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ABSTRACT BOOK

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ANALYSIS OF CARDIOVASCULAR TOXICITY OF TYROSINE-KINASE INHIBITORS IN-VIVO AND IN-VITRO IN ANIMAL MODELS

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Abstract

Introduction: Approximately one in 40 human genes codes protein kinase, while over 30% of all new drugs are kinase inhibitors. Accumulated data on cardiovascular adverse reactions, combined with insufficient data from pre-clinical phase, necessitate further research. Aim: We conducted pharmacological and toxicological investigation of 3 tyrosine kinase inhibitors in-vivo and in-vitro via monitoring of vital parameters and biochemical measurements. Materials and methods: We conducted single center, prospective, interventional, controlled trial for a period of 4 weeks. We conducted the interventions on male sexually mature mice line H (19÷44g), grown in standard laboratory environment in plastic cages with 12 hour bright/dark cycle, unlimited access to rodent food and water, in a room with optimal humidity, temperature and ventilation. We measured vital and biochemical parameters including body weight, systole and diastole arterial pressure, creatine kinase (CK), MB-fraction of creatine kinase (CK-MB). For conducting this trial we obtained a positive opinion №259 from Committee on ethics towards animals within Bulgarian food safety agency (BFSA) and decision №343 in accordance with article 155 line 7 of the Veterinary medicine affairs law for using animals in trials from executive director of BFSA. Results: We found changes in measured parameters in test groups compared to the control group and we investigated dose-dependency and causal relationship. Conclusion: Non-clinical data reveal acceptable safety profile of investigated drugs, but further investigation of mechanism of toxicity and causes of discrepancy between pre-clinical and clinical safety data is necessary.

Keywords: tyrosine kinase inhibitors, cardiovascular toxicity, tofacitinib, baricitinib, pazopanib.

COMPETENCIES OF BULGARIAN MEDICAL STUDENTS FOR RATIONAL DRUG PRESCRIBING

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Abstract
Aim: The purpose of this study was to assess the competencies of Bulgarian medical students from Medical University-Sofia (MU-Sofia) for rational drug prescribing after completion of their cycle in clinical pharmacology.
Materials/Methods: A total of 154 Bulgarian medical students from two consecutive cycles in clinical pharmacology in 2024 took part in the study. On a random base each student was presented one simulated patient case with either infectious (hospital acquired pneumonia or pyelonephritis), cardiovascular (stable angina) or endocrine disease (diabetes mellitus type 2) and was asked to write appropriate prescription(s) with a detailed explanation of both - drug(s) choice(s) and their specific characteristic (indications, MOA, PK's, ADR's contraindications and drug interactions). The competencies of medical students were assessed by two clinical pharmacologists on the basis of 3 criteria: appropriateness of the drug(s) chosen for the specific patient case, writing a prescription and their knowledge about the drug(s) prescribed.
Results: The competencies for rational drug prescribing of 48.05% of the students were rated as "very good". The competencies of 39.61% of the students were rated as "satisfactory", due to established non-essential gaps in the above mentioned criteria. 12.34% of the students' competencies for rational drug prescribing were rated as "unsatisfactory", due to significant gaps in one or more of the criteria listed above.
Conclusion: The majority of medical students from MU-Sofia showed a good level of competence for rational drug prescribing indicating, that they are prepared to navigate the complexity of drug prescribing in real clinical settings.
Keywords: prescribing competencies, drugs, Bulgarian medical students.

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IN VITRO STUDY OF TΦHE ANTIOXIDANT ACTIVITY OF NEWLY SYNTHESIZED N-PYRROLYL HYDRAZONES

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Abstract
Oxidative stress is involved in the etiology and pathophysiology of many socially significant diseases, including neurodegenerative, liver, malignant, and others. The development of new effective antioxidant agents for the prevention or suppression of the progression of pathological processes is of increasing importance. Targeted synthesis of pyrroles and their derivatives, which exhibit good antioxidant properties, offers a promising perspective for practical application in medicine.
The objective of this study is to investigate the antioxidant effects of newly synthesized N-pyrrolyl hydrazones in an in vitro model of induced oxidative damage on the neuroblastoma cell line SH-SY5Y and the hepatocellular carcinoma cell line HepG2. The SH-SY5Y cell line is a suitable model for studying neurotoxicity and neuroprotection processes in models of neurodegenerative diseases, including Parkinson's and Alzheimer's diseases. The HepG2 cell line is used in a wide range of studies, from oncogenesis to the evaluation of the cytotoxicity of substances on the liver. To assess the safety profile of the newly synthesized compounds, we monitored their effects on the viability of SH-SY5Y and HepG2 cells using the MTT assay. Screening tests showed low or no cytotoxicity in both cell lines, indicating a good safety profile. The results of the study in an oxidative stress model induced by H2O2 (1 mM, 15 min) in the neuroblastoma cell line SH-SY5Y and the hepatocellular carcinoma cell line HepG2 demonstrated good antioxidant protection by the compounds.
In conclusion, this in vitro study found that the newly synthesized N-pyrrolyl hydrazones exhibit low toxicity and good antioxidant activity, making them promising candidates for further experimental pharmacological and toxicological studies aimed at discovering new molecules with potential antioxidant activity, including against oxidative stress induced in neurodegenerative pathological processes.
Acknowledgements: This research was funded by the European Union’s NextGenerationEU through the National Recovery and Resilience Plan of the Republic of Bulgaria (project No. BG-RRP-2.004-0004-C01).
Keywords: oxidative stress, antioxidant agents, N-pyrrolyl hydrazones, in vitro, neuroprotection

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NIGELLA SATIVA OIL ALLEVIATES PAIN IN PACLITAXEL-INDUCED NEUROPATHY IN RATS

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Abstract

Objective: to investigate the analgesic effect of Nigella sativa oil (NSO) in an experimental model of paclitaxel-induced neuropathy.

Material and methods: male Wistar rats were randomly divided into 6 groups (n=8): saline, negative control (paclitaxel), positive control (gabapentin) and three experimental groups treated with NSO 1; 3 and 5 ml/kg. Paclitaxel (2 mg/kg) was injected every other day to reach a cumulative dose of 8 mg/kg. Thereafter, rats were treated with NSO or gabapentin for 14 days. Thermal hypersensitivity (plantar test), cold and mechanical allodynia were tested. Criteria for analgesic effect: increase in withdrawal latency in the plantar and cold plate test at 60, 120 and 180 minutes, and lack of response to needle touch, respectively. High performance liquid chromatography was used for quantitative determination of thymoquinone in the oil.

Results: the amount of thymoquinone in NSO was 21.37 ± 0.38 mg/ml. Paclitaxel notably decreased latency in both tests employing thermal stimuli and caused removal of the paw in response to needle touch. In the plantar test, significant increase in latency compared to negative control was recorded in NSO treated animals at 180 minutes. In the cold plate test, NSO treatment led to an increase in withdrawal latency at 60, 120 and 180 minutes. A significant percentage of rats treated with NSO, along with gabapentin, did not remove the paw in response to needle touch. There was no statistical difference in the effect between gabapentin and NSO treated rats in all tests.

Conclusion: NSO exerts analgesic effect that is comparable to that of gabapentin.

Keywords: neuropathy, analgesia, thymoquinone, allodynia.

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EFFECTS OF ARONIA MELANOCARPA-BASED FRUIT JUICES ON THE BIOCHEMICAL MARKERS OF LIVER FUNCTION IN RATS A FED HIGH-CALORIE DIET

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Abstract
Introduction. Unhealthy diet is a serious risk factor for a variety of non-communicable diseases and requires a constant search for safe and effective methods for prevention of complications.
Aim. The aim of the present study was to investigate the effects of four Aronia melanocarpa-based polyphenol-rich fruit juices in rats fed high-calorie diet (HCD).
Materials and methods. The experiment was conducted on male Wistar rats for 60 days. The HCD contained 17% lard and 17% fructose added to the standard granules, and 10% fructose solution instead of drinking water. Rats were allocated to 6 groups: Control (standard diet), HCD, HCD+AM1, HCD+AM2 (aronia fruit juices produced at 20°C or 60°C, respectively), HCD+AMRC (AM2 with Rosa canina extract) and HCD+AMAV (A2 with Alchemilla vulgaris extract). Each juice was applied daily at a dose of 10 ml/kg. After sacrifice, blood serum was obtained for spectrophotometrical measurement of liver enzymes.
Results. HCD significantly increased the levels of AST ($p<0.01$ vs. Control), ALT ($p<0.001$ vs. Control) and ALP ($p<0.05$ vs. Control). AST levels were not significantly different from the control value in groups HCD+AM1 and HCD+AM2, and were elevated in HCD+AMRC and HCD+AMAV ($p<0.001$ and $p<0.05$ vs. Control for HCD+AMRC and HCD+AMAV, respectively). ALT levels were not different in all juice-treated groups compared to Control. ALP levels were increased in HCD+AM1 ($p<0.01$ vs. Control), and were not different from Control in other juice-treated groups.
Conclusion. Aronia melanocarpa-based fruit juices demonstrated a tendency to prevent high calorie diet-induced liver damage in rats.
Keywords: Aronia melanocarpa, Wistar rats, high-calorie diet, liver function, biochemical markers.

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THE TRADITIONAL BULGARIAN HERBS LOVAGE, SAVORY, FENUGREEK – POTENTIAL HEALTH BENEFITS IN RELATION TO THEIR HIGH POLYPHENOLIC CONTENT

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Abstract
Introduction. Lovage (Levisticum officinale), savory (Satureja genus) and fenugreek (Trigonella foenum-grecum) are traditional and underutilized Bulgarian herbs.
Aim.The aim of the present study is to highlight the potential health benefits of these traditional Bulgarian herbs.
Materials and methods. The study was performed by searching different internet-based databases (Google Scholar, ScienceDirect, PubMed, etc.).
Results. Levisticum officinale (lovage) is a perennial aromatic plant belonging to the family Apiaceae. Savory is a common name for different perennial plants from Satureja genus, family Lamiaceae. In Bulgaria mainly Satureja montana („mountain savory“) and Satureja hortensis („summer savory“) are grown. Trigonella foenum-grecum is an annual herb belonging to the family Fabaceae. The most commonly used parts for seasoning are the leaves and seeds. All these three plants are rich in the flavonoids quercetin and kaempferol. Rutin, apigenin and luteolin are found in two of these. The phenolic acids chlorogenic and ferulic are present in all three plants, while gallic, caffeic and vanilic are found in two of them.
For all of these plants, as well as for their main polyphenolic components, antioxidant, anti-inflammatory, anticancer, neuroprotective, antibacterial, metabolism improving and organoprotective effects have been reported. Savory and fenugreek affect positively also cardiovascular and reproductive functions. Many authors find a correlation between the high polyphenolic content of these herbs and their biological effects.
Conclusion. Lovage, savory and fenugreek are traditional Bulgarian polyphenol-rich herbs which had demonstrated various health-promoting properties. Amongst them lovage stands out as the least well studied and worth further scientific and clinical investigation.
Keywords: lovage, savory, fenugreek, polyphenols, health benefits.

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NEUROPROTECTIVE EFFECTS OF GLP-1 RECEPTOR AGONIST TREATMENT – FUTURE PERSPECTIVES

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Abstract

Introduction: GLP-1 and glucose-dependent insulinotropic peptide (GIP) are incretin hormones that are secreted from the intestinal tract during feeding and contribute to glucose-dependent insulin secretion. GLP-1 receptor agonists are used to treat type 2 diabetes mellitus, and their pleiotropic effects are determined by their binding to receptors in cells of the central and peripheral nervous system, muscle tissue, vascular endothelium, and multiple organs.

Methods: A literature review was performed, focusing on the potential neuroprotective effects of GLP-1 receptor agonists, molecular mechanisms, and activated signaling pathways in the CNS.

Results: The GLP-1 receptor is widely distributed in the CNS, including the striatum, hypothalamus, cortex, subventricular zone, and substantia nigra, as well as in the brainstem, with expression of GLP-1 receptors detected in endothelium, microglia, astrocytes, and neurons in humans and experimental animals. Results from *in vivo* and *in vitro* studies have demonstrated improvement of cognitive function, neuronal signaling, and insulin sensitivity, reduction of pro-apoptotic factors and neuronal death, as well as dose-dependent increase of neovascularization through activation of different intracellular signaling pathways.

Conclusion: These findings may be of clinical relevance for the administration of GLP-1 receptor agonists in patients with cognitive deficits and after stroke to improve prognosis and quality of life.

Keywords: neuroprotection, GLP-1 receptor agonists, CN.

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EFFECT OF TANACETUM VULGARE ESSENTIAL OIL ON SERUM BIOCHEMICAL PARAMETERS

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Abstract
Tanacetum vulgare L. is an aromatic herbaceous plant with a rich background in the traditional medicine of many nations. Its rich phytochemical content (phenolic compounds, sesquiterpene lactones, essential oil (EO)) contributes to various biological effects – antioxidant, anti-inflammatory, antimicrobial, cytotoxic, and antihelmintic. However, data on the in vivo pharmacological activity of the EO is limited. The present study aimed to evaluate the subacute toxicity of T. vulgare EO by observing serum biochemical parameters. We used 20 male rats, divided into two groups (n = 10). The animals were treated orally for 28 days as follows: control group – Oleum Helianthi (1.0 g/kg BW), test group - T. vulgare EO (1.5 ml/kg BW). At the end of the experiment, blood samples were drawn for the examination of serum biochemical parameters. In the test group was observed a significant increase in creatinine, AsAT, total bilirubin, HDL-cholesterol, albumin, and calcium, whereas a decrease in glucose, uric acid, ALAT, LDL-cholesterol, lactate dehydrogenase, creatine kinase-MB, iron, and phosphorus were detected. In conclusion, due to the low number of animals and short period of time, further investigations are needed to precisely evaluate the chronic effect of T. vulgare EO on biochemical parameters.
Acknowledgements: The authors gratefully acknowledge the support of Medical University of Plovdiv, project DPDP-07/2023.
Keywords: Tanacetum vulgare, essential oil, serum biochemical parameters.

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EFFECT OF TANACETUM VULGARE ETHANOL EXTRACT ON COGNITIVE FUNCTIONS IN AN EXPERIMENTAL MODEL OF SCOPOLAMINE-INDUCED AMNESIA

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Abstract
Tanacetum vulgare L. is a perennial plant, widely distributed in the northern hemisphere. The species is characterized by an affluent content of secondary metabolites such as flavonoids, sesquiterpenoids, and essential oil, contributing to its anti-inflammatory, antioxidant, antibacterial, and cytotoxic properties. However, literature data about the cognitive effects of the herb is scarce. The aim of the present study was to evaluate the pro-cognitive effects of two doses Tanacetum vulgare hydroalcoholic extract in an experimental model of scopolamine-induced amnesia in rats. We used 40 male Wistar rats, divided into 5 groups (n = 8) as follows: C-veh, C-Scop, Gly-Scop, T.vulgare-Scop 200 and T.vulgare-Scop 1000. All rats were subjected to two passive avoidance tests (step-down and step-through) and an object recognition test (ORT). Statistical evaluation was done by one-way ANOVA and Tukey post hoc test. We found that in the step-down task only the low dose of 200 mg/kg T. vulgare improved the short and long-term memory, while in the step-through test both doses of T. vulgare showed a longer latency time in the light chamber compared to the Scop-treated groups. No effect was observed during both passive learning sessions. In the ORT, the two groups treated with T. vulgare managed to increase the discrimination index compared to the animals with drug-induced amnesia. In conclusion, we found that T. vulgare applied in two doses, 200 and 1000 mg/kg, showed cognitive-enhancing properties including improved formation of short- and long-term memory traces and better recognition memory in an experimental model of scopolamine-induced memory impairment.
Keywords: Tanacetum vulgare, hydroalcoholic extract, cognitive function, scopolamine, amnesia**.**

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TREHALOSE: MECHANISMS AND THERAPEUTIC POTENTIAL IN NEURODEGENERATIVE DISORDERS

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Abstract
Introduction: One among many leading hypotheses about the cause of neurodegenerative diseases is the neuron damage induced by various mutant and misfolded proteins. Several studies concluded that trehalose a naturally occurring disaccharide consisting of two molecules of glucose linked via an α,α-1,1 glycosidic bound has neuroprotective properties in different experimental models of diseases like Parkinson's and Huntington's.
Aim: To summarize the current information about the neuroprotective effects of trehalose and to present some of the suggested mechanisms by which these effects are achieved.
Materials and Methods: A search across different scientific publication platforms including PubMed, ScienceDirect, ResearchGate, and SpringerLink was performed using keywords such as trehalose, neuroprotection, autophagy, induction, inflammation, protein, stability, etc. for articles published in the last fifteen years.
Results: A substantial number of studies agreed on several mechanisms. Of those the main are autophagy pathways modulation, anti-inflammatory properties, stabilization of proteins, oxidative stress reduction, and involvement of gut microbiota.
Conclusion: The results can serve as a basis for further investigation on identifying other possible mechanisms of neuroprotection in neurodegenerative disorders by trehalose.
Keywords: trehalose, neuroprotection, autophagy, oxidative stress, protein stabilization.

