# PHARMACY

## PLENARY LECTURE

### INTERACTIONS OF PHYTOMEDICINES AND NATURAL PRODUCTS WITH CONVENTIONAL DRUGS

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## Summary

Natural products medicines, plant extracts and the corresponding herbal medicines and supplements are commonly used by many patients with chronic diseases. Supplements are not subjected to the same rigorous safety and efficacy trials as conventional drugs. Some of them as *St. John's wort, Ginkgo biloba, Garlic, Licorice, Ginseng* among others have significant drug interactions. Deleterious effects are most pronounced with anticoagulants, cytostatic drugs, antiretrovirals, antidepressants, antiepileptic, and some other CNS-drugs, which could lead to serious safety issues in patients. Most pharmacokinetic herb-drug interactions involve drug metabolizing cytochrome P450 (CYP) enzymes, in particular CYP3A4 and CYP2C9. The aim of this overview is to assess the severity of adverse drug reactions due to herb-drug interactions in patients taking herbs and prescribed medications based on published evidence. The second focus is on recommendations for close monitoring of pharmacological effects as a strategy to avoid toxicity and ensure adequate therapeutic coverage in patients.

**Key words:** drug interactions, phytomedicine

## ORAL PRESENTATIONS

### BULGARIAN MEDICINAL PLANTS

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## Summary

The aim of the present study is to outline some peculiarities of the plants from the flora of Bulgaria and especially of the Bulgarian medicinal plants. The rich plant diversity of more than 7835 species of lower and higher plants, which are grouped in segments - algae, lichens, mosses, plains, fowls, ferns, angiosperms, gymnosperms are distinguished. The reasons for the richness of the Bulgarian flora are given, compared to other countries are different environmental conditions, altitude, terrain, water basins, rivers, soil cover, climate, etc. The geographical situation of Bulgaria is a crossroads of floristic influences from all directions of the world. In our flora, there are paleoendemites (*Haberlea rhodopensis, Ramonda serbica*) and others. Relicts are distributed – *Pinus peuce, Taxus baccata, Castanea sativa* and others. Over 170 species of endemics plants are present on the territory of Bulgaria. Bulgaria is unique in the use of medicinal plants. Of the Bulgarian flora, about 20% of the higher plants are known and used as medicinal plants, while only 2.4% of the higher floras are used as medicinal plants worldwide. These data stand out for BULGARIA as a unique country with nearly ten times better knowledge and use of medicinal plants. There is also a widespread use of our medicinal herbs in folk medicine. Bulgarian folk medicine has given the

world a Bulgarian treatment (the "Cura bulgara") for Parkinson's disease of the folk healer Ivan Raev, with the roots of *Atropa belladonna.* The Bulgarian medicinal plants are unique in the chemical composition of the biologically active substances due to their healing effect. For example, Bulgarian rose oil, which is one of the most expensive and sought after perfume essential oils in the international market and differs from all others in the quantitative content of the ingredients. Dependencies between the specific Bulgarian conditions and the qualitative and quantitative composition of the biologically active substances in the Bulgarian plants can be mentioned with *Digitalis lanata, Tribulus terrestris, Leucojum aestivum*, etc. The scientific researchers conducted in Bulgaria have led to the creation of some unique and world-famous healing phytoproducts, which are durable in action, healing effect and application for more than half a century – Nivalin, Tribestan, Tabex**,** and others. Though thousands of tons of herbs are exported annually, Bulgaria is unique in that it is the only country in the world where there is an adopted and effective „Law on Medicinal Plants".

