
INVESTIGATION OF THE EFFECT OF ARONIA MELANOCARPA FRUIT JUICE AND CHLOROGENIC ACID IN A RAT OVARIECTOMY-INDUCED DEPRESSION MODEL

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Introduction: Ovariectomy can be used as an animal model of menopause-induced depression. Aronia melanocarpa fruits are one of the richest sources of polyphenols, amongst them proanthocyanidins, flavonoids and phenolic acids, mainly chlorogenic acid. Polyphenols can cross the blood-brain barrier and thus act centrally.

Aim: The aim of the present study was to investigate the effects of Aronia melanocarpa fruit juice (AMFJ) and one of its active ingredients – chlorogenic acid (CGA), on depression-like behavior in subchronically treated ovariectomized female Wistar rats utilizing the force swim test (FST).

Materials and methods: Experimental animals (n=70) were divided into 5 groups: Control, OV, OV+AMFJ5, OV+AMFJ10 and OV+CGA. Rats from OV, OV+AMFJ5, OV+AMFJ10 and OV+CGA were ovariectomized, control animals were sham operated. After 14 days recovery period, animals were treated daily orally for 30 days as follows: Control and OV groups – with distilled water (10 ml/kg), OV+AMFJ5 and OV+AMFJ10 groups – with AMFJ at doses of 5 and 10 ml/kg, respectively, and OV+CGA group – with CGA 20 mg/kg. After the treatment period, FST was carried out. The immobility time (IT) shortening served as a measure of an antidepressant effect.

Results: In ovariectomized rats IT was significantly prolonged ($p<0.01$) compared with that of the controls. AMFJ treatment at the lower dose (5 ml/kg) and CGA had no significant effect on IT. IT of ovariectomized animals treated with AMFJ at the dose of 10 ml/kg was significantly shorter ($p<0.05$) than that of OV group.

Conclusion: AMFJ applied subchronically showed an antidepressant-like effect in ovariectomy-induced rat depression model.

Keywords: *Aronia melanocarpa, chlorogenic acid, ovariectomized rats, antidepressant*

ANXIOLYTIC AND SEDATIVE PROPERTIES OF MYRTENAL IN EXPERIMENTAL RODENTS

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Introduction: Myrtenal is a monoterpene with a variety of biological effects.

Aim: To investigate the anxiolytic and sedative properties of Myrtenal (M) in experimental rodents.

Materials and methods: Influence of M in single dose (30 mg/kg b.wt. i.p.) on the narcotic effect of two barbiturates (hexobarbital - metabolized by hepatic monooxygenases and barbital excreted by kidney unchanged) was studied on male Wistar rats. In ICR mice acute effects of M on sedation duration of Diazepam also were studied. Flumazenil was used to stop this sedation. Anxiolytic property of M was evaluated after single and repeated treatment (7- and 14- days) of mice using Marble burying test- MBT (Kung'u Njung'e, Sheila I. Handley, 1991) in compare to diazepam as referent. Statistical processing of the results was performed with ANOVA and GraphPad Prism.

Results: M significantly influenced sleeping time of barbital and did not change hexobarbital sleep duration. Probably this mechanism is central rather than metabolic. M applied in combination with diazepam produced narcosis (for average 16 minutes), whereas diazepam alone produced only sedation. Administration of Flumazenil led to a rapid recovery of the animals which confirms our conclusion for a central mechanism of action of M. According MBT test M demonstrate significant short-term anxiolytic effect ($p < 0.01$) after acute treatment which decreased after 7- and 14-days application.

Conclusion: Myrtenal has promising sedative and anxiolytic effect as a potential pharmacological agent.

Keywords: *anxiolytic effect, sedation, Myrtenal, rodents*

STUDY OF SPECTRAL CHARACTERISTICS OF ION ASSOCIATES CARMOISINE WITH SOME MEDICINAL SUBSTANCES FROM THE GROUP OF MYOTROPIC SPASMOLITHICS

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Modern pharmaceutical market is characterized by high competition between producers of the medicines. In order to make their product memorable and recognizable by consumers, companies are trying to give it a spectacular appearance. One of the most common way is covering tablets with a bright, effective colored shell, which means using dyes. Most often for this purpose use synthetic dyes, which are derivatives of diazotized sulfonaphthalenes. Theoretically anions of these dyes can form ion associates with some cations of medicinal substances.

The aim of our work was studying interaction between synthetic dye carmoisine with some myotropic spasmolytics.

Methods: For studying associates was used absorption spectrophotometry in UV and visible areas of the spectrum.

Results: It was established that the hydrochlorides of papaverine and drotaverine form ion associates with carmoisine, which are extracted by chloroform. The formation of the associate leads to a redistribution of the electron density, which produces to a change in the spectral characteristics of the dye entering the associate and manifests itself in a change in the absorption spectrum of the dye in the visible area, where a specific minimum appears in the differential spectrum of the associate, taken from a solution of a dye of similar concentration, observed specific minimum and maximum absorption.

Molar ratios of the components are determined for the formed associates.

Conclusion: Synthetic a zo dye carmoisine forms ion associates with papaverine and drotaverine hydrochlorides, which make changes in their physicochemical properties and spectral characteristics.

Keywords: *carmoisine, papaverine hydrochloride, drotaverine hydrochloride, ion associates, spectrophotometry*

PERSPECTIVES OF GENERIC MEDICINES MARKET DEVELOPMENT IN BULGARIA

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Over the last decade, global healthcare has been faced with problems connected with the increase of the cost in medicines, medical services and health protection of the increasingly aging population. One possible solution is the development of the generic drug products market. In many countries, the market of generic drug products is largely dependent on the functioning healthcare model and the regulatory mechanisms applied by the relevant health authorities. From 1996 to 2001, the sale of generic medicines has grown by 15%, while the growth in the innovative drug products is only 6%. This article presents analysis of the market for generic medicines in Bulgaria compared to selected countries of the European Union. The need to expand the generic medicines market is justified with the aim of limiting the costs and rational distribution of financial resources in the healthcare sector.

Keywords: *generic drug products, healthcare, costs, market, aging population*

THREE-DIMENSIONAL PRINTING OF DRUG PRODUCTS - AN INNOVATION FOR A PERSONALISED APPROACH IN PATIENTS' TREATMENT

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The development of innovations in this sector is helped by the the rapid improvement and the entry of technology in medicine and pharmacy. The three-dimensional printing of drug products is an innovation that can open up new opportunities for pharmaceutical research and biotechnology applications. In 2016, the first drug product for control of epileptic seizures, approved by the U.S. Food and Drug Administration (FDA), was printed on a 3D printer in the United States. The article focuses on the benefits and risks of manufacturing medicinal products through 3D printing, as well as the potential of innovation to change the traditional approach in patients' treatment to personalized medicine.

Keywords: *three-dimensional print, drug products, innovation, personalised medicine, patients*

LOCAL STUDY ON COMMUNITY PHARMACY EXTERIOR

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Introduction: There is a great recognition that community pharmacy exterior attracts consumers and patients. It can affect the consumption of different pharmaceutical and cosmetic products, which is very beneficial for the business. Another important point is that exterior can have an important reinforcing effect on loyalty of patients.

Materials and Methods: In this study it is mainly aimed to explore the exteriors of the community pharmacies in the city of Varna. In addition, we aimed to determine whether any difference exist between them. A total of 60 community pharmacies were randomly selected from 116 registered in Varna region. A uniform multicriteria research tool was applied to analyze the differences between exteriors by using a standard technique of photograph snaps.

Results: There are differences in terms of exterior between the community pharmacy in central and upper part of the city. More owners and managers attach importance to the attractive sight of their pharmacy. In addition, there is a very pronounced trend the green crosses to be instalated somewhere at the exterior. We indicated higher importance level of selection of the decoration equipment and the presence of illuminating elements.

Conclusions: Our study suggests that some community pharmacies pay more attention to exterior and its elements and others do not. There is a difference in terms of attaching importance to some elements (i.e. green cross, decoration equipment, illuminating elements, etc.) between pharmacy settings in central and upper part of the city.

Keywords: *Exterior, Community pharmacy, Varna, Marketing*

RADIONUCLIDES IN THE PLANT *MATRICARIA CHAMOMILLA L.* GROWN UP IN TWO REGIONS

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Common used medicinal plant in traditional and conventional medicine is *Matricaria chamomilla L.* The plant contains different types of biologically active substances among which the most important role for the therapeutic effect have hamazulen and α - bizzabolol. Concentration of radionuclides in the plant gives information of the safety level of using it.

Methods and materials: Samples of flowers of *Matricaria chamomilla L.* were collected in July 2016 from Yagnilo, Varna region and Debeli rut, Veliko Turnovo region. They were open air exsiccated and levigated. Measurements of dry powdered flowers were carried out with a low-background gamma-ray Ge(Li) spectrometer at the University of Shumen. The obtained gamma spectra were processed with the Anges software. Radioisotopes are determined by their energies.

Results: Values for the specific activities of natural radioisotopes in flowers of chamomille were obtained. In the samples from the two regions were found approximately levels of ²²⁶Ra, ²²⁸Ac, ²⁰⁸Tl and ⁴⁰K. The highest levels in the plants from Yagnilo and Debeli rut were found to be for ⁴⁰K. A natural radionuclide with low specific activity in the plant from Yagnilo was ²⁰⁸Tl and for the plant taken from Debeli rut - ²¹²Pb.

Conclusion: The levels for the specific activities of natural radioisotopes were within the limits of Regulation 25 for the protection of people from chronic exposure from the use of materials with increased radionuclide content. Therefore, public health is not at risk having in mind these levels.

Keywords: *gamma – ray spectrometry, Matricaria chamomilla L., natural radionuclides*

SYNTHESIS, STRUCTURAL ELUCIDATION AND ANTIMICROBIAL ACTIVITY OF A NEW ORGANOHALIDE DERIVATIVE OF EUDESMIC ACID

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Introduction: During the last few decades, halogens have had an important role in the development of pharmaceuticals. It is a well - known phenomenon that insertion of halogen radicals into many drug molecules enhance significantly both their effectiveness and metabolic stability. The majority of halogenated drugs are organofluorines (making up approx .20% of all pharmaceuticals), followed by organochlorine and organobromine therapeutics. Only a few iodine - containing drugs are known, e.g. thyroid hormones Levothyroxine sodium and Liothyronine sodium, antiarrhythmic agent Amiodarone , antiviral drugs Idoxuridine and Riodoxol , and Cloquinol - a drug for Alzheimer's disease interfering specifically with brain metal metabolism.

On the other hand, there is a group of iodinated compounds categorized as diagnostic agents - Odixanol, Iohexol, Iopamidol, Iotrolan and Iopromide - used usually to improve the visibility of body structures on images obtained by X - ray techniques.

Materials and Methods: The main structural features of the obtained aryl iodide were investigated by Fourier Transform Infrared Spectroscopy (FTIR), and by ¹H and ¹³C NMR Spectroscopy. The reagents eudesmic acid (99 + % , Alfa Aesar), trifluoroacetic acid (Merck) , iodine (99.8%, Sigma - Aldrich) and silver nitrate (>99.5%, Fluka) were used without further purification. The solvents chloroform, cyclohexane, toluene and dichloromethane were received from Sigma-Aldrich and dried by standard methods. The antimicrobial activity of the title compound was also evaluated against Gram - negative (E.coli spp.) and Gram - positive (Staphylococcus aureus spp.) bacteria strains as well against fungi belonging to Candida spp. class. A minimum inhibitory concentration (M.I.C.) was determined by the serial dilution method in a nutrient broth.

Results: The structure of the obtained aryl iodide has been characterized in detail by FTIR, ¹H and ¹³C NMR Spectroscopy. The presented synthetic procedure is a convenient route to the direct and high - yield synthesis of fully substituted eudesmic acid.

The new organohalide compound exhibited antimicrobial activity against all bacterial strains selected, but did not have a similar effect against all fungal strains tested

Conclusions: Low toxicity and high antibacterial activity define the present organohalide compound as a promising building block for further development of drugs with a good safety profile.

Keywords: halogenated drugs, antimicrobial activity, low toxicity

OIL FROM ROSA DAMASCENA – EXTERNAL APPLICATION AND ANTIBACTERIAL ACTIVITY

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Introduction: *Rosa damascena mill L.*, is one of the most important species of floral flowers. In Bulgaria the oil-bearing rose is grown in certain areas. This oil is one of the symbols of our country. Due to the low oil content of *R. damascena* and the lack of natural and synthetic substitutes, rose oil is also one of the most expensive in world markets.

Many of the beneficial effects of this oil on the skin, including antiseptic, antibacterial, disinfectant, are already proved. Different products are made out of rose extract – Rosewater, white cosmetics and many other. There are products with rose against acne too. During the last few years are done studies about its antibacterial properties. Some of them prove its bactericidal and bacteriostatic effect.

Aim: The aim of this study was to experiment the potential antibacterial effects of rose oil. We used rose oil, isolated by the method of water extraction of leaves of *Rosa damascene* by Clevenger apparatus.

Materials and Methods: We used water extraction by Clevenger apparatus, microbial food among and microbacteria. Literature was accessed through PubMed, Science Ditect and Google Scholar. Results: Successfully extracted rose oil from oil-bearing rose and proving of antibacterial effects. Conclusion: The use of rose oil as part of the composition of various cosmetic products would contribute to controlling microbial growth. The bacterial effect of the oil is particularly important for its widespread use in cosmetic and medical practice.

