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Second Pharmaceutical Business Forum with Scientific and Practical Conference  
Faculty of Pharmacy, Medical University of Varna, Bulgaria  
October 30-31, 2015  

PROGRAMME  

October 30, 2015  

09:00 – 10:00 Registration  
10:00 – 10:15 Opening ceremony  
10:15 – 15:30 Oral presentations  

Session 1. Research and Innovations in Pharmacy  
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10:30 – 10:45 Lydia Mihaylova  
Investigating the quality of water used in HPLC and LC-MS  
10:45 – 11:00 Temenuga Trifonova, Gergana Simeonova, Plamen Biyachev  
Option for increased yield of the 18F-FDG synthesis process  
11:00 – 11:15 Nadezhda Ivanova  
Therapeutic drug delivery systems. Transdermal drug delivery systems (TDDS) – advantages, recent achievements and current status of the Bulgarian and global market  
11:15 – 11:30 Stanitsvet Penev, Neli Markova, Valentina Stoilova, Tanya Stoeva, Irena Hineva, Maria Misheva  
Innovation of products with general and local antioxidant effect, based on the results of independent studies on the antioxidant potential of the Bulgarian medicinal plants  
11:30 – 11:45 Antoaneta Georgieva, Iren Belcheva, Steliana Belcheva, Roman Tashev, Stefka Valcheva-Kuzmanova  
Effects of chlorogenic acid, ferulic acid, gallic acid and quercetin on learning and memory in the two-way active avoidance task in young/healthy rats  
11:45 – 12:00 Ivo Kumanov  
Pharmaceutical care – challenges of a new paradigm of our millennium
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13:45 – 14:00 Katya Nedeva, Viktoria Ivanova
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Antimicrobial properties and use of star anise
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14:30 – 14:45 Patrisiya Georgieva, Stanila Stoeva, Krasen Tonev, Dayana Gergova, Totka Cherneva, Svetlana Georgieva, Ivo Kumanov
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14:45 – 15:00 Liliya Bogdanova, Evgeni Grigorov, Ilko Getov, Petko Salchev
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15:00 – 15:15 Radosveta Georgieva
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Radionuclides and radiopharmaceuticals for PET/CT. On-site production of [18F] from cyclotron
3. Olga Antonova, Rada Staneva, Zora Hammoudeh, Savina Hadjidekova, Vedat Sabriev, Elenko Popov, Chavdar Slavov, Draga Toncheva
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4. Bogdan Hadjiev, Bistra Galunska
Molecular mechanisms of vitamin D and androgens in prostate cancer
5. Djeni Cherneva, Dobri Ivanov, Mariana Filipova-Marinova
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6. Galina Vasilieva, Antoniya Kondova, Iliya Zhelev, Kaloyan Georgiev
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7. Stela Dragomanova, Lyubka Tancheva, Marieta Georgieva, Almira Georgieva, Svetlana Stoeva, Reni Kalfin
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12. **Gabriela Kehayova**, Marieta Georgieva
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13. **Simeonka Ivanova**, Marieta Georgieva
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14. **Valentina Belcheva**, Evgeni Grigorov
    Usage of Rx-to-OTC switch as an effective pharmaceutical marketing strategy
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    Clinical Aspects of pro-inflammatory factors MCP-1 and IFN-γ
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    Liposomes - transporters of drugs, destroying cancer cells
24. **Aleksandra Stefanova**, Elena Stoyanova, Dimana Mitsova, Natasha Ivanova
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25. **Erskin Ismail**, Georgi Shopov, Natasha Ivanova
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METABOLOMICS – A NEW ERA IN BIO(PHARMACEUTICAL) ANALYSIS

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The major aim of metabolomics is to identify and quantify all endogenous and exogenous small molecule metabolites in a biological system in a high-throughput manner. Metabolomics has the potential to deliver diagnostic biomarkers for the detection and prognosis of diseases, and the prediction of the efficacy and safety of pharmaceutical treatment. Metabolomics can also provide insights into the biochemical mechanisms of diseases and their modulation by drugs.

The analytical platforms include NMR spectroscopy, mass spectrometry combined with gas or liquid chromatography. Due to the complexity of the metabolome, no single analytical platform can be applied to detect all metabolites in a biological sample.

Different conceptual approaches are used in metabolomics. Targeted (specific) metabolomics is a quantitative approach where a set of known metabolites are quantitated. The identities of metabolites were initially established based on the available databases and using standard compounds; the identified metabolite peaks are then quantified based on internal or external reference compounds. Targeted metabolomics can provide greater insights into the dynamics and fluxes of metabolites. Non-targeted (global) metabolomics aims for a quick and reliable identification of small molecule biomarkers characteristic for a particular physiological state in response to internal or external stimuli. This approach is often used in pharmacokinetic studies of drug metabolism and when looking at the effect of therapeutics or genetic modifications on a specific enzyme.

The development of personalised metabolomics in the future, will give the opportunity to track the trends of the metabolome for personalised drugs and improved treatment strategies.

Keywords: metabolomics, analytical platforms, targeted and nontargeted analysis
INVESTIGATING THE QUALITY OF WATER USED IN HPLC AND LC-MS

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Ninety percent of all difficulties in HPLC systems and columns are caused by column problems, and that most of those problems are caused by contaminated water. Water could be contaminated with particles, bacteria, organics, and ions. Benefits and disadvantages for different water purification technologies are summarized (distillation, reverse osmosis, ion exchange resins, EDI and activated carbon treatment). Contaminants in water, that affect reversed phase HPLC (particles, organics, metal ions and bacteria), are discussed in the focus of sources and recommendations to control them are given.

Trace amounts of pharmaceutical molecules detected in HPLC- and LC-MS-grade bottled water were demonstrated and recommendations for maintaining the quality of high purity water to avoid contamination issues in HPLC are discussed.
OPTION FOR INCREASED YIELD OF THE $^{18}$F-FDG SYNTHESIS PROCESS

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Introduction: 2-$[^{18}]$Ffluoro-2-deoxy-D-glucose ($[^{18}]$FDG) is the most commonly used radiopharmaceutical in clinical molecular imaging. The process of FDG synthesis is under constant development to optimise and increase yields.

Aim: Review of $[^{18}]$FDG radiopharmaceutical production with ABT cyclotron and chemistry module. Materials and methods: The $^{18}$F radionuclide we work with, is the product of a $^{18}$O (p, n)$^{18}$F nuclear reaction by irradiation (30-45 min) of enriched $[^{18}]$O$\text{H}_2\text{O}$. Our process of choice for FDG production is nucleophilic fluorination using mannose triflate as precursor and Kryptofix because of the proven high yields and short reaction time. Synthesis itself is achieved by nucleophilic substitution and acid hydrolysis with passive cooling (air at room temperature) or an active one (CO$_2$ gas). The quality of each dose is checked by an automatic QC system and 4 manual QC tests. The QCM automatically performs pH determination, residual solvents (acetonitrile and ethanol), radiochemical identity/purity, Kryptofix 2.2.2. determination, and filter integrity test.

Results: We have observed a huge difference in dose activity when using the two different types of cooling. Between 10 and 16 mCi with passive cooling and 14 and 26 mCi when using active CO$_2$ cooling. The heightened dose activity is a result of cutting the overall synthesis time.

Conclusions: Active CO$_2$ gas cooling leads to shorter synthesis times and higher yields without affecting the quality of the end product $[^{18}]$FDG.

Keywords: $[^{18}]$FDG, Radiopharmaceuticals, PET/CT biomarkers, $[^{18}]$FDG synthesis
Therapeutic systems (TS) are contemporary drug delivery forms, designed to improve the therapeutic potential of drugs through maintenance of therapeutic drug levels for extended period of time. TS provide controlled or sustained drug release, intended to reach the systemic circulation or remain and act locally on the site of application. Transdermal Drug Delivery Systems (TDDS) are pharmaceutical preparations to be applied to the intact skin for systemic absorption and occupy more than 30% of the global market share of TS. TDDS ensure a constant plasma concentration of the active ingredients in the therapeutic window from 24 hours to 7 days by non-invasive and easy administration. Important advantages of TDDS include avoidance of first-pass metabolism and gastro-intestinal adverse effects, improved drug stability and etc. First generation TDDS (Transderm-Scop, Transderm-Nitro, Estraderm, Nicoderm and etc.) accomplish remarkable success and benefits in the treatment of motion sickness, angina pectoris, quit smoking and contraceptive therapy. The constantly growing scientific interest and adjustment of well-known physical and chemical methods (as iontophoresis, sonophoresis, microneedles and etc.) to TDDS as additional force to enhance drug permeation through stratum corneum, leads to next TDDS generations by overstepping beyond the preferable TDDS stereotype of the small, less than 300 Da, molecule with balanced lipophilicity. The number of the TDDS on the market increases every year, as the highest progress is observed in the field of Central Nervous System’s diseases - dementia, depression, Parkinson, migraine. The market share of TDDS on the global pharmaceutical market reaches up to 12% and is estimated to be approximately 31.5 billion, while their role and disposal on the Bulgarian market is still limited.
INNOVATION OF PRODUCTS WITH GENERAL AND LOCAL ANTIOXIDANT EFFECT, BASED ON THE RESULTS OF INDEPENDENT STUDIES ON THE ANTIOXIDANT POTENTIAL OF THE BULGARIAN MEDICINAL PLANTS

Stanitsvet Penev, Neli Markova, Valentina Stoilova, Tanya Stoeva, Irena Hineva, Maria Misheva

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Based on the results of an independent study of the antioxidant properties of aqueous extracts from traditional Bulgarian medicinal plants by the research team of the Department of Biochemistry, Molecular Medicine and Nutrigenomics of the Faculty of Pharmacy in the Medical University of Varna, Pharmaceutical laboratories THALLODERMA presents two new products with local and general antioxidant focus - Thallderma VITA, Face Cream, Antioxidant and Thallderma NUTRICA, tincture, Antioxidant developed.
EFFECTS OF CHLOROGENIC ACID, FERULIC ACID, GALLIC ACID AND QUERCETIN ON LEARNING AND MEMORY IN THE TWO-WAY ACTIVE AVOIDANCE TASK IN YOUNG/HEALTHY RATS

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The phenolic acids chlorogenic (CA), ferulic (FA) and gallic (GA) and the flavonoid quercetin (Q) are polyphenols abundant in natural food sources. Polyphenols exhibit strong antioxidant properties. There are data that they cross the blood-brain barrier and accumulate in the brain. These substances are tested in different models of impaired memory. The aim of the present study was to investigate their effects on learning and memory processes in young/healthy rats.