## CANNABINOIDS: DESIRED FRIENDS OR UNDESIRED FOES OF THE IMMUNE SYSTEM IN PATIENTS UNDERGOING CANCER IMMUNOTHERAPY

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**Summary**
This mini-review aimed to unravel the most current scientific data related to the use of cannabinoids, and especially the effect of cannabidiol on the immune system of different cancer patient populations. In recent years, the interest in cannabis use, and cannabidiol in particular of patients undergoing cancer treatment has been increasing. A critical evaluation of the existing evidence of cannabis use in patients treated with conventional chemotherapy and cancer immunotherapy is necessary. Evidence-based data of such use is still insufficient, and the results from many pilot trials regarding concomitant use of cannabinoids and cancer treatment are controversial. In this mini-review, we tried to find the most recent evidence-based literature Science direct and PubMed from 2018-2019, related to cannabinoids usage in concordance with chemo or immunotherapy. We came across ten articles and one case report with human-based data of low and very poor quality due to the nature of the trial design. Evidence-based medicine, related to cannabis use in cancer patient still needs better designed and lager RCT and systematic reviews, so that clinicians can obtain results that they could apply in their everyday practice. Nevertheless, cannabinoids usage in patients undergoing conventional chemotherapy is linked with improved disease-related symptoms and no influence on cognitive skills. On the other hand, some data suggest that cannabinoids administration with cancer immunotherapy may lead to a lower therapy response rate in those individuals. More extensive and more representative studies should be carried out to investigate this field further.
**Key words:** cannabinoids, cannabidiol, immunotherapy

## DRUG REPURPOSING IN THE MODERN TREATMENT OF COMPLEX DISEASES

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## Summary

Drug repurposing or redirection of already approved drugs for new indications has recently been intensified concerning time and cost-saving, when compared to *de novo* drug development and facilitated bringing of well-established pharmacological knowledge from existing clinical use to other potential treatments by modification and repositioning of medication use to unexplored desirable targets. Although saving 5-7 years in drug developmental process, drug repurposing has been continuously challenged by pathological signalling pathways, specific disease phenotypes, varying treatment responses and methodological efforts in efficacious selecting and combining drug candidates for new therapies. Various compound libraries and big data repositories have served as a base for experimental screening and *in silico* analysis of available drug information along with developing computational methods of machine-learning approach to molecular target identification. In this review, we aimed to elucidate the basic strategies in drug repurposing and describe the modern methods in revisiting older drugs for new treatments of complex diseases with a focus on oncology. We also provide a literature-based selected categorization of the latest evidence on efficient drug repurposing with discussion on the proper access to existing information and how clinicians and pharmacists may collaborate in the successful finding of appropriate new medication candidates. The problem with "off-label" drug use is presented as well. We consider our analysis useful for better understanding the modern advantages, discrepancies and challenges of redirecting and combining drugs with already approved or failed preceding indications to new strategic regimens in pharmacotherapy.

**Key words:** drug repurposing, signalling pathways, machine-learning methods, drug-redirection repositories, repurposed indications

## PRIMARY PHARMACOGNOSTIC ANALYSES OT 88 TRADITIONAL HERBAL SUBSTANCES

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## Summary

This study was designed to evaluate the quality of herbal substances traditional for the Bulgarian market and freely available commercially. Eighty-eight herbal substances were investigated using the pharmacognostic methods of macroscopic and microscopic analyses. They were selected as representatives of all main groups of biologically active compounds with curative or supportive qualities in various diseases and health conditions. These herbal substances were derived from 85 species or groups of species affiliated to 83 genera, 45 families and five divisions (Lichenophyta, Lycopodiophyta, Equisetophyta, Pinophyta, Magnoliophyta). Many of the substances under investigation do not meet the requirements of purity, and, some of them, for identity. In many cases, the names of the substances are not correctly labelled according to the requirements of Pharmacopoeia. For a significant part of the substances, we found that the gathering is carried out through an unsuitable phenological phase of

the plant and their specific characteristic colour is altered as a result of improper drying and/or storage. Our study showed that the quality control of the traditional herbal substances available on the Bulgarian market does not match the required level. More studies in this area are much needed and could answer questions such as how to improve product control and what changes in the regulatory framework are needed to ensure this in the public interest.

**Key words:** traditional herbal substances, pharmacognostic analyses, quality control

## POISONOUS MEDICINAL PLANTS AND HERBAL SUBSTANCES – REGULATORY AND SAFETY ISSUES IN BULGARIA

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## Summary

The aim of this study was to find out if poisonous medicinal plants (PMP) and herbal substances are adequately regulated in Bulgaria to ensure population health. Literature review and content analysis of the current legal framework governing PMP and herbal substances in Bulgaria were performed along with an online survey of market access for 17 randomly selected items from the list of PMP. The supply and use of medicinal plants and herbal substances for treatment and prophylaxis are regulated partially by the Law on medicinal products for human use. These issues are not covered by the Law on medicinal plants. Ordinance №5 on the requirements for herb processing facilities and herb warehouses provides a list of PMP only for their workers' safety. There is a list of PMP banned for use in food supplements. There is no official PMP classification as is the case with medicinal products. Prescription status of PMP is not regulated. There are free market access and free consumption of PMP and herbal substances in Bulgaria. Currently, fragmentary regulatory mechanisms are governing the supply and use of PMP, entailing direct and indirect risks for the population health. Hence there is an urgent need for revision of the relevant Bulgarian legislation that should fill the PMP regulation gap in order to guarantee population safety.