Keywords: *Rosa damascene, rose oil, antibacterial effects*

SYNTHESIS AND STRUCTURAL CHARACTERISATION OF PYRROLE DERIVATIVES AS POSSIBLE SELECTIVE MAO-B INHIBITORS

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Introduction: Monoamine oxidase (MAO) is recognized as an enzyme of crucial interest to pharmacologists due to its main role as catalyst of the major inactivation pathways for the catecholamine neurotransmitters. MAO inhibitors are discussed as the first and for some time the only treatment, for depressive illness. As recently reported the selective inhibitors of MAO-B have found a therapeutic role in the treatment of Parkinson's disease.

Recent modeling studies of the the possible binding modes of MAO inhibitors, through molecular docking of a group of pyrrole derivatives within the active site of human MAO-B defined the aim of our study.

Materials and Methods: The design of the target structures was directed to condensation of three 1H-1-pyrrolylcarbohydrazides with 4 carbonyl compounds and formation of 12 hydrazones, according to the following Scheme:

Results and Conclusion: The initial N-pyrrolyl hydrazides were synthesized via classical Paal-Knorr cyclization. The final hydrazones were obtained in a micro synthesis apparatus, assuring about 65 – 95% yields, low harmful emissions and reagent economy. The twelve compounds, divided into three series, were elucidated by IR, 1H NMR, 13C NMR and MS spectral analyses and the obtained results were consistent with the assigned structures. The purity of the substances was proven by TLC characteristics and corresponding melting points. The possible selective MAO-B inhibitory effect will be additionally determined, and the results will be published elsewhere.

Keywords: *catecholamine neurotransmitters, MAO-B inhibitors, structural characterization*

Acknowledgements: *Medical Science Council of Medical University of Sofia*

CAFFEINE - A PSYCHOACTIVE AND HIGHLY ACCESSIBLE STIMULANT

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Introduction: The positive effects on the central nervous system make caffeine a widely-spread substance in beverages and medications, but its psychoactive stimulation can cause mild tolerance which indicates a psychological and physical addiction.

Methods: The aim of the study is to focus the attention over the addictive aspect of caffeine as a biologically active substance.

Results: Caffeine is a psychoactive substance and a central nervous system stimulant which can be extracted from coffee beans. As a methylxanthine alkaloid it can be found in coffee, tea, cola, chocolate and energy drinks. The pharmacological effect of it is centered on the activity of adenosine receptors and caffeine functions as a nonselective receptor antagonist. Adenosine is an inhibitory neurotransmitter that suppresses the activity of the central nervous system, therefore, the antagonistic effect of caffeine is caused by the similar structure and in this way the alkaloid can bind with the receptors and block the action of adenosine. A study found that after the absence of a regular intake of 235 mg - approximately 2.5 cups of coffee per day - the subjects experienced high fatigue scores, abnormally high Beck Depression Inventory scores and low vigor scores.

Conclusion: The accessibility of this stimulant and its numerous positive effects on learning, memory, reaction time, concentration, motor coordination, makes caffeine a highly-desired psychoactive drug in our everyday lives. However, mild physical dependence and withdrawal symptoms may occur after the full reduction of caffeine intake, which is why raising awareness over the subject is of real importance.

Keywords: *caffeine, adenosine, methylxanthine alkaloid, addiction*

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THE FIRST DRUG FOR TREATING HALLUCINATIONS AND DELUSIONS IN PATIENTS WITH PARKINSON'S DISEASE - NUPLAZID

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Patients with Parkinson's disease (PD) often experience hallucinations, delusions, dementia, delirium, confusion, insomnia, nightmares usually caused by the drugs for managing the disease (dopaminergic and central cholinolytics) or the degenerative process in the brain due to the disease.

The atypical antipsychotic drug Nuplazid offers a solution for these side effects from the treatment. The drug is a selective inverse agonist or antagonist of the serotonin receptors 5-HT_{2a} and 5-HT_{2c} suppressing them even below their basal level of activity. It doesn't bind to any dopaminergic, muscarinic, adrenergic or histamine receptors. The inverse agonist suppresses the basal and constitutive level of activity of the receptor while the antagonist blocks the ligand-dependent activity, keeping the basal and constitutive activity.

Nuplazid turns out to be more effective than placebo in improving the frequency and severity of the hallucinations and not worsening the initial symptoms of the disease which was proven in a 6-week clinical trial including 199 patients. However, there is a greater risk of death if this drug is applied in elderly patients with dementia-related psychosis. The most common side effects are peripheral edema, nausea, confusion and constipation. Nuplazid is not recommended for patients with chronic kidney and liver diseases, arrhythmia. It can be taken without adjusting the dose of Levodopa/Carbidopa.

More than 50% of the patients with Parkinson's disease experience hallucinations and delusions and results can be seen two weeks after the first intake at the earliest, sometimes it can take more than 6 weeks.

Keywords: *Parkinson's disease, antipsychotic drugs, side effects, Nuplazid*

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TREATING PATIENTS ON DIALYSIS WITH SECONDARY HYPERPARATHYROIDISM WITH THE CALCIMIMETIC PARSABIV

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Secondary hyperparathyroidism is common among patients with chronic kidney disease (CKD). It is characterized with decreased excretion of phosphates and decreased production of calcitriol which leads to hyperphosphatemia and hypocalcemia. These factors increase the secretion of parathormone (PTH) – it lowers the serum levels of phosphates and increases those of calcium. In patients on dialysis the excess amount of phosphates cannot be fully excreted. Common ways of treatment are low phosphorous diet, phosphate binders, vit. D derivatives, calcimimetics or parathyroidectomy.

Parsabiv is a recently approved calcimimetic – a synthetic peptide that binds to an extracellular domain of the calcium-sensing receptor which is separate from the domain where calcium binds. This increases its sensitivity to calcium in an allosteric way. In this way the receptors are activated and the secretion of PTH is decreased. Two 26-week clinical trials have been conducted for testing the drug in which Parsabiv had a greater effect on decreasing the serum levels of phosphates and PTH than placebo (there was a more than 30% decrease in PTH than the initial levels in the group treated with Parsabiv).

Parsabiv is administered intravenously 3 times per week 5 mg/l. Common adverse reactions are hypocalcemia, worsening heart failure, adynamic bone, muscle spasms, diarrhea, nausea, vomiting, headache, paresthesia. Parsabiv is contraindicated for patients with carcinoma of the parathyroids, primary hyperparathyroidism and those who are not on dialysis.

When receiving Parsabiv serum levels of calcium, phosphate and PTH must be regularly monitored in order to avoid life threatening conditions.

Keywords: *Secondary hyperparathyroidism, haemodialysis, Parsabiv*

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INVESTIGATION OF THE USE OF PRODUCTS CONTAINING RHODIOLA ROSEA – NEWLY INTRODUCED IN BULGARIA FOR TREATMENT OF ANXIETY

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Introduction: *Rhodiola rosea* f. *Crassulaceae* (golden root) is a high-altitude herb native to the Arctic areas of Europe and Asia. Commonly used in Chinese, Scandinavian and Russian traditional medicine, it has a long history as a tonic for both mind and body. *Rhodiola rosea*-containing products are recommended against stress, fatigue, exhaustion and mild anxiety.

Aim: The aim of this study was to explore the available on the market in Bulgaria pharmaceuticals and dietary supplements containing *Rhodiola rosea* and to analyze the sales of such products for a one-year period.

Materials and methods: The pharmaceutical market in Bulgaria was investigated in search of the available *Rhodiola rosea*-containing products. The sales of such products were analyzed by collection of sales data from 19 pharmacies in Varna for the year 2016. The use of pharmaceuticals and dietary supplements was compared.

Results: There is one pharmaceutical product containing *Rhodiola rosea* on the pharmaceutical market in Bulgaria. There are also several dietary supplements most of which are mono-products containing *Rhodiola rosea* root extract. The pharmaceutical product was introduced in Bulgaria in 2015. Since then, only low-use dietary supplements containing *Rhodiola rosea* had been present. The sales data from 19 pharmacies in Varna showed that in 2016 the pharmaceutical product had a sales share that was 19 times higher than that of the dietary supplements.

Conclusion: The introduction of the pharmaceutical product in Bulgaria, supported by medical professionals, led to a high increase of the sales of *Rhodiola rosea*-containing products.

Keywords: *Rhodiola rosea*, dietary supplements, pharmaceutical market in Bulgaria

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HERBAL EXTRACTS – OPTICAL METHOD FOR INVESTIGATION AND CLINICAL APPLICATIONS

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Herbal medicines are complex mixtures of different compounds that often act in a synergistic fashion to exert their full beneficial effect. A tea consists compounds that protect cells against the damaging effects of reactive oxygen species, completely inhibit the activity of collagenase, protect blood vessels from rupture or leakage. Green tea lowers total cholesterol, control of body weight, protect from ultraviolet radiation. The tea from white chrysanthemum flower has antioxidant activities and helps the body system lower the high serum lipid levels.

It is difficult for consumers to evaluate the quality and classification of tea beverages or dried tea leaves on the market due to their similar profile or color. Thus, many different methods have been proposed for tea quality analysis like as high performance liquid chromatography, near infrared spectroscopy. The fluorescence spectroscopy has been found to be very efficient for tea classification and quality assessment method. The relation between biologically active substance such as polyphenols and phenolic acids and fluorescence peaks is reported. Two main fluorescence peaks with remarkable difference in fluorescence intensity were found - one was corresponding to flavonoids and another was attributed to chlorophyll-like compounds.

The investigated herbal extracts can be used as food supplements, which are concentrated sources of nutrients or other substances to effect the health of a human's body in a beneficial way. In particular, green tea may lower blood pressure and in addition reduces the risk of stroke and coronary heart disease. The main effect of consuming extracts of white chrysanthemum flower is the boost of the immune system.

Keywords: *Herbal extracts, beneficial effect, food supplements, methods for investigation*

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JARDIANCE - THE NEWEST INNOVATION IN THE TREATMENT OF TYPE 2 DIABETES

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Type 2 diabetes, once known as adult-onset or noninsulin-dependent diabetes, is a long term metabolic disorder. It consists of an array of dysfunctions - hyperglycemia, resulting from the combination of resistance to insulin action, inadequate insulin secretion and excessive or inappropriate glucagon secretion.

Type-2 diabetes mellitus, which accounts for approximately 90% to 95% of all diagnosed diabetes, is a progressive disease associated with serious complications - microvascular, macrovascular and neuropathic. Microvascular complications of diabetes include retinal and renal problems. Macrovascular complications are cardiovascular diseases, which mostly affect coronary artery and peripheral vascular system. Diabetic neuropathy affects autonomic and peripheral nerves.

Jardiance is part of the newest class of oral hypoglycemic agents. The active substance in Jardiance, empagliflozin, works by blocking a protein in the kidneys called sodium-glucose co-transporter 2 (SGLT2). As blood is filtered by the kidneys, SGLT2 stops glucose in the bloodstream from being passed out into the urine. The inhibition of SGLT2 targets glucose directly, thereby reducing the levels of glucose in the blood, and works independently of the β -cell function and the insulin pathway. This drug is the First and only type 2 diabetes treatment approved to reduce cardiovascular death.

Jardiance is contraindicated in people with type1 diabetes, impaired kidney functions or people on dialysis. Jardiance can lead to some serious side effects - dehydration, which may cause people to feel dizzy, faint, light-headed or weak, ketoacidosis and serious urinary tract or yeast infections. Another disadvantage is the bigger average wholesale price.

Keywords: *Type 2 diabetes, hypoglycemic agents, Jardiance*

MULTIPLE SCLEROSIS - THE GREAT MIMIC IN MEDICINE

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Introduction: Multiple sclerosis is autoimmune, chronic, inflammatory and demyelinating disease that causes multiple damages in the brain and the spinal cord. The illness is described with scattered plaques of demyelination in the white matter, relatively preserved axons and initiatory-remitting or constant course. It leads to a major motor disability. Because of the demyelination and lysis of random axons, the implementation of the disease is strictly individual. Therefore the scientists named multiple sclerosis „the great mimic in medicine”. The presence of many and different symptoms, developed individually, prevents the immediate diagnostics.

Materials and Methods: The aim of this study is to present methods of treating multiple sclerosis.

Results: In the last few years in medical practice are used drugs that modify the course of the disease. They have partial efficiency and are not able to suppress completely the illness therefore the main goal is to delay and decrease motor disability in long-term aspect. Treatment with corticosteroids shows most efficiency but it is not recommended for long-term use due to heavy side effects caused by these drugs – high blood pressure, gastrointestinal disturbance, insomnia, depression, mania, acne. Other methods of treatment are the use of interferons in particular beta interferons, DNA vaccines, engrafting stem cells for immediate immunosuppression. The most recent innovation is the peroral treatment via capsules Gilenya – so far the only one of its kind in Bulgaria. Gilenya is a drug for self-medication, modifying the course of the disease in highly active initiatory-remitting form of multiple sclerosis.

Conclusion: Medical research presents that it is impossible to fully heal multiple sclerosis although the progress of the illness can be delayed.