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TREATMENT OF SYPHILIS

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Abstract
Syphilis is a classic sexually transmitted infection caused by the Gram-negative bacterium Treponema pallidum. The bacterium is extremely sensitive to penicillin, which has remained the gold standard for treating syphilis since the introduction of the first penicillin antibiotic. This treatment is effective for all stages and clinical forms of the disease. Although syphilis is a treatable disease with affordable diagnostic tests and therapy, it is still a serious public health problem. The rapidly changing social environment must also be taken into account, including the increase in the number of homosexual individuals and the recognition of the so-called third gender and "gender ideology", which is a global phenomenon in modern society.
In recent years, it has become clear that short-acting penicillin preparations are not sufficient to treat the infection. Depot penicillins, which provide high serum levels of penicillin for two to four weeks, have been shown to be more effective in adequately treating the disease. They are also preferred because of their less frequent dosing (once a week), leading to better treatment adherence. Patients treated with other antibiotics such as doxycycline, ceftriaxone or azithromycin should know that it may take longer to become non-infectious. Data on the effectiveness of these alternative antibiotics are limited, and they should only be used in special circumstances, such as penicillin allergy.
Recently, combined treatment regimens with penicillins and subsequent outpatient treatment with tablet forms have been increasingly used, especially in patients with high antibody titers after standard syphilis treatment. Particular attention should be paid to patients with co-infection with HIV and syphilis, the frequency of which is increasing even during the period of the COVID-19 pandemic, including in Bulgaria. The available data show that these patients should be treated in the same way as people without HIV and respond well to a single dose of benzathine penicillin, but it should not be forgotten that syphilis increases the risk of acquiring and transmitting HIV infection.
Keywords: co-infection with HIV, penicillins, syphilis, Treponema pallidum.

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CLINICAL MASS SPECTROMETRY BECOMES A MAJOR TOOL FOR PRECISION MEDICINE

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Abstract
Introduction. There is an extraordinary flood of new technologies in medicine nowadays - sophisticated diagnostics based on genome assays, mass spectrometry, magnetic resonance spectroscopy and cell sorting platforms promote the entrance of individualized patient management in clinical practice. Aim. This work overviews the role of Clinical mass spectrometry (MS) as a tool for the introduction of precision medicine in routine patient care. Methods. Literature review and personal experience: while genetic testing allows the physician to check personal genetic program and choose appropriate medicine, the performance of MS assays provides the patient's actual phenotype, with all of the environmental, pharmacological and pathological variables; therefore, MS is essential technology for ultimate personalization of patient management. Results. The great technological advance of MS resulted in the introduction of methods with unprecedented identification power, extreme sensitivity and specificity which are based on the current reference analytical principles. Further, the ability to perform panel profiling with simultaneous measurement of bioactive compounds, their precursors and metabolites in a single sample, enormously amplifies the informative value of results, with ultimate improvement of patient care. Typical examples include new born screening, TDM, toxicology, endocrinology, microbiology, clinical omics assays and others. Experience with clinical mass spectrometry in the field of immunosuppressive drug monitoring, assessment of vitamin D status steroidomic, dihydropyrimidine dehydrogenase (DPD) phenotyping and genotyping. Conclusion. Clinical MS paves the introduction of precision medicine and integrates chemical and anatomical pathology via MS imaging and I-knife-MS guidance in surgery, thus opening new horizons for personalized treatment and individualized patient care.
Keywords: mass spectrometry, personalized treatment, precision medicine.

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OPIOIDERGIC MECHANISM OF ANTINOCICEPTION INDUCED BY ANGIOTENSIN 1-7 AND ITS NOVEL ANALOGS

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Abstract
Introduction. Ang 1-7 (Asp-Arg-Val-Tyr-Ile-His-Pro) is an endogenous heptapeptide belonging to the alternative or protective arm of the renin-angiotensin system (RAS). It binds to the Mas1 receptor (Mas1R), which has been found to be involved locally or at the spinal level in the control of experimental inflammatory pain. Our preliminary data showed antinociceptive effects of the precursory angiotensin 1-7 and its novel synthetic analogs in acute and inflammatory phases of the formalin test in mice.
The aim. We aimed to study the participation of the endogenous opioid system in the antinociceptive effects of Ang 1-7 and its novel structural analogs P1, P2, Pc5, and Pc6.
Material and methods. We used pretreatment with the selective opioid receptor blocker naloxone (Nal, 1 mg/kg, IP) to elucidate the involvement of the endogenous opioid system in Ang 1-7-induced antinociception. The new Ang 1-7 analogs were synthesized by solid-phase peptide synthesis (the Fmoc-strategy), dissolved in saline, and injected intraperitoneally (IP) at the effective dose of 1 mg/kg. Experiments were carried out in male ICR mice using the intraplantar formalin test to assess acute and inflammatory nociception.
Results. Ang 1-7 and its analogs P1, P2, and Pc6 produced a significant and naloxone-reversible antinociception in both the acute and inflammatory phases of the test. The Pc5 analog did not show any impact on the nociception.
Conclusion. Our results indicate that the endogenous opioidergic system is involved in the antinociceptive effects produced by the precursor peptide Ang 1-7 and its synthetic analogs P1, P2, and Pc6. The lack of effect of the Pc5 analog suggests the importance of structural changes for the efficacy of the peptide.
Acknowledgments: This work was financially supported by grant No 80-10-15/2024 funded by Sofia University “St. Kliment Ohridski”.
Keywords: Angiotensin 1-7, antinociception, opioidergic system, mice.

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OREXIN-1 ANTAGONISTS IN THE THERAPY OF PANIC DISORDER

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Abstract
Introduction: Orexins are neuropeptides involved in the regulation of sleep-wake behaviour, feeding, emotions, and other physiological processes. In recent years, orexin-1 receptor (OXR1) antagonists have attracted the attention of researchers as a potential new treatment of psychiatric disorders. Panic disorder encompasses spontaneous panic attacks. Main therapeutic approaches are cognitive-behavioural therapy along with SSRIs and benzodiazepines. Disadvantages of current pharmacotherapy have motivated research for a better alternative and OXR1 antagonists appear to be a promising option. Objective: The present research aims to review the available preclinical and clinical studies on the role of OXR1 antagonists in the therapy of panic disorder. Materials and Methods: We performed a search in PubMed and Dovepress databases by using the key words "panic disorder" and "orexin antagonists". 98 publications were screened and 7 were considered relevant to the topic. Results: In animal studies, three OXR1 antagonists demonstrated an ability to attenuate anxiety-like behaviour, assessed by a social interaction test, and cardiovascular responses in two different panic provocation models on rats. The experimental compounds did not present significant sedative side effects. In phase I clinical studies, two OXR1 antagonists showed improvement of panic responses in a CO2-inhalation challenge in healthy volunteers. The compounds demonstrated good safety profile with few reports of adverse effects, mainly somnolence and headache. Conclusion: The preclinical and phase I clinical studies indicate that OXR1 antagonists are promising novel-mechanism-based anti-panic compounds with good efficacy, tolerability and short-term safety. However, further research is needed for confirming their clinical usefulness in patients with panic disorder.
Keywords: panic disorder, orexin-1 receptor antagonists, animal studies, clinical studies.

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2-PHENYL-1,3-INDANEDIONE AND ITS EFFECT ON SPONTANEOUS MOTOR ACTIVITY AND THE PASSIVE LEARNING TEST

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Abstract
Indane and its analogs present a variety of biological applications as pharmacophores for the rational design of medications [1]. Indanone-based medications provide an expeditious profile in the current drug development focused on anti-inflammatory and anti-Alzheimer therapies [2,3]. Therefore, our study aimed to compare the effects of 2-phenyl-1,3-indanedione (PID) on spontaneous motor activity and the passive learning test. Materials and methods: Four groups of male Wistar rats (8 per group) were used. They were treated orally, once daily as follows: 1st group (control) - DMSO 0.1 ml/100g; 2nd group - PID 0.1 mg/kg; 3th group – PID 0.5 mg/kg; and 4th group - PID 1 mg/kg. The Activity cage method was used to evaluate spontaneous locomotor activity in rats using infrared beams. The step-through passive avoidance test was performed in a two-compartment cage divided by an automated, silent sliding door (Ugo Basile). The latency of reactions (animal remaining in the light chamber) was used as a criterion for learning and retention. The statistic evaluation was done in IBM SPSS 19. Results: The experimental group treated with PID 1.0 mg/kg significantly increased the horizontal activity from the first day compared to the control. At the retest on the 15th day, the 0.5 mg/kg- and 1 mg/kg-PID-treated groups showed a significant increase in horizontal movements compared to the groups from the first day of the test. Vertical activity was significantly increased at the retest: control group vs. day 1 control and PID 0.1 mg/kg-treated animals vs. control, while PID 0.5 mg/kg-treated group significantly decreased vertical activity vs. control. In the passive avoidance test, rats treated with 0.1 mg/kg-PID had reduced latency to stay on the first and second days of the training session relative to controls. In the long-term memory retest, animals treated with 0.5 mg/kg showed near-latency times similar to controls. Conclusion: PID stimulates the CNS, with a memory-enhancing effect observed only at the medium dose.
Keywords: cholinesterase inhibitor, activity cage, step-through test.

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COMPARATIVE STUDY OF THE HEPATOPROTECTIVE EFFECT OF ETHANOL INFUSION FROM COTINUS COGGYGRIA HEARTWOOD AND ITS MAIN PHYTOCHEMICAL CONSTITUENT FUSTIN IN A RAT MODEL OF PARACETAMOL-INDUCED ACUTE LIVER DAMAGE

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Abstract

Cotinus coggygria is a medicinal plant, rich in tannins and flavonoids. The main flavonoid in its heartwood is fustin. The aim of the present study was to compare the effects of 1/1000 ethanol infusion from C. coggygria heartwood (EICCH) and its main phytochemical constituent fustin in a model of paracetamol (PCM)-induced liver damage. Two experiments were performed. In the first experiment, 24 male Wistar rats were allocated in 3 groups: Control, PCM and 1/1000 EICCH+PCM. The third group was treated orally for 9 days with 10 ml/kg 1/1000 EICCH (1 g heartwood in 1 L 20% ethanol for 20 days extraction). Control and PCM groups received 20% ethanol. The second experiment included 48 male Wistar rats spread in 4 groups: Control, PCM, F5+PCM, F10+PCM. The rodents were treated orally for 9 days: F5+PCM and F10+PCM received fustin (suspended in Tween 80) at doses of 5 and 10 mg/kg, respectively; Control and PCM received distilled water and the vehicle for PCM. In both experiments, PCM (1.0 g/kg) was injected intraperitoneally on day 8. At the end of both experiments, serum and liver samples were prepared.

PCM caused a severe liver damage confirmed by histopathological and biochemical indices. Compared to PCM group, in F5+PCM and F10+PCM groups, the hepatic necrosis, balloon degeneration and inflammation were reduced. A lack of such hepatoprotective effect was registered for 1/1000 EICCH+PCM group. Fustin decreased serum activities of ALT and GGT. The present study demonstrated a hepatoprotective effect of the flavonoid fustin) at doses of 5 and 10 mg/kg. Such effect was absent for the 1/1000 ethanol infusion of C. coggygria heartwood.

Keywords: Cotinus coggygria; fustin; paracetamol-induced hepatotoxicity; Wistar rats.

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GUARDIANS OF THE MIND: NEUROPROTECTIVE MEROTERPENOIDS FROM FUNGAL REALMS OF LAND AND SEA

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Abstract
Introduction: Meroterpenoids (gr. méros – partial; τερέβινθος – terebinth tree, hēn – with one, oeidēs - resembling) represent a highly diverse group of natural secondary metabolites, partially derived from pathways involved in terpenoid biosynthesis. These compounds have been studied in the recent decade for a wide spectrum of biological activities including anti-cholinesterase, COX-2 inhibitory, antibacterial, antiviral, antidiabetic, antioxidant, anti-inflammatory, antineoplastic, cardioprotective, etc.
Aim: The aim of the current research is to explore the established neuroprotective properties of meroterpenoids from fungal and marine sources.
Material and methods: The data from various sources: PubMed, ScienceDirect, Scopus and Google Scholar have been collected. Research and review articles from the year 1999 onward were thoroughly reviewed. Neuroprotective, fungi, algae, Alzheimer's, dementia in combination with meroterpenoids have been used as keywords to collect the data.
Results: Experimental studies encourage for further in depth research suggesting that meroterpenoids hold promise as therapeutic agents for neurodegenerative disorders involving modulation of different cell signaling pathways and other properties, offering multiple mechanisms of action to combat neuronal damage and dysfunction. Neuroprotective, anti-cholinesterase, antioxidant, BACE1 inhibitory and anti-inflammatory activity with the potential on fighting dementia in various neurodegenerative disorders such as Alzheimer's and Parkinson's diseases by delaying the progression, improving cognitive function and quality of life have been introduced?
Conclusion: Overall, the entities of interest in our research have the potential to be developed as effective adjuvant for neuropathological disorders. Researches, focused on identifying the numerous neuroprotective pathways, is yet to be continued and extended.
Keywords: neurodegeneration, neuroinflammation, meroterpenoids, seaweeds, fungi.

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TERATOGENIC AND EMBRYO/FETOTOXIC EFFECT OF SELECTED MONOTERPENES – AN OVERVIEW

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Abstract
Introduction: Monoterpenes are main components of essential oils known for their diverse actions, including anticarcinogenic, antioxidant, antifungal, antiviral, anti-inflammatory. Some monoterpenes affect the development of the embryo and fetus during pregnancy.
Aim: This review aims to provide a brief summary of existing data on the teratogenic and embryo/fetotoxic effects of selected monoterpenes.
Materials and methods: Web-based databases such as ScienceDirect, Google Scholar and Scopus were used for this purpose.
Results: Dead fetuses were observed after eucalyptol administration at doses of 500 and 1000 mg/kg during the periods of preimplantation and organogenesis in rats. A delay in prenatal development, a higher frequency of mild skeletal deformities, and an increase in fetal spleen weight were noticed in rat fetuses exposed to doses of citral above 125 mg/kg body weight during pregnancy. The administration of thymol had a dose-dependent effect on the development of zebrafish embryos, which led to a decrease in their survival rate. Administration of camphor at a dose of 20 mg/kg to pregnant rats for three weeks resulted in an increased amount of deformed deceased embryos. They were reduced in size, deformity of the face and trunk, abnormal limbs and hypoplasia were observed. Higher doses of Foeniculum vulgare (containing more than 70% anethole) led to skeletal abnormalities, reduced ossification, reduced rib count, and shortened ribs in mice. The administration of high doses of citronellal led to limb deformities on chicken embryos.
Conclusion: The observed effects of selected mootherpenes on the embryo and fetus are noticed on animals, however, it is advisable to avoid them during pregnancy.
Keywords: teratogenicity, embryo/fetotoxicity, monoterpenes.