**Key words:** poisonous medicinal plants and herbal substances, regulation, safety

## HEALTH-RELATED QUALITY OF LIFE OF HYPERTENSIVE PATIENTS TREATED WITH LISINOPRIL AND PERINDOPRIL

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## Summary

The cross-sectional study aimed to assess health-related quality of life (HRQoL) in patients with hypertension (HTN) treated with lisinopril and perindopril. The study was carried out in 2016, as part of Project NO 4/2016 funded by Medical University of Pleven. Hypertensive patients (n=98) admitted to the Clinic of Cardiology of Dr Georgi Stranski University Hospital - Pleven were included in the study. The patients were divided into two groups: 50 patients treated with lisinopril (group A) and 48 patients treated with perindopril (group B). HRQoL was assessed by EQ-5D and MacNew questionnaires after discharge. Data were processed with SPSS.v.24.0. Pearson Chi-Square and Mann-Whitney tests were used. The results obtained with EQ-5D showed that most patients treated with lisinopril experienced impairments in three EQ-5D dimensions (60% in mobility, 70% in pain and discomfort, 53% in usual activities). Seventy-two per cent of the patients in group A had, anxiety and depression, and in group B these accounted for 61%. The QALY for patients in group B (0.36, -0.04÷0.50) was higher, as compared with the group A (0.33, -0.12÷0.50), p=0.087. With MacNew, the mean scores of the emotional well-being (4.6, 1.6÷6.8), physical well-being (4.65, 1.6÷6.7), social well-being (4.9, 1.7÷7.0), MacNew global score (4.5, 1.8÷6.4) were higher in the patients treated with lisinopril than in the patients treated with perindopril, p>0.05. The generic and disease-specific HRQoL questionnaires help to measure the effectiveness of a drug in hypertensive patients in clinical practice. The long-term follow-up study and limited sample selection are necessary conditions for a high validity.

**Key words:** hypertension, lisinopril, perindopril, HRQoL, EQ-5D, MacNew

## COST-UTILITY ANALYSIS (CUA) OF LISINOPRIL AND PERINDOPRIL IN PATIENTS WITH HYPERTENSION

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## Summary

A cross-sectional study was carried out in 2016 to make a cost-utility analysis (CUA) of lisinopril and perindopril used to treat hypertensive patients. The study was a part of Project No 4/2016 funded by Medical University – Pleven. Hypertensive patients (n=98) admitted to the Clinic of Cardiology of Dr Georgi Stranski University Hospital – Pleven were included in the study. They were divided into two groups: 50 patients treated with lisinopril (group A) and 48 patients treated with perindopril (group B). Direct, indirect and total costs were measured and compared, as well as health-related quality of life (HRQoL). EQ-5D was used to measure QALY. The QALY for patients in group B (0.36, -0.04÷0.50) was higher as compared with group A (0.33, -0.12÷0.50), p=0.087. Total costs, most direct and indirect costs were higher in group B than in group A. The treatment with lisinopril was more effective (BGN 76 963.64 per 0.5 QALY) than that with perindopril (BGN 90 781.11 per 0.5 QALY). The results of CUA showed that the treatment with lisinopril is more effective as compared with the other ACE inhibitors.