Keywords: *multiple sclerosis, autoimmune demyelinating disease, Gilenya*

THE NEWEST METHODS OF TREATMENT FOR COLORECTAL CARCINOMA

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The treatment of colorectal cancer (CRC) include surgical procedure and adjuvant chemotherapy, The aim of the last one is to decrease and eradicate the metastatic growth (reducing mortality and the level of recidivism). The overall five-year survival rate for this type of carcinoma in I, II and III stage are accordingly 85-95%, 60-68% and 30-60% due to the histology report during the resection and the number of lymph nodes, which were examined microscopically. The result of the meta-analysis of ten researches shows that delaying the chemotherapy with one month decrease the overall survival with 14%. This evidence is important because earlier chemotherapy can reduce the level of recidivism and progress. The newest cytotoxic drugs, like Oxaliplatin and Irinotecan, extend the duration without tumor progression and the overall survival in patients with metastatic cancer. As a result of that, a lot of clinical trials have been made in third stage of the tumor. Finding new prognostic factors in patients in second stage will be helpful for the therapist for choosing the right chemotherapy.

Keywords: *colorectal carcinoma, adjuvant chemotherapy, survival rate, meta-analysis*

Acknowledgements: *Oncology clinic in "Saint Marina" Hospital, Varna, Bulgaria*

CYSTIC FIBROSIS - BIOPHYSICAL ASPECTS

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Cystic fibrosis is the most common hereditary, life-threatening condition in the European human population - it affects both children and adults. The disease characterizes with severe symptoms which have an influence upon the digestive and reproductive systems in the majority of reported cases. Most often symptoms appear from the infancy period, including persistent dry cough and malnutrition. Subsequently various and more complicated conditions develop – such as pneumonia, emphysema, atelectasis, infertility.

Cystic fibrosis is caused by Delta-f-508 mutation in gene, localized in the long arm of 7th chromosome. Under the control of this gene is synthesized a protein, named Cystic Fibrosis Transport Regulator – CFTR, which in fact has the function of transmembrane channel of chlorine ions. CFTR is expressed mostly on the apical surface of epithelial cells, covering the respiratory tract and exocrine gland channels of the digestive tract. When a mutated protein is synthesized, the chlorine channel does not function and this causes the accumulation of thick mucus layer.

There is no cure for patients, suffering from cystic fibrosis, although some herbs, used in modern phytotherapy have a good effect in relieving the symptoms.

In addition, antibiotics - azithromycin, tobramycin and others are used when persisting infection is observed. Bronchodilators and corticosteroids are also first - line medications.

Keywords: *cystic fibrosis, mucoviscidosis, CFTR, ion channel, phytotherapy*

LEPTIN TREATMENT: FACTS AND EXPECTATIONS

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Leptin has key roles in the regulation of energy balance, body weight, metabolism, and endocrine function. Leptin levels are undetectable or very low in patients with lipodystrophy, hypothalamic amenorrhea, and congenital leptin deficiency (CLD) due to mutations in the leptin gene. For these patients, leptin replacement therapy with metreleptin (a recombinant leptin analog) has improved or normalized most of their phenotypes, including normalization of endocrine axes, decrease in insulin resistance, and improvement of lipid profile and hepatic steatosis. Remarkable weight loss has been observed in patients with CLD. Due to its effects, leptin therapy has also been evaluated in conditions where leptin levels are normal or high, such as common obesity, diabetes (types 1 and 2), and Rabson–Mendenhall syndrome. A better understanding of the physiological roles of leptin may lead to the development of leptin-based therapies for other prevalent disorders such as obesity-associated nonalcoholic fatty liver disease, depression and dementia.

Keywords: *Leptin, energy balance, body weight, metabolism, endocrine function, pathology, Metreleptin*

DYSFUNCTION OF MEMBRANE ION PUMPS. STABLE ANGINA

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Over time, organisms have developed an innate response to different stimuli. This is mainly because of the muscle and nerve cells, which specialize in generating electrical impulses within their cell membranes and passing them on to other cells.

Normally, there is an excess of intracellular negative charges and extracellular positive ones. Stimulation causes them to switch places, which in turn leads to depolarization of the membrane. Repolarization occurs once the process has ended.

The Na⁺/K⁺ pumps consistently maintain a functioning ion homeostasis. They export K⁺ externally and Na⁺ internally in terms of membrane positioning. Normally, this consumes more than a third of a cell's ATP store. Additionally, Ca²⁺ pumps, located in the sarcoplasmic reticulum, are essential to all types of muscle cells being able to work properly.

What unites the aforementioned objects is ATP. Given there is enough ATP within the cell, Ca²⁺ is pumped extracellularly. However, in a case of ischemia, an excess of Ca²⁺ is induced within the cell, which leads to hypercontracture, which damages the myofibrils, leading to structural fragility. It may eventually cause swelling, cell death and respectively necrosis.

Ischemia causes arrhythmia when concerning the heart. This is a major factor, leading to angina pectoris. It usually occurs when there is a lack of blood being pumped into the heart muscle, which may be down to coronary stenosis. Chest and back pain are among the main symptoms. When treating ischemia there is a high probability of reperfusion injury. Treatment of reperfusion and drug development are among the many challenges modern-day medicine faces.

Keywords: ion pumps, functioning ion homeostasis, ischemia, heart pathology.

HYPOTHYROIDISM

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Hypothyroidism is divided in primary, caused by failure of thyroid function and secondary (central) due to the failure of adequate thyroid-stimulating hormone (TSH) secretion from the pituitary gland or thyrotrophin-releasing hormone (TRH) from the hypothalamus. Secondary hypothyroidism can be differentiated in pituitary and hypothalamic by the use of TRH test. In some cases, failure of hormone action in peripheral tissues can be recognized. Primary hypothyroidism may be clinical, where free T4 (FT4) is decreased and TSH is increased or subclinical where FT4 is normal and TSH is increased. In secondary hypothyroidism FT4 is decreased and TSH is normal or decreased. Primary hypothyroidism is most commonly caused by chronic autoimmune thyroiditis, less common causes being radioiodine treatment and thyroidectomy. Salt iodination, which is performed routinely in many countries, may increase the incidence of overt hypothyroidism. The incidence of clinical hypothyroidism is 0.5-1.9% in women and <1% in men and of subclinical 3-13.6% in women and 0.7-5.7% in men. It is important to differentiate between clinical and subclinical hypothyroidism as in clinical symptoms are serious, even coma may occur, while in subclinical symptoms are less and may even be absent. Subclinical hypothyroidism may be transformed to clinical and as recent research has shown it may have various consequences, such as hyperlipidemia and increased risk for the development of cardiovascular disease, even heart failure, somatic and neuromuscular symptoms, reproductive and other consequences. The administration of novel tyrosine kinase inhibitors for the treatment of neoplastic diseases may induce hypothyroidism. Hypothyroidism is treated by the administration of thyroxine and the prognosis is excellent.

Keywords: *hypothyroidism, chronic autoimmune thyroiditis, postpartum thyroiditis, antithyroid antibodies, myxedema coma, congenital neonatal hypothyroidism*

DYSFUNCTION OF THE HYDROGEN-POTASSIUM ATPASE ZOLLINGER-ELLISON SYNDROME

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Introduction: The hydrogen-potassium ATPase is an enzyme, carrying H⁺ outside the cell and transferring K⁺ in the cell. The H⁺/K⁺ pump is located in the parietal cells of the stomach and has a major role in the secretion of HCl. This acid is responsible for the activation of pepsinogen into pepsin (an enzyme that digests proteins).

Materials and Methods: The aim of this study is to present one of the diseases, connected with dysfunction of the hydrogen-potassium ATPase.

Results: Zollinger-Ellison syndrome is associated with the formation of small tumors, called gastrinomas. In most cases they are situated in the head of the pancreas and produce gastrin – a hormone, which stimulates the H⁺/K⁺ pump. As a result, the concentration of H⁺ in the lumen is increased and causes hypersecretion of HCl. Due to the excessive amount of acid there are peptic ulcers in the stomach, duodenum and esophagus.

The ideal treatment for Zollinger-Ellison syndrome is resection of the gastrinomas, which is usually not applicable, because these tumors are difficult to be found. In serious cases a gastrectomy is needed. However, this has a negative effect on the health of the patient.

This is the reason why it is recommended to use medicaments that reduce the amount of acid. These include proton pump inhibitors (PPI) and H₂-blockers. The PPI are more preferable, because they can be used on empty stomach and include lansoprazole (Prevacid), omeprazole (Prilosec, Zegerid), pantoprazole (Protonix), dexlansoprazole (Dexilant), esomeprazole (Nexium), and rabeprazole (Aciphex). Examples of H₂-blockers are cimetidine (Tagamet), famotidine (Pepcid), and ranitidine (Zantac). The PPI bind covalently to the H⁺/K⁺ ATPase via disulfide bond and function about 24 hours. However, on the first usage not all pumps are inhibited. That is why maximum effect is achieved 3-4 days after the beginning of the treatment.

Conclusion: Proton pump inhibitors and H₂-blockers can be used for treatment of Zollinger-Ellison syndrome.

Keywords: hydrogen-potassium ATPase, Zollinger-Ellison, proton pump inhibitors, H₂-blockers

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ANTIOXIDANT PROPERTIES OF JUICE FROM FRUITS OF MULBERRY FRUITS AND ITS INFLUENCE OVER THE CELL METABOLISM

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Antioxidants are widely available as dietary supplements with a range of health influence. They can reduce the production of cytokines, neutralize reactive oxygen samples, promote the process of wound healing. Natural antioxidant molecules such as vitamin E, ascorbic acid, flavonoids and anthocyanins help to protect blood vessels from rupture or leakage. The recommended daily dose of flavonoids in different diets is from 50 mg to 500 mg. Foods with high content of antioxidants are blueberry, different wild berries, Ginko Biloba, black and green tea. In Asia and Africa mulberry fruits are often used in traditional medicine for the treatment of sore throat, fever, hypertension, anemia and in a cosmetic industry.

The aims of this investigation are: It is proposed one nontraditional for Bulgaria berry (mulberry) and is shown its usefulness for our diet as ingredient of marmalades, juices, liquors.

It is demonstrated the nondestructive technique for control of the nutritional quality of fruits during ripening by using optical methods.

Used methods: Near Infrared spectroscopy, visual spectral analysis, acoustic and ultrasonic techniques are often used for these estimations but they are costly and difficult to be proved. Chlorophyll fluorescence is nondestructive method for obtaining estimation of nutritional quality of fruits, including total phenols, total flavonoids and antioxidant activity of mulberry products.

Results: The content of phenols in mulberry is increased with ripping of fruits with maximum in the 3th period. After that, it is reduced and have maximum when the fruit matures. The same results are observed from authors, which are investigated the oils extracted from walnuts in different vegetation periods.

Conclusion: The fluorescence spectroscopy can be used for evaluation of quality of juice from mulberry in different vegetation periods.

Keywords: *fluorescence, mulberry, antioxidant properties*

LIPOSOMAL DRUGS - MODERN AND MORE SECURE WAY TO TREATMENT

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Introduction: Liposomes are microvesicles composed of a bilayer and/or a concentric series of multiple bilayers, separated by aqueous compartments formed by amphipathic molecules such as phospholipids. They enclose a central aqueous compartment. Water soluble drugs are contained in the aqueous compartment and hydrophobic drugs are contained in the lipid layer. Liposomes are non-toxic, flexible, biocompatible, completely biodegradable, and non-immunogenic for systemic and non-systemic administrations. Many liposome formulations are in various stages of clinical trials but some of them have already been commercialized as anti-tumor agents, antifungal agents, vaccines and others.

Materials and methods: Several full-text publications on the technology and action of liposomal drugs were briefly analyzed. The advantages and disadvantages of applying the liposomal analogues of Doxorubicin (LipoDox), Ambisome (Amphotericin B) and Epaxal (Hepatitis A vaccine) were evaluated according to the results of their clinical use.

Results: Compared to a standard Doxorubicin, LipoDox has longer half-life and bioavailability. Also, the cardiotoxicity is eliminated - the drug has increased accumulation in liver, spleen and tumors. Liposomal Amphotericin B - Ambisome has similar fungal eradication rate for *Candida* spp. in addition to lower toxicity (both renal and liver), so it is effective and safe for treating systemic fungal infections. Epaxal is the only aluminum-free and biodegradable HAV vaccine on the market, offering significant advantages in terms of tolerability.

Conclusions: Liposomal drugs have close to same efficacy compared to standard ones but significantly reduced toxicity. Therefore, only the cost and timing of clinical trials remain an obstacle to their wider application.

Keywords: *Liposomal drugs, reduced toxicity, efficacy*

INVESTIGATION OF THE EFFECTS OF ARONIA MELANOCARPA FRUIT JUICE AND CHLOROGENIC ACID ON THE STATE OF ANXIETY IN OVARIECTOMIZED RATS

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Introduction: Aronia Melanocarpa (AMFJ) fruits are very rich in polyphenols, amongst which chlorogenic acid (CGA). AMFJ and CGA have been demonstrated to possess anxiolytic and antidepressant effects in young/healthy rats.

Aim: The present study investigated the effects of AMFJ and CGA on the state of anxiety in ovariectomized Wistar rats using the social interaction (SI) test.

