



YSMU PHARMACY FACULTY

**«ԴԵՂԵՐԻ ՍՏԵՂԾՄԱՆ ԱՌԱՋԸՆԹԱՅԸ
ՆԱԽԱԳԾՈՒՄԻՑ ՄԻՆՉԵՎ ՍՊԱՌՈՒՄ (DDDC-2022)»
ՄԻՋԱԶԳԱՅԻՆ ԴԵՂԱԳՈՐԾԱԿԱՆ ԳԻՏԱԺՈՂՈՎ՝
ՆՎԻՐՎԱԾ ԵՊԲՅ ԴԵՂԱԳԻՏԱԿԱՆ ՖԱԿՈՒԼՏԵՏԻ 50-ԱՄՅԱԿԻՆ**

26-28 ՍԵՊՏԵՄԲԵՐԻ, ԵՐԵՎԱՆ - 2022

ՎԵՅԱԺՈՂՈՎԻ ՊԱՏՎԱԿՈՐ ՆԱԽԱԳԱՐ՝

ԵՊԲՅ ռեկտոր,
բ.գ.դ., պրոֆեսոր Մուրադյան Ա.Ա.

ՎԵՅԱԺՈՂՈՎԻ ՆԱԽԱԳԱՐ՝

ԵՊԲՅ Դեղերի տեխնոլոգիայի ամբիոնի
վարիչ, բ.գ.դ., պրոֆեսոր Թովչյան Յ.Վ.

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դ.գ.թ., դոցենտ Ենոբյան Բ.Զ.

ՏԵՂԱԿԱԼՆԵՐ՝

դ.գ.դ., պրոֆ. Բալասանյան Մ.Գ.
դ.գ.թ., դոցենտ Ժամհարյան Ա.Գ.

ԶԱՐՏՈՒՂԱՐ՝

դ.գ.թ., դոցենտ Մանջիկյան Ա.Պ.

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բ.գ.թ. Դիերյան Լ.Գ.
դ.գ.թ. Սիմոնյան Մ.Յ.
դ.գ.թ. Աֆրիկյան Շ.Գ.
բ.գ.թ. Զիտչիյան Ա.Ա.
դ.գ.թ. Թանանյան Ա.Գ.
դ.գ.թ. Գրիգորյան Ս.Յ.
Աղամալյան Ի.Յ.
Բարսեղյան Ա. Բ.



**“DRUG DEVELOPMENT:
FROM DESIGN TO CUSTOMER (DDDC-2022)”
INTERNATIONAL PHARMACEUTICAL CONFERENCE
IN HONOR OF YSMU PHARMACY FACULTY 50TH ANNIVERSARY**

26-28 OF SEPTEMBER, YEREVAN - 2022

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NEUROPATHIC PAIN ELIMINATION BY GABA-PYROGLUTAMIC ACID SHORT PEPTIDES

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Keywords: *γ-aminobutyric acid, pyroglutamic acid, pregabalin, hot plate, chronic constriction injury.*

Recent decades investigations of neuropathic pain (NP) pharmacological correction indicate the undeniable effectiveness of γ -aminobutyric acid (GABA) derivatives, a striking example of which is the successful use of pregabalin (PGB) for NP elimination. However, the search for new remedies continues to be an urgent problem, since the recommended drugs are not devoid of serious side effects. Based on the above, a combination of new short peptides pyroglutamyl GABA (pGlu-GABA), pyroglutamyl GABA ethyl ester (pGlu-GABA ethyl ester), pyroglutamyl diGABA (pGlu-GABA-GABA) with PGB was investigated, as a possible way to potentiate the effect of PGB and avoid expected sedation. Analgesic activity was studied in rats sciatic nerve chronic constriction injury (CCI) model. The degree of neuropathy was assessed in hot plate test (on the 3rd, 5th, 7th postoperative days and the day before surgery) by evaluating behavioral changes caused by CCI-induced thermal hyperalge-

sia. The drugs were administered intraperitoneally, at a dose of 20mg/kg each. Experimental data analysis revealed the presence of analgesic activity in all the studied agents, but in different manner. Thus, maximum licking latency was observed in the PGB and pGlu-GABA receiving animals on day 3, whereas the longest jumping latency was noted in the PGB and pGlu-GABA ethyl ester treated rats on the same day. The highest locomotor latency was observed on the 7th day of the CCI for PGB and pGlu-GABA-GABA combination. Licking frequency compared to the control group was lower in pGlu-GABA and pGlu-GABA ethyl ester and PGB receiving animals, but jumping frequency was reduced in all groups. It is noteworthy that all registered effects were accompanied by an increase in locomotor activity without sedation. The obtained data indicate that GABA derivatives could serve as potential sources for combination with PGB in purpose to potentiate analgesic activity and eliminate its side effects.