**Key words:** hypertension, lisinopril, perindopril, QALY, CUA

## ONE-STEP ROUTE TO NOVEL BENZO[A]QUINOLIZIDINES AS POTENTIAL DPP–IV INHIBITORS

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## Summary
Dipeptidyl peptidase IV (DPP-IV) is a highly specific serine protease enzyme whose inhibition has been widely explored for its potential to treat chronic metabolic type 2 diabetes mellitus. Recent studies have outlined the benzo[a]quinolizidine ring system as an essential heterocyclic framework in the structure of potential DPP-IV inhibitors. In light of this prospective application, the development of novel methods for the construction of these heteropolycycles would be of considerable significance to both organic and medicinal chemistry. Our investigation was focused on the reaction of dihydroisoquinolines with monocyclic enolizable anhydrides (glutaric, diglycolic and thiodiglycolic) as a one-step approach to the benzo[a]quinolizidine system and its analogues. Molecular docking was used to determine the binding potential of the compounds prepared to the active site of human dipeptidyl peptidase IV enzyme. The docking analysis revealed that the energy minimized poses of the studied compounds are in contact with some of the most crucial selectivity cliffs for the enzyme inhibition. The minimum energy values were compared to the binding energy of Carmegliptin – a highly potent inhibitor currently on clinical trials. The compounds prepared bear the potential to become building blocks for future synthetic bioactive molecules.

**Key words:** heterocyclic synthesis, DPP-IV inhibition, docking studies

# SOME EFFECTS OF NEW NEUROTENSIN ANALOGUE ON ULTRASOUND VOCALIZATIONS AND NOVELTY STIMULUS REACTIONS IN RODENT MODELS WITH ANXIETY

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## Summary
Neurotensin is tridecapeptide secreted in the brain and the gut and acts as a neurotransmitter and neuromodulator. However, neurotensin is rapidly degraded in the body by the endopeptidases. Therefore, new synthetic analogues of neurotensin are needed to prolong its bioavailability and effects in the body. A new neurotensin analogue, resembling the smallest bioactive part of the neuropeptide – the neurotensin (8-13) fragment was synthesized. Anxiety and fear are important emotions with significant adaptive value for the individual. However, the maladaptive anxious behaviour in related anxiety disorders can significantly impact the performance and wellbeing of the individual. The aim was to study the effects of a new neurotensin analogue on the anxiety in two disease models in rats. A standard solid-phase method was used for the synthesis, and the terminal Arg unit was replaced by

canavanine (CAV). The two models with anxiety disturbances were used in this study induced either through social deprivation or impairment of the dopaminergic system. A battery of tests based on unconditional novelty and conditional ultrasound vocalizations were applied. The results showed that the new neurotensin analogue has various anxiolytic effects in most of the applied tests. Therefore, the new neurotensin analogue can be a promising agent in the treatment of such symptoms.

**Key words:** neurotensin, ultrasound vocalizations, USV, anxiety, social deprivation

POSTERS

## RISK COMMUNICATION IN COMMUNITY PHARMACIES

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### Summary

The study aimed to assess community pharmacists' approach to risk communication on self-medication. An anonymous, questionnaire-based, descriptive study was performed. A pre-validated close-ended questionnaire was distributed among a random sample of community pharmacists. Data were analyzed using SPSS v.19. A total of 99 valid questionnaires were collected, in which 60.6% of the responders claimed that patients very often consult them about their self-medication practices but rarely about possible adverse drug reactions and other drug-related problems such as drug interactions. Also, 51.5% of pharmacists consider presenting information about risks as a mandatory part of the pharmaceutical consultation, and the majority of them (87.9%) believe that it could affect patients' decisions. According to 18.2% of the responders, up to 80% of self-medicating patients do not use their over-the-counter medicines as recommended in the patient leaflet. 63.6% of the responders believe that over-the-counter medical products have a high potential for drug misuse and abuse, and 12.1% consider them with substantial potential for drug interactions. Data suggest that patients consider over-the-counter medicines safe and rarely seek information about possible risks. The conducted pilot study showed that pharmacists should be the primary and pro-active source of information about the dangers of self-medication products.

