РЕЗЮМЕТА НА НАУЧНИТЕ ТРУДОВЕ

на Доц. д-р Мариета Петрова Георгиева, д.м.

представени за участие в конкурс за заемане на академична длъжност „Професор“ в област на висшето образование 7. Здравеопазване и спорт, професионално направление 7.1. Медицина, специалност „Фармакология“, катедра „Фармакология, токсикология и фармакотерапия“, факултет „Фармация“ Медицински университет - Варна.

Научните трудове след заемане на академична длъжност „Доцент“ включват:

I. Монография – 1 брой;

II. Пълнотекстови публикации в български научни списания и сборници – 24 броя;

III. Пълнотекстови публикации в чужди научни списания – 5 броя;

IV. Резюмета на доклади от научни форуми, публикувани в български научни списания и сборници – 27 броя;

V. Резюмета на доклади от научни форуми, публикувани в международни научни списания и сборници – 6 броя;

VI. Участие в книги – 2 бр.;

VII. Участия в справочник, учебници и учебни помагала – 75 броя;

Общият **Импакт фактор** на научните трудове е **16,042**.

I. МОНОГРАФИЯ

1. **Георгиева, М.** Пробиотиците – лекарство и храна. Варна, МУ-Варна, Стено, 2018. 167 стр.
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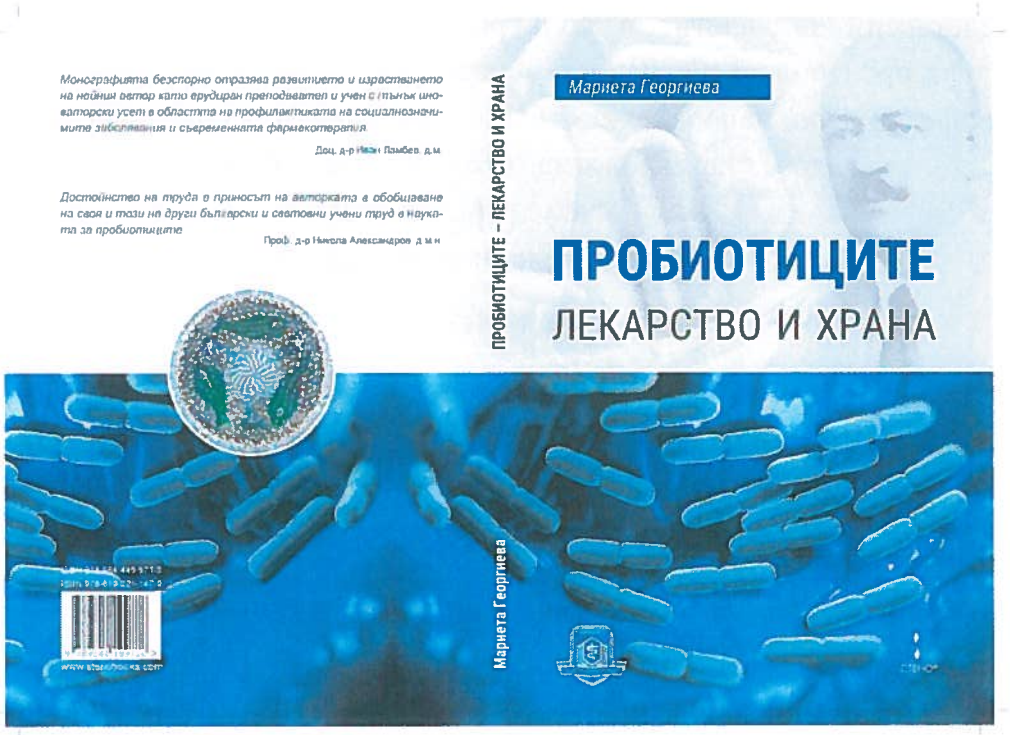


Монографичният труд е в обем 167 стр., съдържа 6 авторски проучвания, онагледен е с 8 таблици и 51 фигури. Използваната литература включва 200 източника.

Авторът представя в обобщена форма съвременните разбирания за пробиотиците, пречупен през призмата на личния си опит. Очертава историята, проучванията, успехите и възможните приложения на пробиотиците – „добрите" микроорганизми, обещаващи здраве и по-добро качество на живот през XXI в. Обосновано се представят здравословните ефекти, свързани с рационалното използване на тези продукти и основните показания за профилактика и фармакотерапия с тях. Приложението им обхваща широк спектър от заболявания на храносмилателната система, тумори (вкл. малигноми), метаболитен синдром, атеросклероза, урогенитални инфекции, имунни заболявания, психически заболявания и др. Новите перспективи в научните изследвания на пробиотиците са създаването на модерни форми на храни, добавки и терапевтици, покриващи изискванията за безопасност и полезност, съгласно Европейските регулаторни рамки, както и да се предоставят знания за генетичните основи и молекулни механизми на полезно действие, които да осигуряват оптимално здраве за всеки индивид.

В монографията са отразени обобщени данни от многобройни рандомизирани проучвания у нас и по света, които потвърждават здравословните ефекти на пробиотиците. В съвременното глобално общество, където хората са подложени на ежедневен стрес, на повсеместна употреба на антибиотици, на неправилно хранене и редица вредни външни фактори, балансът на стомашно-чревната флора търпи непрекъснати нарушения. А гениалната догадка на Хипократ, че „всички болести започват от чревния тракт", намира своето съвременно потвърждение. Пробиотиците са особено ефикасни при съвременните заболявания, свързани с физически и психически напрежения, сърдечно-съдови увреждания, нарушения на имунната система, метаболизма и др. Най-новите изследвания сочат, че хората с психоневрологични заболявания (депресии, хронична умора и други психични заболявания) страдат от тежка дисбактериоза. Коригирането на дисбиозата с пробиотици повлиява благоприятно основното заболяване.

В монографията са представени оригинални резултати от дългогодишни задълбочени авторски изследвания върху използването на пробиотиците като храни, добавки и терапевтици. Обхванат е широкия спектър на протекция на заболявания: хепатопротективен, лъчезащитен, антимутагенен, антитуморен, имуномодулиращ и други.

Възможността да се контролират и предвиждат ефектите на пробиотиците, базирайки се на строги научни изследвания, би позволила както на потребителите така и на производителите да избират и предлагат продукти с доказани лечебни качества и по този начин да се удължи пълноценно човешкия живот. Защото „Здравето не е всичко, но без здраве всичко е нищо" (А. Шопенхауер).

Монографията е адресирана към работещите в сферата на здравеопазването. Тя може да бъде използвана и при специализираната подготовка на студенти, специализанти и докторанти.

II. ПЪЛНОТЕКСТОВИ ПУБЛИКАЦИИ В БЪЛГАРСКИ НАУЧНИ СПИСАНИЯ И СБОРНИЦИ

1. **Георгиева, М.** Лъчезащитен ефект на пробиотика Biomilk. – *Военна медицина*, 59, 2007, № 2, 30-33.

Пробиотикът Biomilk се състои от живи клетки *Lactobacillus Bulgaricus*, млечни протеини, мазнини и въглехидрати, естествени витамини и минерали. Известно е, че млечнокиселите продукти, съдържащи живи клетки *Lactobacillus bulgaricus*, оказват благоприятен ефект при чернодробни и жлъчни заболявания, върху имунната система и др.

Целта на настоящата работа е изследване влиянието на пробиотика Biomilk върху резистентността на организма към нелетално радиационно въздействие. Ефектът се оценява чрез промяна в най-чуствителната към радиационно въздействие система - кръвотворната. Пробиотикът Biomilk е въвеждан на мъжки плъхове порода Wistar чрез перорална сонда в доза 1600 mg/kg в продължение на 30 дни до гама облъчването (с изотоп ®°Co с тотална доза 3 Gy). На 4-ия и 10-ия ден след радиационното въздействие се определя броят на кръвните клетки в периферната кръв.

Получените резултати показват, че третирането с пробиотика Biomilk, съдържащ *Lactobacillus bulgaricus*, повишава резистентността на кръвотворната система към нелетално гама облъчване.

2. **Georgieva, M.,** G. Bekyarova, M. Gabrovska. Influences of probiotic "Biomilk" on indomethacin-induced oxidative injuries of some tissues. – *Acta morphologica et anthropologica,* 2008, № 13, 144-148.

The effect of probiotics Biostim LBS (Biomilk) and LBB of pure culture on ulcerogenesis in Indomethacin-induced oxidative stress by means of a model of Indomethacin-induced ulcer in white male rats was studied. Indomethacin was subcutaneously injected in a dose of 20 mg/kg bw 4 hours prior to taking for examination the biopsy material such as blood, liver and brain. Both probiotics Biostim LBS and LBB were introduced per sondam in a dose of 1600 mg/kg bw for 30 consecutive days prior to modelling the Indomethacin-induced ulcers. Malonyldialdehyde (MDA) as a marker of lipid peroxidation was examined in plasma, liver and brain homogenate. The results from the morphometric study of gastric lesions were presented as index of lesions. Indomethacin caused the formation of numerous lesions and haemorrhages and enhanced MDA level in plasma and tissues. Both probiotics Biostim LBS and LBB introduced for 30 days restrict the lipid peroxidation and protect the gastric mucosa from Indomethacin ulcerogenic action.

3. **Georgieva, M.**, E. Softova, M. Gabrovska. Role of the probiotic Biomilk on Induced Ulserogenesis. – *Acta morphologic et anthropologica,* 2010, № 15, 108-111.

The effect of probiotic Biomilk in a dose of 1600 mg/kg b.w. for 30 consecutive days in Indomethacin-induced gastric ulcer in white male rats was studied, Indomethacin was s.c. injected in a dose of 20 mg/kg b.w. Malondialdehyde (MDA) was examined in plasma, liver and brain homogenates. Indomethacin caused the information of numerous lesions and haemorrhages and enhanced MDA level in plasma, liver and brain tissues. The probiotic Biomilk restricted the lipid peroxidation and protected the gastric mucosa from Indomethacin ulcerogenic action. Thus it could represent a non-pharmacological alternative for the prevention and treatment of gastric ulcer in man.

4. Милев, Е., **М. Георгиева**. Чуждестранно военномедицинско участие в България по време на Балканската война (1912-1913 г.). – *Социална медицина*,18, 2010, № 1, 39-41.

В статията се прави кратък преглед на Балканската война като военен конфликт между Османската империя и съюзниците България, Сърбия, Гърция и Черна гора и на последиците – падналите на фронта жертви и тежката съдба на цивилното население. Първата балканска война нанася големи поражения на жителите на районите, през които преминават войските. В Тракия и Родопите са опустошени редица села. Десетки хиляди българи са принудени да търсят закрила в районите, завзети от техните сънародници.

Освен участието на българския военномедицински персонал, важна роля в медицинското обслужване на българската армия и на целия български народ по време на Балканската война играе помощта, оказвана от чуждестранните медицински и

червенокръстки организации на редица европейски страни. Авторите изтъкват задачите, историята и дейността на Българското дружество „Червен кръст" през този период, като акцентират на изпратените санитарни мисии от десет страни: Русия, Австро-Унгария, Англия, Франция, Германия, Холандия, Италия, Белгия, Швейцария и Румъния. Най-характерните черти на помощта, дадена от тези санитарни мисии, са високата квалификация на ръководителите - лекари хирурзи, повечето от които са професори и доценти от медицински факултети, възможността за разкриване на лечебни заведения, което се обуславя от добрата материална база, с която чуждестранните мисии идват - инвентар за разкриването на походни болници, лазарети, хирургически инструментариум, медикаменти и превързочни материали. Не се подценява и осигуряването на среден медицински персонал - фелдшери и медицински сестри, което позволява доброто и правилно гледане на болните и ранените в лазаретите и болниците.

5. **Георгиева, М.** Пробиотици – исторически преглед на изследванията в България. – *Известия на Съюза на учените - Варна. Серия „Медицина и екология"*, 15, 2010, № 2, 6-10.

Статията е посветена на пробиотиците – откриването на ***Lactobacillus bulgaricus*** от д-р Стамен Григоров през 1905 г. в Женева, неговите последователи в България, множеството им изследвания върху лечебните и профилактични свойства на киселото мляко и лактобацилите и индустриализирането на млечната промишленост в страната.

6. **Георгиева, М.,** Д. Ставрев. Фармацевтични препарати включени в обзавеждането на медицинските звена на ВВС. – *Авиационна, морска и космическа медицина*, 2011, № 1, 50-53.

През 1928 година е създадена първата професионална водноспасителна команда към общината на гр. Варна. Изгражда се медицинската служба с лекарски кабинет, оборудван с необходими средства за първа помощ. Така още с възникването на водното спасяване, медицинската служба е неотменима част от него. Съвременното водно спасяване се регламентира от Наредба за водноспасителната дейност и обезопасяването на водните площи, приета с постановление на Министерския Съвет. Медицинските звена се обзавеждат съгласно изискванията, определени в Приложение № 5 към чл. 18, ал. 2. Към медицинското осигуряване се включва и списък със задължителни медикаменти за водоспасителна дейност. Всички медикаменти, консумативи, апаратура и оборудване, включени в изискванията към устройството и обзавеждането на медицинските звена са изключително важни за спасяването на човешкият живот и здраве.

7. **Georgieva, M.**, M. Gabrovska. Double Staining Technique for Rat Foetus Skeleton in Teratological Studies. – *Acta morphologic et anthropologica*, 2011, № 17, 109-113.

The characteristic staining of the skeleton is an important part of the toxicological studies on the individual development. The precise and full interpretation of the data regarding the

skeletal toxicity is possible only if using the "double staining method" with alizarin red and alcian blue. The Wilson section method, which is standard teratological method and still represents the most utilized technique to examine the visceral organs, was used to explore the soft tissues.
The study of teratogenicity required application of the studied substances on pregnant female Wistar rats during the organogenesis. On day 21 after conception were extracted via caesarian section and were explored for skeletal toxicity, using the method of "Double skeleton staining".
The double staining method used in the current study is a fundamental part of the teratological studies for assessment of the toxicity of the xenobiotics and non-chemical factors for the individual development.

8. **Georgieva, M.,** N. Alexandrov. Effect of the probiotic Biostim LBS in acute intoxication after industrial accidents. – *Scripta Scientifica Medica*, 43, 2011, № 1, 39-41.

A probiotic is a "live microbial food ingredient that, when ingested in sufficient quantities, exerts health benefits on the consumer". The profound research of a range of Bulgarian scientists has allowed for the development in the last 15-20 years of original Bulgarian probiotic, milk-acid low-lactose products, united in the Biosim LBS (Lactoflor, Biomilk) series. This survey gives an overview of the effect of probiotic Biostim LBS in acute intoxications after industrial accidents. The mean energy values in kcal of the nutritional therapy applied intravenously and via oral route in 186 patients with intoxications with moderate severity are presented. The data show that Biostim LBS covers a mean energy value of 45.36% of the food applied orally in the group with moderate and 70.86% in the group of patients with severe intoxication. These results have been achieved owing to the correct choice of therapy which have included mutually additive enteral and parenteral medications. In none of the patients adverse events have been observed regarding the parenteral medications and the enterally introduced Biostim LBS as well. They exerted beneficial effect on the metabolism, improved body energy levels and contributed to the absorption of energy and proteins. A special attention should be paid to the probiotic properties of the viable cells of *L. bulgaricus,* which favorably influence on the organism of the patients by improvement and regulation of the internal bacterial equilibrium.

9. **Georgieva, M.,** M. Gabrovska. Morphological studies of rat foetus skeletons: test for teratogenicity of nootropic drug pyramem. – *Acta morphologica et anthropologica*, 2012, № 19, 53-57.

The teratogenic effect of the nootropic drug Pyramem on the skeleton and internal organs of rats was investigated. Pregnant Wistar rats were treated orally by 200 mg/kg b. m. Pyramem and 200 mg/kg b. m. during the period of organogenesis since the 7th until 15th day of pregnancy. The effect of Pyramem on the fetuses in terms of malformations, skeletal fragility and abnormalities in the internal organs (lungs, liver, spleen and kidneys) close to delivery (day 20-21) was analyzed. The nootropic Pyramem failed to prove to be embryotoxic agents at all.

10. Milev, E., **M. Georgieva.** The training of medical students in the field of Phytotherapy. – *Scripta Scientifica Medica*, 44, 2012, № 1, 47-49.

Now in its eigth year at the Medical University - Varna run elective course in the teaching discipline of Phytotherapy. Together with the study of medicinal plants and essential phytopreparations, during the course were monitored interests and attitudes of participants towards phytotherapy as a whole, and to individual phytotherapeutic methods and fields. At the end of each course in 2003 - 2011, a questionnaires were filled from the students-participants. Questionnaires and collected data are processed. According to them, average 94% of participants demonstrated considerable interest in the topics, and an average of 98% of the students wish to use phytopreparations in their future practice. Despite still tentative attitude of the Bulgarian phytotherapy for clinicians, medical students demonstrate a specific interest in the area of phytotherapy and willing to update their knowledge on it in the future. Given the increasing use of phytopharmaceuticals and phyto supplements in the world is glad, that the future doctors have a very constructive attitude towards them. We believe it would be reasonable and practical to include some phytotherapeutic topics in the regular training in pharmacology.

11. **Georgieva, M.**, M. Gabrovska, N. Manolov. Andreas Vesalius (1514-1564) – the founder of modern human anatomy. – *Scripta Scientifica Medica*, 45, 2013, Supplement 1, 13-18.
Andreas Vesalius was a Belgian physician and anatomist, whose work revolutionised anatomy and contrib-uted to enhancement of knowledge how the human body functioned. Vesalius was born in Brussels in 1514. He studied medicine and anatomy in Paris (1533-1536). He obtained a post of lecturer at the University of Padua and remained there as professor (1537-1542). His important innovations were to perform postmortem dissections and to make use of illustrations in the teaching of anatomy. In 1543 Vesalius published his revolutionary book De humani corporis fabrica (on the structure of the human body). Vesalius helped es-tablish surgery as a separate medical profession. Scientific findings of Vesalius are in field of: skeletal system, muscular system, vascular and circulatory systems, nervous system, abdominal organs, heart, brain. Andreas Vesalius, died June 1564, island of Zacynthus (now in Greece).

12. Vidinova, H., **M. Georgieva**, G. Aleksandrov. Effect of probiotic product Laktera Vision with Lactobacillus bulgaricus and extract of bilberry on the syndrome of dry and tired eye. – *Scripta Scientifica Medica*, 45, 2013, Supplement 1, 101-104.

Technology development and penetration of computers in life lead to refractive anomalies of the eyes in more young people. Excessive congestion of eyes at a young age led to the occurrence of new syndromes in ophthalmology - dry eye syndrome and tired eye syndrome.
Purpose of this study is to examine the effect of bilberry on the vision of young people.
Object of observation were 41 people aged between 21 and 44 years (men and women). All of them wear glasses for vision correction and work in offices from 4 to 9 hours a day in front of computers an average 5 hours a day. All wear anti-reflecting glasses while working on a

computer. Most frequent syndromes that oc-cur in these people are the dry eye syndrome and the tired eye syndrome.

The study was carried out within 8 weeks (56 days). 35 of people have taken 2 capsules Laktera Vision every day before meal. 6 of the observed people have taken Laktera Vision irregularly - on average 2.5 times a week. After administration of the product manifestations of the syndromes are put under control for a period of 12 - 24 hours.

The probiotic product with bilberry extract controls successfully the syndromes of dry and tired eye, occurring in young people wearing glasses for vision correction, who work on a computer more than 4 hours a day.

13. Стоева, С., Л. Танчева, Ст. Драгоманова, Т. Пайпанова, **М. Георгиева.** Ноцицептин и пилотни опити за откриване фармакологични ефекти на негови късоверижни аналози. – *Варненски медицински форум*, 2, 2013, № 2, 9-13.

Ноцицептин (орфанин) е ендогенен лиганд, свързващ се с ноцицептинов рецептор (NOP, ORL-1). Той притежава антианалгетични ефекти. Рецепторът е широко експресиран в мозъчните структури. Пептидомиметиците са молекули с къса верига, наподобяващи пептиди, с характерни фармакокинетични свойства. Целта на изследването е да се проучат основните фармакологични и токсикологични ефекти на два новосинтезирани пептида (PI и P2) при мишки. Анализирана беше активността им върху ЦНС, както и влиянието им върху хексобарбиталов сън. Аналгетичната активност на двете вещества беше изследвана с тест с оцетна киселина. По същия метод бе проучен и дозо-зависимият ефект на аналгетичната активност на P2. Установи се, че P2 притежава антиноцицептивни свойства, което го прави подходящ за по-нататъшни проучвания в тази насока.

14. Dragomanova, St., **M. Georgieva**, S. Alexandrova. Alzheimer's disease – treatment research trends. – Proceedings of Vth Workshop on Experimental models and methods in biomedical research. Sofia, Bulgaria, 7-9 April 2014. pp. 162-169.

Alzheimer's disease (AD) is a type of dementia causing problems with memory, thinking and behavior. Scientists have identified factors that increase the risk of AD - the most important are age, family history and heredity. Two abnormal structures have key role in damaging and nerve cells apoptosis: beta-amyloid plaques and tau tangles (twisted fibers).