UDC: 615.21:612.824

RECOVERY OF IMPAIRED CEREBRAL CIRCULATION BY NICOTINOYL L-PROLINE

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Keywords: *nicotinoil L-proline, brain ischemia, cerebrocortical microcirculation, antihypoxic activity.*

Discovered in our laboratory effects of new synthesized nicotinoil L-proline (NLP) to stimulate the cerebral blood flow both in acute and chronic ischemia formed the basis for investigation its effects on cerebrocortical microcirculation changes under the ischemic condition and antihypoxic activity. Experiments were carried out on inbred male white rats weighing 170-230g and mice weighting 18-20g. Cerebrocortical microcirculation was evaluated by the calcium adenosine triphosphate method in rats anesthetized by chloral hydrate (400 mg/kg, i/p), under the acute cerebral ischemia caused by left carotid artery occlusion (LCAO). Antihypoxic activity of NLP was assessed by the registration of mice survival time in hypercapnic, hemic and cytotoxic hypoxia models. Conducted experiments evident, that

in a background of LCAO after 60min of NLP i/p injection at a dose of 10mg/kg cerebrocortical microcirculation was changed both in ipsilateral and contralateral hemispheres compare with control as follows: the number of functioning capillaries was increased about 52.53% in left and 60.32% in right hemispheres, whereas the number of compressed capillaries was decreased by 25.95% in left and by 26.2% in right hemispheres. Obtained data manifested the antihypoxic activity of NLP at a dose 10mg/kg, which was appeared by its ability to increase animals survival time about 28.53% in sodium nitrite mediated experimental hemic model of hypoxia. Thus presented data concerning the antihypoxic activity of NLP and its ability to stimulate cerebrocortical microcirculation allow to considered its as a potential agent for recovery of impaired cerebral circulation.

UDC: 615.322:582(479.25)

PHARMACOGNOSTIC ANALYSIS AND ANTIOXIDANT ACTIVITY OF NEPETA MUSSINII (SPRENG.) AND NEPETA SULPHUREA (C.KOCH.) GROWING IN ARMENIAN FLORAArshakyan N.I.^{1*}, Dumanyan K.H.¹, Chichoyan N.B.¹

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Keywords: *Nepeta mussinii* (Spreng), *Nepeta sulphurea* (C.Koch), essential oils, copaene, antiradical activity.

Nepeta is multiregional genus of the Lamiaceae or (Labiatae Mint) family. Species of *Nepeta* are extensively used in traditional medicine, particularly in India, China and Iran. *Nepeta mussinii* (Spreng.) and *Nepeta sulphurea* (C. Koch.) species as a medicinal raw material has a significant potential and population in Armenian flora. From this point of view, the aim of this was the pharmacognostic analysis and the study of biological activity of *Nepeta mussinii* and *Nepeta sulphurea* harvested from 3 regions of Armenia. As research materials were served *Nepeta mussinii* (Spreng.) collected from the areas of Tsakhkavit, Vayk and *Nepeta sulphurea* (C.Koch.) gathered from the bank of river Mantash. The determination of the chemical composition of the essential oil was performed by the gas chro-

matography-mass spectrometry (GC-MS) method. For the evaluation of the antiradical activity of *Nepeta* herb was used the spectrophotometric method. In the essential oils of the plants 148 compounds were identified, in which dominant compounds were monoterpenes and their oxygen derivatives (61.29 %). The dominant components in the essential oils obtained from the raw materials collected from 3 regions of Armenia were *Copaene* and β -*Elemene*. The result of the investigation showed that *Nepeta mussinii* and *Nepeta sulphurea* herbs growing in different climatic condition express antioxidant and free radicals eliminating activity. According to pharmacognostic parameters and qualitative composition of essential oils, the studied species of *Nepeta* growing in Armenia, which possessed antioxidant activity were endemic species, they did not belong to any of the three known chemorases.