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RETROSPECTIVE STUDY ON THE DRUG UTILIZATION OF BIOSIMILAR MEDICINAL PRODUCTS CONTAINING MONOCLONAL ANTIBODIES IN BULGARIA

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Abstract
The introduction of biologics has raised complex regulatory issues and pharmacoeconomic concerns due to the associated high costs of therapy compared to conventional drugs. As periods of "data exclusivity" expire, biosimilars are emerging on the market that are expected to lower costs and increase patient access to biologic treatments. The aim of the study is to analyze the use of BSMP containing monoclonal antibodies in Bulgaria. Materials and methods: We conducted a retrospective study of data from the public registers of the EMA, the National Council on Prices and Reimbursement of Medicinal Products and the NHIF in Bulgaria for the period 2015 - 2023. The results were processed using descriptive statistical methods. Results and discussion: At EU level, BSMPs granted marketing authorization are within 10 INNs. The positive drug list of Bulgaria includes 32 BSMPs with the same INNs. The total expenditure on BMPs for the period was BGN 1,274,568,089, of which the share of BSMPs was 9%. BSMPs are available, but despite falling in the lower price range, the reference medicinal products remain the preferred therapeutic choice. The reason could be the lack of national standards for interchangeability, the mistrust of prescribers to the so-called replacement therapies and aggressive drug promotion to medical professionals.
Keywords: Biosimilars, availability, affordability, drug utilization, monoclonal antibodies.

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EFFECT OF ANETHOLE ON BODY WEIGHT AND ADIPOSE TISSUE DEPOSITS IN RATS ON A HIGH-CALORIE DIET

Elis Rafailova, Klementina Moneva-Marinova, Mehmed Reyzov, Silvia Gancheva, Milena Todorova, Miroslav Eftimov, Maria Zhelyazkova-Savova, Stefka Valcheva-Kuzmanova
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Abstract
Introduction: Anise and fennel essential oils contain anethole. Aim: To evaluate the effect of anethole on body weight and adipose tissue deposits in rats with an experimental model of obesity induced by a high-calorie diet (HCD). Materials and Methods: Male Wistar rats were divided into 5 groups (n=10): control, HCD, HCD+62.5A, HCD+125A, HCD+250A. The control group received standard diet and drinking water, while the other groups received HCD and 10% fructose solution instead of drinking water. The treatment was daily oral: control and HCD groups received sunflower oil, while the remaining groups – anethole at doses of 62.5 mg/kg, 125 mg/kg and 250 mg/kg, respectively, dissolved in sunflower oil. After euthanizing the experimental animals (in the 10th week), the mesenteric, paranephral, perigonadal, retroperitoneal and total adipose tissue were weighted and the adipose tissue indices were calculated in relation to body weight. Results: The indices of retroperitoneal, mesenteric and total adipose tissue were increased significantly in the HCD group compared to the control level. Treatment with anethole dose-dependently decreased all adipose tissue indices except that of paranephral fat tissue. In group HCD+250A, the indices of total and retroperitoneal adipose tissue did not differ significantly from the control values, as the index of retroperitoneal adipose tissue was significantly lower ($p<0.05$) in comparison to that of HCD group. Body weights of all experimental groups remained close in values throughout the experimental period. Conclusion: Anethole reduced adipose tissue deposits in rats in an experimental model of obesity, with the most pronounced effect on retroperitoneal and total fat tissue.
Keywords: anethole, obesity, adipose tissue, body weight.

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A CLINICAL CASE OF RESISTANT HYPERGLYCEMIA AND LIVER INJURY IN AN ELDERLY PATIENT WITH ACUTE LYMPHOBLASTIC LEUKEMIA

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Abstract
L-asparaginase is part of highly effective chemotherapy for the treatment of acute lymphoblastic leukemia (ALL) in children. In recent years it has been included in modern chemotherapy protocols in adults. It realizes a selective action on the lymphoblastic population by blocking malignant protein synthesis and cell proliferation. L-asparaginase is associated with numerous adverse drug reactions (ADRs). Significant are rapid-type hypersensitivity, hepatotoxicity, pancreatitis, hypercoagulation with pathological thromboses, and bone marrow suppression. Their incidence is significantly higher in adults compared to childhood, which limits the use and requires careful preliminary assessment.
Our clinical case presents resistant hyperglycemia and hepatotoxicity in an elderly patient with ALL. A 69-year-old man with B-ALL, high risk (CNS infiltration), was treated with induction chemotherapy according to protocol DFCI 91-01/Al.4. On day 8 of the regimen, PEG-L-asparaginase was administered. Hyperglycemia, discrete bilirubinemia, and elevated transaminases were recorded two days later. It followed a daily increase in glycemia with a lack of effect of insulin infusion, advancing liver toxicity with hyperbilirubinemia and impaired protein synthetic function against the background of severe drug-induced pancytopenia. Despite the complex treatment of overcoming pancytopenia, on day 12, the patient was somnolent, with jaundice, persistent hyperglycemia, manifestations of respiratory failure, and death followed. The potential of polychemotherapy to induce multiorgan toxicity is well known. Hepatotoxicity and hyperglycemia are characteristic ADRs of L-asparaginase. Age, discrete pre-existing liver damage, and dosage regimen can be considered as risk factors.
The clinical case confirms the need for a preliminary systematic assessment of risk factors and an individual benefit-risk assessment in adults.
Keywords: L-asparaginase, acute lymphoblastic leukemia, hepatotoxicity, hyperglycemia.

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COMPARATIVE STUDY OF ANTIOXIDANT EFFECTS OF RESVERATROL AND RESVERATROL-LOADED NANOPARTICLES IN SCOPOLAMINE INDUCED DEMENTIA IN RATS

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Abstract
Plant extracts and different natural products have been used effectively in traditional medicine for over 2000 years. Resveratrol (RVT) is a natural polyphenol which exhibits a wide range of beneficial effects – antioxidant, anticancer, anti-inflammatory, neuroprotective etc. However, its poor bioavailability is a challenge for therapeutic application. Nanoparticles are promising systems capable to solve this limitation. The aim of our study was to investigate and compare antioxidant effects of resveratrol and resveratrol-loaded nanoparticles (nRVT) in cortex in scopolamine induced dementia in rats. Male Wistar rats were divided into following groups: 1) Controls; 2) Scopolamine (Sco); 3) Sco + RVT; 4) Sco + nRTV. Sco 2mg/kg was applied i.p. for 11 days, RVT and nRVT 10 mg/kg i.p. 1h before Sco. After verification of the model with behavioral tests the animals were decapitated, cortex dissected and prepared for spectrophotometrically measurement of main antioxidant parameters: levels of lipid peroxidation (LPO) and total glutathione (GSH), antioxidant activities of superoxide dismutase (SOD), catalase (CAT) and glutathione peroxidase (GPx). The results showed that Sco induced oxidative stress in all studied markers. RVT and nRVT significantly decreased the elevated from Sco LPO and SOD. GSH levels were restored from nRTV, and GPx from RVT. As a conclusion, in our preliminary study we observed strong antioxidant potential of nRVT that suggested its potential for treatment of neurodegenerative disorders.
Keywords: resveratrol, nanoparticles, antioxidants, oxidative stress, neurodegeneration.

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INHIBITION OF THE BALANCING ARM OF THE RENIN-ANGIOTENSIN SYSTEM AFFECTS MOTIVATIONAL BEHAVIOR IN MICE

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Abstract
Introduction. The renin-angiotensin system (RAS) is a key regulator of body homeostasis that modulates many brain functions. Two opposing arms are thought to constitute the RAS: the pressor arm consists of Ang II, and AT1 receptors, mediating vasoconstrictor, proliferative, and proinflammatory effects, and the AT2 receptor, which opposes the effects of the AT1R. The depressor arm includes angiotensin-converting enzyme type 2 (ACE2) and Ang-(1-7), which mediate vasodilatory, antiproliferative, anti-inflammatory, and neuroprotective effects through the Mas1 receptor (Mas1R).
Aim. This study aimed to elucidate the complex effects of systemic ACE2 blockade on the control of anxiety- and depression-like behaviors and motor coordination in mice.
Methods. Male ICR mice were injected acutely or chronically (14 days) with the selective ACE2 inhibitor MLN-4760 (1 mg/kg, intraperitoneally), and subsequently tested for exploratory (“open field”) and anxiety-like behavior (“elevated plus maze”), depression-like behavior (“tail suspension”), and motor coordination (“rota rod”).
Results. Data analysis showed that chronic ACE2 inhibition induced depression-like behavior in "tail suspension" and impaired motor coordination in "rota rod" tests in mice. Acute enzyme inhibition stimulated exploratory and anxiolytic behavior expressed by greater total ambulation in the "open field" and more time spent in the open arms of the "elevated plus maze".
Conclusion.These preliminary data indicate that acute and chronic ACE2 inhibition affects the regulation of behavioral motivation, but further study is needed to elucidate their structural and cellular mechanisms of action.
Acknowledgments: This work was financially supported by the Bulgarian National Scientific Fund project КП-06-Н71/9.
Keywords: ACE2, anxiety, depression, mice.

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SPECIALIZED ANTI-INFLAMMATORY PHARMACOTHERAPY IN THE PATHOGENESIS OF CYTOKINE STORM IN SARS-COV-2 AND COVID-19

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Abstract
Coronaviruses are RNA viruses, causing inflammatory infectious diseases of the respiratory tract, with different clinical symptoms with complete or partial recovery, post-CoViD syndrome, or fatal outcome. The main cause of mortality in SARS-CoV-2/CoViD-19 is the genetically determined overreaction of the immune system to its viral irritation, expressed in excessive secretion of pro-inflammatory cytokines such as TNF-α, IL-1, Il-6, IL -8, IL-12, Il-18, IL-23 inducing a cytokine storm. The development of a large-scale inflammatory process with a cytokine storm can affect to varying degrees the parenchyma of the lower respiratory tract, endocrine organs, kidneys, heart and brain, with subsequent structural and functional disorders. During the course of the pandemic, the European Medicines Agency (EMA) approved several medicinal products for use in the treatment of SARS-CoV-2 infection. Active substances or monoclonal antibodies with different mechanism of action such anakinra, tixagevimab, cilgavimab and ragdanvimab could limit the inflammatory response and cytokine storm. OBJECTIVE: To elucidate different mechanisms by which cytokine storm occurs but can be suppressed by anakinra, tixagevimab, cilgavimab, or ragdanvimab therapy. MATERIALS and METHODS: A scientific review of various mechanisms by which the cytokine storm occurs and develops in SARS-CoV-2 infection, as well as the mechanisms by which anakinra, tixagevimab, cilgavimab or ragdanvimab act, was performed. CONCLUSION: Cellular pro-inflammatory cytokine mediators play a key role in the development of the cytokine storm in SARS-CoV-2 infection, but active substances or monoclonal antibodies such as anakinra, tixagevimab, cilgavimab or ragdanvimab can pharmacotherapeutically suppress the inflammatory process by different mechanisms.
Keywords: Cytokine storm, SARS-CoV-2/CoVid-19, Monoclonal pharmacotherapy, Pro-inflammatory and anti-inflammatory mechanisms.

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LEVETIRACETAM, BRIVARACETAM, SELETRACETAM AND SV2A IN THE THERAPY OF EPILEPSY

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Abstract
Epilepsy is a chronic disease of the brain, characterized by permanent predisposition to generate repeated short-term epileptic seizures at different time intervals. Epilepsy therapy is difficult because of the specific congenital or acquired structural-functional disturbances occuring in the damaged nerve tissue. Often, monotherapy is not sufficient, which necessitates the combination of several antiepileptic drugs to limit epileptic seizures.
The group of "racetams" is one of the most relevant in combined epilepsy's therapy, including levetiracetam, brivaracetam and seletracetam, who are indicated for the treatment of various types of epileptic seizures with genetic or acquired etio-pathogenesis, in patients under and over 18 years of age. These three antiepileptic active substances have an atypical mechanism of action. They do not affect epileptic seizures by acting on ATP-ase ion channels, but by acting on the poorly studied synaptic vesicle protein SV2A. OBJECTIVE: To elucidate the mechanisms through which „racetams" interact with SV2A to affect epileptic seizures. MATERIALS and METHODS: A comprehensive scientific review of specialized publications concerning the pharmacomechanisms between "racetams" and SV2A was performed. CONCLUSION: This report presents the molecular mechanisms of antiepileptic action of the main group of antiepileptic drugs, expressed in the modulation of voltage-gated and ligand-gated ion channel receptors, in contrast to the mechanisms through which levetiracetam, brivaracetam and seletracetam suppress epileptogenic activity of neurons in the epileptogenic focus, and their association with synaptic vesicle protein SV2A. The genetics, structure, and function of the synaptic vesicle protein SV2A itself in the pathogenesis and pharmacotherapy of epilepsy are also discussed.
Keywords: Epilepsy, Levetiracetam, Brivaracetam, Seletracetam, SV2A.

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ONCOPHARMACOLOGICAL STUDIES OF BIOLOGICALLY ACTIVE COMPOUNDS FROM THE GENUS HYPERICUM

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Abstract
Species of the genus Hypericum (St. John's wort) comprise a rich and promising source of biologically active substances of different structural classes, including condensed anthraquinones, benzophenones, xanthones, whereby of particular interest are the prenylated phenolic compounds incorporating a phloroglucinol fragment in their structure. In the framework of a long-term research program to identify promising natural bioactive substances with antineoplastic activity, detailed oncopharmacological studies of prenylated phloroglucinols, xanthones, benzophenones and their glycosides isolated from Hypericum aucheri, H. annulatum Morris subsp. annulatum, H. elegans, H. maculatum. The pharmacological exploration has allowed the identification of analogues with promising antineoplastic, antiangiogenic, apoptogenic effects or agents with the potential to overcome the multidrug resistance. Combinations of these newly isolated compounds and anticancer agents have also been investigated with a view to establishing synergistic effects in tumour models or reducing toxicity to non-malignant cells and tissues. For some of the most promising biologically active compounds, in-depth virtual screening has been conducted for in silico evaluation of their drug likeness, physicochemical properties and ADME profiles.
Keywords: Hypericum, natural products, antineoplastic activity, MDR, drug likeness, ADME.

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NOCICEPTIN ANALOGUES AND THEIR EFFECTS ON THE ENDOCANNABINOID AND OPIOID SYSTEMS AFTER CHRONIC IMMOBILIZATION STRESS IN RATS

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Abstract
Introduction: Stress influences neuroendocrine, autonomic, and immune functioning. Opioid peptides are released during stress, leading to antinociceptive effects. This is a phenomenon, referred to as stress-induced analgesia (SIA). The endocannabinoid system (ECS) has a well-established role in the modulation of pain perception and behavioral responses after stress. Nociceptin and analogues are neuropeptides, and neuromodulators, that have been found to play a role in pain perception.
This study aimed to investigate the analgesic effects of novel nociceptin N/OFQ(1-13)NH2 analogues on nociception after chronic immobilization stress (CIS) and the involvement of the opioid and endocannabinoid system in these effects.
Materials and Methods: The experiments were carried out on male Wistar rats. Analgesic effects were examined by paw-pressure (PP) test. All drugs were dissolved in saline and were injected intraperitoneally (i.p.). Statistical analysis was performed using one-way ANOVA.
Results: Our results showed that nociceptin and analogues decreased pain threshold after CIS, which is most pronounced for [Orn9, Orn13]N/OFQ(1-13)NH2. Co-administration of the peptides with CB1 antagonist (AM251) as well as of the peptides with Naloxone significantly decreased the pain threshold compared to a group that underwent chronic stress only.
Conclusions: Our experiments confirmed the participation of the opioid and endocannabinoid systems in the analgesic effects of nociceptin analogues after CIS.
Keywords: AM251, immobilization stress, naloxone, nociceptin analogues, pain.

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NOVEL BENZO[A]QUINOLIZIDINE ANALOGUES AS POTENTIAL DPP-IV INHIBITORS

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Abstract

Dipeptidyl peptidase IV (DPP-IV) is a specific serine protease enzyme whose inhibition has been widely used for type 2 diabetes mellitus treatment. Recent studies have outlined the benzo[a]quinolizidine ring as an important heterocyclic framework in the structure of potential DPP-IV inhibitors.

Material and methods. Our earlier studies were focused on the development of a one-step approach toward the benzo[a]quinolizidine system and its heterocyclic analogs based on the reaction between enolizable anhydrides and 3,4-dihydroisoquinolines. The results from molecular docking of previously synthesized compounds were used to optimize the structure, and a series of benzo[a]quinolizidine derivatives with varying molecular complexity were successfully synthesized. A fluorescence-based method for screening DPP IV inhibitors was applied to assess the synthesized compounds' inhibitory activity. The viability of stem cells derived from adipose tissue (ADSCs) at 6, 24, and 48 h was evaluated at 10, 100, and 1000 µmol compounds' concentrations.

