOQ. The average recovery was 100.22 % and the BSS was 1.492 %. The HPLC method has been validated with linearity and range between 16.19-48.26 µg/mL concentrations, the determination coefficient of 0.999 and 3.703 µg/mL LOD, 11.221 µg/mL LOQ. An average recovery of 99.88% with BSS 0.94% was achieved. Quantification analysis of Naftifine HCl was performed in Exoderil® cream with the developed UV-VIS spectrophotometry and HPLC methods. The high rate of recovery showed that the additives did not affect the methods and excipients contained in the drug formulation and that the method was valid and feasible.

Conclusions: The pharmaceutical preparation of Naftifine HCl was applied to Exoderil® cream and the results obtained in both methods were compared. Due to the t-test results, it was seen that there was no significant difference between the methods. The developed and validated methods were successful in finding the quantity of Naftifine HCl in the pharmaceutical products and active ingredient. The developed methods can be used in quality control laboratories because they are simple, economical and do not cause waste time. The procedures do not require any separation step.

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OP139: LC-MS/MS AND LC-DAD METHODS FOR ROBUST DETERMINATION OF GLYCEROL PHENYLBUTYRATE IN BIOLOGICAL FLUIDS AND HIGH-RESOLUTION MASS SPECTROMETRIC IDENTIFICATION OF FORCED DEGRADATION PRODUCT

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Introduction: Glycerol phenylbutyrate (GPB) has been approved in the US by the FDA in 2013 for the treatment of urea cycle disorders that cannot be managed by protein restriction and/or amino acid supplementation only in patients 2 months and older in 2017 (1). In the current study; a novel fully validated liquid chromatography method has been developed for the analysis of GPB in pharmaceutical formulations, human plasma and urine.

Methods: The liquid chromatographic separations were succeeded with using a Supelco Ascentis® Express F_5 reversed-phase column (100 × 4.6 mm, 2.7 µm I.D). The mobile phase was composed with 1 mM ammonium acetat buffer and acetonitrile (25:75, *v/v*, pH=5.3). The flow rate was 0,5 mL/min, injection volume was determined as 1 µL. Compounds were monitored at 200 nm using PDA detector. In the mass detection, the maximum ionization peak obtained in the positive mode was observed in the Q3 scan, and so the MRM+ mode was selected. The precursor ion m/z 548.35, and m/z 367.10 and 147.05 daughter ion were observed.

Results: The method was fully validated according to ICH Q2 (R1) guideline and also forced degradation studies were carried out comprehensively. To determine the linearity of the developed, GPB standard solutions corresponded to 2.8-111.7 µg/mL for PDA detector and 1.40-55.84 ng/mL for mass detector. Regression coefficient was found to be more than 0.99 for both systems.

Conclusion: To sum up with the analysis of pharmaceutical formulation, human urine and plasma and detection of degradation products was made successfully in HPLC, LC-MS/MS, and LCMSMS-IT-TOF. This newly validated method was transferred to another laboratory with its stationary phase for interlaboratory comparison study in HPLC. In the other HPLC instrument, the validated method was examined and proved method suitability.

Acknowledgements

This study was supported by a grant of Anadolu University Scientific research Projects Commission (Project No: 2005S061).

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OP140: DETAILED ELECTROCHEMICAL BEHAVIOR AND THERMODYNAMIC PARAMETERS OF ANTICANCER DRUG REGORAFENIB AND ITS SENSITIVE ELECTROANALYTICAL ASSAY IN BIOLOGICAL AND PHARMACEUTICAL SAMPLES

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Introduction: Regorafenib (REG) is a broad-spectrum tyrosine kinase (TK) inhibitor with antineoplastic and antiangiogenic activities due to its dual-targeted VEGFR2-TIE2 TK inhibition (1, 2). Multiwalled carbon nanotubes modified glassy carbon electrode (MWCNTs/GCE) was developed for the sensitive electrochemical determination and the evaluation of thermodynamic and electrooxidation properties of REG. This study provides a sensitive sensor for REG determination with a low LOD value in a wide linear range also the application to the tablet dosage form with satisfactory recovery results provides an advantage in terms of the applicability of the sensor. This is the first study that comprehensively examines the sensitive determination of REG in biological and pharmaceutical samples.

Materials and Methods: Stock solution (1×10^{-3} M) of REG was freshly prepared in acetonitrile, MWCNTs/GCE was formed by dropping 5 µL of suspension (1mg/1mL dimethylformamide) on the electrode surface and dried at room temperature. An accumulation time of 120 s and an accumulation potential of 0.1 V was used for AdsDPV measurements.

Results: Thermodynamic study revealed the endothermic nature of the REG oxidation processes. The electrochemical oxidation of REG was found pH-dependent. The maximal anodic response was observed at pH 1.0. MWCNTs/GCE shows a higher response current, approximately two times higher compared to the bare GCE. The accumulation process has a significant enhancing effect on the oxidation peak current of REG (nearly 4 times higher than the bare GCE). The linear range is between 5×10^{-7} M and 2.5×10^{-5} M with LOD and LOQ values of 2.08×10^{-8} M and 6.93×10^{-8} M. It was also seen that ascorbic acid, dopamine, Na^+, Cl^-, and paracetamol have no interfering effect on the current response of REG.

Conclusions: This study demonstrates the first comprehensive and the most sensitive electroanalytical assay for the determination of REG. Its applicability was also proved in human serum and tablet dosage form samples with satisfactory recovery results of 103.46% and 101.89%.

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OP141: EFFECT OF GEOGRAPHICAL DIFFERENCES ON THYMOQUINONE CONTENT AND CYTOTOXICITY OF BLACK CUMIN SEEDS

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Introduction: Thymoquinone (TQ) is the dominant bioactive component of Black cumin (*Nigella sativa* L.) which has a wide range of biological activities including anti-cancer, antioxidant, anti-inflammatory and hepatoprotective effects (1). The aim of this study was to evaluate the potent cytototic effect of black cumin extracts derived from India, Iraq, Turkey, Syria, Saudi Arabia on colorectal carcinoma cell line Caco-2 and associate with the TQ content.

Materials and Methods: Black cumin seeds were obtained from different geographical regions; India, Syria, Turkey, Saudi Arabia and Iraq. Methanol extracts of the seeds were prepared and TQ amounts analysed with HPLC. Caco-2 cells were incubated with the methanolic extracts for 24 hrs, where cytotoxicity was evaluated through different pathways, using MTT (mitochondrial), neutral red (lysosomal), lactate dehydrogenase (membrane integrity) assays. MDA levels, were also evaluated on the cells treated below IC50 concentrations.

Results: TQ amounts differs from 0,03-0,001%. The highest and the lowest TQ amount belong to India and Turkey samples respectively. IC50 values ranged between 74.04-499.67 µg/ml by MTT test and 172.63-1211.35 µg/ml by neutral red assay, indicating a potential mitochondrial related cellular death. Highest cytotoxic effect were found for Indian sample in MTT assay where the lowest were for Turkish samples in both assays in accordance to the TQ content. LDH activity ranged between 70.29-115.04 U/l. MDA content were found to increase dose dependent in Turkish, Syrian and S. Arabian samples; ranging 7.59-10.68 µM/ml in all treatments.

Conclusions: The amount of TQ effected the cytotoxic potential of the black cumin extract on

Caco-2 cells. Indian black cumin were found to induce highest cytotoxic effect with highest TQ levels. This preliminary experiment provides evidence that the geographical differences were found to have an effect on the efficacy of the anticancer potency of black cumin.

Acknowledgements

This study was supported by Near East University, (SAG-2018-1-014).

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OP142: MICROWAVE-ASSISTED *IN SITU* SYNTHESIS OF A NOVEL DEEP EUTECTIC SOLVENT FOR THE LIQUID-LIQUID MICROEXTRACTION OF BETA BLOCKERS

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Introduction: Deep eutectic solvents (DESs), as a green alternative to toxic organic solvents commonly used in liquid-liquid microextraction (LLME), have attracted considerable attention lately (1). The aim of this study was to develop a vortex-assisted LLME method for the determination of beta-blockers based on the microwave-assisted *in situ* formation of a new DES consisting of azelaic acid and thymol.

Materials and Methods:

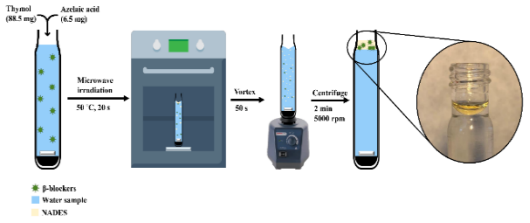

Fig. 1. Schematic representation of the proposed microextraction technique.

Results: The effect of 7 parameters on extraction was investigated by fractional factorial design. Significant parameters, namely pH, DES volume, and vortex time, were optimized using Box-Behnken design. Twenty seconds of microwave irradiation was sufficient for the *in situ* DES preparation, which is significantly shorter than previous reports (2). An enrichment factor of about 145 was obtained for both analytes. The intra- and inter-day accuracies were within 90.8-100.2%, with RSDs of 0.49-5.15%. LODs for metoprolol and propranolol were 0.2 and 0.1 µg/L, respectively.

Conclusions: A green vortex-assisted LLME method for beta-blockers was developed by employing a novel DES as an extraction solvent. In situ preparation of DES was achieved in only 20 s by microwave irradiation. This study proves that the proposed method can be employed as a rapid and green alternative for the enrichment of beta-blockers from environmental samples.

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OP143: INHIBITION OF TYROSINASE BY NON-STEROIDAL ANTI-INFLAMMATORY DRUG: AN ELECTROCHEMICAL APPROACH

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Introduction: Tyrosinase (Tyr) which catalyzes the biosynthesis of melanin and other pigments through oxidation, is a copper-containing enzyme. Tyr causes hyperpigmentation and hypopigmentation in mammals, and it is vital to control enzyme activity with Tyr inhibitors (1). Therefore, biosensing platforms decorated with different nanomaterials have often been suggested. Moreover, conducting polymers can be coupled with quantum dots. Hence in this work, a novel amperometric nanobiosensor was prepared from poly(3,4-ethylenedioxythiophene) nanoparticles (PEDOT NPs) decorated graphene quantum dots (GQDs) for the dual determination of catechol and anti-inflammatory drug diclofenac.

Materials and Methods: GQDs nanomaterial suspension was dropped onto the working surface of the screen-printed electrode (SPE) and allowed to dry at room temperature. PEDOT NPs were dropped onto SPE/GQDs surface and allowed to dry at room temperature in the next step. Then, the Tyr enzyme was dropped on the surface of SPE/GQDs@PEDOT NPs by crosslinking with a 0.25% GA crosslinking agent.

Results: Before detection and inhibition studies, amounts of GQDs, PEDOT NPs, Tyr, pH, and measuring temperature were optimized. Dual detection and determination of catechol and diclofenac were further investigated using SPE/GQDs@PEDOT NPs/Tyr nanobiosensor. In the linear range of 0.5-10 mM diclofenac, the inhibition effect of diclofenac on Tyr was followed.

Using this inhibition strategy, the inhibition effect of diclofenac can be observed with the LOD value of 0.2 mM.

Conclusions: The developed biochemical strategy of this electrochemical nanobiosensor would provide excellent potential for analysis of other substrates of Tyr, immobilization of different enzymes, and inhibition studies for other drugs, pesticides, ions, etc. Hence, it is suggested that the designed sensor is a perfect marker to show Tyrosinase inhibition using electrochemical methods. This way, a diclofenac-based cosmetic cream formulation can be an alternative to the cosmetic market.

Acknowledgements

The authors would like to thank VEM İlaç San. ve Tic. A.Ş, (Istanbul, Turkey) for chemical substances and their pharmaceutical dosage form support.

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OP144: CHROMATOGRAPHIC DETERMINATION OF IRINOTECAN RESIDUES IN URINE SAMPLES BY USING A NEW SYNTHESIZED SORBENT MATERIAL

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Introduction: Irinotecan is a semi-synthetic chemotherapy agent with the same properties as camptothecin, originally extracted from the Chinese ornamental tree Camptotheca acuminata. Camptothecins, which specifically target DNA topoisomerase I, are used as a broad-spectrum anticancer drug (1). Topoisomerase inhibitors are widely used in cancer treatment. Irinotecan, the most effective topoisomerase inhibitor, blocks the topoisomerase I enzyme, preventing the proliferation and division of cancer cells (2, 3).

Materials and Methods: The method that we developed is based on monitoring the interactions of a new magnetic material and Irinotecan. HPLC-DAD instrumentation was optimized with isocratic conditions by means of methanol, acetonitrile, 0.1 % TFA. Analysis of irinotecan in urine samples was performed via a simplicity, precisely and rapidly approaches. The used magnetic sorbent material was developed and characterized during experimental studies.

Results: After optimizing the method required by HPLC-PDA for irinotecan, peak area of target molecule was recorded at two different wavelengths (255 and 358 nm). A linear working range of 10 to 500 ppb was provided for irinotecan. The LOD and LOQ values of irinotecan were calculated as 3.03 and 3.96 ppb, respectively. The relative standard deviation of the developed method for irinotecan was found lower than 3.2%.

Conclusions: Experimental parameters were optimized step by step in order to obtain accurate, precise, sensitive, and quick results. These factors include adsorbent amount, eluent type and its volume and pH effect. Then, the method was applied to urine samples and recovery studies were carried out by using spiked samples. Finally, satisfactory results were obtained between 95 and 102 % for recovery values.

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OP145: DEVELOPMENT OF ANALYTICAL METHOD FOR SENSITIVE SIMULTANES DETERMINATION OF AMITRIPTYLINE AND VENLAFAXINE BASED ON MAGNETIC PHASE EXTRACTION

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Introduction: Many antidepressants exert their effects by inhibiting the reuptake of norepinephrine and serotonin substances in the brain. Generally, these drugs are used for treatment in case of mental depression. It is important to analyze the low concentrations of these molecules in terms of monitoring the therapeutic dose of antidepressants and the follow-up of excretion products after use (1).

Materials and Methods: A sensitive and readily deployable analytical method has been reported for the simultaneous analysis of Amitriptyline(AMT)

and Venlafaxine (VEN) antidepressant drugs residues in simulate urine and normal urine samples using magnetic solid phase extraction (MSPE) followed by high-performance liquid chromatography combined with photodiode array (HPLC-PDA) detector. Both drugs were successfully determined with a Luna omega C18 column under isocratic elution mode by means of acetonitrile and phosphate buffer (pH 3.0) as the mobile phase.

Results: The quantitative data for AMT and VEN were obtained via PDA detector at their maximum wavelengths of 238 nm and 228 nm, respectively. The calibration plots were obtained as linear for both target molecules in the range 5.0–500.00 ng mL^{-1} with correlation coefficient of 0.9873 and 0.9954 for AMT and VEN, respectively. Experimental variables were investigated in detail, such as contact time with the MPSE membrane, pH and electrolyte concentration, and the volume and type of desorption solvent. Under the optimized conditions, the developed method showed satisfactory reproducibility with relative standard deviations less than 3.5% and LOD values were lower than 1.43 ng mL^{-1}.

Conclusions: The combined procedure allows for enhancement factors ranging from 88 to 113, with pre-concentration values of 125 for both analytes. The chromatographic resolutions were approx. 12 for AMT (retention factor of 9.63) and VEN (retention factor of 3.78), respectively, with a selectivity factor of 1.73. Finally, the validated method was successfully applied to simulate urıne and normal urine samples for the determination of these antidepressant drugs.

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OP146: THE PRELIMINARY ETHNOBOTANICAL STUDY OF GÖKÇEADA/ÇANAKKALE

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Introduction: Ethnobotany is the study of the relationship between plants and humans. Plants have been selected and used by mankind through trial-and-error for centuries, the acquired invaluable information may give some clues about interesting properties (1). Gökçeada (Imroz) is the largest island of Turkey and a district of Çanakkale Province. It is located in the North Aegean Sea (2). The aim of this study was to document the ethnobotanical uses of plants in Gökçeada.

Materials and Methods: There are 11 villages on the island. The field studies were held in the region at different times between April 2017-June 2019. The information about plants was collected from both the elder and the young local people (total 71 people) through interviews and recorded. The plants were collected with the help of the informants and photographs were taken. The collected samples were prepared to be kept in the Herbarium of Istanbul University Faculty of Pharmacy (ISTE).

Results: According to this preliminary research, the ethnobotanical uses of 78 taxa (13 of these were cultivated) belonging to 41 families were determined. The most common families were Asteraceae, Lamiaceae, and Apiaceae. Among these plants, 51 taxa are used as food and 29 taxa are used for medicinal purposes. In addition, some other plant species are used as dye, fuel, animal feed, veterinary medicine, etc.

Conclusions: In this study, the ethnobotanical uses of plants of Gökçeada were recorded for the first time. Some recorded plants are used both in Gökçeada and in other parts of Turkey, either for the same or for different purposes. The information on the use of plants obtained from villages reveals the cultural, ethnobotanical richness of the island that has not been investigated until today and sheds light on the emergence of new and beneficial results.

Acknowledgements

This study was supported by the Research Fund of Bezmialem Vakif Univ Project no: 12.2016/20.

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OP147: ESSENTIAL OIL COMPOSITION AND ANATOMICAL STRUCTURE OF *FERULA TINGITANA* L. (APIACEAE)

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Introduction: The use of *Ferula* L. species for therapeutic purposes is known since the early days of humankind (1). Many biological activities, -such as cytotoxic, antibacterial, antiviral, and anti-inflammatory- have been attributed to the

sesquiterpene coumarin content of the genus (2). In this study, *Ferula tingitana* L. (Apiaceae) naturally distributed in Turkey, has been investigated to highlight its anatomical structure and the essential oil composition.

Materials and Methods: *F. tingitana* was collected from Antalya in 2019. The specimens were deposited at the AEF Herbarium. The characteristic anatomical elements in the cross-sections of leaf, stem, peduncle, and rays were determined by Leica CME (Germany) camera. The flowers and the leaves were hydrodistilled for 3h using a Clevenger type apparatus. The analysis processes of GC and GC-MS systems were performed according to Demirci et al. (3).

Results: The characteristic anatomical elements in *F. tingitana* were angular collenchyma cells in the cortex, a visible cambium in the stem and peduncle in the contrast to rays, between 20-30 secretory canals in the stem, 16-22 in the peduncle and 4-6 in the rays, The leaf is amphistomatic, monofacial and the stomata are anomocytic. A total of 36 components in essential oils were identified. The main essential oil constituents for the flowers and the leaves were found as germacrene D (23.6%–5.3%), 1,3,5-trimethylbenzene (10.0%–18.4%) and 1,2,4-trimethylbenzene (8.5%–16.0%), respectively.

Conclusions: Chemical analysis of the essential oil of *F. tingitana* represents some differences and similarities compared to literature (4). Its major component for the flowers was germacrene D and 1,3,5-trimethylbenzene for the leaves. In a similar study, the main components were 3-carene, δ-cadinol and α-Thujene (4). Besides, obtained anatomical results compared to related species (5) were provided detailed information on the leaf, stem, peduncle and rays, which will contribute to the taxonomy of *F.tingitana* and the genus.

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OP148: COMPARATIVE LEAF ANATOMY OF SOME *OPOPANAX* SPECIES

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Introduction: Members of *Opopanax* W. Koch genus (Apiaceae) are being used traditionally for epilepsy treatment (1), infertility in woman, hemorrhoids (2) and paralysis (3) due to the coumarins and essential oils (4) that they contain. This study aims to show anatomical differences of leaves of 3 *Opopanax* species.

Materials and Methods: Plant materials *O. hispidus* (OH)*, O. persicus* (OP) and *O. siifolium* (OS) were collected from the wild and voucher specimens are kept in AEF. Cross and surface sections were taken by hand with razor from the plant materials preserved in 70% alcohol and microphotographs were taken by Leica DM 4000B camera.

Results: In the cross sections of all leaves, the lower and upper epidermis cells were of the same size and in oval shape. In OP, the outer wall was sinuous. Collenchyma tissue was found on the abaxial and adaxial surfaces. Collenchyma tissue in OH and OP midrib protruded in both surfaces, however in OS, protrusion was only seen on the abaxial surface. In the main vein, phloem enclosed the xylem in an arc-shape, but in OH, phloem tended to cover the xylem completely. All species had a secretory canal in the abaxial and adaxial direction of the main vein in the midrib. OH and OP were monofacial, however OS was bifacial. In the surface section of OH, OP and OS, stomata were observed on lower and upper surfaces. The stomata were surrounded by 3 epidermal neighboring cells. Anticlinal walls of epidermal cells were sinuous. Dendroid hairs were observed on the surface of the OH.

Conclusions: In terms of leaf anatomy, OH and OP were similar to each other, OS showed different features. OH and OP were monofacial, however OS was bifacial. Stomata were observed on both surfaces in all species. Dendroid hairs were only seen on the epidermis of OH.

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OP149: DEVELOPMENT OF A CELLULAR MEMBRANE AFFINITY CHROMATOGRAPHY COLUMN CONTAINING IMMOBILIZED TRKB RECEPTORS FOR THE IDENTIFICATION OF PHYTOCHEMICALS MIMICKING THE EFFECTS OF BDNF

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Introduction: Tropomyosin-receptor kinase B (TrkB), one of the most widely distributed neurotrophic receptors in the central nervous system, is the key receptor for brain-derived neurotrophic factor (BDNF). BDNF signaling has a therapeutic prominence for the management of various neurodegenerative diseases including Alzheimer's and Parkinson's diseases. While several phytochemicals show their neuroprotective effects by increasing the expression of neurotrophins and their associated receptors, only a few compounds are able to mimic the effects of neurotrophins (1). In this study, we aimed to develop a Cellular membrane affinity chromatography (CMAC) column that allows to screen complex natural matrices such as plant extracts for the presence of pharmacologically active specialized metabolites mimicking the effects of BDNF.

Materials and Methods: SH-SY5Y Neuroblastoma cells overexpressing TrkB were used to prepare CMAC columns (CMAC (+)). Homogenization, solubilization, dialysis, packing, and characterization steps required for developing a functional CMAC column were performed respectively (2) with some important changes. Negative control CMAC columns (CMAC(-)) were also prepared using SH-SY5Y TrkB-NULL cells, to be able to discern specific and non-specific interactions.

Results: We succesfully developed a novel CMAC column containing immobilized cell membrane fragments with fully-functional TrkB receptors for the first time. We proved the presence of the functional TrkB receptors in CMAC (+) compared to CMAC (-) by using frontal affinity chromatography and confocal microscopy.

Conclusions: In the drug discovery process, CMAC columns with the immobilized TrkB receptors can be used to characterize known ligands and to screen plant extract to find new ligands binding to TrkB receptors and mimicking the effects of BDNF.

Acknowledgements

Z.C.A was supported by TUBITAK (2219-Fellowship Program). This work was supported by American of Pharmacognosy Research Starter Grant and Regis Technologies grant to L.C.

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OP150: *IN VITRO* BIOLOGICAL EFFECTS OF ENDEMIC ANATOLIAN SPOTTED NEWT DERMAL VENOM: A POTENTIAL ACTIVE PHARMACEUTICAL INGREDIENT (API) FOR DRUG DELIVERY SYSTEMS

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Introduction: *Neurergus strauchii strauchii* Steindachner, which is a member of the *Salamandrid* genus, has a haemolytic dermal venom (1). Previously, the dermal venom microflora of *Neurergus* sp. has been reported to exhibit antimicrobial activities against pathogene microorganisms (2) The main goal of this study is research on the *in vitro* anti-inflammatory, antioxidant and antimicrobial activities of dermal venom of *Neurergus strauchii*.

Materials and Methods: *In vitro* anti-inflammatory, antioxidant and antibacterial effects of dermal venom of *Neurergus strauchii* were determined by using *in vitro* COX-1 & COX-2, DPPH scavenging assays and agar microdilution method. SC-560, celecoxib, Vit C and chloramphenicol were used as positive controls. *Bifidobacterium animalis ssp lactis* B94 was used as obligatory as well as *Lactobacillus reuterii* DSM 17938 was used as a facultative anaerobic microorganism.

Results: The total protein amount of the secretion was found at 1700 µg/mL. IC_{50} results of venom were calculated as 157.9770, 96.84, 11.6873 µg/mL for *in vitro* COX-1 & COX-2, DPPH inhibitons respectively. Antimicrobial activity MIC results of venom were determined as >400µg/mL against both of the microorganisms.

Conclusions: Venom inhibited all enzyms and DPPH on related concentrations. It is safe on obligatory and facultative anaerobic microorganisms. This result supports the texistence of probiotic dermal venom microflora (2). The results of this study indicated that link

between related enzyme activities and probiotic microorganism protective activity. More detailed analysis will be cconducted in the future stages of the study, and different drug delivery systems will be designed and characterized by using the relevant substance as an API.

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OP151: PHYTOCHEMICAL ANALYSIS AND BIOLOGICAL ACTIVITY OF *NEPETA CADMEA* BOISS

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Introduction: The members of the *Nepeta* genus, which grow in the mountainous regions of Europe, Asia, North Africa, North America and tropical climates, are popularly used due to their wound healing, antihelmintic, antirheumatic and cough sedative features (1). *Nepeta cadmea* Boiss. which is an endemic species of Turkey grows naturally in West and South Anatolia (2). In the current study, phytocemical and *in vitro* enzyme inhibitory studies were performed on the methanol extract of the aerial parts of *N. cadmea*.

Materials and Methods: *N. cadmea* was collected from Denizli in June, and deposited in the Herbarium of Ankara University Faculty of Pharmacy (AEF28879). Methanol extract was obtained using magnetic stirrer at room temperature. *N. cadmea* was examined qualitatively and quantitatively for the phenolic compounds characterization using HPTLC and reverse phase HPLC methods. Also, *in vitro* alpha-glucosidase and alpha-amylase enzyme inhibitory activity tests were performed to evaluate the antidiabetic potential (3, 4).

Results: As a result of TLC analysis, optimal two solvent systems were determined and HPTLC analysis were carried out. Qualitative analysis revealed that TLC and HPTLC findings were found to be parallel with HPLC results. According to the HPLC outcomes, tremendous amount of rosmarinic acid (0,6290±0,0095%) together with chlorogenic acid (0,0429±0,0012%) and caffeic acid (0,0027±0,0002%) were detected and quantified in the extract. In a previous study, it was indicated that methanol extract of the plant was lack of rosmarinic acid, which was contrary to our findings (2). Alpha-glucosidase and alpha-amylase inhibitory values were recorded as 17,14±2,18% and 36,74±7,23% at 1mg/mL concentration, respectively.

Conclusions: It was concluded that *N. cadmea* was found to be rich in phenolic acids such as rosmarinic acid, which possibly contributed to the promising enzyme inhibitory activity.

Acknowledgements

Thanks are due to Mehmet Çiçek, Pamukkale University, for supplying the plant material.

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OP152: METABOLOMICS AND ACETYLCHOLINESTERASE INHIBITORY ACTIVITY STUDIES ON *DACTYLIS GLOMERATE* L. AND *HORDEUM MURINUM* L.

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Introduction: Metabolomics (Phytomics in plants) is defined as a comprehensive quantitative and qualitative analysis of all metabolites present in a particular cell, tissue or organism (1). Alzheimer's disease is an age-related, irreversible, progressive neurodegenerative disease (2). Acetylcholinesterase inhibitory compounds and extracts can be effective on Alzheimer's and are used (3). In this study acetylcholinesterase inhibitory activities and metabolic profiles of *Dactylis glomerata* L. and *Hordeum Murinum* L. (Poaceae) were investigated.

Materials and Methods: In this study methanolic extracts of aerial parts from *Dactylis glomerata* L. and *Hordeum Murinum* L. were used. GC-MS and LC-QTOF-MS is used to determine metabolic profiles and an enzymatic assay is applied for acetylcholinesterase inhibitory activities.

Results: 296 primary metabolites by using gas chromatography-mass spectrometry (GC-MS), 305 secondary metabolites by using liquid chromatography quadrupole time of flight mass spectrometry (LC-QTOF-MS) and 1394 and 25332 unknown metabolites were detected respectively. Acetylcholinesterase inhibitory activities are defined %18.15 and % 13.13 for *D. glomerata* and *H. Murinum* respectively.

Conclusions: According to metabolic profiles of two plants we expected acetylcholinesterase inhibitory activities because of many possible active metabolite that we determined. But, it is a fact that synergy and antagonism play a important role of the whole metabolite instead of single metabolite. That's why there is no significant acetylcholinesterase inhibitory activity. Further studies will be performed for investigate antagonistic interactions.

Acknowledgements

This study was supported by grant from Afyonkarahisar Health Sciences University Scientific Research Projects (Project No: 19.TEMATİK.007)

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OP153: A COMPARATIVE ANALYSIS ON ANTIOXIDANT PROPERTIES, PHENOLIC COMPOSITION AND HPTLC EXAMINATION OF *SIDERITIS SCARDICA* SPP. *SCARDICA* INFUSION AND HYDROALCOHOLIC EXTRACT

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Introduction: On account of an imbalance between antioxidative protective systems and the generation of oxidizing substances, including free radicals, the human body is continuously exposed to significant oxidative stress (1). The production of free radicals leads to cell damage and death, speeds up aging, and causes a variety of diseases such as cardiovascular diseases, cancer, Parkinson's disease, and others (1). Various phytochemical analyses focused on the occurrence of flavonoids and phenolics, as these chemical substances are partly responsible for pharmacological activity of *Sideritis scardica* (2). In this study, we aimed to comparatively determine the antioxidant potentials of EtOH extract and infusion prepared from the aerial parts of *S. scardica* spp. *scardica* by using various *in vitro* methods as well as to characterize their phenolic compositions by High Performance Thin Layer Chromatography (HPTLC) technique.

Materials and Methods: Infusion and 80% ethanolic extracts were prepared from the aerial parts of the plant. The extracts were investigated for their antioxidant capacities using DPPH radical scavenging activity method and FRAP, CUPRAC, TOAC assays. Total phenolic, phenolic acid, and flavonoid contents were also assessed spectrophotometrically. Quantification of chlorogenic acid was performed by using HPTLC.

Results: Total phenolic, flavonoid and phenolic acid contents were measured as 198.60±5.83 mg gallic acid equivalents (GAE)/g, 29.27±1.44 mg quercetin equivalents (QE)/g, 99.27±3.00 mg caffeic acid equivalents (CAE)/g for ethanolic extract, and 209.91±9.34 mg (GAE)/g, 20.66±3.65 mg (QE)/g, 227.93±3.82 mg (CAE)/g for infusion, respectively. The IC_{50} values for DPPH radical scavenging activity were measured as 2047.84 and 1981.38 µg/ml with comparison of BHT for ethanolic extract and infusion, respectively. CUPRAC, FRAP and TOAC antioxidant capacities were determined as 228.15±2.93 mg ascorbic acid equivalents (AAE)/g, 0.97±0.02 Mm $FeSO_4$ equivalents/g, 338.60±5.23 mg AAE/g for ethanolic extract and 208.53±9.09 mg AAE/g, 0.95±0,03 Mm $FeSO_4$ equivalents/g, 323.25±2.76 mg AAE/g for infusion, respectively. Ethanolic extract and infusion of *S. scardica* spp. *scardica* were found to contain chlorogenic acid as 1.31 and 1.52 w/w%, respectively.

Conclusions: The antioxidant activities of ethanolic extract and infusion of *S. scardica* spp. *scardica* were virtually comparable, but the total phenolic acid contents differed significantly. Furthermore, HPTLC analysis showed that chlorogenic acid content is higher in infusion when compared to ethanolic extract. These results support the folkloric use of *S. scardica* spp. *scardica* as infusion. Moreover, HPTLC analysis was conducted on *S. scardica* spp. *scardica* extracts, for the first time to our knowledge.

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OP154: *SAMBUCUS EBULUS* L. VERSUS *S. NIGRA* L.: COMPARATIVE ASSESSMENT OF THE PHENOLIC COMPOSITIONS AND BIOACTIVITY PROFILES OF FLOWERS, LEAVES AND FRUITS

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Introduction: Among the 25 species of *Sambucus* genus (Adoxaceae family), *S. nigra* and *S. ebulus* are widespread in Turkey (1). Although medicinal use of *S. nigra* flowers has been approved by the official authorities, i.e. World Health Organization (WHO), *S. ebulus* has remained only in the folk medicine documents (2). Traditionally, different parts of *S. ebulus* are used to treat gastrointestinal disorders, influenza infection, symptoms of arthritis, and wounds. Recent studies have shown that these pharmacological effects might be attributed to its high phenolic content, including anthocyanins, quercetin and caffeic acid derivatives (3). This study aimed to compare *S. ebulus* and *S. nigra* plant parts (flowers, leaves and fruits) insight of their chemical compositions and antioxidant activity.

Materials and Methods: The fingerprinting profiles of *S. ebulus* and *S. nigra* plant parts were determined by HPTLC. Then, rutin, chlorogenic acid, neochlorogenic acid, hyperoside, isoquercitrin and kaempferol-3-*O*-glucoside contents were quantified by a newly developed and validated HPLC method. Additionally, total anthocyanin content was calculated by spectrophotometry in fruit samples over cyanidin-3-*O*-glucoside (C3G). *In-vitro* antioxidant activity of the extracts were investigated by DPPH, CUPRAC and FRAP methods. Lastly, HPTLC-direct bioautography was applied to evaluate contribution of the separated compounds on the chromatogram to the antioxidant activity of the extracts.

Results: In all samples, neochlorogenic acid, chlorogenic acid, rutin, and isoquercitrin were identified as the common phenolic contents by HPTLC. On the other hand, hyperoside was only detected in *S. ebulus* plant parts. The highest neochlorogenic acid and hyperoside contents were found in *S. ebulus* leaves as 21.57±0.82 mg/g and 6.15±0.13 mg/g, respectively. Besides, the highest kaempferol-3-*O*-glucoside amount was calculated as 13.33±0.0 mg/g in *S. ebulus* flowers. C3G was not detected in *S. ebulus* fruits by HPTLC. However, its fruits were found to be rich in other anthocyanins as total anthocyanin content was calculated as 6.55±0.13 mg C3G/g. In the perspective of antioxidant activity studies, *S. ebulus* leaves showed similar activity to *S. nigra* flowers. Accordingly, DPPH, CUPRAC and FRAP results were 101.31±1.56 mg TE/g, 289.18±1.22 mg TE/g, and 108.90±2.24 mg TE/g, respectively in its leaves. In HPTLC-DPPH, all the investigated phenolic components appeared as yellow-colored bands on a purple background, indicating their contribution to antioxidant activity.

Conclusions: *S. ebulus* plant parts might have a potential to be included in the official herbal monographs due to their rich content of phenolic acids, flavonoids and anthocyanins. Besides, chromatographic and spectrophotometric techniques applied in this study would be useful for the qualification of *Sambucus* species.

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OP155: THE RADICAL SCAVENGING ACTIVITIES AND ENZYME INHIBITION EFFECTS OF THE EXTRACTS FROM *ORIGANUM ONITES* L.

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Introduction: The genus *Origanum* L. (Lamiaceae), which is widely distributed in the world, especially Mediterranean regions, is represented by around 40 species and more than half of them are found in Turkey with high endemism ratio (1, 2). *O. onites* L., which is one of the most popular oregano as perennial herb, is known as "İzmir mercanköşkü" and grows southwest of Turkey. The aim of this study was to use *in vitro* methods to assess the antioxidant and inhibitory activities of the methanol and water extracts prepared from *O. onites* against tyrosinase.

Materials and Methods: The antioxidant function of *O. onites* methanol and water extracts was investigated using *in vitro* methods, DPPH and ABTS radical scavenging, iron chelating, and total phenol and flavonoid content determination. Using an in vitro spectrophotometric process, the extracts were also tested for enzyme inhibition effects against tyrosinase, which is linked to hyperpigmentation.

Results: The methanol extract of *O. onites* had the highest flavonoid content (60.62 mg QE/g), while

the water extract had the highest phenolic content (156.40 mg GAE/g). Despite the fact that both the methanol and water extracts showed increasing antioxidant activity depending on the cocentrations, the methanol extract was found to be more active than the water extract in DPPH assay. Otherwise, radical scavenging potential of the water extract was detected as higher than the methanol extract using ABTS, and iron chelating methods. Antityrosinase activity was also exhibitied in both the methanol and water extracts with less than 50 % inhibitions.

Conclusions: Our findings suggest that the extracts of *O. onites* could be helpful for the discovery of new bioactive constituents to use food and pharmaceutical industiries.

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OP156: IN THE FIGHT AGAINST BACTERIA: AERIAL PARTS OF PEGANUM HARMALA L.

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Introduction: The increase in the rate of bacterial diseases caused by multi-drug resistant bacterial strains has become a global health problem in recent years. The research and development of new antibacterial agents effective against Gram-positive and Gram-negative bacteria has been reported as a priority by WHO to deal with this public health threat (1). Recently, there has been increased interest in studying the phytochemicals effective in treating bacterial infections caused by resistant microorganisms (2).

Materials and Methods: In this study, *in vitro* antibacterial activity of the methanolic extract prepared from the aerial parts of *Peganum harmala* L. on some Gram-positive and Gram-negative bacteria was investigated. In addition, the inhibitory activity of the extract on the swarming motility, which plays a role in the pathogenicity of *Pseudomonas aeruginosa* PAO1, was also examined. The phytochemical content of the extract was determined by HPLC analysis.

Results: The minimum inhibition concentration that the extract had an effect on the studied bacteria was determined as 1.76-0.9 mg / mL. The extract was found to inhibit the swarming motility of PAO1 at a concentration of 58 µg / mL by 85 %. According to the results of HPLC analysis, it was determined that the major components of the extract are protocatechic acid and chlorogenic acid.

Conclusions: Considering the literature data on the antibacterial and anti-swarming effects of phenolic acids (3), it is obvious that the activity of the extract and its phytochemical content are related.

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OP157: INVESTIGATION OF *in vitro* ANTIMICROBIAL EFFECTS OF *TRIPLEUROSPERMUM CALLOSUM* (BOİSS. & HELDR.) E. HOSSAIN EXTRACTS ON URINARY SYSTEM PATHOGENS and *in vivo* TOXICITY IN *Caenorhabditis elegans* MODEL

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Introduction: The endemic *Tripleurospermum callosum* Boiss. & Heldr. E. Hossain is naturally distributed in the northern parts of Turkey and used in respiratory and urinary system ailments in folk medicine (1). In the present study, we demonstrated, for the first time, the antimicrobial effects of *T. callosum* extracts by *in vitro* microdilution method and *in vivo* toxicity in *Caenorhabditis elegans* using the life span assay.

Materials and Methods: In this study, infusion, decocsion and ethanol (96 %) extracts of aerial parts of *T. callosum* were prepared and analyzed by LC-MS/MS system. The extracts of *T. callosum*

were evaluated for their antimicrobial activity against *Escherichia coli* ATCC 8739 *Staphylococcus aureus* ATCC 6538, *Pseudomonas aeruginosa* ATCC 6538, *Klebsiella aerogenes* ATCC 1348 and *Candida albicans* ATCC 10231 by broth microdilution methods, and minium inhibititory concentration (MIC, µg / mL) values were determined. Non-toxic concentrations of the extracts were determined *in vivo* using the life span assay in *C. elegans*.

Results: 5-caffeoylquinic acid, quercetin glucoside, luteolin-7-glu, 4,5-dicafeoylquinic acid, quercetin acetyl glucoside, isoramnetine glucoside, apigenin glucoside, luteolin acetylglucoside, apigenin acetylglucoside, isoramnetine and luteoline were defined as the main compounds for infusion, decoction and alcohol extracts. MIC values were determined at 312.5 to 5000 µg / mL for all strains. All concentrations of infusion and decoction extracts of *T. callosum* (5000, 2500, 1250, 625 and 312 µg / mL) were found to be non-toxic for *C. elegans*, while 96% alcohol extract was found to be non-toxic only at 312 µg / mL.

Conclusions: The initial evidence gathered in this study shows that *T. callosum* extracts have antimicrobial activity and are non-toxic for *C. elegans.* Further experiments on antimicrobial activity of *T. callosum* extracts are ongoing in *C. elegans* model.

Acknowledgements

This study was supported by a grant of Tübitak (No: 218S812)

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OP158: LAMIACEAE MEMBERS USED IN ANATOLIA TRADITIONALLY FOR RESPIRATORY DISEASES FROM THE PERSPECTIVE OF BACTERIAL AND VIRAL INFECTIONS

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Introduction: Anatolia is the host of most old civilizations besides the rich flora, a wide range of topography and climate. Since ancient times there are so much documented or not documented information related to using the medicinal plants in this area. Respiratory diseases are among the globally most common diseases, in which the majority of the population experiences at least one of them from mild to severe annually (1). This study aimed to evaluate the documented Lamiaceae plants from Anatolia used traditionally to treat respiratory diseases from the perspective of bacterial and viral infections.

Materials and Methods: In this context, we evaluated 187 ethnobotanical researches (between 1991-2020) to prepare the list of most frequently used Lamiaceae species in Anatolia. Then we studied the books, reviews and scientific studies on biological activities and phytochemical analysis of these taxa too.

Results: According to our results, Lamiaceae is the most prominent family with 18 genera and 101 citations as traditional therapeutics for the treatment of respiratory diseases such as cough, bronchitis, asthma, colds & flu, shortness of breath. The genera that showed the highest citation frequency were *Thymus* L., *Mentha* L., *Salvia* L., *Origanum* L., *Sideritis* L., *Teucrium* L., *Melissa* L., *Rosmarinus* L., *Stachys* L., *Thymbra* L., respectively. Generally, herba or leaves of these plants were applied internally as tea. Most of these taxa have antibacterial, antiviral, antitussive, antipyretic, and anti-inflammatory activities. Due to high phenolic contents, the extracts and/or essential oils obtained from different parts of the plants exhibited a broad spectrum of antimicrobial and antiviral activities (2-5).

Conclusions: The presence of a wide range of therapeutic compounds in these medicinal plants has shown beneficial advantages in terms of antioxidant, antibacterial, antiviral, antitussive, antipyretic, and immunomodulatory activities. According to results, some taxa that have a higher potential for the development of new drugs is suggested concern to the common use of taxa by local people in different area, wide distribution and availability of them.

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OP159: COMPARATIVE STUDY OF ANTIHYALURONIDASE ACTIVITIES OF HYBRID NANOFLOWERS OF *ROSMARINUS OFFICINALIS* METHANOL PLANT EXTRACT

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Introduction: Interest in natural resources and biotechnological products via using green chemistry increasing day by day in the dermocosmetic field. *Rosmarinus officinalis* is a widely grown medicinal plant with different purposses. In this study, we aimed to synthesis hybrid nanoflowers of *R. officinalis* and to evaluate the hyaluronidase enzyme inhibition activity of both the extract and the hybrid nanoflowers in order to establish new generation, effective dermal preparations.

Materials and Methods: Leaves of *R. officinalis* were dried and extracted with methanol. Evaporated extract was used to synthesis copper and zinc organic-inorganic hybrid nanoflowers (*Ro*-CuNf, *Ro*-ZnNf) (1,2). PBS, $CuSO_4$ solution and *R. officinalis* plant extract in different concentrations were used for the synthesis of copper hybrid nanoflowers. The synthesis of the zinc hybrid nanoflowers was carried out by mixing the plant extract, PBS and zinc acetate solution by magnetic stirrer for 6 hours. Scanning Electron Microscope (SEM) analysis of the obtained nanoflowers was conducted at Erciyes University, TAUM. The hyaluronidase inhibition activity of these nanoproducts were conducted based on the turbidity measurement resulting from the reaction of hyaluronic acid with albumin solution (3,4).

Results: The optimal forms of nanoflowers at different concentrations were determined by analyzing the SEM images of the copper (*Ro*-CuNf) and zinc (*Ro*-ZnNf) hybrid nanoflowers of the extract. According to the preliminary results, the hyaluronidase enzyme inhibition of hybrid nanoflowers were higher than the only plant extract used.

Conclusions: Preliminary anti-hyaluronidase activities of the *R. officinalis* extract and the copper (*Ro*-CuNf) and zinc nanoflowers (*Ro*-ZnNf) of the plant will be presented comparatively. In order to obtain promising products in dermocosmetics, characterization of hybrid nanoflowers with different chromatographic methods and different *in vitro* biological activity studies will be continued.

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OP160: 5-LIPOXYGENASE ENZYME INHIBITORY ACTIVITY OF *ORIGANUM MINUTIFLORUM* O. SCHWARZ ET P.H. DAVIS VARIOUS EXTRACTS

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Introduction: *Origanum minutiflorum* O. Schwarz et P.H. Davis belonging to the Lamiaceae used as 'Oregano' in Turkey. *O. minutiflorum* is an endemic species that has been sustainably collected for years from Sütçüler, Isparta, Turkey. Although *O. minutiflorum* is among the commercial Oregano and is widely used with various nutrients in Turkey and in many exporting countries, there are not enough studies on its pharmacological effects (1). Lipoxygenase (LOX) enzymes are associated with inflammation-related, and neurodegenerative diseases (2). This study is aimed to the determination of *in vitro* LOX enzyme inhibitory activity of *O. minutiflorum*.

Material and Methods: Plant material was collected from Sütçüler in 2017. Crude extract was prepared air-dried aerial parts of the plant with 70% ethanol and was subjected to liquid-liquid extraction according to the polarity of the following solvents; *n*-hexane, dichloromethane, ethyl acetate and *n*-butanol, respectively. LOX enzyme inhibitory activity was performed spectrophotometrically by modifying the Baylac and Racine method (3). NDGA was used as positive control. All measurements were repeated three times and the results were expressed as Mean ± Standard deviation.

Results: Dichloromethan extract (100 µg/mL) showed the highest inhibition on the LOX enzyme (82.33±0.94%), while % inhibition of the other extracts (100 µg/mL) was founded at 65.80±2.00% (ethanol), 40.94±1.81% (ethyl acetate), 24.50±0.50% (*n*-butanol) and 17.45±0.55% (*n*-hexane). No activity found in the residual extract. NDGA was determined as 99.00±0.00%.

Conclusions: As far as our knowledge, the present work is the first contribution into the LOX enzyme inhibitory activity of *O. minutiflorum*.

Acknowledgement

We are grateful to Prof. Dr. Yavuz Bulent Kose, Faculty of Pharmacy, Department of Pharmaceutical Botany, Anadolu University, Eskişehir, Turkey, for determination of the plant specimen.

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OP161: THE IMPORTANCE OF *DROSOPHILA MELANOGASTER* AS A MODEL ORGANISM IN PHYTOCHEMICAL ACTIVITY BIOASSAY FOR NEUROLOGICAL DISEASES

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Introduction: *Drosophila melanogaster* "fruit fly" is one of the well understood, high-throughput and cost effective model organism being used more than 110 years to study the different biological aspects related to the development and diseases. Most of the developmental and cell signaling pathways and 75% human diseases-related genes are conserved between human and *Drosophila* (1). Pharmacological properties of phytochemicals can be studied by performing the fly behavior assays, memory and learning studies in the diseased model organism without ethical concerns.

Materials and Methods: We have been investigating the effects of phytochemicals on SMA (spinal muscular atrophy), Alzheimer's and Parkinson's via following assays, in Hacettepe University, Department of Biology, Drosophila Genetics Laboratory. We carry out assays including survivorship, life span, behaviour assay, AChE and BChE enzyme inhibition, histone acetylation levels using the *Drosophila* strains which developed to study human diseases from the *Drosophila* Genetic Reference Panel (DGRP), which includes 205 strains with different genetic backgrounds (2).

Results:

Survivorship assay: In flies feeding with desired phytochemicals any extension in survival will suggest the life extension associated with phytochemicals.

Behavioural assays

-Larval behavioural assays are helpful for early detection of the disease.

-Adult behaviour assays include courtship, locomotor and phototaxis. These are important identification of neuroprotective potential associated with many phytochemicals.

Courtship behaviour assay is being used to examine flies sexual behaviour and neuronal coordination.

Locomotor behaviour, in neurologic disease such as Alzheimer's (AD), Parkinson's (PD) and Huntington's disease (HD), SMA motor dysfunctions/locomotor impairment is one of the key parameters of the disease progression.

Phototaxis assay is a visual behaviour assay which is associated with learning and memory of the fly. The phototaxis response supplemented with phytochemicals will suggest the neuroprotective potential of these substance.

In vivo AChE and BChE enzyme inhibition

AChE and BChE enzyme inhibition are also studied to determine non-alkaloid effective phytochemicals in Alzheimer's disease (3).

Rpd3 and histone acetylation levels in *D. melanogaster* model of SMA

This study aimed to determine the treatment conditions that can be used in HDAC inhibitor research in the *D. melanogaster* model of SMA (4, 5). With this method we adapted to our laboratory, started to identify phytochemicals with HDAC inhibitory potential.

Conclusions: These studies and our references emphasize the advantage of *D. melanogaster* as a model organism for its use in pharmacological activity studies specifically related to neurological diseases, with our previously reported or ongoing experiments in our laboratory.

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OP162: *NEPETA TRANSCAUCASICA* GROSSH.: CHEMICAL COMPOSITION AND *ALPHA* GLUCOSIDASE INHIBITORY ACTIVITY OF ESSENTIAL OIL AND ANATOMICAL PROPERTIES OF DIFFERENT PARTS OF THE PLANT

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Introduction: *Nepeta transcaucasica* Grossh. (Lamiaceae), named as 'kaf pisik otu' in Anatolia, belongs to *Nepeta* genus that is represented in Turkey by 33 species and 40 taxa, 19 of them are endemic. In previously studies showed that *N. transcaucasica* has antibacterial and anticandidal activities (1-3). The aim of our study was characterizing essential oil obtained from aerial parts of the plant and evaluating for *α*-glucosidase inhibitory activity, as well as making anatomical examination of different parts of the plant.

Materials and Methods: Essential oil was obtained with Clevenger apparatus and analyzed by Gas Chromatography and Mass Selective Detector. The enzyme inhibitory effect of essential oil was determined according to method of Bachhawat (4). Sections were taken manually from plant parts in 70% alcohol, and prepared with Sartur reagent for anatomical examinations.

Results: The major compounds of essential oils were found as *cis*-nepetalactone (92.5%) and *trans*-nepetalactone (5.5%). Essential oil exhibited *α*-glucosidase inhibitory activity with an IC_{50} value of 7966.88 µg/mL compared to the positive control, acarbose (IC_{50} = 4199.05 µg/mL). The stem cross section was quadrangular. There were glandular trichomes with bicellular heads and unicellular stalk on stem. Stomatas were on the upper and lower surface of the leaf. There were glandular trichome with unicellular head, unicellular stalk and Lamiaceae type glandular trichomes on leaf. In addition, Lamiaceae type glandular trichomes were found on petals and sepals.

Conclusions: Nepetalactones were determined as major compounds of essential oil of *Nepeta transcaucasica*. Essential oil was not found as a potent *α*-glucosidase inhibitor. Essential oil was found at different types of glandular trichomes of the plant. These data will contribute to the taxonomic classification of the plant.

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OP163: *IN VIVO* ANTI-ANGIOGENIC AND ANTI-INFLAMMATORY POTENTIALS OF R(+) OR S(-) LIMONENE LOADED EUDRAGIT® RS 100 NANOPARTICLES

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Introduction: R(+) and S(-) limonene are major compounds of *M. spicata* essential oil have been reported to be used in treatment due to their antimicrobial, anticancer, anti-angiogenic, anti-inflammatory and antioxidant effects and as well as in cosmetics and as sweetener in drinks (1). We aimed to design and characterize R(+) or S(-) limonene loaded nanoparticles (NPs) and investigate their *in vivo* anti-angiogenic and anti-inflammatory potentials.

Materials and Methods: Eudragit RS 100-based NPs were prepared by following the nanoprecipitation technique with some modifications (2). The *in vivo* anti-angiogenic and anti-inflammatory activities of R(+) and S(-) limonene NPs were evaluated by using *in vivo* CAM and HET-CAM assays respectively (3,4).

Results: According to the results, NPs at the concentration of 50 µg/pellet including R(+) limonene and S(-) limonene as 4 µg/pellet showed strong *in vivo* anti-angiogenic potentials with anti-angiogenic scores of 0.93 ± 0.1 and 0.74 ± 0.05 and no membrane irritation and embryotoxicity compared with (±)-Thalidomide (0.8 ± 0.05) (Figure 1). R(+) and S(-) limonene NPs also exhibited strong *in vivo* anti-inflammatory activities with 75.00 ± 12.50% and 80.00 ± 11.18% inhibition values compared with 81.25 ± 8.84% (Figure 1).

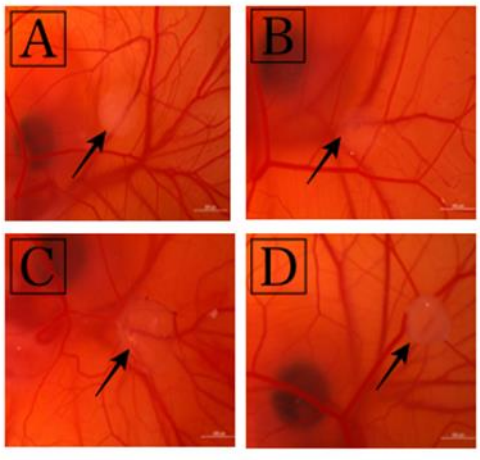

Figure 1. *In vivo* anti-angiogenic and anti-inflammatory effects of R(+) and S(-) limonene NPs. **A:** strong anti-angiogenic effect of R(+)

limonene NP, **B:** strong anti-angiogenic effect of S(-) limonene NP, **C**: strong anti-inflammatory effect of R(+) limonene NP, **D:** strong anti-inflammatory effect of S(-) limonene NP.

Conclusions: Plant derived natural angiogenesis inhibitors including plant extracts, essential oils and their volatile compounds used to treat cancer and inflammatory diseases, are seen promising as good alternatives to synthetic ones due to their low side effect profiles and different mechanisms of effect.

Acknowledgements: This study was financed by Anadolu University Scientific Research Project Foundation (No: 1905S054).

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OP164: SEARCH OF POTENTIAL MARINE NATURAL PRODUCTS AGAINST COVID-19

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Introduction: The development of vaccines has come to a certain point to end the new coronavirus (SARS-CoV-2) pandemic that has affected humanity for more than a one and a half. Scientists continue to research in order to develop an effective drug against the virus that has killed more than 3 million people (1). The aim of this study is present our findings and bring together the result of other studies on marine secondary metabolites from the studies carried out to end COVID-19 epidemic and to draw attention to the importance of studies on marine natural products for drug research.

Materials and Methods: Docking study was done using the procedure reported in literature (2). Tested compounds were downloaded from Pubchem (pubchem.ncbi.nlm.nih.gov) or built form the 2D structures. Ligands and proteins were prepared as reported in literature. Docking analysis and image preparation was done using PyMol. The proposed binding mode of the isolated compounds with neutrophil elastase (NE) and SARS-CoV-2 main protease (Mpro) was studied using Autodock Vina (3).

Results: Thousands of compounds were subjected to preliminary evaluations in studies and hundreds of compounds with drug-like properties were studied. As a result, it has been found that some marine natural products have a potent inhibitory effect by binding to COVID-19 M^{Pro} (Main Protease) (4). In this study four compounds isolated from marine derived *Aspergillus terreus* fungi were assessed for their in silico COVID-19 main protease (Mpro) inhibitory activities. Among the tested compounds, only butyrolactone I revealed significant activity that makes butyrolactone I a potential lead entity for developing new remedy to treat and/or control the currently devastating COVID-19 pandemic. It has also been shown from other studies that sulfated polysaccharides from marine organisms inhibit different stages of the viral infection process within the host cell and Plitidepsin is a peptide found in *Aplidium albicans* tunicate, which is currently used in cancer treatment, has also been found effective against COVID-19 and phase 3 clinical studies have been initiated recently (5).

Conclusions: The marine habitats are excellent homes to countless organisms and microorganisms and thousands of bioactive marine natural products have been isolated from these sources until now. The results revealed in the compiled studies show that marine natural products have a very important place in efforts to develop new drugs against the COVID-19 virus. Despite the reported antiviral activity of isolated marine metabolites, structural modifications showed the importance in targeting and efficacy.

Acknowledgements

Authors declare that there is no conflict of interest in this study.

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OP165: THREE NEW ANTIMICROBIAL NATURAL COMPOUNDS FROM *Scorzonera aucheriana*

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Introduction: *Scorzonera aucheriana* (Asteraceae/Compositae), a perennial herb, belongs to the genus *Scorzonera* which consists of over 52 species, and 32 of these are endemic to Turkey. Scorzonera L. species are consumed as a vegetable and the use of complementary medicine in the world and Turkey (1, 2). In the literature, flavonoids, phenolic acid derivatives, dihydroisocoumarins, lignans, neolignans, bibenzyl derivatives, benzyl phthalates, triterpenes, and sesquiterpenes were obtained in phytochemical studies from Scorzonera (1, 3). As a result of ongoing investigations, we report the isolation and structure elucidation of three new natural compounds from the water extract of *S. aucheriana* species which is endemic to Turkey.

Materials and Methods: *S. aucheriana* was collected in July 2018 from Sivas Province, Zara District, Yarağıl region in Turkey. The plant was identified by Prof. Kamil Çoşkunçelebi by using Flora of Turkey (2) and taxonomical conspectus of Turkish Scorzonera (1). Voucher (Makbul 244 & Coşkunçelebi) was deposited in the Herbarium of Biology (KTUB) at Karadeniz Technical University, Turkey. The method's extraction, chromatographic analyses, and antimicrobial activity were made according to our previous study (3). Chromatographic purification on the water fraction yielded compounds **1** (23.9 mg), **2** (12.3 mg), and **3** (14.4 mg).

Results: Chromatographic separation of water fraction of a crude methanol extract obtained from aerial parts of the *S. aucheriana* yielded three new compounds, scorzoaucherin A (**1**), scorzoaucherioside III (**2**), scorzoaucherioside IV (**3**). The structures of the isolated compounds were elucidated on the basis of NMR (^{1}H, ^{13}C, COSY, HMBC, HSQC, and TOCSY), UV, FT-IR, and LC-QTOF-MS spectrometric data.

Conclusions: Water fraction of a crude methanol extract of the *S. aucheriana* gave cannabispiradienone type natural compounds (scorzoaucherin A (**1**), scorzoaucherioside III (**2**), scorzoaucherioside IV (**3**)). All compounds were isolated and identified for the first time from this species. The antimicrobial properties of all isolates were investigated against ten microorganisms. Compounds **1**-**3** showed selective anti-tuberculosis activity within the range of 30.9-47.5 µg/ml (MIC), respectively.

Acknowledgements

The authors are thankful to Karadeniz Technical University for the financial support (KTÜ-BAP 8133).

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OP166: CYTOTOXIC ACTIVITY AND PHYTOCHEMICAL PROFILE of *PIMPINELLA ISAURICA MATTHEWS* ssp. *ISAURICA*

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Introduction: According to the World Health Organization reports, cancer is one of the leading causes of death in the world. The search for new and effective compounds to control the disease is still ongoing. Phytochemicals have been used as anticancer agents and utilized as a structure model for chemotherapeutics obtained by synthesis. Therefore, medicinal plants are important sources for anticancer drug development studies. *Pimpinella* L. (Apiaceae) genus have a broad spectrum of biological activities including anticancer (1). These biological activities are mainly attributed to phenylpropanoid derivatives (2). *Pimpinella isaurica* V.A. Matthews is an endemic species to Turkey. In the literature there is no detailed cytotoxic activity study on *Pimpinella isaurica* Matthews ssp. *isaurica.* The aim of the present study is to evaluate the cytotoxic activity of the methanol extract of the whole plant parts on different cancer cell lines (MCF-7, HeLa, HepG2, A549) and normal human lung cells (BEAS-2B), as well as to determine the phenolic compounds by High Performance Liquid Chromatography (HPLC).

Materials and Methods: The plant was collected from roadside cliffs in Ermenek, Karaman and the whole plant was extracted with methanol. Cytotoxic activity was determined on cervical epithelial carcinoma cell line (HeLa), liver carcinoma cell line (HepG2), breast carcinoma cell line (MCF-7), lung carcinoma cell line (A549) at concentrations of 100, 31.6, 10, 3.2, 1 µg/mL by 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) assay. In addition, the selectivity of the extract in healthy cells and cancer cells was investigated by using normal human bronchial epithelial cells (BEAS-2B). Phenolics and flavonoids in the extract were determined by gradient elution, reversed-phase HPLC method using 23 standards. The quantification of the detected compounds was performed by the external standard method.

Results: Methanol extract of *P. isaurica* ssp. *isaurica* exhibited strong cytotoxic activity on all cell lines. IC_{50} values of the extract on MCF-7, HeLa, A549, HepG2, BEAS-2B were 5.36±0.52 µg/mL, 12.19±1.24 µg/mL, 15.57±1.06 µg/mL, 7.62±0.80 µg/mL, 6.42±0.49 µg/mL, respectively. HPLC analysis indicated the presence of luteolin-7-*O*-glucoside and apigenin-7-*O*-glucoside in the extract.

Conclusions: In the present study, the cytotoxic activity of *P. isaurica* ssp. *isaurica* on MCF-7, HeLa, A549, and HepG2 was investigated for the first time The plant has a potent cytotoxic effect against all tested cancer lines, thus, can be a promising candidate for further anticancer research.

Acknowledgements

This study was supported by Scientific Research Projects Unit of Gazi University. (02/2020-09)

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OP167: POTENTIAL PHYTOCHEMICALS FOR THE TREATMENT OF PULMONARY ARTERIAL HYPERTENSION

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Introduction: Pulmonary arterial hypertension (PAH) is a devastating and incurable cardiovascular disorder triggered by progressive vascular remodelling of the blood vessels in the lung. The main features of this disorder are increased resistance to small pulmonary arteries and abnormal proliferation of endothelial and pulmonary arterial smooth muscle cells which may cause right ventricular dysfunction, heart failure and death (1). Despite the development of new drugs, only symptoms could be treated and there is no curative treatment for PAH at present. Novel therapeutics are intensively needed. Due to their valuable phytochemical content, medicinal plants are still vast sources for the drug researches on PAH.

Materials and Methods: In this study, literature data and our recent research results are reviewed to determine the potential phytochemicals for PAH treatment.

Results: According to literature; nearly 20 phytochemicals have possible effects on the pre-clinical studies for the PAH treatment. The prominent ones among these compounds are Ligustrazine and Tetrandine, both showed effects on regulating the various vasoactive mediators. Ligustrazine decreased pulmonary arterial pressure by upregulating nitric oxide and reducing endothelin levels *in vivo*. Tetrandine showed its effects by downregulating the expression of platelet-derived growth factor and basic fibroblast growth factor *in vivo* and reducing the inducible nitric oxide synthase (NOS) and upregulating the protein kinase-1 expression levels in the lung tissue of rats with PAH (2). There are also new targets for the PAH drug researches like the bone morphogenetic protein (BMP) signalling pathway. The mutations in the *BMPR*2 cause the most of heritable forms of PAH. Rosmarinic acid (RA) that was isolated in our studies increased BMP signalling through BMPRII mediated reporter assay in HEK293T, enhanced the phosphorylation of SMAD1/5 proteins and increased the expression of *Id1* transcripts (3).

Conclusions: Tetrandrine and ligustrazine may have potential in the treatment of PAH, according to the literature. Furthermore, RA could be a drug candidate for further *in vivo* and clinical studies. All these data indicate that natural products are good sources for PAH drug development studies.

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OP168: A SURVEY ON PRACTICE OF DIETARY SUPPLEMENTS AND AROMATHERAPY DURING COVID-19 PANDEMIC IN TURKEY

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Introduction: The absence of a precise confirmed treatment for the symptoms of COVID-19 has led individuals to apply different treatment and protection options. Although their roles on COVID-19 have not been proven, interest in dietary supplements and aromatherapy has increased during the pandemic period (1-3). In this study, usage of dietary supplements and aromatherapy were investigated for COVID-19 among individuals living within the borders of Turkey.

Materials and Methods: A cross-sectional survey study was conducted with total of 310 indivuduals. The study questionnaire was prepared using online forms. The data obtained from the study were analyzed with the commonly used SPSS statistical program. Cross tables were created to correlate the responses and chi-square tests were conducted.

Results: In order for the protection from COVID-19 infection, 31.9% individuals declared that they consume herbal tea / product, 38.1% of them use vitamin/mineral supplements and 18.4% of the indivuduals applied aromatherapy. The rates of those, who used and stopped herbal tea/product, vitamin/mineral supplement, and aromatherapy application during the pandemic period were 15.8%, 20.3%, 5.8%, respectively. As a result of the study, the most commonly used vitamin supplements were vitamin D, herbal tea/product green tea and essential oil thyme. The most increased plant in food consumption determined as garlic. In the study also frequently used herbal products contained ginger, onion as food, peppermint and eucalyptus oils. According to the results of the research, there was no statistically significant relationship between the use of dietary supplement and protection from COVID-19. Participants often report that they find the use of herbs or herbal products safe for COVID-19.

Conclusions: Before the use of dietary supplements and aromatherapy is recommended, their protective effects, side effects, drug interactions should be determined and the public should be informed about this issue.

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OP169: BIOACTIVITY-GUIDED ISOLATION OF CYTOTOXIC COMPOUNDS FROM THE UNDERGROUND PARTS OF *VALERIANA ALLIARIIFOLIA* ADAMS

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Introduction: The genus *Valeriana* (Caprifoliaceae) consists of 14 species in the Flora of Turkey including, *V. alliariifolia* (1). The extracts and isolates from the genus *Valeriana* were shown to possess various biological activities, including anxiolytic, neuroprotective and cytotoxic activity. Iridoids, sesquiterpenes and lignans constitute the major secondary metabolites of the genus *Valeriana*. Among these secondary metabolites, particularly non-glycosidic ester iridoids have received attention recently due to their cytotoxic and antitumor activities (2). This study aimed to isolate the cytotoxic compounds from the underground parts of *V. alliariifolia* through *in vitro* cytotoxicity-guided isolation procedure.

Materials and Methods: The underground parts were extracted with EtOH and then partitioned with $CHCl_3$, EtOAc and *n*-BuOH, respectively to obtain subextracts. The crude extract, subextracts and isolates were evaluated for their *in vitro* cytotoxic activity against four cancer cell lines (MCF-7, HGC-27, PC-3, A549) and one healthy cell line (HUVEC) by MTS assay. The structures of the isolates were elucidated by extensive NMR and MS analyses.

Results: The EtOH extract exhibited cytotoxic activity against all tested cancer cell lines (IC_{50} 12.0-30.7 µg/mL). The $CHCl_3$ subextract showed remarkable cytotoxic activity against the cancer cell lines (IC_{50} 2.5-21.5 µg/mL), while the EtOAc subextract displayed significant activity against only MCF-7 cell line with IC_{50} value of 12.2 µg/mL. Thus, $CHCl_3$ and EtOAc subextracts were subjected to chromatographic separations. Totally 14 secondary metabolites were isolated from the $CHCl_3$ and EtOAc subextracts. The structures were elucidated as didrovaltrate (**1**), IVHD-valtrate (**2**), 7-deisovaleroylvaltrate (**3**), valtrate (**4**), 1-β-acevaltrate (**5**), seneciovaltrate (**6**), valeriotriate B (**7**)**,** valtrate hydrine B2 (**8**), isovaleroxyvaltrate hydrine (**9**), valerosidate (**10**)**,** baldrinal (**11**),

coniferyl aldehyde (**12**), coniferin (**13**), and 8-hydroxypinoresinol (**14**). All isolates were evaluated for their cytotoxicity on the same cancer cell lines. Among the tested compounds, **1**, **2**, **4**, **5**, **8** and **9** exhibited remarkable cytotoxic activities on MCF-7 cell line with IC_{50} values of 2.5 to 8.4 µM. Also, **2**, **4**, **6**, **8** and **9** indicated significant cytotoxic bioactivities on HGC-27 (IC_{50} 2.3-10.2 µM), while only **4** exibited the best activity against A549 (IC_{50} 7.5 µM). Compounds **4, 5** and **8** displayed the best cytotoxicity against PC-3 with IC_{50} values ranging from 3.7 to 9.9 µM. Investigations on the mechanism of cytotoxic activities are in progress. In addition, four polar compounds (eriocitrin, coniferin, xiecaoside E, 8-hydroxypinoresinol 4′-*O*-β-D glucopyranoside) were obtained from *n*-BuOH subextract.

Conclusions: This is the first report on the isolation of cytotoxic compounds from *V. alliariifolia*.

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This study was supported by a grant of TÜBİTAK (Project No: 119Z094)

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OP170: IDENTIFICATION AND CHARACTERIZATION OF DESCHLORO-CHLOROTHRICIN OBTAINED FROM A LARGE NATURAL PRODUCT LIBRARY TARGETING AURORA A KINASE IN MULTIPLE MYELOMA

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Introduction: Multiple myeloma (MM) is a devastating disease with low survival rates worldwide (1). The mean lifetime of patients may be extendable with new drug alternatives. Aurora A kinase (AURKA) is crucial in oncogenesis, because its overexpression or amplification may incline the development of various types of cancer, including MM (2). Therefore, inhibitors of AURKA are innovative and promising targets. Natural compounds always represented a valuable resource for anticancer drug development.

Materials and Methods: We performed virtual screening and molecular docking based on the secondary metabolites with natural origin in the ZINC database in order to identify cytotoxic compounds targeting aurora A kinase. Resazurin assay was conducted to determine the cytotoxicity of the natural compounds obtained from in silico virtual screening and molecular docking results. Microscale thermophoresis was performed for the assessment of experimentally validation of the interaction between the compounds and AURKA. Cell cycle distribution, fluorescence microscopy and western blotting were perused to detect molecular modes of action of the compounds exhibiting cytotoxicity on MM cells targeting aurora A kinase.

Results: In the present study, based on virtual drug screening of more than 48,000 natural compounds, the antibiotic deschlorochlorotricin (DCCT) has been identified to bind to AURKA with even higher binding affinity (free binding energy: −12.25 kcal/mol) than the known AURKA inhibitor, alisertib (free binding energy: −11.25 kcal/mol). The in silico studies have been verified in vitro by using microscale thermophoresis. DCCT inhibited MM cell lines (KMS-11, L-363, RPMI-8226, MOLP-8, OPM-2, NCI-H929) with IC_{50} values in a range from 0.01 to 0.12 µM. Furthermore, DCCT downregulated AURKA protein expression, induced G2/M cell cycle arrest and disturbed the cellular microtubule network as determined by Western blotting, flow cytometry, and fluorescence microscopy.

Conclusions: DCCT may be a promising lead structure for further derivatization and the development of specific AURKA inhibitors in MM therapy.

Acknowledgements

We are grateful for a postdoc stipend given to Nadire Özenver by the Germany Academic Exchange Service (DAAD) (Funding program/-ID: Research Grants- Short-Term Grants, 2019 (57440917)) for a research stay at Johannes Gutenberg University, Mainz, Germany.

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OP171: ANTIMICROBIAL EVALUATION OF JUNIPER BERRY (*Juniperus communis* L.) ESSENTIAL OIL COMBINATION WITH STANDARD ANTIMICROBIAL COMPOUNDS

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Introduction: *Juniper* (Cupressaceae) is an evergreen shrub or tree, usually in the northern hemisphere. *Juniperus communis* L. is traditionally used in medicine because of its diuretic, antiseptic, carminative, digestive, antioxidant, antimicrobial properties and anti-inflammatory activities (1). Several studies have demonstrated the antimicrobial activities of juniper essential oils against different pathogenic microorganisms (2, 3).

Materials and Methods: Juniper berry (*Juniperus communis* L.) essential oil was combined with different antimicrobial compounds with cefuroxime, moxifloxacin, clarithromycin, fluconazole and terbinafin. All combinations were evaluated *in vitro* against pathogenic standard Gram-negative *Escherichia coli* ATCC 8739 and Gram-positive *Staphylococcus aureus* ATCC 6538 bacterial isolates as well as against *Candida albicans* ATCC 10231 for their broad antimicrobial effectiveness. The essential oil were tested in combinations for their minimum inhibitory concentrations (MIC) as well as for their fractional inhibitory concentrations (FIC) against microbial pathogens. Antimicrobial activities were evaluated by microdilution method and antimicrobial interactions were assayed using the checkerboard method.

Results: The essential oil combination of cefuroxime, moxifloxacin, terbinafin and fluconazole showed “additive effect” against *E. coli* ATCC 8739 (FIC=0.625) and *C.albicans* ATCC 10231 (FIC=0.508). Combination with clarithromycin showed “synergistic effect” aganist *E. coli* ATCC 8739 (FIC=0.5). Combination of cefuroxime, moxifloxacin and clarithromycin with essential oil against *S. aureus* ATCC 6538 showed “indifferent effect” (FIC=1.031, 2.016, 1.016, respectively).

Conclusions: Juniper berry essential oil showed promising antimicrobial activity against *E. coli* ATCC 8739, *S. aureus* ATCC 6538 and *C. albicans* ATCC 10231. Our findings from this research showed promising antimicrobial effects as natural alternatives to synthetic drugs for pathogen resistance.

Acknowledgements

This study was partionally supported by a grant of TUBITAK (SBAG-218S812)

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OP172: CONSTITUENTS AND BIOLOGICAL ACTIVITY OF ENDEMIC *CYNOGLOTTIS CHETIKIANA*

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Introduction: Boraginaceae family is represented by 146 genera and 2000 species in the world nearly. Phytochemical studies of these plants have revealed the presence of alkaloids, flavonoids, polyphenols, phytosterols and terpenoids. Their antibacterial, antiviral, antioxidant and anti-inflammatory activities are known mostly due to their phenolic components. *Cynoglottis chetikiana* Vural & Kİt Tan subsp. *chetikiana* (CC) which belongs to Boraginaceae family is an endemic subspecies. The phytochemistry of this plant has not been investigated so far. The aim of the study is the isolation and elucidation of secondary metabolites from CC and also the investigation of their antioxidant and □-glucosidase inhibitory activity.

Materials and Methods: The MeOH extract of the air-dried aerial parts of CC was fractionated with petroleum ether (PE) and then *n*-BuOH. The *n*-BuOH-soluble fraction of the MeOH extract was chromatographed on a polyamide column and five fractions were yielded (Fr. A-E). Fr. E further applied on various columns and the two compounds were obtained (CC-1 and CC-3). Structural elucidation of the compounds was based on NMR spectra. The antioxidant and □-glucosidase inhibitory activities of the four different extracts (MeOH, *n*-BuOH, PE and aqueus) and the isolated compounds from the phenolic-rich Fr.E were determined. As for the detection of antioxidant capacity, DPPH, NO^- SO^-, CUPRAC, FRAP and TEAC methods were used, including total phenolic content assay.

Results: According to the results obtained from this study, the phenolic-rich Fr.E which was found as 285.89 mg/g gallic acid equivalent exhibited stronger TEAC (33,41 mg/g trolox equivalent), SO^- (IC_{50}:18,59 µg/mL), DPPH (IC_{50}: 25,58 µg/mL) antioxidant activity than the other fractions. It was also found that Quercetin 3-rutinoside (CC-3) exhibited the high CUPRAC (218,09 mg/g gallic acid equivalent), FRAP (1668 mg/g trolox equivalent), TEAC (34,69 mg/g trolox equivalent) antioxidant capacities and NO^- (IC_{50}: 190,51 µg/mL), DPPH (IC_{50}: 10,8 µg/mL) radical

scavenging effect. Only MeOH extract showed the noteworthy activity at the □□glucosidase inhibitory acitivity assay comparing with the standard acarbose (IC_{50} values: 608,62, 111,86 µg/mL respectively).

Conclusions: According to the results, Fr.E andCC-3 have high antioxidant and radical scavenging effect. In addition, MeOH exract showed moderate □-glucosidase inhibitory activity. Our phytochemically and different biological activity screening assays are continuing on *Cynoglottis chetikiana.* This endemic plantdeserve further investigations as possible drug candidates.

Acknowledgements:

This study was supported by TUBITAK 2209/A - University Students Research Projects Support Program. The authors would like to thank Prof. Dr. Hayri Duman for collection and identification of plant material and Andras Simon for NMR spectra of the isolated compounds.

OP173: DETERMINATION OF CAFFEINE CONTENT IN WORLD COFFEES BY A NEW, VALIDATED HPLC METHOD AND INVESTIGATION OF THE RELATIONSHIP BETWEEN CAFFEINE CONTENT AND LIPASE INHIBITION

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Introduction: Obesity is evaluated as a serious risk for global health problems and economic burden (1). Coffee has proven to reduce risk for obesity based on caffein content (2). The aim of the study is to determine caffeine content in world coffees by a new HPLC technique and to uncover relationship between lipase inhibition and caffeine content.

Materials and Methods: Coffees growing in five different regions in the world were used as samples. Quantitative analysis was performed by a new, validated HPLC method using C18 column (ZORBAX Eclipse Plus, 4.6 × 150 mm, 5 µm) and gradient program with two solvent systems; A: 100% methanol; B:2.5% acetic acid in deionized water at a constant solvent flow rate of 1.2 mL/min and UV 273 nm as the detector. Lipase inhibition effects of the world coffees were evaluated using spectroscopic method.

Results: The method indicated good linearity (R^2 >0.999) over the assayed concentration range (10-100 µg/mL). Relative standard deviation (RSD) values for intra-day and inter-day precision were detected as 0.14%, and 0.36%, respectively. Accuracy for quality controls was varied from 98.8% to 100.1% (RSD<0.88%). It was revealed that all samples have caffeine content and lipase inhibition for detection ranges while colombian coffee possesses the highest caffeine (86.44 mg/g) content and lipase inhibition (IC_{50}= 54.84 ± 0.9256).

Conclusions: All the parameters of the new HPLC method were acceptable according to current recommendations for method validation. It has been proven to be positive correlation between the caffeine content and lipase inhibition. Colombian coffee is the most remarkable sample but all coffees have therapeutic potential for global health problem obesity.

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OP174: ENZYME INHIBITORY AND PHYTOCHEMICAL STUDIES ON *Pistacia terebinthus* COLLECTED FROM DIFFERENT LOCATIONS

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Introduction: *Pistacia terebinthus* L., known as Menengiç, is a species belonging to the Anacardiaceae family that grows in Turkey. Numerous ethnobotanical uses of different *Pistacia* species have been reported in the literature (1). In this study, *in vitro* antidiabetic (*α*-glucosidase and *α*-amylase enzyme inhibition) and antiobesity (pancreatic lipase enzyme inhibition) potentials of *P. terebintus* leaves collected from different locations were investigated in addition to the inhibition of pancreatic cholesterol esterase enzyme. The phytochemical contents of the extracts tested were examined by HPLC techniques.

Materials and Methods: *P. terebinthus* samples were collected from different locations in 2019. The inhibitory effects of *α*-amylase and *α*-glucosidase, pancreatic lipase and pancreatic cholesterol esterase of extracts with 80% ethanol from leaf parts of the plant were evaluated. General chromatograms were obtained to elucidate the phytochemical content of the extracts. In addition to the qualitative analysis of phenolic acid and flavonoids on leaves collected from Kilis performed by HPLC method, quantitative analysis of protocatechuic acid was conducted.

Results: All extracts showed excellent and dose dependent inhibitory effect on *α*-glucosidase enzyme. The highest *α*-amylase inhibitory activity at a dose of 2 mg/ml was found in leaves (98.31±0.28%) collected from Kilis, and this inhibition was almost at the level of acarbose

(98.91±0.93%). Leaves collected from Siirt province provided the highest inhibition on pancreatic lipase (59.06±2.09%) and pancreatic cholesterol esterase (38.82±1.20%) enzyme at a dose of 2 mg/ml. According to the results of HPLC analysis, Kilis *P. terebinthus* leaf ethanol extract was determined to have a content of 0.060 ± 0.002 protocatecuic acid g/100 g. **Conclusions:** The findings from the experiments revealed the potent antihyperglycemic and potential antiobesity activity of *P. terebinthus* leaves. Within the scope of these results, Antihyperglycemic and antiobesity activity guided isolation studies should be carried on *P. terebintus* leaves.

Acknowledgements

This study was supported by a grant of Gazi University-BAP (02/2019-32)

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OP175: QUALITY-CONTROL OF *HYPERICUM PERFORATUM* L. PREPARATIONS SOLD IN HERBAL DROGSTORES AND PHARMACIES OF ADANA AND INVESTIGATION OF THEIR HYPERICIN AND HYPEROSIDE CONTENT BY HPLC

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Introduction: *Hypericum perforatum* L. is a well-known herbal medicine used mainly for the treatment of moderate depression (1). However the quality of *Hypericum* herbal products sold in the market is bearly known. Due to the complex chemical content of medicinal plants, standardization is the most fundamental issue to be considered in ensuring product quality (2). The aim of this study is to evaluate 6 different preparations (herbs, capsules and extracts) samples claimed as *Hypericum perforatum* L. taken from herbal drogstores and pharmacies using basic pharmacognostic quality-control methods and quantification of hypericin and hyperoside by HPLC in order to investigate their compatibility with the opinion of European Medicine Agency on Herbal Medicinal Products (3).

Materials and Methods: Macroscobic and microscobic investigations together with phytochemical colour tests, total ash, acid-insoluble ash and moisture content of 6 *Hypericum perforatum* samples sold as herbs and food supplements have been determined. An analytical study of methanolic extracts of six samples (**1-6**) was carried out by using an optimised HPLC method for the the detection and quantification of hypericin and hyperoside.

Results: As a result of preeliminary examinations residues belonging to other plant species were found in two plant bundles. The determinations of the samples for loss in drying (7.76%; 7.01%; 6.27%; 5.85%) and the ash values (5.48%; 4.41%; 5.74%; 3.57%) were found appropriate according to the values included in the Turkish Pharmacopoeia II European Pharmacopoeia Adaptation. No hypericin was found in the sample **1**.1As a result of HPLC analysis of the samples (2-6), the amount of hypericin was determined as (0.104%; 0.262%; 0.082%; 0.099%; 0.093%) was determined as respectively. On the other hand the amount of hyperoside of the same samples (**1-6**) were found to be as (%1.645, %3.609, % 3.487, % 1.289, %1.734, %3.022) respectively.

Conclusions: As a result hypericin, one of the major biologically active component of the *Hypericum perforatum* species, was not detected in sample **1**. In three samples, hypericin content were found outside the appropriate range and in very low amounts. The label information of the products offered as food supplements and the content percentages of hypericin do not match, and it reveals the necessity of standardization in these products. When all the analyzes were evaluated, it is concluded that the sample **1** is likely to be a different species than *H. perforatum*. The threats to public health that may arise from the use of inaccurate plant species for health purposes should be carefully evaluated.