UDC: 615.27:577.1

TRIMETAZIDINE AS A MODIFIER OF DOXORUBICIN+CYCLOPHOSPHAMIDE CHEMOTHERAPY MODE-DRIVEN ALTERATIONS IN CHOLESTEROL METABOLISMAvagimyan A. A.^{1,2*}, Kakturskiy L.V.², Aznauryan A.A.¹, Gogiasvili L. E.³¹ Yerevan State Medical University after M. Heratsi, Yerevan, Armenia² FSBI A. P. Avtsyn Research Institute of Human Morphology, Moscow, Russia³ A. Natishvili Institute of Experimental Morphology, TSU, Tbilisi, Georgia

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Keywords: *cardiotoxicity*, *cardio-oncology*, *trimetazidine*.

Cardio-oncology confers a multidisciplinary crisis of contemporary medicine [1]. Doxorubicin+cyclophosphamide (AC) mode of chemotherapy serves as an effective strategy for breast cancer treatment. However, the development of widely variable cardiovascular complications, from sinus arrhythmia to decompensated heart failure, have been noted. The latter is aggravated by the fact that, despite the time map of various multidisciplinary studies conducted within the recent 60 years, the scientific world hasn't reached a consensus on the question - How to protect the heart and vessels from chemotherapy-related failure without reducing the effectiveness of chemotherapy?

The present research is aimed to assess the proatherogenic potential of the AC chemotherapy mode, with substantiation of trimetazidine (TMZ) intake.

The randomized, controlled, experimental *in vivo* study was conducted on 80 Wistar rats which were divided into four equal groups (1 - saline, 2 - AC, 3 - AC + TMZ, 4 - TMZ). The course dosages of doxorubicin, cyclophosphamide, and TMZ were administered at 15, 150, and 42 mg/kg, respectively. The experiment

duration last was 14 days (chronic cardiotoxicity model). TMZ was chosen as a probable stabilizer of cholesterol metabolism. The deviations of the following parameters were evaluated in the framework of this study: total cholesterol (TC), triglycerides (Tg), high-density lipoproteins (HDL), low-density lipoproteins (LDL), coronary risk index (CRI), and atherogenic coefficient (CA).

In group № 2, the concentration of TC is higher by 80.3 and 80.7%, Tg is higher by 80.5 and 88.0%, LDL is higher by 149.3 and 158.6%, HDL is lower by 46.8 and 43.5%, CA is higher by 187.4 and 172.8%, CRI is higher by 115.8 and 113.9% than in groups № 1 and 4, respectively. While the comparative groups № 3 and 2, it was noted that TMZ induces a decrease in the TC level by 26.6%, Tg by 46.4%, LDL by 38.2%, an increase in HDL by 18.2%, as well as a decrease in CA by 55.5% and CRI by 44.2% (Tukey's post-hoc test, $p < 0.05$, one-way ANOVA, $p < 0.0001$).

AC mode of chemotherapy is an inducer of atherogenic hyperlipidemia. TMZ provides a slight but pathogenically important tendency to cholesterol metabolism stabilization.

UDC: 615.454.1

FEATURES OF THE USE OF THE ARMENICUM/EFLORNITHINE MEDICAL COMPOSITION

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Keywords: *Armenicum, Eflornithine, composition, wound, microorganisms, bacteriotoxic action.*

Finding out the causes of various skin wounds, the nature of inflammation, and treatment approaches is one of the fundamental problems of modern medicine. They have various causes, and in particular, depend on the effects of aerobic and anaerobic bacteria, viruses, fungi, burns, low temperatures, and chemical and physical factors.

Over time, studies have revealed that, among other reasons, since the formation of a wound in the wound area, there is an increase in the activity of ornithine decarboxylase - an enzyme that synthesizes polyamines from ornithine, which in turn increases the amount of aliphatic polyamines (putrescine, spermidine, spermine, cadaverine, agmatine) in wounds, thereby promoting the wound healing process.

On the other hand, it has been proven that during wound inflammation, several pathogenic and opportunistic microorganisms actively develop in the wound area, which prevents wound healing. It has been proven that some types of these microorganisms need the presence of polyamines for their survival, and the latter, penetrating the metabolic processes of polyamines in the macroorganism, suppresses the wound healing process.