Results. Two of the studied compounds with the code names A280620 and A191021 were found to possess inhibitory activity in the micromolar range: with IC50 19.4 µM and IC50 2.16 µM, respectively. More than 95% viability of ADSCs was reported with both substances at 6, 24, and 48 h. Results were comparable to controls.

In conclusion, the molecular docking approach allowed us to successfully optimize the structure of the benzo[a]quinolizidine inhibitors and to outline the necessary modifications to increase their potency as DPP-IV inhibitors. Future studies of A280620 and A191021 regarding their selectivity for DPP8 and DPP9 and their in vivo activity are needed.

Keywords: DPP-IV inhibitors, IC50, cell viability.

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REAL WORLD DATA AND REAL WORLD EVIDENCE AND THEIR PLACE IN EVIDENCE BASED MEDICINE

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Abstract
Introduction. In the current medical reality there are a lot of conditions that do not have a treatment alternative, opening highly unmet medical need for a number of patients. Scientific and regulatory societies are searching for ways to fill in the knowledge gaps to be able to meet those new challenges and provide the ones in need with the best possible alternative for their condition, based on evidence for efficacy and safety. When not enough data is available in order a medical or regulatory decision to be made there opens a need of a new tool to help fill in the knowledge gaps. Real world data (RWD) and Real world evidence (RWE) is a new way to generate data adding to CTs accumulated one to help decision-making of regulators and healthcare specialists. Aim. To analyze the advantages and disadvantages of RWD as well as the challenges in using RWE in decision-making. Methods and materials. Using the literature we will review the currently available knowledge and used practices concerning RWD and real world evidence (RWE). Results and conclusions. Real world data (RWD) is increasingly incorporated in the evaluation of human medicines. The need of RWD and RWE to give additional information and supplement the information from clinical trials (CTs) helps decision making in complicated cases where is no strong position standing out.
Keywords: RWD, RWE, decision-making, regulatory.

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BENZIMIDAZOLE METAL COMPLEXES WITH ANTITUMOUR ACTIVITY

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Abstract
Aim: The need for the development of new and innovative antitumor agents has increased tremendously over the past two decades. Adverse reactions accompanying current tarapies such as apoptosis, gastrointestinal toxicity, cardiotoxicity, neurotoxicity, immunosuppression, tumor cell resistance must be overcome. In the present work, a new type of biologically active substances are considered, the advantage of which is, their precise biological activity due to their specific structure and similarity to other biological molecules. Benzimidazole as a pharmacophore used as a basis for the synthesis of selective drugs in multiple therapeutic areas. The development of metallo-drugs based on coordination compounds is rapidly expanding, encompassing a wide variety of transition metals (Cu>Co>Zn>Ni) and ligands with specific structure in their composition. Materials and Methods: A literature review is performed in which the most widely used cytotoxicity assays are briefly described and the results obtained are referenced to scientific articles. Results: The combination of I-row transition metals and benzamidazole ligands reveals new directions for enhancing the cytotoxic or antiproliferative activities of heterocycles, as some of the complex compounds are able to interact with the active center of enzymes, improving their biocompatibility, bioavailability, and lipophilicity. Conclusion: Expanding research around the synthesis of new molecules that integrate benzamidazole as a pharmacophore, an important structural agent found in a large number of natural and biologically active molecules, and metal compounds of the I and II row is providing impetus in the design of new biologically active complexes with potential activity for chemotherapeutic applications.
Keywords: antitumor agents, benzimidazole, metal complexes, biologically active molecule.

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EFFECTS OF THYROID HORMONES ON SKIN PHYSIOLOGY AND PATHOLOGY

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Abstract
The skin is an important peripheral neuro-endocrine organ - a place of synthesis and activation or inactivation of thyroid releasing hormone, thyroid stimulating hormone and peripheral thyroid hormones.
Thyroid dysfunction can lead to oxidative stress in the skin of humans and animals through many different mechanisms. Hyperthyroidism generates abnormal production of reactive oxygen- and nitrogen species (ROS and RNS), respectively, whereas hypothyroidism weaken the antioxidant defense. As an external organ, skin is chronically exposed to the harmful ultraviolet radiation (UVR) that may augment its damage causing premature skin aging or even contributing to photocancerogenesis in patients with thyroid dysfunction.
Both, chronic sun exposure and hypothyroidism can cause independently an oxidative cutaneous damage. We first reported that solar simulated ultraviolet (SSUV) exposure could lead to a higher lipid peroxidation in hypothyroid skin than both factors alone. We found that malondialdehyde (MDA), which is a prototype of thiobarbituric acid reactive substances, was increased but the other lipid peroxidation product F2-isoprostane 15(S)-8-iso-prostaglandin F2α, derived exclusively from arachidonic acid was detected decreased and the reactions were not catalyzed by enzymes in the skin of hypothyroid animals.
It was measured also a markedly decreased total antioxidant capacity toward stable 2,2-diphenyl-1-picryl-hydrazyl radical (DPPH•) in hypothyroid rat's skin. We have observed that SSUV exhausted more hydrogen donating antioxidants than the hypothyroidism, while the combination of the two factors resulted in a very strong decrease of the radical scavenging activity (RSA).
Keywords: hypothyroidism, oxidative stress, phenotypic cutaneous changes, thyroid-associated dermopathy.

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PHARMACOLOGICAL MODULATION OF MITOCHONDRIAL FUNCTIONS IN DIABETES

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Abstract
Mitochondria contribute to much of basic human metabolism, including oxidative phosphorylation, the Krebs cycle, fatty acid oxidation, iron-sulfur center biosynthesis, heme, and amino acid metabolism. Mitochondria are also central to apoptotic cell death and modulate calcium fluxes throughout the cell.
Diabetes is a chronic metabolic disease caused by inadequate insulin production and secretion and, in the case of type 2 diabetes (T2D), by the inability of tissues to respond adequately to insulin. These changes lead to a high concentration of glucose in the blood, which over time leads to various complications. Mitochondrial dysfunctions have long been associated with diabetes as a potential cause of insulin resistance and cellular dysfunction, and more recently in the context of secondary complications of diabetes. There are numerous hypotheses explaining the association of various aspects of impaired mitochondrial function with diabetes, ranging from reduced mitochondrial content and impaired mitochondrial biogenesis to impaired mitochondrial function leading to intracellular accumulation of lipid products and increased production of reactive oxygen species (ROS), which further impair insulin sensitivity and energy metabolism. Mitochondrial functions have been extensively studied in diabetes, especially in skeletal muscle. As a highly metabolically active tissue comprising the largest percentage of total body mass, skeletal muscle, together with the liver, is a key player in the regulation of glucose homeostasis and is severely affected by metabolic disorders such as insulin resistance and metabolic syndrome.
New therapeutic agents targeting mitochondria that have been developed have the potential for a more integrative therapeutic approach to improve energy balance and mitochondrial function in diabetes.
Keywords: mitochondria, oxidative phosphorylation, Krebs cycle, insulin sensitivity, diabetes.

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EXPERIMENTAL STUDY ON THE EFFECTS OF COMBINED PLANT EXTRACTS ANTISTRESS I AND ANTISTRESS II IN AN ACTIVE AVOIDANCE MEMORY TEST

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Abstract

Introduction: Chronic untreated stress can lead to the development of depression, neurodegenerative diseases, and cognitive disorders. Adaptogens are substances that enhance the body's resilience to various types of stress and improve cognitive functions. In phytotherapy, multiple plant products are often combined to achieve better therapeutic effects and fewer side effects.

Aim: This study aims to evaluate the effects on learning and memory of the combined plant extracts Antistress I and Antistress II, as well as the impact of the individual extracts included in their formulations.

Materials and Methods: 64 male Wistar rats, divided into 8 groups of 8 animals each, were treated for 8 weeks with 5 individual extracts—Serratula coronata, Hypericum perforatum, Valeriana officinalis, Crataegus monogyna, and Melissa officinalis—as well as with two combinations, Antistress I and Antistress II, all at a dose of 500 mg/kg body weight. The animals were then tested for their learning and memory processes using the Shuttle box apparatus. The procedure included four days of training, a short-term memory test on day 5, and a long-term memory test on day 12.

Results: The group treated with Antistress II, as well as the groups treated with individual extracts of Serratula coronata and Hypericum perforatum, showed statistically significant (p<0.05) improvements in active avoidance compared to the control group treated with distilled water, in both the short-term and long-term memory tests.

Conclusion: The Antistress II combination improves learning and memory processes in rats and is suitable for inclusion in clinical trials.

Keywords: combined plant extracts, adaptogens, Serratula coronata, learning and memory, active avoidance.

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THE ROLE OF TIRZEPATIDE IN THE TREATMENT OF DIABETES TYPE – 2 AND OBESITAS

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Abstract
Introduction: Obesitas has become a global problem and there are very few drugs, which are simultaneously effective and less adverse reactions. Tirzepatide is a novel molecule that targets for improvement of glycemic control and body weight in patients with diabetes type – 2 and obesitas.
Aim: Evaluation of effectiveness and safety of Tirzepatide, in the treatment of obesitas and diabetes type – 2. The assessment is made against the conducted clinical trials SURPASS 1-6, SURPASS j mono, SURPASS AP combo, SURPASS CVOT and SURMOUNT 1-4.
Methods: We did a research in https://pubmed.ncbi.nlm.nih.gov/, and in clinicaltrials.gov, of the published data for Tirzepatide. The clinical trials have begun with SURPASS program in late 2018 and ended with SURMOUNT program in December 2023.
Results: A total of 10 clinical trials were found. Nine of them have completed, while the 10th is expected to end in 2025 year. From the published data, we can conclude that Tirzepatide is superior, noninferior, with respect to the two primary outcomes – reduction in the glycated hemoglobin and reduction in body weight in patient with type – 2 diabetes, when Tirzepatide is administered as monotherapy and in combination with other antidiabetic drugs. The most common adverse reactions are diarrhea, nausea and vomiting, without clinically significant hypoglycemic episodes.
Conclusion: Tirzepatide has demonstrated superiority, noninferiority against Insulin glargine, Insulin detemir, Insulin lispro and Semaglutide in regard to glycemic control and reduction in body weight in patients with type – 2 diabetes.
Keywords: Tirzepatide, SURPASS, SURMOUNT, GIP, GLP-1

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EFFECT OF VITAMIN D ON RHEUMATOID ARTHRITIS

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Abstract
Introduction. Rheumatoid arthritis (RA) is a chronic autoimmune disease that leads to inflammation and destruction of the joints, as well as systemic effects. In recent years, the role of vitamin D as a potential modulator of the immune system and its impact on inflammatory processes in RA has been studied.
The aim of this study is to evaluate the effect of vitamin D on the inflammatory process in an experimental model of RA and to identify potential mechanisms of action.
Materials and methods. An experimental study was conducted using a collagen-induced arthritis model in mice. The animals were divided into two groups: a control group not treated with vitamin D and a group treated with vitamin D at a dose of 2000 IU/kg orally three times a week for two weeks before arthritis induction (D-CIA). Inflammation was assessed using a plethysmometer and a visual scale. Biochemical and hematological analyses were also performed.
Results. The administration of vitamin D significantly reduced the degree of inflammation. In the D-CIA group, the percentage of affected animals was 64.44% compared to 81.11% in the untreated group. In the D-CIA group, 27.58% of animals were rated "4" on the visual scale; 22.99% were rated "3"; 11.49% were rated "2"; and 37.93% were rated "1". In the control group, 47.95% were rated "4" on the visual scale; 44.29% were rated "3"; 4.56% were rated "2"; and 3.20% were rated "1".
Conclusions. Prophylactic intake of vitamin D reduces the incidence and severity of inflammation in collagen-induced arthritis, warranting further analysis of its potential application in the prevention of rheumatoid arthritis.
Keywords: rheumatoid arthritis, vitamin D, inflammation, immunomodulation
Acknowledgement: We acknowledge the financial support from the Council of Medical Science, Medical University Sofia (Contract No. D-109/2024) for the conduction of the current study.

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ANTICONVULSANT PROFILE OF THREE HEMORPHIN-4 ANALOGUES WITH RHODAMINE B IN MICE

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Abstract
Recently, three novel hemorphin-4 analogs were synthesized and characterized with rhodamine B. The aim of the current study was to evaluate them in the acute seizure test and the pentylenetetrazole (PTZ) kindling model of epilepsy in mice. In addition, the role of opioid receptors in the mechanism of action of the compounds with anticonvulsant activity was investigated. The three novel compounds, R-H4, R-A-H4, and R-M-H4, dose-dependently suppressed 6Hz-induced psychomotor seizures and generalized seizures in the maximal electroshock test. The antiepileptic effect of the compounds in PTZ-induced mice was blocked by naloxone. Docking analysis also confirmed the role of opioid receptors in mediating the antiepileptic activity of the three hemorphin analogs with rhodamine B. Our results suggest that the novel morphine-4 analogs with rhodamine B could be considered promising candidates for the development of novel opioid-related antiepileptic drugs.
Keywords: hemorphin analog, rhodamine, seizure, opioid receptor, mice.

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NOVEL MELATONIN- AND DONEPEZIL-BASED HYBRID ANALOGS TARGETING AB PRODUCTION/CLEARANCE BALANCE AND AB NEUROTOXICITY: A POTENTIAL THERAPEUTIC MOLECULE FOR ALZHEIMER'S DISEASE

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Abstract
Dysfunction of the melatonin system predisposes to neurodegeneration and the pathogenesis of Alzheimer's disease (AD). The role of the melatonin system in the three main hallmarks of Alzheimer's disease (AD) - Aβ plaque formation, p-TAU and cholinergic dysfunction - is attracting considerable attention due to its potential neuroprotective effects. Therefore, the exploration of molecules targeting this system could contribute to the discovery of novel drugs that promote a non-amyloidogenic mechanism known to be mediated by the melatonin (MT) receptor. In the present study, the two most potent melatonin- and donepezil-based hybrid analogs, 3a and 3c, recently synthesized and tested in silico and in vitro by our team, were selected and investigated in a rat model of pinealectomy (pin) followed by icvAβ1-42 infusion. Systemic treatment with melatonin, used as a reference drug, 3a and 3c (10 mg/kg, i.p. for 21 days) was started after the removal of the pineal gland in rats. One week after surgery, Aβ1-42 was infused intracerebroventricularly, while controls were treated with a vehicle. Working and short-term memory were tested in a battery of tests between 17 and 21 days after surgery.
The hybrid compounds showed a beneficial effect comparable to that of melatonin against impairments in spatial and recognition memory in rats. Like melatonin, the two novel hybrid compounds facilitated the non-amyloidogenic pathway via receptor-related signalling (MT1/2/ERK 1/2/CREB and MT1/apoE4/LRP1, respectively). Our preclinical studies in a rat pin+icvAβ1-42 model of AD have demonstrated that melatonin- and donepezil-based hybrid analogs targeting Aβ production are a promising therapeutic approach capable of reducing AD-associated neuropathology and improving cognitive performance in the absence of toxicity.
Keywords: Melatonin analogue; pinealectomy; icvAβ1-42; MT receptors; non-amyloidogenic pathway.

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EXPERIMENTAL STUDY ON THE ANTI-INFLAMMATORY AND ANALGESIC EFFECT OF MICROMERIA FRIVALDSZKYANA (DEGEN) VELEN

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Abstract

Introduction. Micromeria frivaldszkyana is a Balkan endemic species and its extract is particularly rich in linarin, rosmarinic acid, and flavonoids (eupatorin, kaempferol, and apigenin). Aim. To examine the anti-inflammatory and antinociceptive effect of methanolic extract of M. frivaldszkyana. Materials and methods. The antiphlogistic activity was evaluated using the model of carrageenan-induced paw edema in male Wistar rats. They were divided into 6 groups (n = 8) and treated orally with: saline, diclofenac sodium 25 mg/kg bw (positive control group), 250, 400 and 500 mg/kg bw dried methanolic extract of M. frivaldszkyana, and 30 mg/kg bw rosmarinic acid, respectively. The antinociceptive effect was explored using the hot-plate test and Randall-Selitto paw pressure test in 48 male Wistar rats divided into groups as above, except the positive control group, which received 150 mg/kg bw metamizole sodium. Results. Fourteen-day pre-treatment with methanolic extract of M. frivaldszkyana in doses 250, 400, and 500 mg/kg bw induced antiphlogistic effect in the 1st, 2nd, and 3rd hour after the carrageenan administration. This activity was also present in the 4th hour only in the group treated with 500 mg/kg M. frivaldszkyana extract. We did not detect an analgesic effect in the experimental groups. Discussion. Treatment with the methanolic extract of M. frivaldszkyana for 14 days shows an anti-inflammatory potential. Conclusion. These results are a basis for further testing and may find practical application.