Male Wistar rats were treated in the course of 7, 14, 21 and 30 days. Control groups were treated with saline. The other 4 groups received CA, FA, GA or Q at an equal dose of 20 mg/kg. At the end of each period, learning and memory processes were evaluated using the two-way active avoidance task (shuttle box). The number of avoidances was recorded in two learning sessions on two consecutive days and in a retention test 24 h after the 2nd training session. Administered for 7 days, the experimental substances had no significant effects on rat behavior. Applied for 14 days, GA and Q significantly increased the number of avoidances in both training sessions and on the retention test. After 21 and 30 days of treatment all tested polyphenols significantly improved the recorded indices of memory. The onset of the effect after 14/21 days of treatment may be explained by the accumulation of polyphenols in the brain following a long-term consumption. Our results suggest that CA, FA, GA and Q, applied subchronically, improve memory and cognition of young/healthy rats.
More than two decades ago, Charles D. Hepler and Linda M. Stand indicate the necessity of elaboration and practical implementation of an appropriate philosophy of pharmaceutical practice and its organizational structures. They term this philosophy ‘pharmaceutical care’ and its organizational structures ‘pharmaceutical-care system’. Pharmaceutical care provides drug therapy for the achieving of definite outcomes that improve a patient’s quality of life, namely: cure of a disease; reduction or elimination of symptoms; arresting or slowing down of a disease process as well as preventing a disease or symptoms. During the recent years, convincing evidence accumulates of the feasibility and effectiveness of a variety of interventions immediately associated with pharmaceutical care aiming at improving patients’ relationships with master pharmacists in public libraries. The importance of interactive pharmacy students’ learning for enhancement of their pharmaceutical care competences is emphasized. Hospital pharmacists recommend a broader practical implementation of pharmaceutical care while appreciating the organizational, technical and professional barriers in this respect. It is assumed that collaborative efforts between health authorities and educational institutions, along with the integration of innovative approaches in the management of public and hospital pharmacies and pharmacy education, could contribute to the overcoming these barriers.
A REVIEW OF DRUG STEREOCHEMISTRY

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Introduction: Many of the pharmacologically active substances, used in various pharmaceutical products, are chiral organic compounds and can exist in one of several optically active isomer forms. Usually one of the enantiomers is pharmacologically active, while the inactive enantiomer can show unwanted side effects, and in some cases, even antagonistic or toxic effects can be observed. Therefore, a need for resolution of the enantiomers and for enantiomeric purity control arises.

Aim: To overview the bases of drug stereochemistry with regard to pharmacokinetic and pharmacodynamic parameters of chiral pharmaceuticals, used as single enantiomers or racemates, as well as the analytical methods for isolation and separation of the different enantiomer isoforms.


Results: The different enantiomers and diastereomers of chiral pharmaceutical substances can vary in the terms of their absorption and bioavailability, protein binding and distribution throughout the organism, metabolism pathways and excretion, as well as the extent of the pharmacological activity, therapeutic effect and toxicity. Since obtaining pure drug enantiomers through enantioselective synthesis is not always practical, separation of the racemic mixtures can be achieved with chromatographic and electroseparation techniques, which prove to be more cost-effective.

Conclusions: A better understanding of the pharmacological differences between drug enantiomer forms is required. Furthermore, administration of single enantiomer products rather than racemates or vice versa can lead to treatment options that are more successful. The required resolution of drug enantiomers can be achieved to a desirable extent using modern analytical methods.

Keywords: stereochemistry, chiral drugs, analytical methods, pharmacology
THERAPEUTIC RANGES OF VISCUM ALBUM

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Introduction: Phytotherapy is a method for prevention and treatment in the initial stages of many diseases. There are still many herbs whose medicinal properties are not sufficiently studied and applied in the pharmaceutical industry.

Aim: To present the positive effects of treatment with the medicinal plant Viscum album (mistletoe); to study what part of the population today uses herbs as a method of treatment and to inform about the various effects of Mistletoe.

Methods: An inquiry among people of different ages was conducted and the data was processed; different sources were used to gather information about the researched topic and certain publications in recent years were selected and summarized.

Results: The therapeutic properties of viscum are known and used in folk medicine for many years. Phyto-preparations are more easily used and do not cause toxic changes in the body. However, much of the population today does not know the actions of viscum on the body.

Conclusion: By correct application in the treatment of disease or prevention, viscum not only heals, but also strengthens the body as a whole.

Keywords: mistletoe, treatment, positive effects
ANTIMICROBIAL PROPERTIES AND USE OF STAR ANISE

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Introduction: Star anise (Illicium verum, Schisandraceae) is a Chinese native evergreen tree with wide uses in medicine, perfumery, culinary and other fields. The star-shaped fruit, along with the seeds, has shown to have various pharmacological properties such as carminative, stimulant, diuretic, antirheumatic, antioxidant, analgesic, antibacterial, antifungal and antiviral.

Aim: In the wake of a worldwide antibiotic resistance epidemic it is important to explore various sources of antibiotic alternatives. The aim of this report is to examine the diverse properties of star anise, describe its current use and suggest further research into its potent qualities.

Materials and methods: Gathering and systematizing of information using various research papers from around the world.

Results: The properties are attributed to the numerous compounds including essential oil, polyphenols, anthocianins, tannins and phenolic acids. Around 90% of the world's star anise crop is used for extraction of shikimic acid, a primary precursor in the pharmaceutical synthesis of anti-influenza drug oseltamivir (Tamiflu®). Numerous in vitro studies have shown that extracts from the fruit of star anise show antimicrobial activity against infamous pathogens such as Staphylococcus aureus, Escherichia coli, Pseudomonas aeruginosa, Candida albicans and Aspergillus flavus. A study reports that crude extract of star anise is also active against some of the most common fish pathogens and could be used instead of antibiotics to treat fish.

Conclusions: These facts could serve useful by diminishing the antibiotic overuse and thus help against the development of antibiotic resistant "superbugs".

Keywords: star anise, antimicrobial, resistance
SOFOSBUVIR/LEDIPASVIR – NEW PHARMACEUTICAL APPROACH AGAINST HEPATITIS C

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Introduction: Hepatitis C is an inflammation of the liver, which is caused by a hepatitis C virus (HCV). Over 170 million people worldwide are infected with HCV. The present treatment of hepatitis C includes pegylated interferon alpha and ribavirin for 24 to 48 weeks.

Aim: Review of the new medicines against hepatitis C.


Results: On October 10, 2014, the fixed-dose combination ledipasvir-sofosbuvir (Harvoni®) was approved by the FDA for the treatment of chronic hepatitis C genotype 1 infection in adults. Ledipasvir is a potent inhibitor of HCV NS5A, a viral phosphoprotein that plays an important role in viral replication, assembly, and secretion. Sofosbuvir is a nucleotide analog inhibitor of hepatitis C virus NS5B polymerase – the key enzyme mediating HCV RNA replication. The treatment with this combination is suitable for naïve and treatment-experienced patients. Its duration depends on prior treatment experience and the presence or absence of cirrhosis. Genotype 1 treatment-naïve patients with or without cirrhosis: 12 weeks. Genotype 1 treatment-experienced patients without cirrhosis: 12 weeks. Genotype 1 treatment-experienced patients with cirrhosis: 24 weeks.

Conclusions: The fixed dose combination of ledipasvir-sofosbuvir provides a very attractive and effective one pill once a day option for treatment of genotype 1 chronic hepatitis C infection. This regimen is the first FDA-approved interferon- and ribavirin-free regimen to treat hepatitis C.

Keywords: ledipasvir, sofosbuvir, hepatitis C, HCV NS5A, HCV NS5B polymerase
ADVANCED DRUG TREATMENT OF CHRONIC LYMPHOCYTIC LEUKEMIA (CLL)

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Introduction: In the context of the increasing number of neoplastic diseases, which have become a leading reason for death during last years, and the related to that drug resistance, it is important new pharmaceutical approaches to be found. CLL is the most commonly diagnosed adult leukemia and approximately one-third of all cases of leukemia. Chemotherapy has been the standard-of-care for CLL, but a considerable progress in treatment has been made with the introduction of anti-CD20 monoclonal antibodies, B-cell receptor (BCR) kinase inhibitors and PI3Kδ kinase inhibitors.