That is why, in the course of the fight against polyamine-dependent microorganisms, inhibition of the synthesis of polyamines thanks to new and targeted drugs has become relevant

today. This effect has the drug Eflornithine, the main active ingredient of which is alpha-difluoro-methyl ornithine (DFMO), an inhibitor of ornithine decarboxylase.

The preparation "Armenicum" of domestic production has pronounced antibacterial and anti-inflammatory properties. Based on the characteristics of these two drugs, the staff of the SRC YSMU proposed to use the combined preparation "Armenicum /Eflornithine" by combining these two ointments, which have a spectrum of antimicrobial action against pathogenic and opportunistic resident microbes, and, unlike polyamine-dependent microorganisms, has the properties inhibition of polyamine synthesis. Following this recommendation, technological investments in the preparation of the drug were made at the initiative of the pharmaceutical company ArpiMed.

We have conducted pharmacokinetic studies of the claimed drug and the results obtained allow us to conclude that the pharmacokinetics of the drug "Armenicum /Eflornithine" in rats is characterized by slow absorption of Eflornithine (DFMO). At the same time, when Armenicum/Eflornithine paste is applied to the wound surface, the active component of the DFMO paste penetrates the blood relatively slowly and remains on the wound surface for a longer time, providing pronounced regenerative properties than when applied separately. the use of drugs Eflornithine and Armenicum.

UDC: 618.11-006.2:618.177

INFLUENCE OF OVARIAN CYSTS ON OVARIAN RESERVE AND FERTILITY

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Keywords: *Adolescent girls, ovarian cysts, Anti-Mullerian hormone (AMH), Antral follicle count (AFC), fertility.*

Ovarian cysts are very common findings in adolescent girls. The vast majority of them are benign and self-resolving, with less than 10% of these cysts being malignant. The impact of ovarian cysts on an ovarian reserve and fertility depends on the nature, size, number, laterality, surgical intervention and risk of recurrence of the cysts. The objective of the study was to investigate the influence of ovarian cysts on the ovarian reserve and fertility rates. This is a prospective case control study. In total, 500 adolescent girls were included in the study. Anti-Mullerian hormone, follicle stimulating hormone was determined and ultrasound was performed. The median age was 15.5 (range = 13-18) years. A statistically significant reduction in anti-Mulle-

rian hormone from 4.23 ± 3.77 to 2.67 ± 1.78 ng/mL ($p= 0.03$), increase in follicle stimulating hormone level from 6.46 ± 2.46 to 8.65 ± 2.67 mIU/ml ($p= 0.02$), reduction in antral follicle count by 2.22 ($p= 0.01$) was seen in cysts with a diameter of 5 cm and more persistent for 4 months or more. Our data showed a significant and long-term reduction in ovarian reserve 5 months after surgery on the ovaries and 3 months after the recurrence. The size of the cysts, long-term maintenance, recurrence and surgery on the ovaries had an influence on the ovarian reserve. The larger the size of the cyst the greater the statistically significant damage to the ovarian tissue and ovarian reserve. The potential reduction in fertility might be dependent on the extent of the ovarian damage.

UDC: 615.256:502/504

ENVIRONMENTAL EXPOSURE ON THE OVARIAN RESERVE IN ADOLESCENT GIRLS*Bareghamyan H.H.^{1,2}, Harutyunyan A.G.^{1,2}, Shahverdyan N.B.^{1,2}, Ghazaryan A.S.³*¹“Beglaryan” MC, Yerevan, Armenia.²Department of Obstetrics and Gynecology № 1, YSMU³Hospital N2Corresponding author e-mail: hasmik3185@gmail.com**Keywords:** *Adolescent girls, environmental pesticides, Anti-Mullerian hormone (AMH), fertility.*