Materials and methods: Experimental animals (n=70) were divided into 5 groups: Control, OV, OV+AMFJ5, OV+AMFJ10 and OV+CGA. Rats from OV, OV+AMFJ5, OV+AMFJ10 and OV+CGA were ovariectomized, control animals were sham operated. After 14 days recovery period, animals were treated daily orally for 30 days as follows: Control and OV groups – with distilled water (10 ml/kg), OV+AMFJ5 and OV+AMFJ10 groups – with AMFJ at doses of 5 and 10 ml/kg, respectively, and OV+CGA group – with CGA 20 mg/kg. After the treatment period, SI test was carried out. The increase of SI time served as a measure of an anxiolytic effect.

Results: In OV rats, SI time was not significantly different from that of the controls. SI time of OV+AMFJ5 and OV+AMFJ10 rats was significantly shorter ($p<0.05$) compared to that of OV group. SI time of OV+CGA group did not differ significantly from that of OV group.

Conclusion: Neither AMFJ nor CGA demonstrated an anxiolytic effect in OV rats. AMFJ decreased the time of active social contacts in OV rats, probably due to the inhibition of the general locomotor activity of these animals, registered in the open field test.

Keywords: ovariectomized rats, anxiety, Aronia melanocarpa fruit juice, chlorogenic acid, rats

Acknowledgement: This research was funded by Science Fund-MU-Varna, 2014

RATIONALE FOR CHOOSING OF EXTRACTION SOLVENT FOR OBTAINING LIQUID EXTRACT FROM THE ROOTS OF HARPAGOPHYTUM PROCUMBENS DC

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Improvement of extraction process of herbal raw materials for the purpose of enhancing of the yield of biologically active substances is one of the main tendency of the development of pharmaceutical science. Creation of liquid preparation from the herbal raw materials includes selection of many criteria, such as choice of extraction solvent and its concentration.

Aim: The aim of this work was to determine extractive substances in the extracts obtained from the roots of *Harpagophytum procumbens*, to choose optimal extraction solvent for the creation of new dosage forms.

Materials: Liquid extracts of the roots of *Harpagophytum procumbens* were the object of research («Starwest Botanicals», USA). Ethanol in different concentrations (20 %, 40 %, 60 %, 80 %) was used as extraction solvent. Duration of extraction using magnetic stirrer was one, two and three hours.

Methods: Determination of extractive substances (residue on evaporation) in the extracts was done in accordance with the procedure of State Pharmacopoeia of Ukraine 2.0 (2.8.16).

Results. Obtained data indicate that maximum yield of extractive substances in the extract of the roots of *Harpagophytum procumbens* was obtained after the extraction for two hours for all used concentrations of extraction solvent: 20%, 40%, 60%, 80% ethanol (74.74±0.41%; 68.65±0.29%; 53.33±0.21%; 54.48±0.32%; 50.61±0.35 %, respectively).

Conclusion: Experiments proved that ethanol (20%;v/v) is an efficient extraction solvent for preparation of liquid extract from the roots of *Harpagophytum procumbens* , if a duration of extraction (with the use of magnetic stirrer) is two hours.

Keywords: *Harpagophytum procumbens*, Liquid extracts, extraction solvent, extraction duration

TEIXOBACTIN - A HOPE IN THE FIGHT AGAINST MULTIDRUG RESISTANT BACTERIA

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Multidrug-resistant bacteria are a growing worldwide public health problem. Uncontrolled and sometimes unnecessary use of antibiotics for human therapy and prophylactic use on animals in farms, resulted in the selection of pathogenic bacteria resistant to all available antibiotics. Teixobactin is an antibiotic of a new class produced by a soil microorganism undescribed and unknown until 2015, named *Eleftheria terrae*. Teixobactin is active against gram positive but not gram negative bacteria. The studies show that the new antibiotic can be used against Multidrug-resistant *Staphylococcus aureus* and Multidrug-resistant *Mycobacterium tuberculosis*. It also showed a good activity against *Streptococcus pneumoniae*, *Clostridium difficile* and *Bacillus anthracis*. The mechanism of action is different compared to other antibiotics used for human therapy. Teixobactin inhibits peptidoglycan biosynthesis by binding to lipid II (a precursor of peptidoglycan) and lipid III (a precursor of teichoic acid). Studies on *Staphylococcus aureus* with subinhibitory concentrations of teixobactin show no development of resistant strains. That leads to the suggestion that if it is used for human therapy it will be difficult for the pathogenic bacteria to become resistant. More clinical trials must be done to make sure that the antibiotic is safe and effective to use. Even if teixobactin itself does not make it to the market, the research done around it could lead to discovery of new antibiotics.

Keywords: *multidrug-resistant bacteria, antibiotics therapy, Teixobactin*

STENTS FOR TREATING OPEN-ANGLE GLAUCOMA

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Introduction: Micro-bypass stents are micro-invasive glaucoma surgery (MIGS) devices used to treat open-angle glaucoma.

Aim: The aim of this article is to present a randomized clinical trial that was conducted to evaluate gel microstents for treatment of primary open-angle glaucoma (POAG).

Materials and methods: This clinical study was conducted by the Institute of Ophthalmology in Cairo. 13 eyes with POAG underwent gel implantation with subconjunctival mitomycin-C. Of those eyes, 3 were pseudophakic and 10 underwent simultaneous phacoemulsification and gel implantation. Patients had uncontrolled IOP, had intolerance to therapy, or had maximal therapy but undergoing cataract extraction. Complete success was defined as IOP reduction $\geq 20\%$ from preoperative baseline at 1 year without any glaucoma medications while partial success as IOP reduction of $\geq 20\%$ at 1 year with medications.

Results: IOP dropped from 16 ± 4 mmHg pre-op to 9 ± 5 , 11 ± 6 , 12 ± 5 , 12 ± 4 , and 12 ± 3 mmHg at 1 week, 1, 3, 6, and 12 months. LogMAR was 0.33 ± 0.34 and improved to 0.13 ± 0.11 at 1 year. Mean number of medications dropped from 1.9 ± 1 preoperatively to 0.3 ± 0.49 ($p=0,003$) at 1 year. 42% of eyes achieved complete success and 66% qualified success.

Conclusion: Gel implants are effective surgical treatment for POAG with significant reduction in IOP. They reduce the need to apply glaucoma medications.

Keywords: *stent, glaucoma, Mitomycin-C, IOP*

RANIBIZUMAB MONOTHERAPY OR COMBINED WITH LASER VERSUS LASER MONOTHERAPY FOR DIABETIC MACULAR EDEMA

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Aim: To demonstrate superiority of ranibizumab 0.5 mg monotherapy or combined with laser over laser alone based on mean average change in best-corrected visual acuity (BCVA) over a 12-month, randomized, double-masked, laser-controlled study with patients with diabetic macular edema (DME).

Methods: 345 patients aged ≥ 18 years, with type 1 or 2 diabetes mellitus and visual impairment due to DME were randomized to ranibizumab + sham laser (n = 116), ranibizumab + laser (n = 118), or sham injections + laser (n = 111).

Results: Ranibizumab alone and combined with laser were superior to laser monotherapy in improving mean average change in BCVA letter score from baseline to month 1 through 12. At month 12, a significantly greater proportion of patients had a BCVA letter score ≥ 15 and BCVA letter score level > 73 (20/40 Snellen equivalent) with ranibizumab (22.6% and 53%, respectively) and ranibizumab + laser (22.9% and 44.9%) versus laser (8.2% and 23.6%). The mean central retinal thickness was significantly reduced from baseline with ranibizumab (-118.7 μm) and ranibizumab + laser (-128.3 μm) versus laser (-61.3). Ranibizumab monotherapy or combined with laser was not associated with an increased risk of cardiovascular or cerebrovascular events in this study.

CONCLUSIONS: Ranibizumab monotherapy and combined with laser provided superior visual acuity gain over standard laser in patients with visual impairment due to DME.

Keywords: Diabetic macular edema, Ranibizumab, laser.

FEBUXOSTAT AND THE DESEASE OF KINGS

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Introduction: Febuxostat, is a medication used in the treatment of chronic gout and hyperuricemia. It inhibits xanthine oxidase, thus reducing production of uric acid in the body.

Aim: The aim of this article is to present a randomized clinical trial that was conducted to compare the efficiency of Febuxostat and Topiroxostat in the treatment of patients with gout and cardiovascular disease.

Materials and methods: In this study, patients with cardiovascular disease and hyperuricemia, in whom serum uric acid (s-UA) was controlled at ≤ 6 mg/dL, were eligible for enrollment. Fifty-five patients were randomized to receive either febuxostat or topiroxostat for 6 months and were switched to the other drug for the following 6 months. The primary endpoint was s-UA. Secondary endpoints included serum creatinine, estimated glomerular filtration rate, urinary albumin, cystatin-C, oxidized low-density lipoprotein, eicosapentaenoic acid/arachidonic acid ratio, lipid biomarkers, high-sensitivity C-reactive protein and B-type natriuretic protein.

Results: Although s-UA level was similar for both drugs, significantly more patients required dose escalation during treatment with topiroxostat. There were no differences in renal function, inflammatory and lipid markers between the 2 drugs. A biomarker of oxidative stress was significantly lower after 3 months of febuxostat compared with topiroxostat.

Conclusion: Febuxostat causes more marked and more rapid reduction of s-UA than topiroxostat. With regard to the antioxidant effect, febuxostat was superior to topiroxostat after 3 months.

Keywords: *Febuxostat, gout, hyperuricemia*

ANALYS OF HYDROXYCINNAMIC ACIDS *PULSATILLA PRATENSIS* (L.) MILL.

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Pulsatilla pratensis (L.) Mill. (Ranunculaceae) distributed in the Central and Eastern Europe. The plant has a diuretic, expectorant, bactericidal, sedative and analgesic action.

Aim: The purpose of this work was the quantitative determination of o-dihydroxycinnamic acids in the grass and extracts of *Pulsatilla pratensis* with the object of studying groups of biologically active substances and developing a phytotherapeutic agent.

Materials: The object of our research were grass of *Pulsatilla pratensis* («Mir trave», Ukraine) and obtained from it water extraction (1:10) and tincture (1:5). Ethanol was used as extracting agent in the following concentrations 10%, 30%, 50%, 70%, 96%.

Methods. Determination of the quantitative content of o-hydroxycinnamic acids was carried out according to the European Pharmacopeia 8.0 method “Black horehound”. The content of the sum of dihydroxycinnamic acids, calculated as acteoside, was determined as a percentage.

Results: As a result of the obtained experimental data it was established that the content of the sum of dihydroxycinnamic acids, in terms of acteoside in tinctures of *Pulsatilla pratensis*, obtained using 10%, 30%, 50%, 70%, 96% ethanol, and constitute $3,65 \pm 0,01\%$, $5,16 \pm 0,02\%$, $2,78 \pm 0,01\%$, $2,99 \pm 0,01\%$ and $2,03 \pm 0,02\%$ respectively. In an aqueous extract, the content of dihydroxycinnamic acids was $3,07 \pm 0,02\%$.

Conclusion: The quantitative content of dihydroxycinnamic acids in aqueous extract (1:10) and tinctures (1:5) from *Pulsatilla pratensis* grass was established. The greatest content of the investigated group of substances was established in 30% tincture ($5,16 \pm 0,02\%$).

Keywords: *Pulsatilla pratensis*, hydroxycinnamic acids, aqueous extract, tinctures

GLP 1- ANALOGS (LIRAGLUTIDE) - NEW WEIGHT LOSS OPTION FOR OVERWEIGHT AND OBESE

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Aims/Objectives: The aim of this literature review is to present the current knowledge about the injectable glucagon-like peptide-1 (GLP-1) receptor agonist liraglutide, approved for management of overweight and obese in adults.

Methods: The conducted research includes articles without any constriction in the years of publishing.

Results: Liraglutide is a long-acting human glucagon-like peptide-1 (GLP-1) analog, which is approved for treatment of diabetes type 2. Liraglutide stimulates insulin release, inhibits glucagon secretion and slows gastric emptying. The incretin-based therapy for diabetes type 2 is associated with a significantly reduction in HbA1c and body weight reduction without risk of hypoglycemia. Liraglutide is indicated as an adjunct to a reduced-calorie diet and increased physical activity for management of overweight and obese in patients with BMI $\geq 27 \text{ kg/m}^2$, dysglycaemia (pre-diabetes or type 2 diabetes mellitus), dyslipidaemia, hypertension or obstructive sleep apnoea. GLP-1 analogs regulate appetite and food intake, reduce fasting and post-prandial blood glucose levels by stimulating insulin secretion and lowering glucagon secretion. The weight-loss effect is greater in patients with dysglycaemia. In conducted trials, liraglutide in combination with a reduced calorie diet and increased physical exercise, 50.4 to 67.5% of patients achieved $\geq 5\%$ weight loss after 12 weeks of treatment with liraglutide 3mg.

Conclusion: GLP 1 - analogues (liraglutide) are a new class antidiabetic medications, which improve fasting and post-prandial blood glucose levels and lead to weight loss in patient with pre-diabetes or type 2 diabetes mellitus.

Keywords: GLP 1 – analogues, diabetes type 2, Liraglutide

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CARDIOVASCULAR DISEASE AS A RISK FACTOR FOR DEPRESSION

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Introduction: Depression is the most common mental illness affecting more than 300 million people worldwide. In recent years, there has been much evidence of the link between depression and cardiovascular disease. Depression and cardiovascular disease (GCC) are the two most serious health problems in developed countries. According to the latest World Health Organization (WHO) predictions in 2020, depression will be second among the causes of disability. And in 2030 it will be the second most prevalent and fatal in the world after cardiovascular disease.