Two types of medications are approved - cholinesterase inhibitors and memantine. The available treatments of AD are only symptomatic, cholinesterase inhibitors being the most widely used drugs. Several natural compounds with anticholinesterase activity can be used as leader compounds for the synthesis of new drugs.

Today, there is a worldwide effort (by WHO) to find better strategies of treating the AD, delay its onset, and prevent it from developing. Researchers are developing medications aimed at in amyloid processing. Recent studies have indicated the critical importance of tau in the pathomechanisms of neurodegeneration in AD and related tauopathies. There is a theory of novel anti-inflammatory treatments for AD. The results from several studies provide strong evidence in

support of the hypothesis that AD represents a form of diabetes mellitus that selectively afflicts the brain.
Researchers hope various brain imaging techniques studies will soon provide methods to diagnose AD in its earliest stages – even before symptoms appear. Biomarkers may also offer better ways to monitor response to treatment.

Despite of that many theories and experimental efforts there still is an enormous need for more effective therapeutic strategies for the purposes of successful treatment of AD and other dementias.

15. **Georgieva, M.**, G. Aleksandrov, M. Peneva, N. Manolov. Lactobacillus Bulgaricus – the contribution to modern healthy nutrition. – *Scripta Scientifica Pharmaceutica*, 1, 2014, № 1, 25-27.

Lactobacillus bulgaricus is part of the traditional Bulgarian food. It was known to the Thracians - the ancient population that lived on the territory of present Bulgaria.

At the beginning of 20th century, the Russian scientist and Nobel prize winner Ilya Metchnikov, in his work „The Prolongation of Life: Optimistic Studies" relates the long and healthy life of Bulgarians to the yoghurt consumption and in particular to the local bacterium in yogurt.
In the 90s of the 20lh century Lactobacillus bulgaricus was used in the production of probiotic functional food for astronauts. Using modern biotechnologies, certain Bulgarian companies sheathe strains of Lactobacillus bulgaricus and other probiotic microorganisms with a natural coating, consisting of components of the growing medium during fermentation. The isolation of new probiotic strains from spring water, which normally survive under the changing climatic conditions in nature, helps the production of probiotic products in which the strains of Lactobacillus bulgaricus and other probiotic microorganisms retain their stability and vitality when passing through the gastrointestinal tract.

Bulgaria becomes famous in the world for Lactobacillus bulgaricus and the Bulgarian territory is still an important reservoir for the isolation of natural strains of lactic acid bacteria which after an additional selection are used as starter cultures for the production of various fermented foods and probiotic products.

Lactobacillus bulgaricus is the ancient contribution of mankind to the modern agricultural science and the creation of the first healthy foods in the world.

16. Georgiev, K., **M. Georgieva**, P. Marinov, D. Radkova. Acute poisonings with neuroleptics in clinic of toxicology of military medical academy Varna/Bulgaria registered for 20 year period. – *Scripta Scientifica Medica*, 47, 2015, № 1, 70-72.

This retrospective study was conducted to follow out acute intoxications with neuroleptics in Varna region, to assess the frequency and proportion depending on other drug and non-pharmacological poisonings.

The objects of the study are 193 patients with acute neuroleptic intoxications treated in the Clinic of toxicology of the Military Medical Academy - Varna, Bulgaria. The study is retrospective and covers a period of 20 years (1991-2010).

The incidence of acute poisonings with neuroleptics was 7.5% of all drug poisonings and 2.5% of general poisonings. Poisoning occurs more commonly in women and the majority of poisonings were in people of working age.

In recent years, there is a trend for an increase in the absolute number and the proportion of poisonings with neuroleptics. Lethality in these poisonings is not high - 0.4 percent.

17. Marinov, P., K. Georgiev, **M. Georgieva.** Some aspects of the modern antihypertensive drug therapy and most common side effects. – *Scripta Scientifica Pharmaceutica*, 2, 2015, № 1, 7-14.

Hypertension or high blood pressure is one of the most common diseases worldwide affecting people and is a major risk factor for stroke, myocardial infarction, vascular disease, and chronic kidney disease. Health care professionals must not only identify and treat patients with hypertension but also should have a good understanding of the side effects that accompany antihypertensive therapy. The aim of this review is to represent the most common adverse drug reactions (ADRs) of the most prescribed antihypertensive drugs.

18. Georgiev, K., **M. Georgieva.** New pharmacological approaches in the treatment of oncological diseases. – *Journal of IMAB*, 21, 2015, № 3, 818-822.

Malignant diseases are significant and growing health problem in almost all countries of the world. Besides the results achieved in reduction of morbidity and mortality in individual countries, significant progress of science and practice of oncology medicine and the application of new methods of diagnosis and treatment, cancer remains the second leading cause of death after cardiovascular diseases. The past decade has seen breakthroughs in personalized cancer medicine, where new targeted therapies are being developed which inhibit cellular proliferation and survival in tumors with certain specific oncogenic mutations. These new treatment approaches have shown progress in the understanding of the origin and pathogenesis of tumors, and offer hope for a good outcome of neoplastic diseases. In this review the idea is to present up-to-date report on these new molecular mechanisms and to identify their advantages and disadvantages from the pharmacological point of view.

19. Dragomanova, S., K. Georgiev, **M. Georgieva**. Advanced pharmacy practice experiences for pharmacy students in the field of cosmetology. – Сборник статии от Юбилейни научни конференции по фармакология и клинична фармакология за млади учени. Scientific papers of Jubilee Conferences of Pharmacology and Clinical Pharmacology for young scientists. Цигов Чарк, България, 5-7 юни 2015. стр. 6-8.

Counseling in dermatology and cosmetology at pharmacies is an usual practice. Therefore, to provide competent intervention in advising patients with cosmetic disorders, pharmacists should have considerable expertise in the field of dermatology and cosmetology. The рифове of this investigation was to determine the need and benefits for conducting the training courses in the field of cosmetology for pharmacy students and to improve the future training, based on the student's feedback. In this study, 58 participants (pharmacy students) took part. After conducting training courses in cosmetic parlor, all participants completed questionnaire with 10 questions. 97 % of them are of the opinion that the course was very useful and will help them to practice pharmacy. The majority of them 60 % feel capable and confident to serve patients with cosmetic disorders. The main recommendation, which the participants have made, was to include in the training courses pharmacists with experience in cosmetics.

20. Georgiev, K., **M. Georgieva**, P. Marinov. Increasing knowledge of pharmacists in substance abuse prevention, education and assistance. – Сборник статии от Юбилейни научни конференции по фармакология и клинична фармакология за млади учени. Scientific papers of Jubilee Conferences of Pharmacology and Clinical Pharmacology for young scientists. Цигов Чарк, България, 5-7 юни 2015. стр. 15-17.

Pharmacists have unique knowledge, skills, and responsibilities for assuming an important role in substance abuse prevention, education, and assistance. Pharmacists, as health care providers, should be actively involved in reducing the negative effects that substance abuse has on the society, health systems, and the pharmacy profession. Therefore, to increase their knowledge we have organized second consecutive year free-elective discipline - Drug addiction, which is held after completing the course in pharmacology. In this survey 30 participants, pharmacy students have taken part (first year of the survey - 18, and the next year - 12). After the course of lectures, they completed a questionnaire with 10 questions. The most of them, 90 % were satisfied with the lecture course. During the course, the students visited the Clinic of Toxicology and Clinic for addiction and all of them 100 % gave a positive assessment of the initiative.

21. **Георгиева, М.**, Н. Манолов. Николай Иванович Пирогов – велик руски хирург и анатом (1810-1881). – *Варненски нефрологичен форум,* 3, 2016, № 2, 34-39.

Николай Иванович Пирогов (1810-1881) е изтъкнат руски хирург, основател на клиничната анатомия, учен педагог и общественик. Той въвежда обучението по приложна топографска анатомия, и е един от първите въвел етерната наркоза в Европа. Той е основоположник на военнополевата хирургия. По време на Кримската война (1853-1855) той пръв разработва гипсовата превръзка. Той е първият хирург, приложил анестезия на бойното поле (1847), и изобретил различни видове хирургични операции. Пирогов създава своя знаменит анатомичен атлас „Топографска анатомия на човешкото тяло" (1851-1854), който представлява първата публикация на замразени срезове в анатомичната илюстрация.

22. Хвърчанова, Н., **М. Георгиева**, Б. Каназирев. Тенденции в медикаментозното лечение при хоспитализирани болни по повод на хронична обострена сърдечна недостатъчност със запазена и редуцирана фракцияна изтласкване. – *Варненски медицински форум*, 7, 2018, № 1, 53-58.

Целта на нашето проучване беше да се установят тенденциите в прилаганото медикаментозно лечение при хоспитализирани по повод на сърдечна недостатъчност (СН) пациенти със запазена и потисната фракция на изтласкване. Това е постигнато чрез обобщаване и сравняване на информацията за предписваните медикаменти и потенциалните противопоказания и причини за неспазване препоръките за лечение на сърдечна недостатъчност.
Материали и методи: Това е ретроспективно проучване, обхващащо 535 пациенти, хоспитализирани в УМБАЛ „Света Марина“ - Варна за периода от януари 2010 до декември 2014 година с диагноза хронична обострена сърдечна недостатъчност. Сравнени са процентите на предписваните кардиоактивни медикаменти - блокери на РААС, бета-блокери, антагонисти на минералкортикоидните рецептори и калциеви антагонисти при пациенти с хронична СН и редуцирана и запазена ФИ.

23. Хвърчанова, Н., **М. Георгиева.** Морски тропически организми – източници на опасни токсини. – *Варненски медицински форум*, 7, 2018, приложение 1, 23-28.

Сакситоксин и тетродотоксин са сред най-мощните познати морски неврогпоксини. Специфични са за някои морски организми характерни за тропиците, но поради гпобапното затопляне и смяната в температурата те мигрират към необичайни за тях води. Рибата фугу се среща вече и в Хърватска - в южната част на адриатическото крайбрежие.
Сакситоксин и тетродотоксин могат да бъдат използвани за убийство или самоубийство. Сакситоксин е включен в списък 1 от конвенцията за химически оръжия, което засилва инте-реса на правителствените агенции към него, но отдръпва учените, проучващи морски токсини, а също така и производителите на морска храна. Тетродотоксин е познат от рибата фугу (риба балон) и от историята на Хаити - като главен елемент от ритуалите за създаване на зомбита от вуду шаманите там. Предумишлена интоксикация с тези токсини се наблюдава ряд-ко, като по-често се касае за зле приготвени ястия с рибата фугу или миди, съдържащи сакси-токсин. Прецизно поставената диагноза е от съществено значение.
На клетъчно ниво сакситоксин и тетро-дотоксин имат идентичен механизъм на действие, като основният им ефект е мускулна слабост, която може да прогресира до тотална парализа, наблюдават се и сензорни смущения. Двата токсина имат директно парализиращо действие върху напречно набразденатa скелетна мускулатура, както и върху нервните влакна.

24. Хвърчанова, Н., **М. Георгиева**, Б. Каназирев, В. Вълков. Полови различия в лечението на пациенти с хронична сърдечна недостатъчност и запазена или редуцирана фракция на изтласкване за периода 2010-2014. – *Наука Фармакология*, 2018, № 1.

Целта на проведеното проучване е да се установят половите различия в медикаментозното лечение на пациентите със сърдечна недостатъчност (СН) със запазена (СНзФИ) и редуцирана (СНрФИ) фракция на изтласкване (ФИ) на лявата камера.

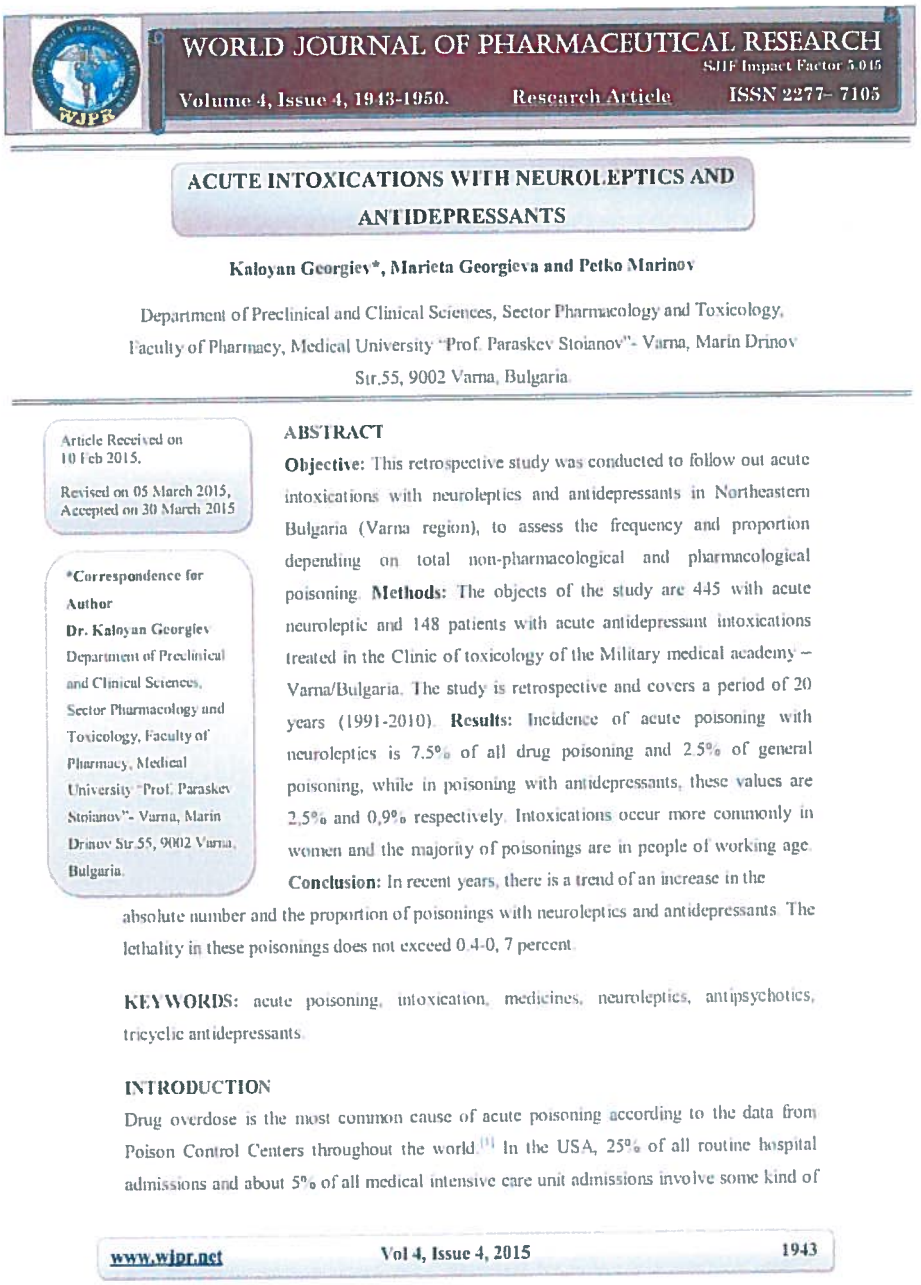
Материали и методи: Това е ретроспективно проучване на 535 пациента със СН, хоспитализирани за периода от януари 2010 до декември 2014 година. Анализирано е предписването на АСЕ инхибитори/ангиотензин рецепторни блокери, бета-блокери, минералкортикоидни рецепторни антагонисти, блокери на калциевите канали, статини, Ivabradine, Trimetazidine, Acenocoumarol и ацетилсалицилова киселина. Пациентите са разделени на групи - според техния пол и ФИ.

Резултати: Установени са много разлики между предписването на проучените медикаменти на групите пациенти с установяване на статистическо ниво на значимост за някои от тях.

Заключение: Има много разлики между пациентите със СНзФИ и СНрФИ, а също така и между мъже и жени със СН. Това обяснява различията в медикаментозното им лечение.

III. ПЪЛНОТЕКСТОВИ ПУБЛИКАЦИИ В ЧУЖДИ НАУЧНИ СПИСАНИЯ

1. Georgiev, K., **M. Georgieva**, P. Marinov. Acute intoxications with neuroleptics and antidepressants. – *World Journal of Pharmaceutical Research*, 4, 2015, № 4, 1943-1950.



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ACUTE INTOXICATIONS WITH NEUROLEPTICS AND ANTIDEPRESSANTS

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ABSTRACT

Objective: This retrospective study was conducted to follow out acute intoxications with neuroleptics and antidepressants in Northeastern Bulgaria (Varna region), to assess the frequency and proportion depending on total non-pharmacological and pharmacological poisoning. **Methods:** The objects of the study are 445 with acute neuroleptic and 148 patients with acute antidepressant intoxications treated in the Clinic of toxicology of the Military medical academy – Varna/Bulgaria. The study is retrospective and covers a period of 20 years (1991-2010). **Results:** Incidence of acute poisoning with neuroleptics is 7.5% of all drug poisoning and 2.5% of general poisoning, while in poisoning with antidepressants, these values are 2,5% and 0,9% respectively. Intoxications occur more commonly in women and the majority of poisonings are in people of working age. **Conclusion:** In recent years, there is a trend of an increase in the absolute number and the proportion of poisonings with neuroleptics and antidepressants. The lethality in these poisonings does not exceed 0.4-0, 7 percent.

KEYWORDS: acute poisoning, intoxication, medicines, neuroleptics, antipsychotics, tricyclic antidepressants.

INTRODUCTION

Drug overdose is the most common cause of acute poisoning according to the data from Poison Control Centers throughout the world.[1] In the USA, 25% of all routine hospital admissions and about 5% of all medical intensive care unit admissions involve some kind of

2. Georgiev, K, **M. Georgieva**, I. Iliev, M. Peneva, G. Alexandrov. Antiproliferative effects of Bulgarian spring water probiotics (Laktera Nature Probiotic®) against human colon carcinoma cell line. – *World Journal of Pharmacy and Pharmaceutical Sciences*, 4, 2015, № 6, 130-136.

WORLD JOURNAL OF PHARMACY AND PHARMACEUTICAL SCIENCES
SJIF Impact Factor 5.210
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ANTIPROLIFERATIVE EFFECT OF BULGARIAN SPRING WATER PROBIOTICS (LAKTERA NATURE PROBIOTIC®) AGAINST HUMAN COLON CARCINOMA CELL LINE

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ABSTRACT

Colorectal carcinoma is a malignant disease, from which more than 1 million people worldwide suffer. Over the past two decades, its social significance attracts more attention. Colorectal cancer is the second leading cause of death from malignancy and the third most frequently diagnosed malignancy. It has been estimated that nutrition is the main reason for the high incidence of cancer. Probiotics are live microorganisms with proven health benefits in a variety of gastrointestinal diseases, and disorders outside the gastrointestinal tract. The aim of the present study is to explore cytotoxic and anti-proliferative effects of the new Laktera Nature Probiotic® on non-cancerous cell lines (BALB/3T3 and BJ) and colon adenocarcinoma cell line – HT-29. Laktera Nature Probiotic® has weak direct cytotoxicity against BALB/3T3 and BJ cells, but inhibits their proliferation in a dose-dependent manner. On carcinoma cell line – HT-29, in low concentration range (2-125 µg/ml) Laktera Nature Probiotic® stimulates proliferation; at high concentrations (250-1000 µg/ml) we detected concentration-dependent inhibition of proliferation. Laktera Nature Probiotic® has shown

3. Hvarchanova, N., **M. Georgieva**, B. Kanazirev. Changing trends in heart failure patient's hospitalization and treatment in 2010-2014. – *Internation Journal of Medical and Health*

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Changing trends in heart failure patient's hospitalization and treatment in 2010-2014

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Abstract
Introduction/Aim: The aim of this study was to look for trends in demography and treatment of patients with both heart failure (HF) with preserved and reduced ejection fraction (EF) and to establish the extent of adherence to ESC guidelines for heart failure treatment.
Materials and Methods: This is a retrospective study involving 535 heart failure patients hospitalized for the period from January 2010 to December 2014. It involves age, gender, left ventricular EF, drug treatment prohibiting comorbidities and medical treatment with renin-angiotensin system blockers, beta- blockers and mineralocorticoid receptor antagonists.
Results: Patients in general tended to become older, and females and HFrEF to be prevalent over time in the investigated period. Patients with HF with preserved EF (HFpEF) were older than those with reduced EF. Male gender prevailed in the group of patients with HF with reduced EF (HFrEF) and female – among those with HFpEF. When estimating the annual percentage of non-adherence to therapy recommendations for heart failure, taking into account contraindications as well, a trend to better adherence to treatment recommendations over time was found. Still, there was a high percentage of non-adherence to heart failure therapy recommendations for both HFpEF and HFrEF.
Conclusion: There was increasing predominance of HFpEF, older age and female gender in heart failure hospitalizations over time with a tendency to improve adherence to ESC recommended treatments for heart failure in 2010-2014.