**Key words:** risk communication, community pharmacy, patients, pharmacovigilance

## FUTURE TRENDS IN PHARMACY EDUCATION AND MEDICAL UNIVERSITY - PLEVEN PHARMACY CURRICULUM

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### Summary

This report aimed to study the future trends in pharmacy education as outlined by the International Pharmaceutical Federation (FIP) and the European Association of Faculties of Pharmacy (EAFP) and the MU – Pleven pharmacy curriculum conformity with them. We performed

a content analysis of the Nanjing Statements on Pharmacy and Pharmaceutical Sciences Education of the International Pharmaceutical Federation (FIP) and the European Pharmacy Competences Framework (EPCF) of EAFP and compared them to pharmacy curriculum at Medical University – Pleven. The Nanjing Statements (67 statements, grouped in 8 clusters) represented the FIP requirements for effective pharmaceutical education. In the EPCF, the requirements for pharmacy practice are defined and ranked as 50 competences in 11 domains. We found that the pharmacy curriculum in Medical University – Pleven is in line with the Nanjing Statements and the EPCF, as well as with the four EAFP pillars of relevant pharmacy education that are based on workforce market needs in all settings: community and hospital practice, industry, regulatory bodies, and research institutions. The Faculty of Pharmacy at Medical University – Pleven should continue redesigning its curriculum, using the principles of competency-based education in order to keep up with the changes in the profession, technology and society, and provide pharmacy students with knowledge, skills and attitudes that prepare them for their new professional roles in healthcare.

**Key words:** pharmacy education, curriculum, competencies

## FIXED DOSE-COMBINATION OLMESARTAN AND HYDROCHLOROTHIAZIDE – TECHNOLOGICAL AND BIOPHARMACEUTICAL STUDIES

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## Summary

Olmesartan medoxomil is an angiotensin II antagonist. These medicines are often combined with diuretics, e.g. hydrochlorothiazide) in practice. The aim of this study was to evaluate the possibilities for developing a fixed-dose combination of Olmesartan and Hydrochlorothiazide in a pharmaceutical form of a tablet, from which the drug release is similar to those of originator Olmetec plus. This raises the problem of drug release from tablets, which was resolved in our studies by the method of dissolved active substance spraying in a fluid-bed apparatus. Most often, during the process, the drug substance is in an amorphous form with a high dissolution rate. The suitable co-solvent, which completely dissolves olmesartan (such as methanol and acetone), and a binding polymer (hydroxypropyl cellulose) were chosen. At the same time, granules without dissolving of active substance were produced using conventional technology. The comparison of drug release from tablets, produced by both technological methods, demonstrates significant and rapid dissolution rate from tablets produced by dissolving of olmesartan in a granulated solution. The possibility for intra- or extra granular addition of a second drug (hydrochlorothiazide) is studied. These dissolution profiles are similar to those of the originator Olmete plus. The final assessment can be done after thoroughly evaluating the stability of the finished product. In conclusion, the experiments performed proved the possibility to develop a generic drug product, with a similar release of the active substances as the original product Olmetec plus.

## MINERAL CONTENT AND RADICAL SCAVENGING ACTIVITY OF HELIANTHUS TUBEROSUS

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## Summary

The mineral content as represented by the concentrations of K, Ca, Mg, P, Na, Fe, Zn, Mn, Cu and Se in various plant parts (leaves, stems and tubers) of *Helianthus tuberosus L* is presented in this study. The bioavailability of the elements was investigated by water infusions from the leaves of the plant, as well as through their concentrations in the extracts imitating the stomach juice obtained from plant tubers. The radical scavenging ability of 30, 50 and 70% alcoholic extracts prepared from plant leaves and stems was assessed using a 2,2-diphenyl-1-picrylhydrazyl (DPPH) in vitro assay. Results obtained showed relatively high antioxidant activity. High concentrations of K in alcoholic extracts, derived from all plants parts suggest high potential bioavailability of this element in pharmaceutical preparations, based on them. The profile of basic chemical components in Helianthus tuberosus L was assessed by using ATR-Infrared Spectroscopy. Overall, the results obtained justify the application of all plant parts in non-traditional medicine, increasing the knowledge for their chemical composition and also supported the conclusion that *Helianthus tuberosus L.* might be accepted as adequate functional food.