Material And Methods: Make a literary review to explore the connection between depression and cardiovascular disease. A review of literary sources available in electronic databases such as ScienceDirect, PubMed has been made.

Results: The incidence of clinical depression in patients with coronary artery disease is three times higher than in the general population. It is believed that a number of medications such as non-selective beta blockers may provoke depressive symptoms. Approximately every sixth patient with acute myocardial infarction unfolds a major depressive episode, which in one third of cases does not respond satisfactorily to the usual treatment. Myocardial infarction combined with depression results in much higher mortality within 6 months compared to patients who are not affected by depressive disorder.

Conclusion: The diagnostic of depression is a very serious and complex problem. Particular attention should be paid to patients suffering from cardiovascular disease treated with non-selective beta blockers.

Keywords: *depression, cardiovascular disease, non-selective beta blockers*

STUDY OF THE OPINION OF LOCAL POPULATION REGARDING THE DEGREE OF THREATENING OF THE MEDICINAL PLANTS IN THE NORTHERN BLACK SEA COAST REGION

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The growing interest in medicinal plants nowadays raises serious questions about the status of their populations and their exploitation potential. That was our motive to investigate the opinion of the local population about the status of the medicinal plants localities in the Northern Black Sea coast.

The study was conducted in different cities and villages from April to June 2015 using the technique interview face to face. Respondents were selected randomly.

In order to investigate the opinion of the local population how endangered are medicinal plants in the area they live, we asked them the following question: "Are there any herbs that are harder to find during the last ten years in your region?"

According the results, relatively small number of respondents have indicated herbs that are harder to find. The most frequently quoted species are *Matricaria chamomilla* (16 times), *Thymus serpyllum* (14 times), *Hypericum perforatum* (12 times) and *Origanum vulgare* (9 times). Whether the opinion of the respondents is objective and true should be verified by specific studies and, if it is necessary to clarify the reasons for the limited distribution of the listed medicinal plant species.

Keywords: *medicinal plants, Northern Black Sea coast, interview, plants distribution*

POSITIVE INFLUENCE OF CURCUMIN ON THE HUMAN BODY

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Curcuma longa is a perennial herbaceous plant of the Zingiberaceae family. For its homeland it is considered to be Southeast Asia, which is still in China, Vietnam, India, and is cultivated in our country for decorative purposes. The so-called "sacred dust" for thousands of years is used mostly by traditional healer practitioners, Chinese medicine and Ayurveda.

Turmeric root has a variety of biological and pharmacological activities - anti-cancer, antioxidant, anti-inflammatory, antibiotic, analgesic. It has a beneficial effect on immunity by supporting immune activity and strengthens the response to persistently attacking viruses and infections. In its use, tumor markers were decreased in various oncological indications (colon cancer, breast cancer, lung and prostate). Helps the cardiovascular system, lowers levels of cholesterol and triglycerides, regulates metabolism.

Curcumin (CUR) [1, 7-bis (4-hydroxy-3-methoxyphenyl)-1,6-heptadiene-3,5-dione] is a naturally occurring hydrophobic polyphenol extracted from the plants of the *Curcuma longa*. It is highly lipophilic drug that shows degradation at alkaline pH, which restricts its oral bioavailability. Different hydrophilic polymers such as PVP K-30, PEG 4000 and PEG 6000 have been tried for solubility and dissolution rate enhancement of CUR by different solid dispersion (SDs) techniques. Solid dispersions (SDs) of CUR in aqueous and organic solvent using Eudragit EPO (EuD) were prepared by spray drying and rota evaporation technique. CUR in pH 1.2 showed negligible release even after 120 min (2-5%) whereas, SDs showed 20-45% drug release after 60 min.

Keywords: *curcumin, bioavailability, biological activities, pharmacological activities*

ANTI-NOCICEPTIVE EFFECT OF MYRTENAL ON PAIN EXPERIMENTAL MOUSE MODELS

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Introduction: Myrthenal (M) is a monoterpene of natural origin with multiple activities, but scanty studied in experimental pharmacology. In recent years an increased interest to M and its biological activity was documented.

Aim of study: To test the anti-nociceptive properties of Myrthenal on two pain models in mice after acute and repeated treatment.

Materials and methods: Male ICR Albino mice were treated with M in acute and repeated treatment (7 and 14 days, 30 mg/kg b. wt. i.p.). Anti-nociceptive activity of M was examined on two established experimental pain models - Acetic acid writhing test (antipyretic type analgesia) and Hot plate test (narcotic type analgesia). Piracetam was used as a referent (Suelen A., Navarro et al., 2013). Statistical processing of the results was performed with ANOVA.

Results: In acute trials Myrthenal significantly decreased the number of abdominal writhing (Acetic acid test) at 15th and 20th minute. The effect was better than this of Piracetam. After repeated treatment the anti-nociceptive effect of M decreased and lost its significance (as well as the effect of the referent).

According Hot plate test, M demonstrated again significant anti-nociceptive effect occurred after 7 and 14 days treatment. The number of jumps of animals decreased significantly (by 40 %) in compare to controls. Established stable anti-nociceptive effect of M is better than this of the referent Piracetam.

Conclusion: At present, the mechanism of observed significant anti-nociceptive effect of M is not clear. Obviously it is complex and deserves further experimental studies.

Keywords: *anti-nociceptive effect, pain models, Myrthenal, mice*

Acknowledgements: *Fund Science - Medical University of Varna; Institute of Neurobiology, Bulgarian Academy of Sciences*

POLYCYSTIC OVARY SYNDROME - CAUSE AND TREATMENT

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Polycystic ovary syndrome (PCOS) is a common endocrine system disorder among women of reproductive age. Women with PCOS may have enlarged ovaries that contain small collections of fluid (follicles) located in each ovary.

While the exact cause of PCOS is unknown, it is believed that hormonal imbalances and genetics play a role. Overproduction of the hormone androgen may be another contributing factor. Women with PCOS often produce higher-than-normal levels of androgen. This can affect the development and release of eggs during ovulation.

Symptoms of PCOS typically start soon after a woman begins to menstruate for the first time. The type and severity of symptoms varies from person to person. The most common characteristic of PCOS is irregular menstrual periods. Because PCOS is marked by a decrease in female sex hormones, this condition may cause women to develop certain masculine characteristics, such as: excess hair on the face and other body parts, decrease in breast size, deeper voice, hair loss. Other symptoms may include: acne, weight gain, pelvic pain, depression, infertility.

Early diagnosis and treatment along with weight loss may reduce the risk of long-term complications, like type 2 diabetes and heart disease.

PCOS can be treated, but there is no cure. Certain lifestyle changes, such as diet and exercise, are considered first-line treatment for adolescent girls and women with polycystic ovarian syndrome. Treatment focuses on controlling symptoms and managing the condition to prevent complications. The treatment will vary from woman to woman, depending on specific symptoms.

Keywords: *Polycystic ovary syndrome, hormonal imbalances, complications, treatment*

RISK OF HYPERKALEMIA IN HEART FAILURE AND NEW TREATMENT OPTIONS

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Introduction: Hyperkalemia is a serious medical condition that can cause muscle weakness, paralysis and cardiac arrhythmias. This condition occurs especially frequently in patients with heart failure (HF), in part due to existing comorbidities, such as chronic kidney disease (CKD) and in part because of medications, used to treat HF – inhibitors of the renin-angiotensin-aldosterone system (RAASi) and mineralcorticoid receptor inhibitors (MRIs).

Materials and Methods: This retrospective study reveals the risk factors, the stratification of the risk of hyperkalemia and its significance among the patients with HF. Patients hospitalized for HF at the St. Marina University Hospital in Varna in the period January 2010 - December 2014 were included in the study. The objective was to review the demand of the patients with HF for medications reducing potassium levels in the blood serum.

Results: Significant part of the patients with HF have CKD as a comorbidity and are taking medications that increase the serum potassium level, leading to a risk of hyperkalemia. The same situation is observed with the patients, who are receiving a combination of RAASi and MRIs, which leads to the aforementioned risk as well. There are also a few patients per year who have hyperkalemia as a comorbidity. They must be treated with the same medications, despite the possible risk of hyperkalemia.

Conclusion: Two new potassium binders – patiromer and sodium zirconium cyclosilicate, are included in the current guidelines as medications under consideration for regulatory approval. They are new therapeutic options for managing hyperkalemia in patients with HF and a risk of hyperkalemia. The current study reveals the importance of minimizing this adverse effect in order for the patients with HF to be able receive their optimal pharmacological treatment.

Keywords: hyperkalemia, heart failure, treatment

PHARMACOEPIDEMIOLOGICAL STUDY OF GINKGO BILOBA-INDUCED TOXICITY

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Introduction: *Ginkgo biloba* is a popular supplement and one of the most widely sold botanical dietary supplements worldwide. Commonly health effects of *Ginkgo biloba* leaf extract are improved blood circulation and improved memory. Usually it is labeled as a memory ‘panacea’. *Ginkgo* leaves have also been used in treatment of cognitive disorders, arrhythmias and ischemic heart disease, cancer, diabetes, thromboses, pyogenic skin infections and intestinal tract worm infections. This study based on information collected from scientific journals and electronic databases presents updated information on the toxicological effects of the plant. *Ginkgo biloba* leaf extract has been classified as a possible human carcinogen by the International Agency for Research on Cancer. There are studies on *Ginkgo biloba* leaf extract, which provide evidence of a carcinogenic effect in mice revealed by increased incidence of hepatocellular carcinoma and hepatoblastoma.

Materials and Methods: Isolation and chemical analysis of ginkgotoxin (4-o-methoxypyridoxine) were accomplished by implementing different chromatographic techniques. The chemical analysis of different *Ginkgo biloba* products has been also performed. *Allium cepa* test was used to investigate potential cytotoxic and genotoxic effects of ginkgotoxin.

Results: This study presents information on new, unknown till now harmful side effects of phyto preparations of *Ginkgo biloba* and it is an attempt to monitor side effects of a well-known and widely used product.

Conclusions: Currently, there is an increasing global interest in the use of botanical products because of people’s belief in “natural” products being only health beneficial. Despite this common belief, many botanical dietary supplements have been reported to have potential health risk and should be taken with caution.

Keywords: *Ginkgo biloba*, dietary supplements, beneficial effects, side effects

HEPATOPROTECTIVE EFFECT OF PROBIOTIC FOOD, CONTAINING LACTOBACILLUS BULGARICUS DWT1 IN ACUTE ETHANOL INTOXICATION IN EXPERIMENTAL ANIMALS

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Probiotics are live microorganisms, which have a beneficial effect on human health and contribute to the intestinal balance. In 1905 the Bulgarian Dr. Stamen Grigorov discovered the microorganism *Lactobacillus bulgaricus* in yogurt. Later Russian physiologist Ilya Mechnikov concluded that the secret of longevity of Bulgarians lies in eating yogurt.

Lactobacillus bulgaricus is the only microorganism, named after a particular geographic territory. It reproduces only in the territory of Bulgaria. Nowadays probiotics are subject of increasing interest because of their proven hepatoprotective, immunostimulating, antioxidant and anti-tumor effect. For the first time in the world, Professor Nikola Aleksandrov managed to isolate natural probiotic bacteria from water source in Stara Planina. The probiotic association contains wild strains of lactic bacteria.

In the present experiment, we first investigated a hepatoprotective effect of a new strain of *Lactobacillus bulgaricus* DWT1. We used 30 male Wistar albino rats. The rats were treated within 14 days with Laktera Nature probiotic, and on the 12th day an acute liver damage was induced with a high dose of ethanol. After laboratory and histological analysis of rat blood and liver, we found that animals receiving only ethanol had extensive necrosis zones and elevated liver enzymes. In the Laktera Nature pretreated and then subjected to ethanol groups, ALT and alkaline phosphatase levels were significantly lower than those in the ethanol group. Histologically, a preserved liver structure was established. The present experiment demonstrates the hepatoprotective effect of Laktera Nature. It can improve significantly the treatment of the patients suffering from liver disease.

Keywords: *probiotics, ethanol, liver damage, hepatoprotective effect*

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SIDE EFFECTS OF TOPICAL RETINOIDS

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Since introduction of topical Retinoids in 1971, they have been extensively used for treatment of acne, psoriasis, skin aging, and certain types of cancers. The first-generation retinoid tretinoin (all-trans retinoic acid), isotretinoin (13-cis retinoic acid) and the synthetic third-generation polyaromatics adapalene are approved for acne treatment in Europe. These compounds result in proliferation and reduced keratinization of skin cells. Retinoids also contribute greatly to intercellular communication, allowing signaling to nearby cells by binding the nuclear receptors, therefore regulating epithelial cell growth and rate of proliferation. Topical Retinoids have a favorable safety profile distinct from the toxicity of their systemic counterparts. Local adverse effects, including erythema, dryness, itching, and stinging, occur frequently during the early treatment phase. The irritation side effects from topical Retinoids occur mainly from prolonged, high dose use. Side effects occur in a dose and concentration dependent fashion, with higher doses and concentrations contributing to the negative effects of these medications. These include excessive dryness of the skin, skin redness, scaling of the skin, pruritus (itching).