Acknowledgements:

This study was supported by a grant of TUBITAK 2209A

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OP176: QUANTIFICATION OF FATTY ACIDS IN CHIA SEED OILS OBTAINED WITH SFE-CO_2 AND COLD PRESS TECHNIQUES

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Introduction: Chia (*Salvia hispanica* L.; Lamiaceae family) is a herbaceous plant in nature and grown semi-annually (1). Chia seeds are currently consumed not only as seeds, but also as source of the fixed oil rich in valuable fatty acids. Chia seeds and chia seed oil are consumed as a food commodity and the oil is used as a dietary ingredient recommended in various dietary supplements (2). Chia seeds gained increasing commercial importance as a nutraceutical and food medicine in Turkey for recent decades. Chia seed oil offers a great future perspective for feed, food, medical, pharmaceutical and neutraceutical sectors (3).

Materials and Methods: Chia seed oils have been obtained from the black and white seeds by supercritical fluid extraction (SFE) and cold press techniques for comparison and quantification of the oil yields and fatty acid profiles. The conditions for SFE technique: pressure 200 bar, at 40 °C during 60 min and 210 min period. The chemical composition analysis and quantification of the fatty acids have been performed with C18 column, 1.9 um (150×3.3 mm), 60 °C, back pressure of 1700 psi, mobile phase 0.1 M formic acid in 2-propanole using ACQITY UPC2 system (Waters) programmed with Empower III software equipped with QDA detector.

Results: The highest oil yield (17.9%) was found for the oil obtained under SFE conditions during 210 min from the white seeds, while the lowest yield (10.27%) was from the black seeds under SFE during 60 min. α-Linolenic, linoleic, palmitic, oleic and stearic acids have been found as the main constituents in all the oils obtained. The percentage of the fatty acids varied according to applied extraction technique and seed variety. α-Linolenic acid content tends to increasing under SFE conditions (from 55.2% to 72.16% in white seeds, from 66.02% to 67.96% in black seeds). Extraction during 210 min resulted by increasing in percentage of α-linolenic acid (from 72.16% to 73.2%) and decreasing amount of linoleic acid (from 20.33% to 18.63%) in white seeds.

Conclusions: The chia black and white seeds were evaluated for the oil yields and fatty acids profiles, the effects of extraction techniques were investigated. The potential of application of SFE-CO_2 technique for chia seed oil extraction was evaluated.

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This study was supported by a grant of Eskisehir Technical University Scientific Research Projects (Project №19ADP063)

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OP177: QUALITATIVE AND QUANTITATIVE ANALYSIS OF ISOORIENTIN IN *LINUM ARBOREUM* AND *LINUM FLAVUM SSP. SCABRINERVE*

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Introduction: *Linum* (Linaceae) consists of 230 species that are widely distributed around the World. Lignans are widely distributed in the plant kingdom and show a wide variety of biological activities: antitumour, anti-HIV, immunosuppressive, hipolipidemic, antifungal, phytoestrogenic and antiasthmatic activities (1). Aryltetralin type lignans (podophyllotoxin derivatives) as the major secondary metabolites of *Linum* species play an important role in the production of chemotherapy drugs (etoposide, teniposide and Etopophos® are semisynthetic derivatives of podophyllotoxin). The genus *Linum* is usually divided into the following five sections: *Syllinum*, *Cathartolinum*, *Dasylinum*, *Linum* and *Linastrum* (2). Generally, aryltetralin types of lignans have been reported in the section *Syllinum*. In Turkey, genus *Linum* is represented by 39 species. The aim of this work was to identify and quantify phenolic acids and flavonoids content of two *Linum* species are member of section *Syllinum* (3).

Materials and Methods: In the present study, we examined phenolic acids and flavonoids content of methanol extracts of *Linum arboreum* and *Linum flavum* ssp *scabrinerve*. Reversed phase high performance liquid chromatography (RP-HPLC) with UV detection was employed for the identification and quantification of the phenolic acids and flavonoids. In total 22 standards including p-coumaric acid, syringic acid, catechic

acid, gallic acid, ferulic acid, chlorogenic acid, quercetol, orientin, isoorentin, galangin, luteolin, hyperoside, hesperetin, arbutin, rutin, genistein, apigenin, isoquercitrine, quercitrine, kaempferol, naringin, naringenin were examined.

Results: As a result of our work, only isooirentin was determined out of 22 standards. The amounts of isoorientin at concentrations of 1 mg / ml of methanol extracts of *Linum arboreum* and *Linum flavum* ssp *scabrinerve* are 34.83602 ± 0.276315 (µg ± standard deviation) and 12.48527 ± 0.02729 (µg ± standard deviation), respectively.

Conclusions: As a result of the study, it has been proven that *Linum arboreum* and *Linum flavum* ssp *scabrinerve* contain significant amounts of isoorientin. In further studies, it is recommended to investigate other flavonoid and phenolic acid standards.

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OP178: CYTOKINE-BASED ANTI-INFLAMMATORY STUDIES ON *Acanthus spinosus*-L.

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Introduction: *Acanthus* L. represented by 30 species in the world (1). The species are used in the treatment of different diseases such as rheumatism, hepatitis, and injury, in Turkey and globally due to their anti-inflammatory effects (2, 3). In the current study we aimed to investigate the anti-inflammatory potential of *Acanthus spinosus* and its active compounds via proinflammatory cytokine levels.

Materials and Methods: Aerial parts of *A. spinosus* were extracted with methanol. Water-soluble part of methanolic extract partitioned with petroleum ether. Aqueous extract was subjected to polyamide column for main fractionation to get Frs. A-C. Isolation studies were conducted on these three fractions to get four pure compounds. Anti-inflammatory potential of the aqueous extract, fractions and pure compounds were determined on LPS induced RAW 264.7 macrophages via proinflammatory cytokines; nitric oxide (NO), prostaglandin E2 (PGE2), interleukin-6 (IL-6), tumor necrosis factor-α (TNF-α). Cytotoxic activities of tested samples on RAW 264.7 cells were also examined by MTT method.

Results: Concentrations of extract (20-400 µg/mL), fractions (10-200 µg/mL), and isolated compounds (1-50 µM) with no cytotoxic effects were selected for the anti-inflammatory effect assay. Structures of the isolated compounds were elucidated as *β*-hydroxy acteoside [**1**], acteoside [**2**], 2,4-dihydroxy-1,4-benzoxazine-3 (2H)-one [**3**], 2-*O*-*β*-glucopyranose-4-hydroxy-1,4-benzoxazine-3(2H)-one [**4**] according to advanced spectroscopic methods. The aqueous extract decreased PGE2 and NO levels in LPS stimulated RAW 264.7 cells significantly at the concentrations of 10 and 100 µg/mL, respectively ($p<0,001$). Fr. B, one of the active fractions, inhibited significantly production of all tested cytokines at 10 µg/mL ($p<0,001$). Compound **3**, from Fr. B, significantly reduced NO and PGE2 levels at 5 µM ($p<0,001$) compared to LPS treated group.

Conclusions: In this study, the anti-inflammatory effect of *A. spinosus* has been proven, the compounds that may be responsible for the effect and the cytokines that play a role in the effect were discussed.

Acknowledgements

This study was supported by a grant of Hacettepe University Scientific Research Project Coordination Unit (THD-2019-18123)

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OP179: ESSENTIAL AND FIXED OILS OF SICILIAN PLANTS AS PHYTOTHERAPEUTIC SOURCES

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Introduction: The floristic peculiarities of Sicily and its satellite islands make these insular territories an independent phytogeographical entity of the Mediterranean floristic region. The Italian

vascular flora checklist reports 3010 for Sicily, mostly native but with naturalized elements. Of these taxa 137 species, over 4%, are protected by national and international regulations (1). Our interest is aimed at the study of essential oils and fixed oils obtained from endemic, anthropic and spontaneous Sicilian plants, such as *Ridolfia segetum*, *Anthemis secundiramea*, *Elaeoselinum asclepium* (L.) Bertol subsp. *meoides* and *Ceiba speciosa* (A. St.-Hil.). In particular, antimicrobial activity, antioxidant activity, hypoglycemic and antilipidemic effects, and anti-insecticide activity were evaluated.

Materials and Methods: All plants analyzed were collected during the flowering period and typical specimens have been deposited in *Herbarium Mediterraneum Panormitanum* of Palermo, Italy. All oils, both essential and fixed were characterized by GC-MS, using authentic standards and comparing the RI and MS with those present in different databases.

Results: The *R. segetum* flower EO showed relevant insecticidal activity against *C. quinquefasciatus, Musca domestica* and *Spodoptera littoralis* (2)*;* the fixed oil of *Ceiba speciosa* exerts both hypoglycaemic and anti-obesity effects (3); *A. secundiramea* essential oil has relatively good antibacterial activity against both gram-negative and positive strains tested, and is non-toxic for eukaryotic cells at the applied concentration (4); finally, EO of *E. asclepium* subsp. *meoides* showed promising antimicrobial activities against *B. subtilis*, *S. aureus* and *P. vulgaris* (5).

Conclusions: This study showed how both fixed oils and essential oils of Sicilian endemic or spontaneous plants, can be used for phytotherapeutic purposes, counteracting factors such as obesity, destroying harmful bacterial colonies and inhibiting the birth of insects that carry dangerous diseases.

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OP180: ISOLATION OF SALMONELLA BACTERIOPHAGE IN POULTRY AND ITS CHARACTERIZATIONS

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Introduction: The prevalence of Salmonella in poultry, which is the primary source, should be minimized in order to prevent and control Salmonella infection, which is one of the microorganisms that is an important public health problem. For this, bacteriophages can be used as biological agents (1). In the USA, The Food and Drug Administration (FDA) has authorized commercial phage preparations as additives to prevent foodborne illnesses caused by *Listeria monocytogenes* and Salmonella (2, 3). The aim of this study is to obtain lytic Salmonella phage and evaluated its stability in different conditions.

Materials and Methods: A total of 25 poultry feces samples from 11 poultry farms in Ankara between January 2021 and February 2021 were used in this study. Salmonella phages from these samples were isolated and purified (4). Phage stocks were obtained by reproducing the phages and the host ranges values determined with Salmonella isolates. MOI value of selected phage was measured and its pH (below pH 5 to above pH 9) and thermal (50 °C to 70 °C) stability was evaluated.

Results: Eight phages have been isolated. "A" phage was used in our study. Because of the lytic efficiency of 84% among the phages isolated, it also has a large and clear plaque in terms of plaque morphology. The effective MOI value of this phage is 0.1. In the environmental resistance tests of this phage, it was determined that the pH 5 was resistant to the conditions. Phages were found to be resistant at 50°C and sensitive at 70°C.

Conclusions: These results show that the phage can be active at body temperature and can still be infected and reproduce after exposure to acidic conditions encountered in the stomach. This situation gives hope for the treatment of bacterial infections.

Acknowledgements

This research was supported by the Scientific Research Projects Directorate of Ankara University (Project number: 21L0237004). We would like to thank Dr. Orkun Babacan for Salmonella isolates.

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OP181: THE COMBINATORY ANTIFUNGAL ACTIVITY OF CURCUMIN AND QUERCETIN ON *CANDIDA SPP*.

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Introduction: *Candida spp*. are an important group of opportunistic pathogenic fungi. *Candida albicans* is the most common type in the clinic, nearly 10 species are among the opportunistic agents of mycosis. A wide variety of treatment options include antifungal creams, ointments, instillation solutions or systemic treatment options (1). But the number of agents used is limited. Nowadays, treatment options including natural active ingredients are reconsidered for fungal pathogens as well as for all microbial infectious agents (2). In this study, we aimed to determine the combinatory antifungal activity of curcumin and quercetin on selected *Candida spp*.

Materials and Methods: Antifungal activity of curcumin and quercetin were carried against *Candida albicans* ATCC 10231, *Candida albicans* ATCC 90028, and *Candida parapsilosis* 22019. Minimum Inhibition Concentrations (MIC) evaluated by micro broth dilution test with 1024-1 μg/ml doubling dilutions. Combinatory activity evaluated with checkerboard test (3). Doubling dilutions were determined according to MIC results (4xMIC to MIC/16). Experiments were carried duplicate.

Results: Micro broth dilution test results showed that curcumin and quercetin has antifungal activity at 256 μg/ml concentration for *C. albicans*. MIC values of curcumin and quercetin were 8 μg/ml and 128 μg/ml, respectively for *C. parapsilosis*. According to checkerboard test FICI (Fractional Inhibitory Concentration Index) values were 0.75, 1, and 1.5 for *C. albicans* ATCC 10231, *C. albicans* ATCC 90028, and *C. parapsilosis* 22019, respectively.

Conclusions: Evaluating the experimental results, we think that both curcumin and quercetin can be revaluated in treatment options only after with formulations that will provide stability and increase bioavailability.

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OP182: DETERMINATION OF VIRULENCE AND TRIAZOLE DRUG SUSCEPTIBILITY OF WILD TYPE AND FLUCONAZOLE ADAPTED STRAINS OF *MAGNUSIOMYCES CLAVATUS*

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Introduction: *Magnusiomyces clavatus* is a whitish arthroconial yeast-like fungi. It is an opportunist in humans and regular colonizers of wet in-house environments such as dishwashers. *M. clavatus* is an emerging etiological agent of bloodstream infections in patients with acute hematological malignancies (1). There is an urgent need for more knowledge about virulence and drug resistance profiles of *M. clavatus* in the field. Thus, in this study, azole drugs susceptibility, drug adaptation profiles, and virulence-related enzymatic activities of *M. clavatus* strains were aimed to be evaluated.

Materials and Methods: In this study, minimal inhibition concentrations (MIC) for fluconazole (FLU), voriconazole (VOR), itraconazole (ITZ), and isavuconazole (ISV); biofilm formation, and enzymatic activities of hemolysis, phospholipase, esterase, aspartyl protease were examined for 1 reference (CBS 132759) and 4 environmental *M. clavatus* isolates including FLU-adapted and wildtype groups in comparison to reference clinical strains of *Candida* genus including *Candida albicans* (ATCC 14053) and *Candida glabrata* (ATCC 15126) (1-4).

Results: The MIC values for wild-type *M. clavatus* were in the range of 8-32 μg/mL for FLU, 0.25-2 μg/mL VOR, 0.125-1 μg/mL for ITZ, and 0.06-0.25 μg/mL for ISV. For FLU-adapted strains, MIC values showed rise to 5.84-, 1.94-, 1.31-, and 2.38-fold on average, for FLU, VOR, ITZ, and ISV, respectively. After taking FLU-adapted strains back to drug-free conditions, they continued to show a decreased FLU susceptibility in comparison to those of wild-type strains (2.92-5.84-fold FLU MIC in 7 days). In addition, similarly with those of *Candida albicans* and *Candida glabrata, M. clavatus* strains showed strong phospholipase, however no esterase and aspartyl protease activity were observed. Also, a range of 1.60-2.66-fold increase was observed for biofilm formation for fluconazole-adapted *M. clavatus* strains.

Conclusions: It was determined that *M. clavatus* strains have important features for pathogenicity. The rapid adaptation of *M. clavatus* strain to increasing concentrations of fluconazole, a first-line antifungal drug in the treatment of fungal infections, indicates that it may have the potential to be multi-resistant to other triazole drugs.

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OP183: ANTIBIOFILM ACTIVITY OF TWO NEW GENERATION DISINFECTANTS

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Introduction: Disinfectants are chemical agents which are extensively used in hospitals and other healthcare settings, to inhibit or destroy microorganisms and consequently to prevent infections. New generation disinfectants are defined as products that are completely broken down in nature without harmful residues in the environment. They are also defined as non-carcinogenic products for users. Chlorine dioxide (ClO_2) and hypochlorous acid (HOCl) are powerful oxidizing agents. Both of them are used as new generation disinfectants. Their degradation products are safe for the environment (1, 2). This study aimed to evaluate the antibiofilm activity of two new generation disinfectants against *Staphylococcus epidermidis* and *Pseudomonas aeruginosa*.

Materials and Methods: In this study, Ar-Dez Sniper® (0.2 % chlorine dioxide) and Crystalin® (hypochlorous acid) were used as new generation disinfectants. *Pseudomonas aeruginosa* PAO1 and *Staphylococcus epidermidis* ATCC 35984 were used as biofilm-forming test bacteria. The antibiofilm activity was determined by in vitro microplate-based biofilm model at various contact times. The crystal violet assay was used to determine antibiofilm activity. Optical density values were measured at 620 nm. The percentage inhibition values of biofilms were calculated (3, 4).

Results: Chlorine dioxide-containing disinfectant showed antibiofilm activity against *S. epidermidis* at one and ten minutes (47,1% and 44,2%, respectively). However, no activity was detected against *P. aeruginosa* at the tested contact times. Hypochlorous acid-containing disinfectant showed antibiofilm activity against both Gram-positive and Gram-negative bacteria at one and two minutes (41,8%-35,6% and 41,3%-60,7%, respectively).

Conclusions: The findings indicate that the tested new generation disinfectants may used as antibiofilm agents. Hypochlorous acid-containing disinfectant showed a broad spectrum of antibiofilm activity against both Gram-positive and Gram-negative tested bacteria compared with chlorine dioxide-containing disinfectant.

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OP184: ANTIBIOFILM AND ANTIBACTERIAL EFFECTS OF METABOLITES OF *BACILLUS SP.* ISOLATED FROM SOIL

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Introduction: Bacterial metabolites are products that are produced as a result of metabolic reactions. They can be grouped into two classes as primary and secondary metabolites (1). Bacillus species are industrially important bacteria due to their easy reproduction properties, resistance against unfavorable environmental conditions, and metabolic properties such as the production of antibiotics, enzymes, and toxins. The secondary metabolites produced by these bacteria are widely used in agricultural, pharmaceutical, and industrial fields (2). This study aimed to investigate the antibiofilm and antibacterial effects of metabolites of *Bacillus* sp. isolated from soil.

Materials and Methods: Soil samples were collected from Ankara and Afyonkarahisar. Soil originated *Bacillus* sp. isolates were identified by conventional methods. For obtaining metabolites, the cultures were filter-sterilized. The antibacterial effects of the metabolites were investigated against *Escherichia coli* ATCC 25922, *Pseudomonas aeruginosa* ATCC 27853, *Klebsiella pneumoniae* ATCC 13883, and *Staphylococcus aureus* ATCC 25923 using agar disc-diffusion and well diffusion tests. The antibiofilm activity was determined by in

vitro microplate-based biofilm model against *P. aeruginosa* PAO1 and *S. epidermidis* ATCC 35984 using by the crystal violet assay. The percentage biofilm inhibition values were calculated (3,4).

Results: According to the results of the disc diffusion test, only two metabolites showed weak antibacterial activity against *K. pneumoniae*. No antibacterial effect was detected for the rest of the metabolites. The percentage biofilm inhibition values of the metabolites against *S. epidermidis* (23,47%-22,62%-12%-11,39%-9,55%-7,71%-4,67%) and *P. aeruginosa* (40,83%-27,44%-20,66%-14,57%-14,08%-14,03%-12,16%-4,24%-1,45%) were variable.

Conclusions: Although the tested bacterial metabolites did not demonstrate a strong antibacterial effect against the test bacteria, their antibiofilm effects were found to be variable. More comprehensive studies with more samples are needed to find effective metabolites.

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OP185: ANTIBACTERIAL AND ANTIBIOFLIM ACTIVITY OF NISIN AGAINST METHICILLIN RESISITANT *STAPHYLOCOCCUS AUREUS* ISOLATES

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Introduction: Methicillin resistant *Staphylococcus aureus* (MRSA) is one of the nosocomial infectious agents, usually causes significant morbidity, mortality rates and increase in limited and inefficient antibiotic treatment due to the its multi-drug resistance mechanisms. Biofilm formation is also a resistance factor among the problems that render traditional antimicrobial treatments ineffective. Antimicrobial peptides are among promising candidates for the future treatment of antibiotic-resistant bacterial and biofilm-associated infections. On this basis, the aim of this study was to determine the antibacterial and antibiofilm activity of nisin, an antimicrobial peptide, against MRSA isolates.

Materials and Methods: Antibacterial activity of nisin against 25 MRSA isolates was determined by broth microdilution method as a minimal inhibition concentration. Antibiofilm activity was evaluated according to modified Stephanovic et al.'s method (1) and results were achieved as a percentage reduction. *Staphylococcus epidermidis* ATCC 35984 was used as control.

Results: It was determined that the MIC values of nisin on the isolates varied between 1.95-7.81 µg/ml. It was detected that 20 of the 25 isolates were found to be biofilm producers from weak to strong. The biofilm inhibition of the isolates by nisin varied between 10-91% at MIC/2 and between 0.025-46% at MIC/4 value. It was also determined that MIC/8 concentration of nisin reduced the biofilm formation of a single isolate by 5.8% and this value did not affect the biofilm production of other isolates.

Conclusions: Nisin, as an antimicrobial peptide, was found to have antibacterial and antibiofilm activity in varying degrees on MRSA isolates. It is planned to investigate the utility of nisin in combination with various agents in virulence therapies.

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OP186: ANTIBACTERIAL ACTIVITY OF SOME ANTIDEPRESSANT ACTIVE SUBSTANCES AGAINST CLINICAL *ACINETOBACTER BAUMANNII* ISOLATES

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Introduction: Antidepressants are long-term used drugs that treat the symptoms of depressive disorders. Besides their main therapeutic effects, some of them demonstrate antimicrobial activity. Studies have shown that fluoxetine and sertraline which are belong to selective serotonin reuptake inhibitors (SSRI) have antibiotic modulating activities as well as antimicrobial activities (1, 2). *Acinetobacter baumannii* is one of the primary causes of hospital infections (3). This study aimed to investigate the antibacterial activity of fluoxetine, sertraline, and amitriptyline against clinical *A. baumannii* isolates.

Materials and Methods: In this study, ciprofloxacin, gentamicin, imipenem, and colistin susceptible and resistant clinical *A. baumannii* isolates were used. *A. baumannii* ATCC 1709 and *A. baumannii* ATCC

1799 were used as standard strains. The antibacterial activity of fluoxetine, sertraline, and amitriptyline was determined by using the broth dilution method. The minimum inhibitory concentration test was performed in the concentration range of 25-0,195 µg/ml of active substances (4).

Results: Fluoxetine and sertraline possessed activity having MIC values of 6,25-12,5-25 µg/ml against all test bacteria. Amitriptyline possessed activity having MIC values of 25 µg/ml against only one susceptible isolate and *A. baumannii* ATCC 1709 strain. The antidepressant active substance that has the best antibacterial effect on sensitive test bacteria was found to be sertraline.

Conclusions: The findings indicate that SSRI antidepressants showed better antibacterial activity. In addition to the different usage purposes of these drugs, their effects on microflora should be considered.

Acknowledgments

This study was supported by a grant of TUBITAK (SBAG-119S907)

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OP187: IN VIVO EFFECT OF *Origanum majorana* L. ESSENTIAL OIL ON *Galleria mellonella* LARVAE

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Introduction: The *Galleria mellonella (G.mellonella)* beetle is a member of the Galleriinae subfamily belonging to the Pyralidae family of the Lepidopteran order known as the wax moth (1). *G. mellonella* is among the preferred in vivo models for determining fungal and bacterial load, determining infectious agents and revealing effective treatment options (2,3). This study aimed to determine the infection of *G. mellonella* with *C. albicans* and the effects of the essential oil (EO) of *Origanum majorana* L. on in vivo model.

Materials and Methods: The essential oil (EO) of *O. majorana* was obtained from naturally growing samples of *O. majorana,* collected from the vicinity of Anamur, and then analyzed by GC/MS. The major compound of the essential oil was found to be carvacrol; 75.3%. *G. mellonella* larvaes were treated with *O.majorana* EO (10 µl) after a 2 hour incubation period on 37°C, which infected with *C.albicans* (ATCC 90028). The efficiency level of the *O. majorana* EO as revealed by evaluating the survival times of 24, 48, 72 and 96 hours.

Results: As a result, *C. albicans* -infected control group could not survive at the end of the 24th hour, however, all of the treatment group was still continuing its vital activities at the end of the 96th hour.

Conclusions: We think that the larval model is a reliable model in the investigation of the effects of fungal infections on the host cell. Due to this feature, *G. mellonella* larvae have become a preferred model in fungal pathogenesis and antifungal drug efficacy studies. Origanum etkisi ile ilgili bir cümle eklenebilir.

Acknowledgements

We thank Mr. Halil Bilen for providing *G. mellonella* larvae and sharing her knowledge and skills in production and rearing.

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OP188: ROLE OF EXOSOMAL miRNAS IN IMATINIB RESISTANCE OF CHRONIC MYELOID LEUKEMIA

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Introduction: It has been suggested that exosomes are involved in chemotherapy resistance by transferring genotypic profiles in cancer. In this study, we examined the role of exosomal miRNAs in the acquisiton of Imatinib resistance in chronic myeloid leukemia.

Materials and Methods: First, exosomes and exosomal miRNAs were isolated from K562S (sensitive) and K562R (Imatinib resistant) cells. In the next step,K562S cells were treated with exosomes derived from K562R cells and transmission of these exosomes were shown with flow cytometry and fluorescent microscopy. miRNA expression profiles of groups including K562S, K562R, S/exo, R/exo ve R/exo treated K562S and K562S cells were also determined by microarray analysis.

Results: It was found that hsa-miR-99a-5p exhibited 22.96 fold, 8.63 fold and 5.91 fold increased expression in K562R cells vs K562S cells, R/exo vs S/exo and R/exo treated K562S cells vs K562S cells respectively. Another miRNA hsa-miR-125b-5p also exhibited 20.92 fold, 9.52 fold and 4.63 fold increased expression in K562R cells vs K562S cells, R/exo vs S/exo and R/exo treated K562S cells vs K562S cells respectively. These results reveal hsa-miR-99a-5p and hsa-miR-125b-5p as the only two miRNAs which exhibited increased expression in K562R cells vs K562S cells, R/exo vs S/exo and R/exo treated K562S cells vs K562S cells. It was found that cancer pathways, miRNAs in cancer, drug resistance and some critical pathways regulating CML pathogenesis were among these pathways. In summary, in this study, we examined and found some exosomal miRNAs which may play roles in the transmittance of Imatinib resistance from K562R to K562S cells.

Conclusion: These miRNAs which were found to be transported by exosomes and associated with cancer and resistance profile can further be investigated with in vitro, in vivo and clinical studies and may be used as diagnostic markers. New therapeutic approaches for reversing drug resistance can also be developed with studies by targeting these miRNAs.

Acknowledgements

This study was supported financially by the Scientific and Technological Research Council of Turkey (Project number:115Z400).

OP189: EVALUATION OF THE EFFECTS OF SIRT5 MODULATORS ON THE APOPTOSIS OF K562 CELLS AND SIRT5 AND CYTOCHROME C PROTEINS

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Introduction: SIRT5 is found in the mitochondria and it is responsible for the removal of lysine, succinyl, malonyl, and glutaryl groups from target proteins. The role of SIRT5 in cancer has been least researched among the sirtuin family members until the recent years and it can function as a tumor promoter or suppresor in a cell dependent manner (1, 2). It has been shown that it deacetylates Cytochrome c and regulates the apoptosis of hepatocellular carcinoma (2). Resveratrol and Suramin modulates desuccinylase and deacetylase activities of SIRT5 (1). There are no studies in the literature showing the effects of Suramin and Resveratrol on the SIRT5 protein expression in K562 chronic myleloid leukemia cell line. Although the effects of Resveratrol on the proliferation and apoptosis of K562 cells are known (3), there are no studies evaluating the effects of Suramin on the apoptosis of K562 cells. The aim of this study is to determine the effects of Suramin and Resveratrol on the SIRT5 and Cytochrome c protein expressions and the effects of Suramin on the apoptosis of K562 chronic myeloid leukemia cells.

Materials and Methods: Cell viability was determined by MTT assay, SIRT5 and Cytochrome c protein expressions was determined by western blot analysis. To determine the apoptotic effects of SIRT5 modulators, cells were stained with Annexin V and apoptosis was assessed on Flow cytometry.

Results: According to our results, Suramin did not cause any changes in the cell proliferation and apoptosis of K562 cells. Resveratrol has been found to increase Cytochrome c protein expression while decreasing SIRT5 protein expression. Suramin was found to have no significant effect on SIRT5 and Cytochrome c protein expressions.

Conclusions: The apoptotic effects of Resveratrol may be associated with SIRT5 dependent pathways. Further studies should be performed to reveal this mechanism.

Acknowledgements

This study was supported by a grant of Ankara University Scientific Research Projects Coordination Unit with the project number 18H0237008.

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OP190: INVESTIGATION OF CYTOTOXIC AND APOPTOTIC EFFICACY OF ORCINOL IN SW480 HUMAN COLORECTAL CANCER CELLS

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Introduction: Colorectal cancer (CRC) is a disease that rapidly increases worldwide every year. Almost half of the diagnosed patients lose their lives from this disease every year (1). Therapeutic methods, including surgery, radiotherapy and available chemotherapy options, which are traditional treatment methods for CRC treatment, have low efficacy and many side effects. Due to all these problems, the development of novel agents for the treatment of CRC gains importance (2). In this study, we aimed to investigate the cytotoxic and apoptotic effects of orcinol, a compound which has antioxidant and cytotoxic properties on different cell lines, in human SW480 colorectal carcinoma cells.

Materials and Methods: SW480 human colorectal cancer cells were cultured in DMEM medium and the cytotoxic effect of orcinol at various concentrations was determined by MTT cell viability assay. The phosphatidylserine exposure to outer cell membrane was determined by Annexin V binding assay.

Results: The findings showed that orcinol reduced cell viability significantly at treated concentrations and the IC_{50} concentration was determiend as 12.45 mM. It has also been found that orcinol, a water-soluble polyphenolic compound, increases annexin V binding to cells at treated concentrations revealing the apoptotic efficiency of compound.

Conclusions: As a result of this study, it has been observed that orcinol is promising compound for inhibition of the proliferation of SW480 cells. In order to evaluate the anticancer efficacy of the orcinol according to the results of the study, further studies are planned in the future to elucidate the mechanisms underlying these effects.

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OP191: INVESTIGATION OF *IN VITRO* PHOTODYNAMIC THERAPY EFFECTS OF WATER SOLUBLE Zn (II) PHTHALOCYANINE ON HCT-116 CELLS

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Introduction: Colorectal cancer is the third most common type of cancer in the world (1). Surgery and radiotherapy are applied either alone or in combination with chemotherapy in the treatment of colorectal cancer. The high prevalence of resistance and non-selectivity of antineoplastic agents are leading cause of failure and mortality during chemotherapy in colorectal cancer (2). Photodynamic therapy (PDT) is a new method for the diagnosis and treatment of cancer. In contrast to normal cells, PDT has a greater effect on tumour cells in the patient's body. Phthalocyanines are used in PDT as a photosensitizer which generates cytotoxic reactive oxygen species in the presence of light that leading to cell death through pathways such as apoptosis, necrosis, or autophagy (3). In this study, we aimed to determine the PDT effects of water-soluble Zn(II) phthalocyanine bearing benzenaminium derivatives (**BZnPc**) on human colorectal cancer cells (HCT-116).

Materials and Methods: The DNA photodamage, oxidative photodamage, and topoisomerase I inhibitory effects of **BZnPc** were investigated using agarose gel electrophoresis. In order to determine the DNA photodamage mechanism, the quenching of DNA damage was monitored in the presence of various scavengers (DMSO, SOD, and NaN_3) on agarose gel electrophoresis. The cytotoxic and phototoxic effects of **BZnPc** were assessed using MTT assay on HCT-116 cells for 24 h.

Results: BZnPc showed remarkable DNA photodamage and oxidative photodamage in a concentration/light dose-dependent manner via singlet oxygen pathway. It displayed high inhibitory effects against topoisomerase I. MTT test results indicated that **BZnPc** had a more significant phototoxic effect than its cytotoxicity ($p<0.0001$). The IC_{50} values of **BZnPc** for cytotoxicity and phototoxicity were found to be 0.16 ± 0.01 and 1.26 ± 0.25 µM, respectively.

Conclusions: These results observed that the compound has a promising PDT agent candidate for future research.

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OP192: ANGIOTENSIN II INDUCES NLRP1 INFLAMMASOME ACTIVATION IN HCN-2 CELL LINE

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Introduction: Hypertension affects many organs including heart, kidney and brain. Overactivation of renin-angiotensin system has a critical role in the pathogenesis of hypertension. Recent studies show that increased levels of Angiotensin II (Ang II) contributes to apoptosis, plasticity changes and neuroinflammation. However, the effect of Ang II on NLRP1 inflammasome activation remains unclear. In this study, we aimed to evaluate NLRP1 inflammasome activation in human cortical neuronal cell line (HCN-2) following Ang II treatment.

Materials and Methods: HCN-2 cell line used in this study were suspended in complete Dulbecco's modified Eagle Medium (DMEM) (Life Technologies, Gibco BRL, Grand Island, NY) supplemented with 10 % fetal bovine serum (FBS, Hyclone) and plated in cell culture dishes. The cultures were maintained at 37 °C in 5% CO_2 95% humidified atmosphere. After reaching 85 % confluence, cells were transferred to 6-well plates ($5x10^5$ cells/well) and allowed to adhere for 24 h. Then, cells were treated with 0.1 µM, 1 µM or 10 µM Ang II for 6 or 24 h. Following treatments, NLRP1 and cleaved caspase-1 protein levels were determined by Western Blotting. Statistical evaluation was performed using Student's *t*-test.

Results: At 24h, NLRP1 protein levels were significantly increased by 2.48-fold and 1.85-fold following 1 µM and 10 µM Ang II treatment, respectively, when compared to untreated cells ($p<0.05$). Similarly, Ang II significantly altered cleaved caspase-1 levels at higher concentrations.

Conclusions: Control of inflammation is extremely valuable in terms of both blood pressure regulation and neuronal protection. Our results show that NLRP1 inflammasome activation in brain cells is triggered by Ang II and it can be suggested that the regulation of inflammatory mechanisms induced by Ang II may help to maintain neuronal health.

Acknowledgements

This research was funded by Ege University Research Foundation (BAP) under grant number TDK-2020-22123. The authors acknowledge the Pharmaceutical Sciences Research Centre (FABAL) of Ege University, Faculty of Pharmacy for equipmental support.

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OP193: DEVELOPMENT OF LABEL-FREE ELECTROCHEMICAL IMMUNOSENSOR FOR LEPTIN DETERMINATION

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Introduction: Leptin is a hormone and plays a crucial role in regulating energy intake and consumption (1, 2). Leptin levels are associated with obesity, metabolic abnormalities, infertility, and cancer. Therefore, it is vital to determine leptin to discover not only the functions of leptin but also its relationship with diseases (3). For the determination of leptin, there are various analytical methods. Electrochemical immunosensors can also be used due to their advantages, such as simple pretreatment, low cost, rapid determination, and high sensitivity (4).

Materials and Methods: The label-free immunosensor prepared for leptin determination is given in Figure 1. The measurements in the electrochemical immunosensor system were performed using $[Fe(CN)_6]^{3-/4-}$ redox probe by DPV.

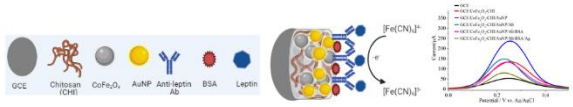

Figure 1. Preparation process of label-free leptin immunosensor

Results: A simple and effective label-free electrochemical immunosensor based on GCE/$CoFe_2O_4$-CHI/AuNP/Ab electrode for leptin detection was developed. The pH of the redox solution and the antibody concentration were optimized. Under the optimal conditions, the approach provided a good linear response range from 1 to 4000 ng/ml with a detection limit of 1 ng/ml.

Conclusions: It has been concluded that the prepared label-free immunosensor is suitable for quantitative analysis of leptin, and it can be developed for medical research as an alternative with its simple, sensitive, easy, inexpensive preparation equipment and rapid measurement.

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OP194: PRENATAL STRESS MAY INCREASE THE RISK OF DEVELOPING ALZHEIMER-LIKE NEUROPATHOLOGY IN THE HIPPOCAMPUS OF RATS

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Introduction: Neuroplasticity is the ability of central nervous system for adapting its structural and functional organization according to developmental and environmental influences. It has been revealed that prenatal stress is affecting brain functions in early life and underlies various diseases during adulthood (1). Alzheimer's Disease (AD) is the most common form of dementia and characterized by progressive cognitive decline. The neuropathologic hallmarks of AD are amyloid plaques (AP) and neurofibrillary tangles (NFT) (2). We searched the effects of prenatal stress on neuropathologic changes specific to AD through amyloid beta peptide generation and tau hyperphoshorylation in hippocampus.

Materials and Methods: Prenatal stress were induced in rats with dexamethasone (Dex), a synthetic glucocorticoid (3). From GD 14 to GD 21, pregnant rats were injected daily with Dex at a dose of 200 µg/kg s.c. (Dex group) or saline (control group). After the birth, at the age of 3 months, male rats were decapitated (n=5) and hippocampuses were dissected on ice. The effects of Dex were investigated by real-time PCR in hippocampus through the mRNA levels of amyloid precursor protein (APP), beta-secretase 1 (BACE1), microtubule-associated protein tau (MAPT), glycogen synthase kinase 3β (GSK-3β). The amyloid beta peptide (1-42) (Aβ(1-42)) and tau levels were measured with ELISA. Statistical analyses were performed by one-way analysis of variance.

Results: Prenatal Dex exposure caused significant increases in mRNA expressions of BACE1 and GSK-3β while decreased MAPT mRNA expression. No signficant differences were found in the mRNA level of APP gene between control and Dex groups. Aβ(1-42) and tau levels were significantly elevated in Dex group when compared to control.

Conclusions: The results of this study showed that prenatal stress induced by Dex caused significant changes in hippocampal Aβ(1-42) and tau levels, and expression levels of genes that involved in APP processing, Aβ(1-42) generation and tau hyperphoshorylation. It was concluded that prenatal stress may trigger development of Alzheimer-like neuropathology in the hippocampus and represent a new therapeutic strategy against AD.

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OP195: DETERMINATION OF THE FIBRINOGENOLYTIC ACTIVITY OF *MONTIVIPERA RADDEI* (RADDE'S MOUNTAIN VIPER) VENOM BY POLYACRYLAMIDE GEL ELECTROPHORESIS

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Introduction: Viper venoms contain some enzymes that play an important role in the blood coagulation process (1). These molecules have become valuable in the laboratory diagnosis and treatment of hemostatic disorders. Thrombin-like fibrinogenolytic enzymes have gained attention in this regard and number of biotechnological products have been developed (eg. batroxobin) (2). In this study, it is aimed to investigate the fibrinogenolytic activity of *Montivipera raddei* venom for the first time and find out the main protease family which is responsible for the fibrinogenolytic activity.

Materials and Methods: Crude venom obtained from *M. raddei* was incubated with human fibrinogen for different times at 37 °C. In addition, inhibition study was carried out with by pre-incubating venom with different protease inhibitors such as Ethylenediaminetetraacetic acid, Phenylmethylsulfonyl fluoride, 1,10-phenanthroline and aprotinin. Fibrinogenolytic activity was assessed by using routine SDS-PAGE and fibronogen zymography methods.

Results: Enzymes cleaving only the Aα chain of fibrinogen were detected in *M. raddei* venom. This effect was observable at 10th minute and Aα chain was completely degraded at the 60th minute. It was concluded that EDTA and 1,10-phenanthroline, which are metalloprotease inhibitors, inhibited the activity of fibrinogenolytic enzymes in the venom, so the bands of the Aα chain did not disappear on SDS-PAGE gels. These results suggest that main enzymes responsible for fibrinogenolytic activity of *M. raddei* venom belong to the metalloprotease family. It was also found by fibronogen zymography

that the main fibrinogenolytic enzymes in *M. raddei* venom have molecular weights of approximately 75 and 50 kDa.

Conclusions: This is the first study revealing the presence of fibrinogenolytic enzymes in *M. raddei* venom. Our results will guide the following isolation and characterization studies of novel thrombin-like enzymes that might have diagnostic and therapeutic potential.

Acknowledgements

This study was supported by Research Fund of the Nevsehir Haci Bektas Veli University (Project Number: ABAP20F28). The presenting author received a TUBITAK 2210-C MSc fellowship during the studies.

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OP196: PROPHYLACTIC EFFECT OF MYRICETIN AND APIGENIN AGAINST LIPOPOLYSACCHARIDE-INDUCED ACUTE LIVER INJURY

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Introduction: Endotoxemia is defined as a common bacterial infection originating from the blood causing excessive damage by spreading from one tissue to another (1). This study has been designed to elucidate the anti-inflammatory and antioxidant effects of myricetin and apigenin in lipopolysaccharide (LPS)-induced acute liver injury and the possible molecular mechanisms involved in such protection.

Materials and Methods: Thirty-six mice were randomly divided into 6 groups as; control, lipopolysaccharide (LPS) (5 mg/kg) (2), LPS + myricetin (100 mg/kg), LPS + myricetin (200 mg/kg), LPS + apigenin (100 mg/kg), and LPS + apigenin (200 mg/kg) groups. Myricetin and apigenin were administered orally for 7 days, and LPS was administered intraperitoneally only on the 7th day of the study. 24 hours after LPS application, all animals were sacrificed and serum biochemical parameters, histopathology and oxidative stress and inflammation markers of liver tissue were examined.

Results: Myricetin and apigenin pre-treatments increased serum albumin and total protein levels, liver GSH level and catalase and SOD activities and decreased serum ALT, AST, ALP, γ-GT, CRP, total and direct bilirubin levels, liver MPO activity, MDA, NOx, PGE2, TNFα, IL-1β, and IL-6 levels, iNOS and COX-2 mRNA levels, phosphorylation of NF-κB p65, IκB, and IKK proteins but not p38, ERK, and JNK proteins in LPS-treated mice. Myricetin and apigenin administration also regained the hepatic architecture disrupted during LPS application.

Conclusions: In conclusion, these phytochemicals may act as a potential agent to prevent acute liver injury. We can conclude that the results of this study may be a new preventive medicine strategy in the prophylaxis of liver damage that may occur as a result of endotoxemia and sepsis.

Acknowledgements

The authors sincerely thank the laboratory assistant in Van Yuzuncu Yil University, Faculty of Pharmacy, Departments of Biochemistry and Pharmaceutical Biotechnology

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OP197: TOLUIDINE BLUE O DECREASES TAU PHOSPHORYLATION AT THR181 AND SER202/THR 205 IN N2A MOUSE NEUROBLASTOMA CELLS STABLY EXPRESSING THE HUMAN SWEDISH MUTANT APP695

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Introduction: Alzheimer's disease (AD) is characterized by intracellular neurofibrillary tangles caused by abnormal phosphorylation of the microtubule-associated tau protein, amyloid plaques composed of β-amyloid peptide (Aβ, 40-42 aa) derived by proteolytic cleavage of amyloid precursor protein (APP) and loss of cholinergic neurons. Currently, most of FDA-approved AD drugs available on the market are cholinesterase inhibitors (ChEIs) that target the cholinergic system. Although ChEIs provide symptomatic therapy, recent findings have shown that some ChEIs can also affect amyloid metabolism and/or tau phosphorylation (1). Recently, we have demonstrated that toluidine blue O (TBO), a phenothiazine-structured compound, is a potent

inhibitor of acetylcholinesterase and butyrylcholinesterase (2) and also decreases extracellular Aβ40, Aβ42, sAPP expression in a dose-dependent manner in PS70 cells (3). Furthermore, our *in vivo* studies have shown that TBO reduces insoluble Aβ plaques while it does not affect tau pathology significantly at the selected treatment conditions in the hippocampus of 3xTgAD mice that mimic neuropathological features of AD (4). The aim of this study was to investigate whether TBO may affect tau pathology in N2a mouse neuroblastoma cells stably expressing the human Swedish mutant APP695 (N2a/APPSwe) cells.

Materials and Methods: N2a/APPSwe cells were treated with 0-5 μM TBO for 24 hours. After treatment, total tau levels were assessed by Western blot using HT7 antibody in cell lysates. Also the levels of tau phosphorylated at residues Thr181 and Ser202/Thr205 were detected using antibodies AT270 and AT8, respectively.

Results: Our findings demonstrated that TBO reduces the levels of total tau and phosphorylated tau at residues Thr181 and Ser202/Thr205 when compared to control.

Conclusions: Overall, our new data support the idea that TBO may be a promising drug candidate in the treatment of AD.

Acknowledgements

This study was supported by a grant from the Scientific Research Unit of Hacettepe University (HUBAB, TSA-2019-17288).

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OP198: INVESTIGATION OF *IN VITRO* ANTIOXIDANT, CYTOTOXIC AND MUTAGENIC ACTIVITIES OF ESSENTIAL OIL DERIVED FROM *Lavandula angustifolia* CULTIVATED in TURKEY

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Introduction: Today, depression is one of the most common diseases and can be described as a reflection of worsening mental conditions on daily activities. Drugs that used for the treatment of depression have several adverse effects such as nausea, constipation. Thus, new treatment strategies must be developed. Due to reasons like presence of adverse effects of drugs, usage of treatments with medicinal herbs (phytotherapy) and essential oils is increased in public-health. Our country has the natural flora that necessary for the cultivation of plants. *Lavandula angustifolia*, which is grown in many areas in our country and is produced efficient essential oil from its flowers, is important in traditional medicine because it is used for depression treatment and has no known adverse effects (1). The aim of this study is to determine the chemical profile of lavender essential oil, investigating probable *in vitro* antioxidant, cytotoxic, mutagenic and antienflamatuar activities of oil.

Materials and Methods: In this context, CCK-8 was used for cytotoxic effects (NIH/3T3) of *Lavandula angustifolia* essential oil (LA). For antioxidant activity both DPPH and TPC were used. In addition, the anti-inflammatory effect was also examined. The AMES test kits (TA98 and TA100) were used to determine the mutagenic activity.

Results: As a result of the cytotoxicity analysis of LA, the IC_{50} value was found to be 0.372 mg/mL. DPPH and anti-inflammatory experiments IC_{50}'s were found to be 6.522 mg/mL and 1.238 mg/mL, respectively. TPC was determined as 1.220 mg/mL. No mutagenic effect of LA was detected even at a concentration of 0.290 mg/mL.

Conclusions: This study provides an important contribution in terms of developing a medical product of standardized lavender essential oil, which is not present in Turkey at the moment.

Acknowledgements: This study was supported by the grants of Istanbul Medipol University (BAP-2020/15, BAP-2019/03).

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OP199: BRAIN-DERIVED NEUROTROPHIC FACTOR LEVELS IN BREAST CANCER

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Introduction: Brain-derived neurotrophic factor (BDNF) is a specific ligand for tropomyosin-associated kinase B (TrkB), a tyrosine kinase receptor, and activates several pathways, including the phosphoinositide-3 kinase pathway, upon binding of BDNF. It is suggested that BDNF-TrkB signaling mediates cancer cell resistance in chemotherapy and promotes the growth of cells through autocrine signaling in primary tumor cells. Autocrine BDNF-TrkB signal transduction is associated with cell proliferation, differentiation, survival, and invasion. We aimed to elucidate the role of BDNF-TrkB activation by examining BDNF levels in breast cancer (1).

Materials and Methods: Gazi University Faculty of Medicine Hospital General Surgery Outpatient Clinic and Dr. Abdurrahman Yurtaslan consists of 110 patients who applied to Ankara Oncology Training and Research Hospital General Surgery Outpatient Clinic and diagnosed with breast cancer and 110 healthy women without any systemic disease. Serum soluble BDNF level was measured in blood samples taken from the study group using commercial ELISA kit. Results were evaluated with SPSS 20.0 statistical program.

Results: Serum BDNF levels (11.12 ± 0.4 ng/mL) in patients with breast cancer were found to be significantly higher than those healthy controls (9.28 ± 0.6 ng/mL) ($p = 0.023$).

Conclusions: BDNF contributes to breast cancer cell survival and can serve as forward targets in attempts to inhibit tumor growth. It has been shown that resistance to apoptosis in breast cancer is stimulated by BDNF via TrkB-T1 (2). BDNF expression has been reported to be significantly higher in breast cancer samples compared to normal tissue (3). In our study, it was found that BDNF levels increased in the serum of breast cancer patients. In the light of these findings, it is thought that BDNF may be involved in breast cancer pathogenesis.

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OP200: THE EFFECT OF NEOPTERIN ON EPITHELIAL MESENCHYMAL TRANSITION DRIVING GENE EXPRESSIONS AT HCC

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Introduction: Increased neopterin (NP) levels is associated with the pathogenesis and progression of various diseases, including Hepatocellular carcinoma (HCC) which is considered the fourth leading cause of cancer deaths worldwide (1-3). Previously, we showed the effects of NP on the biological activities (e.g. proliferation and motility) of 5 different HCC cell lines which we categorized as *sensitive and resistant* on their proliferative and motility responses. NP results in a significant increase in the motility of 3 different HCC cell lines (e.g. *HuH-7, SK-Hep1, and SNU449*)[4]. Depending on these findings, we questioned whether NP involved in the alteration of epithelial-mesenchymal transition (EMT) at the molecular level. Therefore, in this study, we aimed to understand the main driving gene expression in EMT and proliferation/motility under the effect of NP treatment at the mentioned HCC cells lines.

Materials and Methods: RNA isolation, cDNA synthesis, and conventional PCR carried out for HCC cell lines (HuH-7, SK-Hep1, and SNU449) under the effect of NP treatment to assess the gene expressions related to proliferation/motility and EMT.

Results: 1. Decreased expression of c-myc under the effect of NP only found at SK-Hep1 cell line which was the only sensitive cell line among the other HCC cell lines used. **2.** Genes linked with EMT showed different expression patterns on each of 3 HCC cell lines but overall NP molecular signature appears to induce EMT.

Conclusions: C-myc expression showed no change at HUH-7 and SNU-449 cell lines under the effect of NP. Whilst, increased expression of p27(CDKI) and decreased expression of c-myc is compatible with the proliferation arrest at SK-Hep1 cells which have been shown in our previous study.

Different gene expression patterns related to EMT observed in HCC cell lines; increased levels of vimentin at HuH-7, decreased Ecad/increased vimentin/ increased Snail expressions at SNU449 and increased expression of Sox-2 at SK-Hep1 cells, indicating that different NP concentration alters EMT and hybrid epithelial/mesenchymal phenotype activity in these cells.

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This study received no external funding.

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OP201: HEALTHCARE SERVICES AND EMPATHY: EXAMPLE OF PHARMACY STUDENTS

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Introduction: Respect, openness and empathy are the basis of a quality communication process. Also, it's revealed that this has positive impacts on health outcomes (1). The aim of this study is to determine the empathy levels of pharmacy students, who are an important part of healthcare delivery' future.

Materials and Methods: In this study, a survey contained the Empathy Scale were applied to pharmacy students after the permission of the Hacettepe University Ethical Committee. The scale was developed by Baron-Cohen and Wheelwright (2), edited by Wakabayashi et al (3) and translated into Turkish by Bora and Baysan (4). SPSS ver.23 were used for descriptive statistics and performing the statistical tests to find the scale score differences between groups.

Results: The questionnaire was conducted between January 25, 2019 and March 25, 2019 with participation of 323 pharmacy students in Hacettepe University. 306 of them were evaluated for the statistical analysis. The mean score is 41,03 and the Cronbach's alpha internal consistency coefficient is 0,831. 88.37% of the students stated that to have empathy-related lecture on the undergraduate education is beneficial in terms of leaning the qualified healthcare services. The scale score of the students are presented on the Table.

Table 1. Scale score of students

Entrance year	Mean ± SD	Min-Max	p value
2014 and before	48,18±10,33	27-72	0,403
2015	46,69±12,30	24-66	
2016	45,87±10,18	23-66	
2017	45,97±10,24	21-70	
2018	47,33±8,77	25-69	

According to the ANOVA tests results, there are no statistical difference between the students' scale scores in terms of entrance year (p>0,05).

Conclusions: Empathy is a crucial skill for healthcare professionals to prevent medical errors and ensure patients safety. Within the scope of this study, it's revealed that empathy is one of the essential skills for pharmacy students and they stated this is improvable via education. In this sense, to plan and implement training activities are necessary actions for high skilled healthcare profession team members.

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OP202: A STUDY ON PATIENT EXPERIENCE IN COMMUNITY PHARMACIES: ISTANBUL PROVINCE SAMPLE

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Introduction: The number of community pharmacies opened and increasing competition conditions have also affected the community pharmacies as well as all businesses, and since it would not be wrong to describe the term customer experience as patient experience in the field of pharmacy practice. Thus, it is essential to understand customer experience/patient experence in community pharmacies. Understanding of patient experience in community pharmacies is possible with understanding customer engagement, service quality, trust, word-of-mouth, autobiographic memory considering pharmacy and personel. Our aim is to define the critical dimensions for creating a well-designed patient experience in community pharmacies and to evaluate the consequencences of a well-

designed patient experince in community pharmacies in this research.

Materials and Methods: The research was conducted in 414 volunteer patients given informed consent and answered 73 items in Istanbul province. The data obtained from the questionnaire forms were analyzed using IBM SPSS Statistics 23 package program. Confirmatory factor analysis (CFA) was applied using IBM SPSS AMOS 23 package program in the analysis of trust, customer engagement, word of mouth, quality and autobiographical memory scales. The relationships among the scales; trust, customer interaction (impact, information, purchasing), word-of-mouth, pharmacist, personel, design, quality and autobiographical memory (detail, power, impact) were calculated using Spearman's correlation coefficient. The amount of independent variables to explain the dependent variable was determined by linear regression analysis. Since the assumption of normality was not provided, comparisons of two groups were made using the Mann-Whitney U test, and comparisons of more than two groups were made using the Kruskal-Wallis test. The results were evaluated at the significance level of $p < 0.05$.

Results: Our findings show that trust is the most important reason for a patient to visit the same pharmacy. The women's s word of mouth and purchasing habits are more than men. Another finding is that the more visit at the community phamacy the more engaged patients.

Conclusion: It is important to understand the touchpoint of the patient journey at community pharmarcy and the needs of the patients. As well as other health services, patients live a patient journey at the community pharmacy which is the place emotionaly sensitive that affets autobiographic memory, word of mouth and purchasing decision of the patient.

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OP203: THE STATE OF QUALITATIVE RESEARCH IN PHARMACY LITERATURE: A FOCUSED MAPPING REVIEW AND SYNTHESIS

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Introduction: Pluralism and creativity are inherent and important parts of the qualitative endeavour and there are many methodological approaches, each with a different contribution to make (1, 2). The multiplicity of approaches and methods can, however, be confusing. There is a need to examine the extent to which there is congruence between authors' stated qualitative orientation-reconstructed logic (what authors say to do) and the research processes and techniques actually reported (logic-in-use) in pharmacy literature (2). In this study, it was aimed to profile the relationship between qualitative researchers' philosophical claims and their actual methodological practices in the context of reporting in pharmacy and qualitative-based journals.

Materials and Methods: A focus mapping review and synthesis to obtain a snap-shot profile of the stage of qualitative research in pharmacy was undertook. Articles were scrutinized by using the methodology developed by Bradbury-Jones et al. for alignment between researchers' reported orientation (methodological or philosophical positioning) and the techniques used (methods) (3).

Results: In total 22 qualitative articles published between January and March 2021 from seven leading and the most common social pharmacy journals and 8 qualitative articles published in the last 5 years, between the years 2021 and 2015 from 4 leading health and social science journals were retrieved. It was found that 17% of the articles had an explicit statement regarding use of a qualitative approach in their titles. The most used methodological or philosophical approach was generic qualitative. In the sampled articles, nearly half of the articles have high level of alignment, with considerable mastery of qualitative approaches evident.

Table 1. Included articles and analysis of titles

Journal	Number of articles meeting inclusion criteria	Descriptions of qualitative approach in title			Patterning		
		No	Implied	Yes	Level of alignment between orientation and techniques		
					Low	Partial	High
RES SOCIAL ADM PHARM	16	14	1	1	5	2	9
JAPhA	2	2	0	0	2	0	0
CPTL	1	1	0	0	0	0	1
INT J CLIN PHARM	2	1	0	1	1	0	1
J CLIN PHARM THER	1	0	0	1	0	0	1
AJPE	0	0	0	0	0	0	0
IJP	0	0	0	0	0	0	0
SOC SCI MED	2	0	2	0	0	1	1
HEALTH SOC CARE COMMUNITY	6	2	2	2	2	1	3
QUAL HEALTH RES	0	0	0	0	0	0	0
SOCIOL HEALTH ILLN	0	0	0	0	0	0	0
Total	30	20	5	5	10	4	16

Conclusions: It was founded that it is sometimes difficult to determine whether or not an article is qualitative by observing just the titles in pharmacy literature. Much could be done to improve this issue and to make qualitative articles more identifiable and retrievable. In our study, the half of

the articles had high level of alignment, particularly in "generic qualitative studies". As a recommendation, researchers should stay simple to avoid muddling orientation and techniques and QR-LAW (Qualitative Research Level of Alignment Wheel) which is developed by Bradbury-Jones et al. may assist authors' clarity, critique and description while conducting qualitative research in pharmacy.

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OP204: IS THERE ANY DIFFERENCE SINCE 2012: WEB SITES OF PHARMACY SCHOOLS

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Introduction: The internet, which is shaped today's world, has gained importance as a source for a wide-range of areas especially for education, government, health services, e-commerce (1, 2) and its effects on education are remarkable during the COVID-19 pandemic (3). Since the websites have become the main communication tools between the educational institutes and the students, the necessity of quality websites is a significant fact for pharmacy schools. On the other hand, the characteristics of a website differ according to its aim (4). In 2012, it is found that there were missing features on websites of pharmacy schools in Turkey (5). With this study, we aimed to present the current status and development between 2012 and 2021, considering the COVID-19 pandemic.

Materials and Methods: Based on the findings in 2012, the additional evaluation criteria regarding appearance (usage of the visual content, logo) and content (search engine, introduction and/or history, curriculum, weekly program, etc.) are determined with the comprehensive literature search. The descriptive statistics were used for analyzing the websites' current situation and t-test was performed by SPSS ver 23. to compare the scores given the websites in 2012 and 2021.

Results: The total number of pharmacy schools' websites has increased from 16 to 39 in 9-year period. 25 of the schools have accredited and 27 of the schools are public currently. There is a statistically significant difference between the content and visual aspects of websites in terms of 2012 and 2021 scores ($p < 0.05$). However, there is no difference found between public and private or accredited and non-accredited schools.

Conclusions: Digitalization and usage of web-based information have secured their positions in education and online learning suddenly has become the main channel during the COVID-19 pandemic (3). Thus, the place of higher education institutes' websites cannot be ignored. Likewise, all institutions, including universities across the globe reach out to people with their websites. Also, through the websites the visibility of academic research and other scientific events come to be apparent. In conclusion, the content of the website plays an important role in the education in pharmacy schools. Therefore, the current accreditation system should include the websites of these schools as a criterion to enhance the communication between schools and students during the pandemic and after.

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OP205: CINCHONA BARK AND ITS ALKALOIDS IN THE 4TH PORTUGUESE OFFICIAL PHARMACOPOEIA

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Introduction: Cinchona bark, derived from a South American plant, is known for its antimalarial properties (1). Quinine, an alkaloid obtained from cinchona bark which is still in use, was instrumental as a treatment for malaria since its isolation in 1820 (1, 2). Pharmacopoeias are important barometers for current and past therapeutic options and remain a crucial source for the history of pharmacy. This study aims at searching and presenting cinchona bark and quinine references in the *Farmacopeia Portuguesa* IV, the 4th Portuguese official pharmacopoeia. The *Farmacopeia Portuguesa* IV was written by a self-appointed commission of pharmacists and is one of the most important pharmacopoeias for the history of pharmacy in Portugal.

Materials and Methods: The references to cinchona bark and quinine in the 4th Portuguese official pharmacopoeia's 2 editions (1935 and 1946, plus the 1961 Supplement for the 2nd edition) were identified and analyzed. The total number of medicines in each edition was also identified.

Results: *Farmacopeia Portuguesa* IV's first edition has a cinchona bark monograph (which characterizes yellow and red bark, indicating the species that belong to each "type" of cinchona bark). It has 10 medicines made with cinchona bark (1,37%), 17 medicines made with quinine (2,34%), and 1 medicine with quinidine (0,14%) (3). The second edition and its Supplement also have a cinchona bark monograph, but with a different quinine dosage method. It has 10 medicines made with cinchona bark (1,20%), 19 medicines made with quinine (2,29%) and 1 made with quinidine (4,5).

Conclusions: Cinchona bark and quinine were included in several different pharmaceutical formulations presented in the 4th Portuguese official pharmacopoeia. The cinchona bark monographs are detailed in both editions, with species characterization, dosage methods for total alkaloid content and quinine content, and minimum accepted quinine content for each type of cinchona bark (yellow or red).

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OP206: DETERMINATION OF PRESCRIBED MEDICINE BORROWING BEHAVIOR OF INDIVIDUALS

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Introduction: Medicine sharing behavior, which is also important in terms of rational drug usage and patient safety, is divided into borrowing medicine from someone else and lending medicine to someone else (1). The study aims to determine the prescribed medicine borrowing behavior of individuals for medical purposes and the sub-factors affecting this behavior.

Materials and Methods: An online survey was conducted on individuals who borrow at least one prescribed medicine before (n=393). In the first section of the survey 6 open-ended questions were asked to determine the demographic characteristics of the participants. The second section is including a measurement tool consisting of 39 items prepared with a 5-point Likert Scale, adapted from relevant literature according to the Theory of Planned Behavior. Exploratory factor analysis (EFA), t-test, and ANOVA were conducted via SPSS 22.0.

Results: As a result of the EFA, a 6-factors structure was determined, which explained 72.604% of the total variance. The Cronbach's alpha values of the factors were between 0.756 and 0.940, which indicates that the reliability of the measurement tool is high. The average responses given to the expressions in the factors obtained are below 3. According to t-test results, gender is found effective on the factor scores. The averages of the men participants are higher than women. As a result of ANOVA, it was determined that the education level and income made statistically significant difference on some factor scores.

Conclusions: To the best of the authors' knowledge, it is the first study investigating this issue in Turkey. It is seen that the participants do not have a very positive attitude to borrow drugs from someone else for medical purposes. Borrowing prescription medications is not a common practice. The findings will shed light on healthcare professionals in preventing the public health harms of medicine borrowing behavior.

Acknowledgements

Authors want to thank individuals participated in this study.

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OP207: COVID-19 ANXIETY OF THE STUDENTS AND ACADEMICIANS OF PHARMACY SCHOOLS IN TURKEY AND ITS EFFECTS ON THEIR PSYCHOLOGICAL WELL-BEING

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Introduction: The state of anxiety seen during the Covid-19 pandemic needs to be evaluated and controlled. Studies show that high anxiety reduces students' academic performance (1). The productivity and scientific studies of academicians have also been negatively affected during the pandemic (2). Psychological conditions of students and academicians need to be improved as high anxiety levels can affect academic achievement. In

this study, the effects on psychological well-being of the Covid-19 anxiety levels of students and academicians in Pharmacy Schools in Turkey have been determined.

Materials and Methods: The research is quantitative. As a data collection tool in the research, a questionnaire consisting of three parts was applied to the academic staff and students of Pharmacy Schools. After the first part of the questionnaire aiming to determine general information, there are questions about the Pandemic Anxiety Scale (PA) developed by Çiçek and Almalı (2020) and the Psychological Well-Being Scale (PWB), which was translated into Turkish by the same researchers and whose validity and reliability studies were conducted (3).

The universe of the study consists of 1563 academic staff working in Pharmacy Schools and 17101 students in these faculties. The level of significance (α) was determined as 0.05 in the analyzes made in the study.

Results: 247 academicians and 1698 students participated in the research. Data is analyzed by SPSS ver. 25.0 programme. 79% of the academic staff participating in the study are women, 21% are men; 77% of the students are women and 23% are men. Female academicians have significantly higher (p=0.001) pandemic anxiety level than male. Female students have significantly higher levels of pandemic anxiety (p=0.000) and psychological well-being (p=0.027) level compared to male students.

Conclusions: In the study, pandemic anxiety of academicians is generally lower than students, and psychological well-being is higher. When the relationship between pandemic anxiety and psychological well-being is examined, the relationship between pandemic anxiety and psychological well-being of the academicians is very low and positive; students were found to be very low and negative.

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POSTER PRESENTATIONS

P001: HPLC METHOD DEVELOPMENT AND VALIDATION OF CHLORHEXIDINE GLUCONATE AND BENZYDAMINE HCL FOR BUCCAL DELIVERY

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Introduction: Benzydamine hydrochloride (BZD) and Chlorhexidine gluconate (CHG) are active pharmaceutical ingredients mostly used in combination for the treatment of oral diseases as mouthwash or sprey. BZD is an analgesic, antipyretic and antimicrobial drug which is beneficial to oral and buccal conditions (1). CHG, which is regarded as gold standard for oral hygiene, is an antiseptic with a broad spectrum that can display bacteriostatic or bactericidal effect (2). The aim of this study to develope an analytical method and validate for quantificiation of BZD and CHG involved in buccal drug delivery systems to be improved.

Materials and Methods: The quantificiation method of BZD and CHG was developed based on the study of Dogan and Bascı (3). The device and the column used are Agilent 1100 HPLC and C18 (5µm, 150x4.6mm). The flow rate, volume of injection and the wavelength were 1 mL/min, 20µL and 219 nm, respectively. The mobile phase was prepared in proportion as 35:65 Acetonitrile:Phosphate Buffer (included 0.5% Triethylamine, pH adjusted as 3 using o-phosphoric acid). The concentration range was selected in between 0.25-30 µg/mL for both active ingredients. In order to validate the method; accuracy, precision, repeatability, reproducibility etc. parameters were assessed according to ICH guideliness.

Results: The correlation coefficient of BZD and CHG, which is a proof of the linearity level, was found to be 0.9998 and 0.9970, in turn. Retention time of BZD and CHG were detected as 4.8 and 2.7 seconds respectively. As a result of the validation parameters, the method was evaluated to be suitable with high recoverability, low standard deviation values and a coefficient of variation less than 2%.

Conclusion: The analytical method developed with this study can be used successfully for the quantificiation of BZD and CHG.

Acknowledgements

CHG (%20) was gifted from Merkez İlaç and BZD was gifted from Pharmactive İlaç San. Tic. A.Ş.

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P002: EVALUATION OF BERBERINE PHYTOSOME STABILITY IN SIMULATED BODY FLUIDS BY HPLC METHOD

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Introduction: Phytosomes (PSs) are structures formed by complexing plant-derived active ingredients with natural phospholipids (PLs) (1). Berberine (BER) is a quaternary benzylisoquinoline alkaloid that can be obtained from many different plants. In recent years, antihypertensive (2), hypoglycemic (3) and anticancer (4) effects of BER have also been studied by various researchers. However, the oral bioavailability of BER is low. Therefore, BER-PSs were prepared by a reverse phase evaporation method. The objective of the study is to determine the BER-PSs stability in simulated gastric fluid (SGF) and simulated intestinal fluid (SIF).

Materials and Methods: BER was dissolved in mixture of ethanol and distilled water. PL was dissolved in dichloromethane. BER solution was added onto the PL solution and mixed in magnetic stirrer at 60 °C and 400 rpm for 1 hour. Organic solvents were removed in the rotary evaporator. BER-PSs was lyophilized. SGF pH 1.2 medium and SIF pH 6.8 medium was prepared according to the European Pharmacopoeia. BER-PSs and BER powder were incubated in SGF for 2 hours at 37 °C and for 6 hours at 37 °C in SIF. The amount of BER which remained without disintegration was determined by HPLC.

Results: BER-PSs were prepared by a reverse phase evaporation method to increase the bioavailability of oral BER. The BER-PS showed a small particle size (236 ± 8.71 nm) and a well-dispersed structure with 76.4±3.41% encapsulation efficiency. SGF and SIF stability of BER powder and BER-PS were given in Table 1.

Table 1. Stability of BER powder and BER-PS in SGF and SIF

Sample	BER powder	BER-PS
SGF stability	91,0±0.01 %	79.9±0.01 %
SIF stability	79.8±0.04 %	70.7±0.05 %

Conclusions: BER-PSs were prepared by reverse phase evaporation method in success. In our study, it was aimed to determine how the PS drug delivery system affects the stability of the BER in body fluids. It has been observed that the PS structure reduces the stability of BER in SGF and SIF mediums. The stability of PL decreases with the increase of unsaturated chains in their structure. PLs can make the PS structure more susceptible to fragmentation in the body fluids. Hence the difference in stability between BER powder and BER- PSs may due to this.

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This study was supported by a grant of TUBITAK (SBAG-215S664).

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P003: THE EVALUATION OF THE POTENTIAL EUDRAGIT-BASED DELAYED RELEASE NANOFIBERS FOR COLON TARGETING

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Introduction: Ornidazole is a nitro-imidazole derived anti-protozoal drug (1). Nanofibers can be used for colon targeting due to their high surface area and superior mechanical properties (2). The aim of this study is to prepare delayed release ornidazole loaded electrospun nanofiber formulations for colon targeting.

Materials and Methods: Three different polymer solutions were prepared in methanol and N, N Dimethylformamide (7:3) solvent system at room temperature. Formulations were coded as E1 (15% Eudragit S100), E2 (15% Eudragit L-100-55) and E3 (7,5% Eudragit S100-7,5% Eudragit L-100-55). Viscosity, surface tension and conductivity properties of polymer solutions were determined. Nanofibers were examined in terms of mechanical properties, contact angles, mucoadhesion properties and in-vitro drug release behavior.

Results: Viscosity values of polymer solutions were found to be 3418 ± 205, 3790 ± 53 and 3115 ± 76 cP. s for E1, E2 and E3 polymer solutions, respectively at 25 rpm. The highest mechanical properties and work of mucoadhesion values were found in the E2 fiber formulation. The contact angle values of all formulations were found to be high due to the hydrophobic nature of the polymers (Table 1). According to the in vitro drug release results, at the end of 24 hours, the E1, E2 and E3 fiber formulations released 98.63%, 78.57% and 73.31% of ornidazole, respectively. Formulation E1 was chosen as the optimum fiber formulation showing a more appropriate release profile for colon targeting compared to the E2 and E3 formulations.

Table 1. Results of in-vitro characterization studies of nanofiber formulations

Nanofiber Formulations	Tensile Strength (mPa)	Elongation of break (%)	Contact angle (°)	Work of mucoadhesion (mJ/cm²)
E1	0,972 ± 0,190	3,23 ± 1,07	102,46 ± 0,75	0,050± 0,040
E2	1,898 ± 0,06	6,76 ± 0,59	67,84 ± 5,20	0,244± 0,097
E3	0,741 ± 0,010	4,42 ± 0,98	120,23 ± 0,75	0,065± 0,027

Conclusions: The E1 nanofiber formulation containing 15% Eudragit S100 showed optimal delayed release property at the end of 24 hours. Eudragit-based nanofibers demonstrated suitable mechanical and mucoadhesive properties for colon targeting in the treatment of intestinal diseases. Delayed release delivery systems have been prepared Eudragit-based polymers.

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P004: EFFECTS OF PRODUCTION METHOD VARIATIONS ON PARTICLE SIZE DISTRIBUTION OF ETHYL CELLULOSE NANOPARTICLES

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Introduction: The development of nanoparticular systems is a frequently used approach to deliver drugs to the side of action and increase their bioavailability (1). In this study, the effects of changes in process parameters on particle size and polydispersity index (PDI) of ethyl cellulose nanoparticles (EC-NP) were investigated.

Materials and Methods: ***Preparation of EC-NP:*** EC-NP were prepared by solvent evaporation and extraction method (2). The water phase was formed from PVA and water (0.2 or 1 %, w/v) while the organic phase contained ethyl cellulose and dichlorometane. These two phases were mixed, and the droplet sizes were reduced by two different methods. In the first method, after the ultrasonic probe application for 30 seconds, the organic phase was evaporated and nanoparticles were

formed. In the second method, both homogenization using Ultraturrax and high pressure homogenization with different pressure were applied and the organic phase was evaporated (6 or 24 h) to form nanoparticles. Filtration through cellulose acetate filters (0.20 µm) was employed to some of the samples. Particle size and PDI values of EC-NP were measured using a Malvern Zetasizer ZS.

Results: As for EC-NP applied first preparation method, the particle size were between 199.3-248.4 nm while PDI values were below 0.2 depending on concentration of PVA used (Table 1).

Table 1. Particle size and PDI values of EC-NP obtained by first preparation method (n=3).

PVA (%)	Santrifuge (rpm)	Evaporation Time (h)	Mean Particle Size (nm)±SD	PDI±SD
0.2%	10.000	4	230.5±1.36	0.127±0.02
1%	10.000	4	248.4±12.88	0.180±0.04

For the EC-NP prepared by second method, the particle sizes of the formulations were between 154.8-179.8 nm and PDI values were less than 0.3 (Table 2) depending on the different process parameters used.

Table 2. Particle size and PDI values of EC-NP obtained by using different process parameters (n=3).

Pressure (bar)	Cycle	Evaporation time (h)	Filtration	Mean Particle Size (nm)±SD	PDI±SD
800	8	6	+	154.8±7.33	0.207±0.01
1200	8	24	-	177.0±8.38	0.248±0.01
1200	8	24	+	179.8±5.51	0.271±0.01

Conclusions: It was concluded that process parameters such as pressure, cycle, evaporation time, filtration and PVA amount have critical effects on the particle size distribution of EC-NP.

Acknowledgment

Beril Tas is supported by TUBITAK 2244 grant, covering the co-operation between Hacettepe University and Novagenix Bioanalytical Drug R&D Center.

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P005: A NOVEL RP-HPLC METHOD TO DETERMINE IRBESARTAN AND HYDROCHLOROTHIAZIDE IN FIXED DOSE COMBINATIONS: METHOD DEVELOPMENT AND VALIDATION

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Introduction: Hypertension is an important public health problem because of its worldwide prevalence and its potential for death when combined with other diseases (1). The active pharmaceutical ingredients irbesartan (IRB) and hydrochlorothiazide (HCT) have been approved by the U.S. Food and Drug Administration (FDA) for the treatment of hypertension. In our study, we will perform quality control (QC) tests on combined all IRB/HCT tablets available in the Turkish market.

Materials and Methods: IRB/HCT (300/25 mg) fixed dose combination drug product from the Turkish pharmaceutical market were chosen for the studies. IRB and HCT were quantified using HPLC with photo-diode array detection at 230 nm in the presence of avanafil (AVA) as an internal standard. C_{18} core-shell column (SUPELCO® Ascentis Express, 100 × 4.6 mm, 2.7 µm i.d.) was used for separation. 30 mM sodium acetate buffer: water: acetonitrile (40:40:20, *v/v/v*) was used as the mobile phase in gradient separation mode. The developed method was fully validated in accordance with the ICH Q2 (R1) guidelines (2).

Results: The retention times of HCT, IRB and AVA were 2.8, 4.6, and 5.3 min respectively. The regression coefficients of the calibration lines were found to be 0.9996 and 0.9980 for IRB and HCT. The recovery values of one of the randomly selected market preparations were 99.0% - 100.1% for IRB and 98.6%-100.9% for HCT. All tablet data has been evaluated and interpreted in accordance with USP standards.

Conclusions: The full validated method was successfully applied to studies of content uniformity and dissolution. It was discovered that the method we developed can be used to determine both IRB and HCT at the same time.

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P006: PREPARATION AND EVALUATION OF LYSOZYME LOADED POLYCAPROLACTONE MICROPARTICLES USING THE FULL FACTORIAL DESIGN

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Introduction: The growing problem of multidrug-resistant bacteria has encouraged the search for therapeutic alternatives to conventional antibiotics. To this end, there is a growing interest in the use of antimicrobial peptides (1). Lysozyme is a monomeric protein that can be used in the treatment of microbial infections due to its antimicrobial activity, but the relatively narrow antimicrobial spectrum, instability and easy inactivation make the practical application of free lysozyme quite limited (2). Considering these reasons, poly-ε-caprolactone (PCL) microparticles of lysozyme were prepared using the full factorial design in this study.

Materials and Methods: Lysozyme, egg white was obtained from Vivantis (Oceanside, CA). Poly-ε-caprolactone (PCL), poly(vinyl alcohol) (PVA) and dichloromethane (DCM) were from Sigma (Germany). Lysozyme loaded microparticles were prepared by w/o/w double emulsion solvent evaporation method. Based on a 2^4 full factorial design, different lysozyme concentrations, DCM volumes, PVA volumes and stirring rates were used as independent variables. Particle size of microparticles were measured with a laser diffraction particle size analyzer (Mastersizer 3000, Malvern Panalytical, UK). The encapsulation efficiency (%) was calculated using following equation. Encapsulation efficiency (%)=(Calculated drug concentration)/(Theoretical drug concentration)×100.

Results: The effects of DCM volume, PVA volume and stirring rate on particle size were found to be significant ($p<0.05$). Otherwise, the effects of lysozyme concentration and PVA volume on encapsulation efficiency is significant ($p<0.05$).

Conclusions: The PCL microparticles containing lysozyme were prepared successfully by using w/o/w double emulsion solvent evaporation method. As a result, lysozyme loaded PCL microparticles can be used in the treatment of microbial infections.

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P007: EVALUATION OF IN VITRO-IN VIVO RELATIONSHIP: BOSENTAN-LOADED LIPID BASED FORMULATION VERSUS COMMERCIAL PRODUCT

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Introduction: In the U.S. FDA guidance, In Vitro-In Vivo Relationship (IVIVR) is defined as a relationship between in vivo bioavailability and the in vitro release profiles, which can be described by a relationship other than that of a straight line (1). A stronger relation provides a prediction of in vivo results using in vitro data. Moreover, IVIVR allows a decrease in the number of in vivo studies, formulation optimization, enhance product quality, reduce costs of drug development (2). The aim of this study was to investigate IVIVR for Bosentan-loaded SNEDDS, S-SNEDDS tablet, and commercial product (Tracleer®).

Materials and Methods: Piecewise Cubic Hermite Interpolating Polynomials (PCHIP) method was used to develop point-to-point relation between in vitro dissolution data and in vivo plasma concentration by MATLAB Version 9.10 (MathWorks, MA, USA). With this method, the unknown intermediate values (the missing points) were found at any unknown intermediate time points (3). With this method, the data set was generated by applying interpolation to 5, 10, 15, 20, 25, 30, 35, 45, 50, 55, and 60 minutes. The relationship between in vitro and in vivo data at these time points was evaluated.

Results: The relationship between fasted group plasma concentration and FaSSIF, FaSSIF V2, FDA-recommended media (a distilled water media containing 1% SLS), and the relationship between fed group plasma concentration and FeSSIF, FeSSIF V2, FDA-recommended media were evaluated. The correlation coefficient (R^2) was given in Table 1.

Table 1. The correlation coefficient for reference, SNEDDS, and S-SNEDDS tablet in the fed and fasted states

	Reference			SNEDDS			S-SNEDDS Tablet		
Fasted state	FaSSIF	FaSSIF V2	1% SLS	FaSSIF	FaSSIF V2	1% SLS	FaSSIF	FaSSIF V2	1% SLS
	0,918	0,896	0,773	0,869	0,820	0,936	0,974	0,950	0,957
Fed state	FeSSIF	FeSSIF V2	1% SLS	FeSSIF	FeSSIF V2	1% SLS	FeSSIF	FeSSIF V2	1% SLS
	0,548	0,463	0,442	0,965	0,807	0,990	0,940	0,906	0,914

The biorelevant media simulate gastrointestinal fluids better than FDA-recommended media. Compared to 1% SLS, the stronger relation was obtained in biorelevant media.

Conclusions: The positive relations were successfully obtained between in vitro dissolution data and in vivo plasma concentration. Since the SNEDDS and S-SNEDDS tablet increased solubility, dissolution, and lymphatic absorption of bosentan, a higher relation was observed between in vitro dissolution and plasma concentration. The lower correlation coefficient was obtained in the

fasted state than in the fed state for reference, since bosentan is a BCS Class IIa drug with a weak acidic property.

Acknowledgements

This study was supported by a grant from The Scientific and Technological Research Council of Turkey (TUBITAK) Project No: 217S602.

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P008: DoE BASED APPROACH FOR THE DESIGN OF PIROXICAM LOADED POLYMERIC NANOPARTICLES

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Introduction: Hepatocellular carcinoma is the third most common solid organ malignancies cause of death from cancer and the fifth most commonly occurring cancer due to the high prevalence of chronic liver damage caused by hepatitis or cirrhosis in the world. Although surgical resection, liver transplantation, local ablation therapies, and chemotherapy which are the basic treatment strategies, it can not be obtain significant survival rate in patient with metastatic disease or advanced local disease. For this reason, there is a significant need for new treatment strategies (1). The aim of this study is to develop the polymeric nanoparticulate drug delivery systems of piroxicam which is a chemopreventive active substance and to evaluate the in-vitro characteristics for the first time.

Materials and Methods: Nanoparticles were prepared as a per 3^2 full factorial experimental design to optimize the amount of PLGA (X1) and Poloxamer 188 percentage ratio (X2) investigated based on the encapsulation efficiency of nano-sized systems (2). The particle size and size distribution, surface charge, morphological structure and in-vitro drug release profile were carried out for the characterization of nano-sized particles.

Results: In this study, it was found that nano-sized particles were produced with high encapsulation efficiency in the range of 29.65–98.88%. The particle size of PLGA nanoparticles ranged from 184.6 to 323.4 nm with polidispersity index between 0.051-0.249. On the basis of the statistical evaluations carried out in the 3^2 full factorial experimental design performed in the prepared nanoparticles, the optimum piroxicam loaded formulation was selected and then the morphological structure and in-vitro release profile of this formulation were obtained.

Conclusions: This study demonstrated that the various physicochemical properties of polymeric nanoparticles loaded with piroxicam could be optimized by changing the polymer amount and surfactant concentration according to the full factorial design studies, which established the optimal formulation conditions with a reduced number of experiments.

Acknowledgements

This work was supported by Ankara University Scientific Research Projects Coordination, (21L0237008).