Many studies have investigated the effects of pesticides on female fertility. Similar to other agents present in the environment, exposure to pesticides may occur in occupational settings, through water consumption and dietary exposures, and from agricultural or gardening activities. Additionally, exposure may occur in populations residing next to crops and other agricultural fields, via sprayed pesticides spread by wind. The duration and timing of exposure to pesticides is likely to play a significant role in the severity of associated fertility disturbance. As the world has faced a significant reduction in fertility during the last few decades, the aim of this study is to investigate the association between environmental and occupational exposure to pesticides and fertility disturbances in adolescent girls and determine exposure to pyrethroid pesticides on ovarian reserve. This is a prospective case control study. In total, 150 adolescent girls were included in the study. In this study pesticides, including organochlorine pesticides (OCPS), such as dichlorodi-

phenyltrichloroethane (DDT), as well as contemporary organophosphate-based agents, pyrethroids, and serum anti-Mullerian hormone was determined. In a prospective study of 150 adolescents aged 13-18 years old from Armenia, found that pyrethroid exposure is associated with a greater prevalence of delayed pubertal onset. Greater concentrations of organochlorine pesticides (OCPS) were associated with decreased antral follicle count ($p=0.02$) and levels of anti-mullerian hormone (AMH) ($p=0.03$) and increased follicle-stimulating hormone (FSH) ($p=0.04$) amongst adolescents. Synthetic pyrethroids may affect female ovarian reserve. Pesticide exposure and ovarian toxicity may lead to female infertility, including premature ovarian insufficiency (POI), menstrual problems, polycystic ovary syndrome (PCOS). At present, fertility evaluations are not routinely incorporated into adolescents' health surveillance programs, which might play an important role in prevention of infertility and in reduction to the adverse effects of environmental pesticide exposure.

UDC: 616.211/231:616.857

COMPARATIVE ANALYSIS OF SELF-MEDICATION FOR ACUTE UPPER RESPIRATORY TRACT INFECTIONS AND HEADACHE SYMPTOMS*Barseghyan A.B.^{1*}, Simonyan A.R.¹, Nazaryan L.G.¹, Simonyan M.H.¹*¹Department of Pharmaceutical Managment, Yerevan State Medical University after M. Heratsi, Yerevan, ArmeniaCorresponding author e-mail: anushikbarseghyan@gmail.com**Keywords** *acute upper respiratory tract infections, headache, self-medication, pharmacy employee.*

Acute upper respiratory tract infections (URI) and headache symptoms are the most frequently self-treated symptoms by consumers. Self-medication contains many dangers: misdiagnosis, improper use and wrong combinations of drugs, complication of the disease, etc.

Purpose of the study was to evaluate the self-treatment process for URI and headache symptoms and to make a comparative analysis.

This study was a cross sectional, questionnaire-based survey, participants (1308 people) were randomly selected without repetition. The number of questionnaires was determined by The Survey System Version 11.0, the first type error is with 5% probability, the evaluation accuracy is 3%, $P = 0.5$. The data were registered in SPSS program (12.0), analyzed by SPSS and EXCEL programs.

The results revealed that consumers in general when buying medicines take into account their previous experience (34%), advertising (7%), Internet (6%), advice of neighbors and friends (10%), professional advice from doctors (29%) and pharmacy employees (14%).

According to the results of the study 35% of consumers seek professional advice in case of URI, 45% in case of headache, in other cases self-treatment is performed 65%, 55%, respectively, using various non-official consultation sources.

The discussed symptoms are mainly self-medicated, but the comparison shows that self-medication is more often carried out in the case of URI. Pharmacy employees should carry out adequate management of consumers self-treatment, paying more attention especially to the self-treatment of URI. A qualified, knowledgeable pharmacist will help avoid self-medication errors by providing advice on Over-the-Counter drugs.

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PHARMACIST'S ROLE IN NONCANCER PAIN MANAGEMENT

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Keywords: *noncancer pain, pharmacotherapy, over-the-counter analgesic, pharmacy employees.*

Pain is a general reason for self-medication with over-the-counter (OTC) analgesics. Common risks of self-medication include inappropriate use and overdose of drugs, drugs interactions and adverse effects, other pharmaceutical errors. Pharmacists can assess the type and severity of pain, monitor treatment and guide medication regulation to improve the treatment of the pain. Purpose of the study was to study and analyze professional abilities and role of pharmacy employees during the noncancer pain management. This was a descriptive cross sectional research conducted with Questionnaires. The study was carried out among 285 pharmacy employees selected randomly. Number of questionnaires was determined by The Survey System Version 11.0., the reliability coefficient $t=1.96$, the first type error is with 5% probability ($\alpha = 0,05$), and the evaluation accuracy is 5% ($\Delta = 5\%$), $p=0.5$. Data obtained as a result of sur-