**Key words:** *Helianthus tuberosus L*, mineral content, bioavailable, radical scavenging ability, IR spectra

## EFFECTS OF A NEW NEUROTENSIN ANALOGUE ON THE AFFECTIVE BEHAVIOR IN A PARKINSON'S DISEASE MODEL

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## Summary

Neurotensin (NT) is a small neuropeptide which is secreted in the central nervous system and in the gut. In the nervous system, it acts as neurotransmitter and neuromodulator. However, natural neurotensin is quickly degraded in the body; therefore, artificial analogues are necessary to prolong the bioavailability and effects. Parkinson's disease (PD) is a neurological disease with specific motor disturbances along with cognitive and affective ones. It is associated with mitochondrial dysfunction and degeneration in the dopaminergic system. The study evaluated some of the new neurotensin analogue effects upon the behaviour in rats with a model of PD induced with a striatal injection of 6-hydroxydopamine (6-OHDA). 6-OHDA (12

µg in 2 µl saline) injection in the striatum was applied to produce a PD model in male Wistar rats. Treatment with the Neurotensin analogue was applied at a dose of 5 mg/kg i.p. for five days. The neurotensin analogue effects were evaluated via behavioural tests for anhedonia, depression and anxiety. The Student t-test was used at $p<0.05$. Verification of the PD-model was made by a rotarod test on the 2nd and 3rd week after surgery and compared to sham-operated animals. A significant performance decrease in the mood and affective disturbances was observed. Reduction in depression- and anxiety-related parameters in the neurotensin analogue-treated animals was observed (both on 2nd and 3rd week) in comparison to the PD-controls. Neurotensin is a neuromodulator and immune-modulator. Therefore, this Neurotensin analogue probably modulates some of the transmitter systems related to the studied behaviour and contributes to a reduction of apoptosis and necrosis in the area of 6-OHDA trauma.

**Key words**: neurotensin, depression, anhedonia, Parkinson's disease

## PROTECTIVE EFFECTS OF LACOSAMIDE ON LEARNING AND MEMORY AND LOCOMOTOR ACTIVITY IN THE PILOCARPINE-MODEL OF TEMPORAL LOBE EPILEPSY IN RATS

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### Summary

The present study aimed to investigate the effects of the new anticonvulsant Lacosamide (LCM) on learning and memory and locomotor activity in naïve rats and with Pilocarpine (Pilo)-induced status epilepticus (SE). Male Wistar rats were randomly divided into four groups (n=8), and SE was evoked by a single administration of Pilo (320 mg/kg) i.p. in half of them. For one month, all animals were daily treated per os as follows: group 1 (C-veh)–with saline, group 2 – with Pilo-veh, group 3 (C-LCM)– with LCM 30 mg/kg, and group 4 (Pilo-LCM)– with LCM 30 mg/kg. In a step-down passive avoidance test, a learning session was held for one day. On day 2 was the test for short-term and on day 7 – for long-term memory. The latency of reactions was accepted as a criterion for learning and retention. The activity cage automatically recorded the number of horizontal and vertical movements. The Pilo-veh rats were hyperactive compared to C-veh animals ($p<0.05$). The Pilo-LCM group decreased the number of horizontal movements, compared to Pilo-veh animals ($p<0.01$). Pilo-veh group had a shorter latency reaction than C-veh animals during the learning session ($p<0.05$). In the short- and long-term memory retention tests, both groups Pilo-veh and C-LCM decreased the time spent on the platform than C-veh animals ($p<0.01$ and $p<0.05$, respectively), while Pilo-LCM group had a better performance than that of the Pilo-veh animals ($p<0.01$). LCM alleviated Pilo-induced hyperactivity and restored spontaneous locomotor activity. The drug has a protective effect on memory deficits in a model of temporal lobe epilepsy, but not in naïve rats.

**Key words:** Lacosamide, learning and memory, pilocarpine, rats

## PHYTOCHEMICAL COMPOSITION AND BIOLOGICAL ACTIVITY OF *TANACETUM VULGARE L.*

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### Summary

*Tanacetum vulgare L.* is a medicinal plant of the Asteraceae family with a distribution range in the temperate geographical area. Folk medicine uses a decoction of the plant as an antiseptic, spasmolytic and antihelminthic

agent. Scientific studies have found that plant extracts contain several groups of biologically active compounds: flavonoids 18%, coumarins 7.5%, tannins 7.5%, and sesquiterpene lactones. The antioxidant and anti-inflammatory activity of the plant is due to alpha-khumulen, and the antibacterial activity against *Escherichia coli* and *Staphylococcus aureus* is mediated by alpha-pinene and caryophyllene oxide. Experimental data have shown that the essential oil has a strong convulsive effect, and aqueous extracts have a diuretic effect. Literary data suggest that the pharmacological effects of individual plant components are poorly studied. Future experimental studies on T.vulgare's biological activity could reveal possibilities for the therapeutic application of the plant extracts.