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P009: ATORVASTATIN-ENCAPSULATED CORE-SHELL TYPE HYBRID NANOCARRIERS FOR LOCAL THERAPY OF BREAST CANCER: FORMULATION AND OPTIMIZATION STUDIES

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Introduction: Breast cancer is most commonly diagnosed cancer and the second leading cause of death among women. The major treatment strategy of breast cancer is surgical intervention followed by radiotherapy, chemotherapy or hormone therapy. Most of these strategies, especially conventional chemotherapy, can lead to a variety of undesirable side effects such as the development of cardiac or systemic toxicity in healthy tissues and drug resistance against anti-cancer drugs. These drawbacks have limited the therapeutic effectiveness of anti-cancer drugs. To overcome these limitations, the efficacy of drug delivery strategies such as nano-sized drug carriers have been investigated with great interest in recent years (1).

Materials and Methods: Core-shell type hybrid nanocarriers were produced through one-step self-assembly approach. DSPE-PEG-COOH 2000 was

utilized as a PEG-conjugated phospholipid, lecithin was used as a lipid material and PLGA was chosen as a biodegradable polymeric core material. The 3^2 full factorial design was utilized to understand the influence of independent variables including drug/polymer ratio (X1) and phospholipid/polymer ratio (X2) on the mean particle size of nanoparticles (2). Encapsulation efficiency, PDI, surface charge, particle morphology, and in-vitro release performance studies were carried out through in vitro characterization.

Results: The encapsulation efficiency of nanocarriers varied widely from 33.49% to 91.27%. The prepared lipid–polymer hybrid systems exhibited an average particle size from 122.7 nm to 219.0 nm with polydispersity in the range from 0.070 to 0.179, which inhibited a narrow size distribution. Hybrid particles successfully produced with a spherical shape and negative zeta potential values ranged from -22.5 mV to -32.8 mV.

Conclusions: In the present research, the core–shell-type hybrid nano-sized carriers of Atorvastatin were successfully produced through DoE approach. The influence of the critical formulation factors on the quality of a final feature of Atorvastatin-encapsulated hybrid systems, the mean particle size, was evaluated within the scope of this 3^2 factorial statistical design in the context of this study.

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P010: DEVELOPMENT AND OPTIMIZATION OF AN ANTIHYPERTENSIVE FIXED-DOSE COMBINATION USING PLACKETT-BURMAN DESIGN

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Introduction: Fixed Dose Combinations (FDCs) have frequently been preferred in the treatment of hypertension in cases where blood pressure needs to be reduced in the ratio of 20/10 mmHg [1]. Angiotensin Converting Enzyme Inhibitors (ACEIs) and Calcium Channel Blockers (CCBs) have been commonly prescribed together due to their additive effects. Besides, improved patient adherence by taking fewer pills make it rational to develop an FDC product containing ACEI and CCB. Experimental design is the strategy of planning the effect of selected independent variables on the responses at determined levels as a result of a series of experiments. Commonly, screening designs such Plackett-Burman Design (PBD) are preferred at the earlier stages of the process to eliminate the insignificant factors, In this study PBD was used in the formulation development of FDC tablets including amlodipine besylate as a CCB and enalapril maleate as an ACEI. This study aims to show how to use screening designs to determine the most effective factors on product quality while preparing an antihypertensive fixed-dose combination tablet.

Materials and Methods: The formulation contains pregelatinized starch, crospovidone, hydroxypropyl cellulose, and glyceryl distearate. Experimental design table was created in Design-Expert®. PBD was used to examine whether the independent variables selected as a result of the risk assessment have a significant effect on CQAs. The evaluated factors were disintegrant ratio, lubricant ratio, binder ratio, blending speed, blending time, lubrication speed, and lubrication time. Tablets were directly compressed in TDP 5 (China).

Results: Results were evaluated in terms of assay, relative standard deviation of content uniformity of active substances, friability, disintegration and dissolution. According to the statitical evaluation, blending time, lubrication time, and lubrication speed had significant effects on content uniformity of enalapril ($p<0.05$). Additionally, the amounts of the lubricant and disintegrant had significant effects on disintegration time ($p<0.05$).

Conclusions: According to the PBD results, the amount of lubricant (glyceryl distearate) (1-3%) and disintegrant (crospovidone) (1-5%) were proven as the critical material properties, and the blending time was exhibited as a critical process parameter. Based on these results, an optimization design could be performed and a design space could be established.

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P011: DEVELOPMENT AND OPTIMIZATION OF SELF-NANOEMULSIFYING DRUG DELIVERY SYSTEM OF BOSENTAN USING BOX BEHNKEN DESIGN

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Introduction: Bosentan (BOS) is an orally active endothelin receptor antagonist and

Biopharmaceutics Classification System (BCS) Class II drug for the treatment of pulmonary arterial hypertension (1). Lipid-based systems such as self-nanoemulsifying drug delivery systems (SNEDDS) have been extensively investigated to improve the bioavailability and dissolution rate for poorly soluble drugs. The aim of this study was to evaluate the lipid-based formulation properties before the BOS loading. Design Expert® Version 10 was used to examine and optimize the effects of formulations.

Methods: According to the solubility results, Maisine and Peceol were selected as oil. In addition, Cremophor RH 40 and Labrasol were selected as surfactant and co-surfactant, respectively (2). The most appropriate combination was created using BBD and investigated the system characterization properties before drug loading. In the pseudo ternary phase diagram, the shaded area was the area in which the self nanoemulsion was formed by a system that did not contain any active substance and was determined by water titration. The ratio of S_{mix} was selected as 9:1. The optimized SNEDDS was characterized with respect to dispersibility, self-emulsification time, transmittance%, droplet size, polydispersity index (PDI), dilution and pH effect, turbidity, viscosity, morphology, thermodynamic and long-term stability studies. After these evaluations, optimum SNEDDS formulation was selected to load the drug.

Results: The prepared SNEDDS formulations were thermodynamically stable with a droplet size of 17.11 nm and 16.76, a PDI of 0.180 and 0.200, for Maisine-SNEDDS and Peceol-SNEDDS, respectively. The emulsification times were <1 min for the rapid rate of emulsification and dispersibility. TEM images illustrated the formation of a spherical shape with a size range of 10–100 nm. The formulations exhibited no sign of precipitation, robust against dilution and effect of pH, and also showed acceptable %transmittance (≥99%), turbidity, and viscosity values. There were no significant differences in the stability results of various test conditions.

Conclusions: The results showed that both formulations were found to be proper for the drug loading. 30 mg and 28 mg of BOS were successfully loaded to 1 g of Maisine-SNEDDS and Peceol-SNEDDS, respectively.

Acknowledgments

This study was supported by a grant from The Scientific and Technological Research Council of Turkey (TUBITAK, SBAG-217S602). The authors would like to thank Gattefossé for providing Maisine, Peceol, Labrasol, and Abdi İbrahim for providing Bosentan.

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P012: COMPARISON OF BIORELEVANT DISSOLUTION OF MEDIUM CHAIN MONO AND DIGLYCERIDES BASED BOSENTAN-LOADED SELF-NANOEMULSIFYING FORMULATIONS

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Introduction: Self-nanoemulsifying drug delivery systems (SNEDDS) among lipid-based systems are one of the most widely used approaches for drugs with a limited dissolution rate of absorption. Bosentan (BOS), which is an endothelin receptor antagonist treatment of pulmonary arterial hypertension, is categorized as Class II in Biopharmaceutics Classification System (1). The aim of this study was to compare the biorelevant dissolution performance of BOS-loaded SNEDDS and commercial products (Tracleer®).

Materials and Methods: In our previous studies, the SNEDDS components were chosen and formulations were designed with Box-Behnken Design (2). It was observed that the solubility of BOS was significantly higher in the long-chain mono and diglyceride derivatives which were Maisine and Peceol comparing to the other oils (3). 30 mg and 28 mg of BOS were loaded to 1 g of blank SNEDDS formulation containing Maisine or Peceol, respectively. The formulations were filled with a hard gelatin capsule. The in vitro dissolution studies were performed USP Apparatus II at 50 rpm at 37±0.5°C in 1% SLS in distilled water, Fasted State Simulated Intestinal Fluid (FaSSIF), and Fed State Simulated Intestinal Fluid (FeSSIF). Samples were analyzed by HPLC. The dissolution profiles were compared to BOS-loaded SNEDDS versus reference tablet. The dissolution data were evaluated using DDSolver®.

Results: For both Peceol and Maisine-SNEDDS, more than 80% of the drug was released from SNEDDS and a reference tablet within 15 min and 100% release was obtained from both within 30 min in 1% SLS. Additionally, more than 80% of releases were obtained within 30 min in FaSSIF and FeSSIF for SNEDDS. However, reference tablets, approximately 32% and 11% in 90 minutes were able to release in FaSSIF and FeSSIF, respectively. The Peceol-SNEDDS and Maisine-SNEDDS increased the percentage of cumulative

dissolved by 2.98, 7.88-fold, 3.0, and 7.97-fold in FaSSIF and FeSSIF compared to the reference tablet, respectively. The similarity factor (f_2) was also determined (Table 1). The dissolution profiles of SNEDDS formulations and Tracleer® did not give similar dissolution curves in biorelevant media.

Table 1. f_2 values of BOS-loaded SNEDDS formulations and reference

	BOS-loaded Peceol SNEDDS vs reference	BOS-loaded Maisine SNEDDS vs reference	BOS-loaded Peceol SNEDDS vs BOS-loaded Maisine SNEDDS
1% SLS	83	63	68
FaSSIF	13	11	60
FeSSIF	8	9	69

Conclusions: Our results showed that the in vitro dissolution profiles of SNEDDS and reference tablet was only similar in 1% SLS in distilled water which was not mimic the in vivo media. In biorelevant media that mimic fast and fed conditions, bosentan was almost completely dissolved according to the commercial product. According to the results, the bioavailability of bosentan could be enhanced in fasted and fed states compared to the commercial products because of the lipid-based formulation effect.

Acknowledgments

This study was supported by a grant from TUBITAK (SBAG-217S602). The authors would like to thank Gattefossé for providing Maisine, Peceol, Labrasol, and Abdi İbrahim for providing Bosentan.

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P013: POLYMERIC MICRONEEDLES FOR NASAL DRUG DELIVERY

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Introduction: Epilepsy is a neural disorder mostly characterized with seizures that occurs due to unbalanced production of stimulant and inhibitory signals in neurons of the brain (1). Lacosamide increases frequency of seizures in patients with epilepsy however it has low transition through BBB [2]. Microneedles, have great potentials to overcome membrane barriers to achive sufficient doses at the targetted sites of the body. Therefore in this study, microneedles were formulated for nasal route in order to reduce the applied dose of Lacosamide to minimize the severe side effects while maintaining enhanced brain transition with the help of nasal olfactory pathway.

Materials and Methods: Lacosamide (gifted by Santa Farma, Turkey). Eudragit® S 100 (ES100) (Röhm Pharma, Darmstadt, Germany). All other chemicals were in analytical grade. Microneedles were prepared by micro-molding method [3]. A modified HPLC method was used for the determination of Lacosamide [4]. Lacosamide amounts were determined and *in vitro* release, SEM (Zeiss Ultra Plus FE-SEM, Germany), FT-IR (IR Affinity-1S Shimadzu, Japan), DSC (DSC-60, Shimadzu USA) and ^{1}H-NMR (Fourier 300 NMR Bruker, USA) analyses were performed.

Results: Microneedles were prepared successfully with micro-molding method. Lacosamide amounts (Table 1), *in vitro* release (Fig.1) SEM (Fig. 2), FT-IR (Fig. 3), DSC (Fig. 4), ^{1}H-NMR (Fig. 5) analyses results were presented.

Table 1. Compositions of microneedles (Mean ± SE, n=3)

Code	ES100 (%)	PEG 400 (%)	Lacosamide Practical (%)
EL0	7.5	0.5	-
EL1	7.5	0.5	0.6 ± 0.0
EL2	7.5	0.5	1.1 ± 0.0
EL3	7.5	0.5	1.5 ± 0.0

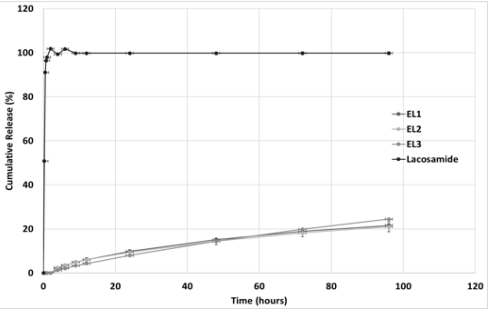

Fig. 1. *In vitro* release (Mean ± SE, n=3)

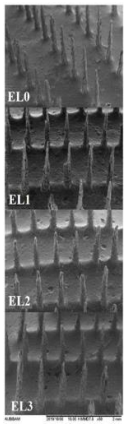

Fig. 2.

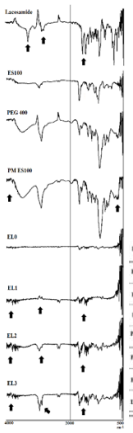

Fig. 3. FT-

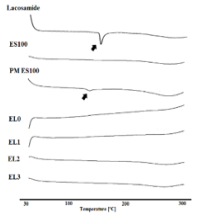

Fig. 4.

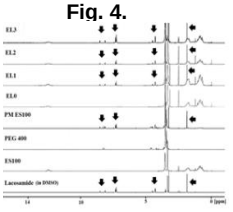

Fig. 5. ^{1}H-

Conclusions: ES100 based microneedles are promising candidates for the nasal application of Lacosamide for epilepsy treatment.

Acknowledgements

DOPNA-LAB for FT-IR and ^{1}H-NMR analyses and BIBAM for SEM Analyses.

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P014: PREPARATION AND OPTIMIZATION OF B-CYCLODEXTRIN INCLUSION COMPLEXES OF ATOMOXETINE HYDROCHLORIDE

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Introduction: Atomoxetine hydrochloride (ATO), which is used for the treatment of attention deficit/hyperactivity disorder (ADHD), has an extremely bitter taste (1). The aim of this study is to prepare beta cyclodextrin (β-CD) inclusion complexes of ATO by experimental design method in order to mask the bitter taste of the drug and formulate it as an oral dosage form (2).

Materials and Methods: Inclusion complexes of ATO have been prepared using five different molar ratios and two different mixing times were prepared using the kneading method. With the experimental design, the mixing time in the process and the optimal molar ratio of ATO and β-CD in the preparation of inclusion complexes have been optimized. In the study, ATO: β-CD molar ratio and mixing time independent variables, loaded ATO amount and cumulative dissolved ATO amount have been selected as dependent variables and evaluated by ANOVA.

Results: In the solubility studies performed with the USP II method in the inclusion complexes, it was observed that all of the ATO dissolved in 10 minutes. Determination of the amount of ATO in inclusion complexes was performed by UV spectrophotometric method. Results showed that the optimum inclusion complexes in terms of the cumulative amount of solute ATO and the amount of ATO loaded have been determined as 2: 3 (ATO: β-CD) and 7: 3 (ATO: β-CD) molar ratios with mixing times for 20 minutes and 40 minutes, respectively.

Conclusions: The kneading method was used to prepare β-CD inclusion complexes of ATO, which has a very bitter taste, and the experimental design was used to optimize the β-cyclodextrin complexes of ATO. It has been concluded that with the preparation of the inclusion complexes, ATO can be formulated as an oral dosage form.

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P015: PREPARATION OF LAMOTRIGINE SOLID DISPERSIONS WITH DIFFERENT POLYMERIC AND SURFACTANT CARRIERS TO ENHANCE SOLUBILITY

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Introduction: Lamotrigine (LMT; BCS Class II drug) is used in the treatment of epilepsy, bipolar disorder and neuropathic pain caused by anticancer drugs (1). Poor aqueous solubility of LMT limits not only its oral administration due to slow and insufficient absorption but also formulation development studies. The aim of this study was to prepare LMT solid dispersions using different polymeric and surfactant carriers to improve its poor aqueous solubility.

Materials and Methods: LMT solid dispersions were prepared by melting method. For this purpose, various carriers with polymeric (polyethylene glycol 4000, polyethylene glycol 6000) and surfactant properties (poloxamer 188, poloxamer 407) were used in different ratios (drug:carrier; 1:2, 1:4, 1:6, 1:8, 1:10). After melting each carrier, LMT dispersed in the molten mass, and then cooled at room temperature. The solid mixture was powdered and sieved through a 60 mesh screen. To determine entrapment efficiency, each formulation was weighed (5 mg), dissolved in the mobile phase, and analyzed by a validated HPLC method. Shake-flask solubility study was conducted according to the World Health Organization (WHO) guideline (2). An excess amount of drug and LMT solid dispersions were placed into amber glass vials, and sealed after adding 2 mL of distilled water. Vials were placed in a water bath (37±1°C, 80 rpm), and three samples taken at end of 24 h, filtered (0.45 µm), and then analyzed by HPLC.

Results: Entrapment efficiency was high for all solid dispersion formulations (82.7-117.2%). Aqueous solubility of LMT solid dispersions (0.46-0.66 mg/mL) was higher than LMT (0.29 mg/mL). The highest solubility was achieved in the presence of poloxamer 407 (1:6, drug: carrier). Surfactant carriers resulted in higher solubility enhancement in solid dispersions than polymeric carriers. Additionally, solubility increased as the proportion of carrier in the solid dispersion increased.

Conclusions: Solid dispersions prepared with various polymeric or surfactant carriers successfully increased the solubility of the LMT, and have high entrapment efficiency.

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P016: DEVELOPMENT AND VALIDATION OF AN HPLC METHOD FOR DETERMINATION OF LAMOTRIGINE

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Introduction: Lamotrigine (LMT) is a phenyltriazine derivative compound used in the treatment of diseases such as epilepsy, simple and complex seizures, generalized tonic-clonic seizures, and bipolar disorder (1). In this study, we aimed to develop and validate a High Performance Liquid Chromatography (HPLC) method suitable for the quantitative determination of LMT.

Materials and Methods: To determine the optimum chromatographic conditions, different mobile phase mixtures and ratios, column temperature and flow rates were tested in the preliminary studies. HPLC analyses were performed using Agilent HPLC system (Agilent 1200, Germany). An Inert Sustain® C18 (250 mm × 4.6 mm, 5µm) (GL Sciences, Tokyo, Japan) HPLC column was used as a stationary phase. The mobile phase consisting of mixture of acetonitrile : monobasic potassium phosphate solution (containing orthophosphoric acid to adjust pH to 4.5) in the ratio of 30:70 (v/v) was used throughout the analysis, and delivered at a flow rate 1.0 mL/min**.** Detector signal was monitored at 201 nm wavelength, and the injection volume was 20 µL. The column temperature was kept at 40°C. Validation studies were carried out according to the International Conference on Harmonization guidelines (ICH) (2), and the chromatographic method was validated for linearity, accuracy, precision and sensitivity.

Results: The retention time was determined to be 4.6 min with the optimum HPLC conditions used. The linear regression equation and determination coefficient (R^2) for standard curve in the mobile phase were $y = 196.06x + 29.917$ and $R^2=0.9997$, respectively. Our results indicated that the relationship between concentration and peak area was linear within the concentration range of 0.39-12.5 µg/mL. The limit of detection and the limit of quantification values were 0.18 µg/mL and 0.61 µg/mL, respectively. The results of the accuracy and precision studies for the HPLC method revealed that the relative standard deviation values were less than 2%.

Conclusions: The results obtained from this study clearly showed that HPLC method is accurate, precise and reproducible. Therefore, developed HPLC method is suitable for the quantitative determination of LMT.

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P017: POSACONAZOLE LOADED EUDRAGIT® FS 100 NANOPARTICLES

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Introduction: Posaconazole is a second generation antifungal agent among the triazoles, stands out with its powerful effect even on itraconazole resistant strains (1). Nanoparticles create significant differences with topical application in maintaining the desired drug levels in targeted areas of the eye (2). Therefore in our study Eudragit® FS 100 (FS100) nanoparticles were formulated for ocular application of Posaconazole for better treatment of severe ocular fungal disorders.

Materials and Methods: Posaconazole (gifted by Abdi İbrahim, Turkey), Eudragit® FS 100 (Evonic, Germany). All other chemicals were in analytical grade. Nanoparticles were prepared by o/w emulsion-solvent evaporation method [3]. A modified HPLC method was used for the determination of Posaconazole [4]. Particle size (PS), polydispersity index (PDI) and zeta potential (ZP) analyses (Malvern Zetasizer, UK), SEM (Zeiss Ultra Plus FE-SEM, Germany), FT-IR (IR Affinity-1S Shimadzu, Japan), DSC (DSC-60, Shimadzu USA) and ^{1}H-NMR (Fourier 300 NMR Bruker, USA) analyses, Posaconazole amounts and *in vitro* release studies were performed.

Results: Compositions, PS, PDI, ZP, Posaconazole amounts (Table 1), SEM (Fig.1), FT-IR (Fig. 2), ^{1}H-NMR (Fig. 3) and *in vitro* release analyses results (Fig. 4) were presented.

Table 1. Compositions and PS, PDI, ZP, Posaconazole amount analyses results of the nanoparticles (Mean ± SE, n=3)

Code	FS100 (mg)	EA (mL)	T80 (mg/mL)	PVA (mg/mL)	DW (mL)	PS (nm)	PDI	ZP (mV)	Posaconazole (%)
FT0	90	3	10.6	5	30	381±2	0.2±0.1	-38±1	-
FT1	90	3	10.6	5	30	132±3	0.4±0.3	-39±4	1.7±0.0
FT2	90	3	10.6	5	30	192±5	0.3±0.5	-30±7	3.4±0.1

WA:Ethyl acetate, T80: Tween® 80, PVA: Polyviniyl alcohol, DW: Distilled water

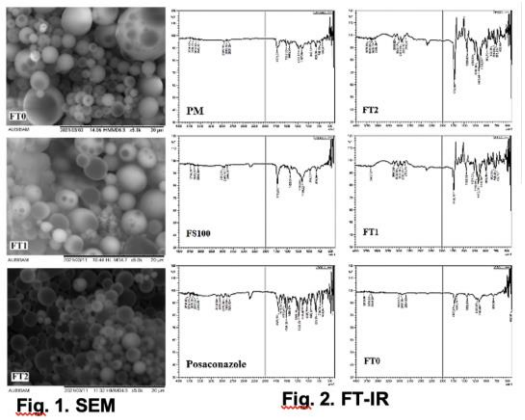

Fig. 1. SEM

Fig. 2. FT-IR

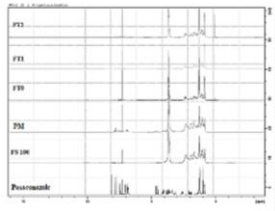

Fig. 3. ^{1}H-NMR

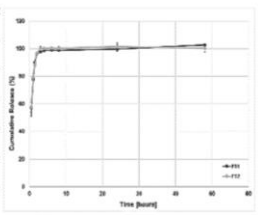

Fig. 4. *In vitro* release (Mean ± SE, n=3)

Conclusions: FS100 based nanoparticles were formulated successfully for the ocular application of Posaconazole for enhanced topical fungal treatment.

Acknowledgements

To DOPNA-LAB for FT-IR and ^{1}H-NMR analyses. To BIBAM for SEM Analyses. Anadolu University Scientific Research Project Foundation (Project Number: 1901S006)

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P018: CAFFEINE LOADED CHITOSAN GEL: FORMULATION AND IN-VITRO EVALUATION

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Introduction: Being the second most abundant and renewable natural resource after cellulose in nature is Chitosan (CH), which is obtained from chitin [1]. Hydrogels with CH has biocompatibility that enables them to be used frequently in the

cosmetic field. Skin aging is caused by internal or external factors or their combination and it is a complex biological process that inevitably occurs. Caffeine (CF) is similar to sunscreens, is one of the gold standards for delaying photoaging symptoms [2]. Its use aims to meet the increasing cosmetic expectations of societies. In this study, chitosan gel formulation containing caffeine against skin aging has been prepared and characterized.

Materials and Methods: CF is gifted by Novartis, Turkey, CH is from Sigma/Aldrich, Germany. All other chemicals were in analytical grade. Briefly, chitosan was dissolved in acetic acid solution (0.5%, v/v) under a magnetic stirrer at 250 rpm for 4 h [3]. CF was added to the selected formulation up to the final concentration of %1 (w/w). Formulations prepared were kept at 3 different conditions (25 ± 1 ◦C, 4 ± 1 ◦C, 40 ± 1 ◦C) for better evaluation of the stability for 3 months. A modified UV-VIS method was used for the determination of CF. All samples were observed for appearance, pH and viscosity. *In vitro* skin permeation studies were performed using a modified Franz diffusion cell (Hanson, USA).

Results: Characterization studies DSC (Fig 1.), FTIR (Fig. 2) *in vit*ro permeation (Fig.3) and viscosity (Fig.4) studies results (Fig. 4) were presented. After 3 months storage the pH of the gel formulaion was found 5.53.

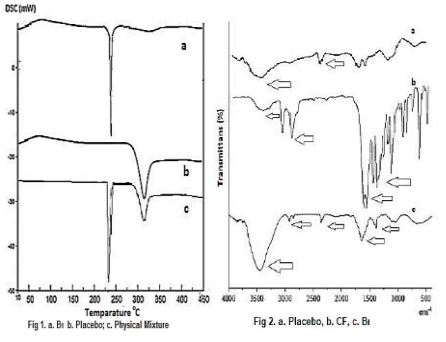

Fig 1. a. Bı b. Placebo; c. Physical Mixture

Fig 2. a. Placebo, b. CF, c. Bı

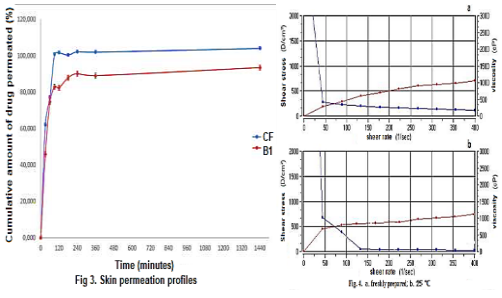

Fig 3. Skin permeation profiles

Fig 4. a. freshly prepared, b. 25 °C

Conclusions: Caffeine-loaded chitosan gel prepared and *in vitro* characterization studies have been done. With DSC and FTIR analysis the physicochemical structure has been enlightened. UV spectrophotometer method used is relatively easy, fast, inexpensive and quite useful for determining caffeine content. UV-method developed for caffeine is selective for analytical quantification of caffeine and it has proven to be an accurate method. As a result of the analysis, the formulation (B_1) stored at room temperature is found to be stable and is a suitable system for caffeine's cosmetic usage. In order to say that the formulation is an effective as anti-skin aging product, testing *in vivo* human volunteers is essential.

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P019: ANALYTHICAL METHOD DEVELOPMENT AND VALIDATION FOR SIMULTANEOUS QUANTIFICATIONS OF BRUSATOL IN DRUG LOADED LIPOSOMES

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Introduction: Nuclear factor E2-related factor (NRF2) plays a role in redox metabolism and antioxidant defense. Recent studies have shown that NRF2 is frequently activated in many types of cancer and NRF2 inhibition can be considered as a promising strategy for cancer treatment (1). Brusatol was shown to suppress NRF2-mediated defense mechanism and lead tumor-suppression in various types of cancer (2, 3). However, brusatol formulations with high efficacy and specificity for clinical applications have not been found and formulated yet. Preparation and in vitro characterization of a tumor targeted thermosensitive liposome formulation of brusatol is a focus of our research interest. Current study covers analytical method development and validation studies of brusatol using reverse-phase high-performance liquid chromatography (RP-HPLC) and UV spectrophotometric methods to be used in the formulation development studies of brusatol.

Materials and Methods: RP-HPLC method was developed using ACE C18 (50mm x 4.6 mm x 5µm) column with a flow rate of 1 mL/min using an Agilent 1260 Infinity series HPLC (Santa Clara, USA). The injection volume was set to 10µL and the mobile phase was consisted of acetonitrile and water. The spectrophotometric analysis was carried out using Agilent Carry 60 UV-Vis (Santa Clara, USA). Both the HPLC and UV analytical methods were developed with standard solutions

of brusatol in methanol and a λmax of 220 nm was used. Calibration curves were obtained and proposed methods were further validated according to ICH Q2 Validation of analytical procedures in terms of precision, accuracy, linearity and range. The limit of detection and quantification values were also calculated.

Results: The linearity range of the HPLC and UV-spectrophotometric methods were 0.5-20 µg/ml (r^2 :0.997) and 5-50 µg/ml (r^2 :0.992) respectively. The precision of the methods was shown (% Coefficient of variation< 2). Detection limits were 0.03 µg/ml and 0.06 µg/ml, respectively.

Conclusions: The r^2 values and validation results obtained at 95% confidence interval showed that the developed methods are validated and can be used for formulation development studies.

Acknowledgement

ZSB acknowledges the support of the Turkish Academy of Sciences, Ankara, Turkey, as young academy member.

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P020: INCREASING RIBOFLAVIN SOLUBILITY WITH SULFOBUTYL ETHER-B-CYCLODEXTRIN AND FORMATION OF DRUG- CYCLODEXTRIN INCLUSION COMPLEXES

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Introduction: Keratoconus is a degenerative disease that causes cone-shaped swelling of the cornea and causes thinning in advanced stages. Since riboflavin is susceptible to light, it has been used to initiate ultraviolet-induced collagen cross-linking in the diseased cornea since 2003 (1). The commonly used method to facilitate riboflavin-mediated corneal cross-linking is an invasive technique with removing the epithelium performed under local anesthesia. It is essential to develop formulations that can increase riboflavin penetration due to increased riboflavin solubility without removing the epithelium surgically. In this study, we investigated the effects of Sulfobutyl ether-β-cyclodextrin (SBE-β-CD) on riboflavin solubility and whether the drug-cyclodextrin inclusion complex was successfully produced.

Materials and Methods: Phase-solubility studies were carried out using Loftson and Brewster methods (2). Briefly, abundant riboflavin was added to SBE-β-CD solutions with increasing concentrations (0–10 mM), and the mixtures were stirred at room temperature for seven days with a magnetic stirrer. Later, each mixture was filtered through a 0.22 µm membrane filter, and the riboflavin amount in the supernatant was determined by HPLC. The riboflavin inclusion complexes: SBE-β-CD; were prepared by kneading methods. Fourier transform infrared spectroscopy (FTIR-ATR), and Differential scanning calorimetry (DSC) analyzes were conducted to determine the successful formation of drug-CD inclusion complexes.

Results: According to the defined methodology, the diagram of SBE-β-CD was classified as "AL-type''. From the straight lines of SBE-β-CD (r2 = 0,9765). The determined slopes were 0,0135. The complexation efficiency (EC) was 0,013 and the stability constant (KS) 62 M^{-1}. Furthermore, when the FTIR-ATR and DSC results were taken into consideration, it was determined drug-CD inclusion complexes were successfully formed by the kneading method.
Conclusions: This study has demostrated the the solubility of riboflavin could be enhanced using SBE-β-CD. Further studies will be conducted to investigate whether increasing the solubility of riboflavin by complexing with SBE-β-CD enhances corneal permeation of the drug ex-vivo and in vivo.

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P021: THERMODYNAMIC STABILITY TESTING OF KETOCONAZOLE AND CAFFEINE LOADED NANOEMULSION FORMULATIONS FOR DERMAL APPLICATION

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Introduction: Ketoconazole and caffeine are shown as effective at different pathophysiological disorder belongs to hair loss. Although the solubility of ketoconazole in water is very low, the solubility of caffeine in water is very high.

Nanoemulsion formulations are recently preferred for dermal application due to their features like small droplet size, increased thermodynamic stability and enhanced drug penetration through the skin. The aim of the study is to investigate the ketoconazole and caffeine loaded nanoemulsion formulations durability and to evaluate their capability for further studies and for dermal usage on hair loss.

Materials and Methods: Coconut oil, miglyol 818 were used as the oil phase. Cremophor rh40 and transcutol p were used as the surfactant and the co-surfactant. Distilled water was used as the water phase of the formulations. Self-nanoemulsifying method was used for the formation of the nanoemulsion systems. The centrifugation test with 3500 rpm 30 min was applied on the formulations. The freeze-thaw test with the process of the freezing at -20 ºC and the thawing at 25 ºC was applied. The heating-cooling test with the process of the heating at 45 ºC and the cooling at 4 ºC was applied.

Results: All the formulations were evaluated for their droplet size and polidispersity index, homogeneity and phase separation properties before and after the tests application. The phase separation and the homogeneity problems didn't occur in any formulations. The droplet size were 30 nm below and the polidispersity index properties were obtained 0.3 below.

Conclusion: All the studies showed that, the results remained within the desired range and the formulations are stable. All the systems are promising for dermatological use as a new carrier system.

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2. Follicular Penetration of Topically Applied Caffeine via a Shampoo Formulation N. Otberga A. et all.

P022: DEVELOPMENT&VALIDATION OF HPLC METHOD FOR TOPICAL DELIVERY OF FINASTERIDE USED IN HAIR LOSS TREATMENT

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Introduction: Finasteride has a strong selective antagonist effect on 5α-reductase type II enzymes and acts by preventing the conversion of testosterone to its active metabolite, dihydrotestosterone. Finasteride was initially approved for benign prostatic hyperplasia and prostate cancer. With recent developments, finasteride has been found to be useful in the treatment of various dermatological conditions such as androgenetic alopecia (1). Orally administered finasteride causes side effects such as erectile dysfunction, impaired reproductive function, gynecomastia and impotence. Topical application of finasteride may be considered for various dermatological conditions to eliminate these side effects (2). In this study, it was aimed to develop and validate an analytical method for topical delivery of finasteride.

Materials and Methods: Agilent 1100 HPLC system including UV detector was used for the quantification of finasteride. Analyses were performed using a C18 (5µm, 4.6x150mm) column for HPLC with isocratic elution. Detection was carried out at 210 nm with a mobile phase of Methanol:Water (70:30, v/v) (included 0.5% Triethylamine, pH adjusted as 6,38 using o-phosphoric acid) and the flow rate was 1.0 mL/min^{-1}. The concentration range was chosen as 0.5-20 µg/mL. To validate the method, parameters such as precision, recoverability, repeatability, durability etc. were evaluated according to the ICH guideline.

Results: The correlation coefficient of finasteride was found to be 0.9998. Retention time of finasteride were detected as 6.0 minute. The high recovery and a coefficients of variation less than %2 confirm the effectiveness of process.

Conclusion: The results suggested that developed method is suitable method for quantification of finasteride.

Acknowledgements

Finasteride was gifted from Koçak Farma İlaç ve Kimya San. Tic. A.Ş.

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P023: LACOSAMIDE LOADED MICRONEEDLES AS NASAL DRUG DELIVERY SYSTEMS

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Introduction: Epilepsy is one of the most common neurological disorder mostly characterized with seizures due to the abnormal induction of neurons (1). Lacosamide, an antiepileptic drug has low transition rate into the brain because of blood brain barrier (BBB) (2). In our study Carboxymethyl cellulose sodium salt (CMC) based microneedles were formulated for nasal application of Lacosamide to overcome the BBB by the help of olfactory pathway with less invasive way (3).

Materials and Methods: Lacosamide (gifted by Santa Farma, Turkey), Carboxymethyl cellulose sodium salt (CMC) and hydroxylpropyl gamma cyclodextrin (HPGCD) (Sigma-Aldrich, Germany). All other chemicals were in analytical grade. Micro-molding method was used for the preparation of CMC microneedles (4). SEM (Zeiss Ultra Plus FE-SEM, Germany), DSC (DSC-60, Shimadzu USA), FT-IR (IR Affinity-1S Shimadzu, Japan), ^{1}H-NMR (Fourier 300 NMR Bruker, USA) analyses were performed. A modified HPLC method was used for the determination of Lacosamide (5).

Results: Water soluble microneedles were prepared successfully with micro-molding method and API amounts, *in vitro* release, SEM, FT-IR, DSC and ^{1}H-NMR analyses results were presented in Table 1 and Figure 1-Figure 5 respectively.

Table 1. Compositions of microneedles (Mean ± SE, n=3)

Code	CMC (%)	HPGCD (%)	Lacosamide Practical (%)
CL0	6.0	2.0	-
CL1	6.0	2.0	0.6 ± 0.0
CL2	6.0	2.0	1.1 ± 0.0
CL3	6.0	2.0	1.6 ± 0.0

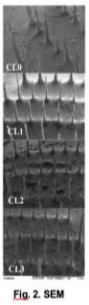

Fig. 2. SEM

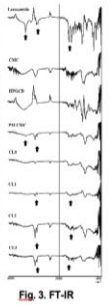
Fig. 3. FT-IR

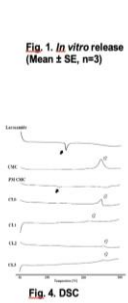
Fig. 1. *In vitro* release (Mean ± SE, n=3)

Fig. 4. DSC

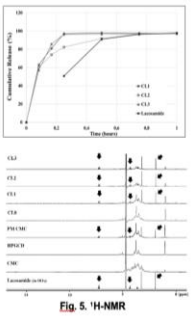
Fig. 5. ^{1}H-NMR

Conclusions: CMC based water soluble microneedles were prepared successfully for nasal application of Lacosamide.

Acknowledgements

DOPNA-LAB for FT-IR, ^{1}H-NMR and BIBAM for SEM Analyses.

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P024: DEVELOPMENT OF OROMUCOSAL FORMULATIONS - EVALUATION OF THE STRUCTURAL AND MECHANICAL PROPERTIES

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Introduction: Oromucosal formulations are gaining increasing interest as drug delivery products. They can be formulated e.g. as fast-disintegrating oral films (ODF) or mucoadhesive preparations intended for prolonged transmucosal absorption of an active substance. Mechanical properties of these formulations, related to their microstructure, are of a great importance according to the technological and biopharmaceutical aspects (1-3). Aim of the study was to determine the physical properties of two types of formulations: ODF composed of hypromellose obtained during casting process and mucoadhesive oral discs (MucD) formulated with sodium carmellose by freeze-drying method.

Materials and Methods: In orded to obtain MucD the aqueous solutions of sodium carmellose (CMC, 1-5%) were freeze-dried in PVC blisters (15 mm diameter and 6 mm height). Formulations "placebo" and with lidocaine HCl were prepared. ODFs were composed of hypromellose (HPMC) as the matrix forming polymer and polyethylene glycol (PEG, m.w. 200 - 4000) used as a plasticizer, in concentrations 0-30% (w/w of dry mass). The casting height was approx. 500 µm. Using a texture analyzer (TA.XT plus) the viscoelastic properties of ODF were evaluated, while resistance to compression and mucoadhesiveness (gelatin model) of MucD were analyzed. Moreover, microscopic observations were performed.

Results: During freeze-drying process porous MucD were formed. Depending on the CMC content in freeze dried solutions, the following values of resistance to compresion were measured for MucD: 1% (0.8 N), 2% (6.2 N) and 5% (47 N). Incorporation of the drug caused even 3–fold increase in these values. On the other hand, mucoadhesiveness, regardless of MucD composition, was similar ranging 0.27-0.43 mJ. The tear resistance of ODF depends directly on PEG concentration and its molecular weight. PEG 200 and 400 diminished tear resistance but

increased elasticity. The concentration limit for PEG 4000 was below 30% due to recrystallization.

Conclusions: The measurements performed with a texture analyzer are a convenient tool for assessment how appropriate is a choice of the particular additives in the development of ODF and MucD formulations.

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P025: VALIDATION OF AN HPLC METHOD FOR THE DETERMINATION OF CARFILZOMIB AND NILE RED FROM PLGA NANOPARTICLES

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Introduction: Carfilzomib is an epoxomicin derivate that induces apoptosis and inhibits tumor growth (1). Analytical validation is an important step in formulation development. This study is aimed to develop and validate an HPLC method for the determination of Carfilzomib (CFZ) and Nile Red (NR) from poly(lactic-co-glycolic acid) (PLGA) nanoparticles for tumor inhibition.

Materials and Methods: The selective assay of CFZ was carried out by RP-HPLC according to the combined method of Lamprecht and Benoit (2) and Gopireddy et al. (3). HPLC system consisted of Agilent 1200 Separations Module equipped with Diode Array Detector (DAD) (200 nm for CFZ and 560 nm for NR) and a C18 column (300 nm x 4,6 mm x 5 µm). The mobile phase was water: methanol: acetonitrile in the ratio of 20:40:40 a flow rate of 0,9 mL/min. In order to determine the amount of CFZ and NR in PLGA nanoparticles, the drug-loaded nanoparticles were dissolved in 1 mL of dimethylformamide and diluted to 10 ml with acetonitrile:water (80:20). The solutions were separated and filtered through 0.45 µm membrane filters and then injected into the HPLC column. The amount of CFZ and NR in nanoparticles was calculated through the peak area values by the calibration curve.

Results: The retention time was about 7 min for CFZ and 14.75 min for NR. Calibration curve was linear over the concentration range of 0,35-71,20 $\mu g.mL^{-1}$ for CFZ and 0,01-0,97 $\mu g.mL^{-1}$ for NR. The intra- and inter-day precision relative standard deviation was below 2,0 % for both compounds, and the accuracies were within 99,51-100,77 % for CFZ and 99,35-101,08 % for NR.

Conclusions: The developed HPLC method was successfully validated to quantitate CFZ and NR in PLGA nanoparticles.

Acknowledgment

Melih Zeki Kaya is supported by TUBITAK 2244 grant, covering the co-operation between Hacettepe University and Novagenix Bioanalytical Drug R&D Center.

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P026: A NOVEL UV/VIS SPECTROSCOPY METHOD FOR THE DETERMINATION OF ATEZOLIZUMAB: METHOD DEVELOPMENT AND VALIDATION

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Introduction: Atezolizumab is a monoclonal antibody and has been approved by FDA for various cancer treatments (1). Regarding the atezolizumab, there is no UV spectrophotometry methodology published for the quantification of atezolizumab in pharmaceutical preparations. The aim of this study was to develop and validate a simple, fast, and reliable UV visible methodology for the determination of atezolizumab in pharmaceutical products.

Materials and Methods: First, the maximum wavelength and the calibration curve of atezolizumab were determined using a UV/Vis spectrum. Then, validation studies were carried out to determine the reliability of the spectrophotometer method used in quantification for atezolizumab according to the criteria recommended by the FDA (2).

Results: According to the experimental data, the maximum absorbance for atezolizumab was found as 280 nm (Figure 1). The method developed was linear in a range varying from 0.10 to 1.50 $mg.mL^{-1}$ determined by 6 individuals calibrations points (Figure 2). The r^2 value was 0.9995 indicating a 99.95% correlation in linearity and precision. The robustness showed good and similar values and the limit of detection and limit of quantification were 0.005 $mg.mL^{-1}$ and 0.018 $mg.mL^{-1}$, respectively.

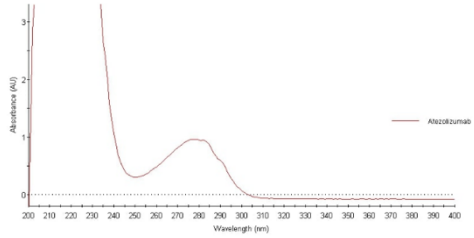

Fig 1. UV/Vis spectrum of atezolizumab.

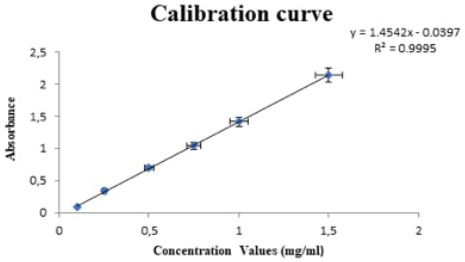

Fig 2. Calibration curve of atezolizumab.

Conclusions: The data corroborates the reliability as applicability of the developed UV/Vis spectroscopy method for quantitatively determining the amount of atezolizumab in pharmaceutical products.

Acknowledgements

This study was supported by a grant of TUBITAK (SBAG-220S361) within the scope of the PhD thesis of Meliha Ekinci.

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P027: DEVELOPMENT AND OPTIMIZATION OF R-HPLC METHOD OF OXICONAZOLE NITRATE FOR TOPICAL DRUG DELIVERY

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Introduction: Oxiconazole, an imidazole derivative, is used as a topical antifungal for treating fungal infections such as *tinea pedis*, *tinea corporis*, and *tinea cruris* (1). Commercially available forms of oxiconazole in 1% lotion and cream formulations can be used for large and hairy areas (2). The hydrophobic nature of oxiconazole limits the development of formulations. And also, it causes poor water solubility and bioavailability. Additionally, side effect problems seen in systemic administration require the development of new topical formulations for the safe use of oxiconazole. Therefore, innovative approaches are needed to overcome these problems (3). This study, it was aimed to develop and validate a current HPLC method for the analysis and formulation of oxiconazole nitrate in novel drug delivery systems.

Materials and Methods: This study used C18 (5µm, 4.6x150mm) column in Agilent 1100 HPLC device. The column temperature was set to 25°C, and the flow rate to 1 mL/min. The mobile phase was at the ratio of 90:10 Methanol: Ammonium acetate buffer (0.02 M) in gradient mode, and the injection volume was 20 µL. The absorbance of oxiconazole nitrate was monitored at 212 nm wavelength. The method validation, following ICH requirements, contains parameters such as linearity, precision, accuracy, repeatability, reproducibility.

Results: The calibration curve showed satisfactory linearity at the concentration range 0.5-60 µg/mL. The linearity equation was found $y = 97.244x + 14.618$ with $r^2 = 0.9990$. Also, the retention time of oxiconazole nitrate was determined approximately 4.1 minutes.

Conclusion: An accurate, repeatable, and current HPLC method has been developed and validated with this study for use in the quantitative analysis of oxiconazole nitrate.

Acknowledgments

Oxiconazole nitrate was generously gifted from Pharmactive İlaç San. Tic. A.Ş.

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P028: FORMULATION AND CHARACTERIZATION OF TEDIZOLID PHOSPHATE LOADED LIPOSOMAL GEL FORMULATIONS FOR TOPICAL TREATMENT ABSSSIS

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Introduction: Acute bacterial skin and skin structure infections (ABSSSIs) are complicated skin and soft tissue infections with a broad range of disease severity (1). Tedizolid (TDZ) is a second generation oxazolidinone antibiotic and comercially available as tablet or intravenous injection formulations (2). The aim of this study was to develop TDZ phosphate loaded liposomal gel formulations for topical treatment of ABSSSIs which reduces systemic side effects and shows high patient compliance.

Materials and Methods: Liposomes were prepared with phosphatidylcholine:cholesterol mixture by film-hydration method (3). They were characterized in terms of particle size, polydispersity, zeta potential and encapsulation efficiency. Then, liposomes were incorporated to Methocel K4M gels to obtain appropriate properties for topical application. Liposome loaded gels were characterized in terms of their rheological/mechanical properties, pH, viscosity and in vitro release.

Results: TDZ phosphate liposomes were developed and characterized. The results of characterisation studies were given in Table 1.

Table 1. The characterisation of liposomes.

Formulations	Particle Size (nm, ±S.D.)	Zeta Potential (mV, ±S.D.)	Polydispersity Index	Encapsulation Efficiency (%)
Blank liposomes	172 ± 3.9	0.02 ± 0.01	0.62	-
TDZ phosphate liposomes	201 ± 7.1	0.05 ± 0.09	0.49	30.6 ± 3.5

TDZ phosphate liposomes incorporated gels showed the non-Newtonian pseudoplastic flow and strong elastic gel behavior. The mechanical properties proved that the addition of TDZ phospate loaded liposome did not significantly affect the adhesiveness, cohesiveness, hardness, compressibility and elasticity of the formulations. The in vitro release results indicated that the formulations give a controlled release over 6 hours with first order drug release kinetic model.

Conclusions: TDZ phosphate loaded liposomal formulations were successfully prepared and dispersed in Methocel K4M (3%) gels for topical treatment of ABSSSIs. The results of these preformulation studies were found to be promising and it was decided to proceed further microbiological and cell culture studies.

Acknowledgements

This study was supported by Izmir Katip Celebi University, Scientific Research Projects Coordination Unit (2018-ONAP-ECZF-0002).

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P029: PREPARATION AND CHARACTERIZATION OF CREAM-GELS BASED ON HYDROXYETHYL ACRYLATE / SODIUM ACRYLOYLDIMETHYL TAURATE COPOLYMER INCORPORATED WITH FIXED OR ESSENTIAL OILS

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Introduction: The use of natural vegetable oils is common in pruritic skin diseases such as eczema, rosacea, urticaria, atopic dermatitis, and some pregnancy related skin diseases (1,2). However, due to the greasy feeling on the skin, the rate of non-adherence to treatment is high.
Hydroxyethyl acrylate/sodium acryloyldimethyl taurate (SEP) is a thickener, stabilizer and texturing agent for medical applications. SEP has self-gelling and emulsifying properties, which makes it preferred for various formulations such as gel, cream-gel, emulsions, powder, patch and foam. SEP provides a fresh, non-sticky, smooth feeling on the skin. It has a shear thinning profile and thus has good spreadability (3,4). The aim of this study was to develop SEP based stable semi-solid formulations with emollient and anti-pruritic effect.

Materials and Methods: Cream-gel formulations were prepared by dispersing fixed oil (olive oil, safflower oil, jojoba oil or almond oil), essential oil (peppermint oil or tea tree oil) or liquid paraffin (20% w/w) in distilled water containing SEP (3% w/w). The gel formulation was also prepared using glycerine instead of oil. The morphological analysis, pH and spreadability analysis were conducted as characterization studies.

Results: SEP based semi-solid formulations were successfully prepared. Physically; homogeneous, opaque and white-beige coloured cream-gel

formulations were obtained. The gel formulation prepared with glycerine was transparent. The pH range of the formulations was 4.01±0.02 – 6.09±0.04. The lowest pH values were obtained with the formulations containing essential oils. According to the spreadability data, the highest firmness (455.04±19.58 g) and work of shear (395.40±8.67 g.sec) values were obtained with glycerine gel formulation. However, formulations prepared with fixed and essential oils were spread more easily than gel formulation. The spreadability of the formulations, according to the type of oil are listed as follows: Glycerine gel> Liquid paraffin> Olive oil> Safflower oil> Jojoba oil> Almond oil> Peppermint oil> Tea tree oil

Conclusions: Smooth and uniform cream-gel and gel formulations of SEP were successfully prepared with all used type of oils. The easy spreadability of cream-gels compared to glycerine gel was preferable in terms of ease of application and high patient compliance to the treatment. In further studies, the developed formulations would be used as a base for preparations containing antihistamines, anti-inflammatory agents or corticosteroids for itchy skin diseases.

Acknowledgements

Hydroxyethyl acrylate/sodium acryloyldimethyl taurate copolymer was a kind gift of Nobel Pharmaceuticals (İstanbul, TURKEY).

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P030: DEVELOPMENT OF BIODEGRADABLE NANOPARTICLES FOR THE BRAIN DELIVERY OF FLURBIPROPHENE

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Introduction: The blood-brain barrier is the most critical barrier that selectively restrains the molecules and drug delivery to the brain (1). Nonsteroidal anti-inflammatory drugs (NSAIDs) are potent molecules that are commonly used to treat pain and inflammation. In a glioma cell cultures study, flurbiprofen (FB), one of the NSAIDs, demonstrated beneficial effects; however, when administered systemically, FB is unable to reach the brain a sufficient amount (2). The aim of this study was to develop and characterize in vitro FB loaded poly lactic-co-glycolic acid (PLGA) nanoparticles (NPs) in order to improve brain delivery of FB.

Materials and Methods: PLGA NPs were prepared by W/O/W multiple emulsion solvent evaporation method (3). Briefly, an inner aqueous phase containing 0,1% Polyvinyl alcohol (PVA) was added to the organic phase ((0.1%(w/v) PLGA 50:50 Resomer RG 504 or Resomer RG 504H in dichloromethane), after that it was emulsified through sonication for 3 min at 60 watts (Bandelin Ultrasonic Probe). This emulsion was dispersed in the first outer phase that contains PVA (2,0% (w/v)) and sonicated for 5 min at 60 watts, and then it was diluted in the second outer phase including 0,36% PVA. The resulting dispersion was stirred for 4 h at room temperature. Finally, collected NPs were frozen at -80°C and lyophilized for 48 h.

Results: Characterization results of FB loaded NPs were demonstrated in Table 1. Drug loading values were calculated as 77,96% and 91,27% for F3 and F4. formulations, respectively. Cumulative FB release from F3 and F4 formulations were found as 94,92% and 98,62%, respectively, at 24 hours. Particle sizes of the all formulations were below 200 nm.

Table 1. Characteristic of FB loaded nanoparticles

Code	Drug Amount (mg)	PLGA Type	Size (nm ± SD)	PDI ± SD	Zeta Potential (mV ± SD)
F1	-	504	181,1 ± 2,28	0,169 ± 0,01	-15,4 ± 0,51
F2	-	504 H	175,7 ± 4,16	0,094 ± 0,01	-9,30 ± 0,24
F3	15	504	169,6 ± 2,84	0,100 ± 0,03	-7,77 ± 0,29
F4	15	504 H	177,3 ± 2,48	0,173 ± 0,02	-2,66 ± 0,20

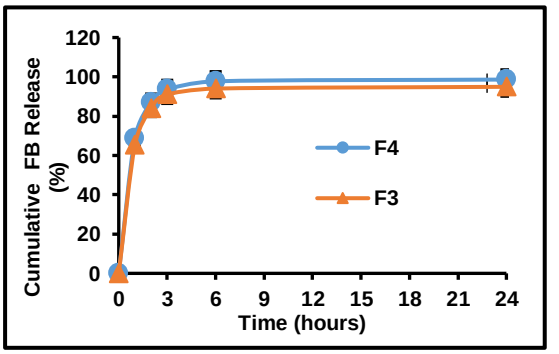

Fig 1. Cumulative drug release from PLGA formulations.

Conclusions: It could be concluded that the developed formulations were promising for the delivery of FB to the brain considering their characterization such as particle size, drug loading

value, drug release properties and zeta potential values.

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P031: PREPARATION AND *IN VITRO* CHARACTERIZATION OF LIPID-COATED NANOPARTICLES CONTAINING CARBOPLATIN AND DECITABINE

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Introduction: Silencing of critical tumor suppressor genes by DNA hypermethylation is the major epigenetic cause of chemoresistance of cancer cells. DNA methyltransferase inhibitors, such as decitabine (DEC), allow silenced critical tumor suppressor genes to be re-expressed by demethylation [1]. In this regard, the combination of DNA methyltransferase inhibitors and conventional chemotherapeutics is thought to be promising approach for modulating drug resistance by sensitizing of cancer cells. The aim of this study is to develop carboplatin (CRB) and decitabine loaded lipid-coated albumin nanoparticles for the treatment of platinum-resistant ovarian cancer and evaluate the physicochemical properties of the nanoformulations.

Materials and Methods: The production method of lipid-coated nanoparticles consisted of two steps. In the first step CRB-loaded albumin-based nanoparticles were prepared by desolvation method. Then these nanoparticles were coated with a DEC-containing lipid layer [2]. To optimize the lipid-coating procedure, the effects of various lipid:nanoparticle ratios, lipid film compositions and rehydration medium volumes on the physicochemical properties of the nanoparticles were examined. Developed nanoparticle formulations were evaluated in terms of encapsulation efficiency, particle size and size distribution (PDI), surface charge, particle morphology and thermal behaviors.

Results: Multidrug-containing lipid-coated nanoparticles were obtained 1:1 (w:w) lipid:nanoparticle ratio, 1:0.5 (w:w) soy phosphatidyl choline:cholesterol ratio and 2 ml rehydration medium volume. The optimum nanoparticle formulation showed 272.3 nm particle size, 0.298 PDI, -10.9 surface charge and 35.4% and 36.6% encapsulation efficiency for CRB and DEC, respectively.

Conclusions: The thin film hydration method-based two-step preparation method was successfully applied to the DEC-loaded lipid coating of CRB-loaded albumin nanoparticles with desired physicochemical properties and relatively high encapsulation efficiencies.

Acknowledgements

This study was supported by a grant of TUBITAK (SBAG-116S395)

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P032: DEVELOPMENT AND CHARACTERIZATION OF BUCCAL FILM CONTAINING HYDROCORTISONE NANOSUSPENSIONS

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Introduction: Aphthous ulcers are oral mucosal inflammatory ulcers that occur in the oral cavity and antibiotics, antiseptics, and topical corticosteroids are often used for treatment (1). Hydrocortisone (HC) is an anti-inflammatory compound with low solubility in water (1). The aim of this study to increase the solubility of active substance drug by preparing a nanosuspension (NS) formulation. HC nanosuspension loaded buccal film has been developed for the treatment of aphthous ulcers. Characterization studies of NS and buccal films were carried out.

Materials and Methods: Wet milling method was used to prepare the NS formulations (2). In this method, HC-NS was prepared with using 0.5mm sized zirconium oxide beads and different processing times (0.5, 1 and 2 h). Different concentrations (0.25% and 0.5%) of hydroxypropyl methylcellulose E4 (HPMC) and polyvinylpyrrolidone K90 (PVP) were used as stabilizers. Particle size (PS), polydispersity index (PDI), zeta potential (ZP) values of nanosuspensions was measured with Malvern Zetasizer. Solvent casting method was used to develop a buccal film formulation containing nanosuspension. Pectin (3%) was dispersed into the optimum nanosuspension (PVP 0.5%, 2 h) selected for film formulations and Plasdone K12 and glycerin (3%) were added and poured in petri dishes. Mechanical properties, mucoadhesive

properties and moisture content of the film formulation were investigated.

Results: The characterization results of the nanosuspension formulations are given in Table 1. NS formulation with best properties was achieved with a 0.5% PVP concentration and a two hour process time. The optimum formulation's PS, PDI and ZP values were found 148.9 ± 3.134 nm, 0.301 ± 0.006 and -28.9 ± 1.78 mV, respectively.

Table 1. Characterization results of the nanosuspension formulations

Stabilizer Type	Process Time (h)	0,25% Stabilizer Concentration			0,5% Stabilizer Concentration		
		ZP (mV)	PS (nm)	PDI	ZP (mV)	PS (nm)	PDI
PVP	0.5	-16.9 ± 0.404	278.9 ± 21.41	0.449 ± 0.052	-19 ± 1.20	230.7 ± 25.62	0.478 ± 0.048
	1	-6.08 ± 0.870	444.2 ± 17.02	0.576 ± 0.070	-17.6 ± 1.06	232.9 ± 52.49	0.451 ± 0.132
	2	-6.63 ± 0.350	325.5 ± 6.691	0.386 ± 0.019	-28.9 ± 1.78	148.9 ± 3.134	0.301 ± 0.006
HPMC	0.5	-14 ± 6.29	482.7 ± 4.981	0.646 ± 0.054	-6.23 ± 0.752	322.3 ± 72.66	0.510 ± 0.065
	1	-10.2 ± 1.69	441.6 ± 38.30	0.570 ± 0.014	-5.47 ± 0.929	266.1 ± 11.71	0.443 ± 0.019
	2	-16.1 ± 0.586	280.1 ± 17.73	0.458 ± 0.055	-4.45 ± 3.70	210.0 ± 25.80	0.417 ± 0.007

The mechanical properties of the film formulation were 19.8±0.02 mPa, and the elongation at break value was 17.7±4.02%. Moisture content was 14.56% and work of mucoadhesion value was 0.067±0.015 mJ/cm^2.

Conclusions:
Process time and the choice of stabilizer used in the production of nanosuspensions affected ZP, PDI and PS. The buccal film formulation containing HC loaded NS has been successfully developed. The film formulation was found suitable for buccal application in terms of mechanical and mucoadhesive properties.

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P033: MODELING AND COMPARISON OF IN VITRO DISSOLUTION PROFILES OF NAPROXEN SODIUM TABLETS IN BIORELEVANT MEDIA

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Introduction: In vitro dissolution tests are used to define the effect of formulation factors on bioavailability during drug development. Naproxen sodium (NS) is a widely used non-steroidal anti-inflammatory drug, which Biopharmaceutics Classification System (BCS) Class II (1). The pH and composition of the dissolution medium are have a great impact on its solubility. This study was aimed to compare the dissolution profiles of NS tablets using DDSolver® (2).

Materials and Methods: NS 550 mg tablets were purchased from the local market. The solubility studies were carried out for pH 7.4 and the dose number was calculated. Dissolution studies were carried out in USP Apparatus II, according to the USP 30. All collected samples were analyzed with validated UV spectrophotometric method at 330 nm. The dissolution data analysis was performed model-independent (similarity factor (f_2)) and model-dependent using DDSolver®. The dissolution test in biorelevant media (Fasted State Simulated Intestinal Fluid (FaSSIF) and Fed State Simulated Intestinal Fluid (FeSSIF)) were performed with the generic product (G), which was determined to have the highest similarity factor calculated as a result of the dissolution tests performed in pH 7.4. The adjusted determination coefficient (r^2 adj), Akaike information criterion (AIC), and model selection criterion (MSC) were used to determine the most appropriate release model. The model with the lowest AIC, highest MSC, and r^2 value was evaluated as the most appropriate model.

Results: In pH 7.4 at 37°C, the solubility and dose number were found 50.4±4.38 mg/mL and 0.044, respectively. The reference and all generic products were dissolved in the range of 78-83% in FeSSIF medium at pH 5.0, 100% in FaSSIF medium at pH 6.5, and 101-103% in pH 7.4, respectively. f_2 values and the suitable mathematical models obtained via DDSolver® are presented in Table 1.

Table 1. Dissolution data analysis of model-independent and model-dependent with DDSolver®

Medium	pH 7.4				FaSSIF	FeSSIF
	G1	G2	G3	G4	G2	G2
f_2	59 Similar	69 Similar	62 Similar	41 Different	79 Similar	42 Different
Medium	**pH 7.4**				**FaSSIF**	**FeSSIF**
	Reference	**G1**	**G2**	**G3**	**G4**	**Reference**	**G2**	**Reference**	**G2**
Model	Weibull-1	Weibull-2	Weibull-1	Hopfenberg	Hopfenberg	Hopfenberg	Probit-1	Logistic-2	Logistic-2
r^2adj	0,997	0,998	0,991	0,996	0,989	0,996	0,994	0,996	0,976
AIC	39,4	31	50,6	40,9	50,8	41,7	46	38	60,5
MSC	4,87	5,42	3,76	4,54	3,33	4,68	4,28	5,03	3,21

Conclusions: Biorelevant media were preferred because it mimics in vivo better. NS shows pH-dependent solubility, so as pH increased, solubility increased. The dissolution profiles of all generic products, except for G4, were found to be similar to the reference product at pH 7.4. Biorelevant media comparison was made for G2 with the highest f_2 and the reference. Model fitting of reference and G2 produced good fits for the same model in each case in pH 7.4 and FeSSIF media.

Acknowledgments

The authors would like to thank Pharmactive for providing naproxen sodium. Nebahat Ayşe

ERMAN was supported by a scholarship from The Scientific and Technological Research Council of Turkey (TUBITAK) 2247-C Intern Researcher Scholarship Program (STAR) (Project ID: 217S602).

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P034: VALIDATED HPLC METHOD FOR THE DETERMINATION OF TENOFOVIR AND ITS APPLICATION FOR *IN-VITRO* AND *EX-VIVO* INVESTIGATIONS OF TENOFOVIR LOADED DOUBLE NANOEMULSION

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Introduction: Tenofovir disoproxil fumarate (TDF) is a nucleotide reverse transcriptase inhibitor used for the treatment of hepatitis B and HIV infections [1]. The purpose of this study was to develop a validated HPLC method for the determination of TDF and assess its application for the *in-vitro* and *ex-vivo* studies on TDF formulations.

Materials and Methods: The HPLC system (Agilent Technologies 1200 Series) was operated using acetonitrile:ultrapure water (47:53, v/v) as a mobile phase at a flow rate of 1 mL/min. The injection volume was 20 µL. The detection wavelength was 259 nm [2]. Separations were carried out using Waters XSelect HSS C18 column (250x4.6mm, 5µm) at room temperature. The method was validated according to ICH guideline in distilled water and compendial media (0.1N HCl, pH 4.5, and pH 6.8) and has been successfully applied in solubility, dissolution, and permeability studies of TDF formulations [3]. The solubility studies were carried out in distilled water and compendial media. All collected samples were filtered using a 0.45 µm syringe filter (Sartorius) and analyzed by HPLC.

Results: The method was linear in the range of 1-35 µg/mL for all media ($r^2 \geq 0.999$). The retention time of TDF was 3.10-3.96 min in all media. The limit of quantification ranged from 0.394 to 1.140 µg/mL. Recovery ranged from 94 to 107%. Within day precision expressed as RSD% were in the range of 0.134 to 1.120. The solubility, dose number (D_o), relative sink condition (C_S/C_D), dissolution, and permeability results are presented in Table 1.

Table1. The solubility, D_o, C_S/C_D, dissolution [3] and permeability [3] results

	0.1N HCl	pH 4.5	pH 6.8	Distilled water
Solubility	197 ± 56	30.6 ± 15.8	9.78 ± 0.774	16.4 ± 2.25
D_o	0.00609	0.0392	0.123	0.0731
C_S/C_D	591	91.8	29.3	49.2

Dissolution: 0.1 N HCl		pH 4.5		pH 6.8	
Reference	Formulation	Reference	Formulation	Reference	Formulation
106 ± 0.754%	98.6 ± 0.935%	97.9 ± 0.813%	91.9 ± 1.53%	95.4 ± 0.783%	88.5 ± 2.82%

	Reference		Formulation	
	Flux*	Permeability coefficient**	Flux	Permeability coefficient
Ex-vivo	181 ± 98	90.5±48.9 x 10^{-4}	12.9 ± 6.53	6.47±3.26 x 10^{-4}
Dialysis membrane	758 ± 103	379±52 x 10^{-4}	30.5 ± 15.3	15.2±7.63 x 10^{-4}

* µm.cm^{-2}.min^{-1}, **cm.min^{-1}

Conclusions: In conclusion, the HPLC method proved to be sensitive, simple, reproducible, rapid, and precise, making it valuable in the formulation development studies for TDF.

Acknowledgments

Seval Olgac was supported by a scholarship from The Scientific and Technological Research Council of Turkey (TUBITAK) 2211-C National Ph.D. Scholarship Program in the Priority Fields in Science and Technology. Nebahat Ayşe ERMAN was supported by a scholarship from TUBITAK 2247-C Intern Researcher Scholarship Program (STAR) (Project no: 217S602).

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P035: EVALUATION OF POLYVINYL ALCOHOL NANOFIBERS AS VAGINAL DRUG DELIVERY SYSTEM

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Introduction: Polyvinyl alcohol (PVA) is a hydrophilic polymer used for biomedical and pharmaceutical applications with biodegradable, biocompatible, mucoadhesive, and water-soluble properties (1). The aim of this study is to develop a nanofiber formulation for vaginal applications using different PVA types. Electrospinning method was used to produce PVA nanofibers.

Materials and Methods: N,N-Dimethylformamide (DMF) : distilled water (1:1) was used as solvent system to prepare nanofiber formulations. Studies were carried out with three different concentrations (5%, 7.5% and 10%) for each type of polymer. The codes and content of the formulations are given in the table 1. The surface tension, viscosity (at 20 rpm) and conductivity properties of the polymer solutions were examined. The mechanical

properties and mucoadhesive properties of the nanofibers were investigated and compared.

Table 1. Concentration and codes of nanofiber formulations

Concentration	PVA M 13/140	PVA G 26/140	PVA G 40/140
5%	A1	B1	C1
7.5%	A2	B2	C2
10%	A3	B3	C3

Results: The results of the characterization studies of polymer solutions and nanofibers are given in Table 2. Viscosity increased with increasing polymer concentration. Since the solvent system is the same in polymer solutions, the surface tension values were found to be close to each other. The highest mucoadhesion, tensile strength and elongation at break values were found in the B3 nanofiber formulation.

Table 2. Characterization of nanofiber formulations and polymer solutions. ND: Not detected

Formulation Code	Characterization of Polymer Solutions			Characterization of Nanofiber Formulations		
	Viscosity (cP.s)	Conductivity (µS/cm)	Surface Tension ($mN.m^{-1}$)	Tensile Strength (MPa)	Elongation of break (%)	Work of mucoadhesion (mJ/cm^2)
A1	41.42 ± 2.87	174.73 ± 4.97	43.74 ± 0.20	ND	ND	0.033 ± 0.005
A2	349.67 ± 2.89	152.27 ± 0.51	43.00 ± 0.03	4.755 ± 0.029	65.067 ± 4.013	0.118 ± 0.097
A3	542 ± 0	129.47 ± 2.26	42.11 ± 0.08	3.035 ± 0.988	45.743 ± 8.468	0.054 ± 0.007
B1	183.89 ± 4.97	18. 46 ± 0.11	46.01 ± 0.10	1.910 ± 0.416	31.043 ± 7.454	0.075 ± 0.005
B2	699.11 ± 2.87	32.31 ± 0.30	43.01 ± 0.02	1.383 ± 0.065	125.423 ± 36.801	0.039 ± 0.005
B3	1740.16 ± 93.91	36.49 ± 0.23	44.78 ± 0.07	5.438 ± 1.062	170.677 ± 73.885	0.144 ± 0.030
C1	805.14 ± 24.85	67.51 ± 0.14	44.92 ± 0.04	2.747 ± 0.158	69.030 ± 13.643	0.025 ± 0.005
C2	1960 ± 5.739	97.82 ± 0.35	42.72 ± 0.13	2.993 ± 0.237	51.343 ± 16.004	0.027 ± 0.005
C3	2909 ± 80.29	95.61 ± 0.74	45.67 ± 0.03	8.00 ± 1.29	122.54 ± 42.41	0.090 ± 0.024

Conclusions: The nanofiber formulations showed different mucoadhesive and mechanical properties depending on the molecular weight and production process. The B3 formulation showed suitable mechanical and mucoadhesive properties for vaginal applications according to these results.

Acknowledgements

This study was supported by Gazi University Scientific Research Projects Coordination Unit under grant number 02/2020-17.

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P036: PREPARATION AND EVALUATION OF ALPHA TOCOPHEROL/ CYCLODEXTRIN COMPLEXES

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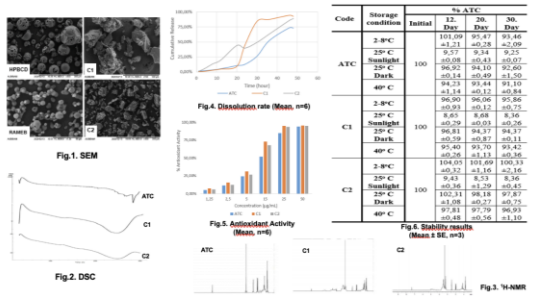
Introduction: The alpha tocopherol (ATC) uses commonly in cosmetic products. It has antioxidant, antibacterial, skin regenerating and antiaging properties, but it is sensitive to light, oxygen and heat. It may be irritating for skin in high concentrations. ATC must be in low concentration with high efficiency in an ideal cosmetic product. Therefore in our study, ATC: cyclodextrin complexes were prepared with hydroxypropyl beta cyclodextrin (HPBCD) and randomly methylated beta cyclodextrin (RAMEB) (1,2).

Materials and Methods: ATC (Fluorochem, UK), HPBCD (Applichem, Germany) and RAMEB (CTD, Inc. USA) were used as received for preparing ATC:CD complexes. All other chemicals were in analytical grade. The inclusion complexes were prepared by freeze drying method [3]. A modified HPLC method was used for the determination of ATC [4]. SEM (Zeiss, Supratm 50 VP, Germany), DSC (Shimadzu DSC-60, Japan) ^{1}H-NMR (Bruker Ultra Shield CPMAS NMR)–analyses, dissolution rate, antioxidant activity and stability studies were performed.

Results: SEM (Fig.1), DSC (Fig.2), ^{1}H-NMR (Fig.3) analyses results, dissolution rate studies (Fig. 4), antioxidant activity (Fig.5), stability results (Fig.6) were presented. (C1: ATC: HPBCD Complex, C2: ATC: RAMEB Complex)



Conclusions: Compared to pure ATC, solubility, dissolution rate and antioxidant activity were increased in complexes. ATC: RAMEB was found to be more stable than other complex at different storage conditions during 3 months.

Acknowledgements

To DOPNA-LAB for 1H-NMR analyses. To BIBAM for SEM Analyses. Anadolu University Scientific Research Project Foundation (Project Number: 1903S018)

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3. Güleç K, Demirel M (2016). Curr. Drug Deliv., 13(3), 444-451.
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P037: IN SILICO PREDICTION OF INTESTINAL DISSOLUTION AND ABSORPTION OF CARBAMAZEPINE IN HUMANS

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Introduction: The aim of this study was to predict the intestinal dissolution and absorption of carbamazepine (CBZ) in humans using gastrointestinal simulation technology.

Materials and Methods: Gastrointestinal simulation based on the advanced compartmental absorption and transit model (GastroPlus version 9.6, SimulationsPlus, Lancaster, CA) was used for the prediction. The plasma concentration-time profiles of 200 mg CBZ IR tablet were simulated based on the physicochemical and pharmacokinetic (PK) properties of the drug. The simulation was performed for 72 h using population simulation mode. The input parameters: MW, solubility (at pH 6.5), log P, pKa, human jejunal permeability, unbound percent in plasma, clearance and volume of distribution were 238.29, 0.117 mg/mL, 1.65, 11.83, 4.3 x 10^{-4} cm/s, 30%, 4.91 L/h and 1.26 L/kg, respectively (1-3). Dose volume of 250 mL was selected. The amounts of drug dissolved and regional absorption were obtained in fasted and fed states.

Results: The simulated plasma profiles of CBZ are presented in Fig.1. The predicted $AUC_{0\text{-}72}$, and C_{max} were 38.2 vs. 41.1 µg/mL.h, 1.47 vs. 1.54 ug/mL in fasted and fed states, respectively. t_{max} (4.5 h) was not changed in fasted and fed states. The regional absorption and profiles of drug dissolved in vivo are presented in Fig. 2.

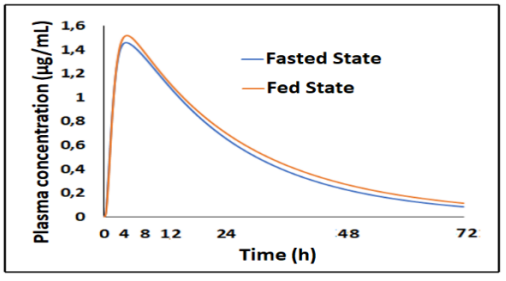

Fig. 1. Simulated plasma profiles.

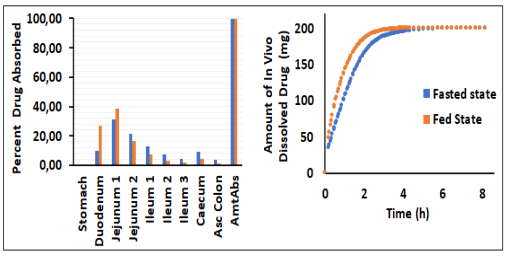

Fig. 2. Regional absorption and in vivo dissolved amount.

Conclusions: The in silico prediction of intestinal dissolution and absorption of CBZ indicated that food intake seems not to effect the oral bioavailability of CBZ IR tablets significantly.

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1. Kovacevic et al., (2009). Molecular Pharmaceutics, 6 (1):40-7.
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P038: EVALUATION OF A BIPHASIC IN VITRO DISSOLUTION TEST FOR LAMOTRIGINE IMMEDIATE RELEASE TABLETS AND CORRELATION TO HUMAN IN VIVO PERFORMANCE

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Introduction: The aim of this study was to characterize the dissolution profiles of two IR tablets of lamotrigine (LTG) with the biphasic dissolution test and explore the correlation to in vivo.

Materials and Methods: IR tablet formulations of 200 mg LTG (Reference, batch no: A8158013 and Test, batch no: 19143001) purchased from the local drug market were tested. Biphasic dissolution tests were carried out using USP apparatus II (708-DS, Agilent Technologies) with the dual paddle modification. pH 6.8 phosphate buffer and octanol were used as the aqueous and organic phases, respectively. Samples withdrawn from the phases at predetermined time points were analyzed spectrophotometrically. f_2 similarity test was used to compare dissolution profiles. Wagner−Nelson method was used to calculate the fraction of LTG absorbed (F_{abs}) from the plasma data of reference (1, 2). F_{abs} was correlated to the fraction of LTG partitioned in octanol (F_{diss}), and used to predict F_{abs} and plasma profiles of test.

Results: Dissolution profiles of LTG determined from two phases for test and reference are

presented in Fig.1. Test exhibited dissolution profile similarity to reference (f_2 > 50). Mean plasma concentration-time profiles of LTG from reference (observed) and test (predicted) are presented in Fig.2. AUC, C_{max} and t_{max} values were 122±28 vs.119±25 ug/mL.h, 2.9±0.5 vs. 2.6±0.4 ug/mL and 2.5±1.2 vs. 3.7±1.1 h for the reference and test, respectively. The bioequivalence (BE) of the test vs. reference was 83.1-111% for AUC and 80.2-100% for C_{max} with a 90% CI, which falls within the 80-125% BE criteria.

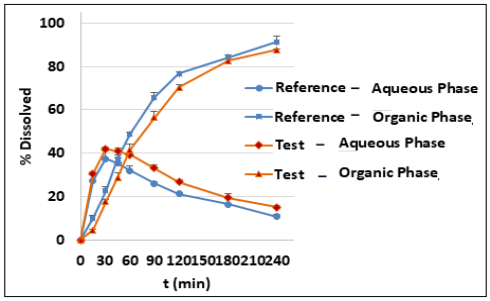

Fig.1. Dissolution profiles of test and reference

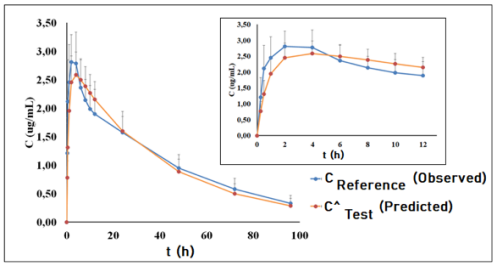

Fig.2. Plasma profiles of test and reference

Conclusions: This study demonstrated that the described biphasic test method provided a discriminative and in vivo predictive power for LTG tablet formulations.

Acknowledgements

The authors would like to thank Sanovel Pharmaceuticals (Turkey) for kindly providing LTG API.

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2. Wagner et al., (1986) Journal of Allergy and Clinical Immunolology, 78:681-688.

P039: DESIGN OF KETOROLAC TROMETHAMINE LOADED NANOPARTICLES AND EVALUATION OF IN VITRO EFFICIENCY FOR BRAIN TUMOR TREATMENT

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Introduction: Inflammation is closely related to cancer, and elimination of inflammation may be a viable strategy for the prevention and treatment of cancer. The purpose of this study is the preparation of PLGA nanoparticles containing Ketorolac tromethamine, an anti-inflammatory drug, and in vitro evaluation of its effectiveness on rat glioma (RG2) cell lines. With the preparation of nanoparticle formulations, it is planned to provide an effective treatment by ensuring that Ketorolac tromethamine passes the BBB and reaches the therapeutic concentration in the target area using a lower dose.

Materials and Methods: Nanoparticle formulations were prepared by water/oil/water emulsification solvent evaporation method (1). In vitro release studies for nanoparticle formulations were carried out using the "Dialysis Membrane Method" (2). RG2 cells was selected to investigate the in vitro cytotoxic effect of Ketorolac tromethamine loaded formulations. "Dulbeccos Modified Eagles" medium (DMEM) containing fetal bovine serum, L-glutamine, penicillin and streptomycin was used as culture medium for RG2 cells.

Results: Ketorolac tromethamine loaded PLGA nanoparticles have been successfully prepared and their particle size were obtained as approximately 155 nm. 35.64 % of the added drug was loaded into the nanoparticles and cumulative release of the drug was completed within 24 hours. İn in vitro cell culture studies, Ketorolac tromethamine solution at high concentrations showed cytotoxic effect on RG2 cells while Ketorolac tromethamine loaded nanoparticle formulations have much higher cytotoxic effect on RG2 cells at lower doses at 24 and 48 hours incubation.

Conclusions: It could be concluded that the developed formulations were promising for the treatment of brain tumors since they provided higher cytotoxic effect on RG2 cells compared to free drug.

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P040: THE EFFECT OF FREEZE DRYING WITH DIFFERENT CRYOPROTECTANTS ON THE CHARACTERISTICS OF KETOROLAC TROMETHAMINE LOADED NANOPARTICLES

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Introduction: Ketorolac tromethamine (KT) is a non-steroidal anti-inflammatory drug (NSAID) from the family of heterocyclic acetic acid. KT is a non-selective cyclooxygenase (COX) inhibitor with higly potent analgesic and moderate anti-inflammatory activity. When administered as a traditional oral dosage form, it carries the risk of many side effects such as peptic ulcer, GI bleeding or perforation. With nanotechnological drug delivery systems, controlled drug release can be achieved, resulting in a reduction in its profile with side effects (1). The purpose of this study is the evaluation of the effect of different cryoprotectants and freeze drying on the characteristics of PLGA nanoparticles loaded with KT.

Materials and Methods: Nanoparticle formulations were prepared by water/oil/water emulsification solvent evaporation method (2). Different cryoprotectants (mannitol, dextran, trehalose, glucose and sucrose) were added to the prepared nanoparticles, and the samples were divided into two groups and half of them were freze-dried. Samples in both groups were stored under different temperature and humidity conditions (4±2 ˚C, 60% ± 5% RH, 20±2 ˚C, 60% ± 5% RH and 25±2 ˚C, 60% ± 5% RH) for different periods (0, 1, 2 and 3 months). At the end of storage periods, particle size, polydispersity index (PDI) and zeta potential values of nanoparticles in all groups were compared with initial values.

Results: In this study, the effect of different cryoprotectants and freeze drying on the characteristics of PLGA nanoparticles were investigated. Particle size increased after freeze drying in nanoparticle formulations in all groups. The aggregation status was evaluated by comparing the particle size ratio of all groups before (first) and after freeze drying (Sf/Si). Significant aggregation was observed in the KT loaded nanoparticles prepared with dextran. No significant change was observed in the zeta potential values after freeze drying.

Conclusions: It can be concluded that different cryoprotectants and freeze drying have a significant effect on the particle size of the prepared KT loaded PLGA nanoparticles.

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P041: SEMISOLID NLC FORMULATIONS FOR COSMETIC USE: EVALUATION OF MECHANICAL PROPERTIES

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Introduction: Nanostructured lipid carriers (NLCs), the second generation of lipid nanoparticles, have been received great attention as cosmetic delivery systems (1). Semisolid NLC dispersions provides advantages such as obtaining a final product with a single-step production process and thus they are cost and time effective. In this study, four different herbal oils that have anti-aging effects were used as liquid lipids for the preparation of semisolid NLC dispersions and the mechanical properties of the formulations were evaluated.