Keywords: Micromeria frivaldszkyana, inflammation, antinociceptive effect, rat paw edema.

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EFFECTS OF CHAENOMELES MAULEI FRUIT JUICE ON LIVER HISTOPATHOLOGY IN A MODEL OF PARACETAMOL-INDUCED HEPATOTOXICITY

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Abstract

Plants from the genus Chaenomeles have been used for their beneficial health effects for thousands of years in traditional Eastern medicine.

The aim of the current study was to evaluate the effects of Chaenomeles maulei fruit juice (CMFJ) on the histopathology of liver in a model of paracetamol-induced hepatotoxicity.

50 Wistar rats were allocated into 5 groups of 10 animals each: Control, PCM, PCM+CMFJ2.5, PCM+CMFJ5 and PCM+CMFJ10. For 12 days, animals were treated with an orogastral tube: groups Control and PCM received water, while the other three groups received CMFJ in increasing doses (2.5, 5 and 10 ml/kg, respectively). On day 11 of the experiment, groups PCM, PCM+CMFJ2.5, PCM+CMFJ5 and PCM+CMFJ10 were intraperitoneally injected with PCM (1 g/kg), while group Control was injected with the solvent for PCM. On day 13, liver probes were taken, fixed in formalin and embedded in paraffin. Tissue slices were coloured with hematoxilin and eosin and observed with light microscopy.

In group Control, a normal structure of the liver was observed. In group PCM, centroacinar necroses, confluent at places, were observed, as well as hydropic degeneration at the periphery of necrotic zones. In group PCM+CMFJ2.5 the zones affected by necrotic and inflammatory changes were reduced. The medium and the high dose of the juice succeed in limiting the paracetamol-induced liver damage to a higher extent without being able to completely prevent it. The current study demonstrates a dose-dependent hepatoprotective effect of Chaenomeles maulei fruit juice that is probably attributed to the rich polyphenolic content of the juice.

Keywords: Chaenomeles, hepatotoxicity, medicinal plants.

MARKETING AUTHORISATION OF MEDICINAL PRODUCTS – STATE OF PLAY AND WAY FORWARD THE ROLE OF THE BULGARIAN DRUG AGENCY

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Abstract
Introduction: Given the upcoming changes in the pharmaceutical regulatory framework, I present an up-to-date status of the processes of marketing authorization of medicinal products and the participation of BDA assessors in European practice.
Objective: to summarize and present the contemporary regulatory framework that defines the procedures for granting marketing authorization for a medicinal product.
In order for a medicinal product to be placed on the market in Bulgaria, it must have a valid marketing authorization in Bulgaria and/or EC, issued by the national competent authority, which is the BDA or the European Commission (EC). The report presents the procedures for issuing a marketing authorization: national, decentralized, and centralized, what are the requirements for the documentation necessary for issuing a marketing authorization, which medicinal products must be considered by the European Medicines Agency (EMA), how they work the separate committees at EMA. Difference between reference and generic products. I present the participation of the BDA assessors in the European procedures for the designation of orphan medicinal products, as well as the participation in multinational teams in the preparation of the scientific assessment of the documentation submitted for the authorisation of new medicinal products in the CHMP: abciximab, bevacizumab (i-Pique), pegfilgastrim and as peer-reviewers of procedures for giving scientific advice to applicants.
Conclusion: The EU's regulatory framework and scientific capacity ensure safe and effective medicines for European patients. The BDA assessors are equal partners in the European procedures for the assessment and granting of Marketing Authorisations of new medicinal products.
Keywords: medicinal products, marketing authorisation, procedures, BDA, EMA.

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EFFECT OF HIGH FRUCTOSE DIET ON URIC ACID LEVELS IN WISTAR RATS

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Abstract
Introduction: A high-fructose diet is among the leading risk factors for the development of many socially significant diseases. Its influence on a number of indicators has been confirmed, and in recent years the relationship between increased carbohydrate intake and uric acid levels has been of interest.
Purpose: The purpose of our study was to determine the effect of a high fructose diet on uric acid levels in male and female Wistar rats.
Materials and methods: 15 male and 15 female Wistar rats aged 2 months were used under standardization of conditions and free, unrestricted access to water and standard laboratory rodent chow for the control groups and using a 15% solution of fructose instead of water in the experimental groups for a period of 12 weeks.
Results: The results of our study showed a statistically significant difference (P<0.05) in the levels of uric acid between the control group of male rats (68.00 ± 4.75 mcmol/l) and the experimental group of male rats fed with high fructose diet (86.63 ± 4.11 mcmol/l). No significant differences were recorded between the control groups of male and female specimens. Between the control (68.00± 4.75 mcmol/l) and the experimental (84.75 ± 24.09 mcmol/l) group of female rats no significant differences were also registered, and the reasons for this are probably complex and include the participation of some sex hormones and other factors.
Conclusion: The role of high-fructose diet in the development of hyperuricemia in male Wistar rats is confirmed.
Keywords: uric acid, high fructose diet.

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MINIMIZING THE TERATOGENIC RISK OF ANTICONVULSANTS IN DESIRED PREGNANCY AND EPILEPSY

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Abstract
The focus of personalized medicine in recent years has been to create rational therapeutic strategies to minimize the risk of using teratogenic drugs that should not or cannot be stopped due to maternal vital risk or long-term treatment of chronic disease syndromes. The actual presentation is devoted to the problems arising from the use of anticonvulsants and protection of reproductive health in women with epilepsy. Can, should, and when should they get pregnant? How and with what drugs should be treated during pregnancy, childbirth and lactation? Do anticonvulsants affect the expectant mother and fetus? Long-term experience with classic and new anticonvulsants has shown a significant teratogenic risk in animals and humans. However, competent pregnancy management by a team of neurologists, obstetricians and clinical pharmacologists allows a woman with epilepsy to have a healthy offspring.
Keywords: anticonvulsants strategies, epilepsy, teratogenesis.

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EFFECT OF CANNABIDIOL ON LEARNING AND MEMORY IN EXPERIMENTAL MODEL OF IMPAIRED MEMORY

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Abstract
Introduction: Cannabidiol (CBD), a non-psychotomimetic phytocannabinoid found in the Cannabis sativa plant, has shown promise in experimental studies for its antioxidant, anxiolytic, and neuroprotective effects, particularly in neurodegenerative diseases such as Alzheimer's disease and multiple sclerosis.
Aim: This study aimed to evaluate the effects of cannabidiol on learning and memory processes in a scopolamine-induced model of memory impairment.
Materials and Methods: Male Wistar rats (n=8 per group) were divided into five groups and treated orally for 14 days. Groups 1 and 2 received olive oil, while groups 3, 4, and 5 received CBD at doses of 2.5, 5, and 10 mg/kg body weight, respectively. After the treatment period, learning ability and memory retention were assessed using the Novel Object Recognition Test (NORT) and the Elevated T-maze Test. Memory impairment was induced on the test days by administering scopolamine (1 mg/kg body weight intraperitoneally) 30 minutes after substance administration to groups 2 to 5. The recognition index and spatial memory index were recorded in the NORT and T-maze tests, respectively. Statistical analyses were conducted using SPSS 19.
Results: In the Novel Object Recognition Test, the group receiving 10 mg/kg CBD exhibited a significantly higher recognition index compared to the scopolamine-treated control group. In the Elevated T-maze Test, animals treated with 2.5 and 10 mg/kg CBD showed a significant increase in the spatial memory index compared to the memory-impaired control group.
Conclusion: Cannabidiol enhances learning and memory in a scopolamine-induced memory impairment model in a non-dose-dependent manner.
Keywords: cannabidiol, learning and memory**.**

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ALGORITHMS FOR ASSESSMENT OF SEVERE CUTANEOUS ADVERSE REACTIONS

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Abstract
Background. Severe cutaneous adverse reactions (SCARs) to drugs are uncommon life-threatening conditions belonging to delayed type hypersensitivity reactions. They include mainly Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN) and drug reaction with eosinophilia and systemic symptoms (DRESS) syndrome.
Aims. To evaluate the relevance of specific algorithms for causality assessment of SCARs in clinical practice.
Materials and methods. A prospective pharmacovigilance study was carried out among patients admitted to the Clinic of Dermatology and Venereology at UMBAL "Prof. Dr. Stoyan Kirkovich", Stara Zagora. Case-causality was scored according to Naranjo et al. (1981). For cases with SJS/TEN the ALDEN algorithm (2010) was also applied, and for those with DRESS syndrome – the ALDRESS algorithm (2024).
Results. Overall 4 cases with SJS/TEN were identified: 2 with TEN and 2 with SJS/TEN overlap. The Naranjo scale scored all cases as “possible” while the ALDEN algorithm differentiated these adverse reactions as “possible” “probable” and “very probable”. The culprit drugs were cotrimoxazole, allopurinol and diclofenac. No specific drug was verified in a patient with TEN due to polypharmacy. DRESS syndrome was detected in 6 patients and was attributed to carbamazepine (5 cases) and sulfasalazine (1 case). Drug causality was scored as “probable” in half of the cases and as “possible” in the rest. The ALDRESS algorithm evaluated causality in these cases as follows: 1 “definite” case, 1 “very probable” case and 4 “probable” cases.
Conclusion. It was confirmed that the ALDEN algorithm and the ALDRESS algorithm are valuable tools for more precise causality assessment of SCARs.
Keywords: severe cutaneous adverse drug reactions, algorithms.

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IN VITRO EVALUATION OF CYTOTOXIC EFFECTS OF BERBERINE, LOADED IN LIPID NANOPARTICLES, IN CHOLANGIOCARCINOMA CELL

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Abstract

Cholangiocarcinomas (CCAs) are malignant tumors that are characterized by a poor prognosis and low survival. Difficulties in chemotherapy are often due to the development of drug resistance. An innovative approach to overcome this problems is using in the therapy natural substances with proven antiproliferative properties, such as the isoquinoline alkaloid berberine and their encapsulation in suitable drug-delivery systems. The aim of this study is to obtain and characterize nanostructured lipid carriers (Nanostructured Lipid Carriers – NLC) loaded with berberine and to evaluate their antiproliferative effects in three cholangiocarcinoma cell lines in vitro. Nanoparticle loading and size were assessed by Nanoparticle Tracking Analysis (NTA). Cytotoxicity was tested in HuCCT1 (iCCA) and TFK-1 and EGI-1 (eCCA) cell lines by MTT-test and Western blot (WB) to analyze the interaction with proteins (eg. AXIN1), involved in pathogenetic pathway of CCA. The obtained results show a high cytostatic and antiproliferative activity of berberine: IC50 for TFK-1 – 6 μM, EGI-1 – 0.4 μM, HuCCT1 – 3 μM. The activity was compared to that of cisplatin: IC50 – 10 μM (approximately in all three cell lines). Berberine-loaded lipid nanoparticles showed cytotoxicity comparable to unloaded berberine and antiproliferative activity was confirmed by HoloMonitor. WB analysis showed a decrease in AXIN1 protein expression after berberine treatment relative to the control. In conclusion, berberine (alone and loaded into lipid nanoparticles) exhibits good antiproliferative activity on CCA cell lines, comparable to that of cisplatin, as well as the ability to affect different cellular pathways. These results show a good perspective for future in vitro and in vivo studies of the effects of berberine in models of CCA.

Keywords: cholangiocarcinoma, berberine, lipid nanoparticles, in vitro evaluation of cytotoxicity.

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CHANGES IN FAT ACCUMULATION, CHOLESTEROL, AND TRIGLYCERIDES IN RATS ON A HIGH-CALORIE DIET AND TREATED WITH ARONIA MELANOCARPA-BASED FRUIT JUICES

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Abstract
Aim. To monitor the weight changes, cholesterol, triglycerides, and fat accumulation in rats fed a high-calorie diet for 60 days and treated with four Aronia melanocarpa-based fruit juices.
Materials and Methods. Wistar rats (n=60) were divided into 6 groups and subjected to a 60-day high-calorie diet (HCD), except for the control group, which received standard food. The HCD contained 17% lard and 17% fructose in standard pellets, as well as 10% fructose instead of drinking water. The animals were treated daily intragastrically with: distilled water – Control and HCD groups; Aronia fruit juices produced at 20°C and 60°C – HCD+AM1 and HCD+AM2 groups, respectively; AM2 with added Rosa canina extract – HCD+AMRC group; AM2 with added Alchemilla vulgaris extract – HCD+AMAV group. The animal weight change was monitored. Fat tissue was measured, cholesterol and triglyceride blood levels were determined.
Results. There were no significant weight changes neither in the HCD group vs. Control, nor in the groups treated with the four types of fruit juice vs. HCD and vs. Control. In the HCD group, fat tissue was not increased compared to the control. Retroperitoneal and total fat tissue in the HCD+AMAV group were significantly reduced ($p<0.05$) vs. HCD. Cholesterol and triglyceride levels were increased in the HCD group ($p<0.05$ vs. Control). Fruit juices, except for AMRC, significantly reduced triglycerides ($p<0.05$ vs. HCD) and all reduced cholesterol to levels similar to those of the controls.
Conclusion. Aronia melanocarpa-based fruit juices show beneficial effects on fat accumulation and lipid profile in rats on a high-calorie diet.
Keywords: Aronia melanocarpa, Wistar rats, high-calorie diet, fat tissue, lipid profile.

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LIRAGLUTIDE ALLEVIATES NEUROPATHIC PAIN AND MITIGATES COMPULSIVE BEHAVIOR IN STREPTOZOTOCIN-INDUCED DIABETIC MICE

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Abstract
Introduction: Diabetes mellitus is a widespread chronic disease. Its most common complication, diabetic neuropathy, causes sensory loss and pain. Additionally, diabetes increases the risk of psychiatric disorders like depression and anxiety. Liraglutide, a glucagon-like peptide-1 receptor agonist, has shown neuroprotective properties.
Aim: This study aims to investigate the effects of liraglutide on cold-induced hyperalgesia and depression- and anxiety-like behaviors in diabetic mice.
Materials and Methods: Experimental studies were conducted on male ICR mice. Type 1 diabetes was induced with a single intraperitoneal injection of streptozotocin (150 mg/kg). Starting on day 8, diabetic mice received daily subcutaneous liraglutide (0.4 mg/kg) for 10 days. Cold-induced hyperalgesia was assessed with the cold plate test. Depression- and anxiety-like behaviors were evaluated using the tail suspension test and marble burying test, respectively. Each group had 9 animals. Data were analyzed using Shapiro-Wilk, one-way ANOVA, Kruskal-Wallis, and Student-Newman-Keuls tests.
Results: Administration of streptozotocin resulted in significant cold-induced hyperalgesia, as evidenced by decreased paw withdrawal latency to cold stimuli. Treatment with liraglutide significantly alleviated this hyperalgesia. Diabetic mice exhibited increased marble burying at both 20 and 30 minutes compared to control mice, indicating enhanced obsessive-compulsive behavior. Liraglutide treatment reduced the number of buried marbles. No significant differences were observed in the tail suspension test among the three experimental groups.
Conclusion: Liraglutide treatment effectively mitigates cold-induced hyperalgesia and reduces compulsive behavior in diabetic mice, highlighting its potential neuroprotective benefits in managing diabetes-related neuropathic pain and anxiety.
Acknowledgement: Bulgarian Science Fund, Ministry of Education, Contract KP-06-H63/9 from 13.12.2022.
Keywords: diabetes, neuropathy, pain, anxiety, liraglutide**.**

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KOCHIA SCOPARIA SEED INFUSION IMPROVES TRIGLYCERIDES LEVELS AND GLUCOSE TOLERANCE IN RATS ON HIGH CALORIE-DIET

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Abstract
Introduction. Kochia scoparia (KS) seeds contain biologically active substances with anti-obesity, antidyslipidemic and antihyperglycemic properties.
Aim. To investigate the effects of aqueous KS seed infusion (KSSI) in three different concentrations on visceral adiposity and lipid and glucose metabolism in rats fed a high-fat high-fructose (HFHF) diet.
Materials and methods. Fifty male Wistar rats were divided into 5 groups (n=10): Control, HFHF, KSSI1.5, KSSI3 and KSSI6. During 10 weeks, the Control group received standard laboratory chaw and tap water, while the other groups received an HFHF diet and 10% fructose dissolved in the drinking water or the KSSI. Groups KSSI1.5, KSSI3, and KSSI6 received KSSI in increasing concentrations – 1.5%, 3% and 6%, respectively, by ad libitum oral administration. The consumption of food and fluids was recorded daily, and animal body weight was monitored weekly. At the end of the experiment, a glucose tolerance test (GTT) was performed and serum levels of triglycerides and cholesterol were measured. Visceral fat depots were weighted and fat depot indices were calculated.
Results. GTT revealed a dose-dependent improvement of glucose tolerance at the 90th minute in KSSI-treated groups ($p<0.05$ for linear trend). Triglyceride levels were increased in the HFHF group compared to Control ($p<0.05$), and decreased in groups KSSI3, and KSSI6 compared to HFHF ($p<0.01$ and $p<0.05$ respectively). There were no significant differences in serum cholesterol levels or final body weight and fat depot indices between the experimental groups.
Conclusion. KSSI showed beneficial effects on triglyceride levels and glucose tolerance in rats on high-calorie diet.
Keywords: Kochia scoparia, high calorie-diet, triglycerides, glucose tolerance.