**Key words:** *Tanacetum vulgare L*, biochemical and pharmacological review

## INSTRUMENTAL ANALYSIS OF METRONIDAZOLE -LOADED NANOSTRUCTERED LIPID CARRIERS

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**Summary**

Nanostructured lipid carriers (NLC) are the new generation of submicron-sized lipid particles where the solid lipid matrix is partially substituted by liquid lipid (oil). Lipids used in the formulation are biocompatible and biodegradable. An antibacterial compound, metronidazole was selected as a model drug. Spectroscopic and chromatographic methods can be successfully applied to quantity identification of metronidazole-loaded nanostructured lipid carriers. We used cetyl alcohol, beeswax, blackcurrant seed oil – as components of the lipid matrix; surfactants- polysorbate 80, span 80, propylene glycol. Metronidazole as the active component, Vanillin 99%, Hydrochloride acid were purchased from Sigma-Aldrich Chemie GmbH, Germany. The method of preparation was high-shear homogenization using Ultra- turrax T25 equipment, followed by ultrasonication. Four different models metronidazole-loaded NLC with different surfactant ratio were prepared. The lipid matrix was composed of Cetyl alcohol- blackcurrant seed oil and beeswax-blackcurrant seed oil. The final lipid particles dispersions were characterized in terms of particle size, zeta potential, surface morphology and in vitro drug release. A few instrumental methods were developed for the determination of metronidazole loaded nanostructured lipid carriers. The proposed methods for preparation and characterization of metronidazole-loaded nanostructured lipid carriers are accurate, sensitive, simple and rapid.

**Key words:** chromatography, metronidazole, nanostructured lipid carriers, spectroscopy

## ESTIMATING MUTAGENIC ACTIVITY OF DERIVATIVES OF THIRD GENERATION RETINOIDS

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## Summary
The aim of this work was to predict the probable mutagenic activity (Salmonella typhimurium) of bexarotene and its five new synthesized derivatives as potential drugs. The chemicals, investigated are a compound of third-generation retinoids (bexarotene) and five new synthesized compounds, which are derivatives of bexarotene. The modular toxicological framework was used to predict is lazar. The main objective of lazar is to provide a generic tool for the prediction of complex toxicological endpoints, like mutagenicity. Lazar uses data mining algorithms to derive predictions for untested compounds from experimental training data. In the present work, lazar was used for identifying probable mutagenic activity (Salmonella typhimurium) of bexarotene and its five newly synthesized derivatives. The data analysis of results showed that bexarotene and its five new synthesized derivatives were not mutagenic (Salmonella typhimurium). Lazar is a flexible modular framework for developing predictive toxicology models and gives the possibility for investigation of mutagenic activity of new derivatives of third-generation retinoids.
**Key words:** Bexarotene, newly synthesized derivatives, mutagenicity, prediction, lazar

## CARCINOGENIC PREDICTION OF BEXAROTENE AND ITS NEW SYNTHESIZED DERIVATIVES AS POTENTIAL DRUGS

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## Summary
The aim of this work was to predict the probable carcinogenic activity (in rat and mouse) of bexarotene and its five newly synthesized derivatives as potential drugs. The chemicals, investigated are a compound of third-generation retinoids (bexarotene) and five newly synthesized compounds which are derivatives of bexarotene. The modular toxicological framework that was used for prediction was lazar. The main objective of lazar is to provide a generic tool for predicting complex toxicological endpoints, like carcinogenicity. Lazar uses data-mining algorithms to derive predictions for untested compounds from experimental training data. In the present work, lazar was used for identifying probable carcinogenic activity (in rat and mouse) of bexarotene and its five newly synthesized derivatives. The data analysis of results showed that bexarotene was not carcinogenic in rat and mouse, but two of the five derivatives were found to be carcinogenic in mice. Lazar is appropriate for discriminating trustworthy, reliable and trustworthy carcinogenic prediction of Bexarotene and its newly synthesized derivatives.
**Key words:** Bexarotene, newly synthesized derivatives, carcinogenicity, prediction, lazar