Materials and Methods: Semisolid NLC formulations were prepared by high shear homogenization and ultrasonication method. Compritol 888 ATO (C) was used as solid lipid and pomegranate seed (P), argan (A), grape seed (G) and coconut (C) oils were used as liquid lipids. The semisolid NLC formulations were produced at different total lipid contents. The particle size, polydispersity index (PDI) and zeta potential values of the formulations were analyzed. TA.XT Texture Analyzer (Stable, UK) was used in Texture Profile Analysis (TPA) mode for evaluating mechanical properties of formulations.

Results: In TPA, lower hardness and compressibility indicate the ease of application while lower numerical value of elasticity and higher adhesiveness indicates enhanced retention of formulation on the skin. The hardness, compressibility and adhesiveness of the formulations prepared with Compritol 888 ATO and pomegranate seed oil were significantly lower than the formulations prepared with other herbal oils (Table 1).

Table 1. Mechanical properties of formulations

	A	B	C	D	E
CP15	21.98	54.24	29.47	0.616	0.993
CA15	61.31	116.01	54.74	0.558	0.976
CG15	64.87	134.99	71.16	0.490	0.995
CC15	77.72	139.13	85.78	0.683	1.000
CP20	50.07	114.67	59.83	0.665	0.976
CA20	147.28	313.17	136.31	0.601	0.990
CG20	128.32	256.75	87.03	0.557	0.996
CC20	142.39	251.68	75.82	0.392	0.990

A:Hardness (N), B:Compressibility (N.sec), C: Adhesiveness (N.sec), D:Cohesiveness, E: Elasticity

Conclusions: Hardness, compressibility and elasticity properties of CP15 and CP20 coded semisolid NLC formulations prepared with Compritol 888 ATO and pomegranate seed oil were found appropriate for ease of application and ease of spreading onto the skin.

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P042: BUDESONIDE LOADED CONTROLLED-RELEASE POLYCAPROLACTONE NANOPARTICLES

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Introduction: Corticosteroids such as budesonide are the drugs of choice for the treatment of inflammatory disorders[1]. However, budesonide undergoes extensive hepatic first-pass metabolism to the extent of approximatelly 85%. This imposes the need for either frequent administration of this drug or high doses[1]. To overcome this constraint and attain controlled release, budesonide was encapsulated in a biodegradable polymer, polycaprolactone (PCL).

Materials and Methods: Budesonide-loaded PCL (molecular weight of 80,000) nanoparticles were prepared by emulsion solvent evaporation with ultrasonification technique. Formulations were prepared based on 3^2 factorial design. Independent variables were the concentration of polymer and oil phase:water phase ratio (1:8, 1:9 and 1:10). While PCL and budesonide formed the oil phase in DCM, Lutrol F68 dissolved in distilled water to form the water phase. Lutrol F68 ratio was kept constant at 5% in all formulations. The amount of budesonide was 1% in drug-loaded formulations. In vitro drug release was performed by the dialysis bag method in a buffer system at pH 1.2, 6.8, and 7.4, respectively, corresponding to the pH in the stomach, upper small intestine, and both ileum and colon, respectively.

Results: The PCL nanoparticle formulations with an oil phase: water phase ratio of 1: 8 had the smallest size and highest zeta potential. The in vitro release study showed that 30% of budesonide was released from the nanoparticles within 24 hours. The nanoparticles exhibited high encapsulation efficiency (approx. 80%).

Conclusions: In conclusion, budesonide encapsulated PCL nanoparticles were prepared by the emulsion solvent evaporation with ultrasonification technique and characterized for controlled drug-release applications. The effect of polymer concentration and oil phase:water phase ratio on the size and zeta potential of particles, were investigated. BUD loaded controlled release nanoparticle drug delivery system was succesfully prepared with emulsion solvent evaporation with ultrasonification technique.

Acknowledgements

This study was supported by Gazi University Scientific Research Projects Coordination Unit under grant number 02/2019-14.

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P043: EFFECT OF POLYMER ON ONDANSETRON HCl LOADED POLYMERIC NANOPARTICLES

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[2] Erzincan Binali Yıldırım University, Department of Pharmaceutical Technology, Erzincan, Turkey

Introduction: Ondansetron HCL (OND) is an antagonist of serotonin (5-hydroxytryptamine) subtype 3 receptor which is used preventing and treatment of nausea and vomiting in neoplastic patients. It is absorbed fastly but has a half life between 2-4 hours that is relatively short, requires multiple dosing during the day. [1-3]. This study aimed to develop sustained release of OND loaded polymeric nanoparticles thus increase patient compliance by reducing the dosing frequency.

Materials and Methods: OND loaded polymeric nanoparticles were prepared by the modified double emulsion solvent evaporation method using different type and molecular weight poly(lactic-*co*-glycolic acid) (PLGA), Poly(vinyl alcohol) and OND and then lyophilized for 48 hours. All formulations

were evaluated in terms of particle size, polydispersity index(PDI), zeta potential(ZP), encapsulation efficiency(EE) and in vitro drug release.

Results: The mean particle size was in the range of 318 to 405nm. It was observed that as the molecular weight of polymers increased, the mean particle size also increased. ZP values of all formulations were measured negative due to negative charged polymer used. The prepared nanoparticles exhibited PDI values ranging between 0.1 to 0.4, which may indicate that they were homogeneous. In formulations prepared with the same type of polymer, the increase in the amount of polymer resulted in an increase in value of EE. However, the increase in the amount of polymer resulted in a slowdown in the in vitro release rate. 72 hours sustained release pattern was obtained for all formulations. On the other hand, when different types of PLGA polymers were used, the EE increased as the lactide / glycolide content in the polymer composition increased and the molecular weight of the polymer decreased.
The result showed that mean particle size, EE and in vitro release rate depend on type and molecular weight of PLGA polymers.

Conclusions: The findings of this study led to the conclusion that the amount and type of polymer have a significant effect on EE, particle size and drug release.

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P044: BIOPHARMACEUTICS CLASSIFICATION SYSTEM (BCS) BASED BIOWAIVER APPROACH IN TURKEY

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Introduction: Current legal regulations on pharmaceuticals take into account the drug properties like solubility and permeability along with biopharmaceutical characteristics such as dosage form and dissolution. Active ingredients for immediate release oral solid dosage forms are classified according to the Biopharmaceutics Classification System (BCS) which is accepted by health authorities like U.S. Food and Drug Administration (FDA), European Medicines Agency (EMA), and World Health Organization (WHO) taking into account these pharmaceutical considerations. Under BCS, holding pharmaceuticals exempt from in vivo bioequivalence and bioavailability studies may only be possible when certain requirements are met (1). Biowaiver applications based on BCS comprise generic drugs. To reduce the cost of bioequivalence studies in human, and at the same time to evaluate the performance of the active ingredient/drug, use of solubility, permeability, and in vitro dissolution studies are supported and recommended. Pursuant to the health policies of our country, manufacturing and registration of generic products are encouraged. In this study, it was aimed to evaluate the biowaiver applications in Turkey.

Materials and Methods: The pharmaceuticals with approved biowaivers were determined, and IQVIA (a Human Data Science Company) data in terms of box numbers and prices have been evaluated and interpreted.

Results: When the total market of drugs containing BCS Class 1 (in total 20) and BCS Class 3 (in total 8) active substances, for which a biowaiver decision has been made by the health authority of our country, was evaluated for 2010 and 2020 on a box and value basis, there was an increase of 243% on a box basis and 78% on a value basis (Figure 1).

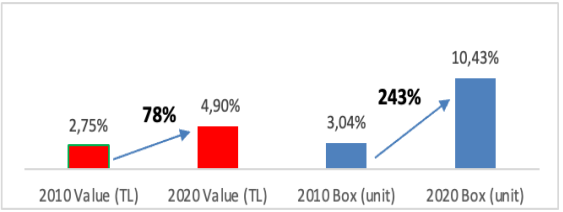

Fig 1. Total market percentage change based on of Value (TL) and Box (unit) in 2010 and 2020 of drugs containing BCS Class 1 and BCS Class 3 active substances.

Conclusions: As a result of the biowaiver assessment, the increase in the total market percentage of BCS Class 1 and BCS Class 3 drugs based on of box and value contributes to the development of the generic pharmaceutical industry. In our country, the health authority also takes into account the biowaiver assessments and, when the necessary criteria are met, it allows for the rapid licensing of generic drugs as a result of the biowaiver assessments. This situation positively contributes to the reduction of health expenditures, considering the budget increases that have a negative effect on the management and sustainability of public health expenditures in our country as in the world. In addition, the increase in the number of drugs for which biowaiver decision is made decreases the number of healthy volunteers ethically and becomes important in replacing in vivo studies with biopharmaceutical tests.

Reference:

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P045: EVALUATIONS OF FASTED AND FED BIOAVAILABILITIES OF SELF DOUBLE EMULSIFYING DRUG DELIVERY SYSTEM OF TENOFOVIR

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Introduction: Water-in-oil-in-water (w/o/w) double emulsions are able to enhance oral bioavailability of BCS Class 3 drugs with high solubility and low permeability. Tenofovir disoproxil fumarate (TNF) is a nucleotide reverse transcriptase inhibitör, which is used for the treatment of hepatitis B and human immunodeficiency virüs infections. It has low permeability while having high solubility, classifying as a class 3 drug in Biopharmaceutics Classification System (BCS). Permeation is the rate limiting step in the oral bioavailability of TNF. The oral bioavailability of TNF is very low and its bioavailability is influenced by fatty food intake (1). The w/o/w emulsion containing TNF was successfully developed and characterized in our previous study (2) The aim of this study was to evaluate the fasted and fed bioavailabilities of Self Double Emulsifying Drug Delivery System (SDEDDS) of TNF compared to the commercial product (Viread®) in rats.

Materials and Methods: Pharmacokinetic studies were conducted in 2 groups as fasted and fed state conditions. The suspension of Viread® tablets and SDEDDS were administered to male Sprague Dawley rats (n=6) at a dose of 61,25 mg/kg by oral gavage. Following oral administration, the blood samples (250-300 µL) were obtained from the tail vein in heparinized tubes at various time points of 0, 0.25, 0.5, 1, 2, 4, 6, 8, and, 24 hours. Blood samples were centrifuged and supernatants were separated and kept at -80ºC until analysis. The LC-MS/MS method was used to determine the concentration of TNF in plasma. The non-compartmental analysis and the pharmacokinetic parameters such as AUC_{0-24}, C_{max}, t_{max}, and $t_{1/2}$ were calculated using WinNonlin® software.

Results: In fasted group, double emulsion formulation showed AUC_{0-24} and C_{max}, 5673±1403 ng.min/mL and 683±130 ng/mL, respectively. In fed group, double emulsion formulation showed AUC_{0-24} and C_{max} 6486±3284 ng.min /mL and 847±214 ng/mL, respectively. The fast and fed states AUC_{0-24} values of the double emulsion formulation were found to be approximately 2-fold higher than the commercial product and C_{max} values increased approximately 1,2-fold. There was no significant difference (p>0,05) between the fast and fed state bioavailability of double emulsion.

Conclusions: The results show that the double emulsion formulation, developed as a lipid-based drug delivery system, increases the oral bioavailability of tenofovir and does not have fast and fed state variations.

Acknowledgements

This study was supported by a grant from TUBITAK (Project No: 115S405). Tenofovir was kindly gifted from Pharmactive from Turkey.

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P046: CHARACTERISATION AND FORMULATION OF MELATONIN INTRANASAL DELIVERY SYSYTEM

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Introduction: Melatonin is a methoxyindole hormone which is present in vertebrates, synthesized in the pineal gland (1) gut, skin, retina, bone marrow and platelets. It is produced by bacteria, protozoa and fungi as well (2). Its structure, especially its two functional groups are crucial for its binding affinity to certain receptors, and its flexibility allowing it to enter any cell, body fluid and the compartment was important to insert its effects (3). Melatonin is gaining popularity due to its many benefits in diabetes, anxiety, cancer, narcolepsy, insomnia, jet lag, anti-aging and neurodegenerative disorders like dementia, Parkinson's disease and Alzheimer's disease (AD) (3). Recent studies showed that intra-nasal route offer many advantages, such as presence of large absorbtion surface area and porous nature of, endothelial membrane high blood flow, avoidance of first-pass metabolism and ease of administration. Melatonin delivery into the brain as a targeted delivery may offer a good opportunity as novel delivery for the treatment of CNS diseases. In this study, the aim was to develop and characterize an intra-nasal niosome melatonin formulation.

Materials and Methods: Melatonin loaded niosomes were prepared by using Cholesterol and Span 60 (sorbitan monostearate) by thin film and

hydration/sonification method. Dicethyl phosphate was also used to modify the surface charges of niosomes. Particle size distribution, zeta potential and polydispersity index of the niosomal formulation were measured by using Anton Paar Litesizer 500. Entrapment efficiency and in-vitro melatonin release profile studies were conducted by using the Franz cell diffusion method, cellulose acetate was the membrane and the donor was PBS pH 7.4.

Results: Some results are summarized in the below table:

Sample	Particle size μm	Zeta Potential	Entrapment Efficiency %
Empty Niosomes	499,4 nm	-63,1 mV	-
Loaded non filtered niosomes 1	357.7 nm	-44,18 mV	%95,70
Loaded non filtered niosomes 2	697,6 nm	-46,78 mV	% 79,17

Sample	Particle size nm	Zeta Potential;mV	Entrapment Efficiency %
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Loaded non filtered niosomes 1	357.7	-44,18	%95,70
Loaded non filtered niosomes 2	697,6	-46,78	% 79,17

The entrappment efficiency differed according to the sonication time, and the size of the niosomes was further reduced by sonication and extrusion through 0,22 μm filter.

Conclusions: Melatonin niosomes could be promising drug delivery sistems for intra–nasal delivery for CNS diseases such as AD.

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P047: DETERMINATION OF EFFECTIVE SURFACE MODIFICATIONS OF SILICA NANOPARTICLES AS VEGF-TARGETED SIRNA CARRIERS

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Introduction: Vascular endothelial growth factor (VEGF) is an endothelial cell-specific mitogen that induces the formation of new capillaries. Tumor cell-derived VEGF-A stimulate angiogenesis and the self-renewal of cancer stem cells (1). Small interfering RNA (siRNA) targeting VEGF is promising in tumor regression. Due to negative charges, large molecular weight and size, and instability or short half-lives in the plasma, siRNAs cannot reach the intracellular target site. In this study, we show that VEGF blocking siRNAs can be carried by PEGylated silica nanoparticles by creation of positive charge on NPs with appropriate surface modifications. Particle size, zeta potential, and degree of complexation of nanoparticles were evaluated.

Materials and Methods: All chemicals were purchased from Sigma-Aldrich or Gelest. Silica nanoparticle synthesis method was adopted from Quan et al (2). 3 experiments were performed as E1 (Surface modification with 3-Triethoxysilylpropylamine (APTES) and PEGylation with Pyridine/ *N*-(3-Dimethylaminopropyl)-*N*′-ethylcarbodiimide (EDC) coupling), E2 (Surface modification with APTES and PEGylation with n-hyroxysuccinimide (NHS)/EDC coupling) and E3 (Surface modification with (3-trimethoxysilylpropyl)diethylenetriamine (TMPT) and PEGylation with PEG-Silane). Particle size determination and zeta potential measurements were done. The agarose gel electrophoresis was performed to evaluate the complexation efficiency.

Results: Silica NPs were synthesized with the size around 20 nm and zeta potential was -15 mV. After PEGylation, particle sizes of E1, E2 and E3 were 33 nm, 138 nm and 31 nm, respectively and all formulations were positively charged according to zeta potential results. Complexations were performed with the concentrations 10/1, 20/1 and 50/1. According the gel electrophoresis results, full complexation was obtained in all ratios of E3 formulation.

Conclusions: Results show that positively charged and PEGylated silica nanoparticles might be promising approach for siRNA delivery.

Acknowledgements

This study was supported by TUBITAK project 118C470

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P048: INVESTIGATION OF THE EFFECTIVENESS OF GLYCOPOLYMER BASED THERANOSTIC NANOSISTEMS IN BREAST CANCER

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Introduction: Nowadays, breast cancer is the most common type of cancer in women in the world. The lack of selectivity of conventional chemotherapeutic agents against tumor tissue, damaging healthy cells and causing serious side effects during treatment have encouraged scientists to develop new targetable drugs and drug delivery systems. Accordingly, new nanoformulations are being developed that allow targeted imaging, molecular therapy and clinical applications that combine diagnosis and treatment in a single material, termed as theranostic. Because of their low toxicity values, easy to synthesize, modification and application with other imaging technologies, upconversion luminescent nanoparticles (UCNP) is a pioneer in theranostic applications. The aim of this study is to prepare a biocompatible new nanoteranostic platform and to obtain an ideal dual drug/gene delivery system against cancer.

Materials and Methods: Glycopeptide polymers (GP) were synthesized via reversible addition-fragmentation chain transfer (RAFT) polymerization and click reactions. Molecular weight of glycopolymers were characterized in terms of gel permeation chromatography (GPC) and proton nuclear magnetic resonance (^{1}H NMR) spectroscopy. UCNP synthesis was carried out by thermal decomposition method. Then they were coated with glycoblock polymers. The morphology and size distribution of the nanoparticles were characterized by transmission electron microscopy (TEM) and dynamic light scattering (DLS) analysis.

Results: UCNP@GP-Dox bionanoprobe and siRNA loaded UCNP@GP-Dox have average diameter in the 102±3.1 nm and 55±2.5 nm, respectively.

Conclusions: The present study showed that UCNPs and GP have low cytotoxicity, siRNA loaded UCNP@GP-Dox have a good cytotoxic and apoptotic effect to human breast cancer cells. The effectiveness of the new nanoteranostic platform in diagnosis and treatment will be demonstrated in future studies.

Acknowledgements

This study was supported by a grant of TUBITAK (SBAG-118S458) and BAP deparment of Bezmialem Vakif University (Project No: 20210209)

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P049: SYNTHESIS OF CISPLATIN AND/OR GEMCITABINE CONTAINING POLYMERIC NANODRUG FORMULATIONS FOR BREAST CANCER TREATMENT

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Introduction: Many anticancer drugs cause serious side effects, have a short plasma half-life and lack of selectivity. Researchers have focused on treatment methods that directly target cancer cells to overcome these problems. In addition to targeting anticancer drug to the tumor site, drug delivery systems also reduce side effects and improve efficiency of treament (1). The aim of this study was to prepare a new dual nanodrug formulation based on polymeric drug delivery systems for breast cancer treatment.

Materials and Methods: Glycoblock polymers composed of (meth)acrylated sugar monomers and methacrylic acid were synthesized via reversible addition-fragmentation chain transfer (RAFT) polymerization by using gemcitabine functionalizied RAFT agent. Glycopolymers were characterized by gel permeation chromatography (GPC) and proton nuclear magnetic resonance (^{1}H NMR) spectroscopy analysis. Then the glycoblock polymers were conjugated with Cisplatin. The morphology and size distribution of the nanoparticles were characterized by transmission electron microscopy (TEM) and dynamic light

scattering (DLS) analysis. Cytotoxycity of nanodrugs were determined by MTT assay.

Results: Molecular weight of glycopolymers were determined by ^{1}H NMR and GPC. Gemcitabine and Cisplatin including nanoparticles have average diameter in the 105±3.148 nm range with narrow particle size distribution. These nanoparticles showed superior uptake and the highest cytotoxicity in-vitro on human breast cancer cells.

Conclusions: The present study showed that well-characterized nanodrug formulations have strong cytotoxycity to human breast cancer cells. A new dual polymeric drug delivery system including gemcitabine and cisplatin together was increased effectiveness of treament.

Acknowledgements

This study was supported by a grant of BAP deparment of Bezmialem Vakif University (Project No: 20200919)

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P050: TRANSCRIPTOMIC CHARACTERIZATION OF THE USNIC ACID (UA) EFFECTS ON TRIPLE NEGATIVE BREAST CANCER (TNBC) WITH NEXT GENERATION SEQUENCING TECHNOLOGY

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Introduction: Triple negative breast cancer (TNBC) represents approximately 20% of all breast cancers and is associated with the worst outcome among all breast cancer subtypes [1]. The most effective treatment method and drug for TNBC cancer has not been developed yet. UA, a lichen secondary metabolite, has been identified as an anti-cancer agent for different cancer types in the literature, it is aimed to examine the therapeutic characterization on TNBC cancer at the transcriptomic level (1).

Materials and Methods: The determined IC_{50} concentration of UA was applied on MDA-MB-231 (Triple Negative Breast) and MCF12A (normal epithelial cell) cells. The mRNA expression profiles were examined using NGS technology (instrument Illumina HiSeq-2000) from the examined cells. Approximately 40 million readings occurred for each library. Readings were filtered and 61057 genes expressed among libraries were identified. The coefficient calculation of these genes among libraries was determined according to p<005 and Log2 criteria. GO and pathway analyzes of genes [-2 <FC <2] in libraries were performed.

Results: As a result, a difference in transcript expression was observed between TNBC cancer and normal epithelial breast cells. This situation is also reflected in the heatmap results. This difference was also observed in the effect of UA on both cells. 4956 (-2≤ FC ≤ 2) genes were identified on UA-treated TNBC cancer and normal cells. 176 genes have been identified, showing only the TNBC cancer-specific effect of UA. Genes (-2≤ FC ≤ 2) showing TNBC effect of UA were found to be related to cellular anatomical structure in terms of cellular component, cellular processes in terms of biological process, and binding activities in terms of molecular function. In addition, using the WNT, Inflammation, Ganodotropin, Intgerin and CCKR pathways, TNBC exerted an anti-proloferative effect on cancer.

Conclusions: Usnic acid has an anti-tumor effect by suppressing genes that are effective in TNBC cancer formation process.

Acknowledgements

This study was supported by a Ankara University Scientific Project (BAP) (19L0415001)

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P051: DETERMINATION THE USNIC ACID (UA) THERAPY EFFECTS ON TRIPLE NEGATIVE BREAST CANCER (TNBC) BY PROTEOMIC APPROACHES

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Introduction: Triple negative breast cancer (TNBC) is characterized by a lack of estrogen receptor (ER) progesterone receptor (PR) expression and an absence of human epidermal growth factor 2 (HER2). Due to the lack of an effective treatment method, it is typically distinguished among other types of breast cancer by its high metastatic and mortality rate [1]. Since UA, a lichen secondary metabolite, has an anti-metastatic and anti-proleferative effect for different cancer cells, it was deemed necessary to enlighten its effects on TNBC cancer at a proteomic level.

Materials and Methods: The IC_{50} concentration of UA for TNBC cells (MDA-MB-231) and normal epithelial breast cells (MCF12A) were determined by XCELLigence real time cell analysis system. The IC_{50} concentration of UA were applied to the cells and the proteins of these cells were determined by LC-MS / MS analysis. GO (Gene Ontology) and KEGG (Kyoto Encyclopedia of Genes and Genomes) pathway analyses were performed to identify the biological functions of differentially expressed proteins.

Results: A total of UA specific proteins (filtered according to p≤0.05) were determined. 70 protein for in MCF12A cell; 349 protein for in MDA-MB-231 cell and 23 protein expressed in both cells were determined. In TNBC cancer, 274 proteins were found with a significant change (-2≤ FC ≤ 2) in UA-specific expression. UA-specific proteins with significant change (-2≤ FC ≤ 2) in TNBC were found to be related to cellular anatomical structure in terms of cellular component, cellular processes in terms of biological process, and binding activities in terms of molecular function. The UA signaling pathways in TNBC cancer were determined as Huntington disease, Glycolysis, Gonadotropin pathway, Integrin signalling pathway, Inflammation pathway, CCKR signaling and Ubiquitin proteasome pathway.

Conclusions: UA directs TNBC cells to apoptosis by separating them from the tumor microenvironment using in particularly integrin and ganodotropin pathways.

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This study was supported by a Ankara University Scientific Project (BAP) (19L0415001)

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P052: SOME NEW 3,5-DISUBSTITUTED 1,3,4-OXADIAZOLE DERIVATIVES WITH IN VITRO ANTI-INFLAMMATORY ACTIVITY

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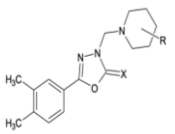
Introduction: Inflammation is the body's defense system response to the stimulation of many factors. Increased vascular permeability, changes in the structure of the membrane and protein denaturation are important factors that trigger the inflammation process. Proteins denaturation is a well-documented reason of inflammation. Therefore, it is recognized that, the compounds that are able to inhibit heat induced protein denaturation, have potential therapeutic remark as anti-inflammatory agents. NSAIDs (Non-steroidal anti-inflammatory drugs) used are also effective by inhibiting albumin denaturation (1). To obtain new anti-inflammatory agents, recent studies have aimed to replace the carboxylate functionality of NSAIDs with many types of less acidic heterocyclic bioisosters like 1,3,4-oxadiazole to protect gastric mucosa from free carboxylate (2). In this study, novel 3,5-disubstiuted-1,3,4-oxadiazoles were synthesized and evaluated for their anti-inflammatory activity.

Materials and Methods: Target compounds were obtained by *Mannich* reaction of previously synthesized 5-(3,4-dimethylphenyl)-1,3,4-oxadiazole-2(*3H*)-thione/one rings with piperidine derivatives (3,4). The anti-inflammatory activity of the synthesized compounds was investigated using *in vitro* albumin denaturation assay (5).

Results: The structures of the newly synthesized compounds were verified by IR and ^{1}H NMR spectral methods. The activity test results demonstrated that while indomethacin showed 86.92% activity, compounds **5b** and **5h** showed inhibition activity with 85.53 and 81.03% at 100 µg/mL, respectively. In addition, at the same concentration, compounds **5a**, **5c**, **5g** and **5i** showed more than 60% inhibition activity (Table 1).

Table 1. Albumin denaturation test results of synthesized compound

Structure of the compounds	Compound	-X	-R	Activity(%)
	Control			100,00
	Indomethacin			86,92
	5a	S	4-Phenyl	67,20
	5b	S	4-Hydroxy-4-phenyl	85,53
	5c	S	4-Benzyl	66,55
	5d	S	4-(4-Morpholine)	25,08
	5e	O	4-Phenyl	23,20
	5f	O	4-Hydroxy-4-phenyl	41,80
	5g	O	4-Acetyl-4-phenyl	69,77
	5h	O	4-Benzyl	81,03
	5i	O	4-Cyano-4-phenyl	64,63
	5j	O	4-(4-Morpholine)	56,27

Conclusions: Compounds **5a**-**c** and **5g-i**, which showed more than 60% inhibition in the albumin denaturation test, were selected for further investigation to elucidate the anti-inflammation mechanism.

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P053: A MONTMORILLONITE CLAY AS AN EFFICIENT AND GREEN CATALYST FOR FUNCTIONAL POLYETHER SYNTHESIS

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Introduction: Green chemistry is the synthesis of substance in such a way that is proper, non-polluting and protected and which requires lowest amounts of resources and energy but generating slight or no waste material. Scientists and Chemists can significantly minimize the risk to environment and health of human by the help of all the valuable ideology of green chemistry (1). The purpose of this paper is to study the copolymerization of cyclic ethers and examine the catalytic activity of an Algerian proton exchanged montmorillonite clay called "Maghnite-H+" (2,3), a new non-toxic and inexpensive catalyst.

Materials and Methods: The preparation of the "Maghnite-H^+" was carried out by using a method similar to that described by Belbachir et al (3). Epichlorhydrin (99%), Tetrahydrofurane (99%) and acetic anhydride were purchased from Prolabo in 99% purity. The ring opening bulk copolymerization of tetrahydrofurane with epichlorhydrine was carried out in sealed tubes at room temperature, using a Maghnite-H^+ as initiator. This solid catalyst can be easily separated from the polymer products and regenerated.

Results: The results of bulk copolymerisation experiments of tetrahydrofurane with epichlorhydrine are reported in Table1. FT-IR,^{1}H-NMR, and GPC analysis show that the polyether is successfully obtained. The ^{1} H-NMR spectra showed three sets of peaks, corresponding to the chloride methylene groups at 3.65 ppm, the central methylene groups at 1.62 ppm and the complex signal that resonates between 3,4 -3,7 ppm corresponds to the methylene protons adjacent to the oxygen.

Table 1: Copolymerization of THF with epichlorhydrine induced by Maghnite-H+.

f	Conversion (%)	Mn	Mw	Mv
0.5	45	2162	5759	5153

Conclusion: Maghnite-H+, proton-exchanged montmorillonite clay, is effective initiator for the ring-opening polymerization of cyclic ethers. The polymerization proceeds smoothly by a very simple procedure, and a simple filtration is sufficient to recover the catalyst.

Acknowledgements

Authors are grateful to Addou, A and Akeb, M engineers of the Chemistry Laboratory of Polymers.

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P054: SYNTHESIS AND STANDARDIZATION OF AN IMPURITY OF ACETAMINOPHEN, DEVELOPMENT AND VALIDATION OF RELATED ULTRA-HIGH PERFORMANCE LIQUID CHROMATOGRAPHIC METHOD

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Introduction: In this study, one of the impurity molecules of acetaminophen, which is not defined in the organic impurities analysis method of acetaminophen in HPLC in American Pharmacopoeia Version 42 (USP 42), has been synthesized, characterized, standardized and a related method in UHPLC including this defined impurity was developed and validated as per ICH Q2(R1).

Materials and Methods: Within the study, after the synthesis of this impurity molecule (N,N'-[Oxydi(4,1-phenylene)]diacetamide: ODAA) using 4,4'-oxydianiline and acetic anhydride, characterization studies were performed by FT-IR, NMR, elemental analysis, HPLC, melting point determination and LC-MS/MS. The potency of the synthesized molecule was determined as a result of the relevant analyses (Singh et.al. 2019). Related method development and validation studies were carried out to transfer the HPLC method of organic acetaminophen impurities to UHPLC.

Results: The chemical structure of the synthesized ODAA molecule was confirmed by characterization studies and its potency value was found to be 99,64%. The organic impurities analysis method of

acetaminophen has been successfully transferred from HPLC to UHPLC by developing the related method. As a result of the validation study, all findings were observed within the acceptance criteria and thus the method was validated.

Conclusions: In this study, one of the acetaminophen impurities which is not defined in USP 42 was synthesized, its potency was determined and standardized. The current organic impurities analysis method of acetaminophen was expanded to include this in-house defined impurity and transferred to UHPLC. It is expected that, this new developed method will be introduced to the literature and pharmacopoeias, as well as the shortened analysis time will save a great deal of time and the chemicals used.

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P055: DEEP EUTECTIC SOLVENTS AS POWERFUL CATALYSTS AND SOLVENTS FOR THE SYNTHESIS OF AMIDES

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Introduction: The amide bond has gained a great position in the pharmaceutical field, representing the main structural motif in small molecule API drugs and therapeutic peptides. The growing need for large amounts of biologically active amides and peptides for the pharmaceutical market has strongly raised the issue of the environmental sustainability of their synthesis. Current methods suffer from low efficiency and sustainability and generate large amounts of waste products, where solvents are the major source [1]. In addition, most common reagents and solvents used have safety concerns that make the environmental profile of these methodologies unfavourable.

Materials and Methods: Deep eutectic solvents (DESs) have been prepared by mixing choline chloride, used ad Hydrogen Bond Acceptor (HBA), and different carboxylic acids used as Hydrogen Bond Donor (HBD). The amides obtained were characterized by spectroscopic methods such as NMR, GC-MS and LC-MS.

Results: deep eutectic solvents (DES) represent a promising eco-friendly alternative to conventional solvents [2]. They can be used not only as reaction media, but also as active catalytic species and, in some cases, as reagents. Herein, we evaluated for the first time the dual role of DESs as reaction media and reagent in the 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide (EDC) mediated synthesis of amides. All the reactions tested proceed at low temperatures and in a short time without the need for a basic catalyst. The reaction conditions demonstrate compatibility with a wide range of carboxylic acids and amines, affording the desired amides in excellent yields.

Conclusions: A highly efficient, mild, catalytic protocol has been developed for the synthesis of amides using a reactive DES. The advantages of this procedure include environmental compatibility, versatility, and easy workup.

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P056: AFFINITY OF THE POLYETHER IONOPHORE MONENSIN A TO BIND MONOVALENT METAL IONS: A DFT/PCM STUDY

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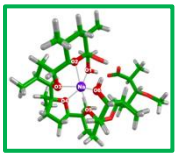
Introduction: The affinity of Monensin A to bind monovalent metal cations was evaluated by means of density functional theory (DFT) combined with polarizable continuum model (PCM) computations. The effect of various factors which may render on complex formation between Monensinate A anion and Group IA and IB metal ions was accessed.

Materials and Methods: All calculations were performed using Gaussian 09 package of programs. All the structures were fully optimized in the gas phase at B3LYP/6-31+G(d,p) level of theory yielding the respective electronic energies of the studied species.

Results: The effect of metal ion radius, its charge accepting power, and dielectric properties of the

medium influencing the complex formation between Monensin A and group IA and IB metal ions was evaluated. The calculations performed reveal the following key determinants of the monovalent metal selectivity in Monensinate A anion:

- The metal ion radius: smaller size cations, with higher positive charge density, are more competitive than their bulkier counterparts;
- The metal cation charge accepting ability: increasing the metal charge accepting ability, especially for d-elements, which translates into increased affinity toward the surrounding ligands (donor atoms), enhances the metal ion selectivity;



- The dielectric properties of the medium: low-polarity solvents favor the smaller ions possessing high ligand affinity (Li+ and Cu+); in polar solvents, characterized with high dielectric constants, the competitiveness of the medium-size cations, particularly Na+, increases.

Conclusions: The metal selectivity of Monensin A can be manipulated by changing the solvent used: the polyether host selectively binds Na^+ in polar solvents (methanol and water) but could become Li^+ or Cu^+-selective in low-polarity solvents such as alkyl ethers, hydrocarbons and their halogenated derivatives.

Acknowledgements

This study was supported by a grant from the National Science Fund of the Bulgarian Ministry of Education and Science (Contract № KP-06-H29/3).

P057: FOCUSING ON C-4 POSITION OF 1,4-DIHYDROPYRIDINE RING: SYNTHESIS AND L-/T-TYPE CALCIUM CHANNEL BLOCKING ACTIVITY

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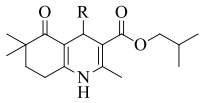
Introduction: 1,4-Dihydropyridines (DHPs), represented by nifedipine and amlodipine, are widely prescribed for the treatment of hypertension (1). Although their primary target in the cardiovascular system is the L-type calcium channel isoform, DHPs can also block low-voltage-activated T-type calcium channels (2). Commercial DHPs generally carry phenyl rings with small substituents at C-4 position. In this study, we aimed to investigate the effects of bulky groups at the mentioned position to the L-/T-type calcium channel blocking activities of DHPs.

Materials and Methods: The target DHPs were obtained by the reaction of 4,4-dimethyl-1,3-cyclohexanedione, appropriate aldehyde, isobutyl acetoacetate and ammonium acetate in absolute ethanol. Calcium channel blocking effects of the compounds were determined on L-type (Cav1.2) and T-type (Cav3.2) calcium channels using patch-clamp assays.



R: Aromatic/Heterocyclic ring/
Phenyl ring with bulky substituent

Results: Some of the synthesized compounds effectively blocked L-/T-type calcium channels with different selectivity profiles. 1,3-Benzodioxole ring at C-4 provided the best selectivity on Cav3.2 over Cav1.2.

Conclusions: In this study, we synthesized DHPs focusing on the modifications at C-4 position. Introducing different rings rather than phenyl, which is common in commercial DHPs, led to the discovery of effective calcium channel blockers.

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P058: THE EFFECT OF COX-2 INHIBITORS ON ACETYLCHOLINE ESTERASE IN TREATMENT OF ALZHEIMER'S DISEASE

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Introduction: Alzheimer's disease (AD), which is one of the neurodegenerative diseases affecting millions of people around the world occurs with the degeneration of neurons and loss of neurons (1). Acetylcholine deficiency, aggregation of tau proteins to form neurofibrillary tangles between neurons, extracellular accumulation of β-amyloid (Aβ) peptide and oxidative stress play important role formation of AD (2). Today, acetylcholinesterase inhibitors are widely used in

the treatment of Alzheimer's disease, which inhibit the hydrolysis of acetylcholine and increase the amount of acetylcholine in the synaptic cleft, but they have limited efficacy and show a variety of dose-related side effects (1). On the other hand, the change of COX activity causes the formation of reactive oxygen species (ROS) and oxidative damage. Elimination of ROS formation may be a new approach to AD treatment (3). For this reason, some COX-2 inhibitors are thought to prevent neuronal damage by suppressing oxidative stress (4).

Materials and Methods: Molecular docking calculations were performed to understand the interactions Cox-2 inhibitors and acetylcholinesterase (pdb: 4EY7) enzyme, by using CDocker method in Accelerys Discovery Studio 3.5 software**.**

Results: The interaction of Cox-2 inhibitors with acetylcholinesterase enzyme, which is considered as a new approach in the treatment of AD, was investigated with docking studies. Interactions of Cox-2 inhibitors with the amino acids Asp74, Trp86, Tyr124, Trp286, Phe295, Tyr337, Phe338 and Tyr341 were revealed.

Conclusions: It is thought that the interactions of Cox-2 inhibitors with acetylcholinesterase as well as their effect of reduction of oxidative stress may play an effective role AD treatment.

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P059: NEW INSIGHTS INTO COVALENT ENZYMATIC INHIBITION MEDIATED BY ELECTROPHILIC SELENIUM COMPOUNDS: THE CASE OF THE SARS-CoV-2 MAIN PROTEASE

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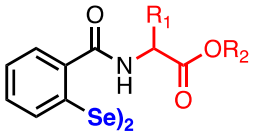
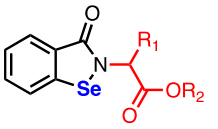
Introduction: The coronaviridae family of viruses are positive-sense RNA viruses. The length of the genome is about 30-kb and it is coated with nucleocapsid protein and enveloped in a lipid bilayer containing three proteins: spike, membrane and envelope. The single coronaviral mRNA encodes for polyproteins, that is cleaved by main protease (M^{pro}) in some non-structural proteins. M^{pro} is formed by two protomers and each protomer is composed of three domains. The substrate binding site is between domain I and domain II and the catalytic dyad is formed by two residues ***Cys145-His41***. The huge importance of M^{pro} in viral life cycle and the absence of close homologues in the human proteasome, makes such protease the perfect target for the design of antiviral drugs. Some of us developed a high-throughput screening (HTS) platform and screened about 10,000 compounds identifying **Ebselen** as the best in class compound.

Materials and Methods: A series of diselenides recently reported as anti-HIV agents (**1**) and the corresponding Ebselen-like derivatives (**2**) were prepared and studied in the inhibition of SARS-Cov-2 virus. The evaluation of their efficiency in the inhibition of the M^{pro} has been investigated and the chemical mechanism simulated by the means of NMR based experiments.



1



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Results: Bio-organic NMR investigations combined with the antiviral activity observed in infected cells afforded the identification of new promising anti-SARS-Cov-2 agents suggesting that the enzymatic inhibition (or at least the antiviral activity) is not solely connected to the electrophilicity of the selenium atom but some level of molecular recognitions are involved.

Conclusions: The results reported in this study clearly indicate that Ebselen and its derivatives are not simply PAINS even if the selectivity is still an unfilled issue and, at the same time, an intriguing perspective for future developments.

Acknowledgements

University of Perugia for financial support (Fondo Ricerca di Base 2019)**.**

P060: SYNTHESIS OF BENZIMIDAZOLE, BENZOTHIAZOLE, BENZOFURANE AND NAPHTOFURANE DERIVATIVES OF AMINOTHIAZOLES

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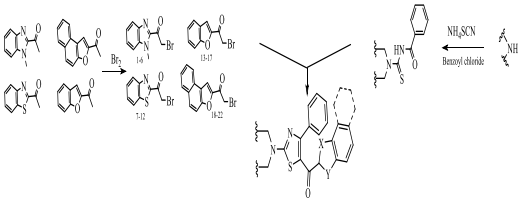
Introduction: Thiazoles are very important class of heterocyclic compounds. In many of the pharmacological groups such as antibacterial, anti-inflammatory, antifungal, anticancer, thiazole containing drugs and drug candidates are exist. Thiazole ring closure usually made by Hantzsch method, however, there are also different ring closure types. In this study, benzoylthioamides are reacted with arylacylbromides, to produce aroyl thiazole derivatives by a methylene-carbonyl condensation. 22 compounds have been synthesized, characterized and antibacterial activity was tested.

Materials and Methods: Amines (dimethylamine, diethyl amine, pyrrolidine, piperidine, hexamethyleneamine and morpholine) were reacted with NH_4SCN/HCl and benzoylchloride to obtain benzoylthioamides (I). Aryl-acyl structures were purchased or synthesized, then they were brominated to obtain bromoacetyl derivatives (II). I and II derivatives were reacted to get final compounds 1-22 by a methylene-carbonyl condensation (1, 2). Compound characterization have been made by IR, ^{1H}NMR, ^{13C}NMR and MS spectra. Antibacterial activity was tested by microdilution method against *E. coli*, *S. aureus* and *Salmonella* species (3).



Results: Compounds were synthesized in 55%-85% yield. Carbonyl peaks were observed in IR spectra around 1600 cm^{-1}. ^{1H}NMR and ^{13C}NMR spectral data were consistent with expectations. Compounds are consist of aromatic and aliphatic hydrogens. Methyl and methylene peaks were observed for amine derivatives. In the antibacterial testing, only few of the compounds exhibited moderate antibacterial activity against tested microorganisms.

Conclusions: 22 aminothiazole derivatives have been synthesized succesfully. Nitrogen containing heterocycles seems to have more potential among the derivatives.

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P061: PREPARATION OF SOME PURINE DERIVATIVES: USE OF THE 2D NMR $^{1}H,^{15}N$ & $^{1}H,^{13}C$ HMBC TECHNIQUES AND X-RAY CRYSTALLOGRAPHY IN ASSIGNING REGIOCHEMISTRY

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Introduction: Purines are basic component of nucleic acids and their many derivatives are used commercially as antiviral and antitumor drugs. Various tautomers of purine bases usually coexist due to the presence of several nitrogen atoms in the molecule. The preferred tautomers of purine derivatives are mainly N^7-H and N^9-H species, probably due to their lower energy. Existence of this tautomerism, in this bicyclic heterocycle has been shown with spectral data, mainly nuclear magnetic resonance (NMR) spectroscopy. This migration is disappeared when the imidazole hydrogen is replaced by alkyl groups (1-3). The aim of this work is to carry out the reaction of 2-(4-fluorophenyl)imidazopyrimidine with 4-chlorobenzyl bromide and the structural elucidation of regioisomeric products.

Materials and Methods: Organic synthesis, structural elucidation using some 1D and 2D-NMR techniques (^{1}H and ^{13}C NMR, COSY, NOESY, gHSQC and gHMBC) including ^{1}H-^{15}N HMBC experiment and X-ray crystallography for further confirmation of **1c**.

Results: In this study, we achieved three regioisomeric products **(1a-c)** and results were confirmed by NOESY and HMBC correlations. Further confirmation of the structure of **1c** was obtained from X-ray crystallography.

Conclusions: Imidazole *N*-alkylated regioisomers were obtained in presence of anhydrous K_2CO_3 in DMF. NOESY experiment is the primary method for structural elucidation of these types of regioisomers. The cross peaks of *N*-CH_2 (at around 5-6 δ ppm) and aromatic protons confirm their spatial proximity as an evidence for which nitrogen atom is substituted. ^{1}H-^{13}C and ^{1}H-^{15}N HMBC techniques can be an effective alternative method for assignment of regioisomers. The complete structure elucidation of all synthesized compounds was performed using 1D and 2D NMR experiments including COSY, NOESY, gHSQC, gHMBC and XRD data.

Acknowledgements

Central Laboratory of Pharmacy Faculty of Ankara University provided support for acquisition of the NMR and mass spectrometer used in this work.

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P062: SYNTHESIS AND MOLECULAR MODELING STUDIES OF SOME NOVEL BENZOTIAZOLE DERIVATIVES AS ANTI-CANCER AGENTS

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Introduction: Cancer is a major public health problem in many areas of the World. It is a complex disease characterized by dysregulation of cell proliferation and cell death, and ultimately transforms into a population of cells that can invade the tissues and metastasize to distant areas, leading to severe morbidity (1). Topoisomerase enzymes have shown unique roles in replication and transcription (2). Inhibitors targeting human topoisomerase I and topoisomerase II alpha have provided a useful chemotherapy option for the treatment of many patients suffering from a variety of cancers (3).

Materials and Methods: In our study, some benzothiazole derivatives were designed to develop new anticancer drugs, in silico activities against Topoisomerase II enzyme were observed with molecular modeling studies; and cytotoxic activities was evaluated by comparison with reference compound etoposide using MTT method on cell lines.

Results: Synthesis of N- (4- (benzothiazol-2-ylmethyl) phenyl) amide derivatives, analysis of their structures; investigation of their anticancer activities were performed. The biological action mechanism elucidation studies were carried out using molecular docking techniques on Topoisomerase-II.

Conclusions: According to the cytotoxic activity results; the activity of compounds 3 and 4 and 6 in the K562 cell line and the compound 4 in the A549 cell line were observed. In docking studies, compounds 3 and 4 show interactions with the Topo II (pdb: 3QX3) proteins at low energies, suggesting that compounds 3 and 4 can act via the Topo II enzyme pathway.

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P063: SYNTHESIS AND ANTICANCER ACTIVITY OF ETODOLAC HYDRAZONES

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Introduction: Deaths from cancer cases tend to increase gradually. In order to break this negative chain, the focus has been on various derivatives that can be strong candidates as cancer drugs. Hydrazide-hydrazone is one of the most prominent structures among these derivatives. The anticancer activity of hydrazide-hydrazone compounds results from its active pharmacophore group (-CO-NH-N=CH-) (1). According to results of many studies, the antitumor effects of hydrazide-hydrazones derived from acitive pharmaceutical ingredients against different cancer cells have been proved (2-5). Therefore, it is aimed to synthesize new hydrazide-hydrazone compounds choosing etodolac as a starting compound and to determine their possible anticancer activity against PC-3, DU-145, LNCaP prostate cancer cells.

Materials and Methods: Etodolac methyl ester [**1**] was obtained by the reaction of etodolac and methanol in the presence of concentrated sulfuric acid. Etodolac hydrazide [**2**] was synthesized by heating compound **1** with hydrazine hydrate in methanol. After compound **2** and substituted benzaldehydes were refluxed in ethanol medium, etodolac hydrazide-hydrazones [**3a-l**] were obtained.

Results: The purity of the synthesized compounds was controlled by TLC and elemental analysis. The characterization of their structures was carried out by FT-IR, ^{1}H-NMR. The cytotoxic effects of compounds **3a-l** and apoptotic effect of compound **3b** on PC-3, DU-145 and LNCaP prostate cancer cells were evaluated in vitro.

Conclusions: As a result of WST-8 assay, compound **3b** was found to display higher cytotoxicity against PC-3, DU-145 and LNCaP prostate cancer cells with IC_{50} values of 10.36, 5.24, 15.53 µM, respectively. Also, compound **3b** caused depolarization on mitochondrial membrane potential from its low concentrations.

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P064: CRYSTAL STRUCTURE OF LITHIUM(I) COMPLEX OF THE ANTIBIOTIC LASALOCID

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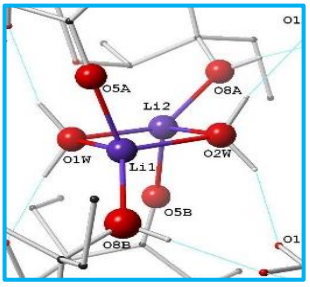
Introduction: In the present study we report the structure of new complex of lithium(I) ions with the polyether ionophorous antibiotic Lasalocid. The crystal structure of the novel compound is discussed and compared with the known dimeric complexes of Lasalocid with monovalent cations and Li(I) complexes of Monensin.

Materials and Methods: Data collection and structure solution were conducted at the X-Ray Crystallographic Facility, Department of Chemistry and Biochemistry, NDSU, Fargo ND, USA, using a Bruker APEX-II CCD diffractometer. The structure was solved and refined using SHELX set of programs with Olex 2 v.1.3 software package.

Results: Lasalocid acid (LasH) reacts with LiOH in a mixed solvent system (H_2O/Et_2O) to produce colourless single crystals of composition $[Li_2(\mu_2\text{-}Las_2)(\mu_2\text{-}H_2O)_2]$. The entire complex possesses a dinuclear structure, formed by the core unit of Li_2O_4, where both metal centres are bridged by two water molecules ($O1^W$, $O2^W$), serving as bidentate ligands and the two Lasalocidate ligands complete the coordination sites of the metal centres. No other solvent molecules are found in the crystal structure's cell. The geometry of Li_2O_2 chromophore represents a planar slightly distorted square; the distance between both metal ions is characteristic for O-bridged dinuclear Li(I) coordination compounds. Additionally, Lacalocidate ligands act in a monodentate coordination manner. The donor atoms are placed in a trans-position with respect to the $Li_2O^w_2$ unit. The inner coordination sphere of lithium(I) cations can be described as having a distorted tetrahedral geometry. Metal-oxygen bond lengths are typical for 4-fold coordinated lithium(I) ions, complexed with oxygen-containing ligands.



Conclusions: We would like to underline that the new Li(I) compound is the first example of binding the smallest alkali metal cation by Lasalocid. Capturing of alkali-metals cations with different sizes is a process with high interest in inorganic and cluster chemistry, which make our success and the reported structure interesting even outside of discussed topic.

Acknowledgements

This study was supported by a grant from the National Science Fund of the Bulgarian Ministry of Education and Science (Contract № KP-06-H29/3).

P065: SYNTHESIS OF SOME NOVEL 4-(1*H*-BENZIMIDAZOL-1-YL)-N'-BENZYLIDENEBENZOHYDRAZIDE DERIVATIVES

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Introduction: Benzimidazole is an essential pharmacophore with wide anticancer potential. Benzimidazole-containing anticancer compounds have selective potential that depends on the substitution of the benzimidazole nucleus (1). Promising anticancer activity of some 1-phenylbenzimidazoles have been reported (2,3). In this study, we aimed to synthesize some novel 4-(1*H*-benzimidazol-1-yl)-*N'*-benzylidenebenzohydrazide derivatives.

Materials and Methods: 1*H*-Benzimidazole ring was built by cyclization of the *o*-phenylenediamine and formic acid (4). Then, reaction of the 1*H*-benzimidazole with ethyl 4-fluorobenzoate in DMF in the presence of anhydrous K_2CO_3 gave ethyl 4-(1*H*-benzimidazol-1-yl)benzoate (5). This compound was treated with excess of hydrazine hydrate to obtain 4-(1*H*-benzimidazole-1-yl)benzoic acid hydrazide. At final step, reaction of the hydrazide derivative with corresponding substituted benzaldehydes gave the final products (Figure 1).

Results: ^{1}H-NMR and ^{13}C-NMR spectra were recorded employing a Varian Mercury 400 MHz FT-NMR spectrometer. Mass spectra were taken on a Waters Micromass ZQ connected with a Waters Alliance HPLC, using the ESI(+) method. Elemental analyses were performed using a Leco CHNS-932. All instrumental analysis results of the

synthesized compounds were found to be consistent with their chemical structure.

Conclusions: Activity studies of these benzimidazole-derived compounds on different cancer cell lines are under investigation.

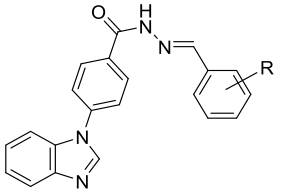

Fig 1. General formula of novel benzimidazole derivatives.

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P066: INDOLE-BENZIMIDAZOLE DERIVATIVES AS ANTIBACTERIAL AGENTS AGAINST HOSPITAL INFECTIONS AND THEIR DOCKING PROFILES

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Introduction: Occurrence of the hospital infections has increased drastically over the last years. These infections lead to high rates of mortality in patients whilst an effective and selective remedy is absent (1). *Staphylococcus aureus* is one of the responsible pathogens causing this disease that is characterised by skin and mucous membrane infections (2). Topoisomerase-II DNA-gyrase and Topoisomerase-IV catalyze the topological modifications in cell thus regulate cell survival. These enzymes become noteworthy targets for antibacterial drug discovery since they exist in bacteria strains and is absent from eukaryotic cells (3). In this study, we implemented design and synthesis of several indole-benzimidazoles (**1-11**) and probed their antibacterial activity on various bacteria strains. Furthermore, we analyzed the docking results of the most potent compound **3** and compared it to the standard compound Ciprofloxacin.

Materials and Methods: For the synthesis of derivatives **1-11**, mixture of the appropriate o-phenylenediamine (1 mmol), related indole derivative (1 mmol) and $Na_2S_2O_5$ (40%) (2 mL) in EtOH (4 mL) was refluxed until starting materials were consumed (determined by TLC, purified with cc) (4). The antimicrobial activity of compounds were determined against *Escherichia coli* ATCC 25922, *Pseudomonas aeruginosa* ATCC 9027, *Acinetobacter baumannii* ATCC 19606, *Klebsiella pneumonia* ATCC 18883, *S aureus* ATCC 29213, Methicillin Resistant *S. aureus* (MRSA) ATCC 43300, *Enterococcus faecalis ATCC* 29212 with using micro-dilution method (5). AutoDock Vina 1.1.2. was used for the docking analysis (6).

Results: According to the antibacterial activity results, compound **3** had MIC value of 0.48 µg/mL on *S. aureus* ATCC 29213 strain. This value was 31.2 µg/mL for MRSA ATCC 43300 and 62.5 for *E. faecalis ATCC* 29212, proving that this compound was selective for *S. aureus*. MIC value of ciprofloxacin was 0.25 µg/mL for *S. aureus* ATCC 29213. Using this standard in docking with DNA-gyrase and Topo-IV, higher activity of this derivative was spotlighted. As a result, this compound was able to bind to the active region of these enzymes with higher affinity (-8.1 kcal/mol for DNA-gyrase B subunit and -8.4 kcal/mol for Topo-IV) than that of Ciprofloxacin (-7.9 kcal/mol for DNA-gyrase B subunit and -7.3 kcal/mol for Topo-IV).

Conclusions: The results of our study has gifted us a prominent candidate with favorable MIC value and good docking profile. This lead compound **3** has given us an idea for SAR studies and in the future we aim to utilize it for discovering novel agents against nosocomial infections that are caused by *S. aureus* strains.

Acknowledgements

This study was supported by a grant of TUBITAK (grant number: 213S037)

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P067: SYNTHESIS AND *IN VITRO* EVALUATION OF THE ANTIOXIDANT ACTIVITY OF IMINES

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Introduction: In recent years, researchers have been interested in the preparation of imines (Schiff bases) by different methods, for the differences in medical, biological and other reactivities that they present. Among these compounds, we were more particularly interested in those endowed with an antioxidant activity (1).

Materials and Methods: Imines are obtained by condensation of vanillin with a diamine. For the synthesis of ligands L1 and L2 we followed the method described by K.H.CHJO et al. Modified for our use (2). The antioxidant test was carried out with the DPPH method and according to the protocol described by Mansouri, A., et al. Modified for our use (3).

Results: The ligands L1 and L2 are obtained by condensation of one or two molecules of vanillin with one molecule of diamine in the presence of ethanol in the form of solids. The products L1 [*(E)*-4-((2-aminoéthylimino)méthyl)-2-méthoxyphénol] and L2 [4,4'-((1*E,* 1'*E*)-(éthane-1,2-diylbis (azanylylidéne)) bis (méthanylylidéne)) bis (2-méthoxyphénol) were isolated after 2h of cooling reflux, with quantitative yields for of the order of 66 % ; 77 %respectively . The purity of these products was confirmed by chromatography (TLC) and characterized by their IR and 1H and 13C NMR spectra. In order to confirm the antioxidant power of our products, we have deduced the IC50 values from the curves % I = f (C). From these results, ascorbic acid is most effective with an IC50 of 0.03 mg / mL compared to synthesized products L1 and L2.The DPPH• antioxidant test of the products in question allowed us to measure the IC50 inhibition concentration. The results show that the imines proved to be the most effective with an IC 50 of the order of 0.77 mg / mL; 0.42 mg / mL respectively.

Conclusion: According to the results obtained we can say that our products have an antioxidant activity in vitro with the DPPH• method.

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P068: SYNTHESIS OF PLATINUM(II) COMPLEXES WITH 2-SUBSTITUTED BENZIMIDAZOLE LIGANDS

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Introduction: The discovery of cisplatin, also known as cis-[PtII(NH_3)$_2$$Cl_2$], was a milestone in the development of platinum(II) and other metal-containing complexes as potential anticancer drugs. Among these complexes, only carboplatin and oxaliplatin have received worldwide approval so far, nedaplatin, loboplatin and heptaplatin have gained regionally limited approval (1). It is well established that cisplatin binds to DNA via covalent bonding, forming mostly 1,2-intrastrand cross-links, which deforms the DNA structure, preventing DNA replication and transcription, and activates the apoptotic pathway, resulting in cell death (2). The replacement of amine groups can result in different structural and formational alterations in target DNA, which may affect the character of biological effects of the anologues (3). One noteworthy approach in the design of new platinum anticancer drugs is to use physiologically active compounds as ligands. The benzimidazole ring is a physiologically active ligand of vitamin B_{12} and its derivatives, purin bases, and several metalloproteins. It also serves as a good ligand in various transition metal complexes (4). In accordance with our previous studies, considering that variations in the chemical structure of the amine groups of cisplatin might have a significant effect on the cytotoxic activity and toxicity of platinum complexes and with the aim of determining the role of the benzimidazole ligands of platinum(II) complexes on cytotoxic properties, we synthesized some platinum(II) complexes with 2-substituted benzimidazole ligands.

Materials and Methods: 2 mmol of corresponding ligands and 1 mmol of K_2PtCl_4 were dissolved in isopropylalcohol-water. The reaction mixture protected from light was heated at 60 ^{0}C for 7 days. The resulting precipitate was filtered off, washed several times with small portions of water, ethanol, and diethylether and dried in vacuo.

Results: In the present paper, two platinum(II) complexes, *cis*-[PtL_2Cl_2] (L=2-

substitutedbenzimidazole as “non-leaving groups), were designed and synthesized. The chemical structures of Pt(II) complexes were elucidated by using IR, ^{1}H- NMR and LC/MS spectroscopic methods. In the IR spectra of synthesized complexes, prominent changes were observed. The ^{1}H NMR spectra of these complexes were consistent with their corresponding protons as chemical shift values and the number of hydrogens. Both the retention times and the MS spectra of the peaks in samples are evidence of the purity and the excepted structures of the synthesized compounds.

Conclusions: As a result, based on the spectral data obtained in this study, synthesized complexes have been shown to have a desired purity and molecular structure.

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P069: 1,4-DIHYDROPYRIDINE-AZOLE HYBRIDS: SYNTHESIS, COMPUTATIONAL STUDIES AND ANTIMICROBIAL ACTIVITY

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Introduction: Heterocyclic compounds hold a significant position not only in organic but also in medicinal chemistry (1). As heterocycles are the core structures of both natural and synthetic products, they efficiently provide strategic pharmacophores to reach novel molecules with a vast variety of biological activities (2). In this study, we aimed to combine two precious rings, 1,4-dihydropyridine (DHP) and azole, in the same molecule.

Materials and Methods: 4-Azolyl benzaldehydes were synthesized through the nucleophilic aromatic substitutions of 4-fluorobenzladehyde with different azoles (pyrazole, imidazole or 1,2,4-triazole). Subsequently, DHPs were obtained according to modified Hantzsch synthesis (Figure 1). Antibacterial and antifungal activities of the compounds were evaluated according to the standard broth micro-dilution assays. Molecular docking studies were carried out using AutoDock in the binding site of *Candida albicans* lanosterol 14α-demethylase (CYP51). Furthermore, optoelectronic properties of the hybrid structures were investigated by computational studies (TD-DFT, electrostatic potential maps, HOMO-LUMO orbital depictions) using Gaussian 09 program package.

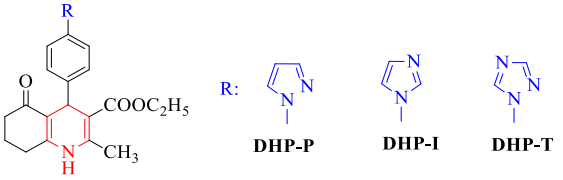

Fig 1. Chemical structures of DHP-azole hybrids

Results: DHP-azole hybrids demonstrated moderate antifungal activities against *Candida* strains. In molecular docking studies, we observed that azole rings could not make the essential interaction through the coordination of the nitrogen atom with the iron of heme in the active site of CYP51.

Conclusions: In this study, we report the synthesis of DHP-azole hybrids carrying azoles directly attached to the phenyl ring at C-4 position of DHP scaffold. Molecular docking studies suggested that providing flexibility to the azole ring can lead to more active antifungal agents.

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P070: SYNTHESIS OF DIHYDROPYRIMIDINE DERIVATIVES WITH L-/T-TYPE CALCIUM CHANNEL BLOCKING ACTIVITIES

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Introduction: 1,4-Dihydropyridines (DHPs) are the most famous group of commercial calcium channel blockers that are used for the treatment of hypertension through blocking L-type calcium channel (1). Recent studies showed that DHPs can

also target T-type calcium channel isoforms (2). In this study, we synthesized dihydropyrimidines (DHPMs) designed by the bioisosteric replacement of DHPs and evaluated their calcium channel blocking activities.

Materials and Methods: DHPM derivatives were obtained by the reaction of isobutyl/benzyl acetoacetates, substituted benzaldehydes (3-nitrobenzaldehyde/5-nitrosalicylaldehyde/5-bromo-3-methoxysalicylaldehyde), and urea in ethanol. Subsequently, N3 position and the phenolic hydroxyl group of the obtained compounds were acetylated via heating in acetic anhydride (Figure 1). Calcium channel blocking effects of these compounds were determined on L-type (Cav1.2) and T-type (Cav3.2) calcium channels by patch-clamp assays.

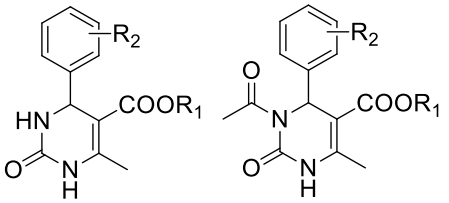

Fig 1. General chemical structures of the synthesized compounds

Results: The results indicated that some of the synthesized compounds produced promising calcium channel blocking activity on both types of calcium channels with different selectivity profiles. Introducing acetyl group to the N3 position of DHPM ring enhanced the ability of the compounds to block calcium current.

Conclusions: In this study, we identified new DHPM-based calcium channel blockers which hold therapeutic value in the treatment of cardiovascular and neurological diseases.

Acknowledgements

We acknowledge the financial support provided by Hacettepe University Scientific Research Projects Coordination Unit through Project THD-2020-18712.

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P071: DESIGN, SYNTHESIS AND ANTIMICROBIAL EVALUATION OF NOVEL ISOQUINOLIN-UREA HYBRIDE MOLECULES

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Introduction: As microorganisms have developed resistance to antimicrobial drugs in recent years, it has become very important to introduce new molecules to medical use. Lack of novel drug molecules and synthesis of molecules without important effects canalized researchers to develop new molecules in this area. It has been reported in studies that molecules with urea structure have antimicrobial activities (1).

Materials and Methods: 1*H*-2-benzopyran-1,3(4*H*)-dione (BPD) was used as the starting compound to synthesis new urea molecules. The reaction of BPD with hydrazine-hydrate in ethanolic medium resulted in 2-aminoisoquinoline-1,3(2*H*,4*H*)-dione (AQD) (2). AQD was refluxed with substituted various isocyanates in toluene at 80 ^{o}C (QU1-22) (3). The synthesized molecules evaluated antimicrobial activity against S. *aureus*, MRSA, E. *faecalis* and E. *coli*.

Results: The structures of the compounds QU1-22 were determined by spectroscopic and spectrometric techniques such as ^{1}H-NMR, ^{13}C-NMR and HR-MS. Two of the targeted compounds showed antimicrobial activity with good results.

Conclusions: New isoquinoline-urea derivatives (QU1-22) were synthesized, characterized and their antimicrobial activity was evaluated. Among the synthesized molecules, two of them were found to have antimicrobial activity.

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P072: STUDIES ON ANTIMICROBIAL PROPERTIES OF SOME BENZOXAZOLES

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Introduction: Infectious diseases caused by bacteria and fungi are still one of the most important threats to public health despite great advances in pharmaceutical and medicinal chemistry. Benzoxazole compounds are important medicinal chemistry because of their wide range of biological activities including antimicrobial activity (1).

Materials and Methods: The benzoxazoles (compounds 2-10) were evaluated for their antimicrobial activity with microdilution technique described by CLSI (2).

Results: The minimum inhibitory concentrations (MIC) of some benzoxazoles were calculated against standard bacterial and fungal strains, as well as drug-resistant isolates, and compared to those of several reference drugs (Table 1).

Table 1. Antimicrobial activity results (MIC µg/ml) of the compounds with the standart drugs

S.a.: *Staphylococcus aureus* ATCC 29213; S.a.*: Methicillin resistant *S. aureus*; E.f: *Enterococcus faecalis* ATCC 29212; E.f *: Vancomycin resistant *E. faecalis*; E.c.: *Escherichia coli,* ATCC 25922; E.c.*: *E. coli* isolate P.a.: *Pseudomonas aeruginosa* ATCC 27853; P.a.*: *P. aeruginosa* isolate (gentamicin resistant); C.a: *Candida albicans* ATCC 10231; C. a.*: *C. albicans* isolate.

Conclusions: In this study, we aimed to develop new effective antimicrobial agents possesing benzoxazoles ring as heterocyclic structure. Microbiological results showed that some benzoxazoles derivatives compounds possess an antimicrobial activity having MIC values of 32-512 µg/ml against the tested microorganisms.

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P073: SYNTHESIS AND STRUCTURE ELUCIDATION OF SOME BENZOXAZOLE DERIVATIVES

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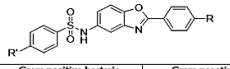
Introduction: Benzoxazoles is an important ring system as it can easily interact with biopolymers in the organism as ring equivalents of purine bases of adenine and guanine, which are in the structure of nucleic acids (1). So that benzoxazoles showed several activities like antitumor, antimicrobial and antiviral.

Materials and Methods: Melting points were determined on a Buchi B-540 melting point apparatus in open capillary tubes and are uncorrected. 1H-NMR and 13C-NMR spectra were recorded on a Varian Mercury 400 MHz spectrometer using $CDCl_3$-d6. Mass spectra were acquired on a Waters Micromass ZQ using the ESI (+) method.

Results: In this study, firstly, 5-Amino-2-(p-ethyl/fluoro-phenyl)-benzoxazole (1) were synthesized by heating 2,4-diamiophenol with p-ethyl/fluoro benzoic acid in polyphosphoric acid (PPA). The target compounds (2-10) (Figure 1)



Compound	R'	R	Gram positive bacteria				Gram negative bacteria				Fungus	
			S. a.	S.a.*	E.f.	E. f.*	E. c.	E. c.*	P. a.	P. a.*	C. a.	C. a.*
N2	-F	$-C_2H_5$	32	256	256	128	128	256	128	256	128	256
N3	$-NO_2$	$-C_2H_5$	256	256	256	128	256	256	128	256	256	256
N4	$-CH_3$	$-C_2H_5$	256	256	256	128	128	256	128	256	256	128
N5	-Cl	$-C_2H_5$	128	256	256	128	256	256	128	256	256	256
N6	-H	-F	256	256	256	128	256	256	128	256	128	128
N7	-F	-F	256	256	256	128	256	256	128	256	256	128
N8	-Br	-F	256	256	256	128	256	256	128	128	128	128
N9	$-CH_3$	-F	256	256	256	128	128	128	128	256	256	256
N10	OCH_3	-F	32	256	256	128	256	128	128	256	256	128
Ampicillin			0,5	>16	2	>16	8	>16	-	-	-	-
Vancomycin			0,5	2	1	> 8	-	-	-	-	-	-
Gentamycin			0,25	>16	4	>8	0,5	>8	0,5	>8	-	-
Ciprofloxacin			0,5	>16	2	>4	0,0156	>2	0,125	>2	-	-
Cefotaxime			1	>16	-	-	0,125	>8	8	-	-	-
Fluconazole			-	-	-	-	-	-	-	-	0,125	>4
Amphotericin B			-	-	-	-	-	-	-	-	0,5	0,5

were then obtained by reaction of the solution of p-substituted benzenesulfonyl chlorides with 5-Amino-2-(p-ethyl/fluoro-phenyl)-benzoxazoles.

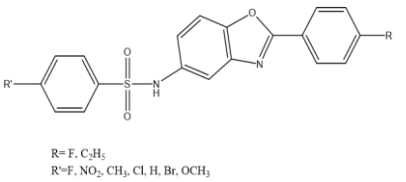


Fig 1. Synthesized compounds

Conclusions: All the results compounds (2-10) were prepared as orginal products. The structures of them were supported by spectral data. The 1H-NMR, 13C-NMR and mass spectra results agree with those of proposed structures.

References:

1. Erol M, Celik I, Temiz-Arpaci O, Kaynak-Onurdag F, Okten S (2020). Journal of Biomolecular Structure and Dynamics, 1-12.

P074: MONONUCLEAR COPPER(II) COMPLEX OF MACROLIDE ANTIBIOTIC TILMICOSIN

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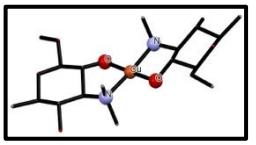
Introduction: The macrolide antibiotic Tilmicosin is an effective drug in veterinary medicine treating pulmonary infections caused by bacterial strains. İn the present study we discuss its ability to bind Cu(II) ions in aqueous solutions and the properties of the complex species formed.

Materials and Methods: Tilmicosin was supplied by BIOVET Ltd. (Bulgaria), $CuCl_2.2H_2O$, $Cu(NO_3)_2.3H_2O$, KOH and the solvents used were purchased from Sigma-Aldrich (Germany). UV-Vis experiments were carried out on Shimadzu UV-1800 (Japan). EPR studies were performed on EMXplus10/12 EPR spectrometer (Bruker BioSpin, Germany). NMR spectra were acquired on Avance II+ 600 NMR spectrometer (Bruker, Germany).

Results: Tilmicosin (HTILM) reacts with Cu(II) ions to form mononuclear violet complex of composition $[Cu(TILM)_2]$. Reaction takes place in aqueous solution at pH 11 and metal-to-ligand molar ratio of 1-4. The complex formed was isolated as violet solid (85% yield), it is soluble in alcohols and acetone, and is insoluble in water. Spectrophotometric studies revealed, that the complex absorbs in EtOH at 520 nm (ε = 108 $cm^{-1}.mol^{-1}.L$) and 600-700 nm (shoulder) due to the d-d* transitions in the Cu(II) center. EPR data lay in line with the formation of mononuclear complex species (EtOH, 100 K, $g_{\|}$ = 2.236, $g_{\perp}$ = 2.037, $A_{\|}$ = 158 G), suggesting the existence of square-planar structure in solution. The NMR studies conducted show that the saccharide moiety containing tertiary amine is the main coordination site of Tilmicosin.



Conclusions: Macrolide antibiotic Tilmicosin coordinates Cu(II) ions in alkaline aqueous solution as neutral mononuclear complex. The ligand acts in a bidentate coordination mode *via* nitrogen atom and one deprotonated hydroxylic group, forming the main chromophore unit of composition $[CuN_2O_2]$.

Acknowledgements

This study was supported by a grant of Sofia University (Contract 80-10-143/2021)

P075: DINUCLEAR COPPER(II) COMPLEXES OF MACROLIDE ANTIBIOTIC TILMICOSIN

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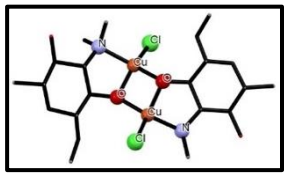
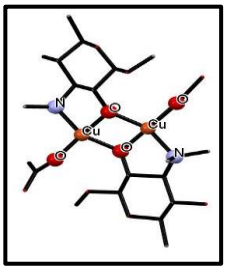
Introduction: The macrolide antibiotic Tilmicosin is a semi-synthetic drug applied in veterinary medicine in case of bacterial infections of various origin. Here we present data on its ability to bind Cu(II) ions in non-aqueous solutions and on the properties of complex species formed.

Materials and Methods: Tilmicosin was obtained from BIOVET Ltd. (Bulgaria), $CuCl_2.2H_2O$, $Cu(NO_3)_2.3H_2O$ and solvents were supplied by Sigma-Aldrich (Germany). UV-Vis experiments were conducted on Shimadzu UV-1800 (Japan). EPR studies were acquired with EMXplus10/12 EPR spectrometer (Bruker BioSpin, Germany). NMR spectra were recorded using Avance II+ 600 NMR spectrometer (Bruker, Germany). The quantum chemical calculations were performed with Gaussian16 and ORCA software packages for optimization of the geometry (Gaussian16) and calculation of the EPR parameters (ORCA).

Results: Tilmicosin (HTILM) reacts with Cu(II) salts to form dinuclear complexes of composition $[Cu_2(TILM)_2X_2]$ (X = Cl^-, NO_3^-). Reactions take place in acetone or ethanol solutions at metal-to-ligand molar ratio of 1-1. The corresponding complexes were isolated as green or blue solids depending on the origin of Cu(II) salt used (chloride or nitrate, respectively). Complexes absorb in



EtOH at 716 nm (green, ε = 125 $cm^{-1}.mol^{-1}.L$) or 676 nm (blue, ε = 97 $cm^{-1}.mol^{-1}.L$) due to the d-d* transitions in the Cu(II) centers. EPR and NMR data revealed that Tilmicosin acts as a bridging bidentate ligand through its tertiary nitrogen atom and closely located deprotonated hydroxylic group of saccharide moiety. The calculations performed corroborate with the proposed distorted planar structure of both complex species.



Conclusions: Macrolide antibiotic Tilmicosin complexes with Cu(II) chloride or nitrate in non-aqueous solutions. The ligand plays a dual function, forming the main chromophore unit of $[Cu_2N_2O_2Cl_2]$ or $[Cu_2N_2O_4]$, respectively.

Acknowledgements

This study was supported by a grant of Sofia University (Contract 80-10-143/2021).

P076: SYNTHESIS OF SOME NOVEL *SCHIFF BASES INCORPORATED WITH INDAZOLE MOIETY*

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Introduction: Since cancer is currently one of the leading causes of death in many countries, new compounds that could affect the molecular mechanisms of cancer need to be designed and synthesized. Indazole derivatives exhibit a wide range of bioactivity, including anticancer, antidiabetic, analgesic, antidepressant and neurodegenerative disorders. Indazole-containing drugs axitinib, pazopanib, and linifanib were approved for clinical use based on their anticancer effects (1). In this study, we aimed to synthesize a number of novel schiff base derivatives incorporated with indazole moiety.

Materials and Methods: Indazole-3-carbaldehyde was synthesized from indole in the presence of HCl (aq.) and $NaNO_2$ (2). Then, final Schiff bases 1-(1*H*-indazol-3-yl)-*N*-substituted-methanimine derivatives were prepared in methanol by using the aldehyde and appropriate amines (3). All of the compounds were purified with silicagel column chromatography.

Results: Structural elucidation of the targeted compounds were performed with LC-MS, NMR, and elemental analysis. Spectral data are compatible with the desired structure.

Conclusions: In this study, novel 1-(1*H*-indazol-3-yl)-*N*-substituted-methanimines were prepared and their characterization were performed. Researches will be conducted to reveal their cytotoxic effects and mechanisms of their actions on cell viability.

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P077: SYNTHESIS OF SOME NOVEL *N'-((ARYL)METHYLENE)-1H-INDOLE-5-CARBOHYDRAZIDES*

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Introduction: The indole ring is an important core of some natural and synthetic molecules with different biological activities. Anticancer effectiveness of indole was described in many studies (1, 2). On the other hand, as a special member of Schiff bases, hydrazones and their derivatives are molecules of interest in medicinal chemistry due to their wide variety of biological activities (3). In this study, we aimed to synthesize a number of novel hydrazone derivatives incorporated with indole core.

Materials and Methods: Methyl-1*H*-indole-5-carboxylate was prepared from 1*H*-indole-5-carboxylic acid in dimethylformamide in the presence of sodium bicarbonate and iodomethane. A mixture of crude ester and hydrazine hydrate in ethanol was heated at reflux to give 1*H*-indole-5-carbohydrazide (4). Then, final hydrazones *N'-((aryl)methylene)-1H-indole-5-carbohydrazides were derived from the hydrazide compound and* appropriate aldehydes according to the process described in literature (5). 1*H*-Indole-5-carbohydrazide and all of the targeted hydrazones were purified with silicagel column chromatography.

Results: Structural elucidation of the targeted hydrazones were performed with LC-MS, NMR, and elemental analysis. The spectral details are in accordance with the final compounds.

Conclusions: In this study, novel *N'-((aryl)methylene)-1H-indole-5-carbohydrazide derivatives* were prepared and their characterization were performed. Studies need to be conducted to determine their effects on different cancer cell lines.

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P078: IN SILICO DESIGN AND SYNTHESIS OF NOVEL 2-ACYLHYDRAZONO-5-ARYLMETHYLENE-4-THIAZOLIDINONES AS enoyl-acyl carrıer proteın reductase INHIBITORS

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Introduction: The synthesis of mycolic acid, which is the essential component of mycobacterial cell wall, is controlled by two systems: fatty acid synthase system type-1 (FAS-I) and fatty acid synthase system type-2 (FAS-II). Since eukaryatic cells produce fatty acids using only the FAS-I enzyme system, the FAS-II enzyme system can be an appropriate target for selective antimycobacterial drugs (1). The FAS-II pathway, which consists of the enoyl-acyl carrier protein reductase enzyme (InhA) (2), is a validated target for antimycobacterial drugs. Within the scope of this work, compounds with high binding affinity were selected, synthesized and their structures were elucidated.

Materials and Methods: Virtual screenings and molecular dynamic simulation (MD) studies were performed on a proprietary library using the MOE (version 2020.04, chemical computing group, Inc., Montreal, Canada) and FlexX (LeadIT, version 4.1, BioSolveIT GmbH, Sankt Augustin, Germany, 2019) software packages. Subsequently, synthesis of selected compounds were performed. N-substituted thiosemicarbazides were obtained from benzoic acid, nicotinic acid and isonicotinic acid hydrazides (4,5). These thiosemicarbazides were cyclized in ethanolic medium containing triethyl amine by the addition of ethyl bromoacetate to achieve N-substituted thiazolidin-4-one compounds (5). The final products bearing the 5-arylidene group were obtained by the reaction of these rings with various aldehydes in methanolic sodium methoxide (5).

Results: Following our molecular modelling studies, N-substituted thiazolidin-4-one compounds bearing arylidene groups from a database containing approximately 15,000 compounds were proposed for synthesis. These compounds were synthesized and elucidated by IR, ^{1}H-NMR and mass spectral techniques. Impurity controls were performed by HPLC and TLC methods.

Conclusions: We selected several new compounds for sythesis using molecular modelling studies. Subsequently N-substituted thiazolidin-4-one compounds bearing the arylidene group were synthesized and their structures were confirmed by IR, NMR and mass spectroscopy after purity checks.

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P079: SYNTHESIS OF SOME NEW 2-PHENOXYACETAMIDE AND 3-PHENOXYPROPANAMIDE DERIVATIVES AND EVALUATION OF THEIR CHOLINESTERASE INHIBITOR ACTIVITIES

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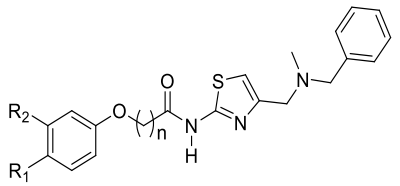
Introduction: Alzheimer's disease (AD) is a chronic neurodegenerative brain disease that affects approximately 50 million elderly people worldwide, and the disease's prevalence will triple by 2050 [1]. Although extensive research has been focused on pathogenetic mechanism of AD, exact cause is still uncertain. Several hypotheses have been proposed as the cause of AD. One of them is cholinergic hypothesis which states the main cause of AD is the reduction in acetylcholine (ACh) synthesis. Therefore, one of the potential therapeutic strategies is to increase the cholinergic levels in brain by inhibiting the activity of cholinesterase enzymes [2]. In the present study, we designed and synthesized three 2-phenoxyacetamide and two 3-phenoxypropanamide derivatives in order to investigate their acetylcholinesterase/butyrylcholinesterase inhibitory activities.

Materials and Method: The chemical structures of synthesized compounds were confirmed by ^{1}H-NMR, ^{13}C-NMR. The inhibitory activities of the synthesized compounds on AChE (from electric eel) and BChE (from equine serum) were determined by the modified Ellman's method. The docking studies of most active compounds were performed to predict the binding conformations and non-covalent interactions with the active sites of the AChE and BChE.



Compound 1	n= 1	R_1= OCH_3, R_2= H
Compound 2	n= 1	R_1= CH_3, R_2= H
Compound 3	n= 1	R_1= OCH_3, R_2= OCH_3
Compound 4	n= 2	R_1= OCH_3, R_2= H
Compound 5	n= 2	R_1= CH_3, R_2= H

Results: According to the biological activity data, compound 1 was identified as the most potent BChE inhibitor with IC50 value of 2.1 µM. However, compound 2 showed selective BChE inhibitory activity with IC50 value of 2.8 µM.

Conclusions: Generally, the synthesized compounds showed better BChE inhibitor activity and selectivity for BChE over AChE, except for compound 3, which has better AChE inhibitory activity compared to BChE inhibitor activity.

Acknowledgements

This study was supported by TUBITAK research grant 118S686.