Aim: The aim of this study is to overview possible side effects of topical retinoid use.

Materials and Methods: Literature were accessed through American Osteopathic College of Dermatology, Google and DermNet.

Results: There are numerous reports of side effects associated with treatment with topical Retinoids, but one of the most frequently reported is excessive skin dryness, which may become chronic.

Conclusions: Retinoids are widely used in medicine and play a very important role in treating disease not just limited to the skin. Although first line for many different skin conditions, therapy should tailored to individual patients based on the side effect profile. Due to individual variability, some people may experience better overall results with the use of different retinoid therapies. It is important not to forget that overuse of this medication can lead to the development of chronic skin dryness, irritation, and discoloration.

Keywords: *Retinoids, side effects, retinoid therapies*

SIDE EFFECTS OF ORAL RETINOIDS

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The retinoids are class of chemical compounds that are vitamin A derivatives. Oral Retinoids have used in the treatment of various dermatoses over the last decade. The most useful drugs have been isotretinoin (13- cisretinoic acid) for nodulocystic acne and etretinate for psoriasis vulgaris.

Retinoids are also effective in the treatment of cutaneous T-cell lymphoma and in chemotherapy and chemoprevention of cancer. However, systemic administration of these compounds is frequently associated with side effects.

The toxicities associated with both short- and long-term treatment with oral Retinoids are significant and include mucocutaneous effects, adverse modulation of serum lipid chemistries, elevation of liver enzymes, and after long-term chronic dosing, skeletal and ligamentous calcification, and hyperostosis. Both etretinate and acitretin, like all Retinoids, known teratogens in animal models, and documented evidence exists for teratogenic activity in humans as well.

Aim: The aim of this study was to overview possible side effects of oral retinoid administration.

Materials and Methods: Literature was access through PubMed, Science Direct and Google Scholar.

Results: There are nomos reports of toxicities associated with treatment with Retinoids. One of the most significant side effects is teratogenicity that assure in Retinoids of all generation.

Conclusions: The safety profile of oral retinoids appears to be well established, although rare new side effects are occasionally reported. Appropriate patient selection, use of the lowest required dose, and adequate follow-up are significant factors in the prevention of these toxicities.

Keywords: *retinoids, oral treatment, toxicity, side effects*

THE ROLE OF THE PHARMACIST IN PROVIDING PHARMACEUTICAL CARE TO PATIENTS WITH TYPE 2 DIABETES MELLITUS

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Type 2 Diabetes mellitus (DM), also known as non insulin-dependent diabetes mellitus” (NIDDM) or “adult-onset diabetes”, is a metabolism disorder, which is characterized with high blood sugar levels. The disease is one of the most serious healthcare problems of our time. Usually type 2 DM is a result of unhealthy diet, excessive body weight and not enough exercise. Type 2 diabetes occurs relatively frequently in young people, including children.

According to the contemporary concepts, type 2 DM’s patients need not only pharmacotherapeutic treatment, but also comprehensive approach to tackle the disease manifestations, prevent complications and improve the patients’ quality of life. The pharmacists’ role in accomplishing different activities in the provision of pharmaceutical care that are crucial in the management and control of the disease.

Data from different surveys show that approximately half of the patients diagnosed with NIDDM, when being prescribed medicinal treatment and regular screening of blood sugar levels, turn to the pharmacist for clarification of rational drug use, training for correct use of the medical devices and for advice with the control of the disease. However, we should note that in the Republic of Bulgaria trainings related to the control of the condition of patients is still in its early stages.

The pharmacists’ participation in multidisciplinary teams for managing the chronic disease, including NIDDM, improves the care for the patients regarding their awareness for the risk factors and achieving better control of the disease.

Keywords: *Type 2 Diabetes mellitus, pharmaceutical care, patients, pharmacist*

RADIOPHARMACEUTICALS FOR BRACHYTHERAPY

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This article presents the use of radiopharmaceuticals in brachytherapy. Brachytherapy is a type of intercellular radiotherapy, where the radiation source is placed inside or next to the organ requiring treatment. Interstitial radium therapy was common in the 1930s. Gold seeds filled with radon were used as early as 1942 until at least 1958. First used in 1958, iridium is the most commonly used artificial radioisotope for brachytherapy today.

The first brachytherapy ward in Bulgaria is founded more than 40 years ago in the University hospital in oncology, Sofia. Radiopharmaceuticals are pharmaceutical drugs that emit radioactive rays. The isotopes used in brachytherapy are Co-60, Cs-137, Au-198, Ir-192, I-125 and Pd-103. The isotopes go through radioactive decay and emit beta - β and gamma - γ rays, which have energy. The three used radioactive sources in remote after-loading devices are Co-60, Cs-137 and Ir-192. Currently the most commonly used source for after-loading is Ir-192, because of its medium average γ -ray energy ($\approx 400\text{keV}$) and its high specific activity.

Depending on the dose of ionizing rays, brachytherapy is divided into several categories: HDR, LDR, PDR, permanent and electronic. LDR seeds (Cianna[®], Varian[®], Bard[®], IsoAid[®], etc.) are used to insert isotopes into or in close proximity to the tumor. The isotope is incased in a titan capsule. HDR balloon-based catheter devices (SAVI[®], MammoSite[®], etc.) use Ir-192 for treating breast cancer. Recently, radiopharmaceuticals have found broader use in the pharmaceutical industry, due to the new ways of treating oncological diseases.

Keywords: radiopharmaceuticals, brachytherapy, oncological diseases

COMPARISON OF GnRH AGONISTS AND ANTAGONISTS IN THE TREATMENT OF ENDOMETRIOSIS

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Endometriosis is a chronic, estrogen-dependent condition that causes dysmenorrhea and pelvic pain. While none of the available treatments resolves the underlying disease process, there are a growing number of alternatives for dealing the symptoms. Successful treatment could be achieved by medications that reduce the levels of estrogen such as gonadotropin-releasing hormone (GnRH) antagonist and agonists. GnRH agonists are potent down regulators of pituitary function, increasing initial release then depletion of gonadotropin FSH and LH. GnRH antagonists work by competitive blocking of pituitary GnRH receptors. Their action onset is immediate, time related and reversible. There is no initial flare of gonadotropins either before or after the onset of action. Complete oestrogen deprivation results in unacceptable side-effects including headache, hot flushes, vaginal dryness, mood disturbances and accelerated bone density loss. These potential side-effects of medical therapy have been effectively managed with 'add-back therapy' using low-dose oestrogen and progestin combinations that limit these effects. Treatment with a GnRH agonist does provide proven pain relief in 80-90% of women with documented endometriosis, but medical treatment is suppressive therapy, not extirpative therapy and pain does recur. Because of the combination with add-back therapy, GnRH agonists deserve consideration as first line therapy. Further development of long acting GnRH antagonists for endometriosis treatment deserves attention due to the immediacy of onset, ease of reversibility and lack of pain increase with utilization.

Keywords: *Endometriosis, gonadotropins, GnRH agonists, GnRH antagonists*

ON THE ITALIAN EXPERIENCE OF PALYTOXIN DETERMINATION AND TOXICITY TESTING

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Marine biotoxins (phycotoxins) find their way through the food chain to the human and may cause severe illness. Emerging phycotoxins are recently detected in Europe, as well as in the edible marine organisms and sea water from the Bulgarian coast of the Black Sea. Most European countries have developed a strategy for overcoming this problem.

Department of Life Sciences (DLS) at University of Trieste in Italy is researching the effect of palytoxins, a marine biotoxins, on human systems.

Palytoxin (PLTX) is a putative toxic marine compound. Oral exposure by ingestion of contaminated seafood is considered to be most dangerous by causing gastrointestinal symptoms, myalgia and spasms and even death. Aim of this overview is to present the experience and experiments carried out at University of Trieste for PLTX toxicity testing.

Methods, results and discussion: Methods used are hemolytic and cytotoxicity assay. Sensitivity of human erythrocytes, peripheral blood mononuclear cells (PBMC) and human DNA to various concentrations of palytoxin were tested. A correlation between the sensitivity, age and gender has been investigated.

Results from this study are expected to be ready in 2018.

Conclusions: As paying attention to shellfish poisoning is a new initiative for Bulgaria the experience of the DLS at University in Trieste would improve the organization and implementation of the procedures.

Keywords: *Marine biotoxins, contaminated seafood, human erythrocytes, PBMCs, human DNA*

GENETICALLY MODIFIED BACTERIA AS A WAY TO REMOVE CANCER

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Introduction: Presently there are many ways to treat cancer, many of which however are harmful not only for the malignancy but also for the organism being treated. Research done on using bacteria as a cancer treatment shows that the negative effects on the organism are far less than the ones on the tumor, which shows promise that bacteria could be used as a viable cancer treatment in the future.

Materials and methods: The information for this scientific review has been gathered using the information provided by eight scientific papers on the topic "Bacteria as cancer treatment" since the year 2010.

Results: The most commonly used attenuated bacteria to treat cancer is *Salmonella typhimurium*. The normal conditions in which the bacteria thrive are provided by the tumor and thus the malignancy can be an environment in which the bacteria grow and replicate. Due to our immune system the bacteria is restricted to and can successfully thrive only in the malignancy. The bacteria have to be administered regularly in situ so as not to be destroyed by our immune system. The cytotoxic agents, cytokines and tumor antigens provided by the bacteria successfully help in reducing the size of the malignant tissue and its proliferation thus prolong the life of the treated organism. The bacteria itself is not a threat to the organism as it is attenuated.

Conclusion: While still not commonly used bacteria provide a viable way of treating cancer as they are cytotoxic only in situ and have relatively small to no harmful systematic effects. Furthermore, genetically modified bacteria can selectively produce cytokines that activate the proliferation of T and NK cell which help the reduction of the malignancies.

Keywords: *bacteria as cancer treatment, cytokines, T and NK cell proliferation*

ANALYSIS OF FACTORS THAT INFLUENCE PHYSICIANS' PRESCRIBING HABITS

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Introduction: The aim of this study is to deduce the main factors which influence on physicians' selection of medicinal products, nutritional supplements, medical devices and cosmetics. Different marketing methods has been studied. In the research also was included the behavior of medical representative and the characteristics of medicinal products.

Materials and methods: The analysis is performed based on anonymous survey, which was conducted among doctors working in regions of Varna, Veliko Tarnovo, Dobrich and Targovishte during April-September 2017.

Results: Variety of factors are reviewed to affect physicians' prescription pattern. Among the leading factors are :data provided by clinical trials, patients' ability to pay medical bills, reputableness of the pharmaceutical company, some experience with a product, marketing tools of pharmaceutical companies and medical representatives' tactics to popularize their products.

Conclusion: Preliminary results show that the role of medical representatives is essential for the drug therapy decision. They are highly respected and accepted by doctors as medical professionals whose knowledge is a reliable criterion for choosing a medicinal product.

Keywords: *factors, prescription, physician, medicinal product*

CHALLENGES FACING THE BULGARIAN HEALTH SYSTEM IN INTRODUCING EHEALTH

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In the health sector, the percentage of the unnecessary medical procedures and laboratory tests that are carried out, or the unnecessary medicines that are prescribed is between 30% and 40%. This is due to the insufficient communication and coordination between the various medical specialists and the units serving a given patient, and to the lack of access to the patient's complete medical history. The experience of many countries of Europe and the world shows that through eHealth, which includes the exchange of information and data between patients and health services providers, hospitals, health professionals and networks, electronic health records and e-prescription, the access to treatment and quality of service is improved, as well as the efficiency of health is increased. The article presents the challenges faced by the Bulgarian health system in the process of introducing e-health.

Keywords: *challenges, health sector, e-health, data exchange, medical specialist, patients*

COST EFFECTIVE ONLY AT A ZERO PRICE IN ONCOLOGY: A REAL TIME SCENARIO?

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Introduction: Incremental cost per a quality-adjusted life year /QALY/ is widely used as a “common currency” to assess cost-effectiveness of medicines although this approach has several well-acknowledged shortcomings. In oncology, innovative therapies often are used as combination with standard of care /SOC/ to gain life-years due to additional time spent in the progression free state /PFS/. Inspired by a real case, this is an example in which a novel technology may not be cost-effective until set at a zero price in oncology.

Materials and methods: The new treatment is an oral adds-on to a SOC, also oral drug, aimed to abrogate resistance which is expected after sixth month following initiation with SOC only. Clinical data from pivotal trial demonstrate incremental Δ PFS of 7 months resulting in Δ utilities of 0.01 for PFS.

Results: Until the new medication is set at a zero price, cost-effectiveness is hard to achieve and finally at zero price cost per QALY arrives at 11 000 €.

Conclusion: Treatments which increase survival in oncology patients with high ongoing standard care cost may result in cost-/in/effectiveness even at zero price. The driver for the high cost per QALY when a novel treatment is administrated as a combination is the additional PFS which is accompanied by the cost of the both drugs. Once efficient technology is cost-effective only at or around zero price, it is justifiable to depart from the cost per QALY approach and adopt optional method/s.