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PHARMACOLOGICAL EFFECTS OF MOMORDIN IC – A REVIEW

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Abstract
Introduction: Momordin Ic (MIc) is a natural triterpenoid derived from Kochia scoparia. Currently, there are no reviews available in the scientific literature about its biological activities.
Objective: Present review aims to summarise the available information about the biological effects of MIc.
Methods: Pubmed and Google Scholar databases were searched using the keyword “momordin Ic”. Nineteen publications were considered relevant to the topic.
Results: MIc has been primarily studied for its effects on GIT. MIc possesses a gastroprotective action and inhibits gastric emptying in experimental animals mainly by activating capsaicin-sensitive nerves. Additionally, MIc suppresses the intestinal glucose absorption, thus producing an antihyperglycemic action, and inhibits pancreatic lipase activity. In a model of acute liver damage, MIc has demonstrated a hepatoprotective effect through activation of the liver antioxidant defense system. Further in vitro studies have confirmed the reported antioxidant action. MIc inhibits intracellular inflammatory pathways mainly by acting as a sentrin-specific protease 1 (SENP1) inhibitor which leads to accumulation of sumoylated proteins in the macrophages and reduced activation of NF-kB signaling. The inhibition of SENP1 is one of the mechanisms of the anticancer activity of MIc that has been demonstrated in recent in vitro and in vivo studies. Furthermore, MIc induces apoptosis of malignant cells through oxidative stress-regulated mitochondrial dysfunction involving pathways like MAPK and P13K.
Conclusion: MIc appears to be a multifunctional bioactive compound with potential applications in various pathological conditions, incl. metabolic disturbances, inflammation, and cancer. However, clinical trials are necessary to clarify its efficacy and safety in humans.
Keywords: momordi Ic, kochia scoparia, inflammation, cancer.

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INTRAVENOUS LIPID EMULSIONS AS A POTENTIAL ANTIDOTE IN OPIOID OVERDOSE

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Abstract
Introduction: In recent decades drug abuse has come increasingly into the focus of public health. To date, fentanyl is one of the most current psychoactive substances, displacing heroin from the illicit drug market. At the same time, a number of clinical cases confirm that the established antidote naloxone is insufficiently effective in acute intoxications with highly lipophilic opioids such as fentanyl.
Objective: To study the potential antidote effect of intravenous lipid emulsions in acute opioid intoxications. Literary sources published in the last 10 years have been selected.
Materials and methods: A thorough review of the literature was performed in scientific databases such as Scopus, Web of Science, PubMed and Google Scholar.
Results: In recent years, intravenous lipid emulsions such as intralipid 20% have been widely used in intoxications with liposoluble drugs. Intralipid 20% is recognized as an antidote for intoxication with local anesthetics and is recommended for acute poisonings with other lipophilic xenobiotics (β-blockers, Ca^{2+}-antagonists, neuroleptics, antidepressants). In addition, in previous studies we have proven the antidote effect of Intralipid 20% in intoxications with verapamil and dimethoate (an organophosphorus pesticide), as well as the absence of serious side effects. Currently, a limited number of studies can be found in the literature that confirm the applicability of intravenous lipid emulsions in acute intoxications with opioid analgesics (tramadol, fentanyl, buprenorphine and others).
Conclusion: Intravenous lipid emulsion therapy as an antidote in acute opioid intoxication shows encouraging results, but further in vivo studies are needed to confirm its efficacy and safety.
Keywords: intravenous lipid emulsion, antidote, intoxication, opioids, fentanyl.

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APPROACHES TO EXPOSURE ASSESSMENT OF COSMETIC PRODUCTS AND COSMETIC INGREDIENTS - SYSTEMATIC REVIEW AND SCOPING REVIEWS

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Abstract
Introduction: Any product directly and/or indirectly related to the health of the general public and which is to be placed on the EU market must be accompanied by clear instructions for use. Directions for normal and reasonable use are defined as cosmetic product claims and are a direct consequence of exposure to cosmetic substances/products. With a view to the foreseeable use of the products, all possible routes of exposure - dermal, oral and inhalation - must be considered. Various parameters (although not exhaustively) have been studied and are available in practice to describe different types of exposure scenarios. The aim of this study is to analyse new approaches for exposure assessment of cosmetic products and cosmetic ingredients. Materials and Methods: We conducted a systematic review and scoping review of scientific and regulatory documents at EU level (directives, guidelines, regulations), regulatory standards of the ECHA and the Scientific Committee on Consumer Safety, etc. Discussion and results: The basic responsibility of the SCCS is to develop and recommend a set of guidelines to be taken into account by the cosmetic industry in developing adequate studies to be used in the safety assessment of cosmetic substances. In order to assess the exposure of end-users, relevant exposure scenarios must be identified which include all relevant functions and uses of a cosmetic ingredient. These scenarios should describe the 'reasonably foreseeable exposure conditions' under which the cosmetic product should be safe. With regard to the foreseeable use of products, all possible routes of exposure - dermal, oral and inhalation - must be considered.
Keywords: cosmetic product, exposure, systemic dose, dermal exposure, inhalation exposure.

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ANALYSIS OF THE RELATIONSHIP BETWEEN ALZHEIMER'S DISEASE AND TYPE 2 DIABETES

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Abstract
Introduction: Diabetes is a chronic disease characterized by high blood sugar levels, which can lead to serious complications, including dementia. Type 2 diabetes (T2D) and Alzheimer's disease (AD) share numerous pathophysiological traits, including insulin resistance, amyloid-β plaque accumulation, and chronic inflammation. The relationship between these two diseases is a subject of research, with some scientists referring to Alzheimer's as "Type 3 diabetes."
Aim: To analyze the potential relationship between diabetes and Alzheimer's disease.
Materials and Methods: A literature review was conducted on PubMed publications based on specific criteria covering the period between March 2017 and December 2023. Results that did not meet the criteria or were duplicated were not included in the analysis.
Results: The search identified 15 publications that met the specified criteria. The results show that newly diagnosed diabetes is associated with an increased risk of developing Alzheimer's disease. Insulin resistance and impaired insulin signaling in the brain contribute to the pathogenesis of AD through metabolic and inflammatory mechanisms.
Conclusion: Understanding these interactions is crucial for developing interventions that can reduce the risk or slow the progression of AD in patients with diabetes and provide new treatment opportunities.
Keywords: Type 2 diabetes, Alzheimer's disease, dementia, insulin resistance.

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TREATMENT OF ACUTE COUGH IN CHILDREN: RECOMMENDATIONS AND REALITY

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Abstract
The best approaches to treating acute cough in children remain unclear, despite knowledge of the cough reflex, the availability of many classes of drugs, and the long history of their use. Studies in the pediatric population are few; there are no clear indications for the dosage and duration of treatment, and a large number of OTC products with numerous active components are used. There is no good evidence for the effectiveness of medicines for acute cough. All this contributes to inappropriate therapy, delay in the diagnostic process, overdose, and adverse events. In 2008, FDA restricted the approval of OTC medicines for the treatment of cough in children under 2 years of age. Manufacturers voluntarily announced their use for children over 4 years. American Academy of Pediatrics recommended avoiding them in children under 6. European Academy of Pediatrics does not support their prescribing and use in young children (December 2023).
Methods. A literature review and review of 20 summaries of product characteristics of approved OTC medicinal products for the treatment of cough was performed.
Results. The number of products indicated for children over 6 years of age is limited. More drugs are recommended for children over 2 years of age. Drug products containing the same active ingredients are recommended for children of different ages.
Conclusion. Clinical trials are needed to elucidate the efficacy and safety of current therapies for acute cough, to better characterize subpopulations of children with cough, and to make corrections in recommendations for use. The responsibility of the pharmacist is great when dispensing OTC products for the treatment of acute cough in children
Keywords: acute cough, children, recommendations, summariy of product characteristics.

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PARACETAMOL POISONING – ANTIDOTE TREATMENT

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Abstract
Paracetamol (acetaminophen) is included in more than 200 medicines of various trade names, including numerous preparations for children used as analgesic and antipyretic drugs.
Poisoning usually occurs after taking a large single dose of paracetamol or combination paracetamol-containing preparations, and as a result of prolonged use of paracetamol in smaller doses by persons with increased sensitivity, alcohol abuse, diet error, or in combination with drugs, which affect its metabolism in the liver. Paracetamol poisoning is among the intoxications that have a latent period. Clinical manifestations of acute poisoning develop in stages. The intensity of the initial symptoms does not always determine the outcome of the disease. Paracetamol poisoning is a common cause of liver damage and is a leading etiologic factor in acute liver failure. The worldwide spread of poisoning with this drug is epidemic.
Keywords: paracetamol poisoning, liver damage, liver failure**.**

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A POSSIBLE ROLE OF BRAIN SEROTONIN AND MELATONIN IN THE DEPRESSIVE BEHAVIOR OF HYPOTHYROID RATS

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Abstract
Disturbances in thyroid function can significantly affect mental status and lead to a variety of neuropsychiatric manifestations, including affecting emotions and cognition.
The present study aimed to measure serotonin and melatonin levels in the brain of hypothyroid rats [untreated and treated with 50mg/ kg 5-hyrdoxy-tryptophan (5-OH-TRP) i.p. or stereotaxically injected in the hippocampus] and to compare them with levels of control animals.
Experimental hypothyroidism was induced by 0.01% Propylthiouracil solution placed in the drinking water of 4 groups of 6 male Wistar albino rats (2 groups of sexually immature and 2 groups of sexually mature rats) for 5 weeks. After reaching a hypothyroid state as confirmed by serum free T4 levels, one of the groups of young and mature hypothyroid animals was treated with 5-OH-TRP in 1% PBS and their respective controls with 1% PBS alone for a period of 10 days .
Proteins in the supernatant of the homogenized brain tissue were measured spectrophotometrically and after their standardization, the serotonin and melatonin levels of the experimental and control animals were determined by ELISA. Brain levels of serotonin and melatonin were measured to be significantly reduced in both hypothyroid age groups rats versus euthyroid controls. Administration of 5-OH-TRP significantly led to an increase in serum levels of serotonin and melatonin, which corresponds to the established reduction of depressive behavior and cognitive disorders in the state of hypothyroidism.
These data allow us to assume the key involvement of serotonergic and melatoninergic mediation in cognitive-behavioral changes in hypothyroidism, and their modulation is essential in the therapy of hypothyroidism -associated depression.
Keywords: serotonin, melatonin, depression, hypothyroidism.

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SAFETY, EFFICACY AND ECONOMIC ASPECTS OF RISDIPLAM AS A SWITCH THERAPY IN SPINAL MUSCULAR ATROPHY TREATMENT

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Abstract
Introduction: Spinal muscular atrophy (SMA) is a neuromuscular disease. It is currently treated by three EMA approved therapies - nursinersen, onasemnogene abeparvovec and risdiplam. Nursinersen and onasemnogene abeparvovec display certain limitations – the first drug being delivered intrathecally, and the second one being restricted by certain criteria. Risdiplam is a survival of motor neuron-2 (SMN2) mRNA splicing modifier that is administered orally.
Objectives: The aim of the present study was to review the data on efficacy, safety, and economic advantages of treating non-naive SMA patients with risdiplam.
Materials and methods: A total of 205 publications were screened through Medline (via PubMed) using the key word “risdiplam“. Nine studies considering treatment of non-naive patients with risdiplam, adverse effects, results after set period, reason for the switch, as well as budget impact were included in the current review.
Results: The research showed there were no additional adverse effects of risdiplam in non-naïve SMA patients compared to naïve patients. Moreover, patients showed motor skills improvement non-inferior to nursinersen over the 12- and 24-month period. Most patients switched to risdiplam due to lack of lumbar access. The oral administration decreased the burden on the caregivers and reduced both hospital stay and travelling costs.
Conclusion: The favorable pharmacokinetic and pharmacodynamic characteristics of risdiplam, as well as its high tolerability and effectiveness, make the drug a good choice for patients unable to receive the other treatments. Moreover, it reduces travelling, hospital stay and the workload of the caregiver.
Keywords: risdiplam, switch therapy, SMA**.**

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NEUROPHARMACOLOGICAL EFFECTS OF LIRAGLUTIDE ON THE STREPTOZOTOCIN MODEL OF DIABETIC NEUROPATHY IN MICE REARED IN AN ENRICHED ENVIRONMENT

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Abstract
Aim. Liraglutide is an incretin mimetic, anti-diabetic, and anti-obesity drug with a proven beneficial effect in some of the complications of diabetes. An enriched living environment is having a protective impact on neuropathological processes. This study aimed to evaluate the neuropharmacological effects of liraglutide on the streptozotocin model of diabetic neuropathy in mice reared in an enriched environment.
Material and methods. The diabetic neuropathy model was established by a single injection of streptozotocin 200 mg/kg i.p. of male ICR mice. The Von Frey test demonstrates the development of neuropathy. Twenty-four mice were administered liraglutide 0.4 mg/kg i.p. once a day for ten days. Of them, 12 mice were raised under standard conditions (DLS-group) and 12 - under enriched environment (DLE-group). The enriched environment was created by placing spinning wheels, tunnels, and igloos in the cages. The evaluation was done using Irwin's test, comparing the DLS and DLE groups with untreated controls without or with diabetes (groups C and D, n=12 each).
Results. Neuropharmacological disorders were demonstrated in the advanced diabetes and neuropathy groups compared to the C-group, and the indicators of spontaneous activity, passivity, grooming, curiosity, heightened reflexes, physical strength, and palpebral opening, the indicators for the three diabetes groups were ranked as follows way: D < DLS < DLE.
Conclusion. Treatment of mice with liraglutide resulted in the improvement of some neurophysiological disorders induced by diabetes. Enriched environment rearing exerts a beneficial synergistic effect with liraglutide in the diabetic neuropathy model.
Acknowledgment: Supported by BNSF, КП-06-Н63/9 of 13.12.2022. and from MU-Sofia No. D -329/19.12.2022
Keywords: Liraglutide, enriched environment, diabetic neuropathy.