Keywords: heart failure, research, RAS blockers, beta-blockers, mineralocorticoid receptor antagonists, calcium antagonists

Introduction

Heart failure (HF) is characterized by high morbidity and mortality rates. It is often a consequence of other disorders of the cardiovascular system, including coronary artery disease, hypertension or valve disease. HF has usually being considered as insufficiency of contractile function of the left ventricle and left ventricular ejection fraction (EF) is used to define cardiac pump function. In the last two decades, it has been established that HF can also occur with normal or borderline EF – named HF with preserved EF (HFpEF) or heart failure with mid-range EF (HFmrEF), which now characterizes the majority of the HF cases [1-3]. The differences between the patients with HF with reduced EF (HFrEF) and those with HFpEF are numerous. The latter group are older and more frequently women. There are comorbidities that often accompany heart failure like diabetes, chronic kidney disease, anemia, iron deficiency, chronic obstructive pulmonary disease and obesity [4]. Compared to patients with HFrEF, hospitalizations and poor prognosis in patients with HFpEF are more frequently related to non-cardiovascular causes [5]. For HFrEF there are approved therapies that improve survival, if there are no contraindications or intolerance, while for HFpEF there are still controversies in treatment approaches [6] These approved therapies include ACE inhibitors (ACEi) and angiotensin receptor blockers (ARB), aldosterone antagonists (MRA), and beta-blockers (BB). They are frequently used in combination with diuretics, prescribed for relief of symptoms and signs of congestion.

Materials and Methods

In this retrospective study, 535 patients hospitalized as from January 2010 to December 2014 with a diagnosis of chronic decompensated heart failure are included. The patients were diagnosed upon admission with HF based on signs and symptoms typical for heart failure and were classified in NYHA III / IV functional class. Ejection fraction was determined by echocardiography and those with HF symptoms and signs and ejection fraction ≥ 50% were considered HFpEF patients. HFrEF patients were defined as having symptoms and signs of heart failure and EF<50%. Demographic, clinical and laboratory data including gender, age, echocardiographic left ventricular ejection fraction, blood pressure, heart rate, creatinine and eGFR, potassium and presence of COPD. Medication at hospital discharge was also collected collected from medical files.

Statistics

Descriptive analysis was used for the interpretation of the main characteristics of the sample and of the indicators included in the study. The basis of the analysis is composed of nonparametric tests, such as cross tabulation and chi-square (Chi) when searching for significant differences in the frequency representation of category values. The statistical significance in nonparametric tests was considered when $p \leq 0.05$.
Correlation analysis was used to analyse dependences between the variables. The estimation of the degree of dependence

4. Hvarchanova, N, **M. Georgieva,** B. Kanazirev. Gender Differences in Comorbidities of Heart Failure Patients with Preserved or Reduced Left Ventricular Ejection Fraction. – *WebmedCentral*, 2018, 1-7. WMC005439

Gender Differences in Comorbidities of Heart Failure Patients with Preserved or Reduced Left Ventricular Ejection Fraction

Author(s): Hvarchanova N, Georgieva M, Kanazirev B

Abstract

Introduction/Aim
The aim of this study was to establish gender differences in the comorbidities of heart failure (HF) patients both with preserved (HFpEF) or reduced (HFrEF) left ventricular ejection fraction Â

Materials and Methods
This is a retrospective study including 535 heart failure patients hospitalized in the period January, 2010 - December, 2014 with the rate of comorbidities in both groups - HFpEF and HFrEF being examined, including diabetes, hypertension, chronic obstructive pulmonary disease (COPD), atrial fibrillation, anemia and impaired kidney function based on the estimated glomerular filtration rate (eGFR).

Results
In this study females with HF tended to be older, more numerous and more likely than men to have comorbid impaired renal function and both genders had similar occurrence of all other comorbidities. Patients with HFpEF had hypertension more often and atrial fibrillation less often, compared to those with HFrEF. Females with HFpEF had hypertension more often and atrial fibrillation less often, compared to their counterparts with HFrEF. Males with HFpEF and HFrEF exhibited no differences in comorbidities whatsoever. Females with HFpEF and HFrEF had more impaired renal function than males and more frequently atrial fibrillation, if with HFrEF.

Conclusion
There was an increasing predominance of HFpEF, older age and female gender in HF hospitalizations over time. Registries and â€œreal-lifeâ€• investigations generally report higher prevalence of comorbidities compared to clinical trials but the impact on mortality seems to be different as mortality rates and causes of death are comparable between both sexes with slightly better survival in women, in contrast to their higher burden of comorbidities.

Introduction

Heart failure (HF) is among the most widely spread cardiovascular pathologies with millions of patients worldwide (1). Its morbidity and mortality rates, hospitalization and rehospitalization rates and financial costs are constantly escalating (2). Several epidemiological studies have shown an increasing incidence of HF with preserved ejection fraction (EF), increased percentage of female patients, and increasing age of hospitalized HF patients (3,4). There are multiple comorbidities associated with HF especially in the group of patients with HF with preserved EF (HFpEF). Both groups have frequent hospitalizations and short-term rehospitalizations, while in the group of patients with HFpEF the lethal outcomes are more frequently related to non-cardiovascular factors compared to patients with HF with reduced EF (HFrEF) (3, 4). There are many differences between HF with reduced and with preserved EF. The latter group presents at a more advanced age, patients are more frequently female, more rarely with ischemic heart disease (IHD) and more often with hypertension (7, 8, 9). This study examines comorbidities associated with chronic HF - diabetes, hypertension, chronic obstructive pulmonary disease (COPD), impaired kidney function based on the estimated glomerular filtration rate (eGFR), atrial fibrillation, and their distribution among the patients with preserved and reduced EF.

Materials and Methods

This is a retrospective study including 535 patients hospitalized in the period 2010-2014 and diagnosed with HF class III/IV NYHA and left ventricular EF verified by 2D echocardiography. Patients with symptoms and signs of HF with EF â‰¥50% were considered HFpEF and those with EF < 50% were classified as HFrEF. Demographic data and prescribed medications at discharge were obtained from medical records and included gender, age, EF, comorbidities, such as diabetes, hypertension, COPD, impaired kidney function based on eGFR, atrial

5. Kehayova, G., **M. Georgieva**, K. Georgiev. Hepatoprotective effect of probiotic, containing lactobacillicus bulgaricus DWT1, in acute paracetamol-induced liver damage in rats. – *World Journal of Pharmaceutical Research*, 4, 2018, 35-42.

HEPATOPROTECTIVE EFFECT OF PROBIOTIC, CONTAINING LACTOBACILLUS BULGARICUS DWT1, IN ACUTE PARACETAMOL-INDUCED LIVER DAMAGE IN RATS

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ABSTRACT

Hepatic impairment is one of the most common organ damage and occurs asymptomatically until damage affects a significant part of the organ. The aim of the present study was to investigate a hepatoprotective activity of a new strain of Lactobacillus bulgaricus DWT1 against paracetamol-induced hepatic damage in Wistar rats. Laktera Nature, containing Lactobacillus bulgaricus DWT1, Lactobacillus helveticus DWT2. Lactobacillus lactis DWT3 and Streptococcus thermophilus DWT 4,5, 6, 7, 8 administered at oral doses of 800 mg/kg and 1600 mg/kg, showed significant hepatoprotective effects by decreasing the levels of serum marker enzymes such as alanine aminotransferase (ALAT), aspartate aminotransferase (ASAT), alkaline phosphatase (ALP), gama-glutamiltransferase (GGT), as compared to standard drug (silymarin) and negative control. Histopathological analysis showed that administration of the probiotic minimized liver damage, by reducing the level of morphological changes and necrosis. Our findings demonstrate the possible use of Laktera Nature, containing Lactobacillus bulgaricus DWT1, Lactobacillus helveticus DWT2, Lactobacillus lactis DWT3 and Streptococcus thermophilus DWT4,5, 6, 7, 8 for prevention of liver injury.

KEY WORDS: probiotic, paracetamol, liver damage, hepatoprotective effect

IV. РЕЗЮМЕТА НА ДОКЛАДИ ОТ НАУЧНИ ФОРУМИ, ПУБЛИКУВАНИ В БЪЛГАРСКИ НАУЧНИ СПИСАНИЯ И СБОРНИЦИ

1. Milev, E., **M. Georgieva**. Phytotherapy in the treatment of immune deficiency. – Фармация, 58, 2011, Supplement, 90.

PHS-P3. PHYTOTHERAPY IN THE TREATMENT OF IMMUNE DEFFICIENCY

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The present review is an attempt to summarize the vast information, related to the problem of phytotherapy and phytoprophylaxy in the treatment of immune deficiency, due to variant reasons. The review contains data about plants and promising substances of plant origin with immunostimulant and immunomodulating effects. At present, little is known about the precise molecular mechanism of action for most of them. As basic data a large number of papers and publications from scientific centers and groups are used. There is a vide variety of newly discovered potential immunostimulant substances, isolated during the last years from medicinal plants, such as Withania, Muira puama, Euphorbia pallasi, Curcuma, Helleborus, species Terminalia, Rhus, some species of fungi, and others. Much of these sources are in their early stages of investigation. A small group of plants and substances are chosen to be presented here. The immunotropic plants and agents are selected so as to fit the following general criteria: Available data about immunotropic activity (in vitro and in experimental models); Available data (incomplete in many cases) about molecular mechanism of action; Relatively low toxicity; Promising use as drug clinically in near future; Participation in clinical trials (in some cases). The presented plants and the substances, isolated from them, are showing efficiency in animal models and tissue cultures. Some of them exhibit activity in clinical trails.

2. **Georgieva, M.**, D. Terziivanov, K. Bozhinova. Effect of Biostim LBS and carbontetrachloride on CYP1A2 activity in rats. – *Фармация*, 58, 2011, Supplement, 94.

PHS-P8. EXPERIMENTAL STUDY OF LEARNING AND MEMORY OF RATS AFTER 45-DAY TREATMENT WITH ATORVASTATIN AND ROSUVASTATIN

Maria Georgieva, Ivanka Kostadinova

Department of Pharmacology and Clinical Pharmacology, MU – Plovdiv

Statins are widely used for the treatment of hyperlipidemia. They have been shown to possess pleiotropic effects apart from their lipid-lowering activity – anti-inflammatory, immunomodulatory, neuroprotective. Opposed to these effects, serious adverse drug reactions are reported: cognitive impairment, insomnia, depression, antisocial behaviour. ***Aim:*** The aim of the present study was to investigate the effect of 45-day treatment with atorvastatin and rosuvastatin on learning and memory processes of rats without brain damage. ***Matherials and methods:*** Wistar rats were treated orally for 45 days with atorvastatin and rosuvastatin in two different doses (10 mg/kg bw and 20 mg/kg bw), in parallel with vehicle-treated group. After that period learning ability and memory retention were evaluated using automatic reflex conditioner (shuttle box) and two types of passive avoidance tests (step through and step down). The following behavioral reactions were investigated with the active avoidance test: conditioned responses (avoidance), unconditioned responses (escapes) and intertrial crossings. The passive avoidance tests were used to observe the latency of reaction. ***Results:*** The results from the passive avoidance tests suggested that rosuvastatin in different doses enhances the formation of short-term memory. The tested drugs didn't improve the preservation of long-term memory on the passive avoidance tests. The results from the active avoidance test also suggested that rosuvastatin prevents the preservation of long-term memory.

PHS-P9. EFFECT OF BIOSTIM LBS AND CARBONTETRACHLORIDE ON CYP1A2 ACTIVITY IN RATS

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The possible role of CYP1A2 in mediating the inducing or inhibitory effects of Biostim LBS and carbontetrachloride (CCL_4) applied separately or in combination was evaluated in an experimental model of hepatotoxicity in Wistar male rats. Comparison of structural population models parameter estimates from the three population pharmacokinetic (PK) models of caffeine (CA), NPEM2-BIOST, NPEM2-CCL4 and NPEM2-BIOST-CCL_4 built-up on data from rats treated with Biostim LBS or CCL_4 alone and in combination, with the parameter values of the population PK model of rats treated with CA only, NPEM2-CAF, revealed statistically significant raise in CYP1A2 activity after Biostim LBS treatment, whereas CCL_4 treatment significantly inhibited enzyme activity. 30-days pretreatment with Biostim LBS prevented CCL_4 inhibitory effect on CYP1A2 activity. The results of the present study unambiguously revealed the ability of the population PK analysis to be used in the so-called evolutionary PK (allometric scaling) for relevant forecasting of drugs PK behaviour in humans based on data derived from animals.

PHS-P10. DENTAL OINTMENT WITH THIOTRIAZOLIN AND CHLORAMPHENICOL (LEVOMICETIN) FOR TREATMENT OF INFLAMMATORY DISEASES OF THE PERIODONTAL TISSUES

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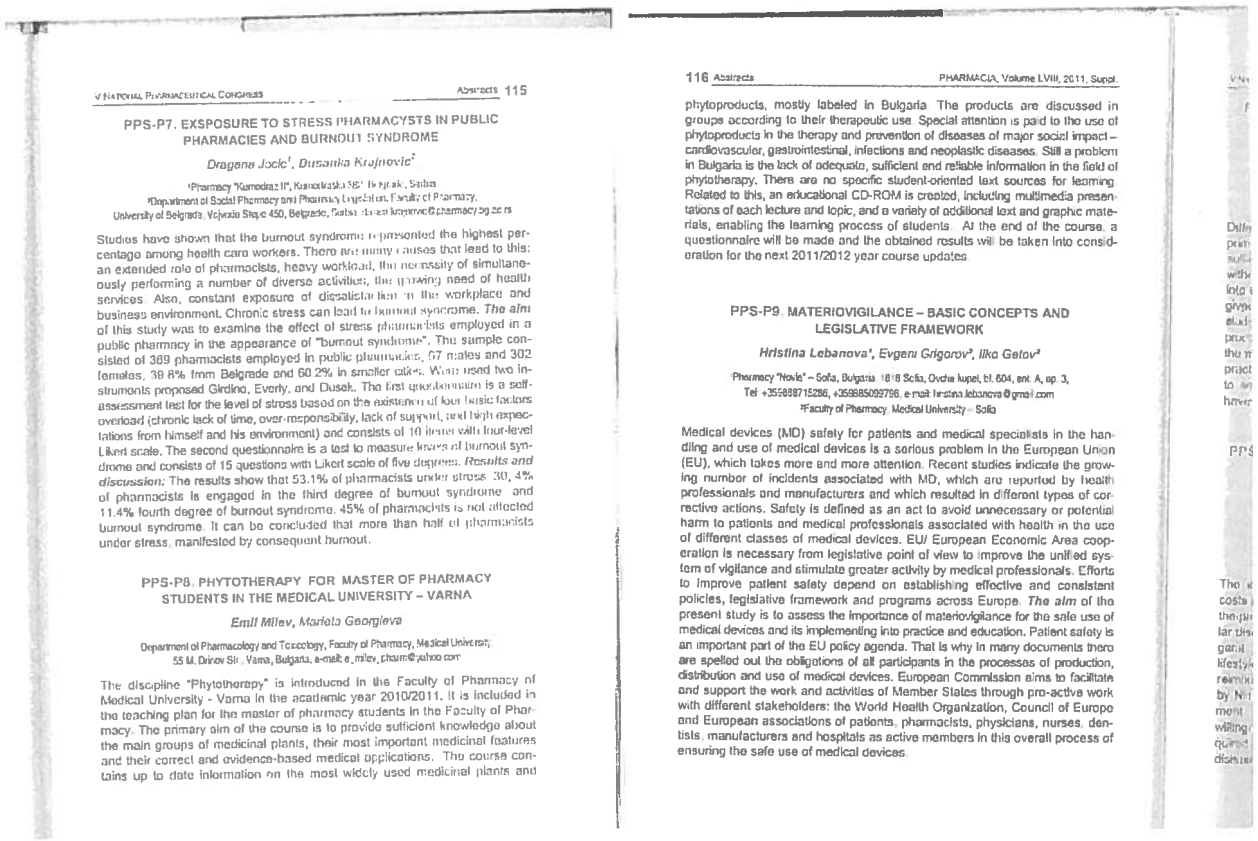
Problems concerned with development of new, more efficient remedies for treatment of inflammatory diseases of the periodontal tissues belong to the most urgent in contemporary dentistry. An application of local dental ointments with antimicrobial and anti-inflammatory ingredients is a promising trend in modern dentistry. Thiotriazolin and chloramphenicol (levomicetin) occupy an important place in the treatment of inflammatory diseases of the periodontal tissues. Thiotriazolin has high antioxidant, immunomodulatory and healing effects. Chloramphenicol is antibiotic of broad-spectrum activity. It is active against gram-positive and gram-negative bacteria. The microbiological investigations have shown that combination of thiotriazolin and chloramphenicol in one dosage form increase the pharmacological effect of each other. For the development of the ointment we have studied a number of carriers possessing properties of adhesion to oral mucosa. It has been determined that the most optimum carrier is 3% solution of methyl cellulose with 10% concentration of glycerine as plasticizer. The efficacy of dental ointment with thiotriazolin and chloramphenicol has been confirmed in clinical conditions. In the case of different periodontitis forms, the remission was achieved after 2-3 visits after its complex treatment. There was a rapid removal of inflammation in generalized periodontitis of mild and medium severity.

3. Milev, E., **M. Georgieva**. Phytotherapy for master of pharmacy students in the Medical University - Varna. – *Фармация*, 58, 2011, Supplement, 115-116.



PPS-P7. EXSPOSURE TO STRESS PHARMACYSTS IN PUBLIC PHARMACIES AND BURNOUT SYNDROME

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Studies have shown that the burnout syndrome represented the highest percentage among health care workers. There are many causes that lead to this: an extended role of pharmacists, heavy workload, the necessity of simultaneously performing a number of diverse activities, the growing need of health services. Also, constant exposure of dissatisfaction in the workplace and business environment. Chronic stress can lead to burnout syndrome. *The aim* of this study was to examine the effect of stress pharmacists employed in a public pharmacy in the appearance of "burnout syndrome". The sample consisted of 369 pharmacists employed in public pharmacies, 67 males and 302 females, 39.8% from Belgrade and 60.2% in smaller cities. We used two instruments proposed Girdino, Everly, and Dusek. The first questionnaire is a self-assessment test for the level of stress based on the existence of four basic factors overload (chronic lack of time, over-responsibility, lack of support, and high expectations from himself and his environment) and consists of 10 items with four-level Likert scale. The second questionnaire is a test to measure levels of burnout syndrome and consists of 15 questions with Likert scale of five degrees. *Results and discussion:* The results show that 53.1% of pharmacists under stress. 30, 4% of pharmacists is engaged in the third degree of burnout syndrome and 11.4% fourth degree of burnout syndrome. 45% of pharmacists is not affected burnout syndrome. It can be concluded that more than half of pharmacists under stress, manifested by consequent burnout.

PPS-P8. PHYTOTHERAPY FOR MASTER OF PHARMACY STUDENTS IN THE MEDICAL UNIVERSITY – VARNA

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The discipline "Phytotherapy" is introduced in the Faculty of Pharmacy of Medical University - Varna in the academic year 2010/2011. It is included in the teaching plan for the master of pharmacy students in the Faculty of Pharmacy. The primary aim of the course is to provide sufficient knowledge about the main groups of medicinal plants, their most important medicinal features and their correct and evidence-based medical applications. The course contains up to date information on the most widely used medicinal plants and

phytoproducts, mostly labeled in Bulgaria. The products are discussed in groups according to their therapeutic use. Special attention is paid to the use of phytoproducts in the therapy and prevention of diseases of major social impact – cardiovascular, gastrointestinal, infections and neoplastic diseases. Still a problem in Bulgaria is the lack of adequate, sufficient and reliable information in the field of phytotherapy. There are no specific student-oriented text sources for learning. Related to this, an educational CD-ROM is created, including multimedia presentations of each lecture and topic, and a variety of additional text and graphic materials, enabling the learning process of students. At the end of the course, a questionnaire will be made and the obtained results will be taken into consideration for the next 2011/2012 year course updates.