Keywords: *Therapies, cost-effectiveness, quality-adjusted life year*

VALUE ADDED MEDICINES - MEASURING HEALTH BENEFIT BY EFFECTIVELY TREATED PATIENT-YEARS (ETPYS) IN FERTILITY PRESERVATION

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Introduction: Value added medicines are defined as “medicines based on known molecules that address healthcare needs and deliver relevant improvements for patients, healthcare professionals and/or payers”. Selective progesterone receptor modulators (SPRMs) are recently approved therapeutic alternative for adult women wishing to preserve fertility. The objective of this analysis is to demonstrate the clinical and economic value of a SPRM considering the inevitable uncertainties within an economic evaluation.

Methods: Unlike the neither empiric nor theoretical cost-per- quality adjusted life years (QALY) approach to assess cost-effectiveness, effectively treated patient-years (ETPYs) is a disease-specific measure of health benefit underpinned by quality of care considerations.

Results: The use of a SPRM is associated with a modest gain in QALY, thus driving total incremental costs vs. monitoring only alone. The incremental cost per ETPY however is significantly less.

Conclusions: The widely used threshold per QALY has many well-acknowledged shortcomings. ETPYs are clinically meaningful measure of patient benefit which recognizes and considers process-oriented factors of value, specifically quality of care.

Keywords: *cost-effectiveness, effectively treated patient-years, quality of care*

REVIEW ON THE PHYTOCHEMICAL COMPOSITION, MECHANISM OF ACTION, BIOMEDICAL EFFECT AND SIDE EFFECTS OF MITRAGYNA SPECIOSA

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Mitragyna speciosa (MS), commonly referred to as Kratom, is a tree-like plant from Southeast Asia that belongs to the Rubiaceae family. It is traditionally used for pain relief and as a treatment for fatigue. Its use in North America and Europe has surged since 2000 with it being used not only for recreational purposes but also for self-management of opiate withdrawal.

Materials and methods: For this review literature from Science Direct and Pubmed was used. Publications were made in the years 2014-2016.

Results and conclusion: The main active compound of MS is mitragynine. The effects of MS include analgesia, euphoria, miosis, constipation, as well as anti-inflammatory and antidepressant-like activity. Although poorly studied, animal trials show interaction between mitragynine and mu- and delta-opioid receptors as well as alpha-2 adrenergic and 5-HT_{2A} receptors. The constipation caused by MS is not fully manageable with opioid antagonists such as naloxone, which suggests a much more complex mechanism of action. Long term use of Kratom can lead to opioid addiction although it's reported to be much less severe than morphine addiction and has milder withdrawal symptoms. Surveys show little to no social impairment in users of the drug. Still its safety has not yet been fully evaluated as new side effects are being reported. These include hallucinations, delusions, depression, myalgia, hepatotoxicity, coma and death. As most of the information comes from surveys and animal trials, more research needs to be done in order to evaluate the benefit: risk ratio of Kratom.

Keywords: *Kratom, opioid, Mitragyna*

OCRELIZUMAB FOR TREATMENT OF MULTIPLE SCLEROSIS – BENEFITS AND RISKS

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Multiple sclerosis (MS) is an autoimmune disease which can affect the brain and the spinal cord. In multiple sclerosis the immune system attacks the myelin that cover nerve fibers. Ocrelizumab is an anti-CD20 monoclonal antibody that targets B cells which are thought to influence the abnormal immune response in MS. The drug is recently approved for treatment of both primary progressive and relapsing multiple sclerosis. In clinical trials, compared to placebo, ocrelizumab showed a pronounced effect on disease activity. At all time points, ocrelizumab showed to be effective in slowing disability progression in comparison to placebo for people with primary MS. At 24 weeks, the percentage of people with disability progression on ocrelizumab was 29,6% compared to 35,7% in the placebo group. In other study, ocrelizumab was compared to interferon beta-1a. Treatment with ocrelizumab reduced the relapse rate by 46% compared to interferon beta-1a. People on ocrelizumab also showed a 40% lower risk of disability progression compared to interferon beta-1a. On magnetic resonance imaging ocrelizumab reduced the number of active lesions by 94% compared to interferon beta-1a. The side effects in both studies were reactions to the infusion, respiratory infections and oral herpes infections. However, by changing the way the infusion was given after the first dose, reactions to infusion were often reduced. Ocrelizumab gives hope for a better treatment of MS but studies must continue to monitor and analyze the safety of the drug.

Keywords: *multiple sclerosis, ocrelizumab, side effects*

SWITCHING OF MEDICINES FROM PRESCRIPTION TO OTC STATUS - ESSENCE, METHODS AND ROLE OF PHARMACIST

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Introduction: Self-treatment is becoming the primary target for healthcare users. The availability of OTC medications makes it possible for patients to treat numerous ailments without constant control of a health care professional. Many of the medications now available without a prescription were previously classified as prescription-only products. The process of reclassification from prescription medications to Over-the-counter medications is known as Rx to OTC switching.

Materials and Methods: This review article contains summarized information from available literature sources in national and international journals about the role of the pharmacist in advising patients on the correct use of new OTC products obtained after the switching process.

Results: To improve easy access to a safe and effective drug, it is possible to 'switch' the Rx medications to over-the-counter status after the initial prescription marketing if the post-marketing safety data of the prescription version of the medication reiterates the safety, effectiveness and ease of use.

Conclusions: The process of Rx to OTC switching, requires pharmacists to focus on counseling patients to properly and responsibly use of this type of medicinal product. Self-treatment provides patients the ability to diagnose their own condition and pick an appropriate medication from the pharmacy to treat their symptoms. This process allows a certain freedom for consumers to actively engage in their own health. In order for patients to self-treat, access to over-the-counter (OTC) medication is of prime importance.

Keywords: *Switch, OTC medication, Prescription medication, Safety, Effective, Pharmacist.*

MODERN METHODS OF EXTRACTION OF BIOLOGICALLY ACTIVE COMPOUNDS

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Introduction: Biologically active compound (BAC) from herbal substances play a key role in the treatment of a wide range of diseases. As many BAC cannot be chemically recreated because of their complex structure, extraction remains the only way to obtain them. The process of extracting BAC is often a difficult one because of the varied chemical structure of BAC, the hard plant cell wall, the presence of accompanying compounds, the low concentration of BAC in most plant substances and the chemically unstable nature of BAC. Methods of extracting BAC are constantly evolving in order to improve the purity, safety and stability of the BAC as well as to shorten the extraction time and lower the costs.

Material and Methods: This review summarizes the most important innovations in the methods of extraction during the last 20 years based on literature found in the Scopus database.

Results and Conclusion: In the foreground of modern extraction techniques are Ultrasound assisted extraction (UAE), microwave assisted extraction (MAE), enzyme assisted extraction (EAE), agitation extraction (AE), pulsed electric field, supercritical fluid extraction (SFE), use of Ionic liquids (IE), pressurized liquid/fluid extraction (PLE or PFE), counter-current Extraction (CCE), liquid nitrogen extraction and others. These techniques of extraction are often used in combination with traditional extraction techniques in order to widen their range and to achieve a higher yield of the BAC. They offer not only better efficacy but also are quicker, economically viable and often more ecological.

Keywords: *biologically active compounds, extraction techniques, herbal substances*

ONE OF THE MOST EXPENSIVE METALS WITH APPLICATION IN IMAGING DIAGNOSTIC

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Tehnetium (Tc) is one of the most expensive metals. It cannot be found in nature, and is fairly unknown for a chemical element, that's given such a boost in the development of nuclear medicine. All of its isotopes are radio active and those which find application in the nuclear medicine are Tc99m and Tc94m. The Tc99m is a gamma emitter with half-life of 6 hours and is used in SPECT and SPECT-CT. The Tc94m is a positron emitter with a half-life of 52 minutes and usually used in PET-CT diagnostics. About 80% of the imaging studies are realized using Tc99m. In Varna, radiofarmaceuticals labeled with Tc99m have been in use for more than 50 years.

Keywords: *Radiofarmaceuticals, Tehnetium (Tc), gamma camera, SPECT-CT, labelling, radiochemistry, nuclear medicine, „cold kits“*

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THERAPEUTIC ROLE OF SV2A LIGANDS – “RACETAM” DERIVATIVES FOR EPILEPSY TREATMENT

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Synaptic vesicle glycoprotein 2 (SV2) is a prototype protein identified in the synaptic vesicles of neurons and endocrine granules. SV2 consists of three isoforms: SV2A, SV2B, SV2C. The most common isoform SV2A is expressed predominantly in the brain including the cortex and the hippocampus. It regulates neurotransmitter exocytosis by enhancing action-potential dependent neurotransmitter release from the nerve terminals and also by modifying the expression of the calcium-sensor protein synaptotagmin on the presynaptic neuronal membrane.

Studies demonstrate that SV2A-knockout mice fail to grow, exhibit severe seizures and die within several weeks, which implies that SV2A takes place in seizure induction. SV2A has been recognized as a binding site for a number of “racetam” derivatives including levetiracetam and brivaracetam. These antiepileptic drugs are indicated in partial seizures, myoclonus and generalized tonic-clonic seizures.

Levetiracetam is a widely used drug in epilepsy, especially in the benzodiazepine-resistant type. This drug binds selectively to SV2A thus modifying the synaptic release of the crucial brain neurotransmitters glutamate and GABA. Brivaracetam, a related newer antiepileptic drug, binds to the same target but with ten-fold higher affinity. Additionally, both drugs inhibit N-type calcium channels and prevent the release of calcium. Levetiracetam and Brivaracetam possess non-classical anti-epileptic mechanisms of action and favorable pharmacokinetic profile (oral use, high oral bioavailability and renal excretion in unchanged form), do not exhibit central depressant effects, and are characterized by low incidence of drug interactions. All these features make them suitable for more vigorous prescribing in some forms of epilepsy.

Keywords: *Synaptic vesicle glycoprotein 2, antiepileptic drugs, mechanisms of action, pharmacokinetic profile*

OBESITY AND DEPRESSION – POSSIBLE CONNECTIONS

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Introduction: Obesity and depression at first sight are two different disorders. Nowadays there is accumulating evidence that they emerge together. Different studies have shown similar biological pathways in their development, and that the presence of one disease increases the chances of developing the other.

Aim: The aim of the present paper is to review the possible cross-link between obesity and depression as two interrelated diseases exploring the similar biological pathways for their manifestation, their mutual influence to each another and the social factors underlying them.

Materials and methods: The literature was accessed through PubMed and ScienceDirect using key words: “obesity”, “depression”, “Indoleamine 2,3-dioxygenase”, “cytokine”.

Results: Several studies have examined a potential link between chronic stress and the hypothalamus – pituitary gland – adrenal axis dysregulation, which has been associated with different eating disorders leading to obesity. Obesity is known as pro-inflammatory state, thus accompanied by elevated levels of cytokines such as IL-6, TNF alpha and CRP. Some inflammatory cytokines may induce indoleamine-2,3-deoxygenase expression that shifts the metabolism of tryptophan from serotonin synthesis to kynurenic acid, 3-hydroxykynurenine and quinolinic acid. As a result, the amount of tryptophan is depleted and serotonin levels decrease. Dysregulation of the kynurenine pathway could result in hyper- or hypofunction of active metabolites, associated with psychiatric disorders such as depression and schizophrenia. We should mention that other factors such as environment and lifestyle, gender and age also play a role in the manifestation of obesity and depression.

Conclusion: Studies in this area are faced with difficulties due to the different types of depression and its extremely varied clinical picture, which may vary from patient to patient. Future researches are needed to recognize different molecular pathways involved in interplay between obesity and depression.

Keywords: *obesity, depression, inflammation, indoleamine 2,3-dioxygenase*

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BORON NEUTRON CAPTURE THERAPY (BNCT) FOR TREATMENT OF HIGH GRADE GLIOMAS

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Boron neutron capture therapy (BNCT) is a unique modality in which neutron beams destroy only boron compound-bearing tumor cells while leaving the surrounding normal tissues intact. BNCT is a highly selective form of radiotherapy in comparison to particle radiotherapy using protons and carbon-ions. It is useful for treating locally invasive malignant tumors such as primary brain tumors – mainly gliomas, especially glioblastoma multiforme, and recurrent head and neck cancer.

The patient is first injected with a tumor-localizing drug which contains the non-radioactive isotope boron-10 and then the patient is radiated with epithermal neutrons, which source is a nuclear reactor or, more recently, an accelerator. Non-radioactive isotope ¹⁰B atoms absorbs low-energy thermal neutrons and subsequently breaks up into an α particle (⁴H) and a recoiled lithium nucleus (⁷Li). These particles provide high energy along their very brief pathway (<10 μ m), and because of that, their energy deposition is limited to the diameter of a single cell. Only neoplastic cells with ¹⁰B are ravaged following thermal neutron irradiation. Targeting is primarily achieved by precisely establishing the boron drugs in the tumor rather than by aiming the beam.

BNCT is an alternative treatment modality for patients with high grade gliomas. Compared with γ -ray and reactor neutron irradiation, a higher relative biological effect can be achieved upon treatment of glioma cells with BNCT. Its success is due to inducing glioma cell apoptosis. All these features make BNCT suitable for vigorous use in treatment of gliomas.

Keywords: *Boron neutron capture therapy; radiotherapy; oncology; tumors; gliomas;*

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OSTEOCALCIN – IS IT JUST A VITAMIN K DEPENDENT PROTEIN?