Aim: To review the drugs' development and the breakthrough therapy for CLL, represented by ofatumumab (Arzerra®), obinutuzumab (Gazyva®), ibrutinib (Imbruvica®) and idelalisib (Zydelig®).

Materials and methods: Systematic review of web databases on the problem.

Results: Four new drugs (two monoclonal antibodies-ofatumumab, obinutuzumab and two kinase inhibitors-ibrutinib, idelalisib) for CLL have been approved by the FDA during the last few years. These targeted drugs can offer the possibility of chemotherapy-free treatment, especially in cases of poor response to chemotherapy, geriatric patients with comorbidities and contraindications. They have shown significant activity in patients with refractory or relapsed CLL. Clinical trials reveal improved progression-free survival in comparison with previous generations anti-CD20 antibodies, kinase inhibitors or chemotherapy.

Conclusions: CLL treatment strategy has changed dramatically with the regulatory approval of ofatumumab, obinutuzumab, ibrutinib and idelalisib in the past 2 years. The introduction and evolution of targeted therapy for CLL has the potential to reduce the need of chemotherapy in future.

Keywords: ofatumumab, obinutuzumab, ibrutinib, idelalisib
DESTRUCTION OF EXPIRED MEDICATIONS – REVIEW OF THE REGULATIONS IN BULGARIA

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Introduction: The proper management of unused and expired pharmaceuticals by community pharmacies, wholesalers and pharma companies in Bulgaria is a long and hard process. Drugs should be treated as dangerous products, so only specially licensed companies for waste transportation and destruction are allowed to deal with expired medicines. In order to protect our natural resources and keep medication out of the hands of our children, animals ect. the best way of drug destruction is incineration.

Materials and Methods: The aim of this study is to compare the Bulgarian regulations for destruction of expired drugs to best practices in other countries, European union and USA.

Results: Before the process of destruction of drugs in Bulgaria, there has to be a set of documentation prepared and submitted to the Bulgarian Drug Agency (BDA). This set consists of several documents, certifying permission by different authorities for destruction of the listed expired drugs. A part of the requested documentation is a list of pharmaceuticals, which must include: brand name, manufacturer, dosage form, package size, batch number. Only after the order is disclosed by the Bulgarian Drug Agency, the expired medications could be submitted for destruction by incineration. In our country we have only one working incinerator in Bulgaria. It is situated in Sofia and unfortunately does not work all the time, which leads pharmaceutical companies to prefer contracting a company for transportation and destruction of expired drugs abroad.

Conclusion: The problem of destruction of expired drugs is ongoing not only in Bulgaria, but also in many other countries. To avoid the risks of abuse and accidental poisoning, as well as other problems that unused, unwanted or expired pharmaceuticals pose, they shouldn't be kept in homes. If thrown away or flushed down a toilet, however, antibiotics, hormones and other drugs can get into lakes, rivers and other water supplies, where they can affect humans and animals, the researchers said. Many countries have implemented national strategies and programs for unwanted drug returns in open pharmacies and then for them to be returned back to sponsor companies. However, considering the current Regulations and situation in Bulgaria, Pharmaceutical companies are not motivated to support drug return.

Keywords: expired drugs, pharmacy companies, patient, medication
DOCTOR SMARTPHONE

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Most people interested in a healthy lifestyle using their smartphones to track the movements during the day, training, food choices, the quality and quantity of sleep using different applications. Do smartphones hold the key to the future of medicine? I assume medical diagnostics will spread outside the hospitals, laboratories, drugstores, etc. Now there is a growing trend of making use of consumer technology to aid medical research and diagnosis. Big IT companies like Apple and Google announced their products to help this project grow. The main advantages of such approach are two: save time and everyone can join. This sort of technology is still in its infancy at the moment but hopefully we are going to see it grow and grow over the next few years.
NOVEL NITRATO COMPLEXES OF PLATINUM(II) WITH EXPECTED CYTOTOXIC ACTIVITY. STRUCTURAL AND SPECTROSCOPIC STUDIES

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The final goal of the present investigation is the development of new cytostatic agents belonging to the class of the non-conventional platinum-based anticancer drugs. Such compounds, more or less, differ in their structure and mechanism of action from the parent drug cisplatin, but, at the same time, retain their activity against cisplatin-resistant tumors.

Main results, materials and methods: In continuation of our systematic studies of N-3-pyridinylmethanesulfonamide (PMSA) and its Pt(II) and Pd(II) complexes, here we report the synthesis and physical characterization at experimental and theoretical level of two novel complexes of Pt(II): cis- (1) and trans-[Pt(PMSA)₂(NO₃)₂] (2). The structure of 1 has been solved by single crystal X-ray diffraction: orthorhombic; Pbcn; a = 19.8017(6), b = 9.8042(3), c = 24.0279(8); Z = 8; R int = 0.044, and compared with the quantum-chemically calculated one (HF ab initio level with 6-31++G(d,p)/LANL08-ECP basis sets). The analysis of the X-ray powder pattern of 2 revealed the following unit cell parameters: triclinic; P1; a = 16.149(6), b = 19.744(7), c = 7.486(4), α = 96.00(4), β = 94.66(2), γ = 93.55(9); Z = 2. The complexes have also been characterized by IR and NMR (¹H, ¹³C and ¹⁹⁵Pt) spectroscopy.

Conclusion: A good agreement between the experimental and calculated physical properties of complexes 1 and 2 has been achieved. Their cytotoxic activity evaluation is now in progress.

Keywords: Platinum; N-3-pyridinylmethanesulfonamide; Cytostatic; Spectroscopy; Crystallography; Quantum chemistry.

Acknowledgements: The work is part of the bilateral cooperation BAS-AUTh, 2012-2015, and was partly supported by the EC programme HORIZON2020, Grant Agreement Number - 675121 – VI-SEEM.
Aim: A brief review of radionuclides and radiopharmaceuticals for PET/CT. Our experience with cyclotron and “dose on demand” production of $^{18}$F FDG. Comparison between workflow with imported $^{18}$F FDG and the FDG produced on site, in our own facility.

Materials and methods: The two raw materials we need for the $^{18}$F production are Hydrogen and $^{18}$O enriched water. The hydrogen gets ionised by high voltage in an ion source. Then the protons are accelerated by the Dee halves (and RF voltage) in magnetic field. The accelerated beam bombards a HAVAR® window target. During the bombardment of the $^{18}$O water inside the target a (p,n) nuclear reaction occurs and $^{18}$F is produced as a result.

Results: With imported $^{18}$F FDG we used to examine 11 to 13 patients per day with 17GBq of activity (on arrival out of initial 37GBq at factory). Now that we produce our own FDG we examine the same amount of patients with no more than 3,7GBq of activity. On average 2000 patients undergo PET/CT imaging at our hospital annually.

Conclusion: Advantages of the on-site production: by producing our own $^{18}$F FDG we gain independence from severe weather conditions, delivery schedules, national holidays, insufficient dose activity, the dose is there when we need it, lower price for a dose, etc.

Keywords: radionuclides, radiopharmaceuticals, $^{18}$FFDG, cyclotron
EXPRESSION ANALYSIS OF BLADDER TUMORS FOR CHEMOTHERAPEUTIC DRUG SENSITIVITY DETERMINATION

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Introduction: Bladder cancer is a multifactorial disease with increasing frequency in the economically developed countries.

Aim: The primary endpoint of this study was the evaluation of the genetic image of bladder tumors in connection to common anticancer drugs.

Materials and Methods: A total of 50 samples were analyzed. 41 samples were from transitorial cell bladder cancer (stages pTa, pT1 and pT2), 6 samples were from chronic inflammatory process (precancerous) and three - negative controls. The gene expression analysis of 168 genes were carried out with two panels for Cancer Drug Resistance & Metabolism PCR Array, Qiagene (84 genes) and PAHS-507 Z - Human Cancer Drug Targets PCR Array, Qiagene (84 genes).

Results: The results showed significant up-regulation of the genes: CYP1A1, CYP3A5, AR, CLPTM1L, CCNE1, MVP, TOP2B, AHR and PPARG in the bladder cancer samples compared to the negative control. A statistically significant difference (p <0.0001) was found in the expression levels of EGFR, ERBB2, ERBB4, ABCC1, ABCC3, ARNT, CYP1A1, CYP3A5, EPHX1, MVP and PPARG genes in muscle invasive (pT2) versus non-invasive bladder tumors (pTa and pT1). These genes are involved in the formation of multi-drug resistance and in the metabolism of steroid hormones, cyclosporins, polycyclic aromatic hydrocarbons, as well as some anticancer drugs like Vincristine, Taxol and Thiopurine. The obtained data show the significance of the genes as possible targets in clinical trials for the treatment of bladder cancer.

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MOLECULAR MECHANISMS OF VITAMIN D AND ANDROGENS IN PROSTATE CANCER

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Introduction: Prostate cancer (PCa) is the most commonly diagnosed non-skin malignancy among men. The recent studies suggest an important role of vitamin D in prevention prostate cancer. Androgens seem to be involved also in the protective effect of vitamin D against PCa, interacting with VDR receptor and other molecular mechanisms that increase the calcitriol protective effect in prostate.

Aim: To review the literature from the last 5 years about the molecular mechanisms of vitamin D and androgens related to PCa.