PPS-P9. MATERIOVIGILANCE – BASIC CONCEPTS AND LEGISLATIVE FRAMEWORK

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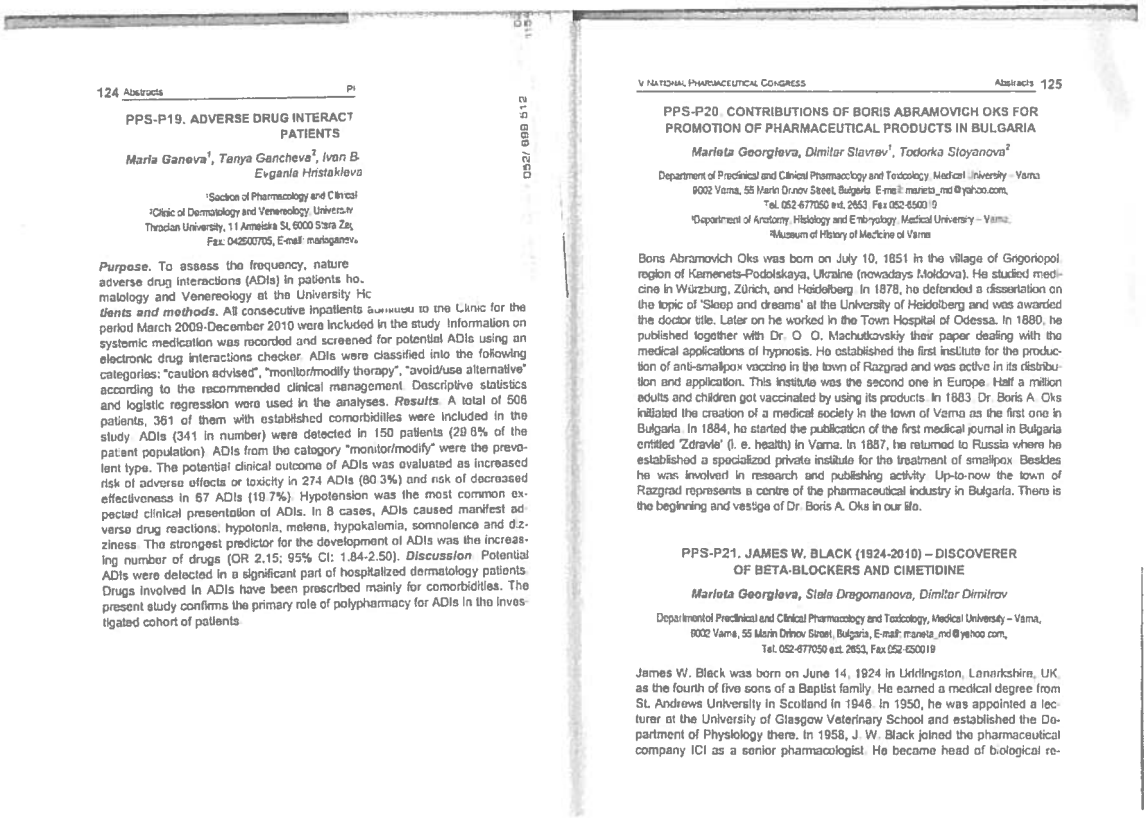
Medical devices (MD) safety for patients and medical specialists in the handling and use of medical devices is a serious problem in the European Union (EU), which takes more and more attention. Recent studies indicate the growing number of incidents associated with MD, which are reported by health professionals and manufacturers and which resulted in different types of corrective actions. Safety is defined as an act to avoid unnecessary or potential harm to patients and medical professionals associated with health in the use of different classes of medical devices. EU/ European Economic Area cooperation is necessary from legislative point of view to improve the unified system of vigilance and stimulate greater activity by medical professionals. Efforts to improve patient safety depend on establishing effective and consistent policies, legislative framework and programs across Europe. *The aim* of the present study is to assess the importance of materiovigilance for the safe use of medical devices and its implementing into practice and education. Patient safety is an important part of the EU policy agenda. That is why in many documents there are spelled out the obligations of all participants in the processes of production, distribution and use of medical devices. European Commission aims to facilitate and support the work and activities of Member States through pro-active work with different stakeholders: the World Health Organization, Council of Europe and European associations of patients, pharmacists, physicians, nurses, dentists, manufacturers and hospitals as active members in this overall process of ensuring the safe use of medical devices.

4. **Georgieva, M.**, D. Stavrev, T. Stoyanova. Contributions of Boris Abramovich Oks for promotion of pharmaceutical products in Bulgaria. – *Фармация*, 58, 2011, Supplement, 125.



PPS-P19. ADVERSE DRUG INTERACT
PATIENTS

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Purpose. To assess the frequency, nature adverse drug interactions (ADIs) in patients ho matology and Venereology at the University Hc ***tients and methods.*** All consecutive inpatients admitted to the Clinic for the period March 2009-December 2010 were included in the study. Information on systemic medication was recorded and screened for potential ADIs using an electronic drug interactions checker. ADIs were classified into the following categories: "caution advised", "monitor/modify therapy", "avoid/use alternative" according to the recommended clinical management. Descriptive statistics and logistic regression were used in the analyses. ***Results.*** A total of 506 patients, 361 of them with established comorbidities were included in the study. ADIs (341 in number) were detected in 150 patients (29.6% of the patient population). ADIs from the category "monitor/modify" were the prevalent type. The potential clinical outcome of ADIs was evaluated as increased risk of adverse effects or toxicity in 274 ADIs (80.3%) and risk of decreased effectiveness in 67 ADIs (19.7%). Hypotension was the most common expected clinical presentation of ADIs. In 8 cases, ADIs caused manifest adverse drug reactions: hypotonia, melena, hypokalemia, somnolence and dizziness. The strongest predictor for the development of ADIs was the increasing number of drugs (OR 2.15; 95% CI: 1.84-2.50). ***Discussion.*** Potential ADIs were detected in a significant part of hospitalized dermatology patients. Drugs involved in ADIs have been prescribed mainly for comorbidities. The present study confirms the primary role of polypharmacy for ADIs in the investigated cohort of patients.

PPS-P20. CONTRIBUTIONS OF BORIS ABRAMOVICH OKS FOR PROMOTION OF PHARMACEUTICAL PRODUCTS IN BULGARIA

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Boris Abramovich Oks was born on July 10, 1851 in the village of Grigoriopol region of Kamenets-Podolskaya, Ukraine (nowadays Moldova). He studied medicine in Würzburg, Zürich, and Heidelberg. In 1878, he defended a dissertation on the topic of 'Sleep and dreams' at the University of Heidelberg and was awarded the doctor title. Later on he worked in the Town Hospital of Odessa. In 1880, he published together with Dr. O. O. Machutkovskiy their paper dealing with the medical applications of hypnosis. He established the first institute for the production of anti-smallpox vaccine in the town of Razgrad and was active in its distribution and application. This institute was the second one in Europe. Half a million adults and children got vaccinated by using its products. In 1883 Dr. Boris A. Oks initiated the creation of a medical society in the town of Varna as the first one in Bulgaria. In 1884, he started the publication of the first medical journal in Bulgaria entitled 'Zdravie' (i. e. health) in Varna. In 1887, he returned to Russia where he established a specialized private institute for the treatment of smallpox. Besides he was involved in research and publishing activity. Up-to-now the town of Razgrad represents a centre of the pharmaceutical industry in Bulgaria. There is the beginning and vestige of Dr. Boris A. Oks in our life.

PPS-P21. JAMES W. BLACK (1924-2010) – DISCOVERER OF BETA-BLOCKERS AND CIMETIDINE

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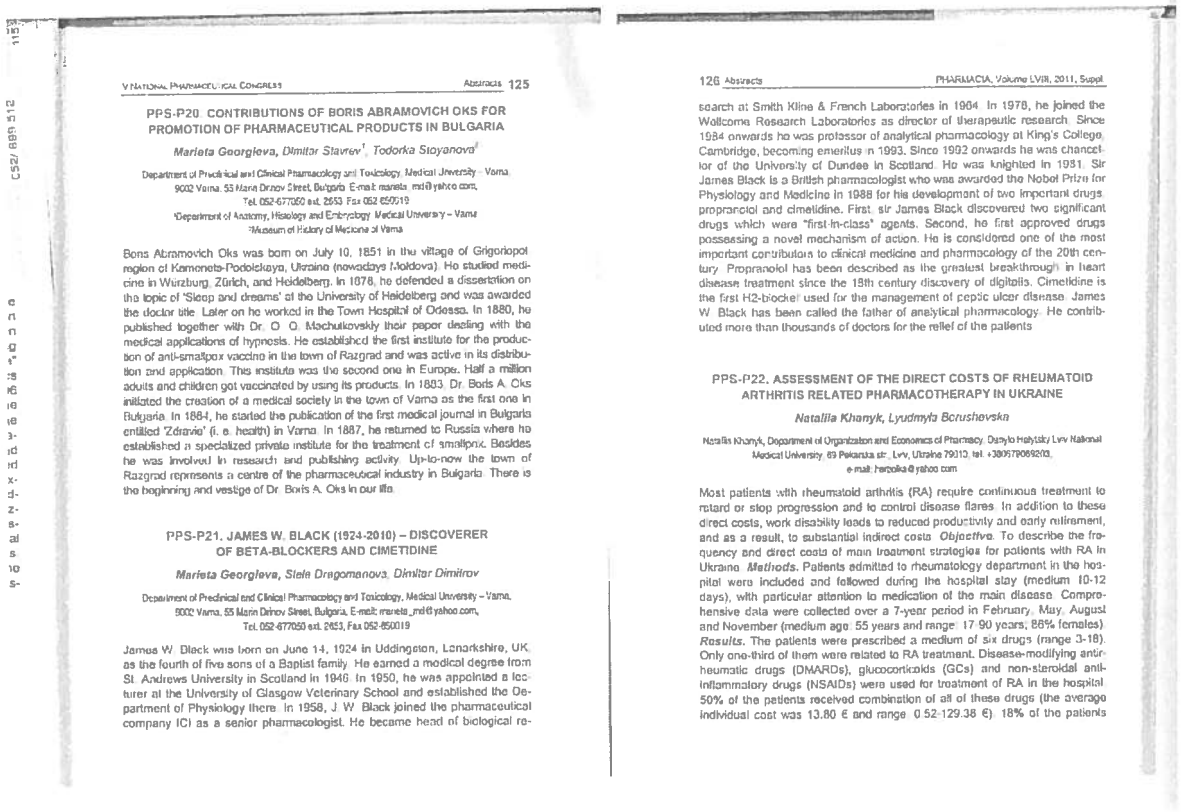
James W. Black was born on June 14, 1924 in Uddingston, Lanarkshire, UK, as the fourth of five sons of a Baptist family. He earned a medical degree from St. Andrews University in Scotland in 1946. In 1950, he was appointed a lecturer at the University of Glasgow Veterinary School and established the Department of Physiology there. In 1958, J. W. Black joined the pharmaceutical company ICI as a senior pharmacologist. He became head of biological re-

5. **Georgieva, M.**, S. Dragomanova, D. Dimitrov. James W. Black (1924-2010) – discoverer of Beta-Blockers and Cimetidine. – *Фармация*, 58, 2011, Supplement, 125-126.



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PPS-P20. CONTRIBUTIONS OF BORIS ABRAMOVICH OKS FOR PROMOTION OF PHARMACEUTICAL PRODUCTS IN BULGARIA

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PPS-P21. JAMES W. BLACK (1924-2010) – DISCOVERER OF BETA-BLOCKERS AND CIMETIDINE

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James W. Black was born on June 14, 1924 in Uddingston, Lanarkshire, UK, as the fourth of five sons of a Baptist family. He earned a medical degree from St. Andrews University in Scotland in 1946. In 1950, he was appointed a lecturer at the University of Glasgow Veterinary School and established the Department of Physiology there. In 1958, J. W. Black joined the pharmaceutical company ICI as a senior pharmacologist. He became head of biological research at Smith Kline & French Laboratories in 1964. In 1978, he joined the Wellcome Research Laboratories as director of therapeutic research. Since 1984 onwards he was professor of analytical pharmacology at King's College, Cambridge, becoming emeritus in 1993. Since 1992 onwards he was chancellor of the University of Dundee in Scotland. He was knighted in 1981. Sir James Black is a British pharmacologist who was awarded the Nobel Prize for Physiology and Medicine in 1988 for his development of two important drugs: propranolol and cimetidine. First, sir James Black discovered two significant drugs which were "first-in-class" agents. Second, he first approved drugs possessing a novel mechanism of action. He is considered one of the most important contributors to clinical medicine and pharmacology of the 20th century. Propranolol has been described as the greatest breakthrough in heart disease treatment since the 18th century discovery of digitalis. Cimetidine is the first H2-blocker used for the management of peptic ulcer disease. James W. Black has been called the father of analytical pharmacology. He contributed more than thousands of doctors for the relief of the patients.

PPS-P22. ASSESSMENT OF THE DIRECT COSTS OF RHEUMATOID ARTHRITIS RELATED PHARMACOTHERAPY IN UKRAINE

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Most patients with rheumatoid arthritis (RA) require continuous treatment to retard or stop progression and to control disease flares. In addition to these direct costs, work disability leads to reduced productivity and early retirement, and as a result, to substantial indirect costs. *Objective.* To describe the frequency and direct costs of main treatment strategies for patients with RA in Ukraine. *Methods.* Patients admitted to rheumatology department in the hospital were included and followed during the hospital stay (medium 10-12 days), with particular attention to medication of the main disease. Comprehensive data were collected over a 7-year period in February, May, August and November (medium age: 55 years and range: 17-90 years; 86% females). *Results.* The patients were prescribed a medium of six drugs (range 3-18). Only one-third of them were related to RA treatment. Disease-modifying antirheumatic drugs (DMARDs), glucocorticoids (GCs) and non-steroidal anti-inflammatory drugs (NSAIDs) were used for treatment of RA in the hospital. 50% of the patients received combination of all of these drugs (the average individual cost was 13.80 € and range: 0.52-129.38 €). 18% of the patients

6. **Georgieva, M.**, G. Haralanova, P. Marinov. Acute intoxications with neuroleptics and antidepressants: survery. – *Journal of Biomedical & Clinical Research*, 7, 2014, Supplement 1, 38.

diabetes in spontaneously hypertensive rats (SHR). Twenty four male and female SHRs, strain Okamoto-Aoki of uniform age were randomly divided into four groups (n=6). Group 1and 2 are non - diabetic control male and female SHR; Groups 3 and 4 are challenged with Streptozotocin (40 mg/kg i.p) rats. Blood pressure and fasting glucose levels were monitored once a day for two weeks. The animals with highest blood pressure and blood glucose levels were chosen for the experiment. Livers were collected for assessment of reduced glutathione (GSH), thiobarbituric acid reactive substances (TBARS), measured as malonedialdehide (MDA), and aniline hydroxylase (AH) activity, a marker enzyme for cytochrome P450 (CYP2E1). There was an increase in the MDA production and the activity of AH, and decrease in the concentration of GSH in diabetic SHR livers, compared with non-diabetic SHR livers. These results are more pronounced in male diabetic rats, compared to female. On the basis of these data we can conclude that the two pathological conditions – diabetes and hypertension, part of the metabolic syndrome interfere not only with the endogenous protective mechanisms but also with the metabolic activity of the liver.

Key words: SHR, diabetes, streptozotocin, metabolism, rats

POSTERS

XANTHATE METABOLISM BY DIFFERENT MONOOXYGENSES AND REACTIVE OXYGEN SPECIES

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Summary
Xanthates (alkyl derivatives of dithiocarbonic acid, ROCS2K) are well known metal ions chelating agents with variety of biological properties as antitumor and antiviral effects. Our previous studies have shown that xanthates were powerful and selective mechanism-based inactivators of some cytochrome P450 isozymes (2B6 and 2E1).Other P450's were either inhibited (1A1, 2D6, 2C9, 4A11) or not affected (3A2, 3A4). The primary side of P450 attack on xanthate molecule is the carbon atom. There are data that some reactive oxygen species are playing major role in the cytochrome P450 xanthates metabolism.
In this study, we are following the metabolism of xanthates (spectroscopically and by HPLC) by some other reactive oxygen dependent enzymatic and non-enzymatic systems like flavine monooxygenase (FMO3), horseradish peroxidase (HRP), hydroxyl radicals (Fe^{3+}/ascorbate/H_2O_2/with or without EDTA) and superoxide radicals (UV-degradation of riboflavine/methionine) producing systems.
FMO3 oxidized one of the sulfur atoms giving perxanthate (the same metabolite is producing by incubation of xanthates with H_2O_2). On the other hand, HRP-compound I (when the ratio enzyme/H_2O_2 is 1:1) oxidizes xanthate mainly to bisxanthate. Xanthates inhibited deoxyribose degradation in Haber Weis reaction mainly by scavenging the hydroxyl radicals concentration. Superoxide generated by the photooxidation of riboflavin, metabolized xanthates to unknown metabolites without oxidation of the sulfur atoms. The same was done by purified CYP2B6.
The readiness of xanthate molecule to interact with different reactive oxygen species reflect in their potent antioxidant and scavenger activity, which could be on the background of their antiviral and anticancer activity.

Key words: xanthates, cytochrome p450, metabolism, reactive oxygen species

ACUTE INTOXICATIONS WITH NEUROLEPTICS AND ANTIDEPRESSANTS: SURVEY

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Summary
Taking into account the increasing use of antidepressants in the world, as well as the vital use of neuroleptics in patients with schizophrenia, we have examined and summarized the data obtained for intoxications with these drugs.
The data available related to intoxications with neuroleptics and antidepressants have been obtained from the Department of Toxicology at the Military Medical Academy - Varna, as well as from additional literature sources, mentioned below in the exposition. On the basis of these data we did our summaries concerning the frequency of the acute intoxications with the indicated medications.
Upon performing a retrospective analysis of the acute poisonings in the Varna region for a 5 year period (2006-2010), based on the adopted for treatment in the Department of Toxicology at the Military Medical Academy - Varna 4960 patients with acute intoxications and acute allergic reactions, was found that the drug intoxications are with a relative share of 18.3% and rank third as a cause of hospitalization.
According to the retrospective analysis, we concluded that is observed a decrease in the drug poisonings, particularly with neuroleptics and antidepressants, compared to data from the recent past, when they have occupied a leading position among the intoxications. It is believed that the reduction of the frequency of the drug poisonings is due to the regular allocation of medicines in the pharmacy network.
Key words: neuroleptics, antidepressants, intoxications, analysis

PPARγ AGONISTS AND LIVER STEATOSIS: MODE-OF-ACTION CHARACTERISATION AND *IN SILICO* STUDY

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Summary
Ligand-dependent activation of hepatic PPARγ has been proposed as a molecular initiating event (MIE) in a prosteatotic mode-of-action (MoA). In this study we aimed at (i) *in silico* study of the PPARγ-ligand interactions as important for elucidation of the MIE; (ii) evaluation of the quantitative evidence supporting key intermediate events within the MoA.
PPARγ-ligand complexes were extracted from Protein Data Bank. For the molecular modelling purposes MOE 2012.10 software was used. The following tools were applied: Protonate 3D, Ligand Interactions, Site Finder and Pharmacophore Analysis. MoA assessment was based on a literature search and followed the AOP/OECD principles.
118 PPARγ-ligand complexes were analyzed. The study outlined important features of the PPARγ ligand-binding pocket, as well as the main interactions with some of the most potent agonists. A pharmacophore model for the PPARγ full agonists was developed and the pharmacophoric features were discussed in relation to their role for the ligand binding to PPARγ. The performed assessment of the developed toxicity pathways outlined PPARγ target proteins relevant to the studied MoA.
The results can be used for: (i) safety evaluation of new compounds targeting PPARγ; (ii) rational design of compounds with controlled activity towards the PPARγ receptor.
Key words: PPARγ; liver steatosis; molecular initiating event (MIE); molecular modelling; pharmacophore
Acknowledgements. The funding from the European Community's 7th Framework Program (FP7/2007-2013) COSMOS Project under grant agreement n°266835 and from Cosmetics Europe is gratefully acknowledged.

RISKS OF ORAL METHOTREXATE ADMINISTRATION IN OUTPATIENTS

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7. Kehayov, D., **M. Georgieva**. Drugs classification during lactation periods. – *Journal of Biomedical & Clinical Research*, 7, 2014, Supplement 1, 41.

The aim of our experiments was to study the effects of benzodiazepine and ethanol administration on reproduction and fetal development of pregnant Wistar rats.
The experimental animals were treated separately or in combination with ethanol, diazepam and medazepam. The number of early fetal deaths and reproductive parameters in male and female rats-generation of the treated animals were observed. We used a reproduction method published by Boyadjieva N, 1988.
Our results show that ethanol potentiated the toxic effects of diazepam and medazepam on fetal development. We observed high frequency of fetal lethality and decreased sexual perception in the generations of rats treated with the combination of ethanol and benzodiazepines. Diazepam and medazepam administrations decreased reproductive abilities in male generations and ethanol potentiated the adverse effects of benzodiazepines.
Our toxicological studies suggest that combined consumption of benzodiazepines and ethanol may cause both early- (fetal lethality) and late-onset (decreased reproductive abilities) adverse reactions on generations of pregnant rats treated with the substances.
Key word: ethanol, diazepam, medazepam reproduction, fetal development

DRUGS CLASSIFICATION DURING LACTATION PERIODS

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Summary
Classification of drugs used during lactation is a poorly explored field in present day pharmacology.
The purpose of this study is to provide practicing health care specialists with a stable and broad qualifications system as the base for making the right choice when administering drugs to beast-feeding patients.
The development of the present qualification scheme is based on logical and statistical methodological approaches keeping in mind the purpose of this study - to classify drugs registered in Bulgaria.
Initially obtained results lead to interesting conclusions, which should be used for further therapy refinement in patients of this high-risk therapeutic group.
Drugs are divided into 4 categories:
1. Considered safe for the infant.
2. Relatively safe for the infant.
3. Safe for the infant after the elimination of the drug out of the mother's body.
4. Considered safe for the mother, but toxic for the infant.
Key words: drugs, lactation, pharmacotherapy

IMMUNOPHARMACOLOGY

ORAL PRESENTATIONS

VITAMIN D, AUTOIMMUNE DISORDERS AND INFERTILITY

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Summary
Studies on vitamin D and its prohormones are increasingly extending beyond the focus and functions related to calcium and bone metabolism. The discovery of the nuclear vitamin D receptor (VDR) in 1974 and its localization in promyelocytes, monocytes, lymphocytes, ovarian, and placental endothelial cells, dermal fibroblasts allow the study of the noncalcemic vitamin D-mediated effects, such as cell proliferation and differentiation and immuno-modulation. VDR is expressed in many cells of the immune system, including monocytes, macrophages, dendritic cells, NK lymphocytes, T and B lymphocytes. Its concentration is high, however, in immature thymocytes and CD8 lymphocytes, regardless of the activation status. Other experimental models, demonstrate the effects of vitamin D on the immune system, some of which are regulated to the differentiation and

8. **Georgieva, M.,** M. Peneva, G. Aleksandrov. Significance of HACCP Plan for Food stuffs and Food Supplements Safety. – *Journal of Biomedical & Clinical Research*, 7, 2014, Supplement 1, 79.