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COMPARATIVE STUDY OF THE EFFECT OF U-74389G AND PREDNISOLONE IN AMIODARONE-INDUCED PULMONARY TOXICITY

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Abstract
Previous *in vitro* and *in vivo* studies have proven the remarkable antioxidative and membrane-stabilizing potency of U-74389G, which is a substituted corticosteroid nucleus derivative. The effect of 21-aminosteroid U-74389G and prednisolone (PR) on amiodarone-induced pneumotoxicity in rats was studied.
Methods The study was carried out on 72 male Wistar rats, divided into four groups: (1) – control; (2) – treated intratracheally (i.t.) with amiodarone (AM); (3) – with AM and U74389G; (4) – with AM and PR. AM was installed i.t. on days 0 and 2 (6.25 mg/kg; 3.125 mg/ml water solution). U-74389G was injected intraperitoneally at a daily dose of 15 mg/kg, PR at 10 mg/kg, from day 0 to day 2. The activity of lactate dehydrogenase (LDH), acid phosphatase (AcPh), alkaline phosphatase (AlPh), total protein content and cytological assays of bronchoalveolar lavage fluid were performed on days 3, 7 and 28. Pulmonary fibrosis was assessed by measuring hydroxyproline (HP) content in lung homogenate (LH) on day 28.
Results. AM treatment led to significant increases in various markers of pulmonary inflammation and damage. However, the treatment with U-74389G and PR effectively attenuated these markers, demonstrating their potential as protective agents. Isolated application of AM significantly increased the HP content on day 28 to 235%. U-74389G and PR significantly decreased this marker (6.82 mcg/ml LH and 7.2 mcg/ml LH, respectively) on day 28, further highlighting their potential.
Conclusion. The results obtained showed that U-74389G reduced early AM-induced lung inflammatory injury and fibrosis and this protective effect is comparable to that of prednisolone.
Keywords: 21-aminosteroid U-74389G, amiodarone-induced pneumotoxicity, hydroxyprolin, prednisolone

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INVESTIGATION OF ANTIOXIDANT AND ANTIPROLIFERATIVE ACTIVITY OF MANGANESE (III) TETRAKIS (4-BENZOIC ACID) PORPHYRIN IN LUNG HOMOGENATE IN AMIODARONE-INDUCED RAT TOXICITY

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Abstract
Introduction. The cell-permeable SOD mimetic, manganese (III) tetrakis (4-benzoic acid) porphyrin (MnTBAP), possesses superoxide dismutase and catalase activity and has been shown to reduce oxidative damage by suppressing both ROS and reactive nitrogen species.
Our goal was to study the effect of MnTBAP on some markers for antioxidant defence system and fibrosis in rat lung homogenate (LH) after amiodarone (AM) treatment.
Materials and Methods. The study was carried out on 72 male Wistar rats, divided into four groups: (1) – controls; (2) – treated intratracheally (i.t.) with AM; (3) – treated with AM and MnTBAP; (4) – treated with MnTBAP. AM was administrated i.t. on days 0 and 2 (6.25 mg/kg). MnTBAP was injected intraperitoneally at a dose of 10 mg/kg from day 0 to day 4. The activity of superoxide dismutase (SOD), catalase (CAT), glutathione peroxidase (GP), and malondialdehyde (MDA) content were measured in LH on days 3 and 5. Pulmonary fibrosis was assessed by measuring hydroxyproline (HP) content in LH on day 28 after AM administration.
Results. The activities of SOD and CAT in group 2 decreased significantly as compared to the control group. The decrease of the same enzymes in group 3 was lower and significant as compared to group 2. Changes in GP activity showed similar dynamics. The content of HP in AM+MnTBAP group (2.25±0.16 mcg/ml LH) was decreased compared to AM alone (3.34±0.15 mcg/ml LH) on day 28 (p<0.05).
Conclusion. MnTBAP reduced the AM-induced generation of reactive oxygen species and protected from AM-induced pulmonary fibrosis.
Keywords: amiodarone, antioxidant defence, lung homogenate, manganese (III) tetrakis (4-benzoic acid) porphyrin, pulmonary fibrosis.

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T_{MAX} AS A PRIMARY ENDPOINT IN BIOEQUIVALENCE TRIALC IN PRODUCT-SPECIFIC GUIDELINES PUBLISHED BY THE EMA: THE EXAMPLE OF TADALAFIL

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Abstract
Similar to the FDA, the EMA has also adopted the practice of publishing product-specific guidelines for bioequivalence trials needed for the registration of generic products. In some of these guidelines (e.g. ibuprofen, tadalafil) the time needed to achieve maximum concentration (T_{max}) is also mentioned as a primary endpoint with the following wording: "Comparable median (≤ 20% difference, 80.00–125.00%) and range for T_{max}.". The suggested wording is problematic both from the statistical and from the pharmacodynamic perspective. From the statistical perspective using the median instead of the arithmetic mean might introduce a bias especially in trials with a relatively small sample size and in addition to that it is not clear why an interval of 80-125% is proposed although no logarithmic transformation is expected for the parameter T_{max}. From the pharmacodynamic perspective the assumption that the effect of any product is closely related to Tmax is highly problematic. An example is provided based on the results of two bioequivalence studies with tadalafil. The provided example challenges the current thinking at the EMA.
Keywords: T_{max}, bioequivalence, tadalafil.

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MOLECULAR APPROACHES FOR STUDYING BIOLOGICAL ACTIVITY IN VITRO

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Abstract
Natural products from plants, animals, microorganisms and newly synthesized small peptides are the common base of novel therapeutic compounds. They are mainly secondary metabolites (alkaloids, terpenoids, polyphenols etc.), which play a crucial role in various developmental and defense processes. To use these molecules for different applications, it is essential to know their structure, concentrations, and biological activity potential. Therefore, it is necessary to select suitable bioassays to evaluate both the cytotoxicity and activity against the disease. For this purpose, target-based screening is mainly used to identify desired compounds. This screening involves different in vitro biological assays designed to measure cellular toxicity like MTT and BALB/c 3T3 NRU test. The combination of this methods with others like FACS analysis, Real Time PCR and Western blotting has allowed us to accelerate the discovery of new bioactive compounds, their effective doses and mechanism of action. This may contribute to the development of various new more efficient medical therapeutics with fewer side effects.
Keywords: peptides, biological assays, therapeutics.

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MODERN APPROACHES IN THE TREATMENT OF HEART FAILURE

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Abstract
Heart failure (HF) is a leading cause of morbidity and mortality worldwide. The 2022 Heart Failure Guidelines provide current evidence-based recommendations for the management of these patients. In order to motivate new approaches in the treatment of HF, the emphasis is on the current understanding and classification of HF. Attention is paid to the complex of diagnostic methods and non-pharmacological approaches in the control of HF. New concepts for the treatment of heart failure (HF) with reduced ejection fraction (HFrEF) have been introduced, with 4 drug classes now included, which include sodium-glucose cotransporter-2 inhibitors (SGLT2i), ARNIs (neprilysin inhibitors), and ARBs (angiotensin receptor blocker)/ACEI inhibitors, β-blockers, MRAs (mineral receptor antagonists). New proposals for the treatment of HF with moderately depressed ejection fraction (HFmEF) and new approaches in the treatment of HF with preserved fraction are presented ejection (HFpEF).
Keywords: heart failure, ARNIs, SGLT2i, MRAs, β-blockers, HfrEF, HfpEF, HfmEF.

SUSTAINABILITY OF MEDICINE USE

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Abstract
The sustainability of medicines use encompasses the efficient and ethical management of pharmaceutical resources to ensure long-term public health benefits while minimizing environmental impact. A comprehensive literature review was conducted, utilizing databases such as PubMed, Scopus, and Web of Science. The review focused on peer-reviewed articles published in the last decade discussing various aspects of pharmaceutical sustainability, including environmental impacts, economic considerations, and public health outcomes. Several critical issues affecting the sustainability of pharmaceutical use were identified:
-Environmental Impact: Pharmaceuticals and their metabolites often enter water systems, leading to ecological disruptions and potential human health risks.
-Economic Considerations: The high cost of sustainable pharmaceutical practices poses a challenge for healthcare systems, particularly in low-income countries.
-Public Health Outcomes: Ensuring access to essential medicines while managing waste and reducing environmental contamination is a complex balance that requires integrated strategies.
Several strategies have been proposed to address these challenges: Improved waste management systems to reduce pharmaceutical contamination in the environment; development of greener pharmaceuticals with lower environmental impact, promotion of the rational medicines use preventing over-prescription and misuse, regulations to support sustainable pharmaceutical practices.
The sustainability of medicines use is a multifaceted issue requiring coordinated efforts across environmental, economic, and health domains.
Keywords: sustainability, rational medicine use.

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DOSE ADJUSTMENT ACCORDING TO RENAL FUNCTION (EGFR/CRCL) IN HOSPITALIZED PATIENTS WITH HEART FAILURE

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Abstract
The present study is designed as a retrospective cohort study based on electronic extraction of data from electronic health records containing information on the treatment of hospitalised patients from hospitals in Bulgaria for the period 2019-2023. The aim is to identify irrational prescribing (IP), defined as incorrect dose/frequency or contraindicated medication according to the patient's renal function. It will also identify potentially nephrotoxic drugs and drugs with high sodium content.
Digitised records from 67 hospitals from all administrative regions in Bulgaria, generated by automated electronic medical record review software, were analysed. Data on pharmacotherapeutic treatment of patients admitted for inpatient treatment between June 2019 and December 2023 were collected. All patients diagnosed with heart failure (ICD I50.0, I50.1, I50.9) and eGFR = or & lt; 50 ml/min/1.73 m2 were identified from the reviewed electronic medical records.
Patients diagnosed with chronic heart failure and abnormal renal function (as assessed by eGFR values) were characterised by a significant incidence of polypharmacy. In this vulnerable group of patients, higher rates of inappropriate drug dosing according to creatinine clearance and/or irrational prescribing are observed, given the risk of drug-drug interactions. The following nephrotoxic medicines have been identified: aminoglycosides, amphotericin B, cisplatin, contrast dye, and cyclosporine.
Keywords: dose adjustment, rational drug use, heart failure.

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IMMUNOTHERAPY IN TRIPLE-NEGATIVE BREAST CANCER – THE NEW THERAPEUTIC APPROACH

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Abstract
Triple-negative breast cancer (TNBC) is challenging from a therapeutic point of view, due to the lack of expression of hormone receptors (endocrine therapy cannot be applied (ER-, PR-)) as well as the lack of expression of HER2 receptors (impossibility to be applied targeted therapy (HER2-)). For a long time, the only option for systemic treatment of this histological variant was conventional chemotherapy. In the last decade, immuno-oncology has experienced a significant development, as evidenced by the increasing number of indications for antitumor immunotherapy and its addition to numerous therapeutic protocols. Immunotherapy is a relatively new indication in the context of the treatment of TNBC. Treatment with immune checkpoint inhibitors in this setting shows good potential, supported by several phase III clinical trials. This report will show the experience of the Department of medical oncology at ACC UMBAL Tokuda - presentation of clinical practice results and specifics related to this type of treatment for triple-negative breast cancer.
Keywords: immunotherapy, triple-negative breast cancer, immuno-oncology.

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COMPARATIVE ANALYSIS BETWEEN PHARMACOVIGILANCE AND COSMETOVIGILANCE

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Abstract
Prior to being placed on the market, products related to population health should first and foremost be safe for human health. Despite the existence of explicit regulatory prerequisites, adverse effects may occur with the use of medicinal products, cosmetic products, food supplements, biocides, etc. Adverse effect reporting, analysis and corrective action should follow standardised formats and internationally accepted standards.
Aim: To comparatively evaluate the different methods of post-authorisation monitoring of the safety of medicinal products (pharmacovigilance) and the safety of cosmetic products (cosmetovigilance).
Materials and methods: We conducted a content analysis, comparative analysis and documentary analysis of European legislation on medicinal products and cosmetic products (directives and regulations).
Results and discussion: Pharmacovigilance and cosmetovigilance require methodological approaches to collect, document, establish causality, and manage adverse effects caused after the use of medicinal and cosmetic products, respectively. We found similarities in the two procedures regarding the requirements under which reported adverse effect information is recorded as a valid individual safety report – there should be an identifiable patient/consumer, an identifiable reporter, a description of the clinical manifestation and the specific medicinal/cosmetic product that led to the adverse effect. However, there is a difference in the regulatory timeframe for reporting the adverse effect – the adverse drug reaction report must be circulated to EU Member States within 15 days, whereas for cosmetic products it is up to 20 days. The similarities between pharmacovigilance and cosmetovigilance facilitate the adverse reaction reporting processes but also ensure that public health and safety are improved.
Keywords: medicinal product, cosmetic product, pharmacovigilance, cosmetovigilance, adverse effect.

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PCR ANALYSIS OF PHARMACOGENETIC POLYMORPHISMS IN PATIENTS WITH NON-OBSTRUCTIVE AZOOSPERMIA

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Abstract
Aim: The aim of our study was to determine a correlation between certain pharmacogenetic polymorphisms and non-obstructive azoospermia in men from the Bulgarian population. Materials and methods: We performed a real-time PCR to determine the following genetic polymorphisms: G681A in CYP2C19 (n = 20), C3435T in MDR1 (n = 21), C677T, and A1298C in MTHFR (n = 71) in men with non-obstructive azoospermia. The allele and genotype frequencies in our patients were compared to those in the Bulgarian/European populations. Results: The results revealed a trend for a significantly higher frequency of homozygotes for the C3435T polymorphism (T/T genotype) in MDR1 (42.8% in the examined patients and 27% in the European population, $p<0.10$) and for the A1298C (C/C genotype) polymorphism in MTHFR (17% in our patients and 8% in the Bulgarian control group, $p<0.08$). No statistically significant differences were established in the frequencies of MTHFR C677T and CYP2C19 G681A polymorphisms in our patients compared to the control populations. Conclusion: The MDR1 gene encodes for the efflux transporter P-glycoprotein, localized in various tissues and organs, including the endothelial cells of the blood-testicular barrier. P-glycoprotein is involved in the detoxification of the organism from toxins and other xenobiotic substances and prevents their accumulation in the male gonads. Methylenetetrahydrofolate reductase is a crucial enzyme for the folate and homocysteine metabolisms. Alterations in its activity lead to disturbances in the proper course of spermatogenesis. The relationship between the MDR1 and MTHFR polymorphisms and the development of non-obstructive azoospermia is worth further, more detailed investigation.
Keywords: pharmacogenetic polymorphisms, azoospermia, MTHFR, MDR1.

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AGONISTIC AUTOANTIBODIES IN CARDIOVASCULAR PATHOLOGY

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Abstract
Antibody formation is a physiological process of high protective value. Autoantibodies are primarily believed to be initiators of a destructive process in autoimmune diseases. Recently, interest in the so-called agonistic autoantibodies (AABs) has been continuously increasing. They target biologically and pharmacologically important receptor structures, mainly G-protein coupled receptors (GPCR). AABs interact with receptors similarly to their endogenous ligands, but with higher affinity and long-lasting receptor activation, which can lead to overstimulation and modification of resulting intracellular signaling.
Our aim is to present the role of AABs in cardiovascular and related diseases through a literature review.
The most studied GPCR-AABs are those directed against adrenergic (α1,β1,β2), muscarinic (M2,M3), angiotensin (AT1), endothelin (ET1A) receptors. These AABs have been associated with dilated cardiomyopathy, pulmonary and essential hypertension, heart failure, preeclampsia, arrhytmias, and others. In patients with heart failure and high serum β1-AAB levels, beta-blocker therapy is often ineffective. AT1R-AABs and ET1AR-AABs are associated with left ventricular remodeling in patients with ST-segment elevation myocardial infarction. In the general population higher serum AT1-AA levels strongly correlate with a higher blood pressure and worse functional measures. In such cases, AT1-blocker application has proved beneficial.
Validation of AABs could be used to stratify patient risk and refine the therapy with AT1-blockers and beta-blockers. Although immunoadsorption is of therapeutic benefits, it is relatively expensive and logistically difficult. Neutralization with peptides and aptamers still remains in the human trials. The creation of molecules targeting receptor signaling pathways stands as a future possibility
Keywords: agonistic autoantibodies, autoimmunity, cardiovascular diseases.