Materials and methods: The MEDLINE database of references and abstracts on life sciences and biomedical topics was used. The data from 155 articles were analyzed for this review.

Results: The results show that vitamin D exerts protective effect against PCa by different mechanisms: cell cycle arrest/inhibition in G1/S phase; activation of pro-apoptotic genes that induce cell apoptosis; anti-inflammatory effect due to its inhibitory effect on cyclooxygenase-2; blockage the angiogenesis by decreasing the vascular endothelial growth factor, and stopping the invasion and metastasis decreasing the α6 and β4 integrins. Androgens promote the growth and regulation of normal prostate cells activating genes related to lipogenesis, thus providing phospholipids for prostate cell membranes. On the other hand there are data showing that calcitriol regulates genes encoding enzymes of lipogenesis including fatty acid biosynthesis. Fatty acid synthase (FAS) was found to be down-regulated by calcitriol. The findings suggest that FAS is involved in the antiproliferative effect of calcitriol in presence of androgens on prostate cancer cells. There are also evidences for interaction between the signaling pathways of calcitriol and androgens.

Conclusions: Further studies need to be done to clarify the molecular mechanisms by which both calcitriol and androgens are involved in PCa development/protection.

Keywords: vitamin D, androgens, prostate cancer, molecular mechanisms
STUDY OF THE CURRENT STATUS OF TRADITIONAL KNOWLEDGE ABOUT HERBS AND THEIR USE AMONG THE POPULATION OF THE NORTHERN BULGARIAN BLACK SEA COAST

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Recent ethnobotanical studies in different parts of the world indicate a trend of gradual reduction of the folk knowledge about herbs and their use. The aim of our study was to examine the current state of that knowledge and the attitude to traditional methods of treatment among the population of the Northern Bulgarian Black sea coast. The study was carried out in different cities and villages from April to June 2015 using the interview technique face to face. Respondents were men and women of different social status and of different age groups, randomly selected.

Descriptive statistical procedures and χ² test were used for the analysis of results. The impact of demographic characteristics on the attitudes of respondents to the herbs and their use was examined by the correlation coefficient of Pearson.

Positive attitude to herbs and their uses were established for 96.85% of respondents, and only 4.32% were indifferent. Among the demographic characteristics only age and gender were ones that affected the answers.

The highest percentage of negative responses to the question „What is your attitude to herbal preparations compared to those of conventional medicine,” was given by people from younger age categories, which outlined the trend of reduced interest to herbs and herbalism among the younger generation. The majority of respondents - 76.68% preferred combined therapy with herbs and synthetic drugs. Relatively large was the share of those who replied entirely on herba treatment - 29.19%.

The results indicated consistent positive attitude of the local population of Northern Bulgarian Black sea coast to medicinal plants and to the traditional methods of treatment. Along with this the impact of modernization of the society on the use of herbs is proven.

Keywords: ethnobotany, folk medicine
AGASTACHE FOENICULUM (PURSH) KUNTZE – CHEMICAL COMPOSITION AND BIOACTIVITY

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Aim: Research of chemical composition and bioactivity of Agastache foeniculum (Pursh) Kuntze.

Materials and methods: Two literary databases (PubMed and Science Direct) were explored.

Main results: The results of the database on the Internet revealed the presence of two groups of biologically active substances in the essential oil: 1. Main volatile compounds: phenylpropanoic and terpene derivatives (estragole, methyl eugenol, pulegone, menthol and isomenthol); 2. Main non-volatile compounds: derivatives of caffeic acid and rosmarinic acid; flavonoids: acacetin and its 3-O-glycoside tilianin; lignans: agastenol and agastinol, diterpenes and triterpenoids, carotenoids, sterols.

The plant is used against gastritis, liver, bile and kidney diseases, headaches and alleviates menstrual pain and pain in facial paralysis. It helps strong recovery after nerve disorders, acts favorably even in the treatment of victims of radiation. The traditional Chinese medicine considers the plants as a symbol of youth and beauty.

Preclinical and Clinical studies of bioactivity of the plant extracts established antimicrobial and antiviral effects, activity, anti-inflammatory and hypocholesterolemic effects, antioxidant and anticancer activity.

Conclusion: Anise is rich in biologically active substances that have various biological effects. There is a need of more in-depth phytochemical studies to identify the single compounds and their biological effects, and possible applications in the medical practice.

Keywords: Anise, chemical composition, essential oil, biological activity
ANTIOXIDANT MECHANISM IN THE PREVENTIVE EFFECT OF MYRTENAL ON ALZHEIMER’S DISEASE PROGRESSION ON EXPERIMENTAL MOUSE MODEL

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Introduction: Alzheimer’s disease (AD) is the most common form of dementia causing problems with memory, thinking and behavior. So far there is no unified theory for AD pathogenesis and effective treatment. Scientific reports indicate many natural substances possessing neuroprotective properties. New studies demonstrated that natural monoterpen myrtenal combines antioxidant and anti-acetylcholinesterase activity. Our unpublished data reveal significant improving effect of myrtenal on cognitive function of rodents.

Aim: Goal of this study is to examine the effect of myrtenal on AD progression using animal model.

Materials and methods: Experimental model of dementia from AD type was produced on male Albino mice via scopolamine treatment (1 mg/kg i.p., 11 days) and was verified with cognitive test (Step through) and biochemical markers: lipid peroxidation and glutathione content in brain. Dement animals were treated simultaneously with myrtenal (20 mg/kg i.p., 11 days). Its preventive effect was evaluated when compared with the effect of lipoic acid (30mg/kg i.p., 11 days) and galantamine (1 mg/kg i.p., 11 days) as referents. Data were analyzed using t-test of Student-Fisher.

Results: Myrtenal produced a significant restoration of cognitive function (with 33%) in dement mice in comparison to scopolamine controls. In healthy rodents, myrtenal had antioxidant activity and decreased significantly brain lipid peroxidation, but in dement animals showed pro-oxidant activity. Administered together myrtenal and lipoic acid demonstrated even better prevention on memory and also decreased established pro-oxidant activity of myrtenal in dement mice.

Conclusion: Analyzed changed parameters (cognitive and biochemical) suggest antioxidant mechanism in myrtenal preventive effect on AD progression.

Keywords: myrtenal, Alzheimer’s disease, lipoic acid, antioxidants, prevention
NEWLY SYNTHESIZED NEUROPEPTIDES WITH CENTRAL NERVOUS ACTIVITY IN MICE

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Aim: Object of present study are two newly synthesized neuropeptides with short chains: analogues of Tyr-MIF – 1 with code P1 and of Nociceptine with code P2.

Materials and methods: On male albino mice we studied the changes in the cognitive functions of animals after 3, 7 and 14-days pretreatment with both compounds (5 mg/kg intraperitoneally- i.p.) via: step through test (for learning and memory), Rot-a-rod test (for muscular coordination) and Hole board test (for exploratory activity). Their potential analgesic effect was evaluated by Acetic acid test and their activity on the central nervous system (CNS) was evaluated via interaction with hexobarbital (HB- 100 mg/kg i.p). Statistics were performed with Student – Fisher test.

Results: On the 3rd day after treatment daily both compounds had no effect on cognitive functions of animals, but on the 7th day the analogue of Tyr-MIF – 1 (peptide P1) significantly improved the memory (by 60%) and decreased also the exploratory activity of treated animals. The analogue of Nociceptine-P2 demonstrated significant dose-dependent analgesic effect. On the 14th day both compounds improved neuromuscular coordination of animals. In single doses two compounds shorten significantly duration of hexobarbital narcosis (P1 by 40% and P2 by 50%) via unknown mechanism, probably related to functional antagonism between the neuropeptides and hexobarbital on CNS level.

Conclusion: Newly synthesized neuropeptides are promising biological active substances with effect on CNS. The analogue of Tyr-MIF– 1 improves cognitive function of animals and the analogue of Nociceptine has significant dose-dependent analgesic effect.

Keywords: neuropeptides, cognition, analogues
Biological toxins are one of the most serious public health threats. They are cheap, easy to disperse and can cause illness and death even in very small doses. The onset of clinical signs may be delayed - from a few hours to a couple of days. Thus, to evaluate the exposure as a cause for complains is sometimes difficult and indistinguishable from a common illness.

Toxins and other biological threat agents are a perfect alert for those, who are trying to cause panic and to weaken the social and economic stability. The health care community at all levels, mainly those in hospital emergency departments and in private practice, needs to identify the occurrence of an intentional toxin release.

The threat of bioterrorism requires economic, political and medical awareness. It is of importance, that governments (federal, state and local) ensure one efficient infrastructure for managing toxic attacks and spend the necessary funds to support the protection of the public's health, in such a manner as to achieve the best possible results.

Keywords: bioterrorism, biological toxins, toxic attacks, governments
MARINE TOXINS - SAXITOXIN (STX) AND TETRODOTOXIN (TTX)

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Saxitoxin (STX) and tetrodotoxin (TTX) are two of the most poisonous marine biotoxins known. They have a very interesting history, both used as a means for suicide and murder. STX has been announced publicly by the world’s governments as a chemical weapon, which made it attractive for many government agencies and no longer interesting for toxicologists and seafood producers. TTX is known as the toxin of “fugu” and also as the main agent in the zombification rituals in some Caribbean cultures. However, intentional intoxications by STX and TTX are not often as much as badly prepared fugu meals or saxitoxin-infested shellfish.