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Summary
The pharmacokinetics of zinc was investigated in broiler chickens after single crop intubation of 50 mg/kg 5% zinc aspartate suspension in 2% carboxymethyl cellulose solution.
Blood serum zinc concentrations were assayed on a biochemical analyzer. The pharmacokinetics of zinc was done using two pharmacokinetic approaches – compartmental method and non-compartmental analysis using pharmacokinetic software (TopFit, v. 2.0.).
After the intraingluvial application, zinc was rapidly absorbed ($t_{1/2abs}$=0.104±0.02 h) by the alimentary system of birds attaining C_{max} of 63.60±3.94 mol/ml by hour 0.77 (compartmental method) and C_{max}=69.27±4.35 mol/ml by hour 0.92h (non-compartmental method). It is characterized with a long biological half-life ($t_{1/2}$) of 13.82±1.63h (compartmental analysis) and 15.96±1.73h (non-compartmental analysis) and long mean residence times (MRT) 20.12±2.35h and 23.00±2.50h, respectively. The distribution in blood and extracellular fluid was good as seen from $Vd_{(area)}$ values – 0.77±0.05 l/kg (compartmental analysis) and 0.65±0.05 l/kg (non-compartmental analysis).
Key words: pharmacokinetics, chickens, zinc aspartate

SIGNIFICANCE OF HACCP PLAN FOR FOOD STUFFS AND FOOD SUPPLEMENTS SAFETY

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Summary
The free market and the quickly changing social and economic circumstances lead to poor control of the foodstuffs' quality and safety. HACCP is a part of the systems for foodstuff's safety management.
The main task of the HACCP system in the food industry is to implement requirements for the manufacture of a safe product meeting the specified qualitative indexes – organoleptic, physicochemical and microbiological. This system follows up, controls and prevents the probabilities during the manufacture various biological, chemical and physical risks to appear.
Ever heavier problem in the present day is the production and consumption of genetically manipulated foods and organisms. Over 50 countries, including all EU member-states, as well as most of the countries in Asia require labeling of the genetically engineered foods.
Important part of the HACCP system is the presentation of objective and full information about the foodstuff on the label, which is improving the consumers' awareness. Thus, the consumers are able to make a conscious and free choice of foods and to lead healthy way of life.
Time and the world experience prove the efficiency of HACCP system and, therefore, it is internationally recognized as the most reliable system of guaranteeing the safety of the foodstuffs.
Key words: Hazard analysis and critical control point (HACCP system), safety foodstuff, genetically manipulated foods and organisms

OXIDATIVE STRESS MARKERS AND HEME-OXIGENASE-1 IN FATTY LIVER, INDUCED BY DIET HIGH IN FRUCTOSE

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9. Yustiniyanova, B., **M. Georgieva**, B. Nanova. Immunofan – characterization and significance as immunomodulator in malignant diseases. – *Scripta Scientifica Pharmaceutica*, 1, 2014, Supplement 1, 17.

fect of 1/100 AICCL, and gastroprotective effect of 2/100 AICCL and EICCW in support of the scarce reports about internal usage of decoctions from *C. coggygria*. The most probable mechanism of these beneficial effects is the significant decrease of lipid peroxidation, due to the antioxidant properties of the plant investigated. Phytochemical analyses showed that the major components of the AICCL are gallotannins and gallic acid. Fustin and sulfuretin were the major bioflavonoid constituents of the EICCW.

IMMUNOFAN – CHARACTERIZATION AND SIGNIFICANCE AS IMMUNOMODULATOR IN MALIGNANT DISEASES

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Immunofan is a modern effective immunomodulator as a product of the newest tendency in world medicine – the molecular nanotechnology. The author and discoverer of the unique patent medicine is Prof. Dr. Vasilii Lebedev. The product is manifectured in three forms: sterile ampullae, spray doses and suppositories in Scientific-manufacture complex "Bionox" in Moscow. Pharmaceutical effect of Immunofan is manifested in three basic directions:

- **Restoration the balance of the oxidation and restoration processes in the organism;**
- **Correct the immune system in cases, when the immune system is destroyed in appearance of malignant formation, disease respectively;**
- **Remove the possibility for multiple drug resistance (MDR), and by this way the effect of the treatment with other drugs is increased in patients with malignant disease.**

For the first time in the world a new medicine is created that give the chance to be used to abolish the multiple drug resistance. In the treatment of malignant diseases it is concerned that during the period of chemotherapy should not be taken immunomodulators, because they increase cellular mitotic activity. Just the opposite is the idea that Immunofan should be taken exactly during the time of chemotherapy, because the multiple drug resistance is avoided, returning the cellular sensitiveness to therapeutic effect of chemotherapy. Overcoming multiple drug resistance, the most powerful effect of medicines is achieved in treatment. The effect of Immunofan is developed and keeps for 2-3 hours (rapid phase) and is continued to 4 months (moderate and prolonged phases). In patients with cancer two ways of therapy is recommended. First: by inclusion in general scheme of multipurpose treatment (chemotherapy and operation), and at that moment start the application of Iimmunofan just before chemotherapy or operation, and second followed by continuing of application the medicine during the whole therapeutic period. It is accepted that Immunofan is a patent medicine that has no analogue among immunomodulators manufactured to this moment in different countries in the world. In patients with cancer Immunofan is with proved effectiveness and is received permission and license for application in medicine. Immunofan is recommended not only for cancer prevention, but for appropriate therapeutic patent medicine with proved effectiveness in secondary and tertiary prevention of cancer. That gives the possibility for prolongation and improvement of life property of patients with cancer.

Keywords: *immunofan, immunomodulator, malignant diseases, prevention, therapy*

10. Dragomanova, S., **M. Georgieva**, R. Pehlivanova, B. Boeva, H. Toncheva, K. Iliev. Problems with prescribing, reading and dispensing of drugs, and education of students of pharmacy, medicine and dentistry. – *Scripta Scientifica Pharmaceutica*, 1, 2014, Supplement 1, 23.

PROBLEMS WITH PRESCRIBING, READING AND DISPENSING OF DRUGS, AND EDUCATION OF STUDENTS OF PHARMACY, MEDICINE AND DENTISTRY

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Medical services and care for patients today are increasingly liberalized and relying on awareness and active participation of the patient. But problems with the spelling and the correct allocation of prescription drugs remain. Many countries have introduced electronic prescriptions, which reduces the possibility of error to a minimum. In Bulgaria such a project is currently in progress.

Will focus primarily on the problems at discharge and dispensing of medicines prescribed on regular ("white") form - Ordinance № 4, Official Gazette No. 3, year LV, Annex 2 to Article 6, paragraph 1.

The recipe is an official document with medical, legal and financial burden. We put emphasis on the responsibility that the pharmacist is often forced to take, performing incorrectly or illegibly written forms for humane reasons and not for financial reasons, as suspected.

Training of medical professionals about the rules of prescription and dispensing of prescription drugs is subject to improvement. In this regard, the project "Updating the curricula of the Faculty of Pharmacy at the Medical University Varna in accordance with the needs of the pharmaceutical business and the requirements of the labor market" is absolutely necessary.

Paying attention to this aspect of the work will improve the performance of pharmaceutical care in pharmacies and reduce the possibility of the occurrence of errors.

Keywords: *recipe, prescribing, reading and dispensing of drugs, improving curricula*

11. Nikolov, Z., S. Dragomanova, **M. Georgieva**. The role of pharmacists in the identification, treatment and prevention of depressive disorders and stress-related pathology. – *Scripta Scientifica Pharmaceutica*, 1, 2014, Supplement 1, 28.

THE ROLE OF PHARMACISTS IN THE IDENTIFICATION, TREATMENT AND PREVENTION OF DEPRESSIVE DISORDERS AND STRESS-RELATED PATHOLOGY

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Bulgaria is a country with high rates of suicide attempts and realized suicides, morbidity from unipolar depression, neurotic and eating disorders. Social instability, low income, and bullying at school and home create a high-stress medium. Chronic stress leads to intellectual and behavioral deficiencies which significantly worsen quality of life and productivity. The exact morbidity and prevalence are unknown because of persistent fear of stigmatization and misunderstanding. Attempts for self-medication with tobacco, alcohol and marijuana worsen the condition and create bigger problems with alcoholism and addictions.

As the most accessible healthcare professionals, pharmacists can play an important role in the treatment and prevention of such disorders. A significant part of the patients prefer visiting the pharmacy for advice or recommendation before a visit to their GP, if such follows.

Review of the tolerability, cost/effectiveness and risk/benefits ratios of the second generation of antidepressants, and especially SSRI's class, shows that they have favorable profile and some meta-analysis show significant decline in suicide rates in countries with traditionally high baseline suicide rates.

Giving pharmacy professionals prescription capabilities for the safest drugs can reduce the burden of the national healthcare and social systems, primarily by preventing serious healthcare issues by an early onset of proper treatment for mild cases and by more efficiently directing moderate-to-severe cases for psychiatric consultation.

Keywords: *Depression, SSRI's, Prevention, Health benefits, Pharmacists*

12. **Georgieva, M.**, B. Yustiniyanova, N. Manolov. Roles of probiotics in cancer prevention: an update. – *Scripta Scientifica Pharmaceutica*, 1, 2014, Supplement 1, 29.

ROLES OF PROBIOTICS IN CANCER PREVENTION: AN UPDATE

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Cancer is a serious global public health problem and incidence and mortality have been steadily rising throughout the past century in most places of the world.

There are several epidemiological evidences that support a protective role of probiotics against cancer. Probiotics are live bacteria that could exert health beneficial effects upon consumption. At least one-half of all cancers are suggested to have a dietary component. Therefore many of the dietary agents and natural health products have attracted the attention of scientists. In addition to regulation of intestinal epithelial homeostasis and immune responses, certain probiotics have been reported to activate anticancer mechanisms.

In vivo and molecular studies have demonstrated encouraging outcomes, mainly attributed to its antimicrobial effects against carcinogen-producing microorganisms, antimutagenic properties, and alteration of the tumor differentiation processes.

The use of probiotics to prevent colon cancer has gained much attention due to positive outcomes. The increased interest in these areas demonstrated the need for further evaluation to better understand the exact mechanisms involved, and to generate uncontroversial experimental evidence.

Keywords: *probiotic, dietary component, cancer prevetion, mechanisms, antimutagenic properties.*

APPROACHES AT UTILIZATION OF HERNIA MESHES

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Aim: **The purpose of the present research is to investigate what Hernia Meshes ("HM") are used within Varna region during hernia surgery and to make estimation of the factors that influences the choice of HM.**

Materials and methods: **During the survey has been collected information on the number and the type of hernias that have underwent surgery in Multiprofile Hospital For Active Treatment – Dobrich, Multiprofile Hospital For Active Treatment – Silistra and Multiprofile Hospital For Active Treatment "St. Marina" – Varna within the period 2012 – June, 2014, as well as on the mesh amount being used in hospitals for active treatment in Sofia, Dobrich, Silistra, Razgrad and Varna. The said survey has involved 55 surgeons from main clinical centers. On the basis of the questions in the survey card there have been clarified with what HM brands the surgeon operate with, which factors influence on the decision to be put a mesh. There has**

13. Dragomanova, S., L. Tancheva, **M. Georgieva**, A. Georgieva, S. Stoeva, R. Kalfin. Antioxidant mechanism in the preventive effect of Myrtenal on Alzheimer's disease progression on experimental mouse model. – *Scripta Scientifica Pharmaceutica*, 2, 2015, Supplement 1, 33.

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*

14. Stoeva, S., L. Tancheva, **M. Georgieva**, A. Georgieva, T. Pajpanova, R. Kalfin. Newly synthesized neuropeptides with central nervous activity in mice. – *Scripta Scientifica Pharmaceutica*, 2, 2015, Supplement 1, 34.

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*

15. Hvarchanova, N., **M. Georgieva**. Biological toxins and bioterrorism. – *Scripta Scientifica Pharmaceutica*, 2, 2015, Supplement 1, 35.

BIOLOGICAL TOXINS AND BIOTERRORISM

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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*

16. Hvarchanova, N., **M. Georgieva**. Marine toxins – Saxitoxin (STX) and Tetrodotoxin (TTX). – *Scripta Scientifica Pharmaceutica*, 2, 2015, Supplement 1, 36.

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*

17. Kehayova, G., **M. Georgieva**. Homeopathic remedies that every home should have. – *Scripta Scientifica Pharmaceutica*, 2, 2015, Supplement 1, 37.

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 substances are being diluted and made dynamic, and afterwards prescribed in infinitesimal doses. Homeopathy is a completely harmless and applicable also to pregnant women and babies, where the traditional medicine 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, Pyrogenium и Ferrum phosphoricum. In case of fever Belladonna is applied, while in case of nausea and vomiting Ipeca 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 intake range from 9CH до 15-30CH, depending on the similarity degree and the strength of complaint on behalf of the patient.

18. Kehayova, G., **M. Georgieva**. Homeopathic options in curing migraine headache. – *Scripta Scientifica Pharmaceutica*, 2, 2015, Supplement 1, 38.

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 painkillers: 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.

19. Ivanova, S., **M. Georgieva**. Pharmacological Treatment of Obesity and Overweight and Adverse Effects Related to Drug Use. – *Scripta Scientifica Pharmaceutica*, 2, 2015, Supplement 1, 39.

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 ≥ 30 kg/m², or with overweight and BMI ≥ 27 kg/m² 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, witch frequency is 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.

20. Stoeva, S., **M. Georgieva**, S. Dragomanova, L. Tancheva. Anxiolytic and sedative properties of Myrtenal in experimental rodents. – *Scripta Scientifica Pharmaceutica*, 4, 2017, Supplement 2, 12.

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 studies 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*

21. Dragomanova, S., L. Tancheva, **M. Georgieva**, R. Kalfin. Anti-Nociceptive Effects of Myrtenal on pain in experimental mouse models. – *Scripta Scientifica Pharmaceutica*, 4, 2017, Supplement 2, 47.

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 Myrtenal 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 Myrtenal 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, Myrtenal, mice*

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

22. Hvarchanova, N., **M. Georgieva**, B. Kanazirev. Risk of Hyperkalemia in Heart Failure and New Treatment Options. – *Scripta Scientifica Pharmaceutica*, 4, 2017, Supplement 2, 49.

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*

23. Kehayova, G., **M. Georgieva**, K. Georgiev, G. Aleksandrov, M. Peneva. Hepatoprotective effect of probiotic food, containing Lactobacillus Bulgaricus DWT1 in acute ethanol intoxication in experimental animals. – *Scripta Scientifica Pharmaceutica*, 4, 2017, Supplement 2, 51.

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 1905the Bulgarian Dr. Stamen Grigorov discovered the microorganism Lactobacillus bulgaricus in yogurt. Later Russian physiologist IlyaMechnikov 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 StaraPlanina. 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 12thday 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 Lactera 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 wasestablished. The present experiment demonstrates the hepatoprotective effect of Lactera 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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24. Кехайова, Г., **М. Георгиева,** К. Георгиев. Хепатопротективен ефект на пробиотична храна, съдържаща съдържаща Lactobacillus Bulgaricus DWT1 при остра интоксикация с парацетамол при експериментални животни. – *Варненски медицински форум*, 6, 2017, приложение 1, 127-128.

ХЕПАТОПРОТЕКТИВЕН ЕФЕКТ НА ПРОБИОТИЧНА ХРАНА, СЪДЪРЖАЩА LACTOBACILLUS BULGARICUS DWT1 ПРИ ОСТРА ИНТОКСИКАЦИЯ С ПАРАЦЕТАМОЛ ПРИ ЕКСПЕРИМЕНТАЛНИ ЖИВОТНИ

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Пробиотиците са живи микроорганизми, които, приложени в достатъчни количества, осигуряват здравна полза за гостоприемника и допринасят за намаляване на риска от заболявания. Употребата на пробиотици се счита за ефективно и безопасно алтернативно лечение на хепатотоксичност. Днес пробиотиците са обект на нарастващ интерес поради доказания си хепатопротективен, имуностимулиращ, антиоксидантен и антитуморен ефект.

През 1905 г. в Женева българинът Стамен Григоров изолира Lactobacillus bulgaricus от кисело мляко, донесено от България. По-късно руският физиолог Иля Мечников заключава, че тайната на дълголетието на българите се крие в консумацията на кисело мляко. Lactobacillus bulgaricus е единственият микроорганизъм, носещ името на определена географска територия. Той се възпроизвежда само на територията на България.

За първи път в света професор Никола Александров успя да изолира естествени пробиотични бактерии от водоизточник в Стара планина. Пробиотичната асоциация съдържа диви щамове млечни бактерии.

В настоящия експеримент изследвахме за първи път хепатопротективния ефект на нов щам Lactobacillus bulgaricus DWT1. Третирахме в продължение на 14 дни плъхове Albino Wistar с помощта на гастрална сонда с пробиотика Лактера Нейчър и приложихме парацетамол на 12-ия ден, за да предизвикаме остро чернодробно увреждане. След лабораторен и хистологичен анализ на кръвта и черния дроб на плъхове открихме, че животните, получаващи само парацетамол, имаха разширени зони на некроза и повишени чернодробни ензими. В групите, предварително третирани с Лактера Нейчър и след това подложени на парацетамол, нивата на чернодробните ензими са значително по-ниски от тези в групата с парацетамол. Хистопатологичният анализ показва, че прилагането на пробиотика минимизира чернодробно увреждане чрез намаляване нивата на морфологичните промени и некроза.

Нашите открития при Albino Wistar плъхове демонстрират възможната употреба на Лактера Нейчър за предотвратяване на чернодробно увреждане. Пробиотикът може да бъде ефективен хепатопротектор в лечението и профилактиката на чернодробни нарушения.

Ключови думи: пробиотици, парацетамол, увреждане на черния дроб, хепатопротективен ефект

25. Хвърчанова, Н., **М. Георгиева**, Б. Каназирев. Тенденции в медикаментозното лечение при хоспитализирани болни по повод на хронична обострена сърдечна недостатъчност със запазена и редуцирана фракция на изтласкване. – *Варненски медицински форум*, 6, 2017, приложение 1, 129-130.

ТЕНДЕНЦИИ В МЕДИКАМЕНТОЗНОТО ЛЕЧЕНИЕ ПРИ ХОСПИТАЛИЗИРАНИ БОЛНИ ПО ПОВОД НА ХРОНИЧНА ОБОСТРЕНА СЪРДЕЧНА НЕДОСТАТЪЧНОСТ СЪС ЗАПАЗЕНА И РЕДУЦИРАНА ФРАКЦИЯ НА ИЗТЛАСКВАНЕ

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Въведение/Цели: Целта на нашето проучване беше да се установят тенденциите в прилаганото медикаментозно лечение при хоспитализирани по повод на сърдечна недостатъчност (СН) пациенти със запазена и потисната фракция на изтласкване. Това е постигнато чрез обобщаване и сравняване на информацията за предписваните медикаменти и потенциалните противопоказания и причини за неспазване препоръките за лечение на сърдечна недостатъчност.

Материали и методи: Това е ретроспективно проучване, обхващащо 535 пациенти, хоспитализирани в УМБАЛ „Света Марина" - Варна за периода от януари 2010 до декември 2014 година с диагноза хронична обострена сърдечна недостатъчност. Сравнени са процентите на предписваните кардиоактивни медикаменти - блокери на РААС, бета-блокери, антагонисти на минералкортикоидните рецептори и калциеви антагонисти при пациенти с хронична СН и редуцирана и запазена ФИ.

Резултати: За последната 2014 година пациентите със СН са били предимно възрастни (средна възраст 72 години) жени (54.5%), по-често със СНзФИ (37.6%). При пациентите със запазена ФИ (сравнени с тези с редуцирана) приеманите бета-блокери, блокери на РААС и антагонисти на минералкортикоидните рецептори са били значимо по-малко (82.3%, 58.1% и 25.8% спрямо 84.6%, 64.1% и 64.1%), докато процентът на приеманите калциеви антагонисти – по-голям (40.3% спрямо 38.5%) в сравнение с групата със СНрФИ. Процентът на неспазване на препоръките за лечение на СНрФИ с оглед на противопоказанията е 25.6%, 12.8% и 17.9% съответно за блокери на РААС, бета-блокери и антагонисти на минералкортикоидните рецептори.