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P080: PREPARATION OF MICROPARTICLES FROM LAVENDER EXTRACT WITH HYDRO/SOLVOTHERMAL SYNTHESIS: CYTOTOXIC AND GENOTOXIC EFFECT ON CANCER CELL LINES

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Introduction: Lavender is a plant species native to the Mediterranean, Middle Eastern countries and the Arabian Peninsula. It is now grown worldwide and has a wide variety of pharmacological properties as a result of the essential oil of its flowers (1). Lavender has complex chemical compositions, especially rich with lipophilic components (essential oil) and hydrophilic components (phenolic compounds, anthocyanins, phytosterols, tannins, flavone glycosides, etc.). There has been a recent increase in the popularity of plant-based natural products as potential therapeutic agents for modern and alternative complementary medicine (2). The studies conducted so far have focused on the direct application of extracts or the production of metal nanoparticles with these extracts. However, today, using the hydrothermal method, nano / microparticles of herbal ingredients can be made directly, apart from standard methods (3). In this way, it can be shown that the particle forms may have a higher effect in various applications, even if the direct effects of the active ingredients have not been determined. For this purpose, in this study, nano / microparticles were synthesized from lavender extracts using two different solvents and their cytotoxic and genotoxic effects on human breast (MCF7) and lung cancer (A549) cells were investigated.

Materials and Methods: Lavender (*Lavandula officinalis L.*) samples were dried at room temperature and ground into coarse powder. Water and 96% ethanol extracts were prepared. The extracts that reached room temperature were centrifuged at 5000xg for 10 minutes and the supernatant was taken. From these extracts, nano and micro sized particles were prepared by hydro/solvothermal synthesis for 150 - 200 ℃, 6 - 24 hours in a certain volume. For characterization, SEM, FTIR, fluorescent / confocal microscopy analyzes were used and the cytotoxic and genotoxic effects of the particles were determined.

Results: Particles sizes between 200 nm and 10 µm were obtained from the *Lavandula officinalis L.* extracts. A cytotoxic effect of the particles was observed in MCF7 and A549 cell lines. The IC_{50} value was determined in cell lines with the study, and genotoxic effects were shown in the experiments against these concentrations.

Conclusions: The results showed that the particles obtained by green synthesis of lavender have a high potential in the biomedical field. In future studies, we believe that the efficiency of the particles can be increased with modifications by detailing the cellular pathways.

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P081: MOLECULAR DOCKING AND SYNTHESIS OF NOVEL BIPHENYL-CHROMONE DERIVATIVES AS *AMPK ACTIVATORS*

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Introduction: Adenosine monophosphate activated protein kinase (AMPK) works like an energy sensor and it activated when the AMP/ATP or ADP/ATP ratio in the body increases in favor of AMP and ADP (1). It is involved in the regulation of carbohydrate, fat, protein metabolism, autophagy, and antioxidant defense during oxidative stress. AMPK has been a potential therapeutic target for many diseases from diabetes to cancer. Thus, various small molecules including flavonoids, which have chromone core, have been investigated and some of them have been found effective on AMPK (2). In addition, the biphenyl structure has been evaluated as an important pharmacophore in some AMPK activators (3). Inspired by these studies, we designed and synthesized some new biphenyl substituted chromone derivatives in order to test their AMPK activator and anticancer activities.

Materials and Methods: Molecular docking studies were carried out by using AutoDock Vina program. Substituted chromone ring is synthesized starting from various acetophenones. Then, suzuki coupling reaction was carried out for the reaction of the chromone ring with the biphenyl structure (4).

Results: The structure of the synthesized compounds was elucidated by ^{1}H NMR, ^{13}C NMR and mass spectral data. All spectral data were in accordance with assumed structures. The designed compounds have been shown to give similar docking poses to known AMPK activators.

Conclusions: In this study, molecular docking studies and synthesis of some new chromone derivatives bearing biphenyl structure were performed. The synthesized compounds will be evaluated for their anticancer and AMPK activator activities in later stages.

Acknowledgements
This study was supported by a grant of TUBITAK (220S193)

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P082: DETERMINATION OF NOVEL UREA AND SULFONAMIDE DERIVATIVES OF ISATIN SCHIFF BASES AS POTENTIAL RECEPTOR TYROSINE KINASE INHIBITOR BY MOLECULAR DOCKING STUDIES

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Introduction: In this study, we have reported the in-silico studies of novel potential active compounds by designing new, urea and sulfonamide derivatives of isatin Schiff bases. These compounds were created by taken into consideration from known active similar structures like urea containing sorafenib and benzylidene containing sunitinib (1). The enzyme-receptor interactions of compounds on VEGFR2 (PDB ID for 4AGD) were studied compared to the reference compound sunitinib.

Materials and Methods: The crystal structures of the receptor protein-tyrosine kinase of VEGFR2 were obtained from the Protein Data bank (PDB, http://www.rcsb.org). The docking study was performed in Auto Dock vina 4.2.6 software and the 3D compound-protein docking possess were analyzed by using Pymol 4.2.6.

Results: Protein-Ligand interaction plays a significant role in structure-based drug design studies (2). Conformations with the lowest docked energy and RMSD value and highest hydrogen bonding capability were chosen as a strongest binding capability. Most of the compounds showed good binding capability in a range between -9.17 and -14.57 kcal/mol and exhibited interactions with the active site amino acids of CYS919. These compounds also showed better interactions upon urea, sulfonamide or Schiff base groups. Compound 2b showed the lowest binding energy (-14.57 kcal/mol) with smallest RMSD (0.31°A).

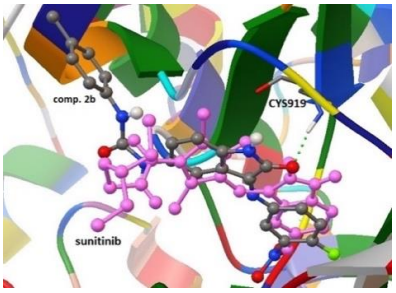

Fig 1. 3D interactions of the compound **2b** (colored by atomic type) and **sunitinib** (pink) with VEGFR2.

Conclusions: The results indicate the possibility of the designed compounds may be biologically active due to similar interactions to sunitinib.

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P083: INVESTIGATION OF POSSIBLE PROTECTIVE EFFECTS OF MOMORDICA CHARANTIA (BITTER MELON) IN LUNG DAMAGE CAUSED BY METHOTREXATE

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Introduction: Methotrexate (MTX), a folic acid antagonist, inhibits the synthesis of purine and thymidine nucleotides by inhibiting the enzyme dihydrofolate reductase (1). It prevents the proliferation of cancer cells by suppressing DNA synthesis. Methotrexate is used in the treatment of many diseases such as cancer, rheumatoid arthritis, psoriasis, and resistant inflammatory bowel diseases (2). The action of methotrexate is not specific to cancer cells, it causes toxicities in the lung, liver, kidney, gastrointestinal, and bone marrow. Momordica charantia (Bitter melon (BM)) plant, which belongs to the Cucurbitaceae family and is widely used in traditional medicine, has anti-ulcer, antidiabetic, antiviral, antitumoral, and antioxidant, hypoglycemic effects (3). In this study, the possible protective effects of the Momordica charantia plant against tissue damage caused by methotrexate in the lung was investigated.

Materials and Methods: 32 Spraque Dawley rats were divided into 4 groups as Control (C), Methotrexate (MTX), BM, and MTX + BM. 20 mg/kg MTX was administered intraperitoneally to rats to cause lung injury. The MTX group was given 50 mg/kg of BM extract orally every day for 10 days. The rats were decapitated on the tenth day and lung tissue samples were taken. Oxidative damage markers glutathione (GSH), malondialdehyde (MDA), myeloperoxidase (MPO), and collagen levels were measured in the samples. GraphPad Prism 5.0 was used for statistical analysis.

Results: MPO activities, MDA and collagen levels in tissues increased, while the amount of GSH levels decreased in the MTX given group compared to the control group. Bitter melon administered group, all of these oxidant responses were reversed significantly.

Conclusions: It's thought that Bitter melon has a protective effect against lung damage caused by methotrexate. In future studies, we think that the use of BM as a therapeutic agent will be beneficial in preventing lung damage caused by oxidative damage caused by MTX.

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P084: INTEGRATING NANOPARTICLE COATED MICROPARTICLES IN THE FIELD OF ELECTROPHYSIOLOGY

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Introduction: Nanoparticles are used to entrap, encapsulate or bind molecules in terms of improving the solubility, absorption and stability of pharmacological agents. It also provides the advantage of avoiding the reticuloendothelial system, leading to protection of the drug from premature inactivation during its transport. Since patch clamp is one of the most sensitive techniques to work on excitable cells, combinig both techniques establishes a promising approach. The aim of this study is to review the final trends concerning this issue.

Materials and Methods: PubMed database was searched up to May 2021 with no date restriction

with the key words “nanoparticles” and “patch clamp”

Results: Less than 100 publications were found in the literature review conducted. Pharmacological properties as well as toxicologic features of nanoparticle coated microparticles has been investigated so far.

Conclusions: Optimization of the complex formation for enhancing the rate of patch clamp applicable cells and gigasealed patch clamp applicable cells is necessary and partly being in the focus of the research (1). A non-viral delivery vehicle – CRISPR-gold nanoparticles- has been shown to edit genes in the brains of adult mice in multiple mouse models (2). Nanoparticles enabling crossing the blood brain barrier, thus can be used as nanocarriers in brain drug delivery accelaretes the scientific progress in the field of pharmacology (3). However there are not enough publications on the effects of nanoparticle coated microparticles of agents on normal cell function. Further research on microparticles and how they efffect the electrophysiological properties of excitable cells should be conducted.

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P085: OPTOGENETICS COMBINED WITH THE PATCH CLAMP TECHNIQUE

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Introduction: In the last decade, combining electrophysiology with optogenetics has became a focal point for researchers. It carries an importance to be aware of the recent progresses and future perspectives.

Materials and Methods: PubMed database was searched up to May 2021 with no date restriction with the key words “optogenetics”, “patch clamp” “and “clamp”.

Results: More than 400 researches involving optogenetic tools together with patch clamp techniques has been published since the combination of these two techniques were conducted for the first time. This time period is almost a decade and the frequency of publishing the research involving the combination of these techniques has been stable after the first years. The interest has not been lost but it is possible that, since both the techniques are complicated and hard to conduct, there is a stable rate per year for the number of the research published.

Conclusions: Optogenetics is the technique which studies the neuronal circuits via use of light to control neurons that are genetically modified to express light sensitive ion channels. It has been considered as a breakthrough of the decade. Combining this technique with patch clamp, which has been a corner stone for research and awarded with Nobel prize, is suggested to improve the investigation and control of cell kinetics and provide the opportunity for collecting robust data for new applications and therapeutic areas (1-3). This combination has been used in identifying cell types being recorded, studying changes in the dynamics of the cells, functional connectivity, synaptic circuits and many more specific areas so far. Automated patch clamp systems and *in vivo* patch clamping combined with optogenetics are the latest trends in this research field.

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P086: ANTIHYPERALGESIC EFFECTS OF LEVETIRACETAM INJECTED INTRA-VPL ON CHRONIC CONSTRICTION INJURY MODEL

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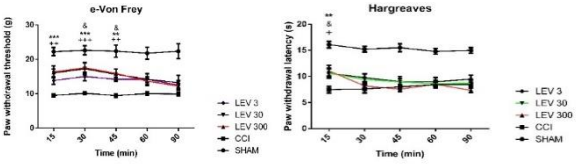
Introduction: There is an evident need for research on more effective treatments for neuropathic pain. Levetiracetam is a promising agent for several indications. This work has aimed to investigate neuroanatomical basis of its antihyperalgesic effects.

Materials and Methods: Male Sprague Dawley rats (n=7) were used. Levetiracetam at doses of 3, 30 and 300 µg were microinjected using stereotaxic apparatus and microinjection pump to the VPL nucleus of thalamus, an important anatomical region for pain transmission (2). Mechanical and thermal hyperalgesia were assesed using e-Von Frey and Hargreave’s

methods, respectively. Neuropathic pain model was established by chronic constriction injury (CCI) to the siatic nerve.

Results: Data obtained introduced the antihyperalgesic effects of levetiracetam in a time-dependent manner. Effects were more evident for the mechanical hyperalgesia.



Conclusions: Levetiracetam has antihyperalgesic effects on CCI model of neuropathic pain and it is partly regulated within VPL nucleus of thalamus. The difference between its effects on thermal and mechanic hyperalgesia may emerge from some possible diversity of the pathways, which will be investigated with further research. Results also emphasize VPL as a promising area for pain research.

Acknowledgements

This study was supported by a grant of EMBO (No:7952)

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P087: PROBIOTICS AND EXPERIMENTAL HYPERLIPIDEMIA

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Introduction: The high-fat diet has a significant role in the pathogenesis of non-alcoholic fatty liver disease. This condition is associated with obesity, diabetes, fibrosis and/or hepatic cirrhosis. In this regard, recently it was assumed that probiotics may influence the lipid metabolism and thus could be used in the treatment of steatosis (1). The aim of the present *in vivo* study was to evaluate the effect of natural probiotic bacteria isolated from a water source in the Balkan mountains (Bulgaria) on the lipid profile of rats fed with a steatogenic diet.

Materials and Methods: The probiotic food, containing *Lactobacillus bulgaricus DWT1*, *Lactobacillus helveticus DWT2*, *Lactobacillus lactis DWT3* and *Streptococcus thermophiles DWT4, 5, 6, 7, 8*, fats, proteins, carbohydrates, minerals, and vitamins, was used for the purpose of our work. 70% fructose solution and *Oleum Helianthi* were used for the induction of hyperlipidemia (2). The experimental study was conducted on 24 male Wistar rats that were divided in four groups (n = 6). All animals were orally gavaged for 30 consecutive days with the relevant substance. Biochemical and histological studies have been performed for the assessment of experimentally induced hyperlipidemia.

Results: The steatogenic diet led to a notable deterioration of the animals' lipid profile (*vs* Control group, $p < 0.05$). On the contrary, the experimental group (on steatogenic diet that was also treated with the probiotic food showed a significant decrease ($p < 0.05$) of VLDL-cholesterol (~ 50 %) and triglycerides (~ 49 %) levels. The histopathological studies correlated with the results reported above, as the probiotic food protected the liver of experimental animals from lipid degeneration induced by the steatogenic diet.

Conclusions: The intestinal microbiota is associated with many different biochemical reactions and is considered as an important regulator of the metabolic status. There is a link between the gut-liver axis, fat metabolism, hormonal balance in fat tissues, and inflammatory mediators. This study proves that probiotics could be used as a nutritional strategy for the management of non - alcoholic fatty liver disease.

Acknowledgements

We express our appreciation for Daflorn Ltd. (Bulgaria), for the providing of probiotic food.

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P088: ANTI-ULCER POTENIAL OF CATECHIN FRACTION OBTAINED FROM *INONOTUS NIDUS-PICI* IN RATS

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Introduction: *Inonotus nidus-pici* is a type of wood fungus from the family Hymenochaetaceae. The best studied member of this family is *Inonotus obliquus*, known as "Chaga" (in Russian), used to brew a curative beverages with different medical properties (1). Catechins are natural bioactive compounds that are widely studied for their potential health benefits, including gastroprotection (2). The aim of the present study was to assess the protective effect of catechin fraction isolated from *Inonotus nidus-pici* in Indomethacin-induced gastric ulcers in rats.

Materials and Methods: Catechins isolated from *Inonotus nidus-pici* were used for the purpose of our experiment. Indomethacin was used for the induction of gastric ulcer and famotidine was used as comparative anti-ulcer drug (positive control). Rats in the control group received saline. The study was carried out on 24 male Wistar rats that were divided in four groups (n = 6). Saline, catechins (low and high dosage) and famotidine were orally administered by gavage for 14 days prior to ulcer induction. Macroscopic evaluation of ulcers and histological analysis have been performed for the assessment of gastric injury.

Results: No gastric ulcers were observed in the control group, while in Indomethacin group extensive gastric ulcers were detected. Macroscopic evaluation and histological analysis show that catechins isolated from *Inonotus nidus-pici* have significant dose-dependent anti-ulcer effect in rats, similar to that of famotidine.

Conclusions: The present study shows that catechins could be used in prevention of gastric ulcers when taken concomitantly with nonsteroidal anti-inflammatory drugs (NSAIDs). More studies are needed to clarify the possible mechanism of the gastroprotective activity of catechins from this species.

Acknowledgements

This study was supported by a National program "Young scientists and postdoctoral students" funded by the Ministry of Education and Science, Bulgaria.

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P089: THE IMPACT OF ANTIMICROBIAL USE ON POTENTIAL MAJOR DRUG-DRUG INTERACTIONS IN THE PEDIATRIC INTENSIVE CARE UNIT PATIENTS

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Introduction: Pediatrics patients in intensive care unit are exposed to potential drug-drug interactions (PDDIs) and suffered from their adverse and side effects. The aim of this study is to evaluate the impact of antimicrobial use on PDDIs, as well as to examine the rate and the risk factors PDDIs, furthermore the management of PDDIs.

Materials and Methods: The present retrospective cohort study included 179 patients under 18 years of age who were hospitalized in Pediatric Intensive Care Unit in Turkey. Drug interactions were evaluated using the Lexicomp® drug interaction tool which provides evidence-based drug information.

Results: Our study results showed that the frequency of the use of antimicrobial drugs (antibiotic, antifungal, antiviral) was found to be statistically significantly higher ($p<0.05$) in the group with PDDIs compared to the group without PDDIs. Especially, the use of carbapenem, cephalosporin among the antibiotic groups significantly increased the frequency of PDDIs ($p<0.05$). While the probability PDDIs statistically significantly increased 3.73 times (OR (Odds Ratio) =3.73; 95% CI= 1.47-9.50) in patients who used a single antibiotic compared to patients who did not use antibiotics ($p=0.006$), the probability of the occurrence of PDDIs by using more than one antibiotic was statistically significantly 8.5 times (95% CI =3.30-21.89) ($p <0.001$).

Conclusions: Our study results showed that the use of antimicrobial drugs (antibiotic, antifungal, antiviral) was found to be statistically significantly higher ($p<0.05$) in the group with PDDIs.

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P090: THE CLINICAL OUTCOMES OF KIDNEY TRANSPLANT PATIENTS USED EITHER AZATHIOPRINE OR MYCOPHENOLATE

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Introduction: To prevent rejection after kidney transplant (KTx), patients are prescribed medications including a calcineurin-inhibitor (tacrolimus or cyclosporin), corticosteroids and an antiproliferative agents (mycophenolate mofetil, enteric-coated mycophenolate sodium or azathioprine) (1). Among the antiproliferative agents, mycophenolate has a stronger immunosuppressive effect and thus it prioritizes the usage (1). While some studies reported that mycophenolate reduced the risk of acute rejection and graft loss compared to azathioprine, other studies showed that acute rejection and mortality were similar between these agents (1,2). This study aims to compare the clinical outcomes of KTx patients who received either azathioprine or mycophenolate.

Materials and Methods: This was a retrospective observational study conducted between 1 January 2011 and 31 December 2019 in the nephrology ward of the Ankara University Ibni Sina Hospital. Patients were eligible if they were ≥ 18 years, prescribed either azathioprine or mycophenolate in their antimetabolite therapy after a KTx and used the same immunosuppressive regimen for at least 1 year. The data was obtained from the patients' electronic medical records.

Results: A total of 271 of KTx patients were included (male: 56% and age (median (interquartile range)): 41 (32-50) years). The majority received a kidney from a living donor (79%) and mycophenolate for antiproliferative regimen (95%). All patients received tacrolimus, glucocorticoids and proton pump inhibitors in combination with antiproliferative agents for their immunosuppressive therapy. After 1 year follow-up period, 15% had biopsy-proven acute rejection. The survival rate within the first year of the transplant was 98%. There was no statistically significant difference among the patients who received either azathioprine or mycophenolate in terms of acute rejection (14% in mycophenolate group vs. 29% in azathioprine group, P=0.135), graft loss (2% vs. 0%, P=1.000), estimated glomerular filtration rate (P=0.067) and overall mortality (2% vs. 0%, P=1.000).

Conclusions: The results of this study showed that there was no difference in acute rejection, graft loss, estimated glomerular filtration rate and overall mortality among the patients who received either azathioprine or mycophenolate during a one-year follow-up period after KTx.

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P091: PATIENT ENGAGEMENT IN THE MANAGEMENT OF MULTIPLE SCLEROSIS

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Introduction: An effective management of Multiple Sclerosis (MS) by disease modifying therapies allows patients to have a sense of control over their disease, which may increase patients' willigness to be actively involved during the treatment (1). The Patient Health Engagement Scale (PHEs) assesses the emotional, behavioral and cognitive competencies of patients in the care process. Understanding the degree of patient's participation allows healthcare services to be tailored according to the patient's needs (2). Therefore, aim of this study was to determine the level of patient engagement in the management of MS.

Materials and Methods: The patients admitted to the Hacettepe University Neurology outpatient clinic between June-September 2020 were included and demographics were collected. The PHEs was applied to the patients who are diagnosed with MS and have been receiving MS medication for at least 1 year. The scale consists of 5 phrases which includes 7 choices each and scored between 1-4; according to the median score, the patients were categorised into four engagement state as blackout, arousal, adhesion, and eudaimonic project. The blackout state represents that patient has no knowledge and desire to learn about the disease and treatment, whereas the eudaimonic project state indicates that patients' knowledge on disease, treatment and self-confidence is increased. The study was approved by the University Ethics Committee.

Results: The data presented here is a preliminary report of an ongoing study in which a total of 50 patients (84% female) were included in initial phase of the study. The mean (±standard deviation) age of patients and duration of MS were 39.22(±12.06) and 7.56(±6.53) years, respectively. According to the PHEs, 6%(n=3) of patients were found in blackout, 40%(n=20) in arousal, 52%(n=26) in adhesion and 2%(n=1) in the

eudaimonic project state. For the further analysis, the patients were grouped as 'more likely to be engaged (adhesion+eudaimonic project)' and 'less likely(arousal+blackout) to be engaged'; no significant differences were found between the groups in terms of age(p=0.147), gender(p=1.000), MS duration p=0.388) and educational status(p=0.309).

Conclusions: The majority of MS patients were found in the arousal and adhesion phases, in which patients are emotionally stable and willing to participate in treatment. However, transition of the patients to the eudaimonic project phase should be aimed in order to engaged patients with active involvement in the treatment process of MS. It can be argued that clinical pharmacists can strengthen the patient participation through patient education on treatment options and coping skills in the management of the disease.

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P092: PERCEPTION OF COVID-19 VACCINATION AMONGST PHYSICIANS: AN ONLINE SURVEY

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Introduction: Physicians' beliefs and attitudes to COVID-19 vaccines are important for the immunization rate of the public (1). This study aimed to evaluate the perception of physicians toward the COVID-19 vaccination.

Materials and Methods: This cross-sectional study was conducted as an online survey between 15 January-12 February 2021 in Turkey. The survey links were shared on online social and scientific platforms. The survey included questions on the physicians' demographics and their perception toward COVID-19 vaccination.

Results: A total of 486 physicians with a mean age (±standard deviation) of 44.64±11.64 years and 55.8% female, were included in the study. Perceived information about COVID-19 vaccines was higher in male physicians (66% vs 53.5%; p=0.030), and female physicians were more concerned about the adverse effects of the vaccine (26.2% vs 14.9%; p<0.001). As the age increased, the percentage of physicians having sufficient knowledge about COVID-19 vaccines also increased significantly (aged between 23-33; 34-44; 45-55; 56-66; 67-77, 41.1%; 51.1%; 63.5%; 82.5%; 100%, respectively, p<0.001). The percentages of physicians of different age scales concerned about the adverse effects of the vaccine were also different (aged between 23-33; 34-44; 45-55; 56-66; 67-77, 23.4%; 29.5%; 21.6%; 5.0%; 8.3%, respectively, p=0.003). The percentage of physicians who did not want the vaccine to be mandatory was found to be higher in younger physicians (age between 23-33) than older physicians (between the ages of 67-77) (48.6% vs 8.3%, p=0.009). Recommendation of COVID-19 vaccines to their patients was higher in physicians who stated that they have sufficient information about vaccines (95.8% vs 86.7%, p=0.011) and not concerned about the adverse effects of the vaccines (98.4% vs 75.7%, p <0.001). While 98.9% of the physicians without concern about the efficacy of the vaccine recommend COVID-19 vaccine to their patients, 85.4% of the physicians with concern recommend the vaccine (p<0.001).

Conclusions: Physicians' age, gender and concerns influence their COVID-19 vaccination perception. Due to common hesitancy and concerns on COVID-19 vaccines, physicians' perception has an important role to vaccination of the public to overcome pandemic.

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P093: SUPPORTIVE THERAPY-INDUCED POLYPHARMACY AND DRUG-RELATED PROBLEMS IN CANCER PATIENTS

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Introduction: "An event or circumstance involving drug therapy that actually or potentially interferes with desired health outcomes'' is defined as a drug-related problem (DRP). Patients with cancer are prone to polypharmacy due to chemotherapy and supportive care which may lead to increase rate of DRPs such as inappropriate medications, dosing and route of administration, drug-drug interactions, drug omissions and lack of monitoring (1-3).Therefore, aim of this study was to emphasize the role of clinical pharmacists in determination and

prevention of drug related problems (DRPs) in an hospital oncology services.

Materials and Methods: In this prospective, cross-sectional study, the patients aged over 18 years and hospitalized in the University Oncology Hospital between December 2020 and January 2021 were included. Drug orders were reviewed by a clinical pharmacist during daily clinic visits along with the physicians; DRPs were identified, recommendations for the problems were documented and the acceptance rate of recommendations were recorded. Drug interactions were detected with the UpToDate software system. Drug related problems were categorised according to the Pharmaceutical Care Network Europe (PCNE) version-9 using subheadings of 'problems' and 'causes' checklists.

Results: Twenty-six patients with cancer were included, of those 13 (50%) were female and the mean (± standard deviation) age was 58.3 (±15.64) years. The mean number of drugs used, concomitant diseases and identified problems per patient was 12.23, 1.62 and 1.15, respectively. During the study period, 318 drugs were assessed by the clinical pharmacist and 42 DRPs were identified, and 42 recommendations were suggested. The majority (n=38; 90.5%) of recommendations were accepted by the physicians and necessary changes were made during the treatment. By the assessment of 318 drugs revealed that prescribed drugs were mainly used for the supportive therapies, such as analgesic, antiemetic, proton pump inhibitors, antifungal and antimicrobials. The most common DRPs identified were dose selection (n=17; 40.5%), followed by drug selection (n=11; 26.2%) drug use process (n=6; 14.28%), dosage form (n=3; n=7.14%), patient transfer related issues (n=2; 4.76%), treatment duration (n=1; 2.38%), drug effectiveness (n=1; 2.38%) and inappropriate monitoring (n=1; 2.38%).

Conclusions:
Polypharmacy status is not always be the result of having multiple chronic diseases. As for the cancer patients, supportive therapies may increase the drug burden in treatment process regardless of chemotherapy. Therefore, this study showed that an involvement of clinical pharmacists in the care of cancer patients creates opportunities to optimize treatment process by identification and management of DRPs.

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P094: IMPROVEMENT OF IMMUNOSUPPRESSIVE MEDICATION ADHRENCE IN NEW RENAL TRANSPLANT PATIENTS

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Introduction: Patient adherence to immunosuppressive medication is one of the most important factors for the survival of a graft in transplant patients (1). Few interventional studies have included approaches aimed at increasing adherence. The objective of this study was to evaluate the impact of clinical pharmacist's behavioral and educational strategy on immunosuppressive medication adherence of new renal transplant patients.

Materials and Methods: A prospective, observational study was conducted in a nephrology outpatient clinic at the Hacettepe University Hospitals between January 2019-April 2020. The new renal transplant patients (n=62) were divided in two groups: control group (n=31; routine transplant education) and educational group (n=31; routine transplant education plus clinical pharmacist education). Treatment adherence was assessed using Immunosuppressive Therapy Adherence Scale (ITAS, which is scored: 12=adherence; ≤11=non-adherence) questionnaire after 3 months (2nd visit). The data on patients' demographics, renal functions and tacrolimus drug concentration were recorded.

Results: A total of 62 patients included in the study. The median (min-max) age in the control and treatment groups was 34 (18-61) and 41 (21-63) years, respectively. The predominant gender was male (61.29%). Triple combination therapy consisting of tacrolimus, mycophenolate sodium or mofetil and prednisolone was used as immunosuppressive drug therapy. After 3 months, adherence rates were 45.16% (n=14) in the control group and 96.77% (n=30) in the educational groups ($p<0.001$). A higher score was observed in the response to the first, second item of the ITAS questionnaire and total median ITAS score for the educational group compared to controls (respectively 3 (2-3) vs 3 (2-3), $p=0.006$; 3 (3-3) vs 3 (2-3), $p<0.001$ and 12 (11-12) vs 11 (10-12), $p<0.001$). Although tacrolimus dose in the control group [6 (2-10) mg] was higher than in educational group [5 (2-8) mg] ($p=0.033$), the mean tacrolimus blood level was higher in the educational group

[9.00 (6.60-14.70) ng/mL] compared to controls [6.00 (3.60-9.00) ng/mL] in 2nd visit ($p<0.001$). Tacrolimus blood level increased by 20% in educational group but decreased by 24% in control group. There was no difference in renal functions between groups (creatinine, spot urine protein/creatinine ratio, BUN, uric acid; $p>0.05$) in 2nd visit.

Conclusions: Adherence to immunosuppressive medication in renal transplant patients is important. Healthcare professionals should be aware of the level of patient's adherence. A clinical pharmacist educational strategy significantly improved the adherence to immunosuppressive therapy.

Acknowledgements

The authors would like to thank all participating patients and hospital staff at the outpatient clinic.

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P095: NEPHROLOGISTS' OPINION ON THE MANAGEMENT OF ASYMPTOMATIC HYPERURICAEMIA IN PATIENTS WITH CHRONIC KIDNEY DISEASE

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Introduction: Hyperuricemia is frequently associated with hypertension, cardiovascular diseases and chronic kidney disease (CKD) (1). However, the management of urate-lowering therapy on asymptomatic hyperuricemia (AHU) differs across the clinical guidelines (2, 3). This study aimed to determine nephrologists' attitudes towards the management of AHU in patients with CKD.

Materials and Methods: An online survey on the management of AHU in CKD patients was designed in the view of literature and clinical guidelines, then e-mailed to the members of the Turkish Society of Nephrology between August 2020- April 2021.

Results: Sixty-five (52.3% female, the mean age: 44.4 ± 7.9 years) nephrologists responded to the survey. The majority (44.6%) of the respondents considered hyperuricemia when serum uric acid level is higher than 7 mg/dL. Fifty-five (84.6%) nephrologists reported to treat AHU with medication in patients with CKD. The most commonly accepted threshold for serum uric acid level to start urate-lowering therapy was 10 mg/dL (28.8%), followed by 9 mg/dL (27.1%) and 8 mg/dL (23.7%). The target level of uric acid for deprescribing was stated as 6 mg/dL and 5 mg/dL by 37.3% and 30.5% of nephrologists, respectively. Allopurinol was the choice of the drug by 98.5% of respondents and the most frequently used maximum dose was 300 mg/day (93.8%). The common reasons for initiation of AHU therapy were prevention of both progression of CKD (87.5%) and cardiovascular events (60.7%), whereas side effects of urate-lowering drugs were stated as the frequent reason (65.9%) for not to initiate the therapy.

Conclusions: In Turkey, the majority of nephrologists prefer to treat AHU in CKD patients to prevent CKD progression or cardiovascular events. Reported threshold and target uric acid levels for initiation and cessation of uric acid-lowering therapy were varied. This might be the result of not having a national guideline for this clinical situation, which highlights the needs in clinical practice.

Acknowledgment

The authors would like to thank the board member of the Turkish Society of Nephrology Prof. Mustafa Arıcı for his help.

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P096: EVALUATION OF DRUG BURDEN IN GERIATRIC PATIENTS: A POINT PREVALENCE STUDY

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Introduction: Higher exposure to anticholinergic and sedative medications is associated with a higher risk of morbidity, mortality and cognitive decline in geriatric patients (1). In addition, polypharmacy is associated with adverse outcomes including mortality, falls, adverse drug reactions, increased length of stay in hospital (2).

This study aimed to determine the prevalence of anticholinergic and/or sedative drug exposure and polypharmacy in hospitalized geriatric patients.

Materials and Methods: A point prevalence study was conducted in internal medicine units of a university hospital on April 30th, 2021. The medications of geriatric inpatients (aged ≥ 65 years) were evaluated by clinical pharmacists to determine anticholinergic and sedative medication exposure which was measured using the Drug Burden Index (DBI). Polypharmacy and hyperpolypharmacy in patients were defined as ≥5 medicines and ≥10 medicines, respectively (2).

Results: A total of 29 geriatric patients (51.7% female) were included in the study. The mean (± standard deviation, SD) age of the patients was 73.8 ± 6.8 years. Sixteen (55.2 %) of them were exposed to at least one sedative or anticholinergic medication. Hypertension, diabetes mellitus and coronary artery disease were the most common chronic comorbidities among patients. Polypharmacy and hyperpolypharmacy were observed in 79.3% and 20.7%, respectively and DBI value was >0 for 55.2% of the patients. The mean number (± SD) of regularly prescribed medications was 6.9 ± 2.9. The median (range) DBI value was 0.42 (0-1.56). Seven patients (24.1%) used 1, eight patients (27.6%) used 2, one patient (3.4%) used 3 different drugs with anticholinergic or sedative effects. The most common medications with associated DBI were detected as sertraline, memantine and tramadol.

Table 1. Patients' Drug Burden Index Value Data

	n (%)
Drug Burden Index	
0	13 (44.8)
0-1	12 (41.4)
≥1	4 (13.8)
The medications associated the drug burden index	
Sertraline	3 (10.3)
Memantine	3 (10.3)
Tramadol	3 (10.3)
Trazodone	2 (6.9)
Escitalopram	2 (6.9)
Quetiapine	2 (6.9)

Conclusions: This study has determined that sedative and/or anticholinergic drugs are frequently used in the geriatric population. Clinicians should be aware of the high burden of these drugs to prevent undesirable outcomes such as poor cognitive and physical functions and mobility impairment in the geriatric population.

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P097: COLISTIN INDUCED NEPHROTOXICITY: EXPERIENCE FROM A UNIVERSITY HOSPITAL

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Introduction: Colistin has been frequently used for the treatment of infections caused by multidrug-resistant bacteria. In this study, it was aimed to determine the frequency and risk factors of colistin-related nephrotoxicity.

Materials and Methods: Patients who were treated colistin between October 2018 and August 2019 in a tertiary care hospital were retrospectively analyzed. Kidney Disease Improving Global Outcome (KDIGO) criteria were used for the staging of nephrotoxicity.

Results: A total of 100 patients, 43% were female, with a median age of 64 years were included in the study. Nephrotoxicity was detected in 52% of patients within the first week and 59% of patients experienced nephrotoxicity at any time of colistin treatment. Serum creatinine increased 1.5 times higher than normal level in median 4 (1-11) days and glomerular filtration rate decreased below 60 mL/min in median 5 (1-42) days. Forty-eight percent of the patients had 'normal' renal function, 20% were 'stage 1', 17% were 'stage 2', 15% were 'stage 3' in colistin treatment according to KDIGO classification. Length of hospitalization (OR: 1.009, %95 CI: 1.001-1.017), age (OR: 1.036, %95 CI: 1.005-1.068), duration of colistin treatment (OR: 1.115, %95 CI: 1.023-1.216), and vasopressor use (OR: 3.012, %95 CI: 1.003-9.042) were significantly associated with nephrotoxicity at any time.

Conclusion: This study showed a high rate of colistin-related renal toxicity. Regular monitorization of renal functions, adequate dosing, and limiting the days of colistin treatment may be useful to avoid nephrotoxicity in older patients, particularly when used with vasopressors.

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P098: PSYCHOMETRIC PROPERTIES OF TURKISH VERSION OF IDENTIFICATION OF MEDICATION ADHERENCE BARRIERS QUESTIONNAIRE IN PATIENTS WITH CHRONIC DISEASES: PRELIMINARY FINDINGS

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Introduction: It is aimed to assess psychometric properties of Turkish version of Identification of Medication Adherence Barriers Questionnaire (IMAB-Q-TR), which is developed based on Theoretical Domains Framework.

Materials and Methods: This descriptive, methodological study has been conducted in community pharmacies (n=6) in Istanbul, Turkey. Convenience sampling method was used to recruit adult patients with chronic disease (diabetes mellitus and/or hypertension and/or dyslipidemia), who used at least one medication for at least a month and are responsible for self-administration of their medication. After appropriate language and conceptional translation, content validity was assessed by expert panel and during pilot study (n=20). Test-retest reliability and internal consistency (by using Cronbach's alpha) were evaluated. Criterion validation was assessed by calculating the correlation (by using Spearman correlation test) between the scores of the scale and validated Turkish version of Medication Adherence Report Scale (MARS-TR).

Results: Among 187 patients (female/male: 124/63) with chronic disease, the mean age of the participants was 60.2±11.0 years. The 2 weeks test-retest reliability of the scale (n=30) was high (r= 0.985; p<0.001). The Cronbach's alpha was 0.643. There was negative correlation between total score of IMAB-Q-TR and MARS-TR (r= -0.463; p<0.001).

Conclusions: Based on preliminary findings, The Turkish version of IMAB-Q could be used to identify medication adherence barriers in patients with chronic diseases.

P099: EVALUATION OF COMMUNITY PHARMACISTS' PRACTICES REGARDING SUPPLYING AND STORAGE OF THE VACCINES

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Introduction: Vaccination is the safest and most effective way in order to immunize against diseases. The effectiveness of the vaccine is achieved by storing the vaccine under appropriate conditions and delivering it to individuals. In the storage of vaccines, breaking the cold chain often poses a problem in terms of the vaccine's effectiveness (1). In this study it was aimed to evaluate community pharmacists' practices regarding supplying and storage of the vaccines.

Materials and Methods: This cross-sectional study was conducted as an online survey among community pharmacists in Turkey. Pharmacists were invited to the study by phone calls between July 2017 and March 2018. The survey link was sent to the e-mail addresses of pharmacists who accepted to participate in the study. Data were evaluated through descriptive statistical analysis. IBM SPSS Statistics for MacOS, version 23.0 (IBM Corp., Armonk, N.Y., USA) was used for the analysis.

Results: A total of 428 pharmacists completed the survey. The median age of pharmacists was 41 (20-74) years and 297 (69.4%) of them were female. Two hundred and forty-two (56.5%) pharmacists preferred to supply the vaccines from the pharmaceutical warehouse upon request, whereas 93.7% tended to stock vaccines at the pharmacy for a short period. The availability of vaccines on-demand was not considered as a barrier by 69.3% of pharmacists in terms of vaccine recommendation. With regards to storage conditions, 345 (80.6%) pharmacists indicated to store the vaccines in a refrigerator and placed them at the mid-shelf (n=200, 57.9%), door-shelf (n=59, 17.1%), top-shelf (n=53, 15.4%) and bottom-shelf (n=33, 9.6%) of the home-type fridge. Eighty-three (19.4%) pharmacists stated that they used vaccine cabinets specially designed for vaccines. Three hundred and forty-nine (81.6%) of the pharmacists indicated that they dispense the vaccine with an ice pack in order to maintain cold-chain.

Conclusions: It has been observed that pharmacists pay attention to vaccine storage conditions. Few pharmacists stored and distributed vaccines improperly. In order to prevent the waste of vaccines and prevent unnecessary re-vaccination of the patients, pharmacists have important responsibilities in storing the vaccines under appropriate conditions and delivering them to the public.

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P100: EVALUATION OF RENAL DRUG DOSING IN HOSPITALIZED PATIENTS WITH RENAL IMPAIRMENT

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Introduction: Drug-related problems (DRPs) are an undesirable patient experience that involves drug therapy and actually or potentially interferes with the desired patient outcome (1). Dose-related errors are common DRPs in patients with renal impairment that require close follow-up and dose adjustment according to renal functions (2). In this study, it was aimed to evaluate the appropriateness of drug doses in nephrology inpatient clinic according to patients' renal functions.

Materials and Methods: This point prevalence cross-sectional study was conducted in the adult nephrology clinic of a tertiary care hospital. Inpatients on the day of the point prevalence (30th April 2021) were included in the study. All orders prescribed during the patients' hospitalization period at the nephrology clinic were retrospectively reviewed by 3 clinical pharmacists. Lexicomp UpToDate® and Rx Media Pharma® were used in the evaluation of drugs' doses. The creatinine clearance was calculated using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation. To summarize the characteristics of the data, descriptive statistics were used.

Results: The data of 22 patients, 9 (40.9%) male, and 13 (59.1%) female, with a mean age of 57.95±14.40 years, were analyzed. The proportion of chronic kidney disease, acute kidney disease, and hyponatremia was respectively 52%, 16%, and 16%. Seven patients were on dialysis; 2 (28.57%) of them were peritoneal dialysis and 5 (71.43%) of them were hemodialysis. The mean number of chronic diseases per patient was 2,09±1.35 and the patients' mean length of stay was 12±8.81 days. Fifty-eight drugs were required dose adjustment according to patients' renal functions. Fourteen (24.14%) drugs' dose was not appropriate in terms of the patients' estimated glomerular filtration rate values. The pharmacological groups of drugs requiring dose adjustment were antimicrobials (42.85%), anticoagulants (21.42%), antihyperuricemics (14.28%), and others (21.45%). It was found that most of the antimicrobial requiring dose adjustment was cefazolin (33.33%). While vancomycin (16.67%) required an increase in the dose, tenofovir alafenamide (16.67%) required discontinuation and other antimicrobials required dose reduction.

Conclusions: In this study, the highest dose error was encountered in antimicrobial drugs. In patients with reduced kidney function, dose adjustment of certain drugs is necessary to prevent toxicity and to provide an effective treatment. The involvement of the clinical pharmacist in the multidisciplinary team in nephrology clinics will contribute to the detection and prevention of DRPs.

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P101: INFLUENZA VACCINATION COVERAGE AMONG PHYSICIANS AND NURSES IN ONCOLOGY SETTINGS

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Introduction: Annual vaccination for healthcare workers (HCW) against influenza has been recommended by the national health authorities. The rate of influenza vaccination coverage among HCW is reported to be less than 30% in Europe (1). Physicians and nurses working with vulnerable patients groups susceptible for infections, such as cancer patients are at risk of transmission the influenza infection to patients. This study was aimed to determine the uptake rate of influenza vaccine by oncology physicians and nurses during the 2018/2019 influenza season and to evaluate their opinions on influenza vaccine.

Materials and Methods: This descriptive study was conducted as an online survey among oncology physicians and nurses working in adult oncology services in Turkey during July 2019-September 2020. A structured survey was sent both to the nurses who are members of the Oncology Nurses Association, and to the physicians in the mail group of oncology physicians via e-mails. The data were analyzed by the IBM SPSS® version 23 program and appropriate tests were used for statistical analysis. A p-value <0.05

with a 95% Confidence Interval was considered significant.

Results: A total of 80 physicians (55% female) and 84 nurses (91.7% female) participated in the study. Thirty percent of physicians' and 36.9% of nurses' age was between 31 and 40 years. Twenty-five (31.25%) physicians and 19 (22.62%) nurses had been vaccinated against influenza in the previous season. There was no statistical difference between the vaccination rates of physicians and nurses (p=0.284). The main reason for physicians not being vaccinated was the lack of time (50.91%), whereas not seeing influenza vaccination as necessary was indicated by nurses (49.23%). Although 38 (47.50%) physicians and 20 (23.81%) nurses considered to have vaccination in the next influenza season (p=0.005), 8 (10.00%) physicians and 16 (19.05%) nurses were undecided about vaccination.

Conclusions: This study demonstrated that influenza vaccination rates among physicians and nurses working in the field of oncology were low. Given the fact that cancer patients are more prone to have infections and at increased risk of associated complications, healthcare workers/professionals should take precautionary actions against infectious diseases in order to maintain the healthy status of their patients and themselves. An awareness on influenza vaccine should be increased and the vaccination uptake should be encouraged among healthcare professionals in oncology settings.

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P102: EFFECTS OF ACRYLAMIDE, HYDROXYMETHYL FURFURAL AND CAFFEIC ACID ON DNA DAMAGE IN V79 CELLS

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Introduction: Acrylamide (AA) and 5-hydroxymethyl furfural (HMF) occurs as a result of Maillard reaction in cooking processes of foods containing carbohydrates under high temperature and low humidity conditions such as frying, baking, roasting, grilling. Both substances have been shown to be carcinogenic in *in vivo* and *in vitro* tests; AA is classified as "possible carcinogenic to humans" by the International Agency for Research on Cancer (IARC) (Group 2A). One of the most important routes of AA and HMF exposure is coffee consumption (1). Caffeic acid (CA) is a phenolic acid compound found in coffee that is thought to have antigenotoxic effects. In our study, we aimed to evaluate the possible genotoxic effect of AA and HMF with/without CA in Chinese hamster lung fibroblast cell lines (V79 cells).

Materials and Methods: Genotoxicity was evaluated by the single cell gel electrophoresis (COMET) assay. The cells were treated with different concentrations of AA, HMF (1, 5, 10, 25, 50 and 100 µM) and CA (25 and 50 µM) and different combinations of AA, HMF, and CA with each other for 1 h. DNA damage was expressed a DNA tail intensity.

Results: The doses of AA (1, 5, 10, 25 and 50 µM) and HMF (1, 5, 10, 50 and 100 µM) did not increase DNA damage alone. DNA damage was increased at the doses of 100 µM AA, 25 µM HMF and 25 and 50 µM of CA. The toxic effects of AA and HMF were potentialized when combined with 50 µM of CA.

Conclusions: Our results show that AA and HMF alone may not cause considerable DNA damage however; CA might induce the DNA damage at high doses in V79 cells. Accordingly, low coffee consumption do not seem to be harmful as thought.

Acknowledgements

This study was supported by Hacettepe University (TDK-2019-17708).

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P103: INVESTIGATION OF THE CYTOTOXICITY OF BISPHENOL A AND ITS ANALOGS (BPS, BPF, BPAF, BPZ) IN MCF-7 AND HSeC CELL LINES

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Introduction: Bisphenol A (BPA), which is known as an endocrine-disrupting chemical, has many application areas such as food containers, making electronic devices, medical equipment and flame retardants. Breast cancer, infertility, cognitive dysfunction, diabetes and cardiovascular diseases are all considered to be associated with BPA (1). Because BPA is now banned in industrial production in many countries, the industry developed and gradually replaced BPA with its chemical analogs, BPS, BPF, BPAF, and BPZ as potentially safer alternatives (1,2). Numerous studies have identified BPA analogs as endocrine-disrupting chemicals since they are structurally similar to BPA, therefore, they may also have the same toxicity (1). However, seeing that there aren't sufficient studies about BPA analogs' effects on human health, we aimed to investigate the cytotoxic effects on MCF-7 and HSeC cell lines.

Materials and Methods: To evaluate the cytotoxicity of BPA and its analogs (BPS, BPF, BPAF, BPZ), an MTT assay was conducted in MCF-7 and HSeC cell lines. The used concentrations of BPs are 0.1, 1, 5, 10, 50 µM and the IC50 values were calculated.

Results: Based on the results of MTT, the IC_{50} values for BPA, BPS, BPF, BPAF, BPZ are respectively 45µM in MCF-7 and 35 µM in HSeC, 450 µM in MCF-7 and 105 µM in HSeC, 435µM in HSeC, 56µM in MCF-7 and 48µM in HSeC, 45µM in MCF-7 and 25µM in HSeC.

Conclusion: According to our results, while BPF is the safest alternative comparing to BPA and its analogs, BPZ is the most cytotoxic compound. Our results also indicated that BPs might be more cytotoxic to HSeC cell line than MCF-7 cell line. However, additional studies are required.

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P104: PROTECTIVE ROLE OF SELENOCOMPOUNDS AGAINST DNA DAMAGE AND OXIDATIVE STRESS CAUSED BY BISPHENOL A IN HUMAN PAPILLARY THYROID CANCER CELL LINE

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Introduction: Bisphenol A (BPA) is a chemical compound that can bind to estrogen receptors with low affinity. BPA shows weak estrogenic activity and is classified as an "endocrine disrupting chemical" (Almeida et al., 2018). It may also disrupt thyroid homeostasis (Moriyama et al., 2002). Selenium has an essential role in thyroid homeostasis as a component of deiodinases. Additionally, it protects the thyroid gland against oxidative stress as a constituent of glutathione peroxidases (Schomburg 2011). In this study, we aimed to investigate the toxic effects of BPA and the modifying effects of selenium supplementation against BPA toxicity in human papillary thyroid cancer cell line (B-CPAP). We also evaluated the cytotoxicity, oxidant/antioxidant parameters, oxidative DNA damage and apoptosis caused by BPA. In addition, the protective roles of inorganic selenium (sodium selenite, SS) and organic selenium (selenomethionine, SM) were assessed.

Materials and Methods: B-CPAP cell line was used throughout the experiments. The study groups were: Control, BPA, SM, SS, BPA+SM and BPA+SS. Cell viability was assessed by MTT assay. The oxidative stress parameters including malondialdehyde (MDA), glutathione (GSH) levels, intracellular reactive oxygen species (ROS) production and levels of apoptosis markers (caspase 3 and 8 l) were measured by using commercial kits. Oxidative DNA damage was determined by single cell gel electrophoresis (COMET) assay. Apoptotic cell count was evaluated using TUNEL assay.

Results: Our results showed that BPA caused significant elevations of intracellular ROS and MDA levels and decreases in total GSH concentrations in B-CPAP cell line. Additionally, BPA also induced oxidative DNA damage and apoptosis.

Conclusions: We can conclude that one of the underlying mechanisms of the toxic effects of BPA in B-CPAP cell line may be significant alterations of oxidant/antioxidant status which can lead to DNA damage. Physiological doses of selenocompounds might be partially protective against BPA toxicity in thyroid cell cancer cell lines.

Acknowledgements

This study was supported by a grant of Hacettepe Scientific Research Projects Coordination Unit, Project number: TYL-2018-17076

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P105: POTENTIAL HAZARD IN THE METFORMIN PRODUCTS, NITROSAMINES

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Introduction: Metformin (MET) has been used clinically for many years as a first-line treatment for patients with type 2 diabetes mellitus (T2D) due to its cost-effectiveness, good safety profile and cardiovascular benefits (Flory et al., 2019). Recently, nitrosamines, known to have probably carcinogenic effects, have been detected above the acceptable intake limits in various extended-release MET products, so the recall of these drug products in the USA caused concern in physicians and pharmacists (FDA, 2021). Nitrosamines are products formed by the reaction of secondary or tertiary amines between a nitrosating agent. Nitrosamines may cause cancer in animals and humans. Dimethylnitrosamine (NDMA) and diethylnitrosamine (NDEA) are classified as probably carcinogenic to humans by the International Agency for Cancer (IARC) (Erkekoğlu et al., 2010, Zmysłowski et al., 2020). In this review, we aimed to inform the recent events to health care providers and pay attention to the potential risk of nitrosamine impurities in human medical products especially metformin.

Materials and Methods: In this review, we compile the scientific data, documents from the European Medicines Agency (EMA), US Food and Drug Administration (FDA) and Turkish Pharmaceuticals and Medical Devices Agency (TITCK) about nitrosamine impurities in human medical products.

Results: It was shown that the medicine authorities recalled the products which contain NDMA and other nitrosamine impurity level higher than acceptable intake limits. Additionally, they published guides and reports to inform the industry and healthcare providers. However, there is still limited data available on the causes and consequences of nitrosamine impurity in human medical products.

Conclusions: In conclusion, FDA and EMA have stated that despite the possible risk of toxic effects of low level of nitrosamines, MET treatment should continue, considering the risks that may occur as a result of the discontinuation of the drug treatment of the patient. The root cause of NDMA impurity for MET have not been identified so far and the risk evaluation is still processing. The elimination of the danger will only be possible by the strict risk evaluation.

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P106: DETERMINATION OF *CYP1B1'3* (LEU432VAL) POLYMORPHISM IN A TURKISH POPULATION

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Introduction: CYP450 enzyme system is the most important enzyme group involved in drug and xenobiotic metabolism. CYP450 enzymes are mostly found in the liver, while CYP1B1 enzymes are found in extrahepatic tissues and cells. Immunohistochemical studies have shown that CYP1B1 was isolated from esophagus, brain, lung and breast cancer tissues (Hood et al., 2007). CYP1B1 is known to be polymorphic. To date, there are 26 different CYP1B1 alleles that have been identified as haploid and also 4 different alleles that have not yet been identified as haploid(https://www.pharmvar.org/gene/CYP1B1). The best known CYP1B1 allelic variants occur at codons numbered 48,119,432 and 453 either alone or in various combinations (Antonarakis et al., 1998). CYP1B1 polymorphisms have been associated with various diseases, including cancer. In this study, the frequency of *CYP1B1'3* (Leu432Val) allele in Turkish population was determined. Identification of polymorphisms occurring in *CYP1B1* gene is very important in terms of taking precautions by determining the

tendencies to cancer, glaucoma, obesity and many other diseases. In this study, it was aimed to determine this polymorphism in healthy individuals, to compare it with other populations and to compare whether there are significant differences.

Materials and Methods: The polymorphism distribution of 150 healthy individuals who do not have any relationship between them was determined by Real-Time PCR method. The study was approved by the ethics committee of Ankara University.

Results: The frequency of Leu/Leu (wild type), Leu/Val (heterozygous variant), Val/Val (homozygous mutant) *CYP1B1*3* genotypes were 39.33%, 50.67% and 10%, respectively.

Conclusions: *CYP1B1 * 3* polymorphism in a Turkish population is similar to other European white races, but differs with Asian and African American races such as China and India.

Acknowledgements

This study was supported by the Research Fund of Ankara University (Grant no: 10B3336003).

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P107: SOME GENE POLYMORPHISMS AFFECTING DIABETES MELLITUS TYPE 2 DEVELOPMENT

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Introduction Type 2 diabetes is a hyperglycaemic metabolic disease related with the decrease of insulin secretion. Genetic and environmental factors are playing major role in the development of the disease. Relationship between the inflammation generation and diabetic complications has been showed in recent studies. Following the formation of the oxidative stress after the disorder of the lipid metabolism, the levels of the reactive oxygen species (ROS) increase and insulin resistance develops consequently. Cytokines are important in regulation of the homeostatic mechanisms such as inflammation and tissue repair. Thus, variations in their levels and structures can cause several diseases. The single nucleotide polymorphisms (SNP) forming on the cytokine genes increase the risk of disease development. Recent studies showed the relationship between some inflammatory cytokine gene polymorphisms and the development of complication in patients with diabetes.

Materials and Methods: Based on this, our aim was searching and the evaluating the possible relations between the TNF-α (-308), Calpain-10 and PPARG gene polymorphisms and the development of the complications in a Type 2 diabetic Turkish patient population by using PCR-RFLP method.

Results: Due to our results all of the studied gene polymorphisms showed significant relationship with the development of Type II Diabetes Mellitus.

Conclusions: The studied gene polymorphisms can be a good indicator for Type II diabetes Mellitus.

P108: POSSIBLE RELATIONSHIPS BETWEEN SOME GENE POLYMORPHISMS AND DIABETES MELLITUS TYPE 2 IN A TURKISH POPULATION

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Introduction Type 2 diabetes is a chronic and complex disease that is characterized by impaired pancreatic beta cell function and insulin resistance. Genetic and environmental factors are playing important role in the development of this disease. Cytokines and chemokines are the keystones in regulation of the homeostatic mechanisms such as inflammation and tissue repair. Thus, variations in their levels and structures are the reasons for the occurrence of various diseases. The single nucleotide polymorphisms (SNP) forming on the cytokine genes increase the risk of disease development. Recent studies showed the relationship between some cytokine and chemokine gene polymorphisms and the development of type 2 diabetes. Based on this, our aim was searching and the evaluating the possible relations between the TNF-α (-308), (+3953), IL-6 (-174), IL-18 (-607) and MCP-1 (-2518) gene polymorphisms and the development of the diabetes in a group of Turkish patient population.

Materials and Methods: Based on this, our aim was searching and the evaluating the possible relations between the IL-1β, KCNJ11 and TCF7L gene polymorphisms and the development of the development of Type 2 diabetic Turkish patient population by using PCR-RFLP method.

Results: Due to our results all of the studied gene polymorphisms showed significant relationship with the development of Type II Diabetes Mellitus.

Conclusions: The studied gene polymorphisms can be a good indicator for Type II diabetes Mellitus.

P109: IDENTIFYING POTENTIAL GENETIC BIOMARKERS OF THE CARDIOTOXICITY INDUCED BY ANTHRACYLINES

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Introduction: Anthracyclines are a mainstay of chemotherapy which are used to treat various type of cancers. Although they have been known as essential cytotoxic medicine, anthracycline-related cardiotoxicity is an important adverse effect of anticancer therapy which restricts the clinical utility (1). This anthracycline-cardiotoxicity association could modified by several demographic and clinical factors, such as age at anthracycline exposure (<4 years); gender (female sex); medication dose; presence of cardiovascular risk factors (diabetes, hypertension) (1-3). However clinical variables might not be predictive enough in detecting cardiotoxicity. Recently, attention has focused on functional genetic differences associated with cardiac dysfunction that might provide a comprehensive understanding of the susceptibility.

Materials and Methods: A survey of the PubMed database for the published papers between the years 2009-2019 was conducted using the syntax included a combination of the following terms: gene, single nucleotide polymorphism, chemotherapy, anthracyclines, and cardiotoxicity. Data from candidate gene association studies examining the role of genetic susceptibility to anthracycline-induced cardiotoxicity are clustered to the molecular mechanisms including oxidative stress, inflammatory pathway, biotransformation autophagy.

Results: The findings support that genetic variations in susceptibility genes contribute to anthracycline-related cardiotoxicity. Genetic variants implicated in anthracycline-mediated cardiotoxicity via candidate gene studies were summarized corresponding to the molecular mechanisms. Here we reported the positively correlated genetic variants in reactive oxygen-buffering genes (Catalase (*CAT)*, Superoxide dismutase (*SOD)*, *and Glutathione S-transferase (GSTP1)*), genes regulating metabolic transformations (CytochromeP450 (*CYP3A5)*), genetic variations in genes regulating solute uptake and efflux (Solute carrier protein (*SLC28A3),* ATP binding cassette transporters (*ABCC1-ABCC2)), and* genes regulating inflammatory process (Human Leukocyte Antigen (*HLA*)) with anthracycline-related with cardiotoxicity in multiple independent studies.

Conclusions: These findings confirmed the importance of the genetic background of the anthracycline-related cardiotoxicity. By identifying the functional genetic variations responsible for cardiotoxicity, we may be able to improve our understanding of the potential mechanisms and pathways of treatment, paving the way for the development of new therapies to target these toxicities and individualization of the cancer treatment.

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P110: COMPUTATIONAL MODEL FOR INVESTIGATING THE TOXICITY OF CHEMICALS USED MAINLY IN COSMETIC PRODUCTS

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Introduction: Skin is the primer target organ that is affected by cosmetic products and immunotoxic effects on skin can be considered as allergic contact dermatitis and irritant contact dermatitis. Although allergic contact dermatitis is the main health problem that was seen after topical application of cosmetic products (1), chronic health effects are also a concern throughout lifetime chronic exposure to the cosmetic ingredients (2). Considering efforts of replacement animal testing with non-animal approaches (EU Cosmetics Directive, California Cruelty-Free Cosmetics Act), in silico tools for skin toxicity assessment are highly demanded. In silico methods also have a potency to give information about other human toxic health effects (3). In our study, we aim to investigate toxicity potency of selected chemicals by using in silico tools.

Materials and Methods: In our study, we have used ProTox-II (4) tool to predict the toxicity of the compounds present in the cosmetics. ProTox-II models are developed integrating cheminformatics-based machine learning (ML) models. ProTox-II contains 33 toxicity end-points models, and is freely available for the academic

community. The 33 models are divided into a five different classification nodes: (i) acute toxicity (oral toxicity model with six different toxicity classes); (2) organ toxicity (one model); (3) toxicological endpoints (four models); (4) toxicological pathways (12 models) and (5) toxicity targets (15 models)

Results: Isoeugenol, DNCB, Formaldehyde, PDD which shows strong EC3 values, are also predicted to be mutagenic and carcinogenic. DNCB which is found to be extremely strong under experimental observation is predicted to be active for four AOPs-Androgen Receptor Ligand Binding Domain (AR-LBD), Mitochondrial Membrane Potential (MMP), Phosphoprotein (Tumor Suppressor) p53, ATPase family AAA domain-containing protein 5 with strong confidence scores. Similarly, the compound-Paraphenylenediamine (PPD) is found to be active for two AOPs- Aryl hydrocarbon Receptor (AhR), Mitochondrial Membrane Potential (MMP) with strong confidence scores.

Conclusions: In summary, the analysis obtained in this study suggests that computational prediction results are in agreement with the experimental observation. Additionally, using a wide range of endpoints, *in silico* methods can help to get deeper insights into the mode of action behind such toxic responses.

Acknowledgements

This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors

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P111: CYTOTOXIC AND GENOTOXIC EFFECTS OF ALUMINUM COMPOUNDS IN ANTIPERSPIRANTS *IN VITRO*

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Introduction: Aluminum compounds have many areas of usage, and one of them is cosmetic products which are topically applied (especially antiperspirants). The widespread production and use of aluminum have led to focus on the effects of this element on human health. According to the results of the in vitro studies, aluminum compounds were non-mutagenic in bacterial and mammalian cells, while some aluminum compounds caused DNA and chromosome damages. Clastogenic effect of aluminum sulphate was also reported at high doses in in vitro studies. The International Agency for Research on Cancer (IARC), which evaluates aluminum in terms of cancer risk, has stated that those who are occupationally exposed to aluminum are more likely to encounter with lung and/or bladder cancer. Under normal handling and use conditions, however, the carcinogenic effect of aluminum has not been proven in humans so far (1). Several studies have been performed to evaluate the toxicity profile of aluminum on different cell lines, however few studies have focused on aluminum mediated effects on L929 or HeLa cells. Accordingly, investigating the cytotoxic and genotoxic effects of aluminum compounds on L929 and HeLa cells will provide new data about the safety of aluminum containing antiperspirant deodorants in humans.

Materials and Methods: In this study, aluminum chloride, aluminum zirconium and aluminum chlorohydrate were tested at 0.5, 5, 10, 50, 100, 500 µM concentrations. MTT assay was performed to investigate the cytotoxic effects and comet assay was used to reveal the genotoxic effects of aluminum compounds. All studies was performed in L929 and HeLa cell lines.

Results: Among the compounds tested in this study, only aluminum zirconium decreased the cell viability in L929 cells at concentrations of 100 and 500 µM, and its IC_{20} was 300 µM. IC_{50} values were not calculated for all tested Al compounds in both cell lines. According to comet assay results, aluminum compounds did not cause DNA strand breaks ($p>0,05$, one-way ANOVA) at all tested concentrations.

Conclusion: Our results demonstrate that aluminum compounds used in our study don't have cytotoxic and genotoxic effects on L929 and HeLa cell lines up to 500 µM.

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P112: ASSESSMENT OF CYTOTOXICITY AND ANTIOXIDANT PROPERTY OF METHANOL AND AQUEOUS EXTRACTS OF *SMILAX EXCELSA*

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Introduction: The genus *Smilax* L. belongs to the Smilacaceae family and comprises about 350 species. *Smilax* species are *distributed* especially in East Asia, South, and North America. *Smilax* sp. is widely used in traditional medicine in Asia and America for the treatment of many diseases such as rheumatism, psoriasis, anemia, and also as a tonic, diuretic, and diaphoretic. *Smilax excelsa* L., which has a local name called "melocan, dikenucu, kırçan, melevcan, merülcen, saparna", grown and consumed mostly in the Black Sea region in Turkey (1, 2). In this study, cytotoxicity and antioxidant properties of methanol and aqueous extracts from aerial parts of *S. excelsa* were characterized.

Materials and Methods: Methanol and aqueous extracts of aerial parts of *S. excelsa* were prepared. 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) assay was performed to determine the cytotoxic effects of the extracts on human lung adenocarcinoma cell line (A549) (3). Antioxidant activity was investigated using 2,2-di-phenyl-1-picrylhydrazyl (DPPH) free radical scavenging assay (3).

Results: The extracts were not cytotoxic on A549 cells based on the results of the MTT cell viability assay. No or low cytotoxicity was noticed up to 1000 µg/mL. Both aqueous and methanol extracts demonstrated significant DPPH radical scavenging activity compared to control. Concentration-dependent inhibition was observed. Methanol extracts exhibited higher antioxidant activity than aqueous extracts (IC_{50}=45,81 and 57,49 µg/ml, respectively).

Conclusions: Our data might serve as a basis for further experiments to explore the biological activities and phytochemical contents of this valuable plant.

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P113: SIMULTANEOUS DETERMINATION OF SOME ANTIFUNGAL PESTICIDES FROM HUMAN BIOLOGICAL SAMPLES BY HPLC

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Introduction: Today, in order to meet the food need arising with the increasing world population, the use of pesticides is widely common in many areas. Fungicide pesticides that used for killing fungi are the most economically important pesticide group. Fungicides are toxic due to their natural chemical structure and are difficult to biodegrade. Pesticides' residue levels on the crops in which fungicides are used can also cause toxic effects on humans. For these reasons, analysis studies to determine the amount of toxic pesticides in human biological samples are important (1). Therefore, the aim of this study is to demonstrate of a HPLC method for the simultaneous determination of thiram, epoxiconazol, hexaconazol, tebuconazol and diethofencarb pesticides from human serum and urine samples.

Materials and Methods: For HPLC study; an isocratic mobile phase with the flow rate of 1 mL min−1 that containing a mixture of methanol: ammonium acetate buffer solution (pH 6.3), 77.5:22.5 (v/v) at 25 °C using LUNA C18 (150 mm × 4.60 mm ID, 5 µm), (Phenomenex, USA) stationary phase with the detection wavelength of 220 nm was used for the separation. A 3600 µL aliquot of human blank serum and urine samples were mixed with sufficient amount from thiram, epoxiconazol, hexaconazol, tebuconazol and diethofencarb stock solutions. The final volume was completed to 10 mL acetonitrile and was vortexed for 3 min. The sample was centrifuged for 15 min at 5000 rpm. Hundred microlitre of supernatant solution was then transferred to a glass HPLC vial for analysis.

Results: The linearity of the proposed method in human serum and urine samples were determined by analysis of different concentrations levels of each pesticides (Fig. 1). The linear ranges were found 0.5–100.0 µg mL^{-1} in all matrix. To demonstrate of method sensitivity, limit of detection (LOD) values were calculated from the equations where the standard deviation of response and the slope of the calibration curve were used. LOD values were found to be between 0.03 and 0.08 µg mL−1 for serum samples, 0.01 and 0.12 µg mL−1 for urine samples. Moreover, when intra-day and inter-day RSD values (less than 4%) were examined, it was seen that repeatability results were obtained in all matrix.

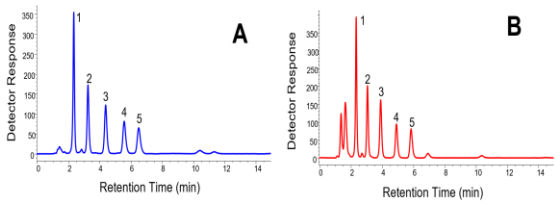

Fig 1. Typical HPLC chromatograms of human serum sample (A) and human urine sample (B), 1:thiram, 2: diethofencarb, 3: epoxiconazol, 4:tebuconazol, 5: hexaconazol

Conclusions: In this work, HPLC method was applied for the simultaneous separation and determination of some antifungal pesticides from human serum and urine samples. The developed method was rapid, highly feasible, reproducible and can be used in research and development laboratories as well as the quality control laboratories where the high throughput analysis is required.

Acknowledgements

This work was produced as a part of B. Bugra Barut's PhD thesis. The authors would like to thank Ankara University Scientific Research Projects Commission for financial support (Project No: 20L0237007)

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P114: A GQDS@PEDOT NPS-BASED ELECTROCHEMICAL TYROSINASE ENZYME BIOSENSOR FOR ADRENALINE DETECTION

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Introduction: An enzyme biosensor is a powerful analytical tool in which an enzyme as the biological sensing element is used to bind analyte(s) and a transducer for converting the recognition event into a measurable signal. Therefore, enzyme-based biosensors have great applications in drug and food analyses nowadays. Recently, graphene quantum dots (GQDs), with their versatile electrochemical and physical properties have attracted many attentions. In addition, poly(3,4-ethylenedioxythiophene) nanoparticles (PEDOT NPs) is a conducting polymer that has received enormous attention due to its high conductivity, good transparency, and stability. Therefore, these materials with such unique properties can be used for designing advanced electrochemical biosensors [1]. In this study, an electrochemical enzymatic biosensor is proposed for the detection of adrenaline. The biosensor design is achieved through immobilization of Tyrosinase (Tyr) in GQDS@PEDOT NPS platform on screen-printed electrodes (SPEs).

Materials and Methods: The surface of SPEs was activated with 0.1 M H_2SO_4 for 120 s at 3 mA using the chronopotentiometric method before each electrode modification. For electrode modification as a first step, GQDs nanomaterial suspension was dropped onto the working surface of the SPE and allowed to dry at room temperature. PEDOT NPs were dropped onto SPE/GQDs surface and allowed to dry at room temperature in the next step. In the final step, the Tyr enzyme was dropped on the surface of SPE/GQDs@PEDOT NPs. Tyr was immediately immobilized by crosslinking the nanobiosensor surface by adding a 0.25% GA crosslinking agent. Chronoamperometric (CA) determination of adrenaline was performed as follows: the prepared nanobiosensor platform was placed in an analytical cell containing 10 mL PBS with KCl (50 mM pH 6.5). 1.0 mM of the adrenaline was added after achieving steady-state current under stirring conditions within a working potential of −0.2 V at 300 rpm.

Results: For the determination of adrenaline, CA response of SPE/GQDs@PEDOT NPs/Tyr nanobiosensor were followed by continuous addition of adrenaline with different and increased concentrations under optimized conditions. The linear range was achieved in the range 0.2−12 µM for adrenaline. Limit of detection (LOD) and limit of quantification (LOQ) based on 3 s/m and 10 s/m principles, respectively, were calculated using a linear curve; where 's' is the standard deviation of the peak current of the lowest concentration of the adrenaline and 'm' is the slope of the related calibration curve. LOD and LOQ values were found as 0.065 µM, and 0.2 µM for adrenaline, respectively, using SPE/GQD@PEDOT NPs/Tyr nanobiosensor.

Conclusions: In summary, an amperometric electrochemical nanobiosensor based on Tyr, GQDs, and PEDOT NPs has been developed for the first time for adrenaline detection. The proposed nanobiosensor offers a wide linear response range for adrenaline. Furthermore, the optimized nanobiosensor exhibited high sensitivity and low detection limit, with good selectivity and stability for detecting adrenaline in a pharmaceutical dosage form.

Acknowledgements

The authors would like to thank VEM İlaç San. ve Tic. A.Ş, (Istanbul, Turkey) for chemical substances and their pharmaceutical dosage form support.

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P115: VOLTAMMETRIC STUDIES ON THE ANTIBIOTIC DRUG CEFPROZIL USING A GLASSY CARBON ELECTRODE

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Introduction: Cefprozil is an orally active, cephalosporin antibiotic. The range of antimicrobial activity of cefprozil is very broad (1). It is effective against gram-positive organisms and some gram-negative bacteria, including *Haemophilius influenzae*, *Moraxella catarrhalis*, *Escherichia coli*, *Klebsiella spp*. Cefprozil is used in the treatment of otitis media, upper and lower respiratory infections, and uncomplicated skin infections (2). In this study, cefprozil was investigated on a glassy carbon electrode using voltammetric methods.

Materials and Methods: All electrochemical experiments were performed using a Autolab Type II potentiostat/galvanostat with GPES 4.9 software (Metrohm, The Netherlands). A three-electrode system was employed including a glassy carbon working electrode, a platinum wire counter electrode, an Ag/AgCl reference electrode. All chemicals and reagents were analytical grade and used without any purification. Stock solutions of cefprozil ($1.0x10^{-3}$ M) were prepared with ultra-pure water. Phosphate, Britton-Robinson, and acetate buffer solutions were used as supporting electrolytes at different pH values.

Results: The electrochemical study of cefprozil was investigated on a glassy carbon electrode on the anodic direction. The dependence of the peak currents and the peak potentials on pH was examined in the range of pH 2.0-12.0. The optimum supporting electrolyte was determined as phosphate buffer at pH 2.0. Scan rate study showed that cefprozil was oxidized by adsorption control on the glassy carbon electrode. The linearity ranges were determined as 1×10^{-7} - 6×10^{-5} M (r = 0.994) for differential pulse stripping voltammetry and 2×10^{-7} - 8×10^{-5} M (r = 0.993) for square wave stripping voltammetry with the detection limits of 5.06×10^{-9} M and 1.12×10^{-8} M, respectively. In the repeatability study, it was concluded that the precision of the methods was good. Finally, to determine the accuracy of the methods used, recovery study was performed using pharmaceutical dosage form of cefprozil and good results were obtained without any separation.

Conclusions: We have described sensitive, simple, rapid, and selective voltammetric methods for the analysis of cefprozil in its pharmaceutical formulation.

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P116: EFFECTIVENESS OF *ACHILLEA GONIOCEPHALA* LOADED NANOPARTICLE ENCAPSULATION ON ANTIOXIDANT AND CYTOTOXIC PROPERTIES

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Introduction: The present study aimed to prepare *A. goniocephala* chloroform extract and evaluate antioxidant and cytotoxic effects. Then, the nanoparticles (NPs) were synthesized on the most efficient extracts and the biological activities of the free forms of the extracts were compared with the NPs forms.

Materials and Methods: Antioxidant capacities of 14 extracts (A-N) by column chromatography were found by FRAP DPPH and CUPRAC methods. Again, the cytotoxic activities of all fractions were evaluated on MCF-7 and HT-29 cell lines using the XTT cell viability assay (1). Chitosan-tripolyphosphate (TPP) NPs were formed using the ionic gelation method of two extracts, which show the most active properties because of biological activities.

Results: The particle size of the NPs synthesized from the two most efficient extracts was found between 274.12 and 296.25 nm. The extract-encapsulation and loading-efficiency of the most active NPs were 77.6± 0.04% and 7.76± 0.01% for F extract and 10.2± 0.02% and 1.39± 0.07% for H extract, respectively.

Conclusions: According to the results of the XTT cytotoxicity and all the antioxidant assays study, F and H extracts showed better antioxidant cytotoxic, and especially anticancer activity Hence, anticancer activity of chitosan NPs gave better results compared to unencapsulated extracts. Based on these results, it can be said that the preparation of NPs containing the chloroform extract of *A. goniocephala*, cell culture studies of

NPs containing the extract, and studies similar to this study will support future studies.

Acknowledgements

This study was supported by a grant of TUBITAK (SBAG-116S509)

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P117: SIMULTANEOUS QUANTITATION OF SULFUR METABOLITES IN CELL EXTRACT BY LC-MS/MS

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Introduction: Sulfur-containing metabolites play critical roles in cellular function. Changes in the levels and metabolism of sulfur compounds have been associated with various disorders such as cancer, neurodegenerative diseases, cardiovascular diseases, liver diseases and diabetes. The quantification of sulfur-related metabolites is essential for monitoring and diagnosing patients with disorders (1, 2). The main separation method used for the sulfur-containing metabolites from biological samples was reverse phase chromatography using C18 columns. However, these methods require a derivatization step to separate these polar metabolites *(3).* In this study, a new method is presented for the simultaneous analysis of metabolites in sulfur metabolism, which has a short analysis time and does not require a derivatization step.

Materials and Methods: A simple, specific, rapid and sensitive LC-MS/MS method has developed for quantitative analysis of sulfur contains metabolites (cystine, cysteine, methionine, glutathione, glutathione reduced, cysteamine, taurine, hypotaurine and serine). The chromatographic separation was carried out on a ZIC®-HILIC (100 x 4.6mm, 5 µm) column with the mobile phase composed of 0.1 % formic acid and 0.1 % formic acid in acetonitrile in gradient elution. MS/MS conditions were optimized by injection of 1 ppm of each metabolite in order to increase sensitivity. Quantification was performed using multiple reaction monitoring mode.

Results: Several chromatographic conditions with different stationary phases (C18, amino and HILIC) were tested in order to obtain a suitable separation with short analysis time. The best separation was obtained with HILIC column. The developed method was found selective, precise, accurate, sensitive, and robust with the validation studies.

Conclusions: A rapid, sensitive, and specific method was developed for the analysis of sulfur-containing metabolites in cell culture without derivatization.

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P118: DEVELOPMENT AN ANALAYTICAL METHODOLGY FOR ANALYSIS OFNAPROXEN SODIUM AT TRACE LEVELS in BIOLOGICAL SAMPLES BY HPLC-DAD

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Introduction: Naproxen sodium (NAS) is a non-steroidal anti-inflammatory drug used for the reduction of moderate to severe aches and pains. Naproxen is a nonselective COX inhibitor. As an NSAID, naproxen appears to exert its anti-inflammatory action by reducing the production of inflammatory mediators called prostaglandins (1). Common side effects include dizziness, headache, bruising, allergic reactions, heartburn, and stomach pain. Development of new analytical approaches is very important in order to follow toxicological and therapeutically effects of drugs. This study presents a simple and sensitive high-performance liquid chromatographic method with photodiode array detector (HPLC-DAD) for the determination of NAS (2). In addition, there several available methods to simultaneously separate NSAIDs by HPLC, but some lack suitable sensitivity. HPLC is a powerful technique for highly specific and quantitative measurements of low levels of analytes in biological samples.

Materials and Methods: A sensitive and easy applicable analytical method was developed for the Naproxen sodium drug residues in simulate urine and normal urine samples using magnetic solid phase extraction (MSPE) followed by high-performance liquid chromatography combined with

photodiode array (HPLC-PDA) detector. A new magnetic solid phase material was synhtezied and characterized in detail. And, HPLC method was also developed and validated.

Results: The quantitative data for Naproxen sodium were obtained via PDA detector at their maximum wavelengths of 219 nm and 256 nm, respectively. The calibration plots were obtained as linear for target molecules in the range with correlation coefficient of 0.9913. Experimental variables were investigated in detail, such as contact time, pH and electrolyte concentration, and the volume and type of desorption solvent. Under the optimized conditions, the developed method showed satisfactory reproducibility with relative standard deviations less than 3.5 % and LOD values were lower than 0.35 ng mL^{-1}.

Conclusions: The developed method was applied to urine samples successively. Recovery values were calculated by means of spiked samples and found in the range of 95.4-103.8 %. The synhtezied material and developed method have a potential to submit very applicable approaches for determination of NAS residues in urine samples.

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P119: ELECTROANALYTICAL ANALYSIS OF GUAIFENESIN ON POLY(ACRIDINE ORANGE) MODIFIED GLASSY CARBON ELECTRODE AND ITS DETERMINATION IN PHARMACEUTICALS AND SERUM SAMPLES

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Introduction: Guaifenesin [(R,S)-3-(2-methoxyphenoxy)-propane-1,2-diol], is an expectorant that is widely used to treat cough and congestion caused the common bronchitis, cold and other breathing illnesses. Guaifenesin provides thinner mucus, increments the lubrication of the respiratory tract (lungs, nose, and throat) and increases the removal of mucus. Also, it used in surgery owing to its additive effect on narcotics and its activity as a muscle relaxant (1).
Acridine orange (AO) (3,6-bis(dimethylamino)-acridine monohydrochloride) is a nitrogen-containing cationic dye, which is usually used in cell biology (2). Due to the aromatic structure of AO, it can be easily electropolymerized on the surface of solid electrodes to obtain poly(acridine orange) (PAO) film serving important catalytic activities to detect electroactive molecules such as uric acid (3), dobutamin (4), and rutin (2).

Materials and Methods: A three-electrode electrochemical cell was used for the experiments. It contained a (BAS, ϕ: 3 mm diameter) glassy carbon electrode as working electrode, a platinium wire as counter electrode and Ag/AgCl electrode as reference. All measurements by cyclic voltammetry and differential pulse adsorptive stripping voltammetry were performed using a computer-controlled Autolab potentiostat/galvanostat with Nova 10.0 software (Metrohm-Autolab, The Netherlands).

Results: The modified electrode was prepared electropolymerisation of monomer AO. Guaifenesin provided highly reproducible and well-defined irreversible oxidation peaks at +1.125 V and +1.128 V (*vs.* Ag/AgCl) in Britton-Robinson buffer solution at pH 7.0 and human serum samples, respectively, by differential pulse adsorptive stripping voltammetry. A possible oxidation mechanism was proposed for guafinesin. The linear response of peak current on the concentration of guaifenesin has been obtained in the ranges of 2.00×10^{-7} to 1.00×10^{-4} M in Britton-Robinson buffer solution at pH 7.0 and 4.00×10^{-7} to 1.00×10^{-4} M in serum samples, under optimized conditions. The precision of the method was detected by intraday and inter-day repeatability studies in the supporting electrolyte and serum samples media. The analytical applicability of the proposed method exhibited satisfying determination results for guaifenesin from pharmaceutical dosage forms (syrup) and human serum samples without any pre-separation procedure.

Conclusions: In this study, cyclic voltammetry and differential pulse adsorptive stripping voltammetry methods were used for voltammetric analysis of GUF in the pharmaceutical dosage forms and human serum samples. The presented method offered high sensitivity and selectivity for the analysis of GUF in pharmaceutical formulations and biological samples without the requirements of sample pre-treatment or time-consuming extraction and evaporation steps before to the analysis.

Acknowledgements

This work is supported by the Karadeniz Teknik University Scientific Research Foundation (Project Number: FAY-2018-7785

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P120: DEVELOPMENT AND VALIDATION OF HPLC METHOD FOR THE DETERMINATION OF IMIDUREA IN CREAM FORMULATION

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Introduction: Imidurea is one of the substance that used as a preservative in pharmaceutical preparations and cosmetic products to prevent microbial growth (1-3). In this study, simple, selective and fast high performance liquid chromatograpic method has been developed and validated for the analysis of imidurea used as anti-microbial agent in cream formulation.

Materials and Methods: The chromatographic separation was carried out on cyano CN (250x4.6 mm; 5 µm) column by using as mobile phase acetonitrile: water (25:75, v/v). The mobile phase flow rate was 1.0 mL/min. Imidurea was detected at 210 nm. The method was validated for system suitability, specificity, linearity, limit of quantification, limit of detection, robustness, recovery, precision and accuracy.

Results: The calibration curve showed a linearity at 0.050-0.150 mg/mL range. The limits of detection and quantification were found to be 62.5 ng/mL and 125.0 ng/mL, respectively. Assay recovery of imidurea from cream formulation at 0.050, 0.100 and 0.125 mg/mL concentrations were evaluated. Intra-day and inter-day relative standard deviation values were calculated to be less than 0.900%. The mean recovery was calculated as 101.86%.