A precise diagnosis can determine whether a victim has been intentionally intoxicated. The treatment of intoxication by STX and TTX is based on gastric evacuation, symptomatic relief and the body’s natural recovery mechanisms. There are some potential treatment options, but they need more examination and financing to advance.

Keywords: saxitoxin, tetrodotoxin, marine biotoxins, chemical weapon, treatment
HOMEOPATHIC REMEDIES
THAT EVERY HOME SHOULD HAVE

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Homeopathy is a therapeutical method using substances of different origin, thus stimulating the natural
potentiality of the human organism to cope with the disease.
Homeopathy is a sector of medicine, which cures the patient with such substances, which may cause in a
healthy person symptoms similar to those observed in a sick one. For the purpose of homeopathy these sub-
stances are being diluted and made dynamic, and afterwards prescribed in infinitesimal doses. Homeopa-
thy is a completely harmless and applicable also to pregnant women and babies, where the traditional med-
icine commands few drugs.
Homeopathy is the perfect addition to every home “First aid kit”. Acute conditions as traumas, are cured
most often with Arnica Montana, virus diseases cured effectively with Influcid, Oscillococcinum, Pyroge-
nium и Ferrum phosphoricum. In case of fever Belladonna is applied, while in case of nausea and vomit-
ing Ipecac и China rubra are efficacious. Allergic conditions like insect bite, urticarial and heat apoplexy are
well influenced by Apis mellifica. Babies’ colic are influenced by Magnesia phosphorica и Colocyntis, while
painful teething most often by Chamomilla и Dentokind. The relevant dilutions and the frequency of in-
take range from 9СН до 15-30СН, depending on the similarity degree and the strength of complaint on be-
half of the patient.
**HOMEOPATHIC OPTIONS IN CURING MIGRAINE HEADACHE**

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Migraine is the most common kind of headache. It is three times more frequently met in women than in men. Migraine affects 10% of the adult population.

The serious and frequent migraines, accompanied by neurological symptoms are being cured either with prophylactic medicines, or surgically, once the main trigger factors, like pressed peripheral nerve, abnormalities in the neuro-transmitting levels have been established.

The migraine attacks should be cured in the very beginning with one or more of the following types of pain-killers: triptans, non-steroid anti-inflammatory agents, anti-emetics and sometimes opioids, or steroids. The triptans are the newest class among these drugs.

Homeopathy is completely harmless and efficient method of treatment, based on the principle of “like cures like” created in 19th century by Samuel Hahnemann. In most cases the headache can be cured successfully. Prophylactic treatment of migraine is aimed at reducing the frequency, heaviness and the duration of the migraine paroxysms, even to their complete extinction.

Homeopathy can soften up and make the paroxysms less frequent. In most of the cases it comes to serious control and even to cure of the disorder (disease).

A wide range of medicines are being used, the choice being on the basis of accompanying complaints of the patient, like vomiting, photophobia, gluttony, in connection with premenstrual syndrome, upcoming stressful situations, “stage-fright”, strong emotions, menopause, etc. Belladonna, Glonoinum, Gelsemium, Ignatia, Nux vomica, Iris versicolor, and Sepia are widely used in appropriate dilutions from 9CH to 30CH prescribed by a doctor-homeopath.
PHARMACOLOGICAL TREATMENT OF OBESITY AND OVERWEIGHT AND ADVERSE EFFECTS RELATED TO DRUG USE

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Obesity is a global epidemic with serious health and economic consequences. In Bulgaria, 62% of men, 51% of women, and 30% of children of school age are overweight and obese. The pharmacological treatment of obesity should be only a part of an overall strategy of treating the disease. Currently, drug therapy is recommended only in patients with a BMI of \( \geq 30 \text{ kg/m}^2 \), or with overweight and BMI \( \geq 27 \text{ kg/m}^2 \) when associated with concomitant diseases (e.g., hypertension, type 2 diabetes mellitus).

Despite the availability of a large number of preparations, due to serious adverse effects, only a small part have shown sufficiently good results, and have been approved for long-term use.

From 2010 Sibutramine is no longer licensed for clinical use, due to concerns about its cardiovascular safety. Results of the SCOUT study demonstrated that long-term administration of the drug resulted in a significant increase in the incidence of non-fatal myocardial infarction and stroke. Headache is the only adverse effect of Lorcaserin, with frequency more than 5% according to placebo. Depression and anxiety appear with less frequency. In 2012 is recorded a new combination of Topiramate/Phentermin, and 2014 combination of Naltrexone / Bupropione. European Commission for the control of drugs used in humans (CHMP) gave a positive opinion for the combination Topiramate / Phentermin, due to mental and cardiovascular risk over time. Regarding another combination (naltrexone/bupropion SR), there is a warning about rare but severe psychological side effects.
The pharmaceutical companies with a strong heritage of Rx-to-OTC switching use this tool as a key opportunity to market a major brand switches. Certain that it had a valuable business case for recommending the relationship and keen to communicate it for receiving the best possible effect.

First of all a completed a detailed assessment of the company’s track record in growing global brands, its experience of Rx-to-OTC switching and the key benefits like dedicated switch team could bring the reclassification to be realized. This must be complemented by an in-depth strategy for switching several of the prospective leading brands, further showcasing the client’s expertise in action.

The regulatory proposition developed by the pharmaceutical company must provide compelling evidence for safety of the product candidate for OTC switching. The potential to secure a best practice launch and implementation a recommended go-to-market strategy should be underpinned by comparing with the gold standard for the medicine and a rigorous marketing analytical process. This powerful articulation of the business rationale served as a critical platform for high-level discussions with the medical professionals and a vital tool for exploring their synergistic potential.
THE APPLICATION OF EUROPEAN PRACTICES TO THE IMPLEMENTATION OF THE ELECTRONIC PRESCRIPTION IN BULGARIA – OPPORTUNITIES AND CHALLENGES

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Introduction: The digitalization of the health systems is a global tendency, which is gradually increasing in Bulgaria. An essential step to achieve an effective computerized system is the introduction of the electronic prescription. So far some activities and services are electronized in our country. Moreover, local registries and databases are already established. However, a complete software solution and integrated information system for electronic management of the pharmaceutical sector is still missing. The electronic prescription is the indispensable integrative component of the healthcare system, which guarantees the information transmission and at the same time combines the selective databases from different parts of the medical and pharmaceutical sectors. Thus, the electronic prescription is not only a digital version of the standard paper prescribing document, but also a key element for the successful development of e-health platform in Bulgaria.

Aim: To elicit the main characteristics of the electronic prescription models used in the European countries and analyze the implementation possibilities in Bulgaria.

Materials and methods: Conduction of a systematic analysis of the e-health practices in some European countries and Bulgaria and summarize data in specific tables and charts.

Results: Our current study focuses on the main characteristics of the models already applied in some European countries. By extensive comparative analysis we emphasize on the similarities and differences, advantages and possible obstacles during the implementation of the exterior practical experience in our country. Furthermore we analyze European experience in respect to the e-services, which use as a base the structure of the electronic prescription. A SWOT analysis was performed. Finally, we shed light on the readiness of the National Health Insurance Fund to implement the electronic prescription.

Conclusion: For the computerization of the health system it is essential to analyze the experience of the countries which already partially or fully use electronic prescription. The best practices should be taken in mind, when establishing a conceptual and working model for Bulgaria.

Keywords: electronic prescription, electronic registers, e-health
SYSTEM FOR SAMPLE INTRODUCTION IN GAS CHROMATOGRAPHY

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Introduction: Gas chromatography is an instrumental method of analysis, allowing the preliminary separation of complex mixtures of substances and their subsequent qualitative and quantitative determination. The aim is to present the main types of devices for introducing samples in gas chromatography and their manner of operation.

Materials and methods: Survey of the available literature on the topic.

Discussion: In gas chromatography the mobile phase is inert gas, called carrier gas. It carries the analyzed sample by the system for sample introduction (injector, sample inlets) and moves it through the chromatography column, in which the separation occurs, to a detector which registers the eluted compounds, leaving the column in the form of pure substances.

In chromatographic system the injector is designed to provide accurate and reproducible introduction of a certain volume from the analyzed sample. For the introduction of gas, liquid and solid samples in gas chromatography are used different types of injectors, tailored for the existing variety of columns and compounds for analysis.

The introduction of the sample is essential for the successful implementation of gas-chromatographic analysis and significantly influences the results that are received. Therefore, the system for sample introduction must ensure rapid introduction of metered quantity without the occurrence of effects of discrimination (introducing only a portion of the sample).

Conclusion: The system for sample introduction in gas-chromatographic analysis is an essential part of the overall chromatographic system and a factor influencing the quality of the analysis.

Keywords: gas chromatography, injector, system, sample inlets.
AMYGDALIN – THE TRUTH BEHIND THE NUT

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Introduction: Amygdalin, a cyanogenic glycoside, is a compound found in the seeds of plants belonging to the Rosaceae family. In recent years the compound provoked scientific disputes because of the controversial data related to its effects on human health.

Materials and Methods: This systematic review is based on the available scientific literature and clinical case reports of amygdalin beneficial and adverse effects.

Results: Some of the studies reveal that amygdalin possesses antitumor potential by inducing the cancer cells apoptosis. The action of the compound on different tumor cell lines is not identical and depends on the tumor cells composition. However, there are many clinical cases of cyanide poisoning after usage of amygdalin as a cancer drug. After a large dose application of amygdalin, the prussic acid and the cyanide acid deliberated in digestive system may lead to a fatal toxicity.