Заключение: Има съществени разлики в лечението на СНрФИ и СНзФИ. Пациентите със СНзФИ приемат по-малко бета-блокери, блокери на РААС и антагонисти на минералкортикоидните рецептори, а повече калциеви антагонисти. Висок е процентът на неспазване на препоръките за лечение на СНрФИ спрямо останалата част от Европа, съобразен с противопоказанията. Тенденцията на хоспитализации по повод на СН е да са по-възрастни пациенти, с преобладаващ женски пол и СНзФИ.

Ключови думи: сърдечна недостатъчност, проучване, блокери на РААС, бета-блокери, антагонистите на минералкортикоидните рецептори, калциеви антагонисти

MEDICAMENT THERAPY TENDENCIES IN HOSPITALIZED PATIENTS WITH CHRONIC ACUTE HEART FAILURE WITH PRESERVED AND REDUCED EJECTION FRACTION

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Introduction/Aim: The aim of our research was to establish the trends in the applied medicament therapy in hospitalized patients with heart failure (HF) and preserved and reduced ejection fraction (EF). The results were achieved by summarizing and comparing the information about the prescribed medicaments and the potential contraindications and reasons for not adhering to the recommendations for heart failure treatment.

26. Хвърчанова, Н., **М. Георгиева**, Б. Каназирев. Бета-блокер и Ивабрадин при хронична сърдечна недостатъчност. – Национална конференция по клинична токсикология. к.к. Слънчев бряг, България, 29 септември – 1 октомври 2017. стр. 34.

БЕТА-БЛОКЕР И ИВАБРАДИН ПРИ ХРОНИЧНА СЪРДЕЧНА НЕДОСТАТЪЧНОСТ

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Бета блокерите, заедно с ACE-инхибиторите (ангиотензин рецепторните блокери) и минералкортикоидните рецепторни блокери са основните медикаменти за повлияване на хроничната сърдечна недостатъчност, според актуалните гайдлайни. Ивабрадин също има своето място в насоките, като той е сред лекарствата препоръчвани само при избрани симптомни пациенти със сърдечна недостатъчност (СН) с понижена фракция на изтласкване. Ивабрадин се прилага в комбинация със стандартната терапия, включваща лечение с бета-блокер или когато лечението с бета-блокер е противопоказано или не се понася.

Това е ретроспективно проучване, проведено сред 535 пациенти, хоспитализирани в УМБАЛ „Света Марина" - Варна за периода от януари 2010 до декември 2014 година с диагноза хронична обострена сърдечна недостатъчност с редуцирана и запазена фракция на изтласкване. В него са изложени процентите на предписваните бета-блокери и ивабрадин за периода и до колко те са били възприети в клиничната практика. Данните за приложение на лекарствата при изписване на пациентите са от медицинската документация.

Установява се нарастваща тенденция в предписването на бета-блокери при пациентите със СН – като от 2010 до 2014 година, процентите на предписаните лекарства от групата са съответно 79%, 85,6%, 77,9%, 81,6% и 83,2%. Ивабрадин е използван в съответно 9%, 0%, 7,1%, 3,9%, 9,9% от пациентите за годините.

Процентът на предписваните бета-блокери в годините се повишава, което сочи, че лечението на СН в България се доближава все повече до това от европейските гайдлайни. Ивабрадин, като едно сравнително ново лекарство (от 25 октомври 2005 г.) все още не е добре възприето в клиничната практика при лечението на хронична СН, но за последните години са достъпни все повече данни за положително повлияване на пациентите, подходящи за терапия с него.

27. Dragomanova, S., L. Tancheva, **M. Georgieva**, R. Klisurov, M. Eftimov, R. Kalfin. Study on the mechanism of neuroprotective effect of Myrtenal on rats with experimental dementia. – AAIC. Satellite Symposia. Abstarct booklet. Varna, Bulgaria, 19-20 October 2017. Poster Location: 1B

Study on the mechanism of neuroprotective effect of Myrtenal on rats with experimental dementia

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Among the leading hypothesis of Alzheimer's disease (AD) pathogenesis are oxidative stress and neuroinflammation. New researches focus on exploring natural substances that affect these processes. Our previous studies found positive effects of the monotherpen Myrtenal (M) on the memory of rodents. Aim of this study is to investigate the role of anti-inflammatory and antioxidant mechanisms in the neuroprotective action of Myrthenal in rodents with experimental dementia. Materials and Methods: On Wistar male rats was induced chemically dementia via administration of scopolamine (1 mg/kg, b.w. i.p., 11 days). Experimental groups received M (30 mg/kg b.w. i.p , 5 days), Ketoprofen (2.5 mg/kg b. w. i.p. 5 days) as a referent for anti-inflammatory effect and Lipoic acid (LA- 30 mg/kg b. w. 5 days) as a referent for antioxidant activity. On the 24th hour after the last treatment next parameters were evaluated: the changes in learning and memory according Step-through test; lipid peroxidation levels in brain supernatants (malondialdehyde content) and anti-inflammatory activity via carrageenan-induced inflammation test. Results: Myrtenal significantly improves the memory of animals compared to demented controls. This effect of M is accompanied by antioxidant activity comparable to those of LA. Co-administration of the two antioxidants although does not improve their effect on the memory and on brain lipid peroxidation. On experimental model of inflammation M shows significant anti-inflammatory activity comparable to the referent ketoprofen (on the 15th hour). On the 24th hour M demonstrates even better effect than ketoprofen. Some changes in the cellular composition of the exudate also are established. Our data shows the complex mechanisms of neuroprotective effect of Myrtenal. At least both activities- antioxidant and anti-inflammatory, are involved in the preventive effect of M on scopolamine-induced dementia. We assume that M can effectively delay the progression of experimental neurodegeneration.

Poster Location: 1B

V. РЕЗЮМЕТА НА ДОКЛАДИ ОТ НАУЧНИ ФОРУМИ, ПУБЛИКУВАНИ В МЕЖДУНАРОДНИ НАУЧНИ СПИСАНИЯ И СБОРНИЦИ

1. Dragomanova, S., L. Tancheva, **M. Georgieva**, A. Georgieva, C. Dishovsky, R. Kalfin, J. Hodjev, D. Atanassova, N. Lazarov, I. Pehlivanov. Preventive effects of the monoterpene Myrtenal on Alzheimer's disease progression on experimental mouse model. – *Amino Acids*, 47, 2015, № 8, 1652. IF = 3,196

Dragomanova S., L. Tancheva, M. Georgieva, A. Georgieva, Ch. Dishovsky, R. Kalfin, J. Hodjev, D. Atanassova, N. Lazarov, I. Pehlivanov. Preventive effects of the monoterpene Myrtenal on Alzheimer's disease progression on experimental mouse model. 14th International Congress on Amino Acids, Peptides and Proteins, Vienna, Austria, August 3-7, 2015, Amino Acids, Springer, Vol. 47, Num. 8, August 2015, p.1652, DOI: 10 1007/s 00726-015-2016-z

Abstract
Preventive effects of the monoterpene Myrtenal on Alzheimer's disease progression on experimental mouse model Stela Dragomanova1, 2, Lyubka Tancheva1, Marieta Georgieva2, Almira Georgieva1, Christophor Dishovsky3, Reni Kalfin1, Jordan Hodjev1, Dimitrina Atanassova1, Nikolai Lazarov1, Ivajlo Pehlivanov 1 - Institute of Neurobiology, Bulgarian Academy of Sciences 2 - Medical University, Varna, Bulgaria 3 –Military Medical Academy, Bulgaria Abstract Background: Alzheimer's disease (AD) is tipe of dementia causing problems with memory, thinking and behavior. At the moment AD pathogenesis is unclear and treatment is symptomatic. Recent studies of some natural products (like terpenes), revealed neuroprotective potential and ability to decrease the risk of AD. The natural monoterpene myrtenal derived from many plant essential oils, combines in its effects both AO and anti-AChE activity. Our previous unpublished data show significant improving effect of myrtenal on cognitive function of rodents. Objectives: To study the effect of Myrtenal on progression of cognitive disorders in dement mice. Materials and Methods:Experimental model of dementia from AD type was produced on male Albino mice via scopolamine treatment (1mg/kg i.p. 11 days). Animals were treated simultaneously with myrtenal (20 mg/kg i.p. 5 and 11 days) or with saline for the controls. Changes in their cognitive functions, after initial training on the 1st day, were described after last treatment with myrtenal, using Step through test (learning and memory) and Holeboard test (exploratory activity), accompanied with AchE-activity and AO status changes in the brain. Relationships among the results were analyzed together with parallel of histological changes in the brain. The preventive effect of myrtenal was compared with two referent compounds: Galanthamine - anti-AChE agent (1mg/kg i.p.), and Lipoic acid (antioxidant) (30mg/kg i.p.). Data were analyzed using t-test of Student-Fisher. Results: Scopolamine – treated animals demonstrated severe memory-loss, accompanied by significant biochemical (increased AchE- activity and lipid peroxidation) and degenerative changes in brain. Co-treatment with Myrtenal of dement mice produced a significant restoration of cognitive function (with 33% - comparable with the effects of both referent compounds) in comparison to mice treated only with scopolamine. The correlations among changed parameters (cognitive, biochemical and histological) discover some new details in preventive mechanisms of Myrtenal on AD progression. Conclusion:Myrtenal can be promising pharmacological agent for AD prevention with complex mechanism. Keywords: myrtenal, Alzheimer's disease, dementia, prevention, lipoic acid

2. Alexandrov, G., K. Georgiev, **M. Georgieva**, I. Iliev, M. Peneva. Anticancer activity of probiotics – experimental and clinical studies. – 6th Southeast European Conference on Chemoterapy and Infection. Scientific program. Solun, Greece, 13-15 November 2015. pp. 23.

Anticancer activity of probiotics – experimental and clinical studies

Georgi Alexandrov[1], Kaloyan Georgiev[2], Marieta Georgieva[2], Ivan Iliev[3], Maria Peneva[4]

Abstract

Introduction: Many scientists have been working on the anticancer effect of probiotics for the past decades. In the middle of the last century I. Bogdanov proved experimentally that Lactobacillus subsp. bulgaricus inhibits the growth and proliferation of tumor cells of Sarcoma 180, implanted in rats. Kitadzava (Japan) ascertained good anticancer effect of fermented milk on rats with implanted tumor cells. A. Hosono (Japan) found out that anticancer effect of fermented milk is due to the lactic acid bacteria and polysaccharides contained in it. Our preliminary studies showed that probiotic Laktera Nature® has an anti-proliferative effect against aggressive colon carcinoma cell line HT-29. The probiotic Laktera Nature® contains original strains of Lactobacillus bulgaricus DWT1 and Streptococcus thermophilus DWT4, isolated from spring water in Bulgaria and 21 natural essential and non-essential lactic amino acids. The aim of this study is to determine the anticancer activity of the different ingredients of probiotic Laktera Nature® and to study the effect of the probiotic formula as a nutritional therapy in patients with colorectal cancer.

Materials and Methods: Four types of cell lines have been used: 3T3, BJ, HT-29 ? MDA-MB-231. Cytotoxicity was determined by MTT-dye reduction assay. The direct cytotoxicity of the tested cell lines, measured at the 24th hour and the antiproliferative activity, measured at the 72nd hour have been studied. Four different samples of Laktera Nature® were used: sample 1 (original probiotic formula containing live cells of Lactobacillus bulgaricus DWT1 and Streptococcus thermophilus DWT4 and 21 lactic amino acids), sample 2 (only the probiotic strains without the amino acids), sample 3 (only the 21 lactic amino acids without the probiotic strains) and sample 4 (the original probiotic formula that has passed ?-sterilization 10 Gy, whereby the probiotic strains are

3. Dragomanova, S. L. Tancheva, **M. Georgieva**, A. Georgieva, C. Dishovski, R. Kalfin, D. Atanasova, N. Lazarov, I. Pehlivanov. Preventive effect of natural monoterpene myrtenal on cognitive disorders in dement mice. – *European Neuropsychopharmacology*, 25, 2015, Supplement 2, 578-579. P.5.a.005 IF = 4,409

several different choice points, enabling possible right or left exits. Food deprived rats (75% of free feeding rate) were released from starting position and the time to reach the goal compartment, containing a food reward, was measured as well as the number of error entries.

Twenty-four hours after the last training, the rats were randomly divided into 5 groups per 8 rats. Cholinergic antagonist QNB (2.0 mg kg^{-1}) was administered 60 min before the test. Rats in groups treated with cholinesterase inhibitors received either one dose of compound 1 (7-methoxy-N-(2-{4-[(3-methylphenyl)methyl]piperazin-1-yl}ethyl)-1,2,3,4-tetrahydroacridin-9-amine trihydrochloride; 25.6 mg.kg^{-1}) or compound 2 (N-(2-{4-[(2-bromophenyl)methyl]piperazin-1-yl}ethyl)-7-methoxy-1,2,3,4-tetrahydroacridin-9-amine trihydrochloride, 12.3 mg kg^{-1}) or standard donepezil (2.65 mg·kg^{-1}) at 30 min after QNB administration. Positive controls were administered with QNB and saline (1 mL·kg^{-1}) instead of cholinesterase inhibitor. Blank controls received saline at 30 min and 1 hr before the test. All compounds were administered via intra-peritoneal injection. The rats were repeatedly subjected to the multiple T-maze test at several time points following QNB administration (1, 24, 48 and 72 hrs). The passage time and number of errors were recorded. Non-parametric statistical test was used for evaluation of the therapeutic effects (Kruskal-Wallis test with post hoc comparisons). Differences were considered at significance level $p < 0.05$.

There was a significant difference between groups within 48 hrs ($p < 0.001$). QNB significantly impaired spatial orientation in rats – non-treated QNB-administered rats showed prolonged passage times through the maze ($p < 0.05$) as well as increased incidence of error entries. Cholinesterase inhibitors attenuated the effect of QNB at 1 hr, 24 hrs and 48 hrs test intervals. Compound 2 significantly reduced passage time of rats in 1 hr test ($p < 0.05$) whereas compound 1 and donepezil reduced passage time of rats in 1 hr test markedly but non-significantly if compared with non-treated QNB group. Number of errors was reduced significantly ($p < 0.05$) throughout all treated groups in 1 hr test. The effect of both novel compounds was equivalent to that of standard donepezil and there was not any statistical difference between them.

Novel 7-methoxytacrine-donepezil like hybrids, especially compound 2, showed their potential in the treatment of QNB-induced cognitive deficit. Further comparable experiments are proposed for the evaluation of novel compounds derived from donepezil as potential drugs for the treatment of Alzheimer's disease.

P.5.a.004 Trasient receptor potential ankyrin 1 (TRPA1): a novel relevant target in Alzheimer's disease?

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Alzheimer's disease (AD) is a neurodegenerative and progressive disease for which there is no current cure or efficient treatment. The search for new targets that could be useful models for drug development is indispensable. TRPA1 arises as a new approach, first considered by our research group to be related to AD due to the fact endogenous molecules that activate this receptor: Reactive Oxygen Species (ROS), Ca2+ and products of inflammation are also up-regulated during the initiation and progression of AD. We aimed to investigate the possible role of TRPA1 in experimental models of AD. We used primary neuronal cell culture from rat cortex (CT) and hippocampus (HP), Swiss mice (3 months-old) injected i.c.v. with Amyloid-β-oligomers (AβO) and also transgenic 5XFAD mouse model of AD. Cells and animals were treated with TRPA1 antagonist (HC030031) in different concentrations and schedules according to the protocol (UFSC Ethics: PP00625). Cells were treated with TRPA1 antagonist (HC030031) 0.03 uM and Aβ oligomers 1–40 (AβOs) 10 uM, and respective vehicles, for further assessment of ROS and neuronal death. Also, Swiss mice were injected i.c.v. with AβOs (400 pmol) and brains were collected after 6 h, 24 h, 7 days and 14 days to analyze TRPA1 expression by immunohistochemistry and western blot. Independently, animals were pre-treated i.c.v. with HC030031 (10 ug/site), 30 min prior to AβOs injections or transgenic mice treated orally, once a day, during 60 days with HC030031 (20 mg/kg). After treatments, behavioral analyses were performed using the object recognition (OR) task to assess spatial memory and brains were collected for molecular assays. Results showed that TRPA1 blockage with HC030031 prevented AβO-induced ROS formation ($F_{3, 14} = 80.48$; $P < 0.0001$) and neuronal death ($F_{3, 11} = 58.83$; $P < 0.0001$) in cells. Notably, when we evaluated TRPA1 expression in Swiss mice CT and HP by immunohistochemistry we observed higher expression after 24 h and 7 days of AβO-treatment in the microglia and surrounding the neuronal body, while blot results confirmed quantifications ($F_{4, 80} = 3.009$; $P = 0.0229$). To answer robustly if TRPA1 activation is required for AβO-toxicity, as we have seen in vitro, we tested the efficacy of HC030031 in vivo. Of note, HC030031 pre-treatment prevented AβO-induced memory deficits in AβO injected Swiss mice ($F_{4, 23} = 5.968$; $P = 0.0019$) while oral treatment during 60 days ameliorated memory deficits in the 5XFAD mice when compared to vehicle-treated mice ($F_{2, 20} = 4.388$; $P = 0.0263$). Besides, 5XFAD animals treated with HC030031 presented low levels of burden amyloid plaques and oligomers. Summarizing, we are reporting for the first time the significant role of TRPA1 in AD related experimental models. Our data suggest TRPA1 as a potential attractive target for the AD therapeutics.

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P.5.a.005 Preventive effect of the natural monoterpene myrtenal on cognitive disorders in dement mice

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Background: Alzheimer's disease (AD) is most common form of dementia causing problems with memory, thinking and behavior, which victims are increasing dramatically. At the moment there is no unified theory for AD pathogenesis and medical treatment is predominately symptomatic – mainly with acetylcholinesterase (AChE) inhibitors with co-treatment with some antioxidants (AO). Recently it was reported that some natural products: polyphenols, terpenes, alkaloids, etc., possess strong neuroprotective effect and

can decrease the risk of AD. Our previous unpublished data reveal significant improving effect of natural monoterpene myrtenal on cognitive function of rodents with unclear mechanism.

Purpose: To study the effect of Myrtenal on progression of cognitive disorders in dement mice.

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 the cognitive test (Step through test) and histological evidences in the brain. Groups of animals were treated with myrtenal in effective doses for 5 days. Control animals received the same volume saline. Changes in their cognitive functions were described after the last treatment with compounds, using Step through test (for learning and memory) and Hole board test (for exploratory activity). Changes in AchE activity and lipid peroxidation in the brains of animals also were studied using classic methods. The preventive effect of myrtenal was evaluated when compared with referent compounds – galanthamine (a well-known anti-AChE inhibitor), and antioxidants in effective doses – ascorbic acid (AA) – water soluble, and lipoic acid (LA) – water and liposoluble, respectively. Experimental data were analyzed using t-test of Student-Fisher and ANOVA.

Results: Animals treated with scopolamine demonstrated severe memory-loss, accompanied by significant biochemical changes in the brain (increased AchE activity – by 15%, increased lipid peroxidation by 83% and decreased glutathione content by 15%), confirmed by histological changes in brain cells. Co-treatment with Myrtenal of dement mice produced a significant restoration of cognitive function. In comparison to Scopolamine treated controls the emotional memory was restored with 35% (Step through test). Orientation was improved with over 50% according Hole board test. Preventive activity of Myrtenal is comparable with the effect of Galanthamine as referent (40%). The effect on memory of Myrtenal in dement mice also was similar and comparable to the effect of antioxidants used (Myrtenal by 35%, LA by 40% and AA by 33%). Compared to controls and the referent compound Galanthamine, Myrtenal has no significant effect on AchE brain activity but it decreased the lipid peroxidation in brain (with 20%). Analyzing relationships between changed parameters (cognitive, biochemical and histological) we discovered some correlations suggesting new details in preventive mechanisms of Myrtenal on AD progression.

Conclusion: Treatment with monoterpene Myrtenal can be promising effective agent for AD prevention. At present its complex mechanism is not clear and deserves further development and future studies.

P.5.a.006 Dimethyl fumarate improves spatial memory impairments in the rat streptozotocin-induced model of sporadic Alzheimer disease – a pilot study

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Alzheimer's disease (AD) is a common neurodegenerative disorder. Prevailing, late-onset, sporadic-form AD (sAD) is related to progressive cholinergic deficits, glucose hypometabolism, oxidative stress and central insulin resistance [1]. This "insulin-resistant brain state" and cognitive disorder accompanying AD is accurately reflected in the animal model of AD evoked by intracerebroventricular (icv) injection of streptozotocin (STZ) [2]. Dimethyl fumarate (DMF) is an oral anti-inflammatory, antioxidative and neuroprotective drug which was recently tested clinically on patients with relapsing-remitting multiple sclerosis. DMF significantly reduced the proportion of patients who had a relapse, the annualized relapse rate, the rate of disability progression, and the number of lesions on MRI [3]. Although both multiple sclerosis and AD are neurodegenerative disorders in which inflammatory processes in the brain contribute to the pathology, there is no study on DMF application in AD or animal models of AD.