Conclusions: The validated method was successfully applied to the determination of imidurea in cream formulation (Figure 1). The developed method is simple, fast, selective, reproducible and reliable can be used safely routine determination of imidurea in pharmaceutical preparations and cosmetic products.

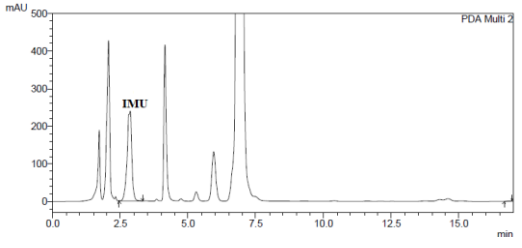

Fig 1: Chromatogram of imidurea (IMU) extracted from cream formulation (0.100 mg/mL)

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P121: DEVELOPMENT OF CE-MS METHOD FOR ANALYSIS OF TRIPTORELIN

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Introduction: Triptorelin is a synthetic decapeptide which, depending on the treatment protocol, may act as an agonist or antagonist at gonadotropin-releasing hormone receptors (GnRH), which causes the secretion of luteinizing hormone (LH) and follicle-stimulating hormone (FSH) from the pituitary gland. LH and FSH induce the synthesis of testosterone and estrogen. While the pharmacological antagonism of triptorelin at GnRH receptors is mainly used in the treatment of oncological diseases, lower doses and longer dosing intervals enhance its agonistic effect at these receptors, which is abused by athletes to achieve better sports performance or to prevent side effects caused by long-term anabolic use. As gonadotropin-releasing hormone and its analogs (buserelin, gonadorelin, triptorelin, etc.) increase testosterone levels in the body, they are referred to as growth promoters and were included in the list of banned substances in 2014 (1). This work aimed to develop a fast, sensitive, cheap, and ecological analytical method for the analysis of triptorelin.

Materials and Methods: The CE experiments were carried out on a CE Agilent 7100 system coupled online with Triple Quadrupole tandem mass spectrometer. Two characteristic m/z transitions were applied in the MRM mode for unequivocal identification and quantification of triptorelin: 656.5 → 328.3 (quantification transition) , and 656.5 → 249.0 (identity confirmation transition). Chemicals were purchased in analytical quality from Merck (Darmstadt, Germany), Sigma Aldrich (Steinheim, Germany), and Fluka (Buchs, Switzerland). Fused silica capillary (ID 50 µm) with the lenght 700 mm was used for all measurements.

Triptorelin was purchased from Caslo (Lyngby, Denmark).

Results: From the tested background electrolytes the best separation conditions (migration time, signal intensity, S/N ratio, separation efficiency) were obtained with the use of 20mM HFo (pH= 2,69). The separation was performed in a cationic separation regime, the applied voltage was set at +25 kV. Electrokinetic injection of the sample was characterized by enhanced intensity of the analytical signal. Such approach led to more then 10 times higher analytical signal when compared to measurements with convenient hydrodynamic injection. The limit of detection was predicted at 50 ng/ml concentration level.

Conclusions: A CE-MS method for determination of triptorelin was developed. Crucial separation and detection parameters were optimized. Favourable separation and operation parameters were obtained. The presented method represents an effective tool for monitoring of triptorelin in model samples.

Acknowledgements

This study was supported by the projects VEGA 1/0463/18 and KEGA 027UK-4/2020.

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P122: APPLICATION OF MAGNETIC SOLID PHASE EXTRACTION FOR PARABEN RESIDUES IN COSMETIC SAMPLES

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Introduction: Parabens have been used as preservatives for long time. Currently, they are widely used preservatives, mainly in cosmetics and pharmaceuticals, but also in food commodities and industrial product (1,2). Human exposure to parabens occurs mostly through the consumption of personal care products containing parabens. Parabens are used in cosmetic industry by various formulations because they have no perceptible odor or taste, are effectively pH neutral, and do not discolor or harden. Main member of this family are methyl paraben (MP), ethyl paraben (EP), propyl paraben (PP), butyl paraben (BP), and benzyl paraben (BzP). These are the most commonly used members, independently and in combination with each other or other biocides. In the last decades, some negative comments about parabens have been published in several studies (3).

Materials and Methods: The method to be developed is aimed to be based on magnetic solid phase extraction (MSPE), which has been widely used in the literature in recent years and offers application practicality. A new magnetic material was synthetized by means of a well-known procedure including a chemical reaction between Fe(II) and Fe(III) ions in basic medium. The developed extraction method provides a very efficient and green sample preparation technique by successfully integrating the advantages of easy phase separation and reusability. PP and BzP were successfully determined with a Luna omega C18 column under isocratic elution mode by means of acetonitrile, methanol, and 0.1% TFA as the mobile phase.

Results: The calibration plots were obtained as linear for both target molecules in the range of with 10-750 ng mL^{-1} with correlation coefficient of 0.9952. Experimental variables were investigated in detail, such as adsorption time, pH and electrolyte concentration, and the volume and type of desorption solvent. Under the optimized conditions, the developed method was applied with satisfactory reproducibility with relative standard deviations less than 4.2 %.

Conclusions: Analytical validation of the developed method was carried out by model solutions including PP and BzP molecules at 200 ng mL^{-1}. Finally, application of method was performed by means recovery tests in cosmetic samples.

Acknowledgements:

This study has been supported by The Scientific and Technological Research Council of Turkey (TUBİTAK) as a 2209-A project with the 1919B012001349 code.

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P123: DEVELOPMENT OF A NOVEL HPLC-DAD-FLD-MS METHOD FOR THE SIMULTANEOUS DETERMINATION OF FIVE ANTICANCER DRUGS

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Introduction: Palbociclib and ribociclib are newly registered anticancer agents often used in combination with anastrozole, letrozole or fulvestrant for the treatment of breast cancer (1). Novel anticancer medicines are potential candidates for therapeutic drug monitoring in plasma in order to avoid drug-related toxicities and enhance therapeutic outcomes (2). Therefore, it is desirable to employ a simultaneous high performance liquid chromatographic (HPLC) method for the selective determination of these analytes in a complex biological sample.

Materials and Methods: Several chromatographic columns were tested, the influence of mobile phase composition and pH was investigated, gradient elution steps, flow rate and column temperature were optimised. Detection was carried out using a diode-array detector (DAD), a fluorescence detector (FLD), and a mass spectrometer (MS).

Results: The optimal conditions were as follows: biphenyl column 4.6x150 mm, 2.6 µm, gradient elution with acetonitrile and water, both containing 0.1 % formic acid, as mobile phase, 25 °C column temperature and 0.5 mL/min flow. All peaks eluted within 12 min and adequate separation was accomplished, as presented in the table:

Name	Retention Time	USP Resolution	DAD absorption maximum (nm)	Main ion ESI+ (*m/z*)	Limit of detection (ng/mL)
Ribociclib	4.163		270	435.45	52.2
Palbociclib	4.911	15.0	366	448.41	39.98
Anastrozole	6.904	37.9	210	294.27	19.8
Letrozole	7.114	3.8	240	217.17	16.6
Fulvestrant	8.748	28.2	210	607.67	1.98

Conclusions: A selective and sensitive new HPLC-DAD-FLD-MS method was developed for the simultaneous determination of five anticancer drugs in human plasma.

Acknowledgments

This work has been fully supported by the Croatian Science Foundation under the project number UIP-2019-04-8461.

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P124: DEVELOPMENT OF FABRIC PHASE SORPTIVE EXTRACTION METHOD FOR DETERMINATION OF AZINPHOS-METHYL AND CHLORFENVINFOS PESTICIDES BEFORE HPLC-DAD ANALYSIS

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Introduction: Nowadays, fierce competition for the production of high quality and healthy agricultural products is a commonly discussed issue. Consequently, farmers use high amounts of pesticides to protect their products against pests and plant diseases. However, the usage of these compounds can result in harmful damages to the environment and may cause many human diseases such as Parkinson's disease, leukemia, asthma, and several types of cancer (1-3).

Materials and Methods: Fabric phase sorptive extraction was developed as an efficient, simple, and reliable method for the extraction of Azinphos-methyl and chlorfenvinfos residues before their analysis with high-performance liquid chromatography combined with photodiode array detector.

Results: The influence of some important factors on the extraction efficiency of azinphos-methyl and chlorfenvinfos was optimized as follows: volume of sample for each fabric phase, 35 mL; kind of salt, Na_2SO_4; concentration of salt, 5%, *w/v*; rotating time in adsorption step, 35 min; kind of elution solvent, methanol; and pH, 6. Moreover, fabric phase sorptive membrane was characterized by scanning electron microscopy and fourier transform infrared spectroscopy.

Conclusions: Ease of operation, high values of EF, suitable RSDs, and low LODs and LOQs are the main advantages of the current method. Finally, fabric phase sorptive extraction was performed on the real samples and its efficiency for adsorption of the analytes from complex matrices has been successfully proved.

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P125: DETERMINATION OF ORNIDAZOLE IN PHARMACEUTICAL DOSAGE FORMS USING BSA COATED FLUORESCENT COPPER NANOCLUSTER

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Introduction: Ornidazol, ORN, (1-(3-chloro-2-hydroxy)propyl-2-methyl-5-nitroimidazole or 1-chloro-3-(-2-methyl-5-nitroimidazole-1-yl)propan-2-ol) is member of third-generation nitroimidazoles which has antiprotozoal and antibacterial properties. Metal nanoclusters and quantum dots, which are luminescent materials, are very promising compared to organic molecules. Metal nanoclusters consisting of several to hundred atoms, they exhibit molecular-like properties such as the HOMO-LUMO transition, stereochemical activity, redox property, and intrinsic magnetism. In this study, a new method has been developed by using BSA coated copper nanoclusters (CuNCs) for the determination of ORN from pharmaceutical dosage forms. Characterization of CuNCs and experimental parameters were made with the following techniques: fluorescence, UV-Vis, FT-IR, TEM, zeta potential measurement and dynamic light scattering.

Materials and Methods: Synthesizes of BSA coated copper nanoclusters: Aqueous $Cu(NO_3)_2.3H_2O$ (1 ml, 20 mM) was added to BSA solution (5 mL, 15 mg/mL). The solution was stirred at room temperature for 5 minutes. The pH was adjusted to 12 by adding NaOH. Then it was stirred vigorously at 55 ° C for 7 hours. Synthesized nanoclusters were stored in the refrigerator. A Varian Cary Eclipse spectrofluorimeter and Specord 50 Plus spectrophotometer with a 10 × 10 mm quartz cuvette was used for the fluorescence and absorption measurements. Fluorescence measurements were carried out with the excitation wavelength of 325 nm in the presence and absence of ORN.

Results: The fluorescence emission of BSA coated CuNCs regularly decreased with the increasing concentration of ORN. A linear response was observed from 0.5 to 13.5 µg mL^{-1} ORN with a LOD value of 0.02 µg mL^{-1}. The quenching mechanism of fluorescence of BSA coated CuNCs by ORN is static and the quenching constant was found as 1.6×10^5 M^{-1}. All the obtained results confirmed that the possible quenching mechanism is based on mainly IFE and partially static quenching effect. High recovery values 99.0%-102.7 were obtained.

Conclusions: In this research, the water-soluble fluorescent CuNCs were synthesized based on the reduction of copper by BSA by one-pot hydrothermal process. The obtained results showed that fluorescence of NCs could be quenched due to the basicly IFE mechanism. The proposed method is simple, selective, sensitive, rapid, and cheap features.

P126: 2D-ITP-CZE-MS/MS METHOD FOR ANALYSIS OF SEROTONIN IN URINE

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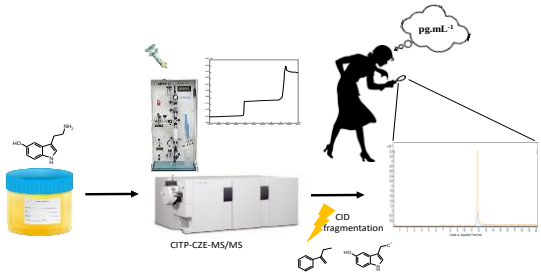
Introduction: Serotonin is a biogenic amine synthetized from amino acid L-tryptophan in enterochromaffin cells of intestinal mucosa. This molecule is predominantly located in the gastrointestinal tract (GIT), blood platelets and central nervous system (CNS). Alterations in 5-HT signaling have impact on inflammatory conditions of gut (e.g. inflammatory bowel disease), allergic airway inflammation or rheumatoid arthritis (1). This work deals with development and optimization of two-dimensional capillary electrophoresis (2D-CE) method with tandem mass spectrometry (MS/MS) detection for determination of serotonin in human urine.



Materials and Methods: A modular capillary electrophoresis analyzer EA-102 (Villa Labeco, Spišská Nová Ves, Slovakia), assembled in the column-coupling configuration of the separation unit, was used in this work for performing the ITP-CZE runs. This CE analyzer was coupled to the triple quadrupole mass spectrometry detector (Agilent Technologies, Santa Clara, CA) via an elution block developed by Foret et al. (2).

Results: The optimized composition of electrolyte systems was: a) ITP stage – leading electrolyte (LE) = 10 mM NH4Ac + 20 mM HAc, terminating electrolyte (TE) = 10 mM HAc; b) CZE stage – background electrolyte (BGE) = 20 mM HAc. The limit of detection was predicted at pg/ml concentration level.

Conclusions: Two dimensional capillary electrophoresis based on on-line combination of capillary isotachophoresis and capillary zone electrophoresis hyphenated with mass spectrometry is an effective and sensitive tool for serotonine determination at very low concentration levels in real biological samples.

Acknowledgements

This study was supported by projects VEGA 1/0463/18, KEGA 027UK-4/2020, 388 APVV-15-0585, VEGA 2/0088/18, VEGA 2/0150/19, and APVV-18-0302.

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P127: DETERMINATION AND POSSIBLE MECHANISMS OF FORMATION LUMACAFTOR DEGRADATION PRODUCTS WITH USING LCMS-IT-TOF

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Introduction: Lumacaftor (LUMA) is used as a combination therapy in cystic fibrosis, especially for homozygous for the F508del mutation patients (aged ≥12 years) (1). In the current study forced degradation products of LUMA were obtained, determined and possible formation mechanisms were proposed using high-resolution mass spectrometric data.

Methods: LCMS-IT-TOF analyses were performed using a hybrid IT-TOF mass spectrometer with ESI interface (Shimadzu, Japan). Analysis conditions were as follows: Nebulizing gas flow: 1.5 L/min; high voltage probe: -3.5 kV, drying gas pressure: 200 KPa, heat block temperature and CDL temperature: 200 °C. CID parameters are chosen 50% for collision gas parameter, 50% for CID energy and argon gas for CID. In addition, the detector voltage of TOF was set to 1.6 kV. The degradation conditions to which the active ingredient is exposed are made according to the ICH Q2 (R1) guideline (2).

Results: The results of forced degradation experiments revealed two new compounds in alkali and acid conditions, and three compounds in oxidation conditions. On the other hand, LUMA had no degradation in forced heat, moisture and UV-light conditions. Three of obtained degradation products had ionization in mass detector and their structure and possible formation mechanisms were proposed. The others had no ionization in mass detector, however detected using DAD detector.

Conclusion: LCMS-IT-TOF method was developed and examined for forced degradation products of LUMA. In addition to the above, new degradation products were added in to the literature.

Acknowledgements

This study was supported by a grant of Anadolu University Scientific research Projects Commission (Project No: 2005S039).

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P128: THE NOVEL APPROACH TOWARDS GRADIENT ELUTION HPLC METHOD DEVELOPMENT

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Introduction: Gradient elution HPLC finds its purpose in simultaneous analyses of solutes covering wide range of polarities. However, the instrument related factors, especially dwell volume,

are frequently responsible for fizzy transfer and short life cycle of the gradient elution method. Therefore, it is advisable to incorporate dwell volume into the optimization stage and avoid transfer related failures. The chemometric approach would enable selection of optimal chromatographic conditions for different HPLC instruments. The aim of this study was to propose and test this approach in gradient elution method's development.

Materials and Methods: The experiments were carried out on three chromatographic systems (UPLC, UHPLC and HPLC), while the separation was achieved on Kinetex C18 Core-shell column (100 mm × 2.1 mm, 2.6 µm particle size). Design of experiments was constructed in Design-Expert 11.0. Indirect modeling, grid point search and graphical presentations were done in Matlab 7.10.0.

Results: Dabigatrane etexilate mesylate and nine structurally related compounds were selected as suitable model mixture due to its complexity and polarity. Method development was supported with experimental design methodology, Placket – Burman for screening and D-optimal design for optimization purposes. Dwell volumes were included in the optimization phase and in this way the same optimal chromatographic conditions for all three instruments were selected.

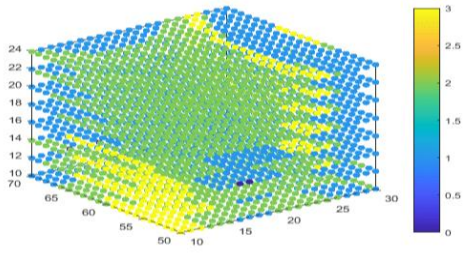

Fig 1: Experimental space overlap of instruments: yellow – 3 instruments, green – 2 instruments, light to dark blue 0 – 1 instrument

They included 10 mM ammonium acetate buffer with pH set to 4.9 using acetic acid, and acetonitrile. The components of the mobile phase were pumped into chromatographic system with flow rate of 400 µL min^{-1} in a linear gradient mode: at 0 minutes 24% (v/v) acetonitrile and 76% (v/v) of buffer solution, at 15 minutes 54% (v/v) acetonitrile and 46% (v/v) buffer solution. At 16 minutes the acetonitrile content was back to 24% (v/v) and 76% (v/v) of buffer solution. The re-equilibration time was set to 5 minutes. The examined chromatographic region is graphically presented and optimal conditions are noticed as the cross sections (yellow dots). The method was validated and confirmed its utility on all instruments.

Conclusions: The proposed methodology demonstrated its ability to predict joint optimal chromatographic conditions for instruments with different values of dwell volume. The potential was confirmed on complex model mixture and instruments significantly differing in dwell volume values. In this way the gap between developing and routine needs could be overwhelmed, followed by facilitated transfer of methods.

Acknowledgements

This study was supported by the Ministry of Education, Science and Technological Development of the Republic of Serbia (Project no. 451-03-9/2021-14/200161).

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P129: CHEMOMETRICALLY SUPPORTED OPTIMIZATION OF RP/WCX-HPLC METHOD

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Introduction: Active pharmaceutical ingredients (APIs) are often used in salt form, which is why the inclusion of weak cation exchange (WCX), in addition to reverse-phased (RP) hydrophobic interactions, could improve APIs' separation (1). Due to the limited knowledge about the RP/WCX bimodal system, the aim was to elucidate the experimental factors' influence on the retention of diverse ionized APIs, and provide efficient method optimization.

Materials and Methods: Acidic (ibuprofen (IB), aceclofenac (AC)) and basic (escitalopram (ES), aripiprazole (AR), atomoxetine (AT)) analytes were tested. Chromatography experiments were performed on Thermo Acclaim Mixed Mode WCX-1 (5 µm, 3x10 mm) column. Mobile phase consisted of ACN (30-50% (v/v)) and acetic buffer (pH 3.8 - 5.6; ionic strength (I) 20-40 mM). Temperature (T) was varied in range 30–38 °C. Variations of these factors were conducted according to Full Factorial Design 2^4. Optimization phase was executed by using face-centered Central Composite Design (Design-Expert 7.0.0).

Results: Screening results showed that %ACN had the greatest impact on analytes' retention factors (k), so increasing in %ACN caused a decrease in k. T had the same effect, but much less pronounced. Changes in mobile phase pH affected k, with the opposite effect on anionic and cationic

species. This is attributed to greater ionization of stationary phases' carboxylic groups at higher pH. As consequence, repulsive interactions with anionic and attractive interactions with the cationic analytes, are enhanced, vice versa (2). Ionic strength had much more influence on cationic analytes than on anionic ones. Due to all the above, all of four factors were included during optimization phase. Optimization goals were set so that k values were in range 1–10 (k(AR)<10, k(AC)>10, k(IB) in range) and selectivity of critical peak pair α(AT/ES)>1.3. All derived mathematical models were statistically estimated (R^2, adj. R^2, pred. R^2>0.95). Set of optimal conditions which is 47% (v/v) ACN, acetic buffer (40 mM, pH 3.8) and temperature 30 °C was determined using Derringer's desirability function.

Conclusions: Experimental parameters with significant influence on retention in bimodal RP/WCX system were evaluated, and upon that method was successfully optimized.

Acknowledgements

This study was supported by the Ministry of Education, Science and Technological Development of the Republic of Serbia (451-03-9/2021-14/200161).

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P130: SIMULTANEOUS DETERMINATION OF SULFACETAMIDE, BETAMETHASONE, METHYL PARABEN AND PROPYL PARABEN IN PHARMACEUTICAL EYE DROP USING RP- HPLC

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Introduction: Sulfacetamide (SFS) is a bacteriostatic topical antibacterial of the sulfonamide group (1). Betamethasone (BTM) is a topical corticosteroid with anti-inflammatory and vasoconstrictive action (1). Methyl paraben (MP) and Propyl paraben (PP) are widely used as an antimicrobial preservative in pharmaceutical formulations (2). These four compounds are pharmacologically active constituents found in an eye drop. There have been numerous publications describing various methods for the quantification of these compounds individually and in combination with other drugs (3, 4). This study involves the development of a novel reversed-phase (RP) chromatographic method for simultaneous determination of SFS, BTM, MP, PP present in a pharmaceutical eye drop.

Materials and Methods: Stock solutions of compounds were prepared in methanol. Standard solutions were prepared from stock solutions by dilution with mobile phase consisted of water and acetonitrile (55:45, v/v). Optimum chromatographic separations of SFS, BTM, MP, PP have been achieved within 7 minutes at flow rate of 0.5 mL/min by using Agilent Zorbax Eclipse XDB C18 (75 x 3.0 mm, 3.5 µm) column and detection was performed at 250 nm using UV detector.

Results: The method was validated in accordance with ICH guidelines. The linear ranges in the RP-HPLC method were 3.0 - 7.0 µg/mL, 1.5 - 3.5 µg/mL, 0.6 - 1.4 µg/mL and 0.6 - 1.4 µg/mL for SFS, BTM, MP and PP, respectively (Fig. 1). The LOD values were found as 0.37, 0.33, 0.021 and 0.012 µg/mL for SFS, BTM, MP and PP, respectively. Moreover, percentage recovery values of each compounds were determined between 95.75% and 104.82% in pharmaceutical eye drop.

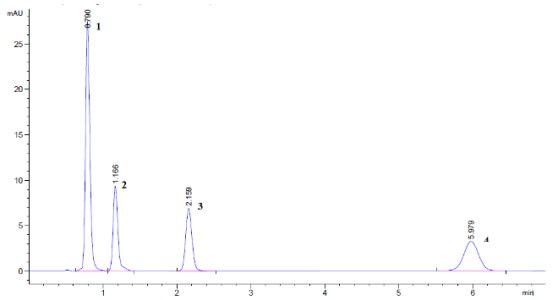

Fig 1. System suitability chromatogram 1: SFS, 2: MP, 3: PP, 4: BTM

Conclusions: In this study, RP-HPLC method is presented for the simultaneous determination of SFS, BTM, MP, PP in eye drop which offers numerous advantages, such as good resolution, accuracy, precision, selectivity and rapidity, ease of operation.

Acknowledgements

This work was produced as a part of Onur Demir's MSc thesis.

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P131: SIMULTANEOUS DETERMINATION OF A BINARY MIXTURE IN A DOSAGE FORM BY CHEMOMETRIC METHODS

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Introduction: In spectrophotometric studies, derivative spectrophotometric methods have been used for the quantitative resolving of binary mixtures. With the development of chemometric techniques many problems of the simultaneous analysis of two-component or multi-component mixtures have been solved (1–3).

Materials and Methods: This procedure is the mathematical basis of the BC method for two-component analysis. As explained here, this calibration model can be applied easily to resolution of the two-component or binary mixtures. The choice of optimum wavelengths plays an important role in the application of this method to a binary mixture analysis. The aim of the present work is the application of BC and MLRC methods to the resolution of a binary mixture containing hydrochlorothiazide and captopril without requiring a chemical pretreatment and a graphical procedure for the overlapping spectra.

Results: The absorption spectra of HCT, CTP and their mixture were observed in the spectral region 215–300 nm. Since the spectra of two drugs overlap in the working wavelength range, it is not possible to determine HCT, and CTP simultaneously in their mixture by conventional spectrophotometric methods. In order to solve this problem, the two methods (BC and MLRC) were applied.

Conclusions: The multivariate spectral calibration methods, two-linear regression-calibration (bivariate calibration (BC)) and multi-linear regression-calibration (MLRC) were applied succesfully for the simultaneous resolution of a binary mixture of hydrochlorothiazide (HCT) and captopril (CTP), which have closely overlapping spectra. The BC and MLRC methods which are very rapid, and easy to apply, yet not expensive, are powerful tools with very simple mathematical contents for the quantitative analysis.

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P132: APPLICATION OF CHEMOMETRIC TECHNIQUES TO THE CHROMATOGRAPHIC DATA FOR DETERMINATION OF ACTIVE COMPOUNDS IN TABLETS

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Introduction: New multivariate approaches have been applied to high-performance liquid chromatography (HPLC) with multiwavelength photodiode-array (PDA) detection. Multivariate calibration techniques such as classical least squares (CLS), and inverse least squares (ILS) was subjected to HPLC data for simultaneous quantitative analysis of synthetic binary mixtures and a commercial tablet formulation (1–3).

Materials and Methods: Chromatographic separation of the two active compounds, was accomplished by means of a 4.6 mm i.d. × 250 mm, 5 µm particle, Waters Symmetry C_{18} reversed-phase column and a mobile phase consisting of 60:40 acetate buffer–acetonitrile (v/v, 60:40).

Results: The CLS, ILS calibration plots for hydrochlorothiazide and losartan potassium were constructed separately by using the peak-area ratios corresponding to the concentrations of each active compound. These multivariate chromatographic methods were also applied to a commercial pharmaceutical dosage form containing HCT and LST.

Conclusions: The chemometric calibration methods were applied succesfully for the simultaneous resolution of synthetic binary mixtures and a commercial tablet formulation. The CLS and ILS methods are rapid, easy and powerful tools for the quantitative analysis of hydrochlorothiazide and losartan potassium mixtures and tablets.

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P133: STUDY OF SPONTANEOUS REGRESSION OF CANCER AND SUBSEQUENT USE OF ADVANCED ANALYTICAL METHODS

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Introduction: Spontaneous regression of cancer is defined as the partial or complete disappearance of a malignant tumor without any treatment or therapy which is considered significant impact on neoplastic disease (1). The mechanism of this phenomenon is still unknown and therefore it is a great challenge for our research team to use advanced analytical methods to help understand its nature. It is probably induced by an autoimmune response to hematopoietic cells to a combination of High-Dose Therapy and Autologous stem cells transplant with the development of aplastic anemia-like syndrome. We assume that research of metabolome and proteome will significantly clarify this phenomenon.

Materials and Methods: In the cell research we used PC3 cells, cultivated on DMEM medium, trypsin passaged and treated with: a) sera from patients with spontaneous tumor regression, b) mouse sera with anti-CAI antibody, c) pure anti-CAI antibody isolated from human erythrocytes. In the analytical research after collecting samples from cell research, we will use UHPLC in combination with detection techniques based on HRMS, MS/MS and commercial kit from Biocrates p180 for targeted metabolomics.

Results: In the cell research, we observe that the simulation of spontaneous tumor regression with three types of treatment has a positive significant effect on PC3 cells- presence of cytopathic effect.

Conclusions: An interesting fact in this area is the presence of antibodies against carbonic anhydrase I in the sera of some patients. It should be noted that the presence of these antibodies was correlated with an increased probability of survival. Our research team also proved this fact. In the future we will focus on metabolomics research, and we will try to understand the mechanism of spontaneous tumor regression, to discover new oncomarkers and develop prognostic or therapeutic tools for oncological diseases.

Acknowledgements

This study was supported by a grant of Comenius University UK/235/2021, grant VEGA 1/0463/18, grant APVV-18-0340.

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P134: SPRAY DRYER OPTIMIZATION OF TEA (*Camellia sinensis* L.) EXTRACT FROM DUST CHAMBER RESIDUES AND OVEN FIBERS COUPLED WITH ARTIFICIAL INTELLIGENCE

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Introduction: Tea is the second most commonly drunk liquid after water (1). The chemical components of tea leaves include polyphenols (catechins and flavonoids), alkaloids (caffeine, theobromine, theophylline, etc.), essential oils, polysaccharides, amino acids, lipids, vitamins (e.g., vitamin C), inorganic elements (e.g. aluminum, fluorine and manganese), etc. (2). Based on the established studies, classical regression tools have been widely used, but they have been generally associated with low accuracy levels, giving room to the development of the AI methods that are considered as accurate and non-linear intelligence tools (3).

Materials and Methods: Green tea samples were dust chamber residues and furnace fibers which were obtained from the ÇAY-KUR company. Thirteen trials were conducted with spray dryer and analysed with HPLC. Beside the spray dryer trials, a non-linear Adaptive neuro-fuzzy inference system (ANFIS) and a classical linear model (Multilinear regression analysis (MLR)) are used for the prediction of yield of extract from dust chamber residues and oven fibers using spray dryer optimization of green tea.

Results: As a result of the spray dryer experiments, 11.5% + 0.3 was the best yield obtained at 85-90^{o}C temperature and 9 ml/min flow rate. From the AI result, it can be observed that both the two models are capable of simulating the yield of extract from dust chamber residues and oven fibers using spray dryer optimization of tea.

Conclusions: According to our knowledge, this is the first study to demonstrate the value of green tea waste residues as a herbal raw material with sprey dryer. Generally, these green tea residues are considered as waste, but based on the results of this study, it is suggested that they can be evaluated as a raw material. The result further shows that ANFIS at the testing phase as non-linear model has outperformed the classical regression model MLR and increases its performance accuracy up to 7% using the determination co-efficient.

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P135: DETERMINATION OF THYMOQUINONE FROM BLACK CUMIN USING HPLC TECHNIQUE: A CHEMOMETRICS BASED APPROACH

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Introduction: Natural compounds have been reported to show promising properties in the prevention of various diseases and disorders. Thymoquinone (TMQ) is the major ingredient found in black cumin and other medicinal plants (1). This bioactive ingredient has been reported in traditional Arab herbal medicine for curing different diseases (2). In this study, both simple and ensemble machine learning techniques were used in modelling both the qualitative and quantitative properties of TMQ using high-performance liquid chromatography (HPLC).

Materials and Methods: The simulation involves the use of the concentration of the standard, the mobile phase, and flow rate as the corresponding input variables. Four performance indices were employed to determine the accuracy of the models namely; Correlation co-efficient (R), Root mean square error (RMSE), Mean square error (MSE) and determination coefficient (R^2).

Results: The results obtained indicated that ANFIS outperformed all the simple models with high performance skills. Moreover, at some instances there is need for boosting the performance of the single models and hence WAE, SAE, ANFIS-E and NNE were proposed. Finally the non-linear ensemble techniques ANFIS-E and NNE were abled to enhance the performance of the simple models.

Conclusions: In conclusion, it is crucial to note that these chemometrics are useful tools in predicting the retention time and peak areas of TMQ as well as other bioactive compounds in HPLC optimization method development, avoiding long and tedious separation optimization (3). In fact, it fulfilled the conditions of green chemistry, which is devoted in developing and constructing novel, cost effective as well as environmentally friendly techniques for chemical elucidations.

Acknowledgements

This study was supported by a Near East University.

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P136: SENSITIVE DETERMINATION OF KETOPROFEN AND IBUPROFEN IN URINE SAMPLES

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Introduction: Non-steroidal anti-inflammatory drugs (NSAIDs) are one of the most common pharmaceutical drug groups used by humans for major relief of inflammatory, chronic and acute pain. Ibuprofen (IBU) and ketoprofen (KET) are chiral drugs belong to this family (NSAIDs) with anti-inflammatory and analgesic activities, being IBU one of the most popular clinically used drugs in the world[1,2]. Sensitive determination of NSAIDs is a challenge due to generally found at very low concentrations in biological and environmental samples. Analytical approaches for determination of these IBU and KET drugs have been developed based on magnetic solid phase extraction and HPLC determination.

Materials and Methods: A new magnetic core-shell was synthetized and characterized in detail. Both drugs were successfully separated and pre-concentrated from urine samples. Determinations of drugs was carried out by gradient elution of methanol, acetonitrile, and 0.1 % TFA. Analytical variables of magnetic solid phase extraction and HPLC were studies and optimized step by step.

Results: The quantitative data for IBU and KET were obtained via PDA detector at their maximum wavelengths of 219 nm and 256 nm, respectively. The calibration plots were obtained as linear for both target molecules in the range with correlation coefficient of 0.9886 and 0.9958 for IBU and KET, respectively. Experimental variables were investigated in detail, such as contact time with the MPSE membrane, pH and electrolyte concentration, and the volume and type of

desorption solvent. Under the optimized conditions, the developed method showed satisfactory reproducibility with relative standard deviations less than 3.5 % and LOD values were lower than 3.48 ng mL^{-1}.

Conclusions: The combined procedure allows for enhancement factors ranging from 76 to 102, with pre-concentration values of 100 for both analytes. The chromatographic resolutions were approx. 12 for IBU (retention factor of 7,9) and KET (retention factor of 5.0), respectively, with a selectivity factor of 1.73. Finally, the validated method was successfully applied to simulate urıne and normal urine samples for the determination of these drugs.

Acknowledgements

This study has been supported by The Scientific and Technological Research Council of Turkey (TUBİTAK) as a 2209-A project with the 1919B012000900 code.

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P137: STABILITY-INDICATING RP-HPLC METHOD FOR ROBUST DETERMINATION OF LUMACAFTOR IN THE PRESENCE OF IVACAFTOR AND ANALYSIS OF ITS PHARMACEUTICAL FORMULATION

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Introduction: The U.S. Food and Drug Administration (FDA) approved lumacaftor (LUMA) /ivacaftor as combination therapy in 2015 for patients aged 12 years and older, who are homozygous for the F508del mutation (1). LUMA combination therapy has been used for cystic fibrosis disease. In this study, LUMA was analyzed by HPLC in the presence of ivacaftor in pseudo-tablet formulation as a pharmaceutical product.

Materials and Methods: Liquid chromatographic separation and quantitation were carried out using a F_5 reversed-phase column (100 × 4.6 mm, 2.7 µm I.D). A simple gradient run was applied; the mobile phase A and mobile phase B were composed with 0.1% (*v/v*) formic acid in water and 0.1% (*v/v*) formic acid in acetonitrile at 40°C. The flow rate was 1 mL/min, injection volume was determined as 10 µL. Compounds were monitored at their maximum absorbing wavelength about 216 nm. The method was applied on pharmaceutical formulation of LUMA.

Results: To determine the linearity of the developed HPLC method, LUMA standard solutions corresponding to 0.5- 20.0 µg/mL in methanol at 10 different concentration levels were prepared and analyzed. Regression coefficient was found to be 0.9977; limits of detection and quantitation values were found to be 200 ng/mL and 500 ng/mL.

Conclusion: HPLC method was developed for pharmaceutical formulation analyzes in the presence of Ivacaftor of LUMA. It is seen that there are very few studies done for LUMA analysis. In addition, there is no comprehensive method in final products and pharmaceutical formulations; therefore, the study will fill a great deficiency in the literature in terms of scope. The method was fully validated according to ICH Q2 (R1) guideline.

Acknowledgements

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P138: ANATOMICAL EXAMINATION OF *FERULAGO PAUCIRADIATA* BOISS. & HELDR.

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Introduction: Apiaceae is among the notable families of flowering plants (1). *Ferulago*, which is a medium size genus of Apiaceae family (3), shows natural distribution especially in the temperate regions of both hemispheres (4). In this study, the anatomical examinations of the fruit, leave, pedicel, peduncle and rays of *Ferulago pauciradiata* were performed.

Materials and Methods: Plant material was collected by Büşra CUMHUR and Hayri DUMAN from Beypazarı, Ankara. Voucher specimen is kept in AEF herbarium with the herbarium number AEF 28670. Plant parts were stored in 70% alcohol until microscopic examination. Cross sections were obtained by hand with a blade. Specimens were investigated in Sartur reagent. Photos of the preparations were taken using a microscope-linked Leica CME (Germany) camera with 4x, 10x, and 40x magnification.

Results: The stem is straight, glabrous and not round. The leaves has amphistomatic and anomositic stomata and spherical aggregations of yellowish acicular crystals (SAC). The pedicel is cylindrical and has crystal sand and SAC. Ray is partially cylindrical. The peduncle is cylindrical. Between 23-30 secretory canals in the endocarp are regular in order. The lateral rib is obtuse. SAC is seen in the mesocarp.

Conclusions: Our results differ in fruit structure and the number of secretory canals compared to a literature study related to fruit anatomy (4). Fruit anatomy and the number of secretory canals are significant for classification for the Apiaceae family, and examination of other plant parts will also provide important information.

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P139: ESSENTIAL OIL COMPOSITION OF ROOTS AND AERIAL PARTS OF *FERULAGO GLAREOSA* KANDEMIR & HEDGE

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Introduction: *Ferulago* W. Koch genus belongs to Apiaceae family and has various medicinal properties important medicinal properties due to their secondary metabolites. This genus is known with the name "Çakşır" in Turkey and 35 taxa of the genus grow naturally in our country. (1, 2). *Ferulago glareosa* is a rare endemic species growing naturally in Erzincan and known with the name "Sürekkişnişi". This species has interesting morphological characteristics compared to other members of the genus (3). In this study we examined the composition of the essential oil of the roots and aerial parts *F. glareosa*.

Materials and Methods: Essential oils of the grounded roots and aerial parts were obtained by hydrodistillation using a Clevenger type apparatus for 3h. Essential oils were analyzed both by GC-FID and GC-MS, simultaneously.

Results: The yield of the essential oils were 0.0.2% and 0.34% for the roots and aerial parts, respectively and 91.3% of the essential oil of the roots and 98.3% of the aerial parts were identified. Major components of these plant organs are given in the following table.

Table 1. Essential oil compositions of roots and aerial parts of *F. glareosa.*

Major components of the roots	%	Major components of the aerial parts	%
2,3,6-Trimethyl benzaldehyde	32.2	*α*-Pinene	33.7
		p-Cymene	14.8
Falcarinol	23.7	*γ*-Terpinene	13.2
Hexadecanoic acid	9.5	*(Z)-β*-Ocimene	12.4
2,5-Dimethoxy-*p*-cymene	5.9	Terpinolene	8.2

Conclusions: Obtained results are generally compatible with the essential oil profiles of different parts of various *Ferulago* species found in the literature, however the presence of falcarinol is quiet interesting for the genus.

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P140: EVALUATION OF *AEGOPODIUM PODAGRARIA* EXTRACTS IN TERMS OF CYTOTOXICITY AND ANTIOXIDANT PROPERTIES

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Introduction: *Aegopodium* L. (Apiaceae) is a genus that grown in Europe to western Asia and Siberia and contains approximately 11 species. *Aegopodium podagraria* L. grow naturally in Turkey. In the Black Sea region, Its local name is "mendek, keçiayağı" and is consumed as food. In traditional medicine, *A. podagraria* is used in gout, rheumatism, hemorrhoids, cancer, inflammation, and joint diseases (1-3). In this study, methanol and aqueous extracts of *A. podagraria* were evaluated in terms of cytotoxicity and antioxidant properties.

Materials and Methods: Methanol and aqueous extracts of aerial parts of *A. podagraria* were prepared. The cytotoxic effects were evaluated on lung (A549) cells using 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) assay (4). 2,2-di-phenyl-1-picrylhydrazyl (DPPH) radical scavenging assay was performed to quantify the antioxidant capacity (4).

Results: MTT cell viability results exhibited that methanol and aqueous extracts were not cytotoxic on A549 cells. No or low cytotoxicity was observed up to 1000 µg/mL. These extracts possessed significant DPPH radical scavenging activity compared to control. Aqueous extracts were more effective than methanol extracts with IC_{50} values of 66,05 and 72,16 µg/ml. The extracts were able to inhibit DPPH in a concentration-dependent manner.

Conclusions: As a consequence, *A. podagraria* has a significat antioxidant capacity without in vitro cytotoxic effect. Thus, our results might provide a basis for further experimentation to explore the biological activities and phytochemical content of this species.

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P141: INVESTIGATION OF ANATOMICAL STRUCTURE OF *PRIMULA VERIS* L.

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Introduction: *Primula veris* L. belongs to the genus *Primula*, is commonly known as 'çuhaçiçeği, tutya, ayıkulağı' in Anatolia. The decoctions prepared from its flowers and roots have been used as expectorant, diuretic, and mild sedative due to its saponin content (1,2).
The aim of our study was to examine anatomy of roots, leaves, stem, and flowers of *P. veris* which is generally used in herbal teas against the common cold.

Materials and Methods: For anatomical examinations, transverse and superficial sections were taken manually from plant parts preserved in 70% alcohol, mounted and stained in Sartur reagent. The samples were examined with light microscope (Zeiss 415500-1800-000) and photographed with a digital camera (Zeiss 51425).

Results: The root and stem cross sections were cylindrical. There were glandular trichomes with unicellular head and multicellular stalks on surfaces of both of them. The central cylinder of root carried starch grains. There were also glandular trichomes with unicellular head and multicellular stalks, as well as unicellular head and unicellular stalks on midrib and both surface of the leaves. The leaves were bifacial, cuticle on the upper surface was wrinkled while cuticle on the bottom surface was rippled. Calyx cuticle was rippled. There were glandular trichomes with unicellular head and multicellular stalks on calyx.

Conclusions: Roots, leaves, stem, and flowers of *Primula veris* were examined anatomically for the first time. These data will contribute to the taxonomic classification of the plant.

Acknowledgements

Bilge AYDIN would like to acknowledge the scholarship during her postgraduate program provided by the Turkish Scientific and Technical Research Council (TUBITAK).

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P142: CHEMICAL COMPOSITIONS OF ESSENTIAL OILS OF *OPOPANAX HISPIDUS* AND *OPOPANAX PERSICUS*

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Introduction: *Opopanax* W. Koch genus is included in Apiaceae family. The genus is distinguished with its compound basal leaves, glabrous fruits, yellow flowers, tall stem with glochidate and stellate hairs (1). The genus was used for epilepsy treatment (2), treatment of infertility in woman (3), hemorrhoid (3) and paralysis (4). Opopanax species contains coumarins (5) and essential oils (5). In this study, chemical composition of the essential oils of *Opopanax hispidus* and *O. persicus* roots were investigated.

Materials and Methods: Plant samples were collected and voucher specimens are kept in AEF. In the present work, essential oils (EOs) of roots of *O. hispidus* and *O. persicus* were obtained by hydrodistillation using a Clevenger apparatus. The essential oils were analyzed by GC-FID and GC-MS.

Results: Hexadecanoic acid (39.2%), linoleic acid (12.6%) and (*E*)-3-butylidiene phtalide were found as main constituents of the EO of *O. hispidus* root. The EO of *O. persicus* was characterized with hexadecanoic acid (28.0%) and cuparene (7.8%).

Conclusions: Chemical composition of the essential oil of *O. hispidus* fruits are found in the literature. In this study, chemical analysis of the essential oils of *O. hispidus* and *O. persicus* roots were investigated for the first time. While the main component of the two essential oils was hexadecanoic acid; chemical composition of fruit essential oil was quite different (5).

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P143: STEM AND LEAF ANATOMY OF FIVE *ARTEMISIA* L. SPECIES THAT GROW IN TURKEY

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Introduction: *Artemisia* L. genus (Asteraceae) represented with 27 taxa, including 21 species, 3 subspecies and 3 varieties in Turkey. The plants in this genus are popularly known as "kâbe süpürgesi, pelin otu, yavşan otu" (1). *Artemisia* L. species comprise mainly terpenoids, flavonoids, coumarins, sterols and acetylenes. Different species of *Artemisia* have several biological activities including antimalarial, cytotoxic, antihepatotoxic, antibacterial, antifungal and antioxidant activities (2). Since, taxonomy of the genus *Artemisia* is highly ambiguous and a challenging task, the aim of this study is make a comparative anatomical analyses of five different *Artemisia* species (*A. annua* L., *A. absinthium* L., *A. incana* (L.) Druce, *A. abrotanum* L. and *A. tournefortiana* Rchb.) grow in Turkey.

Materials and Methods: The voucher specimens were prepared and deposited in the Herbarium of Ankara University, Faculty of Pharmacy (AEF). The materials for anatomical study were preserved in 70% alcohol. Free hand cross sections were taken using sharp razor blades, stained and mounted in Sartur Reagent and Chloralhydrate (50%) solution. Anatomical structures of the stem and leaf of five *Artemisia* species were examined under the light microscope. Their detailed structures were illustrated with photographs.

Results: Results have shown that general stem and leaf anatomical features of Asteraceae family are mostly shared by all species. However, some characters could be considered as species-specific. In cross sections, the stems of all studied species have more or less irregular rounded shapes, but prominent ribs contained collenchyma tissue could be noticed only in *A. annua* stem. The leaves of *A. absinthium* and *A. incana* were covered by glandular and densely T-shape non-glandular trichomes on both sides however, *A. tournefortiana* had no hair at all. Morphology and distribution of secretory canals have been used as diagnostic characters in recognition of the species within this genus (3). With respect to the other

species investigated, there were highly apparent secretory canals located in both the stem (next to the endodermal cells) and the leaf (near to xylem) of *A. tournefortiana*.

Conclusions: Anatomical structure of leaves and stems of *A. tournefortiana and A. incana* growing in Turkey was demonstrated for the first time. Our results revealed that studied species are anatomically distinguishable between each other and also provided valuable features for better species identification and contribute to the anatomy of the genus *Artemisia*.

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P144: THE EFFECT OF CONTROLLED ATMOSPHERE COMPOSITION ON CHANGES OF TRITERPENIC COMPOUNDS OF APPLE PEEL SAMPLES DURING STORAGE

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Introduction: Apples are seasonal fruits, so it is important to prepare them properly for storage and to ensure storage conditions, that the chemical composition of biological active compounds and commercial quality of the apples remain unchanged (1). The aim of the study was to evaluate the variations in the qualitative and quantitative composition of triterpenic compounds in the apple peel sample stored in controlled atmosphere.

Materials and Methods: The study included 'Auksis' apple cultivars. The apple samples were placed in 8 controlled atmosphere chambers of the different O_2, CO_2 and N_2 compositions for 8 months. The apple peels were lyophilized. During the analysis of triterpenic compounds, lyophilisate powder was weighed, added to 10 mL acetone (100%) and extracted in a ultrasonic bath at a room temperature for 10 min. Triterpenic compounds analysis was performed by high performance liquid chromatography method.

Results: The triterpenic compounds were identified and quantified in the analyzed samples of the apple peel: corosolic, betulinic, oleanolic and ursolic acids. The predominant triterpenic compound in the apple peel samples was ursolic acid. Before storage the highest amount of ursolic acid (9.76 ± 0.15 mg/g DW) was determined. The quantitative composition of triterpenic compounds in apple peel samples stored in controlled atmosphere chambers varied. The highest amount of ursolic acid (9.25 ± 0.22 mg/g DW) was determined in apple peel samples stored in II variant (O_2-5%, CO_2-1%, N_2-94%) controlled atmosphere chamber, and did not differ statistically significantly ($p > 0.05$) from the ursolic acid content established in apple samples before storage. The lowest amount of ursolic acid (1.41 ± 0.10 mg/g DW) was found in apple peel samples stored in I variant (O_2-21%, CO_2-0.03%, N_2-78.97%) controlled atmosphere chamber.

Conclusions: The composition of the controlled atmosphere in the chambers influenced the changes in the quantitative composition of individual triterpenic compounds. The amount of corosolic, betulinic, oleanolic and ursolic acids were decreased 73.60%, 87.42%, 89.45% and 85.60%, accordingly during storage in I variant controlled atmosphere chambers.

Acknowledgements

The authors wish to thank the LSMU Science Foundation for the support of this study.

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P145: ANTIOXIDANT CAPACITY AND PHENOLIC COMPOSITION OF WHEAT GENOTYPE

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Introduction: Consumers who eat foods rich in phenolic compounds are at lower risk of diseases such as diabetes, heart disease and cancer caused by free radicals (1). The aim of this study was to evaluate the antioxidant capacity and phenolic composition of wheat samples used to make bread.

Materials and Methods: Kırik genotype was cultivated in Atatürk University Faculty of Agriculture area in dry and wet conditions in 2 consecutive years. The 70% ethanol extracts of samples were prepared and determination of total phenolic compounds of them were carried out using Folin-Ciocalteu's reagent. ABTS radical cation decolorization assay was used to measure the antioxidant capacities of the extracts (2-4).

Results: Wheat samples grown in the second year were higher in terms of antioxidant capacity and phenolic composition.

Conclusions: The bread made from wheat rich in antioxidant compounds can have a protective effect on chronic diseases.

Acknowledgements

Bilge AYDIN would like to acknowledge the scholarship during her postgraduate program provided by the Turkish Scientific and Technical Research Council (TUBITAK).

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P146: ANATOMICAL CHARACTERIZATION OF *CERINTHE MINOR* L. (BORAGINACEAE)

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Introduction: The genus *Cerinthe* belongs to Boraginaceae family and represented with 4 species in Turkey (1). *C. minör* L. is a usually perennial plant, light yellow petals and growing height of 80 cm, which known as "cücegözü" in our country (2). It has been reported that some of its subspecies are consumed as food in Anatolia and decoction prepared from aerial parts is used in the treatment of edema (3,4). The plant contains flavonoids, pyrrolizidine alkaloids and lactones (1). The aim of our study is to investigate the anatomical structure of the plant and to conduct taxonomic research.

Materials and Methods: For anatomical examinations, sections were be taken manually from plant parts in 70% alcohol, and the sections were be prepared with Sartur and chloral hydrate reagents. In this study, characteristic elements of *C. minor* such as stem, leaf, sepal, petal, pedicel, ovary, and stamen were examined anatomically. Their structures were illustrated with photographs.

Results: Leaf bifacial and almost all parts of the plant have parenchyma cells that carry starch. There are two types of stoma on the leaf. The stem is cylindrical, glabrous and crenate. Calyx has secretory cavity. There are papillary on the tip of the theca.

Conclusions: The anatomical properties given in this study provide description of *C. minör.* Our results should be useful in future studies about this genus.

Acknowledgements

Bilge AYDIN would like to acknowledge the scholarship during her postgraduate program provided by the Turkish Scientific and Technical Research Council (TUBITAK).

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P147: ESSENTIAL OIL ANALYSIS OF *HELICHRYSUM ITALICUM (*ROTH) G.DON WHICH IS CULTIVATED IN TURKEY

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Introduction: The *Helichrysum* genus is a large genus belonging to the Asteraceae family. Essential oils of this genus are widely used in phytotherapy, aromatherapy and perfumery (1). Since ancient times, extracts and essential oils from the *H. italicum* have been used in traditional medicine (2). Essential oil extracted from aerial parts, used as an antimicrobial, anti-proliferative purposes (3, 4). In this study; it is aimed to carry

out the essential oil analysis of *H. italicum* species which does not grow naturally in our country but is cultivated for commercial purposes. Thus, it is aimed to determine whether the essential oil of this cultivated plant can be used in treatment or cosmetics.

Materials and Methods: In our experimental study, essential oil was obtained from the *H. italicum*, cultivated in Tekirler Village of Nallıhan district of Ankara province, by water vapor distillation method. Essential oil analysis was performed with GC-MS technique and 94% of the oil composition was identified.

Results: The main compounds of essential oil in the analysis process; neryl acetate 12.9%, ar-curcumene 12.1%, β-selinene 11.1%, β-caryophyllene 7.5%, α- selinene 6.3% and italicene 5.1%. As a result, it has been determined that *H. italicum* essential oil cultured in Turkey has similarities with *H. italicum* essential oil grown in other countries in terms of its major compound relationships.

Conclusions: According to the results of our study, *H. italicum* essential oil grown in our country can be used for medical purposes.

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P148: BIOLOGICAL ACTIVITIES OF *PHLOMIS NISSOLII*

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Introduction: The genus *Phlomis*, which is belongs to the Lamiaceae family, comprises 12 species native to Turkey, Asia, Europe and North Africa. As reported in many studies, *Phlomis* genus has unique therapeutic and aromatic properties. According to the data obtained from traditional uses, *Phlomis* species have a characteristic taste and so can be traditionally comsumed as herbal tea. Also, *Phlomis* species are essentially used as stimulants, tonics, and diuretics, etc (Davis, 1982; Amor et al., 2009). In this present work, it was focused on the evaluation of the *in-vitro* enzyme inhibition and non-enzyme antioxidant activities of the extracts prepared from herbs of *Phlomis nissolii* with ultrasonic assisted method.

Materials and Methods: The antioxidant activities of dichlorometahne (DCM) and methanol extracts of *P. nissolii* herbs was evaluated by 1,1-Diphenyl-2-picryl hydroxyl (DPPH), 2,2'-azinobis-3-ethylbenzothiozoline-6-sulfonic acid (ABTS) radical scavenging assays, and Iron-chelating activity assay. Additionally, total phenol and flavonoid contents of the extracts were also investigated. The inhibitory activities of 80% methanolic and dichloromethane extracts obtained from *P. nissolii* herbs on tyrosinase associated with skin lightening effect were investigated.

Results: 80% methanol extract was found rich in of phenolic compounds (98.17± 3.13mg GAEs/g extract) than dichloromethane extract. Two extracts showed high total flavonoid compounds. The methanolic extract (49.5 %) showed higher DPPH radical scavenging activity while the methanolic extract (68.27%) showed better effect than the DCM extract (42.67%) in ABTS method. Both extracts were demonstrated strong Iron-chelating activities. Tyrosinase enzyme inhibitory activity of dichloromethane extract (38.02%) was more active than 80% methanol extract (13.78%).

Conclusions: Both extracts of different polarity are rich in phenolic compounds and have high antioxidant activities. Especially the high tyrosinase enzyme inhibition of DCM extract is cosmetically promising.

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P149: MICROBIAL TRANSFORMATION OF HESPERIDIN VIA HUMAN PROBIOTICS

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Introduction: Microbial transformations are green biotechnological processes where different microorganisms or their enzymes are used to produce new metabolites from defined substrates. This is common technique utilized in various disciplines including pharmacognosy for the

derivatisation of natural products (1). Hesperidin (hesperetin-7-O-rutinoside) is a member of the flavanone group of flavonoids and can be isolated from the bark of some *Citrus* species in abundance. Preclinical studies and clinical trials demonstrated therapeutical effects of hesperidin and its aglycone hesperetin in various diseases, such as neurological disorders, psychiatric disorders, and cardiovascular diseases and others, due to its anti-inflammatory, antioxidant, lipid-lowering, and insulin-sensitizing properties. There are many different microbial transformation studies in which hesperidin is involved. These studies are usually carried out with plant extracts and quantitative analysis of the metabolites they target (2, 3). This study aims the transformation of hesperidin by using microorganisms.

Materials and Methods: Within the scope of the study, hesperidin subjected to microbial transformation studies by using 5 different bacteria, which are *Bacillus subtilis* var. *clausii* ATCC 9799, *B. coagulans* Snz 1969, *B. subtilis* var. natto BN, *Lactobacillus fermentum* CECT 5716 and *L. rhomnosus* GG.

Results: Biotransformation of hesperidin took place via *Bacillus subtilis* var. *clausii* microorganism. The component isolated using the column chromatography method and was analyzed by NMR. The component identified as a hesperetin, the aglycone form of hesperidin.

Conclusions: Microbial transformation of hesperidin with *Bacillus subtilis* var. *clausii,* which is a human probiotic, occurred for the first time. The rutinoside moiety parted from the flavonoid by microbial transformation. In this way, hesperetin, which is less than hesperidin in nature, obtained by this method.

Acknowledgements

This study was financially supported as a Scientific Research Project (BAP 1901S001) by Anadolu University.

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P150: EVALUATION OF ANTI-INFLAMMATORY ACTIVITY OF FOUR *HERACLEUM* TAXA

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Introduction: *Heracleum L.* (Apiaceae) has been known as “Hogweed” and represented with more than 120 species over the World. It has been used as both food and medicinal plant especially for inflammation and related diseases for many years and utilized for gastrointestinal, respiratory, skin disorders as well as rheumatism, fever and headache in Turkish folk medicine (1-5). In present study, it is aimed to evaluate *in vivo* anti-inflammatory activity of aerial parts and roots of four *Heracleum* taxa growing in Turkey, *H. paphlagonicum* Czeczott*, H. sphondylium subsp. ternatum* (Velen.) Brummitt*, H. sphondylium subsp. montanum (*Schleicher ex Gaudin) Briq.*, H. sphondylium subsp. cyclocarpum* (C. Koch) Davis*,* and also support the traditional usage of *Heracleum* genus for inflammation.

Materials and Methods: Aerial parts and roots of the plant materials were dried at room temperature and powdered, separately. Powdered materials were extracted using dichloromethane and methanol, respectively. Extracts were tested by using carrageenan, PGE2 and serotonin induced hind paw edema models at 100mg/kg doses.

Results: Both extracts of *H. sphondylium* subsp. *cylocarpum* roots displayed the highest activity for carrageenan, PGE_2, and serotonin induced inflammation with range of 24.3-36.9%, 5.4-35.7% and 3.9-17.9% inhibition, respectively. Additionally, roots of *H. sphondylium* subsp.*ternatum* exhibited 8.8-25.4% and 19.6-34.2% inhibition on carrageenan and PGE2 induced edema by following *H.sphondylium* subsp.*cylcocarpum* roots. Inhibition range of reference compound, indomethacin, was 12.8-44.3% for carrageenan test and 2.7-41.3% for PGE_2 test.

Conclusions: Previous investigations have shown the coumarins in *Heracleum* were responsible for their anti-inflammatory activity (1). However, more study has to be carried out to reach active compounds from *Heracleum* and indicate the mechanism of action of these plants.

Acknowledgements

This study was supported by a grant of Ankara University-BAP (20B0237002)

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P151: IN VITRO CARBONIC ANHYDRASE ACTIVITY OF PAEONIA MASCULA (L.) MILLER SUBSP. ARIETINA (ANDERS.) CULLEN ET HEYWOOD EXTRACTS

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Introduction: Carbonic anhydrases (CAs; EC 4.2.1.1) are an essential family of metalloenzymes which catalyze the interconversion between carbon dioxide and bicarbonate (1). CAs express in all life being of three domains of life. Human CA II (hCA II) is found in mammalians and one of the targets for the treatment of many diseases (2).

Materials and Methods: *Paeonia mascula* (L.) Miller subsp. *arietina* (Anders.) Cullen et Heywood was identified by Dr. Ahmet Doğan and deposited in herbarium of the Faculty of Pharmacy, Marmara University with the number of 18080 for future reference. Soxhlet extraction method was performed to obtain petroleum ether, chloroform and ethanol extract of the plant. Then the bioactivities of these extracts on hCA II were performed according to the method of Verpoorte et al (3). After the Inhibition (%) studies, IC_{50} and K_i values were determined. Finally, total phenolic content was determined by Folin & Ciocalteu reagent method (4).

Results: The ethanol extract of the plant showed the highest inhibition characteristic according to inhibition (%) studies. IC_{50} and K_i values of the ethanol extract on hCA II was obtained as 2,8 µg/mL and 1,9 µg/mL, respectively. It was also determined that ethanol extract had highest total phenolic content compared to the other extracts.

Conclusions: Ethanol extract of the plant has showed high inhibition feature on hCA II. Phenolic compounds might be responsible for this activity.

Acknowledgements

This study was financially supported by University of Health Sciences Turkey-BAP (Project number: 2019/073).

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P152: INHIBITORY EFFECT OF SOME MEDICINAL PLANT EXTRACTS ON THIOREDOXIN REDUCTASE

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Introduction: Thioredoxin reductases (TrxR; EC 1.8.1.9) are selenium containing enzymes and found in all organisms. The level of the enzyme is 10-fold in tumorous cells than normal cells. TrxR is one of the key therapeutic target biomolecules for the design of novel anticancer drug due to its overexpression level in tumorous cells (1). We have aimed to investigate the bioactivities of different extracts of some medicinally important plants on TrxR.

Materials and Methods: Petroleum ether (PE), chloroform (CH) and ethanol (EH) extracts of *Achillea setacea*, *Achillea millefolium* subsp. *millefolium*, *Tanacetum macrophyllum*, *Paeonia mascula* subsp. *arietina*, *Plantago lanceolata* and *Hypericum perforatum* were obtained by Soxhlet extraction method. Then bioactivities of the extracts against TrxR, based on the NADPH-dependent reduction of the substrate, reacting with 5,5 -dithio-bis(2-nitrobenzoic acid) (DTNB) (1) were determined. TrxR activity was assayed at 412 nm absorbance by UV–Visible Spectrophotometer. The extract concentrations which caused 50% inhibition (IC_{50}) were obtained from the graphs of % activity-extract concentration.

Results: Bioactivities of 18 different extracts have been investigated. While seven extracts showed inhibitory activities against TrxR, other ones have no meaningful bioactivities. Seven active extracts with IC_{50} values on TrxR are given as (i) EH (75,34 µg/mL) and CH (52,99 µg/mL) extracts of *T. macrophyllum*, (ii) PE (92,62 µg/mL), CH (77,25 µg/mL) and EH (57,05 µg/mL) extracts of *P. lanceolata*, (iii) PE (59,6 µg/mL) extract of *P. mascula* subsp. *arietina*, (iv) EH (53,77 µg/mL) extract of *A. millefolium* subsp. *millefolium*.

Conclusions: This finding illustrates that the extracts as natural product possess good inhibitory features on TrxR. And further studies will be needed to determine the active substances of the extracts.

Acknowledgements

This study was financially supported by University of Health Sciences Turkey-BAP (Project number: 2019/073).

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P153: CHEMICAL COMPOSITION OF *HYPERICUM SCABRUM* L. ESSENTIAL OIL

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Introduction: The genus *Hypericum* L. belonging to Hypericaceae is represented in the Flora of Turkey by 94 taxa (1-3). *Hypericum* species are known as names of kantaron, peygamber çiçeği, kılıçotu, kanotu, kuzukıran and binbirdelik otu (4). *Hypericum* species have traditionally been used in Anatolia for centuries in the treatment of burns, infections, hemorrhoids, diarrhea and ulcers. Various parts of the this species are used in the form of ointments, decoctions and oily maserates. (5). The aim of this study is to determine the chemical composition of *H. scabrum* L. essential oil collected from Tokat, Turkey.

Materials and Methods: *Hypericum scabrum* collected in May, 2018 from Tokat, Turkey. The voucher specimen has been deposited at the Herbarium in the Anadolu Unıversity, (ESSE no: 15467), Eskişehir, Turkey. The plant material was identified by Prof. Dr. Yavuz Bülent KÖSE.
The essential oil from air-dried aerial parts was isolated by hydrodistillation using a Clevenger apparatus. Chemical composition of the oil was investigated using GC-FID and GC-MS techniques.

Results: *α*-Pinene (44.7%), sabinene (14.8%), *β*-pinene (5.5%), limonene (5.2%) and germacrene D (4.7%) were found as main compounds in the essential oil of *H. scabrum*.

Conclusions: To the best of our knowledge with this study, essential oil composition of *H. scabrum* was analyzed for the first time from Tokat in Turkey.

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P154: ANTIOXIDANT CAPACITY AND PHENOLIC COMPOSITION OF HUSKED BARLEY GENOTYPE

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Introduction: Free radicals lead to many diseases by causing DNA damage, lipid peroxidation and protein oxidation in tissues and cells. Foods with antioxidant effects help to protect people from oxidative stress-induced diseases (1). The aim of this study was to evaluate the effect of different conditions during cultivation on the antioxidant capacity and phenolic content of the husked barley genotype.

Materials and Methods: Tokak genotype was cultivated in Atatürk University Faculty of Agriculture area in dry and wet conditions in 2 consecutive years. Antioxidant capacities of 70%

ethanol extracts of these samples were determined by ABTS and DPPH free radical scavenging activities and phenolic content using Folin-Ciocalteu's reagent (2-5).

Results: It was observed that the antioxidant activity and phenolic composition of the husked barley samples grown in the second year were higher.

Conclusions: Foods with high antioxidant content can have a protective effect against free radicals.

Acknowledgements

Bilge AYDIN would like to acknowledge the scholarship during her postgraduate program provided by the Turkish Scientific and Technical Research Council (TUBITAK).

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P155: ESSENTIAL OIL COMPOSITION OF DIFFERENT PARTS OF *ASPHODELUS AESTIVUS* BROT. FROM TURKEY

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Introduction: *Asphodelus aestivus* Brot. is a member of Xanthorrhoeaceae family. There is only a single report on chemical composition essential oil of *A. aestivus* on an extensive search of literature (1). However, there are reports on the secondary metabolites and biological activity of the different extracts of *A. aestivus* in the literature (2). To the best of our knowledge, this is the first report on chemical composition of the essential oil of leaves and aerial parts (flower and stem) of *A. aestivus* from Turkey.

Materials and Methods: The plant material was collected during the flowering period on 1 May 2019 from Kayasehir district in Istanbul. The leaves and aerial parts (flower and stem) were subjected separately to hydro-distillation using a Clevenger type apparatus for 3 h, to produce essential oils. The constituents were determined by gas chromatography-mass spectrometry (GC-MS) in splitless mode.

Results: The essential oils yields of leaves and aerial parts (flower and stem) were very low. Forty-six constituents were identified in aerial parts oil (90.3%). The main compound was 1,4-Diisopropylnaphthalene (10.7%). The major groups of aerial parts essential oil consist of naphthalenes (42.2%) and *n*-alkane derivatives (18.7%). Seventy-six compounds were determined in leaves oil (84.4%). Phytol (13.7%) was found as the main compound in the leaves oil. *n*-alkane derivatives (30.5%), diterpenes (16.5%), and naphthalenes (12.1%) were dominated in the leaves oil.

Conclusions: The previous report indicated that the essential oil of the flower of *A. aestivus* had *n*-alkane derivatives as a major group (1). This study supports the results of the current study. However, naphthalenes and diterpenes were not found as the main group in the previous study. The essential oil composition of the current study showed differences in quality and quantity from the previous research.

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P156: ANALYSIS OF VOLATILE COMPOUNDS OF HAWTHORN TEA

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Introduction: Hawthorn tea is used for stomach disorders, stomach ulcers, bronchitis, shortness of breath, cardiovascular disease, diabetes, blood pressure-lowering, sedative, against cough, heart palpitations, and arteriosclerosis in folk medicine in Turkey (1). The aim of the current study was to analyze volatile compounds of hawthorn tea.

Materials and Methods: The hawthorn tea (flowers and leaves) was purchased from a local market. The essential oil of tea (100 g) was obtained from the Clevenger apparatus (3 h) with the hydrodistillation method. The yield of essential oil was <0.01% (v/v) which was very low. The oil was recovered with 1 mL *n*-hexane and preserved in an amber vial under −20°C until analyzed.

Results: The essential oil of hawthorn tea was analyzed with GC/MS and seventy-one compounds were identified comprising 91.5% of the oil. Nonacosane (20.8%) and phytol (14.8) were the main compounds of the oil.

Conclusions: In the current study, the essential oil of hawthorn had *n*-alkane derivatives as a dominant group and showed a similar chemical profile from the previous studies. However, phytol was not determined as the main compound in the previous reports.

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P157: ESSENTIAL OIL COMPOSITION OF *ONOPORDUM TAURICUM* WILLD. FROM TURKEY

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Introduction: *Onopordum tauricum* Willd. is a biennial plant that grows steppe, open scrub, and fallow fields of North Turkey and adjacent Central Anatolia. The plant is spread mainly in the Balkans, Romania, Cyprus, Crimea, and France (1). There is no report on the essential oil composition of *O*. *tauricum*. The purpose of this research was to determine the essential oil of *O*. *tauricum* for the first time.

Materials and Methods: The aerial parts of the air-dried plant were subjected to hydro-distillation for 3 h, using a Clevenger-type apparatus to produce the essential oil. The oil was kept with 1 mL *n*-hexane and in amber vials under −20°C until analyzed. The essential oil composition was analyzed by means of Gas Chromatography-Mass Spectrometry (GC-MS).

Results: Ninty-nine components were identified in the essential oil of *O*. *tauricum* that represents 82.2% of the oil. The main compounds were 9-hexacosene (14.2%) and hexahydrofarnesyl acetone (7.8%). The major group of oil was *n*-alkane derivatives.

Conclusions: To the best of our knowledge, this is the first report on the chemical composition of the essential oil of *O*. *tauricum*. In the present report, the essential oil of aerial parts of *O*. *tauricum* showed a similar chemical profile with *Onopordum* genus but there are quantitative differences in the major components of essential oils.

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P158: VOLATILE AND PHENOLIC COMPONENTS OF *Anthemis tinctoria* ssp. *tinctoria* GROWING IN TURKIYE

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Introduction: The genus *Anthemis* is the second largest genus of the Compositae family, represented by approximately 210 species worldwide. There are 83 taxa in our country, 54% of which are endemic. Several Anthemis species have been used as herbal medicine to treat diaphoretic, carminative, abdominal pain, kidney disease, psoriasis, fever, gastrointestinal system problems, hemorrhoids, and colds, etc. Some of these species showed various biological activities such as antioxidant, antiproliferative, antidiabetic, antiprotozoal, antispasmodic (1, 2). There are LC-MS and HPLC analyses and phenolic compound studies of *Anthemis* species (2). Phenolic content analysis of *Anthemis tinctoria* ssp. *tinctoria (Att)* with LC-MS reported. Essential oil (EO) analyses of *Att* was not mentioned. In this work, essential oil contents and phenolic compounds analysis of *Att* were investigated by GC-FID/MS and HPLC, respectively.

Materials and Methods: The plant (*Att*) used in the study was collected from the Karadeniz Technical University Campus (Ortahisar-Trabzon) at the height of 130 meters. Identification of the plant was made by Prof. Dr. Salih Terzioğlu, and herbarium number was given. EO analysis, extraction, and HPLC chromatographic analyses of phenolic compounds of *Att* were done according to the literature (3, 4).

Results: GC-FID/MS analyzes for the EO of *Att* revealed 51 natural compounds with in a ratio of 99.7%. Monoterpenes were the primary chemical class for the volatile organic compounds in the EO (36.1%, 13). Borneol (18.1%), camphor (14.9%), and *β*-pinene (11.3%) were the major components in the EO of *Att.* The phenolic constituent analysis for the methanol extract of *Att* gave sinapic acid (26.5 mg/g), benzoic acid (6.36 mg/g), syringaldehyde (2.74 mg/g) as the major compounds.

Conclusions: Terpenes and terpenoids were the main class of compounds in the EO analysis of *Att*. Sinapic acid was identified as the primary phenolic compound for the methanol extract of *Att*.

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P159: BIOLOGICAL ACTIVITY GUIDED INVESTIGATION OF ANTIOXIDANT EFFECTS OF *TANACETUM ARMENUM* (DC) SCH. BIP. EXTRACTS

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Introduction: *Tanacetum* L. species have been reported for different classes of secondary metabolites (1-4). In the present work *Tanacetum armenum* polar extracts have been subjected to comprehensive investigation for chemical profile and biological activities. The extracts have been subjected to HPTLC-bio-guiding investigation to point to substances with antioxidant activity that have been further analyzed by spectroscopic methods.

Material and Methods: The extracts of the aerial parts of *T. armenum* were obtained by maceration with *n*-hexane, methanol and water (TAHE, TAME, TAWE, respectively) and subjected to investigation for antioxidant, antidiabetic and antimicrobial activities. Free radical scavenging and lipid peroxidation inhibition effects were examined with TEAC, DPPH, β-carotene bleaching and ORAC tests. Antioxidant constituents were separated using optimized HPTLC conditions at normal phase mode and were visualized using NPR/PEG and DPPH reagents. Then they were concentrated and subjected to LC-MS/MS analysis for structural evaluation. The antidiabetic potential of the extracts was tested by α-amylase inhibition assay.

Results: The highest TEAC values were obtained for the TAWE (1.67±0.06 mM) and TAME (1.32±0.09 mM). The highest free radical scavenging effect (DPPH) was detected in TAWE (IC_{50} 0.06±0.005 mg/mL) and TAME (IC_{50} 0.10±0.01 mg/mL). The highest β-carotene/linoleic acid oxidation inhibition capacity was detected in TAWE (IC_{50} 0.28±0.03 mg/mL) and TAME (IC_{50} 0.42±0.04 mg/mL). The highest ORAC values were determined in TAWE (221.10±9.24 TEuM) and TAME (164.41±7.60 TEuM). The activity of α-amylase enzyme was moderate inhibited by TAME (%Inh. 33.92±2,38) and TAHE (%Inh. 33.84±1,10) extracts. Bioautographic HPTLC method with subsequent LC-MS/MS analysis allowed to identify 3,5-dicaffeoylquinic acid, 5-caffeoylquinic acid, luteolin glucoside and icariside b/5 as the main compounds responsible for the antioxidant activity of the extracts.

Conclusions: This study revealed that the aqueous and methanolic extracts of *T. armenum* have remarkable antioxidant activity with four bioactive compounds responsible for antioxidant potential of the extracts: 3,5-dicaffeoylquinic acid, 5-caffeoylquinic acid, luteolin glucoside and icariside b/5. The extracts of *T. armenum* have moderate antidiabetic potential.

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P160: ANATOMICAL CHARACTERIZATION AND ESSENTIAL OIL COMPOSITION OF *HYPERICUM SCABRUM*

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Introduction: *Hypericum scabrum* L. pertains to the genus *Hypericum*, is commonly known in Anatolia as 'mayasıl otu, kepir otu, kızılcık otu'. It is used against constipation and hemorrhoids, especially in the infusion prepared from its flowering branches (1-3).

Materials and Methods: For anatomical examinations, sections were taken manually from plant parts in 70% alcohol, and the sections were prepared with Sartur and chloral hydrate reagents. Essential oils obtained with Clevenger apparatus were analyzed by gas chromatography (GC)/Mass Spectrometry (MS) and GC-Flame Ionization Detector (FID).

Results: The secretory canals of aerial parts, flowers, and fruits get more monoterpene hydrocarbons, whereas the canals, existing in the roots are qualified by a higher presence of alkanes. The major compounds of essential oils of aerial parts, flowers, fruits, and roots were found such as α-pinene (17.5%), □-terpinene (17.4%), α-thujene (16.9%); α-pinene (55.6%), α-thujene (10.9%), □-terpinene (7.7%); α-pinene (85.2%); and undecane (66.1%), respectively. The root and stem cross-section is cylindrical. There are stomatas on the upper and lower surface of the leaf.

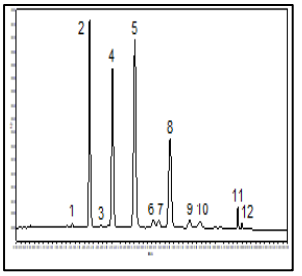

Figure 1. 1-Delphinidin-3-O galactoside, 2-Cyanidin-3-O galactoside, 3-Cyanidin-3-O glucoside, 4-Cyanidin-3-O arabinoside, 5-Peonidin-3-O galactoside, 6-Peonidin-3-O glucoside, 7-Malvidin-3-O galactoside, 8-Peonidin-3-O arabinoside, 9-Cyanidin, 10-Malvidin-3-O arabinoside, 11-Peonidin, 12-Malvidin

Conclusions: α-Pinene was found at the major compound of aerial parts, flowers, and fruits essential oils of *Hypericum scabrum*. Essential oils were found at secretory canals of the plant. These data will contribute to the taxonomic classification of the plant.

Acknowledgements

The authors acknowledge Prof. Dr Hayri Duman for his rewarding assist in diagnosing *Hypericum scabrum*.

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P161: ESSENTIAL OIL AND FATTY ACIDS INVESTIGATION OF *SCABIOSA PSEUDOGRAMINIFOLIA* HUB.- MOR.

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Introduction: The genus *Scabiosa* is widespread mostly in the Mediterranean region and the Near East (1). The phytochemical studies of a various *Scabiosa* species have clearly demonstrated the presence of triterpenes, triterpene glycosides, triterpene saponins, iridoids, monoterpenoid glucoindole alkaloids and flavonoids (2).

Materials and Methods: The plant material was collected in Sivas province of Turkey. The aerial parts have been subjected to hydrodistillation in Clevenger type apparatus to get the essential oil. The fatty acids were extracted with Fatty Acids Microextraction kit from the flowers and leaves separately for further trans-esterification with BF_3. MSD-SPME technique was applied to extract the volatiles from the flowers and leaves separately. Chemical compositions of the volatiles and fatty acids were investigated with GC-FID/MS techniques.

Results: In the essential oil of *S. pseudograminifolia,* hexadecanoic acid (30.2%), linalool (15.6%), dodecanoic acid (10.9%) and tetradecanoic acid (9.1%) were found as the main constituents. In MSD-SPME technique, the flower and leaf volatiles have some different profile due to extraction technique applied. (*Z*)-3-Hexenal (33.3 and 41.2%), 2-ethyl hexanol (5.1 and 3.8%), linalool (5.1 and 6.2%), and terpinen-4-ol (3.8 and 4.6%) were detected in the flowers and leaves, respectively. Benzaldehyde (%5.1) and (*E*)-anethole (2.3%) were found only in the flowers of *S. pseudograminifolia*. In the lipid profile of the flowers and leaves, nonadecanoic (14.6 and 23.4%), hexadecanoic (12.4 and 22.2%), linoleic (8.4 and 6.2%), linolenic (8.2 and 11.0%), and behenic (4.5 and 8.9%) acids were found, respectively.

Conclusions: In the scope of the study, essential oil and fatty acids composition of *S. pseudograminifolia* plant was investigated for the first time.

Acknowledgements

Authors thanks to Scientific Research Department of Anadolu University for financial supporting of the research project. (BAP No: 2103S009)

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P162: QUALITATIVE AND QUANTITATIVE COMPOSITION OF ANTHOCYANINS IN THE FRUIT OF AMERICAN CRANBERRY (*VACCINIUM MACROCARPON* AITON)

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Introduction*:* *Vaccinium macrocarpon* Aiton. (American cranberry) is a plant of the *Ericaceae* A.L. de Jussie (1). Cranberry fruit contain anthocyanins, which give the berries a red color and have anti-inflammatory and anti-cancer properties (2). The anthocyanin profile of cranberries is unique and can therefore be used to assess the identity and quality of cranberries and their products (3). The aim of the study was to determine the qualitative and quantitative composition of anthocyanins in samples of five cultivars of cranberries by UHPLC method, to compare the obtained data with the results of the pH differential method and to evaluate the antioxidant activity *in vitro* of the cranberry extracts.

Materials and Methods: The object of the study was cranberry fruit of cultivars 'Bawfay', 'Bergman', 'Holiston', 'Profilic' and 'Searles'. The samples of lyophilized cranberries extracted with 1% HCl solution in 70% (v/v) ethanol in the ultrasonic bath for 15 min at room temperature. Anthocyanin analysis was performed by UHPLC and pH differential spectrophotometric method. The antioxidant activity was evaluated by spectrophotometric methods using the FRAP assay and the $ABTS^{\bullet+}$ scavenging assays.

Results: Twelve anthocyanins were identified and quantified in cranberry samples (Figure 1). The total anthocyanin content was not statistically significantly different by the pH differential method and the UPLC method. The highest total amount of the anthocyanins was determined in fruit samples the 'Bergman' cultivar of American cranberry using UPLC 5.33 ± 0.49 mg/g and pH differential method 5.60 ± 0.23 mg CGE/g DW. The strongest antiradical activity *in vitro* evaluated by the ABTS assay was observed in American cranberry fruit extracts of the 'Searles' cultivar 607,30±30,69 µmol TE/g DW. When applying the FRAP assay, the strongest reducing activity *in vitro* was found in American cranberry sample extracts of the 'Searles' cultivar 375,75±5,65 µmol TE/g DW, and 'Bergman' cultivar 373,17±3,50 µmol TE/g DW.

Conclusions: Four anthocyanins dominate in cranberries: Cyanidin-3-O-galactoside, Cyanidin-3-O-arabinoside, Peonidin-3-O-galactoside, Peonidin-3-O-arabinoside. The total anthocyanin content was not statistically different by UPLC and spectrophotometric methods.

Acknowledgements

The authors declare absence of conflict of interest.

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P163: BIOLOGICAL ACTIVITIES OF THE EXTRACTS AND ESSENTIAL OIL FROM ANTHEMIS *KOTSCHYANA VAR. GYPSICOLA* (ASTERACEAE)

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Introduction: *The genus Anthemis, which belongs to the Asteraceae family, is widely spread in Europe, especially on the Mediterranean coast (1,2)*. Previous studies reported that *Anthemis* species have antioxidant, antimicrobial, antifungal, anticancer, antiseptic and wound healing activities (3,4). *Anthemis kotschyana* Boiss *gypsicola* taxon is a perennial, herbaceous and endemic subtype (5,6). Phytochemical or biological activity studies done on the species before are not available in the literature.

Material and Methods: The flowers (Fl), leaves (L) and roots (R) of *A. kotschyana* var. *gypsicola* were subjected to maceration to get sequentially hexane (HE) and methanolic (ME) extracts. Also, the plant has been hydrodistilled in Clevenger apparatus to get essential oil. The chemical composition of the essential oil was investigated with GC-FID/MS method. The essential oil and extracts were tested for antioxidant activities (DPPH, TEAC and □□Carotene bleaching assays) and inhibition of porcine pancreatic □-amylase enzyme. The total phenol content was spectrophotometrically determined with Folin-Ciocalteau Reagent, the flavonoids content was determined with $AlCl_3$ reagent.