Conclusions: The in vivo and in vitro studies of amygdalin antitumor effects are at the beginning. The pharmacological mechanism of action of the compound remains to be elucidated. Its effects on normal cells are still unclear.

Keywords: amygdalin, cyanide toxicity, cancer
Atherosclerosis, a degenerative disease of the arterial system, is the №1 killer in the economically developed countries, and is responsible for 65% of mortality in Bulgaria. Multiple studies have shown the involvement of several pro-inflammatory markers, such as Intracellular adhesion molecule-1 (ICAM-1), Vascular cell adhesion molecule-1 (VCAM-1) and NADPH oxidase (NOX) in various stages of the disease. The aim of recent review is to focus on the problem from the nutrigenomics point of view and to propose food products and plant substances, with possible positive influence on the clinical symptoms of the disease.

Through in vitro and in vivo tests it has been discovered that ursolic acid, found in green apple peels, the rich in lauric acid kernel oil, and extracts from the roots of Paeonia suffruticosa (tree peony) and Clematis chinensis can dose-dependently suppress the up-regulatory effect of inflammation mediators on ICAM-1, VCAM-1 and NOX gene expression. It was reported that fruit infusion of Sambucus ebulus (dwarf elder), a medicinal plant used in Bulgarian traditional medicine improves serum antioxidant activity and lipid profile in healthy human subjects. Due to these observations scientists suggested preventive potential of these plant food products against atherosclerotic plaque formation.

The various studies have proven that the abovementioned food products and medicinal substances of plant origin can lower ICAM-1, VCAM-1 and NOX levels, improve lipid profile and antioxidant activity, and can be successfully used in the primary and secondary prevention of atherosclerosis.

Keywords: nutrigenomics, atherosclerosis, ICAM-1, VCAM-1, NOX
MANAGING AGING AND DISEASE BY AN ANTIOXIDANT-RICH DIET

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One of the theories of aging assumes that the progressive decline in physiological functions is a result of accumulation of diverse deleterious changes caused by reactive oxygen species (ROS). Free radical productions is an integral act in the pathogenesis of various diseases and metabolism of xenobiotics during intoxications with halogenated hydrocarbons, phaloid fungi, pesticides, carbon monoxide etc. These radicals damage proteins (including enzyme systems), nucleic acids and set off chain reactions of lipid peroxidation, leading to structural and functional reorganization of the membranes. The membrane permeability is increased with subsequent rupture of membranes and cell death.

If we maintain the levels of antioxidants high enough, most free radicals could be neutralized before they cause any harm to the body. Despite the fact that the human body synthesizes its own antioxidants, the basic antioxidant is supplied with the diet (vitamins C, E and beta-carotene, as well as trace elements selenium, zinc, copper and manganese, thus preventing the changes in mitochondrial pathways of apoptosis that cause the functional tissue changes and aging. We discuss the possibility of delaying the aging process and managing pathobiochemical complications by appropriate diet modifying free radical oxidations and body metabolism directly and on genome level.

Keywords: oxidative stress, diet, antioxidants
THE CLINICAL ROLE OF PRO-INFLAMMATORY FACTORS MCP-1 AND IFN-γ IN THE TREATMENT OF ATOPIC DERMATITIS (AD)

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Introduction: Atopic dermatitis is a common, often long-lasting skin disease that affects a large percentage of the world's population. Atopic dermatitis (AD) is genetically determined inflammatory skin disorder, which is accompanied by marked increases in the levels of inflammatory factors such as the CC-chemokine, monocyte chemotactic protein 1 (MCP-1/CCL2).

Aim: To investigate the role of MCP-1 in the pathogenesis of AD and the ability of IFN-γ to achieve beneficial effects in the above-mentioned pathological condition and to propose foods and plant substances, which can be effective in reducing clinical symptoms of AD.


Results: Different studies demonstrated that CCR2 – CCL2 interaction is a basic inflammatory mechanism in the pathogenesis of AD and IFN-γ has a dual role, because of his dose-dependent effect: 1) attraction of monocytes through the induction of MCP-1 production in keratinocytes; and 2) retention of the monocytes in the skin through down-regulation of CCR2.

Conclusion: Some studies demonstrated that IFN-gamma appears to be a safe long-term therapy for patients with severe atopic dermatitis and diet therapy itself had therapeutic effects on AD and an elimination diet might be essential for the success of IFN-gamma therapy in AD.

Keywords: treatment of AD, MCP-1, INF-γ
**CLINICAL ASPECTS OF PRO-INFLAMMATORY FACTORS MCP-1 AND IFN-Γ**

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**Introduction:** Proinflammatory factors are cytokines-regulators of host responses to infection, immune responses, inflammation, and trauma. MCP-1 is a member of chemokines family-small heparin-binding proteins, whose main function is to recruit monocytes, neutrophils and lymphocytes, which are responsible for the phagocytosis of pathogens. Interferon Gamma (IFN-γ), is a pleiotropic cytokine involved in the regulation of nearly all phases of immune and inflammatory responses, including the activation, growth and differentiation of cells of the immune system.

**Aim:** To explore the clinical role of MCP-1 and INF-γ in the pathogenesis of different diseases and their ability of achieving beneficial effects in some of the mentioned pathological processes.

**Materials and methods:** Web databases: PubMed, ScienceDirect and Google Scholar.

**Results:** Different studies demonstrated that MCP-1 and IFN-γ play an important role in routine immune surveillance and immune modulation. IFN-γ has shown to be crucial for the resolution of allergic-related immunopathologies, tumor development, asthma, etc. MCP-1 has also been associated with many pathological conditions such as multiple sclerosis and insulin-resistant diabetes.

**Conclusion:** MCP-1 and IFN-γ have been shown to be a potential intervention point for the treatment of various diseases.

**Keywords:** IFN-γ, MCP-1, treatment, cancer, allergy, multiple sclerosis
Snakebite is classified by the WHO (World Health Organization) as a neglected tropical disease, envenoming in a significant public health problem in tropical and subtropical regions. Neurotoxicity is a key feature of some envenoming, and there are many unanswered question regarding this manifestation. Acute neuromuscular weakness with respiratory involvement is the most clinically important neurotoxic effect.

We present how the neuroparalytic poison affects the human body and what actually happens when the poison is injected into the human body. Neuroparalytic poisons are one of the most lethal, because they cause paralysis of the eye, throat and pectoral muscles. A well-known member of the Elapidae family is the Cobra. The snakes from this family live in the tropical and subtropical areas of Asia, Africa, Australia, North and South Amerika. Chuan-Chiung Chan is the discoverer of the neuroparalytic substance called bungarotoxin. It consists of three components - α-bungarotoxin, β-bungarotoxin and γ-bungarotoxin. The toxin is also made of proteins and lipids and its effect is due to the curare-like effect of the poison in the synaptic and presynaptic area of the neuron and the following blockage of the neurotransmition.

Bungarotoxins are a group of closely related neurotoxin proteins. α-bungarotoxin inhibits the binding of acetylcholine (ACh) to nicotinic acetylcholine receptors; β- and γ-bungarotoxins act presynaptically causing excessive acetylcholine release and subsequent depletion.

Keywords: Elapidae, action potential, neuromuscular synapse, poison, bungarotoxin
It is a fact that diseases do not strike the entire organism, but they develop in a certain tissues. For more effective treatment, the drug should act over the required section only, without affecting healthy surrounding parts. In the medicine it was necessitated to use liposomes as drug transporters right to the target cells. Why exactly liposomes? Because of their very similar structure with the cell membrane, they are deprived of antigens and reliably are hiding from the immune system.

A liposome is a tiny vesicle, made out of at least one lipid bilayer. It is possible to include a variety of substances in the inner aqueous volume of the liposomes, which allows exchanging these drugs between the liposomes and their surroundings, through the diffusion barrier. A medication like that is Doxorubicin.

Doxorubicin interacts with DNA by intercalation and inhibition of macromolecular biosynthesis. This inhibits the progression of the enzyme topoisomerase II, which relaxes supercoils in DNA for transcription. Doxorubicin stabilizes this complex after it has broken the DNA chain for replication, preventing the DNA double helix from being resealed and thereby stopping the process of replication.

Our study demonstrates the feasibility of Doxorubicin strengthening its antitumor efficacy, but such a tumor-targeted albumin packaging strategy can also be applied to other antitumor drugs.

**Keywords:** liposomes, phospholipids, cell membrane, Doxorubicin, drug transporters
TREATMENT OF PHENYLKETONURIA WITH SAPROPTERIN DIHYDROCHLORIDE

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Phenylketonuria (PKU) is an inherited disorder that increases the levels of an amino acid phenylalanine in the blood. Phenylalanine is found in all proteins and in some artificial sweeteners.

Phenylketonuria is caused by mutations in the PAH gene, responsible for synthesis of the enzyme phenylalanine hydroxylase. This enzyme converts the amino acid phenylalanine (PA) into tyrosine, which is also very important amino acid for the human body. The gene mutations reduce the activity of the enzyme. As a result the levels of PA in the blood increase and can cause a brain damage.

There is no cure for PKU, but treatment can prevent intellectual disabilities and other health problems. People with PKU need to follow a diet that limits food with PA. The diet should be followed carefully and be started as soon after the birth as possible. Experts recommend that people with PKU stay on the diet throughout their lives for better physical and mental health.