The present study aims to determine whether DMF can alleviate spatial reference memory impairment in the STZ-induced rat model of sporadic AD.

Male Wistar rats (n = 20) were randomly divided into four groups: STZ DMF (n = 5) with STZ icv injection (total dose of 3 mg/kg was split into two doses: 2 x 1.5 mg/kg, dissolved in 0.05 mol/L citrate buffer, pH 4.5) and fed with experimental fodder containing 0.4% (by weight) dimethyl fumarate (DMF), STZ CTR (n = 5) with STZ icv injection and fed with standard fodder (CTR), VEH DMF (n = 5) with icv injection of vehicle (VEH; 0.05M citrate buffer, pH 4.5) and fed with DMF fodder, VEH CTR (n = 5) with icv injection of vehicle and fed with CTR fodder. Two weeks after surgery all rats were subjected to behavioural testing in the water maze of Morris (MWM) for four days. Animals were tested in four trials per session, during one session daily for three consecutive days. The platform location changed from session to session (reference memory), but will remain unchanged during each individual session (working memory). During each trial, rats had to swim until they found and climbed onto the platform (latency measurement), or until 120 s have elapsed. EthoVision XT video tracking system was used in this experiment.

STZ DMF rats needed less time to reach the platform in first and second session as compared to STZ CTR rats ($F = 6.88$, $p < 0.05$). There were no differences in latency to reach the platform between STZ DMF rats and control groups not subjected to icv STZ (VEH CTR and VEH DMF). Moreover, STZ CTR rats showed longer latency to enter the platform in each trial as compared to both control groups and in fourth trial as compared to STZ DMF rats ($F = 3.19$, $p < 0.05$).

Oral medication with dimethyl fumarate improves both long-term reference and short-term working spatial memory impairments in the rat streptozotocin-induced model of sporadic Alzheimer disease. Those effects were manifested in lower latency to reach the platform in MWM as compared to STZ CTR rats and in deeper latency reduction in consecutive sessions (reference memory) and in the consecutive trials (working memory).

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4. Dragomanova, S., L. Tancheva, **M. Georgieva**, A. Georgieva, C. Dishovsky, S. Stoeva, S. Pavlov, R. Kalfin. Preventive effect of myrtenal and lipoic acid in combination on progression of Alzheimer's disease. – *European Neuropsychopharmacology*, 26, 2016, Supplement 2, 636. P.5.a.002 IF = 4,239

ysis showed that animals injected with miR-B present a strong reduction in the number of Aβ plaques in the subiculum and hippocampus, as well as a significant reduction in human APP and mouse BACE1 mRNA and protein levels, compared to control groups.

Overall, our study demonstrates that miRNA modulation is a promising strategy to decrease APP and BACE1 expression, leading to a reduction of Aβ deposition and to the amelioration of cognitive function in 3xTg-AD animals. Given the high conservation of the selected miRNAs across species, new significant insights into the ageing process may arise from this study, supporting new diagnostic and therapeutic avenues for Alzheimer's disease and other ageing-related disorders.

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P.5.a.002 Preventive effect of myrtenal and lipoic acid in combination on progression of Alzheimer's disease

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Background: The most common form of dementia is Alzheimer's disease (AD) which victims increase constantly. At the moment there is no unified theory for AD pathogenesis and the available treatment is mainly with acetylcholinesterase (AChE) inhibitors, NMDA receptor blockers and antioxidants (AO). Some natural products (polyphenols, terpenes, alkaloids, vitamins etc.) possess neuroprotective activity and can decrease the risk of AD [1]. New studies demonstrated that Myrtenal, a natural compound of well-known plant essential oils, combines both AO and in vitro anti-AChE activity [2]. Our previous data reveal significant improving effect of Myrtenal (M) on cognitive function of healthy rodents.

Objectives: To investigate the combined effect of Myrtenal with well-known strong antioxidant Lipoic Acid (LA) on the progression of cognitive impairment in AD mice.

Materials and Methods: Experimental model of dementia from AD type was produced on male Albino mice via scopolamine treatment (1 mg/kg b.w. i.p., 11 days) and was verified with the cognitive test (Step through test) and biochemical markers for oxidative stress – lipid peroxidation and glutathione content in brain supernatants. Changes in brain weight for the period of treatment also were studied. Animals were treated simultaneously with myrtenal (20 mg/kg b.w. i.p., 11 days) alone and in combination with the antioxidant LA (30 mg/kg b.w., i.p.) or galantamine – a reversible cholinesterase inhibitor (1 mg/kg b.w., i.p.). The preventive effect of M (alone and in combinations) on declined cognitive functions of dement animals was evaluated, using Step through test (for learning and memory) and Hole board test (for orientation). The changes in AchE activity and AO status (malone dialdehyde content) and glutathione levels in brain homogenate were studied. Data were analyzed by t-test of Student-Fisher and ANOVA.

Results: Animals treated with scopolamine demonstrated severe memory loss and disorientation, accompanied by significant biochemical changes in the brain (AchE- and AO-activity) as well as decreased brain weight in comparison to the controls treated with saline. Co-treatment with Myrtenal of dement mice produced a significant restoration of cognitive function (with 33%) in comparison to scopolamine treated controls. Effect of M is comparable with the effects of both references – Galanthamine (an AChE inhibitor) and of Lipoic acid (an antioxidant). Administered together Myrtenal and LA demonstrated better prevention in combination than when administered alone. Myrtenal administered alone does not reduce the AchE activity in vivo, but its combination with LA reduces significantly the enzyme activity in vivo (with 25%). Combination of M with LA also preserves brain mass of animals and values reach control levels. Analyzing changed parameters (cognitive and biochemical) gave new insight about the preventive mechanisms of the combination Myrtenal and LA on AD progression.

Conclusion: The combination of Myrtenal and Lipoic acid has significant complex preventive effect on declined cognitive parameters in dement mice.

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P.5.a.003 Ethical, legal, and therapeutic aspects in patients with dementia admitted to an acute psychiatric department

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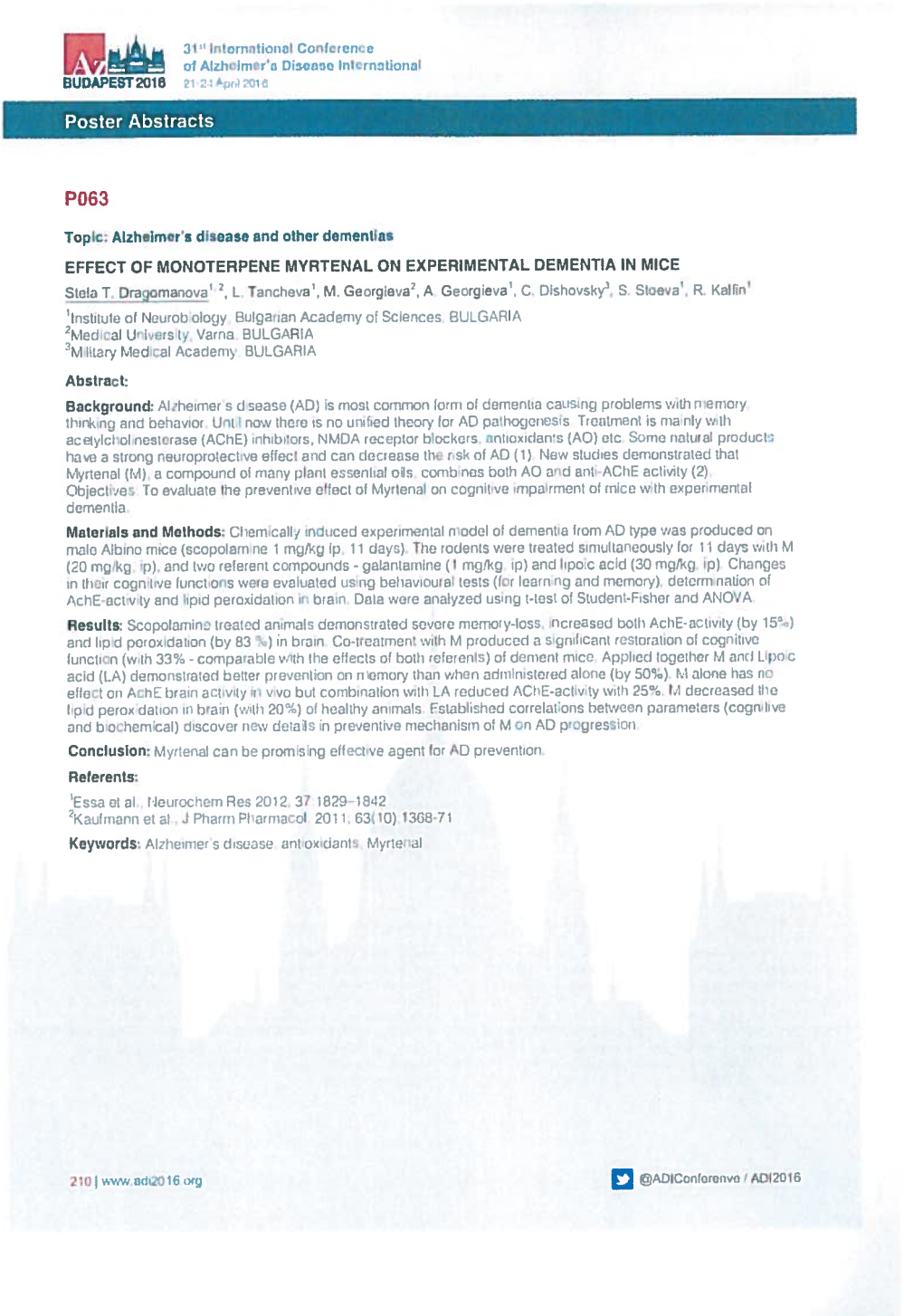
Background: People with dementia have complex medical, social, and psychological needs and can be exacerbated by physical illness and the complex relationships between health care systems, patients and their families or caregivers. They are a vulnerable and fragile population that differs significantly from the population without dementia [1–3]. World-wide studies have concluded that there is significant number of hospitalizations among patients with dementia. However, ethic, legal, moral and therapeutic aspects are still under-explored [4].

5 Dragomanova, S., L. Tancheva, **M. Georgieva**, A. Georgieva, C. Dishovsky, S. Stoeva, R. Kalfin. Effect of monoterpene Myrtenal on experimental dementia in mice. – 31st International Conference of Alzheimer's Disease International. Abstarct Book. Budapest, Hungary, 21-24 April 2016. pp. 210. P063



31st International Conference of Alzheimer's Disease International
BUDAPEST 2016 21-24 April 2016

Poster Abstracts

P063

Topic: Alzheimer's disease and other dementias

EFFECT OF MONOTERPENE MYRTENAL ON EXPERIMENTAL DEMENTIA IN MICE

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Abstract:

Background: Alzheimer's disease (AD) is most common form of dementia causing problems with memory, thinking and behavior. Until now there is no unified theory for AD pathogenesis. Treatment is mainly with acetylcholinesterase (AChE) inhibitors, NMDA receptor blockers, antioxidants (AO) etc. Some natural products have a strong neuroprotective effect and can decrease the risk of AD (1). New studies demonstrated that Myrtenal (M), a compound of many plant essential oils, combines both AO and anti-AChE activity (2). Objectives: To evaluate the preventive effect of Myrtenal on cognitive impairment of mice with experimental dementia.

Materials and Methods: Chemically induced experimental model of dementia from AD type was produced on male Albino mice (scopolamine 1 mg/kg ip, 11 days). The rodents were treated simultaneously for 11 days with M (20 mg/kg, ip), and two referent compounds - galantamine (1 mg/kg, ip) and lipoic acid (30 mg/kg, ip). Changes in their cognitive functions were evaluated using behavioural tests (for learning and memory), determination of AchE-activity and lipid peroxidation in brain. Data were analyzed using t-test of Student-Fisher and ANOVA.

Results: Scopolamine treated animals demonstrated severe memory-loss, increased both AchE-activity (by 15%) and lipid peroxidation (by 83 %) in brain. Co-treatment with M produced a significant restoration of cognitive function (with 33% - comparable with the effects of both referents) of dement mice. Applied together M and Lipoic acid (LA) demonstrated better prevention on memory than when administered alone (by 50%). M alone has no effect on AchE brain activity in vivo but combination with LA reduced AChE-activity with 25%. M decreased the lipid peroxidation in brain (with 20%) of healthy animals. Established correlations between parameters (cognitive and biochemical) discover new details in preventive mechanism of M on AD progression.

Conclusion: Myrtenal can be promising effective agent for AD prevention.

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Keywords: Alzheimer's disease, antioxidants, Myrtenal

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HERBAL PRODUCTS

Effect of Myrtenal on Social Behavior and Memory of Rats

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Plant monotherpen Myrtenal (M) presents in many essential oils and has rich specter of pharmacological activities. Our previous studies established significant effects of M on behavior of mice.

Aim of this study was to investigate effect of M on the cognition and social behavior of rats.

Male Wistar rats were daily injected Myrtenal (40 mg/kg, i. p.) for 9 days. 24 hours after the last treatment the changes in behavior and cognition were tested via Open field test, Step-through test and Mouse-killing test. Brain levels of some neurotransmitters (dopamine - DA, serotonin - 5-HT, acetylcholine - ACh, adrenaline - Adr and noradrenaline - NA) were also measured. Significant improved cognitive performance in M-treated group was established. Learning and memory in this group was better than in the control group at the end of the experiment. Elevated brain neurotransmitter levels of DA, 5-HT and Ach confirmed behavioral data. Interesting changes in social behavior of M-treated animals were recorded, as well. After 3rd day of M-administration increased incidences of dominant and aggressive behavior were established accompanied by vocalization and fighting in the group. We assume that it is due to interaction of M odor with rats pheromones related to animal hierarchy in the group. Brain levels of Adr and NA in M-group were not significantly elevated. At the same time incidences of inter-species aggression were observed according to Mouse-killing test.

Present study indicates significant effects of M on CNS accompanied by changes in brain mediation systems and deserve further studies.

Keywords: cognition, aggression, mediators, monoterpene

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Gentiana Lutea Radix Extract Exerts *In Vitro* Dose- and Time-dependent Response in Peripheral Blood Mononuclear Cells

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Although Gentiana lutea radix extract (GRE) is believed to strengthen organism by stimulating circulation and the activity of many organs, it has certain active components that can cause oxidative and genotoxic stress. The aim of the current study was to estimate which concentration (0.5, 1 and 2 mg/ml) of GRE initiates DNA damage and lipid peroxidation, disrupts oxidative balance following 48h lasting treatment, and whether those parameters modulate survival of human peripheral blood mononuclear cells *in vitro* after 48 and 72h. DNA damage was assessed using alkaline Comet assay, oxidative status by PAB assay, lipid peroxidation by determining MDA levels and cell count by tripan blue dye exclusion test. Obtained results indicate that the lowest tested concentration increases lipid peroxidation along with DNA damage and has a mild cytotoxic effect. Higher concentrations provoke only significant DNA damage, probably due to the other mechanisms involved in initiation of cell death rather than elevated oxidative stress. Albeit cell death after 48h of treatment at the highest tested concentration is not significant, DNA fragmentation is more than doubled compared to control. The impact of detected fragmentation is seen as reduction of cellular survival observed after 72 hours of treatment. According to presented findings DNA fragmentation could be a predictive tool for the cytotoxic effects estimation of GRE treatment since increased fragmentation is observed 24h prior to significant increase in cell death. Parallel monitoring of oxidative status and DNA damage might be valuable parameter in determining sublethal concentrations of GRE in other experimental setups.

Keywords: DNA damage, Comet assay, lipid peroxidation, viability

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VI. УЧАСТИЯ В КНИГИ

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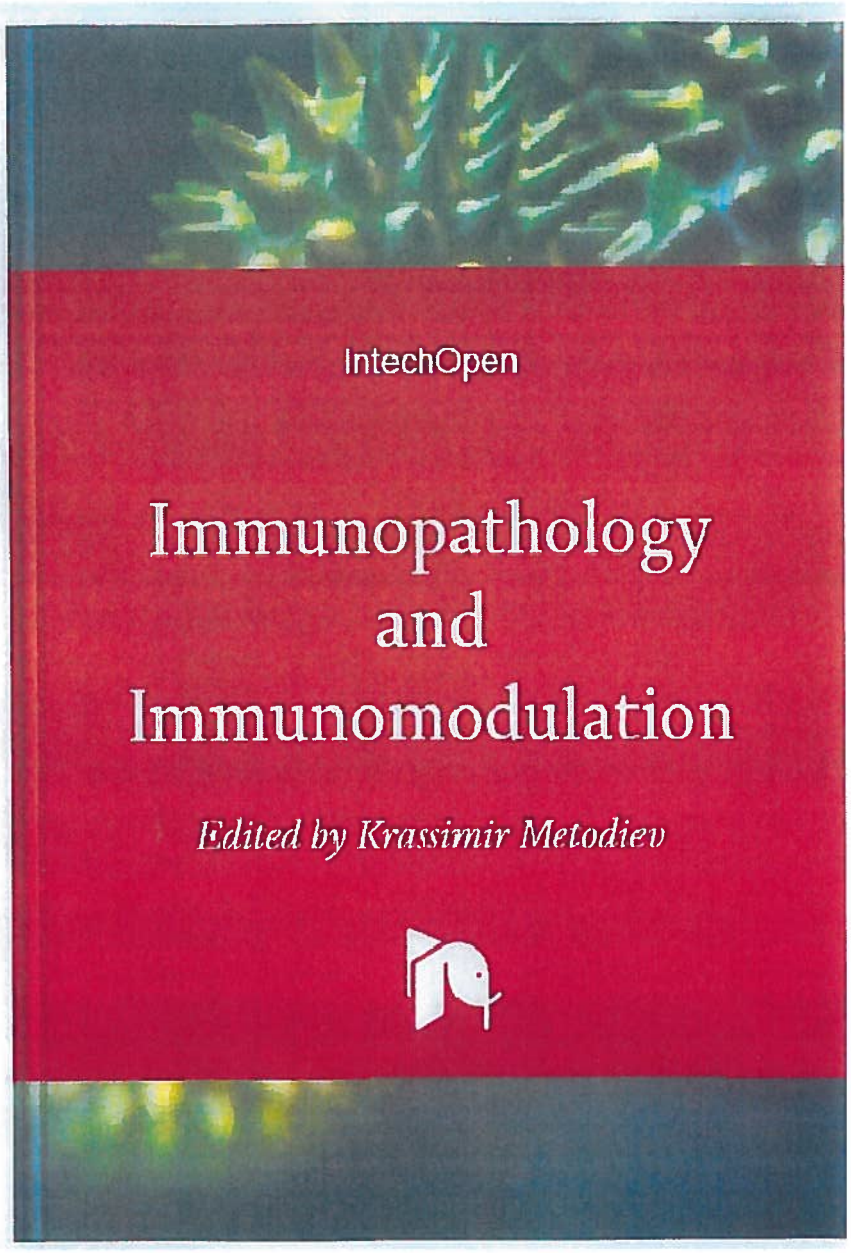

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Chapter 9

Probiotics and Immunity

Marieta Georgieva, Kaloyan Georgiev and Peter Dobromirov

Additional information is available at the end of the chapter

http://dx.doi.org/10.5772/61337

Abstract

Probiotics are "living microorganisms" which exert a prophylactic and therapeutic effect by improving the internal microbial balance. Probiotics play a role in defining and maintaining the delicate balance between necessary and excessive defence mechanisms including innate and adaptive immune responses. The beneficial effects of probiotics have been demonstrated in many diseases.

New therapeutic approaches toward several inflammatory diseases are being developed by affecting the microbial composition of the gut immune system. They are based on the fact that this part of immune system is influenced by many factors, including dietary components and commensal bacteria. An understanding of the molecular mechanisms behind the direct and indirect effects on the gut immune response will facilitate better and possibly more efficient therapy for diseases, although probiotics (live microorganisms) have already shown promise as treatments for several diseases in both clinical and animal studies.

Further, the concept of probiotics and the direct and indirect mechanisms by which they can influence gut immunity are described. Emphasis will be placed on the relationship of microbiota and the gut immune system.

A review of the history of *Lactobacillus bulgaricus*, probiotics, and probiotic functional foods is made and legislation and modern challenges are discussed.

Keywords: Probiotics, immunity, probiotic genomic, history, legislation

1. Introduction

Probiotics are defined by the World Health Organization as "live microorganisms, which when administered in adequate amounts, confer a health benefit upon the host." The main benefit of probiotics is that they help restore balance in the intestinal microbiota. Probiotics play a role in defining and maintaining the delicate balance between necessary and excessive defence

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Chapter 12

Pharmacological Properties of Monoclonal Antibodies Directed Against Interleukins

Kaloyan Georgiev and Marieta Georgieva

Additional information is available at the end of the chapter

http://dx.doi.org/10.5772/61774

Abstract

The road to individualized therapy goes through detecting specific targets (e.g., antigens), suitable for influence, and their selective targeting by using specially designed molecules (e.g., antibodies). A significant advance in this area is the development of therapeutic monoclonal antibodies. This approach enables maximizing the therapeutic effect on one hand, and reducing systemic toxicity on the other hand. In recent years, significant progress was made in improving their pharmacological performance – pharmacokinetics (longer half-life) and pharmacodynamics properties (better efficacy because of stronger affinity to human receptor), and safety profile (less antigenic and immunogenic reactions). Interleukins are a diverse, multifunctional group of proteins that carry out communication between various immune cells and control their gene expression. They manage the intensity and magnitude of an inflammatory response, and control differentiation, proliferation, and secretion of antibodies. Therefore, interleukin network represents an interesting pharmacological target, modulation of which using either biological or small chemical agents could contribute to suppression of excessive activated immune system and successfully treat the diseases that they are involved in.