Results: T-Cadinol (8.0%), camphor (7.8%), □-cadinol (5.7%), eudesma-4(15),7-diene-1-□-ol (4.7%), 1,8-cineole (4.5%), borneol (4.4%) and spathulenol (4.4%) were found as the main volatile constituents in the oil. Nonadecanoic (32.2-22.2%), linoleic (15.4-19.3%), linolenic (1.8-19.0%), stearic (4.5-7.5%), and oleic (5.0-8.3%) acids constituted the lipid profile of the plant. The yields of hexane and methanol extracts obtained from flowers, leaves and roots were calculated as 0,77% (HE_{Fl}), 5% (ME_{Fl}), 0,17% (HE_L), 5,07% (ME_L), 0,88% (HE_R) and 6,6% (ME_R) respectively. The highest

antioxidant activity and TEAC values were detected for ME_R (IC_{50} 0,14±0,06 mg/mL) and (1,1±0,08 mM), respectively. The highest inhibition values in □-carotene bleaching test was obtained for HE_L (0,18±0,02 mg/ml). The highest total phenol content was found in ME_{FI} and ME_R (79,08±2,94 mgGAE/g, 52,94±3,17 mgGAE/g, respectively). The highest total amount of flavonoids was found to be 39,10±2,14 mgRE/g in the ME_R.

Conclusion: The present work revealed that of ME_R of *Anthemis kotschyana* is the good source of effective antioxidants. Antidiabetic activity was not noteworthy.

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P164: BIOLOGICAL ACTIVITIES OF MALABAILA *NYDEGGERİ* (YILD. & DINÇ) MENEMEN

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Introduction: The *Malabaila* Hoffm. genus (Apiaceae) is distributed to Irano-Turanian phytogeographic area and represents by seven species in Turkish flora. Four taxa are endemic (1, 2) to Turkey including the *Malabaila nydeggeri* (Yıld. & Dinç) Menemen. This genus has traditionally been used both as a food and against disorders such as nail disorders, stomach disorders, intestinal diseases, intestinal parasites, hemorrhoids, and be analgesic (2, 3). This study mainly focused on the *in vitro* enzyme inhibitory effects of different aerial parts of *M. nydeggeri*.

Materials and Methods: In this study, the *in vitro* acetylcholinesterase (AChE), butrylcholinesterase (BChE) and tyrosinase (TYR) inhibitory activities of extracts obtained from leaves and fruits of *M. nydeggeri* extracts with two solvents of different polarities by soxhlet extraction 2 mg/mL stock concentration has been investigated using microplate spectrophotometric method. AChE and BChE enzymes are associated with memory problems, dementia and Alzheimer's diseases. TYR enzyme is related to melanin accumulation and skin spots.

Results: TYR inhibitory activity of fruit (42,29%) and leaf (48,06%) ethanol extracts were more active than hexane extracts. AChE inhibitory activity of ethanol (96,21%) and hexane (65,96 %) extracts obtained from fruits were more active than the extracts obtained from leaves. BChE inhibitory activity has not been detected for the fruit and leaf ethanol extracts at 2 mg/mL concentration. Significantly high anti-BChE activity of hexane (71.88%) and ethanol (71.43%) extracts obtained from fruits and hexane (60.77%) and ethanol (62.5%) extracts obtained from leaves was observed at a concentration of 1 mg/mL activity.

Conclusions: It was determined for *M. nydeggeri* that ethanol extracts showed higher biological effect than hexane extracts in related enzyme studies. *M. nydeggeri* fruit ethanol extract particularly showed higher inhibitory effect against all three enzymes than the other extracts. The fruit ethanol extract is promising both against memory disorders and lightening skin blemishes.

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P165: BIOLOGICAL ACTIVITIES METHANOL EXTRACTS OF *SMYRNIUM CONNATUM* BOISS. AND KOTSCHY

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Introduction: *Smyrnium* L. (Apiaceae) contains 6 taxa in the Turkish flora. *Smyrnium* taxa are frequently thought of as diuretic, depurative, and aperient plants, especially because of their roots (1). *S. connatum* is known as ''yabani kereviz'' in Turkey and its roots are used in the treatment of asthma. The most potent radical scavenging activity were found in its methanol extract by 2,2-diphenyl-1-picrylhydrazyl (2). In the present study was to determine the antioxidant and cholinesterase enzyme inhibition activities of *S.*

connatum extracts. Iron-chelating activities and 2,2'-azinobis-3 ethylbenzothiozoline-6-sulfonic acid (ABTS) cation decolorization test were used to determine antioxidant activity.

Materials and Methods: The methanol extracts prepared from *S. connatum* aerial parts (ASC) and *S. connatum* roots (RSC) with soxhlet extractor, ultrasound assisted and maceration methods were tested for their acetylcholinesterase (AChE), butrylcholinesterase (BChE) inhibitory activities and radical scavenging activity using ELISA microplate reader at 2 mg/mL stock concentration (3).

Results: The results of biological activity of *S. connatum* are given in the table.

Methods	AChE (percentage ± S.D.[a])	BChE (percentage ±S.D.[a])	ABTS (percentage ± S.D.[a])	Iron-chelating activities (percentage± S.D.[a])
ASC with soxhlet extractor	73,83±3,30	75,54±2,59	80,88±3,02	16,47±1,36
ASC with ultrasound assissted	93,10±2,09	83,81±7,63	86,29±0,57	81,38±0,70
ASC with maceration	74,68±3,83	69,96±4,60	88,24±0,06	79,25±2,20
RSC with soxhlet extractor	75,09±8,42	99,82±6,23	67,81±2,54	29,87±5,92
RSC with ultrasound assissted	83,64±0,90	61,87±2,03	86,95±0,26	68,65±2,60
RSC with maceration	56,45±4,10	62,83±2,91	86,45±1,31	66,24±4,12
References	99,10±1,18[b]	84,34±4,85[b]	87.51±0.17[c]	87.06±0.34[d]

a: Standard deviation b: Galanthamine hydrobromür (2 mg/mL) c: Ascorbic acid (2 mg/mL) d: EDTA (2 mg/mL)

Conclusions: The biological activity of the aerial parts of *S. connatum* generally was found to be more active than its roots of ASC except for iron chelating activity. We found that the enzyme inhibitors and antioxidant capacity we studied have positive results in treatment of neurodegenerative diseases.

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P166: ANNUAL OUTLINING OF NEUROBIOLOGICAL EFFECT OF THE LEAF AND BERRY EXTRACTS AND ESSENTIAL OIL OF *MYRTUS COMMUNIS* L.

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Introduction: *Myrtus communis* L. (Myrtaceae), locally known as mersin, has been reported to possess a wide range of biological activities. The plant has been recorded to be used against memory dysfunctions in Palestine. Taking of its folkloric use into consideration, aim of the study was to examine neurobiological activity of the plant against cholinesterases, linked to Alzheimer's disease (AD) as well as tyrosinase, a target enzyme for Parkinson's disease (PD).

Materials and Methods: *M. communis* was cultured in Western Mediterranean Agricultural Research Institute (BATEM, Antalya). The leaves were collected from BATEM each month annually (2018). The berries were gathered in September, 2018. The berry and leaf essential oils were obtained through hydrodistillation. The ethanol leaf and berry extracts along with the leaf essential oil of BATEM plant sample and a commercially available essential oil of *M. communis* obtained from Talya Ltd. (Antalya) were tested against cholinesterases (ChEs) and tyrosinase (TYR) using ELISA microtiter assays at 200 □g/mL.

Results: Our data indicated that most of the berries (black and white) and the extracts prepared from the leaf samples from black and white berry types collected throughout the year along with the essential oil displayed a marked inhibition (over 50%) against acetyl- (AChE) and butyrylcholinesterase (BChE), whereas they exerted low inhibition (below 20%) against TYR. The most active extracts against both AChE (87.26 ± 3.33%) and BChE (89.82 ± 5.27%) belonged to the leaf (white berry type) extract collected in January. The commercial essential oil showed a high inhibition towards both AChE (94.50 ± 6.25%) and BChE (95.47 ± 4.62%).

Conclusions: Our findings revealed that the leaves as well as the essential oil of *M. communis* possessed neurobiological effect through inhibition of ChEs. The essential oil showed a more promising inhibition. Particularly, in November and December, ChE inhibitory activity was the lowest. Besides the both extracts obtained from black and white berries of the plant had a very low inhibition against ChEs and TYR below 22%. This data emphasizes that *M. communis* leaves have an auspicious neurobiological effect through ChE inhibition as one of the underlying mechanisms for AD. However, it must be collected in appropriate time for preparing its standardized extract. Our cell culture studies in SHSY5 cells and analyses are going on.

Acknowledgements

This study is part of master thesis of N.E. progressing at the Institute of Health Sciences, Gazi University, Ankara, Turkey. The work was partially supported via the research budget assigned to I.E.O by Turkish Academy of Sciences (TÜBA).

P167: ANTIOXIDANT AND PROOXIDANT PROPERTIES OF *Citrus bergamia* Risso et Poiteau (BERGAMOT) USED FOR THE MANAGEMENT OF HYPERLIPIDEMIA

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Introduction: Hyperlipidemia is a major cardiovascular risk factor (1). Both patients and the scientific societies have an urge to search for natural products (2). This study was designed to evaluate the antioxidant and prooxidant capacities of antihyperlipidemic *Citrus bergamia* Risso et Poiteau juice and bergamot albedo fragment (BA) since there is scarce data on this issue.

Materials and Methods: Bergamot fruit juice (BFJ) and BA of two different commercial samples of bergamot fruit harvested in Antalya, Turkey (named as *Citrus bergamia* risso femminello and Native A41) were tested in our study. Bergamot fruit *Citrus bergamia* risso femminello was designated as 1; while Native A41 as 2. Methanol was used to prepare the extracts from BA. Freshly squeezed BFJ was filtered (BFFJ). Half was lyophilized then stored at -20°C (BFLFJ). The methods used for total phenolic (TPC) and flavonoid content (TFC) were Folin-Ciocalteu, aluminum chloride, respectively. Antioxidant capacity was measured with Iron (III) reduction capacity (IRC), free radical scavenging DPPH IC_{50}, TEAC. Hydroxyl radical scavenging activity was used for prooxidant capacity.

Results: TPC of BFLFJ-1 was as 130.35±8.91 mg GAE/g extract ($p< 0.05$); TFC of BFLFJ-2 was as 65.93±4.31 mg QE/g extract, ($p<0.05$). BFLFJ-1 had the highest IRC and TEAC (2.73±0.12 mM TE/g extract; 1.86±0.086 mmol TE/mg extract; respectively, $p<0.05$,). BFLFJ-2 had the lowest DPPH IC_{50} and TBARP **(**14.18±0.59 µg/mL; 0.144±0.015 µM MDAE; respectively, $p<0.05$). The highest TPC and TFC were in BFFJ-1 as 197.35±6.29 mg GAE/100 mL; and in BFFJ-2 as 94.14±1.39 mg QE/100 mL; $p<0.05$, respectively. The IRC of BFFJ-1 was 2.94±0.031 mM TE/10µL ($p<0.05$); TEAC of BFFJ-1 was 5.14±0.084 mmol TE/10µL, ($p<0.05$), and the DPPH IC_{50} of BFFJ-2 was 10.561±0.17 µL, ($p<0.05$) among the BFFJ samples.

Conclusions: BLFFJ got the highest attention due to high TPC, TFC, AO and low PO capacities. Our study highlights the necessity of clarifying the value of bergamot in this field with further studies.

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P168: ANTIOXIDANT AND PROOXIDANT PROPERTIES OF SELECTED HERBS USED FOR THE MANAGEMENT OF HYPERLIPIDEMIA

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Introduction: Hyperlipidemia is one of the major cardiovascular risk factors (1). Statins are safe for almost all patients (2). However, there may be problems in patient adherence, statin intolerance, doctors' attitude to low cardiovascular risk (3,4). In recent years, there is a search for herbs to aid hyperlipidemia treatment (5). There is scarce data on simultaneous evaluation of antioxidant and prooxidant capacities of antihyperlipidemic herbs. This study was designed to evaluate antioxidant and prooxidant capacities of antihyperlipidemic four herbal drugs.

Materials and Methods: Pharmacy and herbal market commercial samples of hawthorn (*Crataegus* L. spp.) flower-leaf (CFL), hibiscus (*Hibiscus sabdariffa* L.) flower (HF), green tea (*Camellia sinensis* L.) (GT) and myrtle (*Myrtus communis* L.) leaf (ML) were analyzed in our study. Methanol was used to prepare the extracts from dried CFL, HF, GT, ML. The methods used to detect total phenolic (TPC) and flavonoid content (TFC) were Folin-Ciocalteu and aluminum chloride, respectively. Antioxidant capacity was measured with Iron (III) reduction capacity (IRC), free radical scavenging DPPH IC_{50} capacity, Trolox equivalent antioxidant capacity (TEAC) methods. Hydroxyl radical scavenging activity method was used for prooxidant capacity.

Results: The highest TPC was in ML (135.35±3.46 mg GAE/g, $p<0.05$) whereas the highest TFC was in GT (48.76±0.69 mg QE/g, $p<0.05$) both maintained from pharmacy. GT showed the highest antioxidant capacity in IRC and TEAC assays (2.29±0.12 mM TE/g; and 2.32±0.07 mmol TE/mg, $p<0.05$). The lowest DPPH IC_{50} was identified in ML from pharmacy (6.95±0.08 µg/mL; $p<0.01$). GT from pharmacy was associated with the lowest hydroxyl radical scavenger activity (0.171±0.013 µM MDA equivalent, $p<0.05$).

Conclusions: GT from pharmacy got the highest attention due to high TPC, TFC, antioxidant and low prooxidant capacity. Our results highlight the necessity of clarifying the value of GT in this field with further studies.

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P169: AN EVALUATION ON THE KNOWLEDGE LEVEL OF PATIENTS AND FAMILY PHYSICIANS ABOUT HERBAL PRODUCTS

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Introduction: Since the beginning of history, herbs and extracts obtained from plants have been used for healing purposes. Recently, drugs obtained from plant extracts or mixtures are increasingly used in the treatment diseases in Western countries as well as in Eastern countries. Interest in herbal medicinal products is increasing in our country as well. However, researches conducted in the general public, physicians or pharmacists in order to determine their the level of interest are not considered sufficient. Conducting similar studies sheds light on the rational use of medicinal plants.

Materials and Methods: The aim of this study is to evaluate the knowledge levels of patients and family physicians about herbal products in the Ankara sample.578 patients and 24 family physicians participated in our field stud which was conducted as a questionnaire study. Patients were asked 30 and family physicians were asked 10 different questions.

Results: In the evaluation made from the research, it is seen that 61.4% of the patients used herbal products for prevention and treatment of diseases. 84.9% of the patients who applied to family medicine did research before using herbal products; It is seen that 72.7% of them share the herbal products they use with their doctors. 95.8% of family physicians think that they cannot provide sufficient consultancy services to their patients regarding the use of herbal products.

Conclusions: According to the results of the research, the knowledge level of physicians about herbal products is not at the desired level. And another striking finding was that the patient-physician relationship was weak in the use of herbal products. The knowledge level of physicians should be improved with education and publications.

Acknowledgements

This study is part of master thesis of T.E. progressing at the Institute of Health Sciences, Gazi University, Ankara, Turkey.

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P170: ANTIBACTERIAL ACTIVITY OF *TANACETUM PARTHENIUM* (L.) SCH. BIP. ESSENTIAL OIL

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Introduction: *Tanacetum parthenium* (feverfew) is called 'Beyaz papatya' in Anatolia used for the treatment of stomach ache, flu, shortness of breath, throat diseases, menstrual disorders, migraine, and fever (1) due to its antimigraine, antitumor, antileishmanial, antiparasitic, and anti-inflammatory activities. The essential oils of *T. parthenium* displayed variation in their major and minor compounds. The feverfew oil had camphor and *trans*-chrysanthenyl acetate as the main components (2). The aim of this study was to determine the chemical composition of essential oil extracted from aerial parts of feverfew and investigate the antibacterial activity of the oil.

Materials and Methods: The aerial parts of *T. parthenium* were subjected to hydrodistillation for 3 h using a Clevenger-type apparatus to produce the oil. The essential oil components were identified by gas chromatography-mass spectrometry via peak matching and by utilizing their retention indices on an Innowax FSC column. The antibacterial activity of the oil was investigated against two Gram-negative and three Gram-positive bacteria by disc diffusion method.

Results: Forty-six compounds were detected representing 94.1% of the oil. Camphor (37.2%), *trans*-chrysanthenyl acetate (22.3%), and camphene (10.9%) were found as major components in the oil. The disc diffusion results were 11 mm for *Bacillus cereus*, 9 mm for *B. subtilis*, and 8 mm for *Pseudomonas aeruginosa*.

Conclusions: Camphor and *trans*-chyrysanthenyl acetate rich oils were observed which is similar to the previous literature. The essential oil did not show activity against *Escherichia coli* and *Staphylococcus aureus*.

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variation of *Tanacetum parthenium* (L.) Schultz Bip. essential oils from Turkey, 59(4):177-184.

P171: CHEMICAL COMPOSITION AND ANTIBACTERIAL ACTIVITY OF ESSENTIAL OIL OF *CENTAURIUM ERYTHRAEA* RAFN.

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Introduction: *Centaurium erythrae* Rafn. (common centaury) is member of Gentianaceae family. The essential oils of *C. erythraea* are poorly studied concerning their biological effects. Menthol, carvacrol, tricosane, neophytadiene isomer III, toluen, menthone, and terpinen-4-ol were found as main components of *C. erythrae* (1-3). This study aimed to specify the antibacterial activity of the essential oil of *C. erythrae* from Turkey for the first time.

Materials and Methods: The essential oil of aerial parts of *C. erythrae* was obtained by Clevenger apparatus (3 h) with hydrodistillation method. The essential oil composition was analyzed by means of Gas Chromatography-Mass Spectrometry (GC-MS). The antibacterial activity of oil was evaluated against *Escherichia coli* ATCC 14169, *Bacillus subtilis* ATCC 19659, *Bacillus cereus* ATCC 14579, *Staphylococcus aureus* ATCC 25923, and *Pseudomonas aeruginosa* ATCC 27853 by disc diffusion method.

Results: Fifty-eight components were identified in the essential oil of *C. erythrae* that represents 92.9% of the oil. The main compounds were 2-methyl octane (8.1%), 1-tetradecanol (7.8%), caryophyllene oxide (6.5%), and 1-dodecanol (5.6%). The essential oil displayed antibacterial activity against *B. subtilis* (11 mm), *B. cereus* (10 mm) and *P. aeruginosa* (8 mm).

Conclusions: The chemical composition and antibacterial activity of essential oil of *C. erythrae* from Turkey was investigated for the first time. The essential oil composition of the current study showed differences in quality and quantity from the previous researches.

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P172: THE *IN VITRO* ANTIBACTERIAL EVALUATION OF COMMERCIAL ESSENTIAL OIL OF *HELICHRYSUM ITALICUM* FROM SERBIA

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Introduction: The essential oils and extracts of *Helichrysum italicum* (Roth) G. Don are mainly used for perfume compositions and cosmetic preparations, as well as for applications in aromatherapy. The most significant potential of essential oil has been associated with its regeneration properties of collagen, which used in anti-aging creams recently (1). In the current study, the commercial essential oil of *H. italicum* from Serbia was evaluated for antibacterial activity against Gram-positive and Gram-negative bacteria.

Materials and Methods: The chemical composition of essential oil was analyzed by means of Gas Chromatography-Mass Spectrometry (GC-MS). The screening of antibacterial activity of the oil was conducted by a disc diffusion test was determined against *Escherichia coli* ATCC 14169, *Bacillus subtilis* ATCC 19659, *Bacillus cereus* ATCC 14579, *Staphylococcus aureus* ATCC 25923, and *Pseudomonas aeruginosa* ATCC 27853.

Results: The main components of commercial oil were neryl acetate (18.9%), α-pinene (11.5%) and γ-curcumene (11.3%). The oil showed antibacterial activity against all test microorganisms except for *E. coli*. The inhibition zone diameters of oil were 13 mm for *B. cereus*, 12 mm for *B. subtilis* and 10 mm for *S. aureus* and *P. aeruginosa*.

Conclusions: The essential oil composition of the present study displayed a similar chemical profile from the previous studies. Also, the previous studies support the antibacterial activity result of the current research.

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P173: THE SUSCEPTIBILITY OF ESBL POSITIVE KLEBSIELLA SPP. STRAINS TO A NEWLY ISOLATED VB_K1 BACTERIOPHAGE

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Introduction: Extended-spectrum β-lactamase (ESBL) producer *Klebsiella* among the six drug-resistant microorganisms for which new therapies are urgently needed. Furthermore, ESBL positive Klebsiella infections cause serious morbidity and mortality in humans, increasing healthcare costs and treatment burden (1). Alternative or complementary therapies for these infections are required. Bacteriophages are defined as bacterial viruses and they show specific effects to their specific target bacteria. The objective of this work was to isolate potentially therapeutic bacteriophage against to ESBL positive Klebsiella strains. We also determined the in vitro susceptibility of 38 previously characterized ESBL-producing *Klebsiella spp.* to a newly isolated bacteriophage.

Materials and Methods: One ESBL producer Klebsiella strain was used as host for phage isolation and water samples were collected from river in Ankara. Spot test method was applied to determine the possible presence of phage after phage enrichment (2). To confirm the presence of the lytic phage in the filtrate, double layer agar method was applied to spot test positive samples (3). The susceptibility of the harvested phage was determined using in vitro spot test. 38 clinical ESBL positive *Klebsiella spp.* strains were used for this analysis. All strains were spread evenly on the LB agar plate. After drying, 10 µL of the phage culture of 10^8 PFU/mL was dropped onto the overlaid top agar. After cultured for 18 h at 37 °C, the presence or absence of a lysis zone was evaluated (4).

Results: The vB_K1 phage produced visible plaques on the bacterial lawns 1 mm diameter in the initial screening using plaque assay. The susceptibility of ESBL positive *Klebsiella spp.* strains to this phage was determined as 73.7%.

Conclusions: It was proved that a newly isolated phage vB_K1 is very effective to *Klebsiella spp.* strains. However, in vitro bacteriophage susceptibility of characterized isolate is an initial and encouraging development.

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P174: EXAMINATION OF IMMATURE GRANULOCYTE (IG) VALUES COMPLETE BLOOD COUNT IN PATIENTS WITH ACTIVE PULMONARY TUBERCULOSIS

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Introduction: According to the World Health Organization (WHO), 1 in 4 of the world's population is infected with tuberculosis (TB) bacillus (1). Bacillus is located in the droplets of an active TB patient, a latent or active infection occurs when these infected drops are taken by inhalation (2). Bacilli, which can easily settle in the middle of the lung and in areas close to the pleura, forms a very small burn in this area. Neutrophils and leukocytes appear first in the area of combustion, and over time macrophages multiply (3). In this study, immaturate granulocyte (IG) parameters are evaluated in patients who develop active lung TB and how the immune system responds to the disease early with these values.

Materials and Methods: IG values obtained from whole blood count of 154 patients admitted to Mersin University Medical Faculty Hospital between 01.01.2016 – 01.01.2021 and diagnosed with active pulmonary tuberculosis were retrospectively examined.

Results: All patients included in the study had culture positivity in the Löwenstein-Jensen assay with at least 1 solid medium tuberculosis culture. The average age of 154 retrospectively evaluated patients was 50.92 (18-88 years). 36 (23.37%) of the cases are female and 118 (76.63%) are male. IG reference values obtained from the whole blood count were determined as 0-0.09 x10^3/µL and IG% as 0-0.6. The IG value in 23 (14.93%) and IG% value in 33 (21.42%) of the total samples were higher than the reference.

Conclusions: Evaluating the response of the immune system against bacillus in patients with TB infection can offer important contributions before and during treatment of the disease. High IG values obtained from a whole blood count are an important marker for clinicians to start emergency

treatment. For this reason, IG values have an important place and the correlation between TB-IG should be examined with further studies.

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P175: PRODUCTION OF THE HEMAGGLUTININ SURFACE ANTIGENIC PROTEIN OF INFLUENZA A VIRUS AS A SOLUBLE FORM IN MICROORGANISMS

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Introduction: Influenza A viruses, which cause frequent recurring flu outbreaks in humans, are enveloped viruses and carry an eight-part single-stranded RNA genome (1). Influenza viral hemagglutinin (HA) and neuraminidase (NA) proteins are important for the recognition of the virus by the immune system because they are located on the viral membrane. For this reason, inactivated viruses or purified HA and NA surface antigenic proteins are used as vaccines. Both proteins are glycosylated after being synthesized in the host cells. HA proteins have a role in the attachment of the virus to the cells (2). In this work it was aimed is to clone the gene encoding the influenza A virus HA protein into plasmid vectors fused with other genes and to synthesize the HA protein in soluble form in *Escherichia coli* and *Pichia pastoris.*

Materials and Methods: The ful- length HA (HA0) gene or a part of the gene coding HA1 domain of Influenza A/WSN/33 (H1N1) type virus was amplified with polymerase chain reaction. These fragments were fused with the sequence encoding non-variable regions of human IgG antibodies in an intermediate plasmid vector. The fused genes (HA0-Fc and HA1-Fc) were cloned into the plasmid vectors expressing in *E. coli* and *P. pastoris.* The resultant recombinant plasmids were transformed into *E. coli* and *P. pastoris*. The growth curves of transformants were evaluated and the recombinant proteins synthesized in the cells were analyzed with SDS-PAGE/Silver Staining.

Results: For the production of recombinant protein in *E. coli* cells, four different vectors, carrying the T7 promoter (pET-14b-HA0-Fc and pET-14b-HA1-Fc) or the Lac promoter (pLacI-HA1-Fc and pLacI-HA0-Fc), were obtained. It was observed that the growth rate of *E. coli* BL21(DE3) and *E. coli/*Mach1 was significantly decreased after transforming with the plasmids coding HA0-Fc under the control of T7 promoter or Lac promoter. In contrast, the cells transformed with plasmids coding HA1-Fc fusion protein were grown at close rate to the control cells. SDS-PAGE/Silver staining assays showed that HA1-Fc fusion proteins were synthesized at a higher level in bacteria than that of HA0-Fc proteins. In *P. pastris* transformed with pPinkα-HA0.Fc and pPinkα-HA1.Fc plasmids, it was shown that the HA0.Fc and HA1.Fc fusion genes were integrated in the yeast genome by using PCR. However, the expression of the recombinant proteins was not detected with SDS-PAGE analysis.

Conclusions: The result showed that the full-length viral HA proteins synthesized in cells are highly toxic to host bacteria, even when synthesized as fusion with another protein. In contrast, the HA1 domain of the HA protein can be efficiently produced in *E. coli* cells as fusion with human IgG Fc. However, it was observed that the expression system used in the study was not suitable for the recombinant production of viral HA proteins in *P. pastoris* cells.

Acknowledgements

This work was partially supported by a grant from The Scientific and Technological Research Council of Turkey (grant number: 112S518).and a grant from the scientific research foundation of Marmara University (grant number: SAG-C-YLP-080715-0324)

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P176: EVALUATION OF SERUM DEATH RECEPTOR 4 AND CCL5 LEVELS IN BREAST CANCER

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Introduction: Breast cancer is major cause of death related to cancer among women. A study in breast cancer shows that changes in serum levels of TRAIL and in expression of death receptors can be associated with the prognosis (1). Additionally, it is highlighted that CCL5, trigerring cancer microenvironment formation, take part in development and progression of cancer (2). In our study, it was aimed to evaluate serum death receptor (DR4) and CCL5 levels in patients with breast cancer.

Materials and Methods: Our study group includes 62 patients with breast cancer and 62 healthy individuals in the Department of General Surgery, Gazi University Medical Faculty Hospital. Serum levels of DR4 and CCL5 were measured at 450 nm using commercial ELISA kits. Data has been evaluated in SPSS 20.0 package program.

Results: Serum DR4 levels in breast cancer patients were found to be significantly higher than in the healthy control group ($p<0.01$). Although serum levels of CCL5 measured in patients were higher than in control, it was observed no significant change between patient and control groups ($p>0,05$). It were observed that correlation between TRAIL levels measured in previous study and CCL5 ($p<0,01$).

Conclusions: It is thought that increased DR4 levels in breast cancer patients may be associated with an induced extrinsic apoptotic pathway in the cancer pathophysiology. Relationship between CCL5 and TRAIL in our study support the thesis that increasing TRAIL levels may induce CCL5 production (3).

Acknowledgements

This study was supported by Gazi University Scientific Research Projects (02\2020-01).

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P177: LACK OF ASSOCIATION BETWEEN VARIATIONS ON TOLL-LIKE RECEPTOR GENES AND BREAST CANCER IN MERSİN, SOUTHERN TURKEY

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Introduction: Breast cancer has been identified as the second type of cancer diagnosed among women worldwide. Breast cancer is a type of cancer that occurs as a result of genetic changes in cell groups that make up breast tissue. Cancer cells have distinctive features compared to normal cells. At the onset of the disease, it is believed to be the result of an accumulation of genetic damage resulting in activation of protooncogens and inactivation of tumor suppressor genes (1). The pathogenesis of breast cancer and a significant portion of breast cancer risk are thought to occur due to complex interactions and combinations between multiple environmental and genetic factors (2). Genes such as BRCA1, BRCA2, TP53 and ATM, which show a hereditary predisposition to breast cancer, have been identified. Genetic polymorphisms determined in these genes are very common in the general population (3). In recent years, the potential of genetic polymorphisms for breast cancer risk assessment has become increasingly evident and has been used as a marker (4). In the light of the available information, we aimed to investigate whether T399I and D299G polymorphisms are associated with coronary artery disease in the TLR-2 and TLR-4 genes, which is thought to be risk factors.

Material and Methods: In our study, those who applied to Mersin University Medical Faculty Hospital Oncology Department, were diagnosed with breast cancer as a result of routine examinations (n=102) and who were accepted as healthy (n=101) who were not diagnosed with breast cancer were included. The variation was determined using the Tetra-Primer ARMS PCR methodology.

Results: There was no significant difference in the polymorphisms of T>C (rs3804099) on TLR2 gene, and A>G (rs4986790) on TLR4 gene among case and control groups.

Conclusions: This study suggest that both of these polymorphisms of the TLR2 and TLR4 genes does not constitude a risk factor for susceptibility to breast cancer in a sample of Mersin population.

Acknowledgements

This study was supported by a grant of Mersin University Scientific Research Projects Unit (2019-3-TP2-3819).

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P178: CHEMICAL, ANTIOXIDANT AND ANTIMICROBIAL PROPERTIES OF *Alburnus tarichi* ROE PROTEIN HYDROLYSATE

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Introduction: The protein hydrolysates with antioxidant and antimicrobial potential have become a theme of great interest for pharmaceutical industry. On the other hand, chemical composition of fish protein hydrolysates is significant in nutrition perspective of human health (1). Hence, in the present study proximate and amino acid compositions, antioxidant and antimicrobial activities of *Alburnus tarichi* roe protein hydrolysate was estimated.

Materials and Methods: Roe protein hydrolysate was prepared from defatted *A. tarichi* roe powder using Protease N. For chemical analysis of protein hydrolysate, the level of total protein, total lipid, moisture, ash, and amino acid composition was analysed. For determination of antioxidant activity of hydrolysate, DPPH radical scavenging, hydroxyl-radical scavenging, and reducing power assays were performed. Antimicrobial activity of hydrolysate were analyzed by well diffusion method followed by Schillinger and Luke (2).

Results: Protein, lipid, moisture, and ash content were found to be 87.24±0.1, 0.72±0.04, 8.79±0.3, and 7.01±0.09%, respectively. Glutamic acid, aspartic acid, lysine, leucine and alanine were found to be the most dominant amino acids, whereas, cysteine was found to be the lowest amino acid in roe protein hydrolysate. The IC_{50} value of roe protein hydrolysate for DPPH radical and hydroxyl-radical scavenging activities were 54.33 µg/mL and 77.02 µg/mL, respectively. The reducing power of *A. tarichi* roe protein hydrolysate was analysed, the optical density values of roe protein hydrolysate and gallic acid at 700 nm were 0.45±0.03 and 1.14±0.09, respectively. Roe protein hydrolysate had shown maximum zone of inhibition against *Klebsiella pneumoniae* (11.1±0.30 mm) followed by *Salmonella enterica* (10.7±0.46 mm), *Proteus mirabilis* (10.1±0.35 mm) and *Candida albicans* (8.7±0.34 mm).

Conclusions: The results demonstrated the importance of amino acid composition in determining the bioactive potential of the peptides. The results showed that roe protein hydrolysates of *A. tarichi* was proved to show good effect on antioxidant and antimicrobial activities and can be used a source for nutraceuticals and pharmaceuticals.

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P179: PROTECTIVE EFFECTS OF CURCUMIN AND NARINGENIN ON LIVER DAMAGE CAUSED BY COPPER NANOPARTICLES

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Introduction: Copper nanoparticles (CuNP) are ideal products to reduce production costs by replacing more expensive metals compared to itself. The increase in the frequency of use of copper nanoparticles results in an increased exposure of humans to this substance. (1). Curcuma longa L. (Turmeric) is a tropical herb used as a spice and coloring agent. Turmeric consumption reduces the risk of developing cancer types and helps protective biological effects in humans. This effect is thought to be due to the curcumin substance in its structure. (2). Naringenin is one of the dihydroflavanoids and has beneficial effects such as anticancer and antimicrobial found in citrus species and some edible fruits such as tomatoes. (3). In our study, the possible effects of different doses of curcumin and naringenin on the application of copper nanoparticles on rats, oxidative stress and inflammation were investigated in the liver.

Materials and Methods: In this study, 42 rats were divided into 6 groups. One of the groups was the control group, while the other groups were administered different doses of curcumin and naringenin substances as well as CuNP. At the end of the study, after the liver tissue was isolated,

homogenization process was carried out. Superoxide dismutase (SOD), Catalase (CAT) activities, Malondialdehyde (MDA) level and inflammation markers (IL-1α, IL-1B) were investigated in homogenizers.

Results: When the IL-1α parameter in liver tissue was examined, when the control group and different doses of curcumin and naringenin were compared with CuNP, the level of IL-1α decreased, this decrease was not statistically significant ($p > 0.05$). The IL-1β parameter showed a statistically significant increase in the CuNP group compared to the control group ($p < 0.05$). IL-1β level was decreased in different doses of curcumin and naringenin groups compared to CuNP group ($p < 0.05$).

Conclusions: It can be thought that curcumin and naringenine can be used for the protection and treatment against detrimental effects that may occur in case of exposure to copper nanoparticles in humans.

Acknowledgements

This study was supported by a grant of Mersin University Scientific Research Projects Unit. (2020-1-TP2-4062)

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P180: AN INVESTIGATION ON THE ASSOCIATION BETWEEN ATP DEPENDENT POTASSIUM CHANNELS AND CORONARY ARTERY DISEASE

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Introduction: Coronary artery disease (CAD) is the most common cause of mortality and morbidity worldwide driven by both genetic and environmental factors (1). Atherosclerosis, one of the major causes of coronary artery disease, is a complicated disease that begins to develop in early ages and is caused by cholesterol accumulation in the vein walls (2). Various genetic factors and environmental effects are accelerating the development. There are many reasons for atherosclerosis beginning early in life, resulting in coronary artery disease in middle age and later. Smoking, hypertension, hypercholesterolemia, diabetes, advanced age, familial predisposition are risk factors for atherosclerosis. It is important to determine the genetic background of the disease in order to be able to learn and take precautions against the presence or absence of the predisposition to coronary artery disease in terms of increasing the life span and quality of individuals (3). In the light of the available information, we aimed to investigate whether S422L polymorphism is associated with coronary artery disease in the KCNJ8 gene, which is thought to be ampng risk factors.

Materials and Methods: In our study, individuals who applied to Mersin University Medical Faculty Hospital and Mersin State Hospital Cardiology Department, were diagnosed with coronary artery disease after coronary angiography (n = 100) and who were accepted as healthy after coronary angiography (n = 100) were included. Variation was determined using the Tetra-Primer ARMS PCR method.

Results: No significant relationships were found between the S422L polymorphisms and CAD in our study.

Conclusions: Our results does not support the hypothesis that KCNJ8 gene is associated with a significantly increased CAD risk, and point to S422L polymorphism as a possible hotspot mutation.

Acknowledgements

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P181: INVOLVEMENT OF GENETIC VARIANTS ASSOCIATED WITH PRIMARY OPEN-ANGLE GLAUCOMA PATHOGENESIS

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Introduction: Glaucoma is the second cause of blindness worldwide (1). This disease is a neurodegenerative disorder characterized by high intraocular pressure, loss of retinal ganglion cells caused by apoptosis (2). Intra ocular hypertension correlates with the visual field defects and loss of nerve fibres as seen on Optical coherence tomography (OCT), but also the thickness of the cornea. The disease is classified in chronic open-angle glaucoma and chronic closed-angle glaucoma, which in turn have other subtypes. Open angle glaucoma is the most frequent type, found in almost 50% of the patients. The estimated number of patients suffering from this disease is of about 68 million (3). Studies have shown that glaucoma has a genetic predisposition (4). For this purpose, we aimed to analyse a possible association of rs74315329/rs11258194 variations in MYOC/OPTN genes with Primary Open Angle Glaucoma (POAG).

Materials and Methods: 30 individuals diagnosed with POAG (patient group) and 30 healthy individuals (control group) were included in our study. Variations were determined using the Tetra-Primer ARMS PCR method.

Results: No significant association were observed between both the rs11258194 variation on OPTN gene and, the rs74315329 variation on the MYOC gene and POAG.

Conclusions: In this study, we aimed to investigate the involvement of genetic variants associated with POAG. According to results obtained from our sample population, both these variations on OPTN and MYOC genes were not related to reflect the influence of genetic variations predisposing to POAG pathogenesis.

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P182: INVESTIGATION OF BIOACTIVE PHYTOCHEMICALS OF *MATRICARIA CHAMOMILLA* L. AND *MATRICARIA DECIPIENS* K. KOCH AND THEIR *IN VITRO* BIOLOGICAL ACTIVITIES

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Introduction: Chamomile is the common name given to plant species from different genera which are classified in the Asteraceae family Matricaria chamomilla L. is one of the most widely used medicinal plants in the World. However, contrary to Matricaria chamomilla L.'s well defined phytochemicals and biological acitivities there are very few activity-focused studies on Matricaria decipiens K. Koch. (1, 2). The aim of our study is to preliminarily identify and compare the phytochemicals of both species and screen their acetylcholineesterase (AChE) and butrylcholine (BChE) inhibitory activities.

Materials and Methods: Extracts of Matricaria chamomilla L. **(MC)** and Matricaria decipiens K. Koch **(MD)** were prepared and screened for their AChE and BChE inhibitory activities by Ellman method. Phytochemicals of the extracts were analyzed and characterized by LC-MS/MS Tandem Gold Triple quadrupole mass spectrometer.

Results:

BIOLOGICAL ACTIVITY	200 µg extract /mL	MC (Inhibition %)		MD (Inhibition %)	
		AChE	BChE	AChE	BChE
	Butanol	62,19 ± 1,03	66,03 ± 1,42	5,47 ± 0,99	47,97 ± 1,90
	Water	49,90 ± 1,28	NI	15,92 ± 0,86	NI
	Ethanol	2,72 ± 0,15	52,97 ± 1,82	NI	49,68 ± 0,34
	Ethyl acetate	19,19 ± 0,88	63,94 ± 1,40	4,15 ± 0,81	55,95 ± 0,47
	Galantamin*	***71,48 ± 0,50***	***88,06 ± 0,26***	***71,48 ± 0,50***	***88,06 ± 0,26***
BIOACTIVE PHYTOCHEMICALS	**g extract**	**MC (µg)**		**MD (µg)**	
		Apigenin	**Apigetrin**	**Apigenin**	**Apigetrin**
	Butanol	617,38±20,81	5141,85±30,54	1008,9±28,28	247,81±4,03
	Water	217,72±8,11	33,48±1,88	15,74±2,72	ND
	Ethanol	296,55±19,81	1787,07±34,71	548,57±30,70	167,73±6,69
	Ethyl acetate	238,68±13,91	594,86±27,36	409,49±28,27	<LOQ

+: Standart; **ND**: Not Dedected; **NI**: No Inhibition **LOQ**: Limit of Detection; **AChE**: Acetylcholinesterase enzyme; **BChE**: Butyrylcholinesterase enzyme

Conclusions: Highest Apigenin and Apigetrin contents were found for the butanol extracts of two *Matricaria* species in Anatolia, Turkey (617,38±20,81; 5141,85±30,54 and 1008,9±28,28; 247,81±4,03 µg/g, respectively). When compared to *Matricaria decipiens* K.Koch., all *Matricaria chamomilla* L. extracts showed higher AChE and BChE inhibitory activities.

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P183: IN VITRO ACETYLCHOLINESTERASE INHIBITORY ACTIVITY OF COUMARIN-SELENOPHENE HYBRID COMPOUNDS

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Introduction: Alzheimer's disease (AD), defined as a neurodegenerative condition, is characterized by progressive loss of memory. It is common among older people (1). The symptoms of Alzheimer's disease can be reduced by inhibiting acetylcholinesterase (AchE) and increasing the level of acetylcholine. Coumarins (1,2-benzopyrones) are naturally found molecules and widely distributed in plants. Nowadays, to discover and expand the chemical properties of coumarins, many synthetic procedures are developing. They exhibit a wide range of biological activities and applications due to the ability to exert noncovalent interactions with many enzymes and receptors in living organisms. Lactose ring, which is adhered to benzene ring, and also shows AChE and BuChE enzyme inhibition activity (2). In this study, 8 coumarin-selenophene hybrid compounds previously synthesized were investigated for selective anti-AChE activity.

Materials and Methods: All coumarin and coumarin-selenophene derivatives were synthesized based on our previous study (2). In vitro effects on AChE activity of the compounds were studied according to Ellman's method (3). Tacrine (TAC) was used as a reference drug. All experiments were performed in triplicate.

Results: The synthesized coumarin- selenophene compounds showed IC_{50} values in range of 10.21–24.18 nM against AChE.

Conclusions: These results may contribute to the development of new drugs particularly in the treatment of Alzheimer's disease.

Acknowledgements

This study was supported by a grant of Mersin University Scientific Research Projects Unit (2019-3-AP5-3833).

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P184: INVESTIGATION OF BIOCHEMICAL ACTION MECHANISMS OF SOME 2-HYDRAZINOTHIAZOLE DERIVATIVES

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Introduction: Cancer is a group of diseases characterized by the uncontrolled growth and spread of abnormal cells (1). The thiazole nucleus is a fundamental part of some clinically applied anticancer drugs. Thiazole-containing compounds have been proven to exhibit high effectiveness, potent anticancer activity, and less toxicity (2). In this study, it was aimed to evaluate the anticancer activities of newly designed 2-Hydrazinothiazole derivatives.

Materials and Methods: A549 lung cancer cell lines were used in the studies. The cytotoxic activities of the tested compounds were determined by cell proliferation analysis using standard (3-(4,5-dimethylthiazol-2-yl)-2,5-

diphenyltetrazolium bromide (MTT) assay. Detection of apoptosis was performed using Annexin V-FITC apoptosis detection kit (BD Biosciences). Detection of mitochondrial membrane integrity was performed using a Mitoscreen kit (JC-1) (BD Biosciences). Detection of caspase-3 was performed using FITC activate Caspase-3 apoptosis kit (BD Biosciences). All measurements were performed on a CytoFLEX Flow Cytometer.

Results: The IC50 values of the compounds were determined for the A549 cell line. IC50 values of compounds 3d and 3e were respectively, 15 ± 0.51 µg / mL and 6.2 ± 0.46 µg / mL. The percentages of the early apoptotic cell population for compounds 3d, 3e, and cisplatin were respectively 15.50%, 8.28%, and 50.23%. The percentage of cell population showing mitochondrial membrane activity for the compounds 3d, 3e, and cisplatin were 63.31%, 25.46%, 33.57%, respectively. Compound 3d, 1.8-fold higher mitochondrial membrane activity than cisplatin has shown. The percent of cells showing positive caspase-3 activity for the compounds 3d, 3e, and cisplatin were 91.77%, 89.12%, 36.03%, respectively. Compound 3d, 2.5-fold higher positive caspase-3 activity than cisplatin has shown.

Conclusions: It was determined that the synthesized compounds have significant anticancer activity against A549 cell lines. However, compound 3d was the most active compound against the A549 cell line. In addition, our study results showed that compound 3d, and 3e affected A549 cells apoptotically.

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P185: THE EFFECT OF PHARMACIST IN RATIONAL ANTIBIOTIC USE: A META ANALYSIS STUDY

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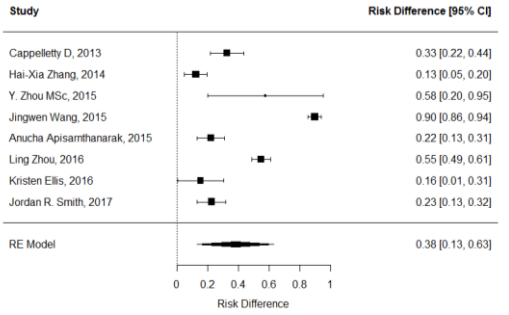
Introduction: Since there is a decrease in the research and development of new antibiotics, antibiotic resistance has become an element that threatens public health (1). Drug counseling is the core element of antibiotic management programs. According to the The United States Centers for Disease Control and Prevention consulting pharmacists should act as antibiotic specialists and program leaders in antibiotic management (2). The purpose of this meta-analysis study is; analyzing the effect of pharmacist-led antibiotic management programs on rational antibiotic use.

Materials and Methods: ScienceDirect, PubMed and MEDLINE databases were searched for analysis. The studies were evaluated in accordance with inclusion and exclusion criteria. Quality assessment was performed via Newcastle-Ottawa and NIH quality assessment scales. Meta-analysis was carried out by means of the R program.

Results: Meta-analysis was performed by calculating the risk difference based on the studies included in the analysis. For the heterogeneity analysis, I^2 statistics were checked. Since the I^2 value is 98.65% and the heterogeneity test Q value is 517.1079 (p = <0.0001), the random effects model was used.



Conclusions: As a result of the meta-analysis, the risk difference in favor of the group with pharmacist intervention was found to be 0.38 [0.13; 0.63]. According to this result, pharmacist leadership increases the rational use of antibiotics in antibiotic management programs in hospitals.

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P186: CANNABIS IN PORTUGAL: THE REBIRTH OF THE ONE THAT WAS ALREADY THE MOST IMPORTANT CULTURE IN THE COUNTRY

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Introduction: Cannabis was once the most important crop in our country. Without it, the Portuguese maritime empire would be nothing more than a mirage. Between ups and downs, with incentives during the new state, in 1970 Portugal

ratified international agreements. The era of prohibitionism begins in our country. (Herer, 2002)After the decriminalization of drugs, at the beginning of the 21st century, recognized as an example worldwide, in 2018 a new milestone in the history of cannabis in Portugal was marked: the approval of the Medicinal Cannabis Law.(Baptista-Leite e Ploeg, 2018)(Fonseca *et al.*, 2019) The aim of the study is clearly tracing the sinuous and peculiar path that has been followed by cannabis in Portugal.

Materials and Methods: The analysis of literature, national scientific articles and national newspapers will be the focus of this work.

Results: After a culture of forgetfulness strengthened by prohibitionist laws, the Medicinal Cannabis Law came to create a paradigm shift. With therapeutic indications approved by Infarmed, cannabis became available in Portuguese pharmacies, from April 1, 2021.

Conclusions: In the year 2020 Portugal had the largest culture of medicinal cannabis in Europe and according to the projects in progress we are only at the beginning.(*Maior Plantação Europeia de Canábis Medicinal Fica no Alentejo*, 2020) Is this the revival of cannabis culture in Portugal?

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P187: PROFESSIONAL EXPERIENCES OF ENTREPRENEUR COMMUNITY PHARMACISTS

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Introduction: Entrepreneurship has become an integral part of pharmacy with the widening the WHO's seven-star pharmacist to nine-star (1). Also, the necessity of developing pharmacy curriculum with this subject is emphasized and its crucial role on transforming pharmacy is underlined. It's aimed to examine the professional experiences of entrepreneur community pharmacists engaged in various entrepreneurship activities on this study.

Materials and Methods: In the light of the entrepreneurship-related literature, researchers prepared interview plan contained 11 question. After the permission of the Hacettepe University Ethical Committee, according to the convenience sampling method, 19 pharmacists were determined among pharmacists whose entrepreneurship activities were accessible on the Internet. Atlas.ti ver.9 were used to determine the codes and themes in accordance with descriptive analysis stages following the transcription of online interviews

Results: Within the scope of this study, 12 of the 19 pharmacists were participated on the online interviews. The number of quotes and codes are presented in the Table with the themes.

Table 1. Themes with the number of quotes and codes

Themes	The number of codes	The number of quotes
Reasons to be an entrepreneur	5	51
Entrepreneurship-related factors	9	60
Characteristics of an entrepreneur	3	22
Total	17	133

The participants emphasized that they focused on innovativeness and learned from the experiences of the other entrepreneurs, while they were at the beginning of their entrepreneurship. Also, it's revealed that the main reasons being an entrepreneur community pharmacist are willingness to be beneficial and serve the society.

Conclusions: Pharmacists are an important professional group that aims to improve the well-being and the health status of society. Besides, some pharmacists are able to see the needs in their field and find solutions with their entrepreneurial activities in the light of professional knowledge, legal limitations and experiences. In order for this to become widespread, the importance of developing activities related to entrepreneurship such as collaboration, innovativeness and productivity starting from undergraduate education in pharmacy is emphasized (2, 3). Therefore, education programs should be updated to support entrepreneurship and provide environments for students and entrepreneur pharmacists coming together.

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P188: THE ROLE OF PHARMACIST JOAQUIM DOS SANTOS E SILVA (1842-1906) IN CINCHONA BARK AND QUININE RESEARCH IN PORTUGAL

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Introduction: Cinchona bark is an antimalarial drug of vegetable origin (1).Its alkaloid quinine is still used in malaria treatment today (2).Cinchona bark and quinine's medicinal value prompted several government initiatives to cultivate cinchona plants outside of its native South America in the 19th and 20th centuries, namely by the British, Dutch, Belgian or the Portuguese (1).This study aims to assess the contribution of the pharmacist Joaquim dos Santos e Silva (1842-1906), manager of practical work at Coimbra University's Chemistry Laboratory, and later Professor at the Coimbra School of Pharmacy to cinchona bark and quinine research in Portugal in the second half of the 19th century.

Materials and Methods: Historical review of Portuguese pharmaceutical and medical literature from the 19th and 20th centuries in databases, physical and digital libraries, as well as books and articles on Portugal's history of pharmacy and medicine.

Results: From 1869, the Coimbra Botanical Garden sent cinchona plants and seeds to the former Portuguese African colonies, particularly to São Tomé and Cabo Verde. Silva performed chemical analysis on cinchona bark samples from São Tomé and Cabo Verde at Coimbra University's Chemistry Laboratory (1,3,4). The results showed that the cinchona bark samples from São Tomé were of good quality (1) with a high alkaloid content and were not inferior to the best quality cinchona bark from the Dutch and British colonies (5). Silva stated that the quinine content was relatively high in the samples he analyzed between 1876 and 1880.Silva concluded that large-scale cinchona cultivation should therefore merit the farmers' attention (4).

Conclusions: Silva's chemical analyses aided the Portuguese cinchona cultivation efforts by showing that cinchona cultivation in São Tomé could be a profitable enterprise. These results may have fostered the expansion of cinchona cultivation in São Tomé. The São Tomé cinchona plantations generated a lucrative business until the beginning of the 20th century.

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P189: DETERMINATION OF PHARMACY STUDENTS' READINESS FOR INTER-PROFESSIONAL LEARNING

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Introduction: Distribution of tasks and collaboration among healthcare professionals are significant in providing qualified, reliable and sustainable healthcare services. Inter-professional learning is defined as a process, which occurs "between students or members of two or more professions to enhance knowledge and competence during inter-professional education" (1). In this study, it is aimed to reveal the readiness of pharmacy faculty students for inter-professional learning.

Materials and Methods: The readiness for inter-professional learning scale developed by Parsell and Bligh (2), edited by McFadyen et al (3) and translated into Turkish by Onan et al (4) were used in this study. After the permission of the Hacettepe University Ethical Committee, the questionnaire was applied to the pharmacy students in Turkey via Google Forms. SPSS ver.23 were used for descriptive statistics and performing the statistical test to find the scale score differences between groups.

Results: The questionnaire was conducted between December 7, 2020 and February 7, 2021 with 812 participants. The mean score is 70,07 and the Cronbach's alpha internal consistency coefficient is 0,935. Some other findings are presented on the Table 1.

Table 1. Differences among students' scale scores

	Mean ± SD	Median	Min-Max	p value
Establishment of the Faculty				
First established ten faculties	70.97±14.82	75	19-95	0.069
Faculties established after 2001	69.14±15.94	74	19-95	
Do you think that inter-professional learning is sufficient in undergraduate education?				
Yes	69.06±14.59	72	19-95	0.008
No	70.50±15.73	75	19-95	

As it's presented on the Table, there are a significant difference between groups which found undergraduate education sufficient and insufficient according to the Mann-Whitney U tests results ($p<0,05$).

Conclusions: Inter-professional learning promotes professional development by increasing awareness of other professions and understanding its role. Also, inter-professional learning leads up to improve patient safety with inter-professional collaboration. The results of this study reveals that participated undergraduate pharmacy students in Turkey think that inter-professional learning process is insufficient on undergraduate education, although they are ready for this. In order to harmonize cooperation with other fields by increasing professional development in the field of pharmacy, inter-professional learning should be included in undergraduate education immediately.

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P190: POTENTIALLY PRESCRIBING OMISSIONS IN OLDER ADULTS WITH CHRONIC KIDNEY DISEASE

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Introduction: Older persons are at significant risk of drug-related problems. This problems can be evaluated by using several tools known as Beers, START/STOPP and MAI. Of this tools only START examines identification and prevalence of potential prescription omissions (PPOs), for patients aged ≥ 65 years. In this study we determined identification and prevalence of PPOs in elderly patients according to START criteria.

Materials and Methods: This was a descriptive cross-sectional study conducted on discharge prescriptions of elderly patients in the nephrology ward of Ankara University Ibn-i Sina Hospital.

Results: In total, 100 patients (51.0% male; mean ± SD age: 73.3 ± 6.9 years) were included in the study. According to START criteria, 92 patients (92.0%; 95% CI: 86.0 - 97.0) had least one PPO. Out of these, 40 (40.0% 95% CI: 31.0 – 50.0) had one PPO, 37 patients (37.0%; 95% CI: 27.0 – 46.0) had two PPOs, and 10 patients (10.0%; 95% CI: 4.0 – 17.0) had three PPOs, and 4 patients (4.0% 95% CI: 1.0 – 8.0) four PPOs, and 1 patient (1.0%; 95% CI: 0.0 – 3.0) five PPOs. Most of these PPOs were related to vitamin D supplement in older people who are housebound or experiencing falls or with osteopenia (86.0%), related to missing of ACE inhibitors although systolic heart failure and/or documented coronary artery (30.0%), documented history of coronary, cerebral or peripheral vascular disease, unless the patient's status is end-of-life or age is > 85 years without statin therapy (13.0%), related to absence of bisphosphonates, and vitamin D and calcium in patients taking long-term systemic corticosteroid therapy (12.0%), and omission of regular inhaled β2 agonist or antimuscarinic bronchodilator for mild to moderate asthma or chronic obstructive pulmonary disease (7.0%).

Conclusions: The prevalence of PPO was high among older adults with chronic kidney disease (CKD) patients according to START criteria. Particularly there was vitamin D indication in most of the patients. Therefore, PPO should be avoided for more effective treatment. Additionally, we believe that developing screening tools specific to CKD patients aged 65 and over will be more beneficial in the treatment of these patients.

13th International SYMPOSIUM ON PHARMACEUTICAL SCIENCES

WORKSHOP

EMPLOYABILITY OF THE GRADUATES OF THE FACULTY OF PHARMACY IN EUROPE

JUNE 24, 2021

16:30-18:00(GMT+03:00)

Luciano Saso

Faculty of Pharmacy and Medicine, Sapienza University of Rome, ITALY

Vice-Rector for European University Networks at Sapienza University of Rome

President of UNICA

Sibel Süzen

Department of Pharmaceutical Chemistry, Ankara University Faculty of Pharmacy, TURKEY

Member of the UNICA Steering Committee

Lilian M. Azzopardi

Department of Pharmacy, Faculty of Medicine and Surgery at the University of Malta, MALTA

President of the European Association of Faculties of Pharmacy

Claire Anderson

Division of Social Research in Medicines and Health, School of Pharmacy, University of Nottingham, UK

Chair of the Royal Pharmaceutical Society English Pharmacy Board

Associate Director for FIPEd

İlkay Erdogan Orhan

Department of Pharmacognosy, Gazi University, TURKEY

Dean of Faculty of Pharmacy, Gazi University

President of the Council of Deans of the Faculty of Pharmacy (ECZDEK)

Nilhan Uzman

International Pharmaceutical Federation (FIP), Netherlands

Global Lead for Education Policy and Implementation at International Pharmaceutical Federation (FIP)

Career paths in the pharma and biomedical sector

Prof. Luciano Saso
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President of the UNICA network of the Universities from the Capitals of Europe (http://www.unica-network.eu)

Given the high number of job and career opportunities available, the main challenge for young students and graduates in the pharma and biomedical sector is to understand which their preferred jobs are and how to get them. To try to help them, UNICA organized a series of webinars involving high level experts from academia and industry[1].

A useful approach is to attend all possible orientation events such as career days, organized nowadays by most universities, in which it is possible to listen to experts coming from different companies.

Some of the biggest pharmaceutical companies, including Abbott[2], AbbVie[3], Amgen[4], AstraZeneca[5], Baxter[6], Bayer[7], Biogen[8], Boehringer-Ingelheim[9], Bristol-Myers Squibb[10], Eli Lilly & Co[11], Gilead[12], GlaxoSmithKline[13], Johnson & Johnson[14], Merck & Co[15], Merck KGaA[16], Novartis[17], Novo Nordisk[18], Roche[19], Sanofi[20], Teva[21], etc., have excellent traineeship programmes for young students and graduates.
Useful websites to find excellent scientific positions in public or private institutions are https://www.sciencemag.org/careers, http://www.nature.com/naturejobs/science/,

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[1] https://www.unica-network.eu/event/unica-student-webinars-pharma-and-biotech-careers-in-europe/
[2] http://www.abbott.com/careers/students/development-programs.html
[3] http://www.abbvie.com/careers/student-opportunities/development-programs.html
[4] http://careers.amgen.com/university-relations/internships-co-ops/
[5] http://www.astrazenecacareers.com/students/programmes/
[6] http://www.baxter.com/careers/programs/healthcare-internships-co-ops.page
[7] https://career.bayer.com/en/career/working-at-bayer/students/
[8] https://www.biogen-international.com/en/careers1/pharmd-fellowships.html
[9] http://careers.boehringer-ingelheim.com/students
[10] http://www.bms.com/careers/university_recruitment/internships_co-ops/pages/graduates_undergraduates.aspx
[11] https://careers.lilly.com/campus
[12] http://www.gilead.com/careers/careers/current-opportunities
[13] http://futureleaders.gsk.com/en-gb/our-programmes/
[14] http://www.careers.jnj.com/explore-careers-student
[15] http://www.merck.com/careers/life-at-merck/students-and-graduates.html
[16] http://www.merckgroup.com/en/careers/graduates_and_students/faq/faq.html
[17] https://www.novartis.com/careers
[18] http://www.novonordisk.com/careers/graduates-students-and-trainees/graduates/graduate-programmes-overview-uk.html
[19] http://www.roche.com/careers/switzerland/ch_your_job/students_and_graduates/trainee_programs.htm
[20] http://en.sanofi.com/careers/join_sanofi/graduates_interns/graduates_interns.aspx
[21] http://www.tevapharm.com/teva_careers/european_leadership_programme/

http://jobs.newscientist.com/, etc.
Another valuable strategy is to apply for a traineeship in a company in another European country participating in the Erasmus+ programme[22]. The programme offers the possibility of spending periods of at least two months in non academic institutions including pharmaceutical companies and research centres[23]. Most universities are active in this programme and students can easily obtain detailed information from their international offices.

Some European Institutions such as the European Medicines Agency (EMA)[24] , the European Centre for Disease Prevention and Control (ECDC)[25] and the European Patent Office (EPO)[26] offer very interesting traineeships.

The Innovative Medicine Initiative (IMI)[27], Europe's largest public-private initiative aiming to speed up the development of better and safer medicines for patients, developed interesting projects in the field of education and training:

- EMTRAIN[28] (European Medicines Research Training Network), a platform for education and training covering the whole life cycle of medicines research, from basic science through clinical development to pharmacovigilance.
- Eu2P[29] (European programme in Pharmacovigilance and Pharmacoepidemiology) which developed numerous courses covering various aspects of medicines research and development, including pharmacovigilance.
- Pharmatrain[30] (Pharmaceutical Medicine Training Programme), which established standards for high-quality postgraduate education and training in Medicines Development.
- SafeSciMET [31](European Modular Education and Training Programme in Safety Sciences for Medicines) which established a new and unique pan-European education and training network, providing master's level courses in safety sciences for medicines.

Another important question often asked by students and graduates is related to the necessary level of education required for the different positions in the pharmaceutical sector. The answer it is not always easy because despite the harmonization of the architecture of the European higher education obtained through the Bologna process since 1999[32] (1st cycle or bachelor's degree, 2nd cycle or master's degree, 3rd cycle or PhD or Doctorate), there are still significant differences in the pharmaceutical field. In most European countries, while chemistry, biology and biotechnology are usually studied in two subsequent cycles (bachelor + master), pharmacy and industrial pharmacy are usually 5 or 6 years integrated master's degree programmes. In addition, in some countries, such as Italy and France for example, it is very common to attend a 'professional master' after the master's degree to obtain the necessary knowledge and skills to be hired by pharma companies for positions in clinical monitoring, pharmacovigilance or regulatory affairs. Finally, concerning the third cycle, despite the existence of many different research and professional PhDs, it should be

[22] https://ec.europa.eu/programmes/erasmus-plus/node_en
[23] https://ec.europa.eu/programmes/erasmus-plus/individuals_en#tab-1-4

[24] http://www.ema.europa.eu/ema/index.jsp?curl=pages/about_us/general/general_content_000321.jsp

[25] http://ecdc.europa.eu/en/aboutus/jobs/Pages/Traineeships.aspx
[26] http://www.epo.org/about-us/jobs/vacancies/internships.html
[27] http://www.imi.europa.eu/
[28] http://www.emtrain.eu/
[29] https://www.eu2p.org/
[30] http://www.pharmatrain.eu/
[31] http://www.safescimet.eu/
[32] http://ec.europa.eu/education/policy/higher-education/bologna-process_en.htm

mentioned that in most countries, the title of PhD is really necessary for careers in research but not for most of the other positions.

Prof. Luciano Saso (luciano.saso@uniroma1.it) is a Member of the Faculty of Pharmacy and Medicine, Sapienza University of Rome, Italy (http://en.uniroma1.it/). He is author of more than 250 original scientific articles published in peer reviewed international journals with impact factor (H-index Google Scholar = 51, H-index SCOPUS = 41, Total Impact Factor > 800) working mainly in the field of **pharmacological modulation of oxidative stress.** He coordinated several international research projects and has been referee for many national and international funding agencies and international scientific journals in the last 25 years. He has been Editor and Guest Editor of Special Issues of different international journals including ANTIOXIDANTS, JOURNAL OF PHARMACY AND PHARMACOLOGY, FRONTIERS IN PHARMACOLOGY, FRONTIERS IN CELLULAR NEUROSCIENCE, MOLECULES, INTERNATIONAL JOURNAL OF MOLECULAR SCIENCES. More information is available at https://www.researchgate.net/profile/Luciano-Saso.

Prof. Saso has extensive experience in **international relations** and he has been Vice-Rector at Sapienza University of Rome in the last 7 years. In the last 15 years, he participated in several projects and has been speaker and chair at many international conferences organised by the UNICA network of the universities from the Capitals of Europe (http://www.unica-network.eu/) and other university associations. Prof. Saso has been Member of the Steering Committee of UNICA for two mandates (2011-2015) and he is currently President of UNICA (2015-2023).

Prof. Saso has extensive experience in **career development for students and recent graduates in the pharma and biomedical sector.** In 2016 he co-authored a book on "Job and Career Opportunities in the Pharmaceutical Sector" which is freely available at https://www.intechopen.com/books/special-topics-in-drug-discovery/job-and-career-opportunities-in-the-pharmaceutical-sector and recently launched a series of international webinars https://www.unica-network.eu/event/unica-student-webinars-pharma-and-biotech-careers-in-europe/

Employability of the Graduates of the Faculty of Pharmacy in Turkey and New Horizons

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Currently, 52 pharmacy programs at undergraduate level are available in Turkey and North Cyprus including the newly opened faculties, which means that number of pharmacy graduates in our country will soon reach up to approximately 4400 *per* year. When a projection is made to the employment areas of pharmacy graduates in Turkey, the most preferable employment is definitely having community pharmacy. To date, it was the most popular reason to choose pharmacy faculties for candidate students, however, situation has changed due to the new legislation in Turkey that there should be one community pharmacy every 3500 people. This restriction by law directed the graduates to relatively less-preferable and new employment areas. Doubtlessly, other areas for employment of pharmacists are pharmaceutical industry, Turkish Medical Device and Drug Agency (TİTCK), academic carrier in pharmacy faculties as well as some other relevant faculties or vocational schools, Social Security Institution (SGK), hospital pharmacies, herbal medicinal products and cosmetic sectors. Although current employment choices seem to be quite variable, recent pharmacy graduates are feeling stuck. As the Deans Council of Faculties of Pharmacy in Turkey (ECZDEK), we closely in touch with Higher Education Board of Turkey (YÖK) to monitor pharmacy education as well as situation of pharmacy graduates nowadays. In fact, YÖK advices us to direct the graduates to the pharmaceutical sector, since the rate of pharmacists working in pharmaceutical companies in Turkey is quite low, which is about 2-3%. Taking this advice into account, pharmacy faculties are also in touch with representatives of Turkish pharmaceutical sector, which is highly strong in technology and production. Relevantly, the pharmacy curriculum has been enriched more with pharmaceutical industry-related courses and compulsory training consisting of minimum 120 work days was extended to cover training in the industry, too, for a maximum 20 work days of total training program. Before that, the pharmaceutical industry training was done by our students on voluntary basis, which has now accepted among the compulsory training options. This important step was mostly achieved by the Deans Council. The disadvantage of getting a job in pharmaceutical industry for the graduates reveals to be that since the drug industry is dominantly located in Istanbul and around it, most of the graduates are reluctant to settle down in Istanbul province.

On the other hand, the governmental bodies such as Turkish Medical Device and Drug Agency (TİTCK) and Social Security Institution (SGK) as well as hospital pharmacies of public and private origins continue to hire pharmacists regularly every year. However, when compared with the increasing number of pharmacy graduates, these positions appear to be insufficient in a near future.

Another option to be employed for pharmacy graduates could be considered to get position at newly opened pharmacy faculties. The reality at new faculties points out to fact that they do not have enough academic staff, particularly they lack pharmacy faculty-graduated academics. The senior pharmacy faculties give hand to new faculties to train new academic staff through joint Ph.D. programs. Nevertheless, most of the new faculties are located in periphery of the country, whereas the young pharmacists being trained in senior faculties in major cities do not want to go back to their own faculties in the peripheral regions. Thus, new pharmacy faculties in Turkey have more chemists or biologists rather than pharmacists especially at the departments of basic pharmaceutical science division. This is also another contradiction to this area of employment.

Realizing this fact, we, as the pharmacy faculties, have been working on extending new professional job areas for our graduates through master or Ph.D. programs. One of them is forensic pharmacy, which is present at two pharmacy faculties as master program, also run by Faculty of Pharmacy, Ankara University as one of the most senior faculties in our country. Forensic pharmacy is observed to get attention from the pharmacy graduates at the moment. Another new horizon seems to be sports pharmacy, which is in progress to set up as master program by Faculty of Pharmacy, Gazi University as another one of the senior faculties, which will be the first example in the country and in the world. For both of the mentioned programs, there are various certificate courses as well. However, we care more about having master programs as an academic degree, which can be later on evolved to Ph.D. programs in upcoming years.

It should be also mentioned that since 2017, two specialty programs in clinical pharmacy and phytopharmacy belonging to Ministry of Health exist for pharmacy graduates. In this concept, some pharmacy faculties were authorized to run these 3-year taking programs, which can be only enrolled *via* passing the central exam organized by Student Assessment and Placement Center (ÖSYM). The exam is quite difficult and, unfortunately, the quota given the authorized pharmacy faculties is highly limited. Beside it is not clear, yet, how and where the graduates of these programs would be employed. At this point, Pharmacy Board in Specialty (EUK) and Ministry of Health have been working closely.

Another obstacle to young graduates is to perform one year-internship as “assistant pharmacist” at community pharmacies in Turkey. After graduating successfully from 5-year pharmacy education with a diploma, graduates who would like to run a community pharmacy must complete this internship during one year according to the relevant legislation. In addition, there is such obligation by law in our country that a second pharmacist have to be employed in community pharmacies with financial turnover passing a certain limit.

Of course, realizing more employment options for our prospective graduates is the primary concern for the Deans Council of Faculties of Pharmacy in Turkey (ECZDEK). We are working more at the moment through some certificate programs in industrial pharmacy for undergraduate pharmacy students to attract their attention for chasing a carrier in pharmaceutical sector. New horizons such as pharmacist employment in nursing homes, prisons, refugee camps, etc. seem to be possibly quite effective and necessary for young graduates. These options are argued at the table by Deans Council, chambers of pharmacists as well as Association of Turkish Pharmacists (TEB). Without doubt, all our efforts in this direction must be in consultation with the state and governmental bodies should be persuaded for these envisaged employment areas.

In conclusion, employment of new pharmacy graduates in Turkey seems to become a difficulty gradually. To slow the problem, establishing new pharmacy faculties should not be allowed by Higher Education Board of Turkey (YÖK) at least for a certain period such as next 10 years. The student quota in pharmacy faculties should be reduced. The senior pharmacy faculties ca be suggested to focus on educating only graduate students and doing R&D collaborating with pharmaceutical industry. The graduates should be encouraged to apply for a job in different scopes such as cosmetic, molecular biology, genetic, basic sciences, etc.

Finally, efforts of the Deans Council of Faculties of Pharmacy in Turkey (ECZDEK) will continue on creating new job possibilities for pharmacy graduates in collaboration with all relevant stakeholders.

Prof.Dr. Ilkay Erdogan Orhan holds a Pharmacist degree (1993) from Gazi University (Ankara, Turkey), 1st M.Sc. degree at Department of Pharmacognosy at the same Faculty in 1996 with young scientist scholarship provided by TUBITAK (Scientific and Technological Research Council of Turkey). Then, she was awarded her second M.Sc. degree in Marine Natural Product Chemistry in 1998 at the University of the Ryukyus in Japan supported by Monbusho scholarship. She earned Ph.D. degree in Pharmacognosy at Faculty of Pharmacy, Gazi University (Ankara, Turkey) in 2002 and visited Department of Chemistry at University of Winnipeg (Canada) in 2003 as post-doc under NATO-TUBITAK fellowship program. She was promoted to Assoc. Prof. position by Higher Education Council of Turkey in 2004 and became full professor in 2009. Dr. Orhan was appointed as “Dean” of Faculty of Pharmacy at Eastern Mediterranean University in the Northern Cyprus for the period of 2011-2014. She is Dean of Faculty of Pharmacy, Gazi University since 2016. She is also member of Traditional Chinese Medicine (TCM) Experts Group in European Pharmacopeia and the International Scientific Board of Austrian Drug Screening Institute (ADSI). Dr. Orhan received several awards. She is author/co-author of 260 scientific papers listed by SCI, 46 papers in other scientific journals, 21 book chapters, 3 patents (Turkish, US, & EP), 5 patent applications, and 3 books. She has supervised 6 Ph.D. theses and 14 M.Sc. theses. Her h index is 44 (Web of Science) and 47 (SCOPUS) with over 7000 citations. Her research interests are as follows; novel enzyme inhibitory compounds from natural sources by in vitro and in silico methods, phytocosmetics, phytotherapy, aromatherapy, and natural product chemistry.

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To ensure the sustainability of pharmacy practice and provide health for all, pharmacy as a profession must embrace the digital transformation that has been changing healthcare at a rapid pace. The International Pharmaceutical Federation (FIP) has conducted a global study on digital health in pharmacy education to describe the readiness, adaptability, and responsiveness of pharmacy education programmes to train the current and future pharmaceutical workforce on digital health and to identify the knowledge and skill gaps of the existing pharmaceutical work-force on with regard to digital health. An online survey was distributed to collect feedback from academics, pharmacy schools, pharmacists, and pharmacy students. The findings showed that a large proportion of pharmacy schools do not offer any digital health education, and the skillsets and knowledge of how to apply digital health technologies to solve existing clinical problems and improve care have been identified as a gap. The future of pharmacy and pharmaceutical sciences is digital and exciting. A digitally enabled and agile pharmaceutical workforce will capitalise on the benefits of digital health to serve the higher purpose of providing good health and wellbeing for all, leaving no one behind. Therefore, pharmacy and pharmaceutical sciences education should act now.

Nilhan Uzman is a pharmacist trained in Turkey. She is the Global Lead for Education Policy and Implementation at International Pharmaceutical Federation (FIP). Her primary focus is developing and delivering FIP's strategy towards advancing pharmaceutical education globally, regionally and at country level by working closely with academics, educators, pharmacy schools, professional associations, health and education partners as well as young professionals and pharmacy students. Nilhan is leading FIP's-Women in Science and Education – FIPWiSE initiative to empower women in these fields to achieve their full potential. She leads the FIP UNESCO-UNITWIN Programme, which aims at improving academic capacity, implementing needs-based education strategies and establishing enabling advocacy environments through educational partnerships to advance education and the profession with focus on LMICs. A key priority area she leads is FIP's Digital health in pharmacy education workstream.

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Sibel Süzen is professor at the Faculty of Pharmacy of Ankara University. Her research is focused on the synthesis and development of antioxidant-based anticancer compounds, their biological evaluation and melatonin-based compounds in drug research. She graduated from Ankara University Faculty of Pharmacy in 1985. After completing her Master's Degree in Pharmaceutical Chemistry at the same university in 1989, she received her doctorate in 1997 from the University of Swansea, UK, Department of Chemistry. She continued her research at Swansea University in various years. She has been a member of European Farmacopea expert in Group (Semi synthetic and synthetic compounds) since 2011. In the last 10 years, she has been working as Institutional Erasmus Coordinator, Internationalization and Foreign Relations Coordinator of Ankara University. She has been coordinating the opening of English taught programs as well as international projects, internship agreements and educational programs of the EU. She was vice-rector for International Relations and Projects at Ankara University since 2019-20. She carried out numerous projects supported by Tübitak and University resources. She is the author of more than 100 scientific articles and many chapters in various books both in Turkey and abroad. She worked as project manager and organized several scientific meetings. She has been a member of the Editorial Board of various scientific journals.

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President of the European Association of Faculties of Pharmacy

Lilian M. Azzopardi is a Professor of Pharmacy and Head of Department of Pharmacy, Faculty of Medicine and Surgery at the University of Malta. Professor Azzopardi serves as chairperson of the Faculty of Medicine and Surgery Doctoral Committee. She has an extensive academic experience and she has spearheaded innovative introductions in pharmacy education that are directed to meet the needs of the health services and the pharmaceutical industry. Professor Azzopardi is well acknowledged in the international field for her ability to ingrain in the education process ways how to combine the basic sciences with the practice areas to meet the needs of stakeholders. Her ability to do this is enhanced by her experience in practice in hospital and community pharmacy and in the pharmaceutical industry. She published several papers and books mainly related to quality systems, pharmacist interventions, and pharmacy education. She has received research awards by the International Pharmaceutical Federation (FIP) and the European Society of Clinical Pharmacy. She served as an ad-interim Director and a member of the Publications Committee of the European Society of Clinical Pharmacy and Deputy Dean of the Faculty of Medicine and Surgery at the University of Malta. Professor Azzopardi was the co-chair of the working group of the FIP Nanjing Statements on Pharmacy and Pharmaceutical Sciences Education and is a member of the advisory group of the Academic Institutional Membership (AIM) within FIP. She currently serves as President of the European Association of Faculties of Pharmacy.

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Claire Anderson is Professor of Social Pharmacy in the Division of Social Research in Medicines and Health at the School of Pharmacy, University of Nottingham. Her research interests include the role of community pharmacists in improving the health of the public, people's experiences of using medicines and pharmacy education. She is chair of the Royal Pharmaceutical Society English Pharmacy Board. She is a past president of the FIP Academic Section of the International Pharmaceutical Federation (FIP). She is currently an Associate Director for FIPEd.

ISOPS 13th International SYMPOSIUM ON PHARMACEUTICAL SCIENCES

PANEL

HAZİRAN 25, 2021
14:00-18:00

Prof. Dr. Hasan MANDAL
Türkiye Bilimsel ve Teknolojik Araştırma Kurumu-TÜBİTAK Başkanı

Doç. Dr. Tolga KARAKAN
Türkiye İlaç ve Tıbbi Cihaz Kurumu -TİTCK Başkanı

Dr. Ecz. Nihan BURUL BOZKURT
Türkiye İlaç ve Tıbbi Cihaz Kurumu -TİTCK Klinik Araştırmalar Daire Başkanı

Prof. Dr. Erhan AKDOĞAN
Türkiye Sağlık Enstitüleri Başkanlığı-TÜSEB Başkanı

Doç. Dr. Rabia ÇAKIR KOÇ
Türkiye Sağlık Enstitüleri Başkanlığı-TÜSEB Türkiye Biyoteknoloji Enstitüsü Başkanı

Prof. Dr. Mayda GÜRSEL
Orta Doğu Teknik Üniversitesi Biyolojik Bilimler Bölümü Öğretim Üyesi

Prof. Dr. Rana SANYAL
Boğaziçi Üniversitesi Yaşam Bilimleri ve Teknolojileri Merkezi Müdürü/RS Research

Prof. Dr. Hülya AYAR KAYALI
DEU İzmir Biyotıp ve Genom Enstitüsü Öğretim Üyesi/
İzmir Biyotıp ve Genom Merkezi-İBG Grup Lideri

Dr. Süha TAŞPOLATOĞLU
Abdi İbrahim İlaç CEO'su

Dr. Hasan Ersin ZEYTİN
Nobel İlaç Biyoteknoloji ve Yeni Ürün Değerlendirme Direktörü

Dr. Ecz. Ferhat FARSİ
CinnaGen İlaç Kurucu Ortağı ve CEO'su

Oturum Başkanları
Prof. Dr. Asuman BOZKIR Doç. Dr. Tolga KARAKAN

DÜZENLEME KURULU

Asuman BOZKIR
Sinem ASLAN ERDEM
İlker ATEŞ
Zeynep ATEŞ ALAGÖZ
Filiz BAKAR ATEŞ
Meltem CEYLAN ÜNLÜSOY
Burcu DEVRİM
Zerrin SEZGİN BAYINDIR
Gülnur EKŞİ BONA
Banu KAŞKATEPE
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ISOPS 13th International SYMPOSIUM ON PHARMACEUTICAL SCIENCES

PANEL

İLAÇ VE AŞI GELİŞTİRME SÜREÇLERİNDE ÜNİVERSİTE-SANAYİ-KAMU İŞBİRLİĞİ

HAZİRAN 25, 2021
14:00-18:00

Oturum Başkanları
Prof. Dr. Asuman BOZKIR Doç. Dr. Tolga KARAKAN

14:00-14:10	**Prof. Dr. Asuman BOZKIR** Ankara Üniversitesi Eczacılık Fakültesi Dekanı	**15:25-15:40**	**Prof. Dr. Mayda GÜRSEL** Orta Doğu Teknik Üniversitesi Biyolojik Bilimler Bölümü Öğretim Üyesi
14:10-14:25	**Prof. Dr. Hasan MANDAL** Türkiye Bilimsel ve Teknolojik Araştırma Kurumu-TÜBİTAK Başkanı	**15:40-15:55**	**Prof. Dr. Rana SANYAL** Boğaziçi Üniversitesi Yaşam Bilimleri ve Teknolojileri Merkezi Müdürü/RS Research
14:25-14:40	**Doç. Dr. Tolga KARAKAN** Türkiye İlaç ve Tıbbi Cihaz Kurumu -TİTCK Başkanı	**15:55-16:10**	**Prof. Dr. Hülya AYAR KAYALI** DEU İzmir Biyotıp ve Genom Enstitüsü Öğretim Üyesi/İzmir Biyotıp ve Genom Merkezi-İBG Grup Lideri
14:40-14:55	**Dr. Ecz. Nihan Burul BOZKURT** Türkiye İlaç ve Tıbbi Cihaz Kurumu -TİTCK Klinik Araştırmalar Daire Başkanı	**16:10-16:25**	**Dr. Süha TAŞPOLATOĞLU** Abdi İbrahim İlaç CEO'su
14:55-15:05	**Prof. Dr. Erhan AKDOĞAN** Türkiye Sağlık Enstitüleri Başkanlığı-TÜSEB Başkanı	**16:25-16:40**	**Dr. Hasan Ersin ZEYTİN** Nobel İlaç San ve Tic A.Ş Biyoteknoloji ve Yeni Ürün Değerlendirme Direktörü
15:05-15:15	**Doç. Dr. Rabia ÇAKIR KOÇ** Türkiye Sağlık Enstitüleri Başkanlığı-TÜSEB Türkiye Biyoteknoloji Enstitüsü Başkanı	**16:40-16:55**	**Dr. Ecz. Ferhat FARSİ** CinnaGen İlaç Kurucu Ortağı ve CEO'su
15:15-15:25	**Ara**	**16:55-18:00**	**TARTIŞMA**

DÜZENLEME KURULU

Asuman BOZKIR
Sinem ASLAN ERDEM
İlker ATEŞ
Zeynep ATEŞ ALAGÖZ
Filiz BAKAR ATEŞ
Meltem CEYLAN ÜNLÜSOY
Burcu DEVRİM
Zerrin SEZGİN BAYINDIR
Gülnur EKŞİ BONA
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Prof. Dr. Asuman BOZKIR

Ankara Üniversitesi

Eczacılık Fakültesi Dekanı

Ankara Üniversitesi Eczacılık Fakültesi, Farmasötik Teknoloji Anabilim Dalı'nda Profesör olarak görev yapan Asuman Bozkır, Ankara Üniversitesi Eczacılık Fakültesi'nden mezun olduktan sonra, 1984 yılında endüstri eczacılığı alanında yüksek lisans, 1989 yılında farmasötik teknoloji alanında doktora eğitimini tamamlamış ve 1991 yılında yardımcı doçent ünvanını almıştır. British Council Doktora Sonrası Araştırma Bursu ile 1997 yılında, İngiltere- Birmingham, Aston Üniversitesi, Farmasötik ve Biyolojik Bilimler Bölümünde, Farmasötik Biyoteknoloji Alanında, araştırmacı olarak, doktora sonrası çalışmalar yapmıştır. 1997 yılında Farmasötik Teknoloji Doçenti, 2004 yılında Profesör olmuştur. Araştırma ve ilgi alanları Farmasötik Biyoteknoloji (aşı/adjuvan formülasyonları, gen/biyomakromolekül taşıyıcı sistemler, aktif hedeflendirilmiş nanotaşıyıcılar, nanobiyoteknoloji, gen/peptid/protein yapılı ilaçların formülasyonu) ile ilaç formülasyonlarının tasarlanması, stabilitesi ve uygulama yolları konularıdır. 1998 yılından beri T.C. Sağlık Bakanlığı TİTCK'de İlaç, Aşı ve Biyoteknolojik Ürünler Teknik İnceleme, Değerlendirme ve Ruhsatlandırma Komisyonu üyesi olarak devam etmektedir. 2002 yılından itibaren Ankara Üniversitesi Biyoteknoloji Enstitüsü/Eczacılık Fakültesinde, Biyoteknoloji/Farmasötik biyoteknoloji Lisansüstü eğitim/öğretim programlarının ve projelerin oluşturulmasında, eğitimlerin verilmesinde görev almaktadır. 2018 yılından itibaren TÜSEB Aşı Bilim Kurul üyeliğini sürdürmektedir. Halihazırda Avrupa Biyoteknoloji Federasyonunun üyesidir. 2004 yılında Novartis Farmasötik Teknoloji Araştırma Ödülünü alan Asuman Bozkır'ın yerli ve yabancı dilde yayınlanmış kitap bölümleri ve bilimsel makaleleri bulunmaktadır.