The U.S. Food and Drug Administration (FDA) has approved the drug sapropterin dihydrochloride (Kuvan) for the treatment of PKU. It is a form of BH4, which is a substance in the body that helps to break down phenylalanine. But even if the medication helps, it will not decrease the PA to the desired amount and must be used together with the PKU diet. If people with PKU do not restrict the phenylalanine in their diet, they develop severe intellectual and physical disabilities.

Keywords: phenylketonuria, phenylalanine, phenylalanine hydroxylase, diet, sapropterin dihydrochloride (Kuvan)
TREATMENT, CLINICAL MANIFESTATION AND BIOPHYSICAL ASPECTS OF KALA-AZAR

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Visceral leishmaniasis (VL), also known as kala-azar, black fever, and Dum-dum fever, is the most severe form of leishmaniasis. It is caused by protozoan parasites of the Leishmania genus. This disease is the second-largest parasitic killer in the world (after malaria), responsible for an estimated 200,000 to 400,000 infections each year worldwide. Kala-azar is an example for harmful positive feedback - interaction between the managing body (immune system) and the object of management (bone marrow) in a biological cybernetic system. The parasite, due to its characteristics is not degraded by enzymes in phagocytic cell. It starts dividing mitotically. Parasites enter the bloodstream and migrate to the internal organs such as the liver, spleen and bone marrow and if left untreated, almost always results in the death of the host. The most common symptoms are: fever, weight loss, fatigue, anemia, and substantial swelling of the liver and spleen, skin lesions.

The available treatment option for visceral leishmaniasis is problematic when it comes to efficacy, adverse effects and cost, making treatment a complex issue. Different methods of treatment are in relation also to toxicity of the drugs, ability to monitor side effects, length of treatment; ability of patients to pay for and stay safe during treatment, ability of the healthcare services to give the right therapy. The main drugs available for treatment of VL are the systemic agents like antimony, amphotericin, paromomycin and now the oral drug miltefosine.

Keywords: visceral leishmaniasis, harmful positive feedback, parasite, amphotericin
Augmentin is a penicillin antibiotic. Penicillin was discovered by Alexander Fleming in 1928. Penicillins are water soluble drugs. The mechanism of incorporation of water soluble drugs represents a passive transport (water diffusion). It is performed in the aqueous pores of the membrane. Pores are disposed in the epithelial lining of the bowel, bladder, and between the epithelial cells of the capillaries. The main route of administration is injecting intramuscularly or intravenously (parenteral). Augmentin is a broad spectrum antibiotic compound comprising amoxycillin and clavulanic acid of ($\beta$-lactam antibiotics) in a ratio of 4:1. It is used in skin and soft tissue infections including dental infections (after extraction of molars), intra-abdominal (abdominal) and pelvic sepsis and respiratory infections, infections affecting the lungs (bronchitis, pneumonia), tonsils (tonsillitis), sinuses (sinusitis), ears (otitis media), genitourinary system, bones, joints. Available in tablets 375-1000mg, suspensions 60-100ml, dry bottles 600 and 1200 mg. It is used in adults and children over 12 years. It is orally administered at a dose of 375 to 625mg/8h for 5-10 days. In severe cases it is injected intravenously at a dose of 1.2-2.4 g every 6 or 8 hours. Penicillins are remarkably nontoxic medicines. This is due to their mechanism of action. This is the reason why penicillins are authorized for use during pregnancy because they are harmless to the fetus.

Keywords: Augmentin, transport, mechanism of action, penicillins
The ultraviolet rays emitted from the Sun have genuine effect on the proteins and DNA in the human body. They destroy their covalent and non-covalent bonds, thus causing the denaturation of proteins and tearing the double helix structure of the DNA molecule. This results in cellular death, manifestation of mutations and inactivation of cells.

The molecules that can absorb light rays are called chromophores. When a light photon is absorbed by the chromophore it can be realized several ways: 1) Emit light (phosphorescence) 2) Radiate warmth 3) Undergo chemical transformations. In protein molecules the role of chromophores are performed by the alpha amino acids tryptophan and tyrosine.

The forming of a photoallergenic factor is divided into several stages:

1) Active stage - Absorption of a light photon by the chromophore (tryptophan or tyrosine) and the activation of the amino acid (this stage can be reversed).

2) Stage of photoionization \( \rightarrow \) the excited molecule decomposes into an electron and radical ion.

3) Third stage – incorporates the chemical reaction of the newly-formed radicals and the reaction of the solvated electron.

4) Fourth stage – includes the process of forming stable products of oxidation. All amino acidic radicals, created in the preceding stages, react with other substances. Those products have toxic properties. They can also react with protein molecules and destroy their structure.

Products created in those processes often show photoallergic or phototoxic properties. These substances are classified under the name photoallergens. There are several diseases caused by photoallergens. The most common are solar dermatitis (eczema) and solar urticaria.

Eczema is caused by chromophores in the skin that either amplify the effects of the UV rays on the skin or directly change their conformation and turn them into a hapten, which induce an immune response. Solar urticarial is also caused by light absorbing chromophores that turn into photoallergenic factor, thus inducing IgE mediated allergic reaction.

Both diseases are characterized by itchy, erythematous, vesicular, weeping, and crusting patches.

Keywords: chromophore, photoallergen, UV rays, mechanism
Aim: The purpose of the research is to show the physiological properties of the hormone melatonin produced by the human body—how it works, and the positive effects of admission of external melatonin.

Materials and methods: The materials and information used are from different scientific articles published on the internet site of the National center for biotechnology information and also from the data collected since the start of the usage of external melatonin as a drug.

Results: They show that melatonin produced in the human body is an important hormone for the regulation of the sleep and wake cycle, and that it is used to send signals to many structures in the organism that can read those signals (they have special receptors). Also if there are sleep disorders or any other sleep-wake cycle differences, external melatonin, most common in the form of pills, can be used to help treat those conditions successfully.

Conclusion: melatonin is an important natural hormone the levels of which in the organism are crucial for a normal and healthy life with regular sleep. More and more people are using external melatonin with positive results.

Keywords: Melatonin, Pharmaceutical properties, Healthy life
Psoralens are furocoumarins that are used in combination with long wave ultraviolet light (UVA) to treat proliferative skin diseases. Important psoralen derivatives include bergapten, xanthotoxin and angelicin. Psoralens for medical purposes are obtained synthetically, but they are naturally occurring substances in a variety of plants – parsley, parsnip, celery and citrus fruits.

Simultaneous use of photosensitizers – psoralens and ultraviolet light with length 320 – 420 nm is used to cure different skin diseases – this method is called photochemotherapy, or PUVA. Psoralens are type I photosensitizers – they produce a chemical reaction in the DNA molecule when exposed to UVA rays and are oxygen-independent.

In most cases of photochemotherapy the psoralen used is xanthotoxin, contained in the patent medicine Methoxalen, Oxoralen, Puvalen, etc. The medicine is resorbed fast by the skin and its highest concentration is in the first 2 – 4 hours. After that a part is disintegrated in the liver and the rest is excreted with the urine. The medicine is applied as a 0.15% solution of ethyl and isopropyl alcohol or in the form of tablets. The patient is exposed to UVA rays one hour after spreading the solution or two hours after the tablet intake.

Psoralens are mainly used to treat psoriasis – genetically determined disease, characterized by patches of abnormal skin – papulo-squamosus dermatosis. PUVA therapy is also used to treat alopecia, cutaneous lymphomas – such as folliculotropic mycosis fungoides, vitiligo and atopic dermatitis. Side effects include itching, erythema, blisters, and skin cancers, caused by the cancerogenic effect of the UVA rays.

Keywords: psoralen, furocoumarins, photosensitizers, photochemotherapy, psoriasis, skin diseases
BONE DENSITY MEASURING DEVICES AND THE ROLE OF PHARMACIST AS A PROVIDER OF OSTEODENSITOMETRIC SERVICE IN THE COMMUNITY PHARMACY

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Introduction: Osteoporosis is a disease where decreased bone strength increases the risk of a broken bone. It is the most common reason for a broken bone among people who are old. Osteoporosis took third place in the world as a socially significant disease. Nowadays over 200 million women suffer from it. In Bulgaria it is estimated that the number of this people is over 500 000. Prevention and the control of risk factors are the best way for fighting with osteoporosis. In 1901 the Bulgarian physicians during their first meeting establish the base of the “Medical Prevention” and since then the healthcare professionals are actively participate in the process.

Aim: To explore the need of additional medical service to patients in the pharmacy for scanning and medical prevention for osteoporosis.

Materials and methods: Some companies for medical equipment are visited: Ilan, Medic OOD, MedAp Consult. I have collected various opinions from Pharmacists working at Pharmacy Galen, Mareshki, Sanita, Mediana – Pavlikeni.

Methods: SWOT analysis, Conversation with Pharmacists, Conversation with Patients

Results: In Bulgaria, there are over 3500 pharmacies, that are very accessible for the patients. Currently, the pressure over our national health system and secondary medical assistance has increased and will be permanent, due to the needs of a first medical assistant.

The basic Osteoporosis scanning is a part of many other pharmacist assistance which could be done/started in the pharmacy.