Keywords: Monoclonal antibodies, pharmacological properties, pharmacokinetics, pharmacodynamics, cytokines, interleukins

1. Introduction

An effective immune response is possible only through the interaction of several cell types. To coordinate this process, there are a number of mechanisms for communication between immune cells, including a plurality of immunomodulating signaling molecules, such as cytokines. An officially recognized definition of the cytokines does not exist. Cytokines are a group of regulatory molecules with protein or glycoprotein structure (relatively small

VII. УЧАСТИЯ В СПРАВОЧНИК, УЧЕБНИЦИ И УЧЕБНИ ПОМАГАЛА

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УДОСТОВЕРЕНИЕ

НА

ДОЦ. Д-Р МАРИЕТА ПЕТРОВА ГЕОРГИЕВА

ПО ПРОЕКТ ВЪЗЛОЖЕН НА МУ-ВАРНА ОТ РЪКОВОДСТВОТО НА МБАЛ „СВ. МАРИНА“ ЕАД, Е ИЗГОТВЕН „ON LINE“ ЛЕКАРСТВЕН СПРАВОЧНИК “LEKARTA” 2011/2012 Г.

НАСТОЯЩОТО УДОСТОВЕРЕНИЕ СЕ ИЗДАВА НА ДОЦ. Д-Р МАРИЕТА ПЕТРОВА ГЕОРГИЕВА В УВЕРЕНИЕ НА ТОВА, ЧЕ ТЯ Е РАЗРАБОТИЛА, ВНЕДРИЛА И ПОПУЛЯРИЗИРАЛА СПРАВОЧНИКА.

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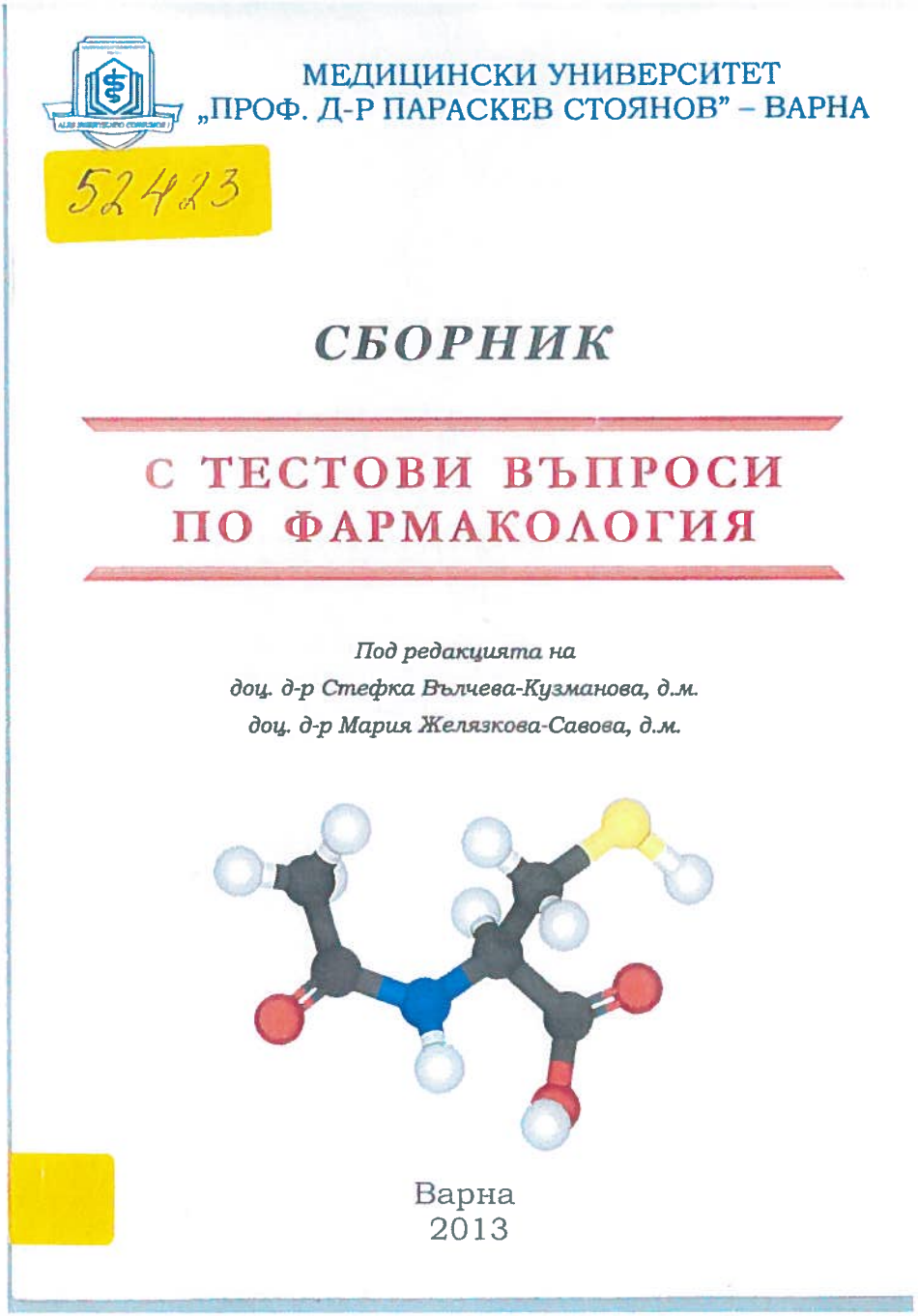

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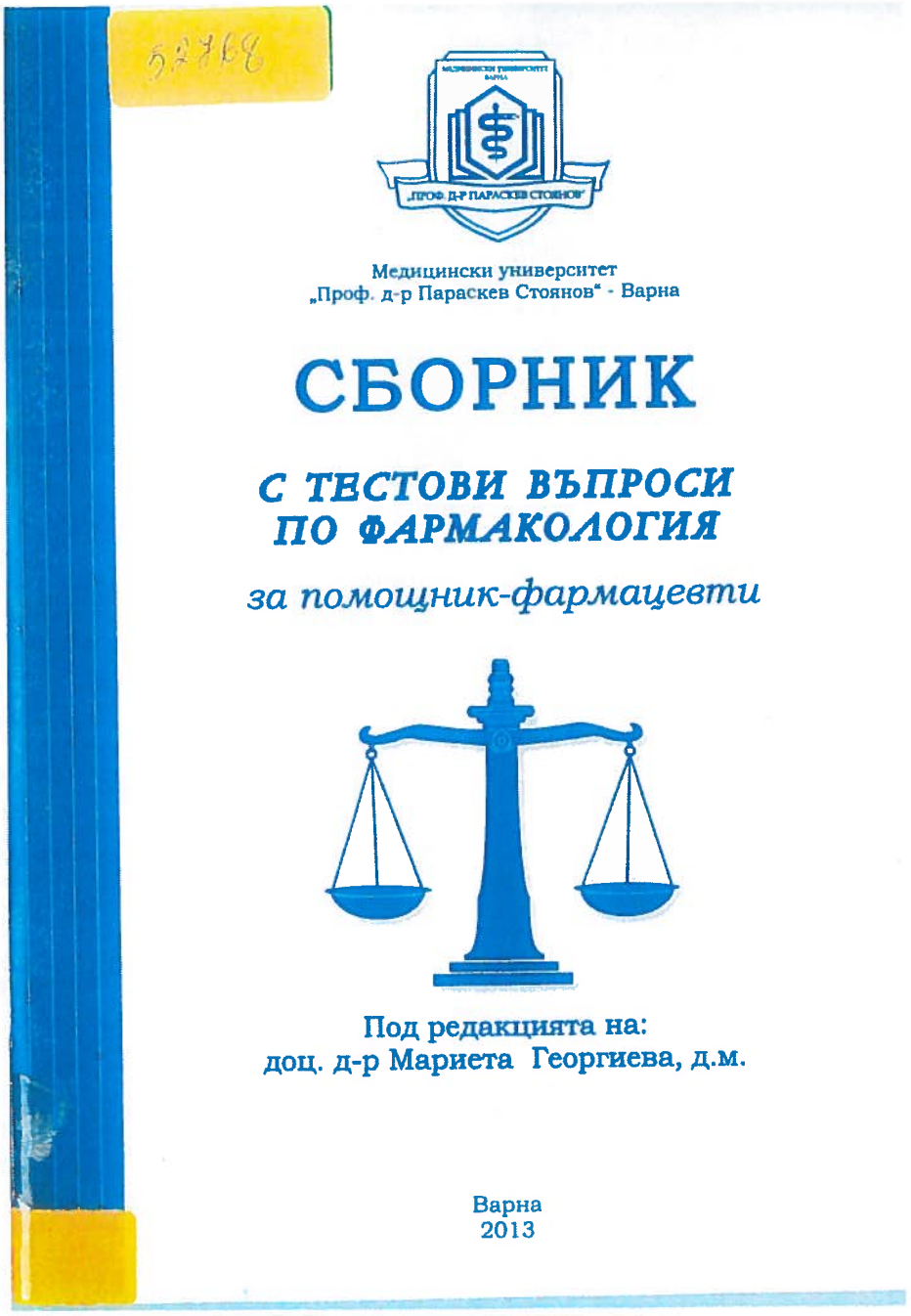

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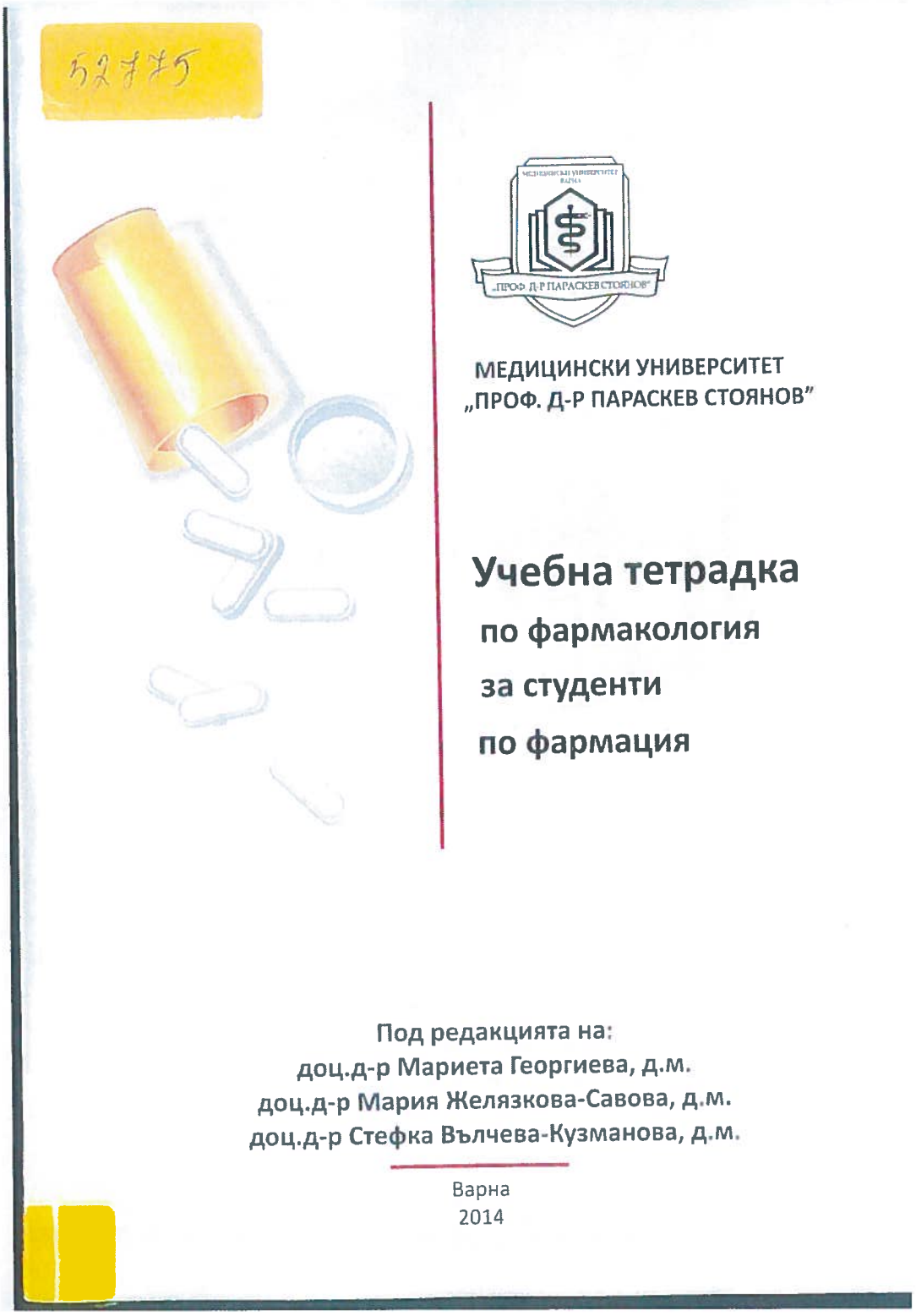

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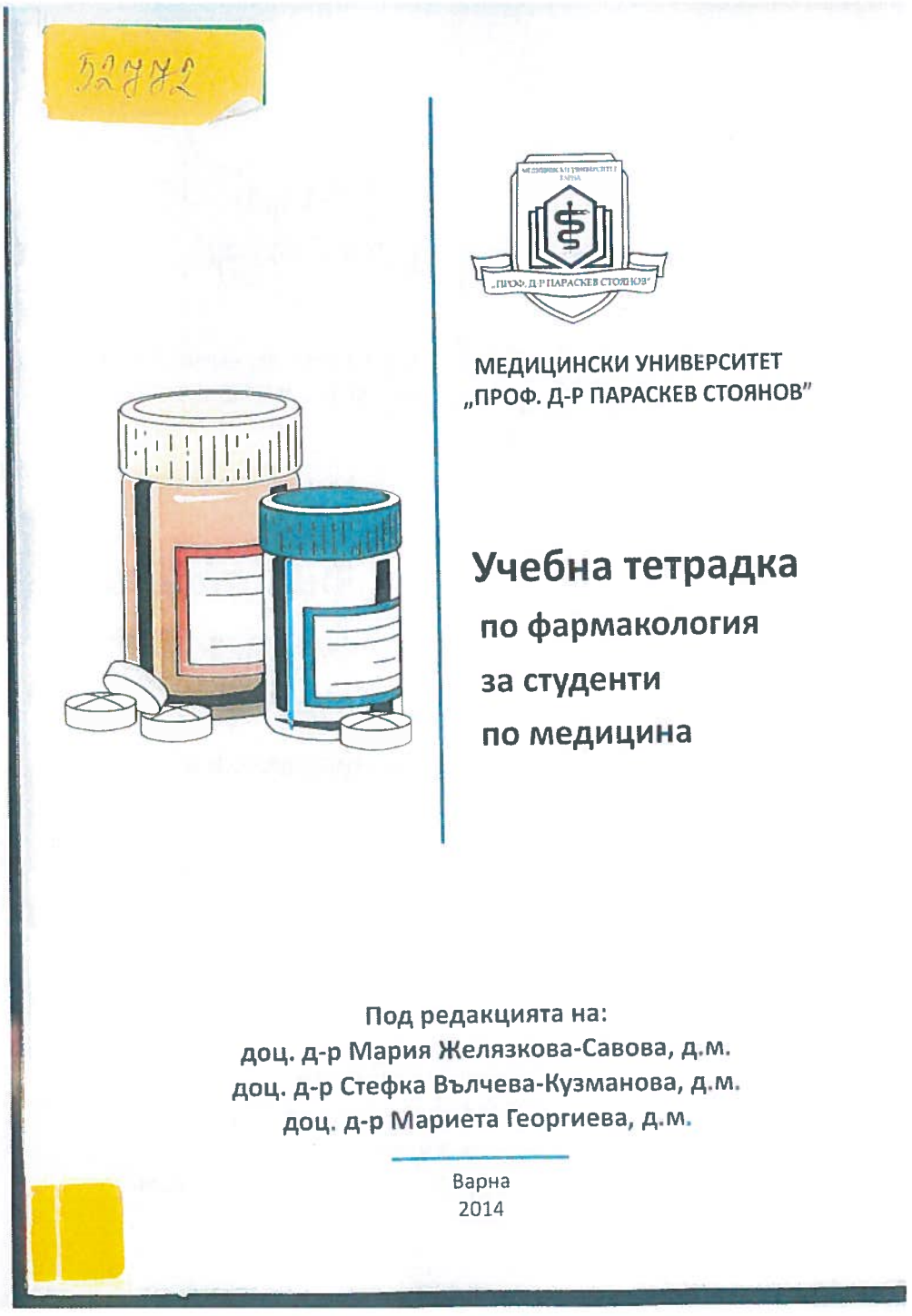

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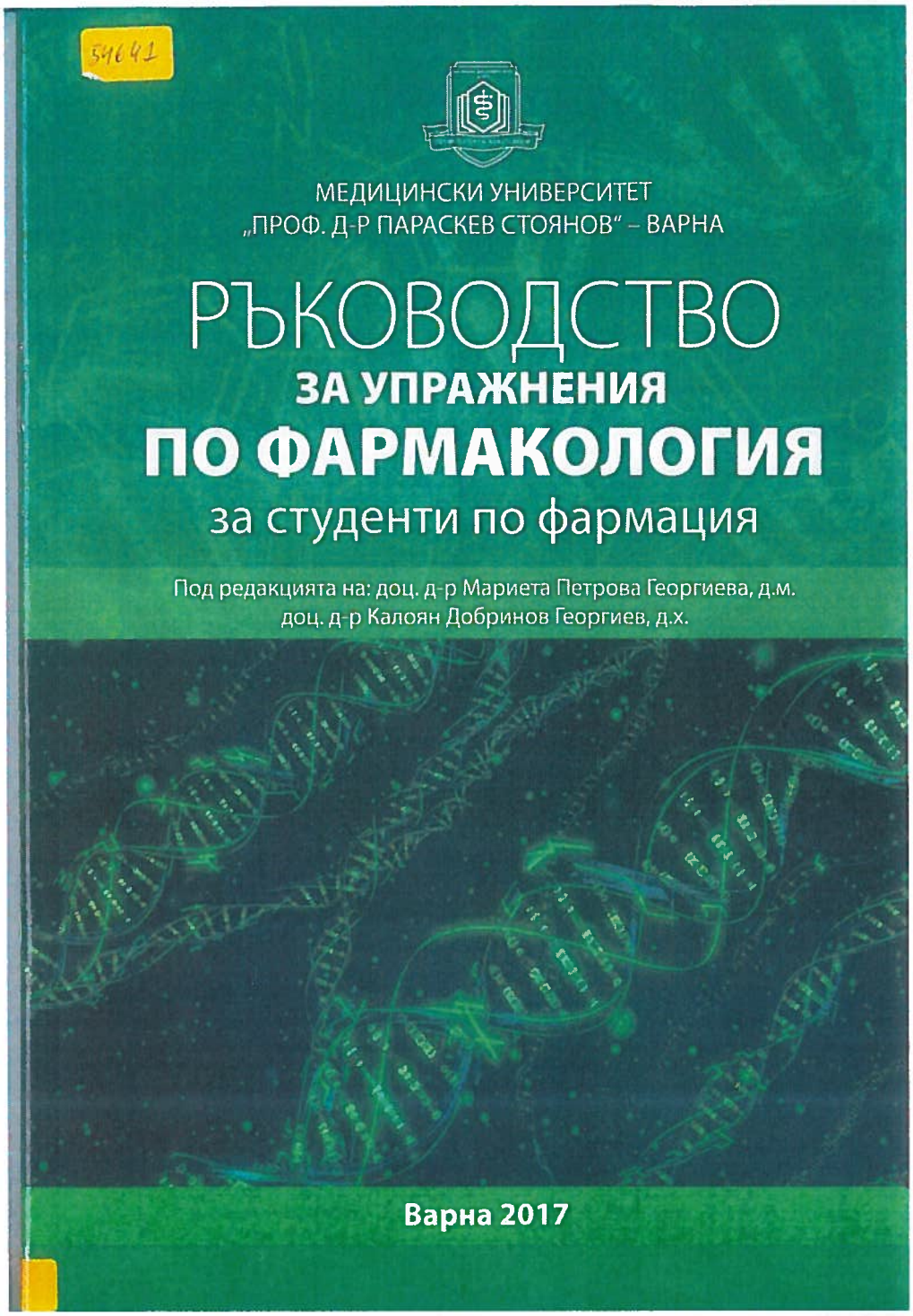

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