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Osteocalcin is a protein, synthesized by osteoblasts, that undergoes a vitamin K-dependent post-translational gamma-carboxylation. The carboxylated form of the protein (cOC) incorporates in the bone matrix. During bone resorption cOC is decarboxylated and is released in the circulation in its un(der)carboxylated form (ucOC).

Although specific to bone, the skeletal functions of osteocalcin remain unclear. The active form of the protein is the carboxylated one due to its ability to bind hydroxyapatite. It has been found to improve mechanical function and to increase the fracture toughness of bones. Clinical and epidemiological studies show efficacy of vitamin K to reduce fracture risk in patients with osteoporosis – an effect believed to be mediated by cOC.

Recent experimental work on genetically modified mice revealed that ucOC possesses hormonal activity. It regulates energy metabolism through stimulation of insulin secretion and improvement of insulin sensitivity in skeletal muscles and adipose tissue. In mice, carboxylated form of osteocalcin seems to be inactive as a hormone. However, human data is not so emphatic. Clinical studies have found positive and negative correlations of both cOC and ucOC with various markers of energy metabolism, suggesting that both forms of the protein might function as a hormone in humans.

Osteocalcin is involved also in the regulation of male murine fertility. Experimental studies reveal that it induces testosterone production by binding to specific receptors in the Leydig cells. Mutations of the same receptor in humans have been found in patients with primary testicular failure, suggesting that osteocalcin modulates reproductive function also in humans.

In addition, osteocalcin seems to be involved in regulation of behavior. It passes through the blood-brain barrier and influences the synthesis of brain neurotransmitters. Deficiency of ucOC in mice is associated with anxiety, depression and cognitive impairment. There is only limited data on the impact of osteocalcin on human cognition.

Keywords: *osteocalcin, posttranslational gamma-carboxylation, effects of osteocalcin*

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CHEMISTRY OF SLEEP: THE ROLE OF MELATONIN AS A DIETARY SUPPLEMENT

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Introduction: Melatonin is a natural hormone produced by the pineal gland, which is located near the middle of the brain. It's sometimes called the "Dracula of hormones" because it's only released in the dark. Melatonin used as medicine is usually made synthetically in a laboratory. Melatonin comes in different forms: capsules, tablets, liquids, sublingual and subbuccal forms. Sublingual and subbuccal forms enter melatonin directly into the bloodstream. This administration may provide better bio-availability.

Melatonin supplements are often recommended for sleep problems involving sleep cycles, such as jet lag or irregular night shift work, for sleep disorders due to side effects from beta-blockers, from stopping benzodiazepine drugs or from quitting smoking. Melatonin may also be given for insomnia linked to attention deficit-hyperactivity disorder and autism in children.

Aim: The aim of this study is to overview possible effects of melatonin supplements used for sleep issues.

Materials and Methods: Literature was accessed through National Sleep Foundation, National Institutes of Health, Office of Dietary Supplements, Google, WebMD and research of melatonin products on the pharmaceutical market.

Results: Research shows that melatonin is likely effective for several sleep issues. Studies mention melatonin can encourage sleep in children who suffer from insomnia related to autism, mental retardation and other central nervous system disorders.

Conclusions: A key factor in how human sleep is regulated is exposure to light or to darkness. Melatonin's main job in the body is to regulate night and day cycles or sleep-wake cycles. Darkness causes the body to produce more melatonin, which signals the body to prepare for sleep. Light decreases melatonin production and signals the body to prepare for being awake. Some people who have trouble sleeping have low levels of melatonin. It is thought that adding melatonin from supplements might help them sleep.

Keywords: *Melatonin supplements, night and day cycles*

MICROSCOPIC EVALUATION OF THE EFFECT OF ANETHOLE IN A MODEL OF TRINITROBENZENESULFONIC ACID- INDUCED COLITIS IN RATS

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Introduction: Trinitrobenzenesulfonic acid (TNBS)-induced experimental colitis in rats is a very popular experimental model for screening of potentially beneficial agents in inflammatory bowel disease.

Aim: Using criteria for microscopic evaluation of colonic damage, the present study investigated the effects of anethole (AN) in a TNBS-induced rat colitis model and compared the effect of AN with that of sulfasalazine (S).

Materials and methods: Male Wistar rats (200-250 g) were divided into 6 experimental groups, each of 10 rats: Control, TNBS, TNBS+AN62.5, TNBS+AN125, TNBS+AN250 and TNBS+S. Colitis was induced by TNBS (10 mg dissolved in 0.25 ml of 50% ethanol) applied in the colon by a soft cannula at a depth of 10 cm from the anus. Control rats received 0.25 ml of 50% ethanol. The oral treatment of the animals began on the 2nd day (24 hours after the induction of colitis) and lasted until the 6th day of the experiment. The animals were treated orally using an orogastric cannula. Groups Control and TNBS were treated with sunflower oil (10 ml/kg). Groups TNBS+AN62.5, TNBS+AN125, TNBS+AN250 were treated with AN at doses of 62.5 mg/kg, 125 mg/kg and 250 mg/kg dissolved in sunflower oil to a total volume of 10 ml/kg. Group TNBS+S was treated with S at a dose of 400 mg/kg dissolved in sunflower oil to a volume of 10 ml/kg. On the 7th experimental day, the animals were sacrificed and colon samples were fixed in formalin. Severity of colitis was microscopically evaluated and scored with numbers from 0 to 3 regarding epithelium injury and inflammatory cell infiltration, respectively.

Results: The results showed that TNBS caused a diffuse or zonal destruction of intestinal wall and inflammatory cell infiltration reaching the muscularis mucosae or the submucosa or muscularis propria. The score of epithelium injury was the highest in TNBS group. In all TNBS+AN groups, gradual but not statistically significant improvement of the epithelium injury score was observed corresponding to the increase of AN dose. The lowest epithelium injury was observed in S-treated rats where the score was significantly lower than that of TNBS group ($p < 0.001$). Regarding the inflammatory cell infiltration, the highest score was observed in TNBS and TNBS+AN125 groups. The score was slightly better in TNBS+AN62.5 and TNBS+AN250 groups. The S-treated rats showed the lowest score with a significant difference ($p < 0.01$) compared to TNBS group.

Conclusion: AN caused a tendency to decrease TNBS-induced damage in the experimental model of colitis probably due to its antioxidant and anti-inflammatory properties. The effect of AN was lower than that of sulfasalazine.

Keywords: TNBS, colitis, anethole, sulfasalazine, rats

PRICING OF MEDICINAL PRODUCTS PREPARED BY A MAGISTRAL AND PHARMACOPOEIAL RECIPES IN PHARMACY

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Introduction: The preparation of various formulations of the magistral and pharmacopoeial formulations is highly specific activity for the pharmacy and its staff. In spite of the faster development and modernization of the production processes, the pharmaceutical forms prepared in the pharmacy settings have unquestionable advantages. Through them, an individual approach to each patient can be acquired and the maximum therapeutic effect can be achieved.

Aim: The main purpose of our study is to look in detail at the legislative pricing aspects of the magistral and pharmacopoeial recipes in Bulgaria. It was also explored the profitability of such kind of activity in one community pharmacy.

Materials and Methods: The study features critical analysis and comparison of current regulations for pricing of medicines prepared by pharmacists in Bulgaria and some other European countries, as well as some practical examples of its application. For the pharmacoeconomic calculations, data was taken from the diary of pharmaceutical extemporaneous.

Results: The results of the study showed, that Bulgaria has a relatively modest pricing legislation for magistral and pharmacopoeial preparations compared to other countries in Europe. Prohibition of putting surplus charge on active pharmaceutical ingredients is a specific rule only for our country. Pharmacoeconomic calculations showed, that running a community pharmacy business only preparing extemporaneous medicinal products is very thorny.

Conclusions: As a conclusion we can say that pricing in Bulgaria is not sufficiently regulated. Changes in the current regulatory framework must be made to clear and precise the criteria laid in the final price of the pharmaceutical forms.

Keywords: *Pricing, medicinal product, magistral, pharmacopoeial, pharmacy*

INTRANASAL APPLICATION OF CORTICOSTEROIDS IN CHILDREN WITH ADENOIDAL HYPERTROPHY

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Introduction: Corticosteroids are steroid hormones that are produced by the adrenal glands. Their synthetic analogs are potent anti-inflammatory drugs. Adenoidal hypertrophy (AH) is the unusual growth of the adenoid tonsil that can cause an obstruction of the nasal airways. The aim of this study is to assess the effect of intranasal corticosteroid application among children with adenoidal hypertrophy.

Method: A statistical meta-analysis about the impact of corticosteroids on adenoid tissue was performed. Results from randomized, controlled studies comparing the effect of intranasal corticosteroids to placebo in children with adenoidal hypertrophy were gathered and resolved. Data were retrieved for 6 trials with a total of 470 patients. Different symptoms and signs of AH like difficulty breathing through the nose, snoring, obstructive sleep apnea, sore throat, dry mouth, ongoing middle ear infections, were compared before and after the application of corticosteroids and placebo. Parameters like adenoid size were taken to serious consideration.

Results: Significant differences were estimated between patients treated with corticosteroids (mometasone, fluticasone and budesonide) and patients given isotonic saline solution. All patients with corticosteroid treatment demonstrated a decrease in adenoid size, compared with a mixed response to placebo. Nasal inhalation of corticosteroids significantly improved the symptoms of AH. Overall, they had positive impact on some asthma-specific symptoms in patients with both AH and asthma as well. No clinically important side effects were reported.

Conclusion: Properly administered nasal corticosteroid in standard doses can significantly reduce adenoidal hypertrophy and eliminate nasal obstructive symptoms in children.

Keywords: *corticosteroids analogs, adenoidal hypertrophy, statistical meta-analysis*

PHARMACEUTICAL ROLE FOR OPTIMIZING PATIENT RECURRENCE WITH POST-OPERATIVE WOUNDS

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Surgical wounds are most commonly treated in today's global practice. Often, patients after surgery do not know exactly how they should treat their wound at home, which, due to possible complications, is a problem not only for the patient but also for our entire health system.

Objective: To investigate the role of the pharmacist in optimizing the recovery of patients with post-operative wounds.

Materials and Methods: Based on literary sources and guides, a Model for Pharmaceutical Care was developed in patients with post-operative wounds. Patient KH was evaluated using a generic SF12 v2 instrument. The tool evaluates physical, mental health and social functions within the last 4 weeks. SF12 v2. was administered to unconsulted patients in a control group and to a consulted group of patients.

Results: The results show an improvement in all measured parameters in the group of patient consulted.

Pharmacists are the most accessible healthcare professionals who, with their knowledge and competencies, can help the faster recovery and improvement of KZ in patients with post-operative wounds.

Keywords: *Surgical wounds, Pharmaceutical Care, Pharmacists competencies*

CARDIOVASCULAR TOXICITY OF NONSTEROIDAL ANTI-INFLAMMATORY DRUGS – COMPARATIVE REVIEW

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Introduction: Nonsteroidal anti-inflammatory drugs (NSAIDs) inhibit cyclooxygenase (COX) enzymes, which exist in at least two isoforms, COX-1 and COX-2. Newer agents termed “coxibs” are selective inhibitors of COX-2. The purpose of our study is to determine if certain non-steroidal anti-inflammatory drugs (NSAIDs) are associated with increased risk of cardiovascular (CV) events: acute myocardial infarction (AMI), stroke, and death from coronary heart disease (CHD).

Method: We examined the randomized, active- and placebo-controlled studies, observational trials, and meta-analyses evaluating the CV adverse effects associated with long-term and short-term use of COX-2 selective inhibitors (rofecoxib, celecoxib) and non selective NSAIDs (naproxen). The mean age of cohort was 69.6 years, with the majority being female (74%) and had no serious illness prior to cohort entry.

Results: The COX inhibitors associated CV toxicity has multiple manifestations, which include the induction of myocardial infarction (MI), edema, thrombosis, blood pressure destabilization and death. In many clinical studies, rofecoxib use was associated with a higher incidence of cardiovascular thrombotic events when compared with celecoxib and non selective NSAIDs. Possible explanation is decreased vascular prostacyclin (PGI₂) production by selective COX-2 inhibitors that may disrupt the homeostatic mechanisms controlling platelet activation. It has been suggested that non selective agents, such as naproxen, may provide some lesser degree of cardioprotection, but conclusive evidence is lacking.

Conclusion: To reduce the risk of cardiovascular complications during long-term coxib therapy, low-dose aspirin supplementation or less COX-2-selective inhibitor (meloxicam) should be considered.

Keywords: *coxibs, COX-2-selective inhibitor, randomized studies, observational trials, meta-analyses*

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Book

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Book chapter

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SCRIPTA SCIENTIFICA PHARMACEUTICA, volume 4, 2017, supplement 2

Editor-in-Chief: Prof. Diana Ivanova, PhD, DSc

Co-Editor-in-Chief: Assoc. Prof. Svetlana Georgieva, PhD

Design and Layout Editing: Emilia Yordanova

Cover Design: Hristina Hristova

Proofreading: Milka Nashar

Publ. Lit. group: III-3

Sent to print: October, 2017

Print sheets: 20

Format: 8/60x84

Approved for print: October, 2017

Publisher: Medical University of Varna

55 Marin Drinov Street, Varna 9002, Bulgaria

www.mu-varna.bg

ISSN 2367-6000 (print)

ISSN 2367-5500 (online)

<http://press.mu-varna.bg/ojs/index.php/ssp>

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