Conclusion: The pharmacy and the pharmacist can be very useful in the part of consulting patients for their health condition. According to Directive 2013/55/EP for the professional duties of the pharmacist/the amendment from 20 November 2013/article 45 paragraph 2 is for the participation of the pharmacist in campaigns which support the medical care of population.

The medical service rendered from the pharmacist to patients in the pharmacy must be very well organized in all aspects and with all medical devices. The pharmacist must be well trained for it.

Keywords: osteoporosis, bone density measuring devices, pharmacy, pharmacist, patient
STUDY OF THE USE OF PRODUCTS CONTAINING OMEGA-3-FATTY ACIDS IN BULGARIA FOR THE PERIOD 2011-2013

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On the Bulgarian market, the products containing omega-3 fatty acids (FA) are: one medicinal product (MP) and a a great number of food supplements (FS).
The purpose of this study was to analyze the use of products containing omega-3 FA in Bulgaria for the period 2011-2013. The market research was done according to data from IMS Health.  
The results from the study showed that in the years 2011-2013 there was a slight increase in the sale of the MP containing omega-3 FA, both in number of packs sold and in terms of value accompanied by a slight increase in the average package price. As a whole, the sales of FS containing omega-3 FA decreased in 2012-2013 compared to 2011 in number of packs sold, and in terms of value accompanied by a slight decrease in the average price per pack. In the study period, the market share of the FS was 500 times greater than that of the MP. The predominant share of FS could be explained by the greater variety and number of these products, as well as by the considerably lower cost of a FS pack compared to that of the MP.

Keywords: omega-3 fatty acids, medicinal products, food supplements, use, Bulgaria
IMPLEMENTATION OF INTERNET PHARMACY TRADE IN BULGARIA

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Introduction: The Internet provides consumers with a global access to health information, services and support. It has revolutionised the sale of medicines so that consumers can self-select, order and buy medicines. They are often delivered across national and state boundaries, without face to face interaction with a health professional. In Bulgaria e-pharmacies are websites selling non-prescription medicines, medical devices, food supplements and cosmetics. They are specially authorized by the Bulgarian drug agency (BDA).

Materials and Methods: The aim of this study was to demonstrate the strengths, weaknesses, opportunities and threats (SWOT) analysis of the internet pharmacy trade in Bulgaria. We identify relevant economic, ecological and societal (EES) issues for the assessment of its sustainable development.

Results: As a major strength can be reported that internet marketing is affordable and convenient method offering competitive prices and the possibility of delivery to remote areas where there is no access to a pharmacy. But as a weakness can be mentioned that it could lead to losing the connection between the pharmacist and the patient, which is a factor for improper diagnosis and treatment.

Conclusion: To satisfy customers in today’s competitive e-marketplace, Internet pharmacies must take a closer look at this kind of trade services. To do this, most online pharmacy companies would be aimed at achieving the following key points - responsiveness, reliability, ease of use, credibility, and perceived cost.

Keywords: Internet trading, analysis, pharmacist, patient, medication
STUDY OF PATIENTS’ COMPLIANCE AND ATTITUDES FOR SELF-MEDICATION WITH ANTIBIOTIC THERAPY

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Introduction: Since the discovery of penicillin by Alexander Fleming in 1928, antibiotics have been used widely and successfully in the treatment of various infectious diseases. However, in recent years, it is increasingly common for bacteria to become resistant to one or more pharmaceutical substances and on multiple occasions, there have been numerous reports for multidrug resistant strains. Some of the explanations for this fact include over-prescription of antibiotics by general practitioners, poor compliance by patients, as well as self-medication.

Aim: To collect information for the treatment habits of the Bulgarian city population, including evaluation of the level of their compliance and willingness to self-medicate.

Materials and methods: A specially designed online questionnaire was applied as well as face-to-face interviews with an identical paper-based questionnaire. The data were processed statistically.

Results: A medium percent of the interviewed population reported use of an antibiotic agent in the last 12 months, and about 20 percent of those reported self-medication. In general, patients who had consulted a doctor and had acquired a prescription showed a high level of compliance. Medication was obtained mainly through a community pharmacy, and information on therapeutic effects and dosage regimen was provided primarily by a physician, followed by pharmacists, patient information leaflets and the Internet.

Conclusions: The reported high compliance level suggests a good probability for positive therapeutic outcome, while self-medication can lead to side effects, poor therapeutic outcome, as well as development of resistant microorganisms. A larger and more comprehensive survey will provide deeper insight into patients’ treatment habits and can investigate the influence of various socio-economic factors in patients’ decision for self-medication.

Keywords: Antibiotics, patients’ compliance, self-medication
The medicines from the pharmacological group of statins are among the most widespread medicinal products in Bulgaria for the treatment of hypercholesterolemia. Separately increased amount of cholesterol in the blood plasma does not represent a disease but it is a significant risk factor for the development of a number of diseases and complications associated with them. Hypercholesterolemia is a prerequisite for many cardiovascular diseases, because it leads to atherosclerosis.

The inclusion of medicinal products in the positive drug list is done by the National Council on Prices and Reimbursement of Medicinal Products, which also sets the level of reimbursement they receive. The reference pricing and the HTA are often implemented policies in most European countries, whose ultimate goal is obtaining a greater benefit for the financial resources invested in medicinal products.

The aim of the study is to evaluate the antihypercholesterolemic drugs from the group of statins which are available in Bulgaria and to estimate their reimbursement status.

According to Annex 1 of the positive drug list, the group of medicinal products used for treating Hypercholesterolemia – Statins is with a reimbursement level of 25%. The most expensive Statin, which NHIF reimburses, is with an International nonproprietary name (INN) – Rosuvastatin. The reason may be that it has been proved to be with the best efficiency compared with other members of this class. As of 02.10.2015 in the positive drug list are included 30 drugs with different trade names, which have INN – Rosuvastatin. Roswera (Produced by the company KRKA) and Tintaros (produced by the company Actavis) provide an advantage of four different dosage forms, which greatly facilitates the process of titration and increases the subject compliance of the patient. The cheapest statin in positive drug list is Torvalipin 10 mg by Actavis with an INN – Atorvastatin.

The low value of reimbursement of the statins (from 0,24 to 5,56 BGN) covering only 25% by NHIF from the value of medicines and 75% co-payment by the patient is irrelevant and inappropriate, considering the proven clinical benefits when administered for the treatment of Hypercholesterolemia. In EU between 75% and 100% of the value of medicines of this class are covered by their health funds.
DIETARY SUPPLEMENTS – LEGAL REGULATIONS IN BULGARIA AND POTENTIAL HEALTH-RELATED RISKS

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Introduction: People nowadays are not just passive consumers of health care. Rather, they are well aware of their personal responsibility for exercising control over their own health. The ever-growing desire to have a better quality of life is intrinsically linked to the heightened health awareness. More and more people opt for dietary supplements as part of their self-medication therapy.

Aim: The aim of this study is to present how supplements are regulated in Bulgaria and to indicate the potential risks related to the improper use of supplements, including dangerous interactions with certain drugs and other supplements.

Materials and methods: The available literature on legal regulations was reviewed and comprehensively analyzed. Some of the most important and common adverse reactions were summarized.

Results: Supplements are considered as food products that contribute to the balanced food diet; therefore they are subject to the corresponding regulation. Unlike drugs, there are no requirements for dietary supplements to be approved by the government for safety and effectiveness before they are marketed. The lack of specific requirements for the production, content and clinical trials is a prerequisite for possible health risks to consumers. As availability has grown, so have sales - supplements constitute the fastest growing segment in the Bulgarian pharmaceutical sector and for the sixth consecutive year (2015) they recorded growth.

Conclusion: Given the tendency of growth in sales of supplements, this segment should be adequately regulated and functioning. Moreover, health professionals and pharmacists in particular, as key advisors to self-medicating patients, ought to provide all available information about proper use of dietary supplements to patients and adapt the consultation individually to the particular case in order to prevent some possible adverse effects and interactions.

Keywords: Dietary supplements, legal regulations, self-medication, health risks, interactions
EXTEMPORANEOUS PREPARATION – PAST, PRESENT AND FUTURE PHYSICIANS’ ATTITUDES AND BELIEFS

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In recent years, major advances in the spheres of computer, automation and robotics technologies have re-shaped the pharmacy practice and have enabled machines to perform various tasks – preparation of medicines, dose verification, choosing the appropriate route of drug administration, distribution and dispensing of medicines. As artificial intelligence (AI) robots have taken over many of pharmacists’ functions in a business environment with a constantly increasing number of nationally-authorized drugs, the focus of pharmacy profession has shifted from the traditional drug preparation and dispensing to the provision of patient counseling on the appropriate drug use.

The purpose of this study was to analyze physicians’ attitudes towards extemporaneous prescribing and dispensing. We performed a direct anonymous survey among general practitioners and medical specialists in the city of Varna, Bulgaria.

Although a dwindling number of pharmacy practices are being registered for extemporaneous preparation in accordance with the current pharmacopoeia and magistral formulae, the necessity and the advantages of extemporaneous medicines are indisputable.

Our study findings show that extemporaneous medications are preferred by physicians to meet the need of a tailored approach to patient care, individualized drug dosing, and selection of the suitable route of drug administration, particularly in young children.

Despite the abundance of industrially manufactured pharmaceuticals, extemporaneous medications are still often prescribed and prepared when there are no appropriate market alternatives.

Keywords: Extemporaneous medications, physicians, preferences, attitudes
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