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MELATONIN TREATMENT OF PREGNANT RATS EXPOSED TO CONSTANT LIGHT THROUGHOUT PREGNANCY IMPROVES WORKING MEMORY AND CORRECTS ANXIETY-LIKE BEHAVIOR IN MALE AND FEMALE RAT OFFSPRING

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Abstract
In recent years, interest in research related to prenatal development and its relationship to the mental and emotional development of the generation has increased tremendously. Melatonin is an endogenous hormone synthesized and secreted by the pineal gland during the dark part of the day. Surgical removal of the pineal gland or exposure to conditions of prolonged illumination suppresses the synthesis of melatonin, which in turn leads to a number of psychosomatic disorders. During embryonic development, the fetus does not synthesize melatonin, but receives the necessary amount of the hormone in an unchanged form from the mother's organism. The aim of the present study was to investigate the emotional state and cognitive processes in the offspring of male and female rats of pregnant mothers exposed to 24 hours of light during pregnancy and treated with melatonin at a dose of 10mg/kg. Melatonin was injected subcutaneously from G0-G21. The state of anxiety was assessed by the light/dark test (LDT) and the cognitive processes by the Y-maze test in both sexes of mature offspring (60 days old) from mothers who spent the entire pregnancy on 24 hours of illumination. The anxiety status of was observed in both genders of offspring of mothers exposed to constant lighting (LL) during pregnancy compared to the control group ($p < 0.005$). Melatonin treatment corrected anxiety in the male offspring with prenatal LL exposure ($p < 0.005$ compared to LD controls). Disorders in working memory were reported in the male and female offspring of mothers who spent the entire pregnancy under conditions in 24-h light compared to the control group ($p < 0.005$). The supplementation of melatonin at a dose of 10 mg/kg improves working memory in both sexes of offspring with prenatal LL regime ($p < 0.005$ compared to LD controls). In conclusion, melatonin supplementation to pregnant mothers exposed to constant light during pregnancy improves emotional status and working memory in male and female offspring with prenatal LL exposure.
Keywords: memory, melatonin, anxiety-like behavior, rats.

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EFFECT OF GR 159897 ON COLONIC MOTILITY IN RATS AFTER ACUTE WATER AVOIDANCE STRESS

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Abstract
Introduction. GR 159897 is a potent, selective antagonist of neurokinin NK2 receptor. It inhibits NK2-mediated contraction of experimental animals' tracheal and intestinal smooth muscle and has anxiolytic properties.
The purpose of this study was to evaluate the effect of GR 159897 on changes in gastrointestinal motility in rats after water avoidance stress (WAS).
Material and methods. Wistar rats received WAS for 1 h and the fecal pellet output was counted; colorectal transit, plasma CTRH, ACTH, cortisol, and pro- and anti-inflammatory cytokines by ELISA were measured. Spontaneous and electrically stimulated motor activity of circular (CM) and longitudinal (LM) colonic muscle was investigated.
Results. Acute WAS accelerated transit time and increased the level of stress hormones. Amplitudes and frequency of spontaneous asynchronous contractions of CM and LM after WAS were higher than controls, while GR 159897 intraperitoneal injection (0.5 mg/kg) significantly suppressed them. Electrical field stimulation (EFS; 0.8 ms, 40 V, 10 Hz, 20 s) elicited contractions of CM were most pronounced in control animals (9.6±0.8 mN), followed by those subjected to WAS (8.41±0.55; p<0.05) and lowest after GR 159897 pretreatment (5.26±0.28). NG-nitro-L-arginine enhanced the contraction of CM from controls by 47.08%, from the WAS rats by 17.59% and by 3.04% after GR 159897 administration, which shows the reduced sensitivity to NO inhibitory transmission. The addition of atropine reduced contractions of CM by 31.30% in controls, by 41.86% after WAS, and by 23.74% after GR 159897 injection.
Conclusion. GR 159897 affected stress hormones and altered spontaneous motor activity after acute WAS. Pretreatment with GR 159897 showed more significant effect on nitric oxide than cholinergic transmission.
Keywords: atropine, neurokinin NK2 receptor, NG-nitro-L-arginine, rat colon, water avoidance stress.

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REVIEW: ANTIOXIDANT, ANTI-INFLAMMATORY, AND ANTI-CANCER PROPERTIES OF SILYMARIN AND SILIBININ IN LUNG DAMAGE

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Abstract
Introduction: Silymarin and its main active ingredient, silibinin, derived from milk thistle (Silybum marianum), have gained scientific interest for their diverse pharmacological properties. This review examines their antioxidant, anti-inflammatory, and anti-cancer effects on lung damage.
Purpose The aim is to evaluate the efficacy of silymarin and silibinin in protecting against lung damage and their potential therapeutic applications.
Materials and Methods: A review of recent studies was conducted, focusing on the antioxidant, anti-inflammatory, and anti-cancer effects of silymarin and silibinin. Studies included those on oxidative lung damage from heavy metals, inflammation from respiratory viral infections, and inhibition of non-small cell lung cancer (NSCLC) cell proliferation.
Results: Silymarin and silibinin are known for their potent antioxidant activities, protecting cells and tissues from oxidative stress. Silymarin shows protective effects against oxidative lung damage and counters oxidative stress in various disease models, indicating broad-spectrum antioxidant actions.
Additionally, their anti-inflammatory properties suggest therapeutic potential in managing inflammatory lung conditions, including those from respiratory infections. Studies show silymarin reduces inflammation, underscoring its utility in these conditions.
Promising anti-cancer effects have also been observed, with silibinin inhibiting NSCLC cell proliferation by modulating cell cycle regulators and signaling pathways like MAPK.
Conclusion: Silymarin and silibinin's antioxidant, anti-inflammatory, and anti-cancer properties make them promising candidates for treating diseases linked to oxidative stress, inflammation, and cancer. The development of water-soluble forms may enhance their clinical applications. Future research should explore their mechanisms, optimal doses, and synergies with existing therapies.
Acknowledgements
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Keywords: silymarin, silibinin, lung, antioxidants, free radicals.

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EFFECTS OF GLP-1 RECEPTOR AGONIST SEMAGLUTIDE ON GUT MICROFLORA IN RATS WITH EXPERIMENTAL MODEL OF OBESITY

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Abstract
Introduction. Obesity if a chronic metabolic disorder characterized by excessive accumulation of subcutaneous and visceral adipose tissue. Latest research shows connection between changes in structure and function of gut bacterial microflora and pathogenesis of the disease. In the previous decade there was great success in pharmacological therapy of type 2 diabetes and obesity with introduction of GLP-1 receptor agonists.
The aim of the current research is to establish effects of GLP-1 receptor agonist Semaglutide on microflora in rats with experimental model of obesity.
Materials and methods: Stage 1 (duration 20 weeks) Implementation of experimental model of obesity in mature male Wistar rats (n=20) – experimental animals received free access to standardized laboratory chow food with high fat content 22% and tap water with high D-fructose content 25% for induction of obesity. Stage 2 (duration 8 weeks) After induction of obesity, experimental animals were divided using the following principle: first group (n=10), treated with Semaglutide and second (n=10) control group, treated with saline solution. During the entire duration of the experiment, we regularly (once weekly) collected biometric data from experimental animals. Results: The data demonstrates successful induction of experimental model of obesity in male Wistar rats. The group treated with Semaglutide shows statistically significant changes in gut bacterial microflora with prevalence of bacteria associated with lean body weight. Conclusion and discussion: The ability of GLP-1 agonists to modulate the gut microbiome can be considered as one of the complex pharmacological mechanisms by which this group of medications influences obesity.
Keywords: Obesity, Semaglutide, Gut microflora.

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PHARMACO-TOXICOLOGICAL ASSESSMENT OF NOVEL SULFONYL HYDRAZONE DERIVATIVES WITH ANTIMYCOBACTERIAL ACTIVITY AND ESTABLISHMENT OF INHA INHIBITING ACTIVITY

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Abstract
Introduction. Tuberculosis continuous to be a serious problem for the health environment, nevertheless the advance in drug discovery in the last two decades. Due to the constantly growing resistance towards currently available antimycobacterials, the development of new chemotherapeutics to combat the infectious agents is still needed.
Aim. The current study presents the toxicological and pharmacological evaluation of novel sulfonyl hydrazone derivatives 3a and 3b with previously proven antimycobacterial activity against Mycobacterium tuberculosis H37Rv strain through in vivo and in vitro methods.
Materials and methods. The acute toxicity of the derivatives has been assessed through p.o. and i.p. admistration on experimental mice in 5 fixed doses to determine LD50. The subacute toxicity has been studied through repeated (14 days) i.p. administration of the compounds. Biomarkers of oxidative stress have been assessed through specific ex vivo methodologies, histological examination has been conducted post-mortem and spectrophotometric study on inhibiting recombinant InhA enzyme.
Results. Derivatives 3a and 3b exhibit good antimycobacterial activity and have a safer profile compared to isoniazid. The tested compounds were classified as slightly toxic, have good tolerability from the experimental animals, do not lead to significant deviations in hematological parameters, and show only isolated pathomorphological deviations in studied organs. The compounds exhibited slight antioxidant capabilities and moderate InhA inhibition capacity, expressed as 57.8% and 53.1% inhibition of the recombinant InhA enzyme.
Conclusions. Sulfonyl hydrazones 3a and 3b exhibit low toxicity and pronounced pharmacological activity and can be considered as promising molecules for further more detailed studies.
Acknowledgement: We acknowledge the financial support from the Council of Medical Science, Medical University Sofia (Contract No. D-109/2024) for the conduction of the current study.
Keywords: Mycobacterium tuberculosis, sulfonyl hydrazones, InhA.

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SILICON DIOXIDE AS A NEXT-GENERATION ENTEROSORBENT AND SOURCE OF BIOAVAILABLE SILICON

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Abstract
Introduction: Silicon dioxide (SiO_2), when taken orally in the form of submicron agglomerates of amorphous non-porous nanoparticles, acts primarily as an enterosorbent and also as a source of bioavailable silicon.
Objectives: To analyze the mechanisms of SiO_2 enterosorption and its conversion into a bioavailable form of silicon, to establish the safety of SiO_2, and to evaluate its effectiveness as an enterosorbent compared to other enterosorbents based on its sorption surface area and sorption properties.
Materials and Methods: Literature review of publications in scientific databases such as PubMed, ResearchGate, and Google Scholar.
Results: Approximately 10-20% of ingested SiO_2 is hydrolyzed into absorbable silicic acids, which serve as a source of silicon, playing a crucial role in various biological processes. The remaining 80-90% passes unchanged through the gastrointestinal tract without being absorbed (demonstrating the safety of SiO_2), while simultaneously adsorbing substances on the surface of its particles at their active centers (silanol groups) due to the lack of pores. SiO_2 has the largest sorption area (over 400 m^2/g) compared to other enterosorbents (activated carbon: 1.5-2 m^2/g). This allows for a lower daily dose (2-4 g) compared to 20-30 g for activated carbon. SiO_2 is selective only for proteins, meaning it effectively adsorbs microorganisms, microbial toxins, allergens, and other proteinaceous substances. Unlike other enterosorbents, SiO_2 does not adsorb beneficial substances such as mono-, di-, and polysaccharides, lipids, minerals, vitamins, and most amino acids.
Conclusion: SiO_2 is a safe and effective enterosorbent and an easily absorbable source of silicon.
Keywords: amorphous silicon dioxide, fumed silica, enterosorbent**.**

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GENETIC VARIATIONS IN CYP2R1 AND CYP27B1 GENES INVOLVED IN 25(OH) VITAMIN D METABOLISM IN PATIENTS WITH PSORIASIS VULGARIS

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Abstract

Introduction: Psoriasis vulgaris (PV) is an immune-mediated skin disease accompanied by different systemic disorders in most patients. Both PV and its comorbidities are associated with low serum vitamin D. Aim: Our study was focused on the influence of single nucleotide polymorphisms (SNPs) of CYP2R1 and CYP27B1 genes on serum 25(OH)D levels in psoriatic patients. Methods: A prospective study covering the autumn/winter period of 2019 and 2020 was conducted. The study sample included 62 patients and 62 controls. The total serum 25(OH)D concentration was measured using electrochemiluminescence assay (ECLIA). PCR-RLFP assay was performed for genotyping of CYP2R1 G/A (rs10741657) and CYP27B1-1260 C/A (rs10877012) SNPs. Results: Serum 25(OH)D had a median value of 15.85 ng/ml (IQR 9.98-21.90) for patients and 18.80 ng/ml (IQR 12.78-25.95) for controls (p=0.03). No significant differences were observed in the genotype distribution and allelic frequencies of CYP2R1 and CYP27B1 polymorphisms between groups. There is no correlation between CYP2R1 and CYP27B1 genotype and serum 25(OH)D concentration in patients and controls. Co-dominant, dominant, recessive, over-dominant and allele models were also used to assess the association between the genotype and vitamin D status. Comparing participants with severe vitamin D deficiency to all other participants only the over-dominant model AG/GG+AA of CYP2R1, showed a significant association between AG genotype and vitamin D status (OR3.19; 95% CI 1.19-8.45, p=0.02). Conclusion: According to the over-dominant model, carriers of the heterozygous AG genotype of CYP2R1 had a 3 time greater chance of severe vitamin D deficiency.

Keywords: vitamin D, psoriasis vulgaris, CYP2R1, CYP27B1.

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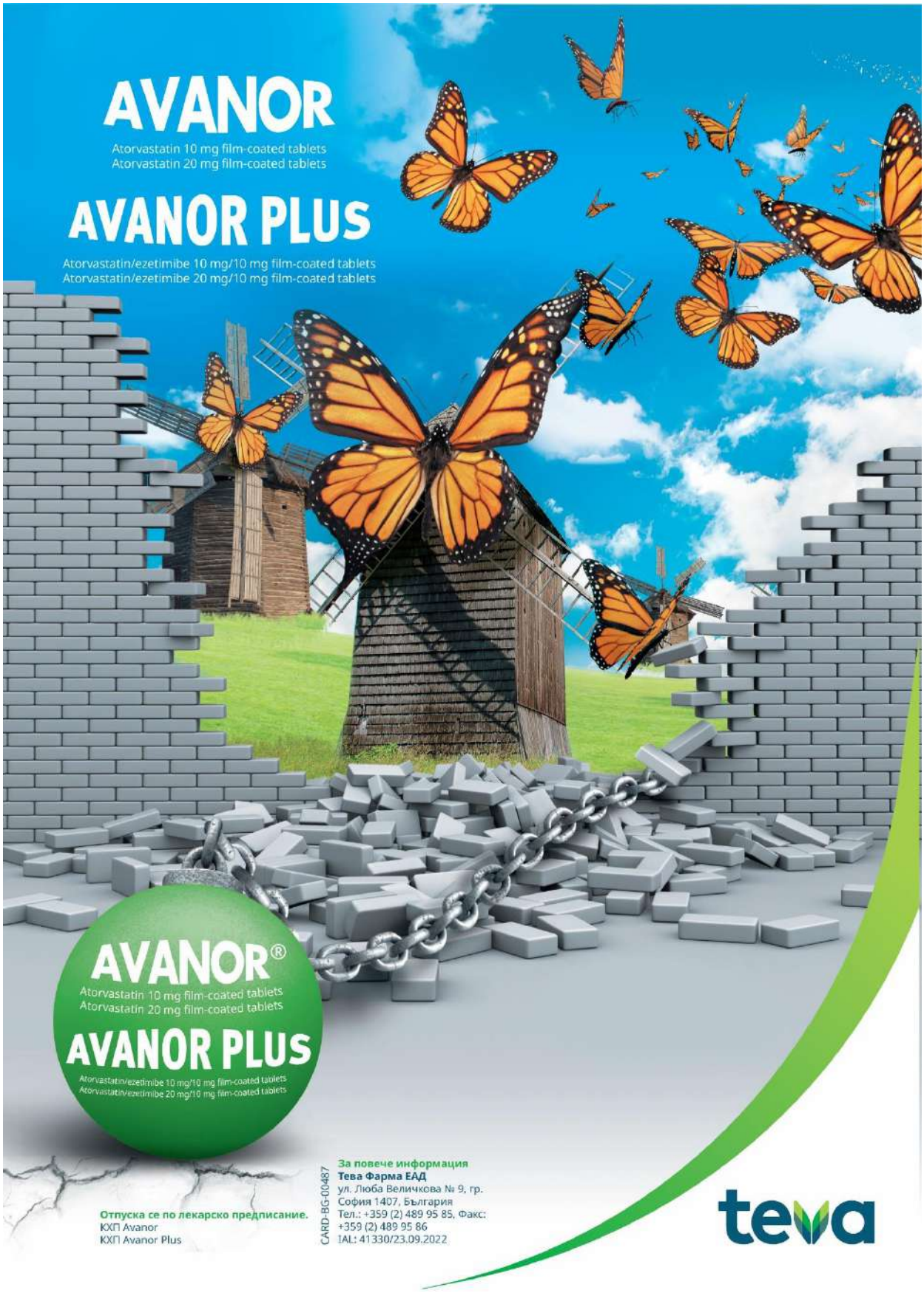
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