Sunum Hakkında

Aşı ve İlaç Geliştirme Süreçlerinde Ar-Ge Ekosistemi Oluşturmanın Önemi

Ülkemizde İlaç ve Aşı geliştirme süreçlerinde gelinen aşamada, Ar-Ge ekosistemini oluşturan paydaşlarca yapılanlar ve geliştirmeye açık yönlerimiz konusunda görüş oluşturmak amacı ile değerlendirmeler yapılması önemlidir.

Bilindiği üzere, 2019 yılı sonunda Çin'de başlayarak tüm dünyayı etkisi altına alan Covid-19 pandemi sürecinin toplum ve iş hayatında oluşturduğu olağan üstü şartlar, her sektör gibi sağlık ve ilaç sektörünü de etkilemiştir.

İlaç sektörü teknolojiyi yakından takip ederek, güncel teknolojileri uygulamaya geçirmek, bu amaçla sürekli yatırım yapmak zorunda olan, üretilemeyen ürünleri üretir hale gelmek için yeni tesisler kurmak ve sistematik olarak yenileme çalışmaları yapmak ihtiyacında olan dinamik bir sektördür.

İzlenen yerelleşme politikalarının ilaç endüstrisi üzerinde olumlu etkileri sonucunda pek çok ilaç firmasında kamu destekleri ile kurulan biyolojik/biyoteknolojik üretim alt yapısı sayesinde yenilikçi katma değerli ürünlerin yanı sıra aşı/biyobenzer ürünlerin üretimi de gündeme gelmiştir.

İlaçlar yüksek katma değeri olan bilgiye dayalı ileri teknoloji ürünleridir. Aşılar ise, ilaç kategorisinde değerlendirilen ürünlerdir. Ancak ilaçtan farkı tedavi edici değil, koruyucu olmasıdır.

Aşı ve İlaç araştırmaları bağımsız etik kurulların uygun bulması durumunda, ilaç ruhsatlandırma otoritelerinin denetiminde gerçekleştirilir. İlaç/Aşı ruhsatlandırma otoritelerinin veriye güvenmediğinde olumlu karar vermesi mümkün olmadığından, araştırmalar sırasında elde edilecek verinin kalitesi otorite açısından büyük öneme sahiptir.

İlaç geliştirme çalışmalarında önde gelen Kuzey Amerika, Avrupa ve Japonya'nın öncülüğünde kurulan, Türkiye'nin de 2020 yılında tam üyesi olduğu Uluslararası Harmonizasyon Konseyi'nin (ICH) klavuzlarına uygunluk, aşı ve ilaç geliştirme süreçlerinde önemli bir güvence sağlamıştır. Bir ilaç yada aşının araştırma safhasından kullanıma geçmesi, etkinlik ve güvenliliğinin her düzeyde ispat edilmesi ile olur.

Sağlık Bakanlığı Türkiye İlaç ve Tıbbi Cihaz Kurumu (TİTCK), gibi sağlık otoritelerinin ilaç ve aşının geliştirme ve üretim aşamalarında hangi verilerin elde edildiğini, etik kurullara uygunluğunu, inceleme ve gerektiğinde her türlü açıklamayı talep etme hakkı ve yetkisi bulunmaktadır. Süreçlerin ne ölçüde şeffaf ve açıklanabilir olduğu aşı ya da ilaca güvenilirliğin bir ölçüsüdür. Aşı ve ilaç geliştirme süreçleri birbirine benzer olsa da başta çocuklar olmak üzere sağlıklı bireylere uygulanması sebebiyle aşıların ruhsatlanması birçok ilaçtan daha sık ve titiz koşullara bağlanmıştır.

İlaç sektörü en yüksek araştırma ve geliştirme (Ar-Ge) potansiyeline sahip küresel bir endüstridir. Küresel ilaç pazarında artan rekabet, farmakoekonomi ve (GMP-GLP) denetim gibi nedenler ilaç endüstrisinin diğer endüstrilerden farklılaşmasına neden olmaktadır.

İlaç sektöründeki Ar-Ge'nin diğer sektörlerle kıyaslandığında, farklı özelliklere sahip olduğu görülmektedir. Bu araştırmaların temel araştırma ve klinik araştırma olarak ikiye ayrılması ve klinik araştırma sürecinin insan katılımlı olması, ilaç sektörü Ar-Ge'sini diğer sektörlerden ayıran başlıca özelliktir.

İlaç sektöründeki Ar-Ge yeni molekül bulma, var olan moleküller için yeni kullanım alanlarının belirlenmesi veya yan etkisi olan bir ilacın tekrar değerlendirilmesini kapsayan temel ve klinik araştırmalar ile uzun ve maliyetli bir süreçtir. Biyoteknoloji ve nanoteknoloji günümüzün ilaç endüstrisinde devrim yaratan/yaratacak teknolojileri arasında görülmektedir.

Ar-Ge ekosisteminin paydaşları; üniversiteler, araştırma merkezleri, kamu, özel sektör ve girişimcilerdir. Paydaşların uygun koşullarda birbirleriyle etkileşmeleri sonucu uygulanabilir yeni

fikirler ortaya çıkmaktadır. Bu ekosistemi destekleyen koşulları ise, finansal kaynaklar ve teşvik mekanizmaları, yasal düzenlemeler, eğitim ve insan kaynakları ile yatırım ortamı faktörleri oluşturmaktadır.

Öneriler;

-Ülkemizde etkin bir Ar-Ge ekosistemi oluşturulması, bu ekosistem içindeki paydaşlar arasında güçlü bir iletişim ağı kurulması sağlanarak birlikte çalışmalarının teşvik edilmesi önemlidir.

-Kamunun öncülüğünde, ilaç endüstrisinin paydaşlarla bir araya gelmesi ile yenilikçi ilaçları geliştirmek için konsorsiyum oluşturmaları sağlanmalı ve Ar-Ge konusunda daha fazla teşvik sağlanarak, teşviklerin patente dönmesi için takip sistemi ve yol haritası oluşturulmalıdır.

-Bu üretimlerin ülke ekonomisine daha fazla katkı sağlaması için; öncelikli alanlarda yetişmiş nitelikli insan gücü olmak üzere, hammadde, yardımcı madde, teknik ve teknolojik destek sağlayan cihazların üretimlerinin de yerelleşmesine ihtiyaç bulunmaktadır.

Panelimizde bu fikirlerden hareketle ilaç ve aşı üretiminde en önemli paydaşlardan olan İlaç Sanayii, Otorite ve Akademinin temsilcilerini bir araya getirerek, ülkemizde bu konuda yapılanlar ve yapılması gerekenleri tartışarak çözüm önerilerinin sunulması hedeflenmiştir.Bu kapsamda yoğun çalışmaları arasında zaman ayıran tüm panelistlerimize değerli görüşlerini , deneyimlerini ve önerilerini bizlerle paylaşacak olmalarından dolayı şahsım ve fakültem adına içtenlikle teşekkür eder, panelimiz sonucu oluşacak görüş ve önerilerin Ülkemiz Ar-Ge ekosisteminin oluşmasına ve gelişmesine katkı sağlamasını dilerim.

Saygılarımla.

Prof. Dr. Hasan MANDAL

Türkiye Bilimsel ve Teknolojik Araştırma Kurumu

TÜBİTAK Başkanı

1965 yılında Eskişehir'de doğan Prof. Dr. Hasan MANDAL, ilk (Yunusemre), orta (Atatürk) ve lise (Motor Meslek) eğitimini Eskişehir'de tamamladı. 1987 yılında ODTÜ, Metalurji Mühendisliği Bölümü'nden Lisans derecesini (Şeref Öğrencisi), 1992'de İngiltere Newcastle Üniversitesi'nden Doktora unvanını aldı. 1992-1994 yıllarında İngiltere Newcastle Üniversitesinde, 1997-1998 yıllarında da Alexander Humboldt Bursu ile Almanya Karlsruhe Üniversitesinde doktora sonrası araştırmalarda bulundu.

1994 yılında Anadolu Üniversitesi, Seramik Mühendisliği Bölümünde Yardımcı Doçent olarak göreve başladı. 1996'da Doçent, 2001'de Profesör unvanını almıştır. Prof. Dr. Hasan MANDAL'ın 70'i SCI kapsamındaki dergilerde yayınlanmış 140'ın üzerinde eseri ve ayrıca 6 adette uluslararası kapsamda patenti bulunmaktadır. Atıf Sayısı 1200, H-index'i 16'dır. Prof. Dr. Hasan MANDAL, arasında TÜBİTAK Bilim Ödülü dahil olmak üzere ulusal ve uluslararası düzeyde farklı ödüllere layık görülmüştür. Kendisi Türkiye Bilimler Akademisi (TÜBA), Dünya Seramik Akademisi (WAC) ve Avrupa Akademisi (AE) üyesidir.

Prof. Dr. Hasan MANDAL, 2011-2015 yılları arasında Sabancı Üniversitesinde, Araştırma ve Lisansüstü Politikalar Direktörü, Ocak 2012 itibaren de aynı zamanda Sabancı Üniversitesi Rektör Yardımcısı olarak da görev yapmıştır.

Kendisinin geçmişte yönetsel görevlerinin arasında, Küresel Mühendislik Dekanları Konsey Başkanlığı, Uluslararası Mühendislik Eğitimi Dernekleri Federasyonu 1. Başkan Yardımcılığı, Avrupa Seramik Derneği Başkanlığı, Anadolu Üniversitesi Rektör Yardımcılığı ile Mühendislik ve Mimarlık Fakültesi Dekanlığı, Türkiye Mühendislik Dekanları Konseyi Genel Sekreterliği, ATAP ve GOSB Teknopark Yönetim Kurulu Üyelikleri, İnovent A.Ş. Yönetim Kurulu Üyeliği, BOREN Yönetim Kurulu Üyeliği, TÜBİTAK, Teknoloji Transferi Mekanizmaları Destekleme Grubu (TEMEG), Mühendislik Araştırma Grubu (MAG) Yürütme Kurulu Üyelikleri yer almaktadır.

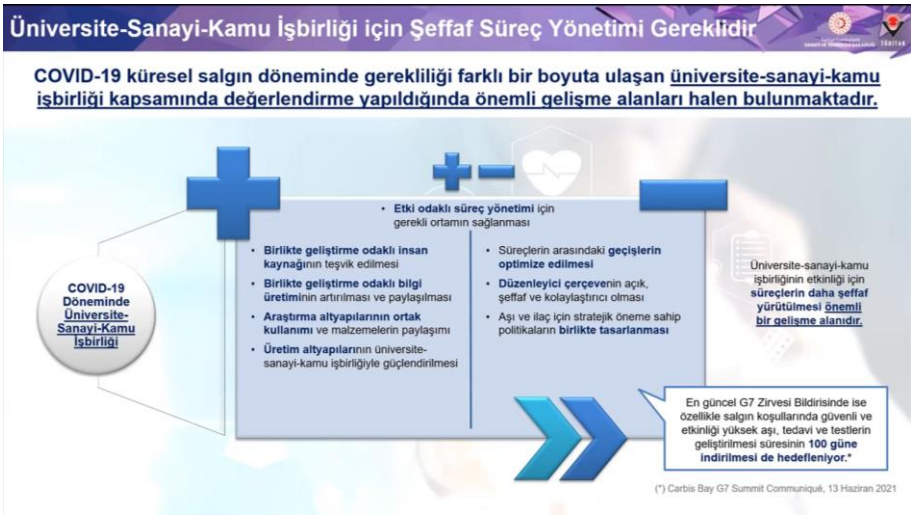
Prof. Dr. Hasan MANDAL, 25.03.2015 tarihinde YÖK Üyeliğine atanmıştır. 1 Nisan 2015 tarihinde YÖK Yürütme Kurulu Üyesi, 21 Temmuz 2016'da YÖK Başkan Vekilliğine seçilmiştir ve bu görevlerini 12 Ocak 2018 tarihlerine kadar sürdürmüştür. Prof. Dr. Hasan MANDAL, 12 Ocak 2018'den 22 Şubat 2018 tarihine kadar Sabancı Üniversitesi Rektör Vekili olarak görev yapmıştır.

22 Şubat 2018 tarihinde TÜBİTAK Başkanı olarak atanmıştır.

Prof. Dr. Hasan MANDAL, 8 Ekim 2018 tarihinde Cumhurbaşkanlığı Bilim, Teknoloji ve Yenilik Politikaları Kurulu üyeliğine atanmış ve 1 Kasım 2018 tarihinde Başkan Vekilliği görevine seçilmiştir.

Prof. Dr. Hasan MANDAL, 27 Nisan 2019 tarihinde YÖK üyeliğine seçilmiştir.

Sunum Hakkında



Doç. Dr. Tolga KARAKAN

Türkiye İlaç ve Tıbbi Cihaz Kurumu -TİTCK Başkanı

1977 yılında Gaziantep'de doğdu. Gazi Üniversitesi Tıp Fakültesi'ni bitirdi.

Meslek hayatına 2005 yılında Ankara Eğitim ve Araştırma Hastanesi'nde başladı. Aynı hastanede Üroloji uzmanlığı eğitimini tamamladı.

Askerliğini 2011 yılında Tabip Asteğmen olarak Ardahan Askeri Hastanesi'nde yaptı. Askerliğinin ardından 2012 yılında Ankara Eğitim ve Araştırma Hastanesi'ndeki görevine geri döndü.

2015 yılında Yenimahalle Eğitim ve Araştırma Hastanesi'ne Başhekim Yardımcısı olarak atandı. 2017 yılına kadar bu hastanede görev yaptı.

Doçentlik unvanını kazandığı Ankara Eğitim ve Araştırma Hastanesi'ndeki görevine iki yıl devam ettikten sonra 2019 yılında Ankara Şehir Hastanesi'nde Onkoloji Hastanesi Başhekim Yardımcısı olarak görev aldı.

Doç. Dr. Tolga Karakan, 2020 yılının Eylül ayından 2021 yılı Mayıs ayına kadar TİTCK Tıbbi Cihaz ve Kozmetik Ürünler Başkan Yardımcısı olarak görev yapmış; 2021 yılının Mayıs ayında Türkiye İlaç ve Tıbbi Cihaz Kurumu Başkanlığına atanmıştır.

Doç. Dr. Tolga Karakan'ın ulusal ve uluslararası bilimsel dergilerde yayınlanmış çok sayıda makalesi, yine ulusal ve uluslararası bilimsel toplantılarda sunulmuş çok sayıda bildirisi bulunmaktadır.

İyi derecede İngilizce bilen Doç. Dr. Tolga Karakan evli ve bir çocuk babasıdır.

Sunum Hakkında

Türkiye İlaç ve Tıbbi Cihaz Kurumu'nun hedefi; insan odaklı, bilimselliği esas alan değer üreten, uluslararası alanda öncü referans bir kurum olmaktır. Kurumun öncelikli görevi; ilaç, tıbbi cihaz, geleneksel bitkisel, destek ve ileri tedavi tıbbi ürünleri ile kozmetik ürünlere yönelik düzenleyici, denetleyici ve yönlendirici icraatlarla topluma hizmet etmektir. Türkiye İlaç ve Tıbbi Cihaz Kurumu, Avrupa Birliği Komisyonu çalışma grupları, Farmasötik Denetim İş Birliği Konvansiyonu (PIC/S) gibi uluslararası platformlarda yer almaktadır. İlaçların etkili, güvenli ve yüksek kalitede olduğunu garanti etmek için dünya çapında regülasyonların uyumlaştırılmasını amaç edinmiş bir kuruluş olan Uluslararası Uyum Konseyine (ICH) üyedir.

2020 yılı boyunca mücadele ettiğimiz COVID-19 pandemisi sorumluluklarımızın gerçekleştirilmesi adına sağlık işgücümüze ve altyapımıza yapılan yatırımların ne kadar isabetli yatırımlar olduğunu göstermiştir. Bu sürecin, ilaçlara ilişkin klinik araştırma, denetim, ruhsatlandırma gibi piyasaya arz öncesi faaliyetlerimizde ve ilaç tedarik, akılcı ilaç kullanımı, ilaç tanıtımı gibi piyasaya arz sonrası faaliyetlerimizde de ilave önlemleri ve uygulamaları zorunlu kıldığı aşikârdır. Kurumumuzca, pandemi ile mücadelede kritik öneme haiz ürünlerin bulunabilirliğine özellikle önem verilmiş ve bu hususta çalışmalarımıza devam edilmektedir.

Yerel üretim çalışmaları ile 2016 yılında kutu bazında % 75 olan imal ilaç oranı 2019 yılında % 87,6'ya çıkmıştır. 2020 yılı değeri ise % 87 olarak gerçekleşmiştir. Değer bazında 2016 yılında % 42 olan imal ilaç oranı ise 2019 yılında % 51,8'e çıkmıştır. 2020 yılında ise bu rakam % 50 olarak gerçekleşmiştir. 2020 yılı Covid19 Pandemisi nedeniyle ayrı olarak değerlendirilmelidir.

Bu zorlu süreçte, Kurumumuz içerisinde yer alan Bilimsel Komisyonlarımız ile üniversitelerimizden değerli hocalarımızla aktif olarak çalışmalarımıza da devam edilmektedir. Aralık 2020'den beridir acil kullanım onayı için çalışmalarımızı sürdürmekteyiz. AKO başvurusu yapılan aşının; yarar/risk dengesinin pozitif olması, kapsamlı klinik verilerin başvuru sahibi tarafından daha sonra sağlanacak olması, karşılanmamış tıbbi ihtiyacın giderilmesi, ek veri gerektirmesine rağmen ilgili aşının piyasada bulunmasının halk sağlığına sağladığı faydanın, bulunmamasının oluşturacağı riske kıyasla daha fazla olması halinde Kurumumuz tarafından AKO verilebilmektedir. Bu süreçte; AKO başvuruları Kurumumuzun üst düzey bir komisyonu tarafından değerlendirilmektedir.

COVID-19 pandemi, aşı geliştirilmesi konusunun ne kadar önemli olduğunu göstermiştir. Kurumumuz, tüm bilimsel gelişmeleri yakından takip etmekte olup uluslararası uygulamalara paralel olarak aşı geliştiren gruplara yol gösterici faaliyetler yürütmektedir. Bu kapsamda, "Viral Aşı Adaylarının Klinik Araştırmalara Geçişi İçin Gereklilikler Tablosu" hazırlanmış ve "Beşeri Aşıların Klinik Dışı Değerlendirilmesine İlişkin Kılavuz"u yayımlanmıştır.

Kurumumuzca, GCP denetimleri eğitici ve bilgilendirici bir şekilde yürütülerek mevcut faz 1 klinik araştırma merkezlerinin kalite standartlarının arttırılması sağlanmış, bununla birlikte söz konusu yaklaşımla yeni açılacak merkezlerin denetim ve belgelendirilme sürecinde zaman kayıplarının önüne geçilmiştir.

COVID-19 Pandemisi kapsamında hem mevcut hem de yeni açılacak olan faz 1 klinik araştırma merkezlerinin her türlü başvuru, denetim ve belgelendirme sürecine öncelik verilmiş, ilgililerle bire bir iletişime geçilerek süreçlerin takibi sağlanmış, süreçler ivedilikle tamamlanmış ve gecikmelerin önüne geçilmiştir. Mevcut durumda aşı çalışmalarındaki son durumda; 1 aşı için Faz III çalışması başlatılmış olup 1 aşıda Faz II çalışma da başlamak üzeredir. 2 aşının Faz I çalışmaları bitmek üzere olup, Faz I çalışmaya başlamak üzere olan 3 aşı vardır.

Sonuç olarak, üniversite, kamu ve sanayi işbirliğinde Kurumumuza düşen görevlere elimizden geldiğince en yüksek önem verilecektir.

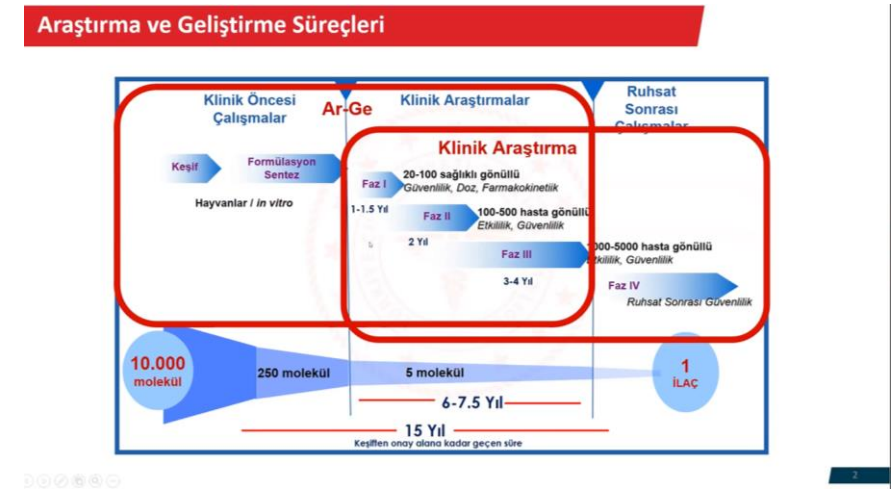
Dr. Ecz. Nihan BURUL BOZKURT

Türkiye İlaç ve Tıbbi Cihaz Kurumu -TİTCK

Klinik Araştırmalar Daire Başkanı

Dr. Ecz. Nihan Burul Bozkurt 1999 yılında Hacettepe Üniversitesi Eczacılık Fakültesi'nden mezun olmuştur. Aynı Üniversitede Famakoloji yüksek lisans ve doktora eğitimini tamamlamıştır. Eğitimi süresince yurtdışındaki farklı üniversitelerde davetli araştırmacı olarak kısa süreli bulunmuştur. Doktora sonrası davetli araştırmacı olarak İsveç Karolinska Enstitüsü Alzheimer Hastalığı Araştırma Merkezi'nde çalışmalar yürütmüştür. Hacettepe Üniversitesi'ndeki görevinin ardından Novagenix Bio-Analitik İlaç Ar-Ge merkezinde Klinik Direktör olarak görev almıştır. Mayıs 2016 yılında Türkiye İlaç ve Tıbbi Cihaz Kurumu'ndaki görevine başlamıştır. Bu tarihten itibaren Klinik Araştırmalar Daire Başkanlığı görevini yürütmektedir.

Sunum Hakkında

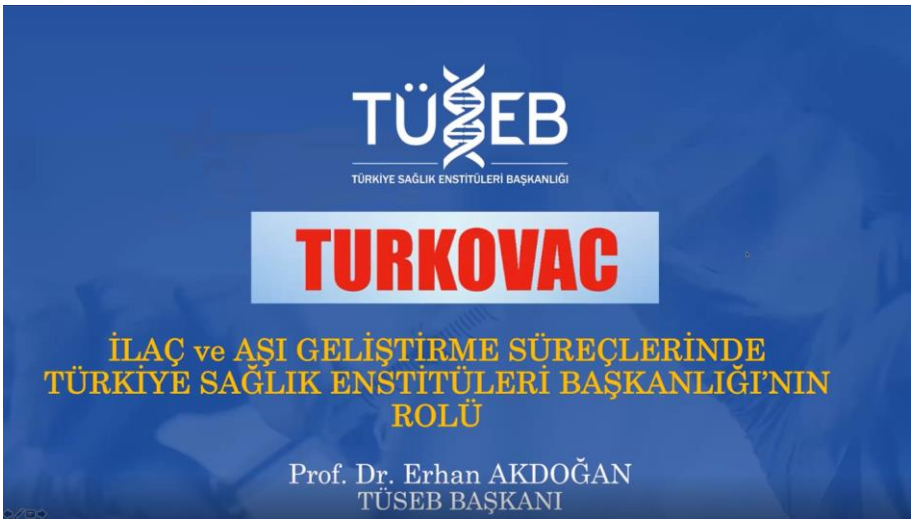


Prof. Dr. Erhan AKDOĞAN

Türkiye Sağlık Enstitüleri Başkanlığı-TÜSEB Başkanı

Dr. Akdoğan, 1999 yılında Yıldız Teknik Üniversitesi, Elektrik-Elektronik Fakültesi, Elektronik ve Haberleşme Mühendisliği Bölümü'nden mezun oldu. Yüksek Lisans ve Doktora eğitimini, Araştırma Görevlisi olarak görev yaptığı Marmara Üniversitesi'nde tamamladı. Doktora çalışmaları esnasında Rehabilitasyon Robotlarının Tasarımı, Üretimi ve Yapay Zeka tabanlı kontrolü üzerine çalıştı. 2008-2009 yılları arasında Japonya Hiroshima Üniversitesi'nde Biyolojik Sistemler Mühendisliği Araştırma Laboratuarı'nda doktora sonrası araştırmalar için bulundu. 2010 yılında öğretim üyesi olarak Yıldız Teknik Üniversitesi Makine Fakültesi Mekatronik Mühendisliği Bölümü'nde göreve başladı. Kurmuş olduğu Biyomekatronik Araştırma Laboratuarı'nda medikal mekatronik alanında birçok araştırma projesi, bilimsel yayın, lisans ve lisansüstü seviyede tez danışmanlığı yaptı ayrıca birçok patent, faydalı model ve endüstriyel tasarım tescilleri aldı. Temmuz 2020'de Yıldız Teknik Üniversitesi'nde medikal teknolojiler, robotik ve yapay zekâ odaklı olarak faaliyet göstermek üzere hayata geçirilen Biyomekatronik ve Robotik Sistemler Uygulama ve Araştırma Merkezi Kurucu Müdürlüğünü üstlendi. YTÜ Teknopark A.Ş.'de Sağlık Teknolojileri dikeyinde yürütülen çalışmaların danışmanlığını yaparak birçok girişimin hayata geçmesini sağladı. Araştırma ilgi alanları medikal cihaz tasarımı, fizik tedavi ve rehabilitasyon robotları, biyolojik işaret işleme ve yapay zekâ konularını kapsamaktadır. TEKNOFEST, TET ARGE PAZARI, IEEE gibi birçok teknoloji odaklı yarışmalarda sağlık kategorilerinde birincilikleri bulunmaktadır. Evli ve bir kız çocuğu babası olan Dr. Akdoğan aynı zamanda Türkiye İzcilik Federasyonu'nun lider eğitimci yardımcısı derecesine sahip izci lideridir.

Sunum Hakkında



Doç. Dr. Rabia ÇAKIR KOÇ

Türkiye Sağlık Enstitüleri Başkanlığı-TÜSEB

Türkiye Biyoteknoloji Enstitüsü Başkanı

İstanbul Üniversitesi, Cerrahpaşa Tıp Fakültesi, Tıbbi Biyolojik Bilimler Bölümü'nde Lisans öğrenimini tamamladıktan sonra, Yüksek Lisans ve Doktora çalışmalarını Yıldız Teknik Üniversitesi Biyomühendislik Bölümü'nde gerçekleştirmiştir. Yüksek lisans tez çalışmasını hücre kültür teknikleri ve sitotoksisite konularında; Doktora tez çalışmasını ise Leishmaniasise Karşı Aşı Geliştirilmesi özelinde, laboratuvar ölçeğinde aşı üretilmesi ve deney hayvanlarında aşı etkinliğinin değerlendirilmesi çalışmaları ile tamamlamıştır.

Doktora sonrası Yeni Yüzyıl Üniversitesi Biyomedikal Mühendisliği Bölümü'nde ve Yıldız Teknik Üniversitesi Biyomühendislik Bölümü'nde Yardımcı Doçent olarak görev almıştır. Doçentlik ünvanını Biyomühendislik Alanından Biyoteknoloji ve Hayvan-Doku Kültürü anahtar kelimeleri ile sözlü sınav sonucu kazanmıştır.

Biyoteknoloji alanında; TÜBİTAK, Bakanlıklar (Sağlık, Tarım vb.), Yükseköğretim Kurumu tarafından desteklenen Aşı, Antikor, İlaç ve Tanı Kiti Geliştirme ile ilgili 15'den fazla araştırma projesinde yürütücü, araştırmacı veya danışman olarak görev almıştır. Ayrıca Food-borne parasites konulu 31 ülke ile ortak yürütülen COST projesinde 3 yıl boyunca Türkiye temsilcisi olarak yer almıştır. Uluslararası indekslerce taranan dergilerde araştırma makaleleri, uluslararası bilimsel kitap bölümleri, ulusal ve uluslararası kongrelerde bildiriler olmak üzere 150'ye yakın bilimsel eseri yayınlanmıştır. Biyomühendislik alanında danışmanlığında aşı, tanı, ilaç ve nanoteknoloji konularında devam eden ve tamamlanmış birçok yüksek lisans ve doktora tez çalışması mevcuttur.

TÜBİTAK, KOSGEB, Yüksek öğretim kurumlarına bağlı proje destek birimleri başta olmak üzere çok sayıdaki projenin değerlendirilmesi ve izlenmesi görevlerinde bulunmuş, uluslararası indeksli dergilere hakemlik ya da editoryal kurul üyeliği yaparak bilimsel makalelerin değerlendirilmesinde katkı sağlamıştır.

Üniversitede görev aldığı süre boyunca akademik çalışmalarının yanı sıra Bölüm Başkan Yardımcılığı, Kalite İç Denetçiliği, Fakülte Akademik Kurul Üyeliği, Etik Kurul Üyeliği, Lisansüstü Koordinatörlüğü gibi görevlerde bulunmuştur.

TÜSEB Türkiye Biyoteknoloji Enstitüsü Başkanı olarak görev yapmakta olan Rabia ÇAKIR KOÇ, evli ve iki çocuk annesidir.

Sunum Hakkında

TÜSEB
TÜRKİYE SAĞLIK ENSTİTÜLERİ BAŞKANLIĞI

TÜRKİYE BİYOTEKNOLOJİ ENSTİTÜSÜ

Üniversite – Sanayi – Kamu İşbirliği için Örnek Proje

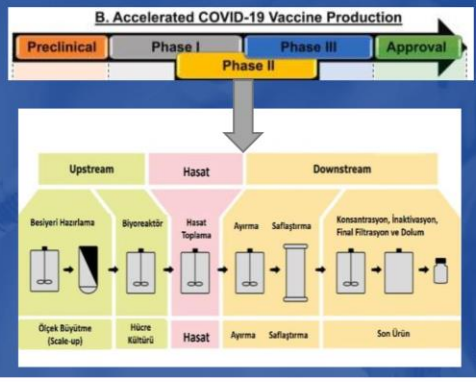
Doç. Dr. Rabia ÇAKIR KOÇ
TÜRKİYE BİYOTEKNOLOJİ ENSTİTÜSÜ BAŞKANI

SARS-CoV-2 Virüsüne Karşı İnaktif Virüs Aşısı ile Rekombinant Aşısı üretimi için Preklinik Sonrası Proses Geliştirilmesi

- Projenin amacı;

Ülkemiz araştırmacıları tarafından geliştirilen ve iki farklı aşı adayının (inaktif ve rekombinant) büyük ölçekli üretimi için

- gereken ölçek büyütme
- saflaştırma yöntemlerinin geliştirilmesi
- optimizasyon çalışmaları



Projenin İşbirliğindeki Rolü

Üniversite

- Aşının *in vitro* ve *in vivo* çalışmalarının gerçekleştirilerek Pre-klinik aşamanın tamamlanması

Kamu/TÜSEB

- Projenin hayata geçirilmesi
- İşbirliği sağlama

Sanayi

- ölçek büyütme
- saflaştırma yöntemlerinin geliştirilmesi
- optimizasyon çalışmaları

Prof. Dr. Mayda GÜRSEL

Orta Doğu Teknik Üniversitesi

Biyolojik Bilimler Bölümü Öğretim Üyesi

Mayda Gürsel, Orta Doğu Teknik Üniversitesi Biyolojik Bilimler Bölümü'nde profesördür. Dr. Gürsel'in araştırmaları, doğal bağışıklık sistemi ve aşılar üzerine yoğunlaşmıştır. 1987 yılında ODTÜ Biyolojik Bilimler Bölümü'nden mezun olan Dr. Gürsel, aynı bölümde yüksek lisansını 1990 yılında tamamlamış ve doktora derecesini 1995 yılında University College London, The School of Pharmacy'den almıştır. 1998-2006 yılları arasında ABD Gıda ve İlaç Dairesi (FDA) Biyolojikler Değerlendirme ve Araştırma Merkezi'nde (CBER) önce doktora sonrası araştırmacı olarak ve daha sonra viral aşı ürünlerini denetleyen deneyimli bilim insanı olarak çalışmalarda bulunmuştur.

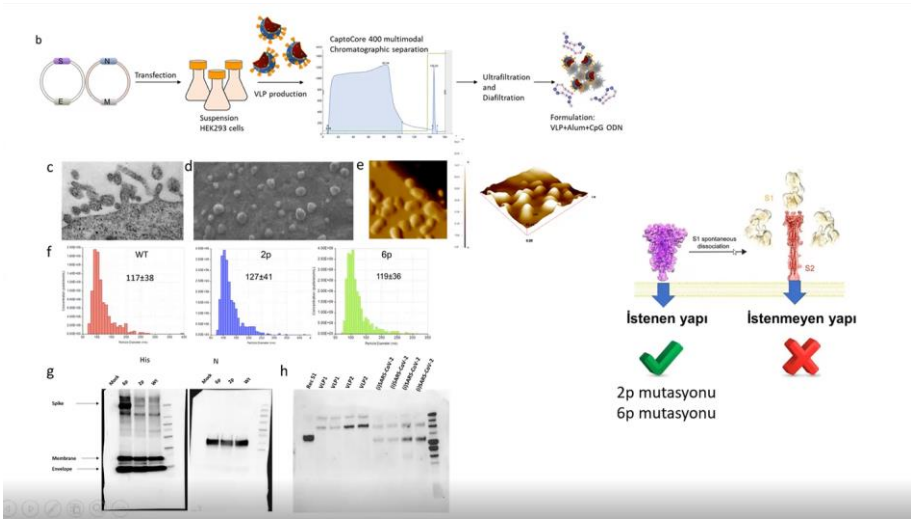
Sunum Hakkında

COVID-19'a Karşı VLP Aşısının Geliştirilmesi

TÜBİTAK COVİD-19 Aşı ve İlaç Platformu

TÜBİTAK MAM

ODTÜ	Bilkent	Hacettepe
MAYDA GÜRSEL (PI)	**İHSAN GÜRSEL(Co-PI)**	**PETEK KORKUSUZ**
İsmail Cem Yılmaz	Muzaffer Yıldırım	Merve Gizer
Emre Mert İpekoğlu	Tugce Canavar	Sefa Burak Çam
Yağmur Aydın	Nilsu Turay	Eda Çiftçi
İlayda Baydemir	Artun Bülbül	
Naz Sürücü	İrem Evcili	
Neşe Güvençli	Bilgehan İbibik	
	Berfu Saraydar	
	Aslı Gülce Bartan	
	Tuğçe Bildik	
	Gamze Aykut (DVM)	



Sonuçların bağımsız veri izleme komitesi tarafından incelenmesi

TİTCK Süreci ve FazII çalışma izni

FazII'de Wuhan ve İngiliz Varyant Aşıların test edilmesi

Delta ve Delta plus Hint Varyantlarına karşı da Hazırlıkların Başlanması

Sürecin iyileştirilmesi ülkemiz için bir kazanç olacaktır

Prof. Dr. Rana SANYAL

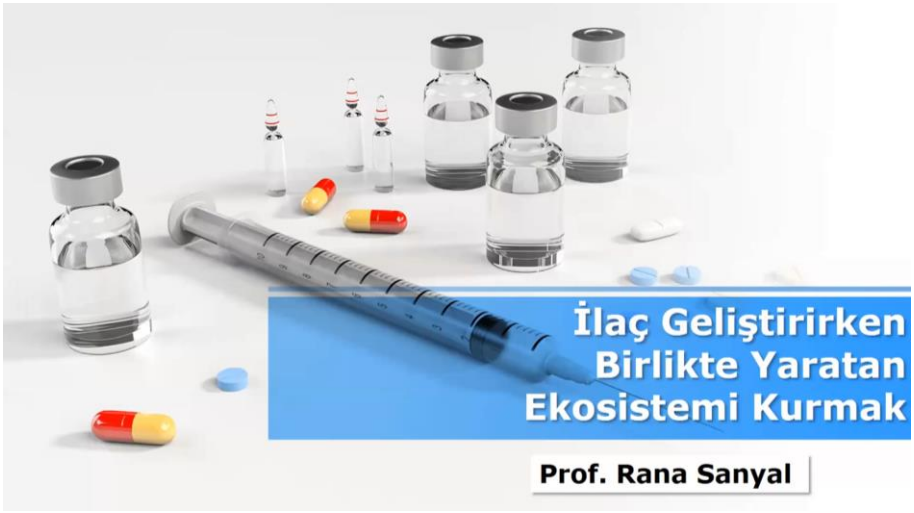
Boğaziçi Üniversitesi Yaşam Bilimleri ve

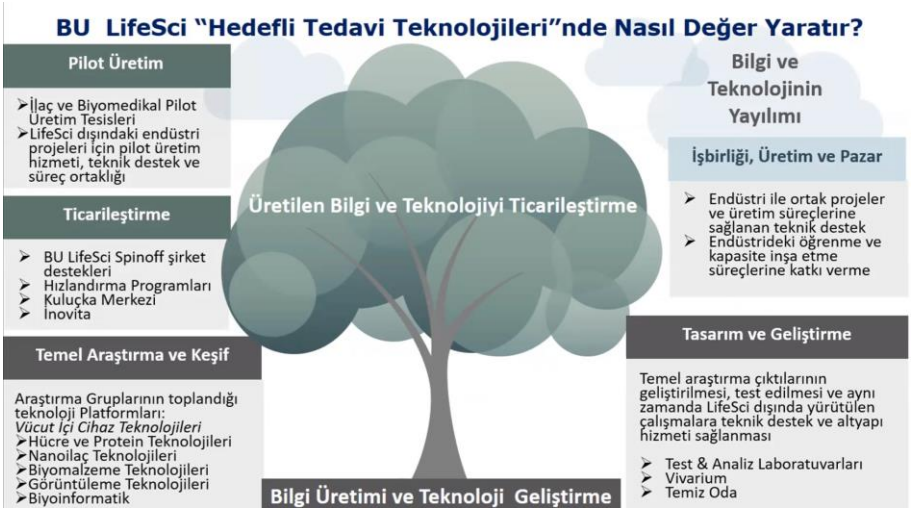
Teknolojileri Merkezi Müdürü/RS Research

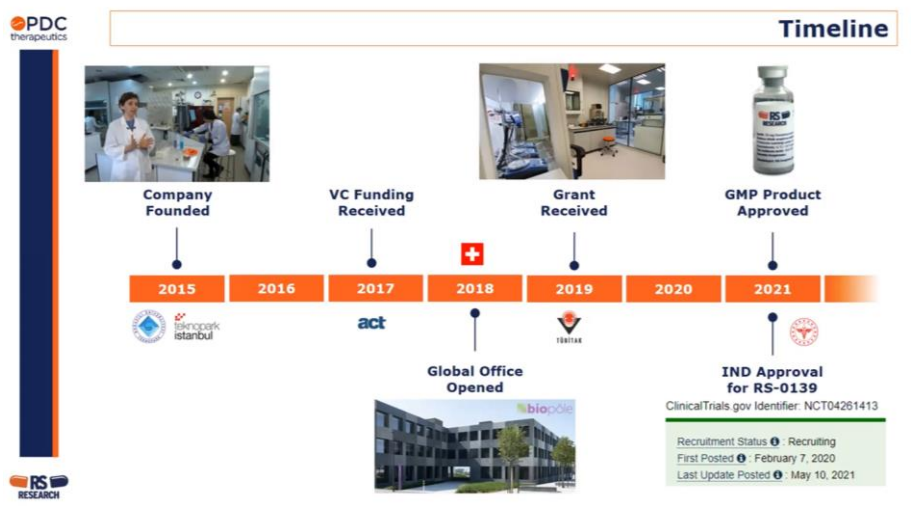
Onkoloji alanında hedefli kemoterapi ilaçları geliştiren Prof Sanyal, Boğaziçi Üniversitesi Kimya Mühendisliği Bölümü'nü bitirdi ve doktorasını Boston Üniversitesi'nden aldı. 2004'te Boğaziçi Üniversitesi Kimya Bölümü'nde öğretim üyesi olarak göreve başlayan Prof. Sanyal, 2015'te ortağı Sena Nomak ile birlikte RS Research'ü kurarak, akademiden girişimciliğe uzandı. Böylece doğrudan tümör hücrelerini hedef alan ilaç geliştirme çalışmalarını kliniğe taşımayı başardı.

Sanyal, çalışmalarıyla 2011 yılında TÜBA-GEBİP ödülüne layık görüldü. 2018 yılında Ekonomist Dergisi, Garanti Bankası ve KAGİDER işbirliğiyle düzenlenen Türkiye'nin Kadın Girişimcisi Yarışması'nda 'Türkiye'nin Gelecek Vaat Eden Kadın Girişimcisi' seçildi. 2021 yılında ise Cartier Women's Initiative tarafından seçilen Bilim ve Teknoloji alanında seçilen 3 global lider arasında yer aldı. Bilimsel yayınlarının yanısıra, 50'yi aşkın uluslararası tescilli patent ve patent başvurusunda buluş sahibi olarak yer alan Sanyal, 2013 yılından bu yana uluslararası bir mükemmeliyet merkezi olan Boğaziçi Üniversitesi Yaşam Bilimleri ve Teknolojileri Merkezi'nin müdürü olarak görevini sürdürüyor.

Sunum Hakkında







Prof. Dr. Hülya AYAR KAYALI

DEU İzmir Biyotıp ve Genom Enstitüsü Öğretim Üyesi/ /İzmir

Biyotıp ve Genom Merkezi-İBG Grup Lideri

Dr. Hülya Ayar Kayalı Dokuz Eylül Üniversitesi Kimya Bölümü'nden (1997) mezun olmuş ve daha sonra yüksek lisans(2001) ve doktora eğitimini de (2005) Biyokimya alanında tamamlamıştır. Postdoc çalışmasını Kanada-McGill Üniversitesinde hücre biyolojisi üzerine gerçekleştirmiştir. Dokuz Eylül Üniversitesi Fen Fakültesine 2008 yılında doçent, 2014 yılında ise profesör olarak atanmış olan Dr.Hülya Ayar Kayalı, 2015 yılından itibaren İzmir Biyotıp ve Genom Merkezinde Biyofarmasötik Teknolojiler ve Biyoanaliz Araştırma Grup lideri olarak çalışmaktadır.
Uluslararası SCI kapsamındaki dergilerde 50 civarında yayını bulunmakta olan Ayar-Kayalı çok sayıda ulusal ve uluslararası toplantılarda bildiri sunmuştur.
Toplam 20 ye yakın ulusal ve uluslararası projede; proje yürütücüsü ve araştırmacı olarak görev almıştır. Bu projelerde özellikle kanser sinyal yolakları ve biyoterapötik ilaçların üretimi, saflaştırılması ve karakterizasyonu konularında çalışmaktadır. İzmir Biyotıp ve Genom Merkezinde, Ayar Kayalı'nın birinde yürütücü, birinde ise araştırmacı olarak görev aldığı iki biyobenzer ilaç üretim projeleri tamamlanarak İlaç Endüstrisi partnerlerine teknoloji transferleri gerçekleştirilmiştir.

Sunum Hakkında

Türkiye'de Biyoteknolojik İlaç Ar-Ge Ekosisteminin Oluşturulması

Ekonomik büyüme ile araştırma-geliştirme (Ar-Ge) faaliyetleri arasında güçlü bir ilişki olduğu bilinmektedir. Ekonomik kalkınma, ülke ekonomilerine yüksek teknoloji isteyen ürünlerin daha düşük fiyatlarla temin edilmesini sağlayan Ar-Ge faaliyetlerinin geliştirilmesi ile mümkündür. Dünyada Ar-Ge'ye en fazla kaynak ayrılan ilaç sektöründe Ar-Ge yapar hale gelmek, yayılma etkisinin yanında sürdürülebilir bir ekonomik büyüme için de önemlidir.

Biyoteknolojik ilaçlar, dünya ilaç endüstrisinin en hızlı gelişen ve yeni yöntemler geliştirmeye açık olan yenilikçi alanıdır. Ülkemizde de Onbirinci Kalkınma Planı dönemi ve 2023 için vizyon, hedef ve politikaları doğrultusunda biyoteknolojik ilaçlar öncelikli alan olarak belirlenmiştir. Özellikle kanser, otoimmün hastalıklar ve nadir hastalıkları da içeren birçok hastalığın tedavisi için hastaların yaşam süresini ve kalitesini artıracak, yasal otoritelerin kabul ettiği ulusal ve uluslararası kılavuzlardaki gereklilikleri sağlayacak hedefe yönelik proteinler, enzimler, monoklonal antikorlar gibi çeşitli biyoteknolojik ilaçların geliştirilmesine devam edilmektedir. Aynı zamanda, patent sürelerinin dolmaya başlamasıyla birlikte ruhsatlı biyolojik referans ilaçlara benzer "biyobenzer" olarak isimlendirilen biyoteknolojik ilaçlar geliştirilmeye de başlanmıştır. Gerek biyobenzer gerekse orijinal ilaçların geliştirme sürecinde kapsamlı Ar-Ge çalışması gerektirmektedir. Ancak bu çalışmalar bilgi birikimi, gelişmiş altyapı, insan kaynağı, kararlı ve büyük yatırımlar gerektirir. Bu kapsamda Ülkemizin Biyoteknolojik ilaç alanındaki çalışmalarında Ar-Ge çalışmalarının hızlandırılması ve etkin hale getirilmesi için biyoteknolojik ilaç ekosisteminin oluşturulması gerekmektedir.

Akademi-Sanayii İşbirliğinin Arttırılması

Akademi ve sanayii iş birliğinin arttırılması için stratejilerinin geliştirilmesi gerekmektedir. Akademik ve sanayinin zayıf ve güçlü alanlarının belirlenmesi sonrası güçlendirilmesi gereken zayıf alanlara yönelik ortak çözüm önerilerinin getirilmesi sonuç almada etkinliği arttıracaktır.

Bu kapsamda, üniversitelerde ders içeriklerinin ilaç sanayinin ihtiyacına göre güncellenmesi, , sanayiide yetkin personelin üniversitede seçmeli dersleri vermesinin sağlanması, ürün geliştirmeye yönelik tezlerin teşvik edilmesi, akademik atamalarda teknoloji transferi gerçekleştiren, ürün protip geliştiren ve patent alan akademisyenlere verilen teşviklerin arttırılması önemlidir. Ayrıca, Fikri Sınai Mülkiyet Hakları komisyonunun kurulması ve üniversitenin FSMH politikasının oluşturulması ve yürütülmesinin sağlanması da araştırmacıların ürün geliştirme yönündeki çalışmalara daha fazla motive olmasını sağlayacaktır. İlaç firmalarına yönelik de Ar-Ge yatırımı yapan firmalara pozitif ayrımcılıkla daha fazla teşvik verilmesi, vergi muafiyetinin uzun süreli sağlanması, kamu alım garantisinin sağlanması, hızlandırılmış onay prosedürlerinin uygulanması ve klinik çalışmalar için destek verilmesi etkin olacaktır.

Biyoteknolojik İlaç Alanında Uzman Araştırmacı Konsorsiyumların Oluşturulması Ülkemizde bu alanda faaliyet gösteren ilaç firmaları, Üniversite ve Araştırma merkezlerinin bilgi birikimi açısından yetkinlik haritalarının çıkarılması önem arz etmektedir. Yetkinlik analizi sonrası biyoteknolojik ilaç alanında çalışan araştırmacıları: nadir hastalıklar, enfeksiyon hastalıkları, bireysel tedaviler, yaşlanma, bio-nano ve kanser araştırma grupları gibi sınıflandırarak bu alanda çalışan araştırmacılardan oluşan alt küme çalışma grupları oluşturulması bilgi paylaşımını hızlandıracaktır. Bu kümeler oluşturulurken kimya, biyokimya, biyoloji, moleküler biyoloji, biyomühendislik ile eczacılık alanlarında çalışan araştırmacılar ve klinisyenler gibi farklı disiplinlerden heterojen grupların kümelerde olması önem taşımaktadır. Alt kümedeki çalışma gruplarının ortak işbirlikli çalışmaları yürütmesi yetişmiş insan gücünün artışını da sağlayacaktır.

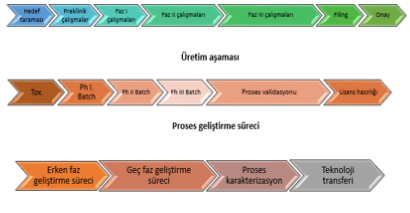
Alt Yapı Ortak Kullanımı

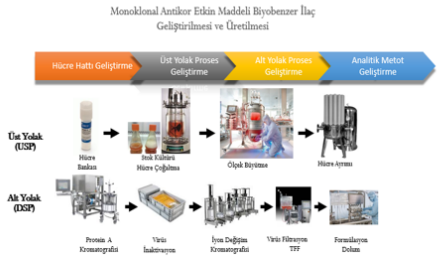
Biyoteknolojik ilaç araştırma geliştirme çalışmaları yüksek teknoloji alt yapısı gerekliliği ve ham maddelerin bütçeleri göz önüne alındığında yüksek bütçeler gerektirmektedir. Bu nedenle, Ülkemizde Kalkınma planları ile biyoteknolojik ilaç üretimi öncelikli alanlar statüsüne alınmış olup Bakanlıklar, TUBİTAK, KOSGEB ve kalkınma ajansları bu alanda Üniversitelere, Araştırma merkezlerine ve İlaç Sanayisine yüksek bütçeli fonlar ile destek olmuşlardır. Bu fonlar ile gerek kamuda gerekse ilaç firmalarında önemli bir alt yapı kazandırılmıştır. Biyoteknolojik ilaç üretim sürecinde teknik ve mevzuatlara uygun hücre geliştirme, üst-alt akım prosesi ve biyolojik ilaç karakterizasyon ve in vivo çalışmaları için oluşturulan mevcut altyapının envanterinin ayrıntılı belirtildiği tek bir noktadan web sitelerinin oluşturulması Ülkemizin farklı kurumlarında çalışan araştırmacıların bu portallara ulaşımı sağlanarak araştırma çalışmalarında kullanmak amaçlı randevu alabileceği bir sisteme dönüştürülmesi Ar-Ge çalışmalarının verimini arttırmada önemli olacaktır. Ayrıca, mevcut alt yapıların kullanıldığı teorik ve uygulamalı çalıştayların düzenlenmesi farklı birimlerde görevli araştırmacıların bu alandaki bilgi birikimini arttırmada ve birbirinden öğrenen ekosistem yapısının geliştirilmesinde etkili olacaktır.

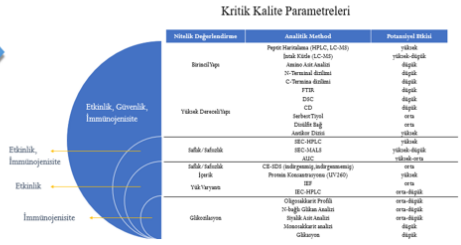
Biyoteknolojik İlaç Hammadde Üretimi

Ülkemizde biyoteknolojik ilaç ürün geliştirme yol haritasındaki eksikliklerin belirlenmesi ve bu eksiklikleri gidererek alt yapı zincirinin tamamlanmasına yönelik yeni fonların ayrılması yerli ve milli ürünlerimizin piyasaya çıkmasını hızlandıracaktır. Örneğin, biyoteknolojik ilaç üretiminde Ülkemizdeki en çok karşılaşılan zorlulardan biri hammadde teminidir. Bu alanda kullanılan hammaddelerin neredeyse tamamı ithal edilmektedir. Özellikle pandemi sürecinde hammadde teminindeki zorluklar katlanarak artış göstermiştir. Bu nedenle, özellikle katma değeri yüksek olacak ham maddelerin yerli üretimi zaman ve bütçe açısından biyoteknolojik ilaç üretim sürecine önemli katkı sağlayacaktır. Bu katma değeri yüksek ürünlerinin de sınıflandırılarak bu alanda uzman nitelikli insan yetiştirme ve mevcut alt yapı ve eksiklikleri belirlemeye yönelik çalışma gruplarının oluşturulması biyoteknolojik ilaç hammadde üretim ekosisteminin oluşturulmasında önemli olacaktır.

Sonuç olarak; kamu kaynaklarının birbirini tamamlayan şekilde organize edilmesi, mevcut alt ve üst yapının verimli değerlendirilmesi, araştırmacı grupların bir arada ortak projelerde yer alması, planlamaların bütüncül bir yaklaşımla araştırma; üretim ve üretim tekniği, yönetim ve organizasyon, pazarlama, finansman, personel yönetimi gibi tüm birimleri dikkate alarak oluşturulması ve bu süreçte hak sahiplerinin fikri hakların korunması sürdürülebilir biyoteknolojik ilaç ekosisteminin oluşturulması için oldukça önemlidir.







Proses Geliştirmede Hedefler

- Ölçeklenebilir, sağlam, tutarlı ve uygun maliyetli bir üretim süreci geliştirilmesi
- Proses adımlarının, önemli çalışma noktalarının ve aralıkların tanımlanması ve gösterilmesi

Bu hedeflere ulaşmak için dikkate edilmesi gereken noktalar;

- Hücre Tipi
- Vektor & Kodon Optimizasyonu
- Sinyal peptit optimizasyonu
- Besiyeri optimizasyonu

→ Sonuç: Yüksek ürün kalitesi ve verimliliği

Dr. Süha TAŞPOLATOĞLU

Abdi İbrahim İlaç CEO'su

Dr. Süha Taşpolatoğlu, Haziran 2013'den bu yana Abdi İbrahim İlaç Sanayi ve Ticaret A.Ş CEO'su olarak görevini yürütmektedir.

Ankara Üniversitesi Tıp Fakültesi mezunu olan Dr. Taşpolatoğlu, 1986-1989 yılları arasında Sağlık Bakanlığı bünyesinde tıp doktoru olarak görev almıştır.

Dr. Taşpolatoğlu, 1990 yılında adım attığı profesyonel iş yaşamında ilaç sektörünün önde gelen ulusal ve uluslararası birçok şirketin satış ve pazarlama bölümlerinde üst düzey sorumluluk üstlenmiştir.

2001 - 2009 yılları arasında Abdi İbrahim'de Satış ve Pazarlama alanında yöneticilik görevini başarıyla yerine getirerek Satış ve Pazarlama Genel Müdürlüğü pozisyonunu üstlenen Dr. Süha Taşpolatoğlu, 2009 - 2013 yılları arasında Roche Türkiye Genel Müdürü olarak görev yapmıştır.

1961 yılında Adana'da doğan Taşpolatoğlu evli ve iki çocuk babasıdır.

Sunum Hakkında

Abdi İbrahim olarak biyoteknoloji alanında uzun yıllardır çalışmalar gerçekleştiriyor, üniversite-sanayi işbirliğinde önemli başarılara imza atıyor, aşı ve ürün geliştirme faaliyetlerimizi aralıksız sürdürüyoruz.

Biz Abdi İbrahim olarak biyoteknolojinin dünya ilaç pazarındaki lokomotif rolünü uzun yıllar önce fark ettik. Biyoteknolojiyi stratejik öncelik alanı olarak belirledik ve yatırım planımıza aldık. 100 milyon USD yatırımla biyoteknolojik ilaç üretim tesisimiz AbdiBio'yu 2018 yılında hizmete açtık. AbdiBio ile dünya standartlarında yüksek teknolojiyle donatılmış bir tesis kurmanın ötesinde; yetişmiş insan gücünün az olduğu biyoteknolojide yurt dışından uzmanlar getirerek know-how transferi sağlıyor, yeni uzmanlar yetiştirerek sektöre ve ülkemize katkıda bulunuyoruz. Biyoteknolojik ürünleri Türkiye'de üreterek, ithal edilen her iki ilaçtan biri olan biyoteknolojik ilaçların ithalatının azalmasına katkı sunmak istiyoruz. Buna bağlı olarak ülkemizde biyoteknolojik ilaçları üretip ihracatını gerçekleştirmemiz ilaç sanayiinin cari açık içindeki payının çift yönlü olarak azalmasını sağlayacak, bunun da bilincindeyiz. Biyoteknoloji alanında yapacaklarımızla çok fazla milli kazanım elde edeceğiz. İhracat ve lokalizasyon ile birlikte dışa bağımlılığın azaltılması, know how transferi, biyoteknolojide nitelikli Ar-Ge ve üretim gücünün oluşturulması, istihdama katkı, FDA ve EMA standartlarında biyoteknolojik üretim üssü konumuna gelinmesi bunların başında geliyor.

Bunların yanında önem verdiğimiz bir diğer konu da aşı ve insülin üretimi. AbdiBio'da mAb geliştirme projelerimizi sürdürüyoruz. Patenti 2026'da bitecek olan dünyanın en önemli biyoteknolojik ürünlerinden birinin ilk biyobenzerlerinden birini geliştirme çalışmalarımıza başladık. Pandemi ile daha da önem kazanan aşı üretimi için de çalışmalarımız sürüyor. Salgını önleyecek aşı alternatiflerinin Abdi İbrahim tesislerinde üretilmesi için mRNA bazlı biyoteknolojik aşılar yanında inaktif aşıların AbdiBio'da üretim ve dolumu için Sağlık Bakanlığı'ndan izin belgesi aldık. COVID-19 aşısını Türkiye'de üretmek istiyoruz, bunu yapabilecek güçteyiz. Aşı üretimi ve dağıtımı için Hindistan, Fransa ve Çin'deki üç ayrı firmayla ön anlaşma yaptık. Bu firmaların şu anda geliştirmenin son aşamasında oldukları aşılarının Türkiye'deki satışı ve üretimiyle ilgili yol almış durumdayız. Ayrıca Acıbadem Üniversitesi'nin geliştirdiği bir inaktif yerli aşının üretimiyle ilgili iş birliğimiz söz konusu.

Biyoteknoloji yatırımlarımız yalnızca AbdiBio ile sınırlı değil. Göz alanında biyoteknolojik ilaçlar geliştiren Amerikalı Ocugen firmasının ortaklarındanız. Hem referans ürün hem de biyobenzer geliştirme konularında kendi içimizde (65 milyon USD değerinde), partner firma Ocugen ile ve Türkiye'deki üniversitelerle proje yatırımlarımız var. Abdi İbrahim her zaman doğru zamanda doğru projelere stratejik yatırım yapmış bir firma. Burada Türkiye'nin konumu itibarı ile Güney Kore gibi bir üretim üssü olma fırsatı var. Bu fırsat çok iyi yönetilir ve devlet koordinasyonu da sağlanırsa Türkiye'de birçok biyobenzer üretilip Avrupa'ya ve Türkiye'nin hintergardenı birçok ülkeye ihraç edilebilir.

Bir diğer önemli adımımızla, geçen senenin sonunda yaptığımız bir yatırımla, İsviçre'deki biyoteknoloji şirketi OM Pharma'nın %28,5'luk hissesine sahip olduk. OM Pharma satınalma hamlemiz biyoteknolojik atılımlarımızı daha da kuvvetlendirecek. Biyoteknoloji ağırlıklı çalışan bir firma olan OM Pharma ile ortaklığımızda 250 milyon İsviçre Frankı (yaklaşık 2,3 milyar TL) gibi ciddi bir Ar-Ge bütçesini, bu ilaçları geliştirmek ve klinik çalışmalar yapmak için harcayacağız.

Abdi İbrahim olarak en önem verdiğimiz konulardan biri de üniversite-sanayi iş birlikleri. Şirketimiz; bilim insanlarının uzman görüşlerini almayı, çalışmalarını desteklemeyi, proje fikirlerinin önceden belirlenmiş şirket kriterleriyle uygunluğunu değerlendirerek araştırma geliştirme faaliyetlerimize dahil

etmeyi her zaman önemsiyor. “Proje İşbirlikleri” grubumuz son 1 yılda 40’a yakın proje fikrini değerlendirdi. Halihazırda fizibilite değerlendirme süreci devam eden projeler de söz konusu. Örneğin; Ege Üniversitesi Eczacılık Fakültesi’nde yerleşik laboratuvar ve personelimiz ile sektörde üniversite işbirliğimizi ileri boyuta taşıdık. Bu laboratuvarda Ege Üniversitesi Eczacılık Fakültesi akademisyenlerinin de danışmanlığında kendi personelimizle Ar-Ge çalışmaları yürütüyoruz.

Ege Üniversitesi ile birlikte gerçekleştirilen 8 yıllık Ar-Ge çalışmalarının bir meyvesi ve üniversite-sanayi iş birliğinin güzel bir örneği olan Dermalix’in lansmanını geçtiğimiz günlerde yaptık. Dermalix, Abdi İbrahim’in üniversite iş birliğiyle geliştirdiği; hem Abdi İbrahim için hem dünya için ilk olan bir ürün. Aslında yerli bir buluştan bahsediyoruz. Ege Üniversitesi Eczacılık Fakültesiyle yaptığımız çalışmalar sonrası, diyabetik ayak yaralarında kullanılan ve şimdiden 41 ülkede patentini aldığımız Dermalix, doku onarımı sağlayan bir yara bakım örtüsü. Yara üzerine konduğunda biyolojik olarak çözünen bir iskele oluşturarak sağlıklı doku oluşumunu sağlıyor. Kollajen, jelatin, laminin yapısındaki matriks yapı içinde hyaluronik asit, DPPC ve resveratrol mikropartiküllerini bir arada içeren ilk ve tek ürün olmasıyla benzersiz bir içeriğe sahip ve etkili bir tedavi sunuyor. Dermalix, insan derisinin kendi bileşenlerinden oluşan süngerimsi ve ağsı yapı ile yara iyileşmesini hızlandırıyor. Dermalix ile bir taraftan Abdi İbrahim’in üniversite iş birliğinin sonucunu görmüş, bir taraftan gerçekten tedavisi çok zor olan diyabetik ayak yaraları tedavisinde yeni bir imkân sunmuş olduk. Yıllarca süren bu çalışmayı sona taşımak bizlere gurur veriyor. Bu ürünle sadece Türkiye'de değil, tüm dünyada da yer alarak Abdi İbrahim markasını daha güçlü hale getirmeyi hedefliyoruz.

Abdi İbrahim olarak, sektörde TÜBİTAK 1004 Mükemmeliyet Merkezi Destekleme Programı kapsamında en fazla konsorsiyum üyesi firma konumundayız. Bu program kapsamında 3 ayrı projede rol alıyoruz. 4 yıl sonunda projelerin pre-klinik/ hayvan denemelerinin tamamlanması akabinde klinik çalışmalara geçilmesi hedefleniyor.

TÜBİTAK 2244 kapsamında da sektörde en fazla üniversite ile iş birliği olan firma olarak 4 ayrı üniversite ile 12 doktora öğrencisini destekleyeceğiz ve AbdiBio’da ve Abdi İbrahim AR-GE Merkezi’nde doktoralı personel olarak kendilerini istihdam edeceğiz.

Şirket olarak attığımız bu adımların yanı sıra Türkiye’de ve dünyada üniversite-sanayi iş birliği ortamını ve bu alandaki gelişmeleri de aktarmak isterim.

Yeniliğin, ekonomik ve sosyal gelişmenin kilidinin üniversite-sanayi iş birliği olduğunu en erken fark eden ülke olan ABD, bu alanda dünyada önde geliyor ve bunu kamu, sanayi ve üniversiteye biçtiği rollerle sağlıyor. ABD’den sona Avrupa da üniversite-sanayi iş birlikleri konusunda önemli aşamalar kaydetmiş durumda. Burada 6 temel politikanın var olduğunu görüyoruz. Öncelikle üniversitelerin özel sektör ile bağlantı içinde, ortak çalışmalar gerçekleştirebileceği mükemmeliyet merkezleri var. Üniversite-sanayi iş birliklerine kolay erişim sağlayan web platformları kuruluyor. Tarafların ortaklık kurabileceği, iletişime hizmet eden aracı yapılar var. Bu üç konu üniversite-sanayi iş birliğindeki en önemli açmazlardan biri olan iletişim sorununu yenmek için önem taşıyor. Uluslararası bilim insanları projelere dahil ediliyor, iş birlikleri onlar için teşvik edici oluyor. Henüz ticarileşmemiş projelerin pilot uygulamaları yapılıyor, böylelikle bu projelerin de know-how’ından faydalanılıyor. Ayrıca ödül programları da uyguluyorlar. Akademik personel, sanayi temsilcileri daha yoğun birliktelikte, her konuda koordineli çalışıyor. Üniversite müfredatları yalnızca teorik bilgiden ibaret kalmıyor, sanayinin de söz sahibi olduğu bir ortam var. Bu durum üniversitelerin sanayiden kopuk olmamasını, her iki taraftaki bilgi akışının sağlanması faydasını getiriyor.

Türkiye’de ne yazık ki ABD ve Avrupa’da olan sistemli yapı mevcut değil. Üniversite sanayi iş birliğinin ülkemizde yeterli olduğunu söylemek oldukça güç. Bu alanda geliştirmeler yapılması elbette hedefleniyor, yapılan çok güzel işler de var ama iş birliklerinin önündeki engelleri görüp, çözüme kavuşturmamız da şart. Bu noktada öneri ve tespitlerimi sıralamak isterim.

Öncelikle bazı yapısal değişimlere odaklanılmalı. Üniversite-sanayi iş birliği kültürünün oturması için gerekli atmosferin taraflarca sağlanması, bilgi paylaşımının, tecrübenin tekrar kullanılabilirliğini sağlayacak mekanizmaların oluşturulması, taraflar arasında güvenin sağlanması, cazibe merkezi olma çalışmaları, teşvik edici eğitim sisteminin kurgulanması başlıca konular olarak karşımıza çıkıyor. Sanayi ve üniversite kaynaklı sorunlar için de değişim gerekli. Sanayicilerin maddi kaygıları ve bu alana ilgi göstermemesi, üniversitelerin özerkliği, yayın yapma ve fon bulma amaçlı iş birliği platformlarına girmek zorunda bırakılmak gerçek anlamda iş birliklerinin önünde bir engel teşkil ediyor. Bürokratik süreçler, müfredatın teorik içerik ağırlıklı olması, projelerin uygulamaya dönük olmaması, endüstrinin problemlerine çözüm olacak şekilde geliştirilememesi ve ticarileştirilememesi iki taraf arasındaki bağın kuvvetlenememesine yol açıyor. Akademik alanda da farklı bir yapılanma sağlanması gerekiyor. Burada "kendilerini" yönetebilen özerk üniversiteler modelinin kurgulanabilmesi önem taşıyor.

Neler yapılmalı konusunda da kısaca önerilerimi sıralamak isterim. Büyük şirket yöneticileri üniversitelerde derslere girerek tecrübelerini aktarmalı. Böylelikle öğrencilere vizyon katan, girişimciliği özendiren, teşvik edilen bir eğitim modeli uygulanmalı. Üniversiteler eğitim ve araştırma kalemlerine öncelik vermeli, müfredatlar ilköğretimden yüksek öğretime kadar bilim ve teknoloji üretimine dönük yeteneklerin geliştirilebileceği eksende tasarlanmalı. Gelişmiş ülkelerde olduğu gibi üniversitelerin, sanayinin ihtiyaçlarını dikkate alarak, sanayi temsilcileri ve akademik kadronun birlikte olduğu bir yapı oluşturulmalı. Üniversitelerdeki akademik programlar, ABD'deki gibi iş dünyasından temsilcilerin de bulunduğu heyetlerle, iş dünyasının ihtiyaçları doğrultusunda kurgulanmalıdır ki bu da sanayinin beklediği insan niteliğinin mezun olan yeteneklerle uyuşmasını sağlayacaktır. Öğrenciler şirketlerde yarı zamanlı çalışmalı ve çabaları notlarına etki etmeli. Akademisyenlerin terfisinde teorik bilgi yanında şirketlere yapacağı danışmanlık ve girişimcilikleri de rol oynamalı. Üniversitelerle kaynaşan iş dünyası bilimsel tabanlı projeden gelecek getiriyi görerek melek yatırımcı şeklinde iyi projeleri desteklemeli. Devlet hukuki düzenlemeleri sağlayarak ve bürokratik işlemleri azaltarak eğitim ve AR-GE giderlerini ilk kaleme aldığı bir iklim oluşturulabildiğinde, üniversiteler, özel sektör ve devletten oluşan ülke çapında bir AR-GE ağı kurulduğunda Türkiye'de üniversite-sanayi iş birliği çerçevesinde yenilikçi üretim sistemi ile arzu ettiğimiz kalkınma sağlanabilir.


AbdiBio
İstanbul, Türkiye
Covid-19 aşı projeleri kapsamında, AbdiBio'da inaktif, vektörel ve mRNA bazlı aşıların formülasyonu ve doldurulması için Sağlık Bakanlığı'ndan onay alındı.
Üretim Kapasitesi
Likit Flakon
11 Milyon Flakon/Yıl
Kartuş
22 Milyon Kartuş/Yıl
Şırınga
9 Milyon Şırınga/Yıl
Liyofilize
1 Milyon Flakon/Yıl
Toplam yatırım tutarı 100 Milyon USD
13.500 m2 kapalı alan
Hücre bankasından nihai ürüne kadar tüm üretim süreçleri
İstihdamda artış
Know-how transferi
Cari açığın azaltılmasında çift yönlü katma değer


Abdi İbrahim & Üniversite İş Birlikleri
Ege Üniversitesi – Abdi İbrahim Ar-Ge Merkezi
• Ege Üniversitesi Eczacılık Fakültesi'nde yerleşik laboratuvar ve personelimiz ile sektörde üniversite işbirliğimizi ileri boyuta taşımış bulunmaktayız.
TÜBİTAK 1004
• Yeni Biyoteknolojik Molekül Geliştirme Projesi
• Yeni Bir Antiviral İlaç Geliştirme Projesi
• HPV Virüslerinde Kullanılmak Üzere Yeni Bir Tıbbi Cihaz Sınıfında Ürün Geliştirme Projesi
TÜBİTAK 2244 Sanayi Doktora Programı (12 bursiyer)
Ankara Üniversitesi : 3 doktora öğrencisi
Ege Üniversitesi : 3 doktora öğrencisi
İstanbul Üniversitesi : 3 doktora öğrencisi
İstanbul Teknik Üniversitesi : 3 doktora öğrencisi


Hayata
Benzersiz
DOKUnuş
DERMALİX
YARA ÖRTÜSÜ
1 ADET 5x5 CM
25cm²'ye Bir Buluş Sığdırdık
Türkiye'de bulunmuş ve geliştirilmiş
İLK YARA BAKIM ÖRTÜSÜ

Dr. Hasan Ersin ZEYTİN

Nobel İlaç Biyoteknoloji ve Yeni Ürün Değerlendirme Direktörü

Dr. Hasan Zeytin, Nobel İlaç San ve Tic A.Ş.'de Tıbbi Araştırmalar Direktörüdür. Trakya Üniversitesi Tıp Fakültesi'nden 1991 yılında mezun olmuş, 2000 yılında Kentucky Üniversitesi'nde immünoloji ve mikrobiyoloji alanındaki doktorasını tamamlamıştır. Yeni antikanser immünoterapi stratejileri ve gen taşıyıcı sistemlerin tasarlanması konularında ABD Ulusal Kanser Enstitüsü'nde çalışmalarda bulunmuştur. Nobel İlaç'taki güncel çalışmaları içerisinde biyoteknoloji ve küçük moleküller ürün geliştirme faaliyetlerinin koordinasyonu yer almaktadır. Türkiye'de piyasaya sürülen ilk biyobenzer Epoetin olan Epoetin Zeta'nın lisanslanmasında ve geliştirilmesinde çalışmıştır. Aynı zamanda 2014 yılında başlatılan ilk Biyobenzer İlaç Geliştirme Devlet hibe programının (1007-KAMAG) proje koordinatörüdür. Pek çok bilimsel yayını bulunan Dr. Hasan Ersin araştırmalarıyla çeşitli ödüller kazanmıştır. Uzmanlık alanıyla ilgili farklı uluslararası etkinliklerde çeşitli konuşmalar yapmıştır.

Sunum Hakkında

COVID-19 tüm dünyada olduğu gibi ülkemizde de yaşamımızı derinden etkilemiştir. Bu salgınının ilk şokunu biyoteknoloji endüstrisi RT-PCR ve antigen kitleri gibi çeşitli olanaklarla karşılamaya çalışmış, COVID19 hastalığına yönelik mücadeleyi sürdürmek ve yoğunlaştırmak için aşı ve antikor tedavileri gibi ek silahlar yaratmak için yoğun bir çaba içine girmiştir. mRNA aşıları, gen terapileri, kişişelleştirilmiş tıp gibi geleceğin teknolojileri olarak adlandırılan bu yeni teknolojiler ile pek çok farklı çalışmalar gerçekleştirilmiş ve gerçekleştirilmektedir. Bu ihtiyaçları karşılayabilmek için, ülkemizdeki pek çok araştırmacı COVID etkilerini minimize etmek için TUBİTAK-TUSEB önderliğinde aşı ve ilaç geliştirme çalışmalarına başlamış ve konsorsiyumlar oluşturulmuştur. Oluşturulan konsorsiyumlar sayesinde de 2 aşı adayımız klinik çalışmalara başlamıştır.

Bir ilaç veya aşı geliştirme süreci; temel araştırma, ilaç keşfi, preklinik çalışmalar, pilot üretim, klinik araştırma olmak üzere 5 ana aşamadan oluşmaktadır. Yerli aşı geliştirme projelerinde ortak olarak karşılaşılan darboğaz ise geliştirilen aşı-ilaç projelerinin iyi üretim teknikleri (GMP) ortamda üretimidir. Bu darboğazın altında yatan nedenler ise geliştirilen ilaçların yerli üretim kaynaklarına uygun olmaması, ilaç endüstrisinde teknoloji transferi prosesi, biyoteknolojik ilaçve aşı üretimine yönelik altyapı yetersizliği ve biyoteknolojik ilaç üretimi alanında uzmanlaşmış insan gücünün yetersizliğidir.

Nobel ilaç olarak, 2014 yılında adım attığımız biyoteknolojik ilaçlar yatırımımız 2019'da Biyoteknolojik ARGE bölümümüzün açılması ile hızlanarak ivme kazanmıştır. Kazandığımız bu ivme sayesinde, biyoteknolojik ilaç geliştirme alanında ülkemizde ilk defa gerçekleştirilen ilaç odaklı teknoloji transfer prosesine öncülük ederek, ODTÜ-Bilkent önderliğinde geliştirilen Virüs benzeri Parçacık temelli aşının GMP ortamda üretimini için büyük bir adım attık. Aralık ayında başladığımız bu serüvene Mart ayında Faz I çalışmalarına başladık. Faz I çalışmalarına göre etkinliği kanıtlanmasının ardından Haziran ayında da Faz II çalışmalarına başlanmıştır. İnovatif bir aşı olan yerli VLP aşımızın Faz III çalışmalarına yönelik inancımız ve desteğimiz ise yüksektir.

Gerek TUBİTAK-TUSEB konsorsiyumlarının gerekse Nobel olarak bizim attığımız bu adımların gelecek nesillere büyük bir örnek teşkil edeceğine inanmaktayız. Oluşturulan bu sinerjinin sürdürülebilirliği ve katlanarak artması için, süreçte elde edilen kazanımların ve tecrübelerin ışığında ilaç endüstrisinde ARGE çalışmaları ve teknoloji transfer prosesine yönelik yeni politikalar geliştirilmesi gerektiği inancındayız.

+

What did / do we have that worked so far for this partnership?

- Common dream
- Strong and unflinched management support
- Continues financial support
- The big picture make sure everybody sees the big picture.

- Open and candid communication.
- Listen before talk. Listen.. Listen.
- Ask help, ask help, ask help. Give help, give help, give help.
- Show empathy, accept others more than you did before.

- Fully dedicated teams
  - Motivate your team
  - Make sure that they take the extra steps (a lot of extra steps)
  - Make quick decisions and pray to be lucky.
  - Accept the failures, have a growth mindset, teach your team to have a growth mind set.

- Do not stop fighting for the best for the project not for your ego, for the project.
  - (get angry, scream, fight, have your blood pressure up, have an urticaria, gastrit, headaches, offend people, be offended) but come to lab/office next day like nothing happened and work.

SAĞLIK İÇİN

Dr. Ecz. Ferhat FARŞİ

CinnaGen İlaç Kurucu Ortağı ve CEO'su

İlaç Sanayinde 1993'den beri sırasıyla Türk ilaç endüstrisinin önde gelen kuruluşlarında görev alan Ferhat Farşi, CinnaGen İlaç'ın kurucu ortağı ve CEO'su olarak kariyerini sürdürmektedir. Hacettepe Üniversitesi Eczacılık Fakültesi'nden mezun olduktan sonra aynı üniversitede 1990 – 1993 yılları arasında Endüstriyel Eczacılık bölümünde yüksek lisansını tamamlamış ve bu süre içerisinde formülasyon geliştirme üzerinde çalışmalar yapmıştır. 1993-1997 yılları arasında doktora programı süresince geliştirmiş olduğu ilaç dozaj formları bağlamında gerek hayvanlar, gerekse insanlar üzerinde yaptığı "*İn Vivo*" çalışmaları ile uluslararası sempozyumlarda ödüllere layık görülmüştür. Bir önceki pozisyonu olan Başkan Yardımcılığı görevi süresince İş Geliştirme, Ruhsatlandırma, Pazar Erişim ve Farmakovijilans departmanları ile başarılı çalışmalara imza atmıştır. Görev aldığı tüm firmalarda Ar-Ge organizasyonu ve Ar-Ge merkezlerinin kurulması ve akreditasyonunda öncülük etmiştir. Türkiye'nin ilk akredite Ar-Ge merkezinin kurulmasında liderlik rölünü üstlenmiştir. Son 7 yıldır biyoteknoloji ile ilgili çalışmalarına devam etmekte olup, teknoloji transferi ve üretim konularında uluslararası projelerde yer almıştır.

Türkiye'de TÜBİTAK'ın öncülüğünde yürütülen İlaç Teknoloji Platformu'nun 2 sene boyunca başkanlık görevini üstlenmiştir. Çeşitli alanlarda uluslararası yayınları ve Freiburg Üniversitesi tarafından verilen ödülü başta olmak üzere, çeşitli ulusal ve uluslararası ödülleri bulunmaktadır. 2011 yılında Barselona'da gerçekleşen "European Business Awards"ta, "İnovasyon" alanında "Ruban d'Honneur" ödülünü almıştır. Kendisinin şu ana kadar ilaç geliştirme ve formülasyon konularında 30 adet patent başvurusu bulunmaktadır.

CİNNAGEN İLAÇ

Sağlığa olan tutkumuz, hayallerin ötesinde...

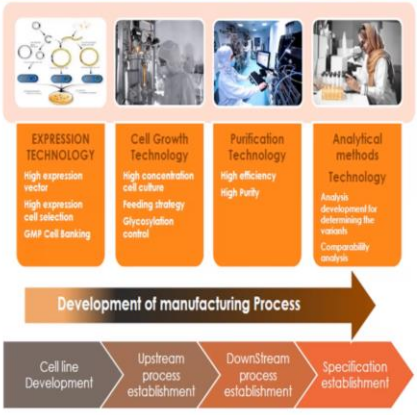
Ankara Üniversitesi
13th Symposium on Pharmaceutical Sciences
25.06.2021

Ferhat Farşi, CEO

CinnaGen İlaç

CİNNAGEN İLAÇ

Sağlığa olan tutkumuz, hayallerin ötesinde...



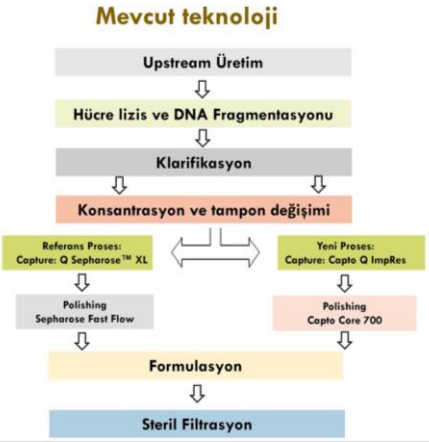
ARGE Departmanımız

- Sadece Biyoteknoloji odaklı AR-GE Laboratuvarımız hazırdır
- Ana Hücre Bankasından bitmiş ürüne kadarki sürecin Çerkezköy tesisimizdeki ARGE Merkezimizde gerçekleştirilecek
- Üniversite-Sanayi işbirliği

CinnaGen İlaç

Adenoviral Vektör Aşısı için Proses Workflow

Sağlığa olan tutkumuz, hayallerin ötesinde...



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