veys were registered in SPSS and EXCEL. According to survey 12% of the pharmacy employees were unable to respond to the question about OTC analgesics recommendations. Responses were divided into two groups according to composition of the medicines: single-agent medicines (81%) and combined medicines (19%). Considering the responses of pharmacists about OTC analgesics recommendations and preferences were the following: ketoprofen 29%, ibuprofen 23%, nimesulide 18%, diclofenac 15%, naproxen 5%, drotaverine hydrochloride 4%, acetaminophen 3%, metamizole sodium 2%, meloxicam 1%. Based on survey data 24% of respondents are unaware of side effects of OTC analgesics. Pharmacy employees have the need for improved pharmacy education on the efficacy and safety of analgesics used at OTC dose and duration when advising on the treatment of pain. They must complete the necessary training to update their knowledge and skills in pain management.

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CONSUMERS' ATTITUDE TO ONLINE TRADE OF MEDICINES IN ARMENIA

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Keywords: *medicines, online pharmacy, pandemic, age group.*

During the pandemic, many pharmacies in Armenia started new activities, in particular, the online sale. In accordance with Directive 2011/62/EU, the sale of certain medicinal products through online pharmacies is allowed, but this type of pharmacy activity has certain advantages and disadvantages.

Purpose of the study is to identify certain problems and regulate the online trade in medicines in Armenia, given the fact that medicine is a special commodity (WHO, Declaration).

A written questionnaire method was used on a voluntary basis more than 270 respondents of different age groups who use the services of online pharmacies.

Among respondents under 35 years old, 85% are satisfied and believe that this service is necessary, given the safety during the pandemic. More than 63.7% of respondents aged 35-65 also gave a positive answer, but 31.5% have some concerns related to the reliability of delivery, and almost 3.8% of

respondents are afraid of buying counterfeit or expired medicines. Respondents over 65, more than 75% believe that it is desirable that this service be carried out by a carrier with a pharmaceutical education, i.e. need to consult a pharmacist. About 13.5% of respondents in this age group, despite the fact that they use this service, are skeptical about online pharmacies, especially in compliance with the rules of delivery conditions, and above 4.3% are afraid of buying fakes.

A certain number of respondents need the delivery person to have a pharmaceutical education, and are concerned about the reliability and the issue of delivery conditions (compliance with temperature and humidity). This requires certain changes in order to improve existing laws. In particular, to tighten existing requirements, ensure proper implementation of requirements, introduce more stringent delivery conditions that will lead to an increase in the quality and consumer confidence in this service.

UDC: 547.7

SYNTHESIS OF NEW DERIVATIVES OF 2-(PYRANO[3,2-C]CHROMEN-5-YL) ACETIC ACIDChernov N.M.^{1*}, Domotskaya M.Yu.¹, Shutov R.V.¹, Yakovlev I.P.¹¹St. Petersburg State Chemical Pharmaceutical University, St. Petersburg, RussiaCorresponding author e-mail: nikita.chernov@pharminnotech.com**Keywords:** 3-vinylchromone, cyanoacetic ester, ANRORC reaction.

Based on the reaction of electron-deficient 3-vinylchromones with cyanoacetic ester, an effective method for the synthesis of pyrano[3,2-c]chromene derivatives was developed. The yields of the compound were 75-87%, the synthesis proceeds under mild conditions (ethanol, 80°C) and is tolerant to the introduction of various substituents. The resulting substances can be used as potential antiplatelet and analgesic agents. Phenanthrene-like 5H-chromeno[4,3-d]pyrimidines derived from 3-formylchromones stand out among new compounds with antiplatelet, analgesic, and anti-inflammatory effects. In earlier works we have shown that electron-deficient 3-vinylchromones are a convenient alternative starting reagent for such heterocycles. Moreover, such chromones in reactions with cyanoacetamide can also lead to other phenanthrene-like systems – chromeno[4,3-b]pyridines and pyrano[3,2-c]chromenes. However, these substances potentially have significant biological effects. A common feature of the systems obtained in this way is the acetic acid fragment, which is convenient for further functionalization of the compounds. The disadvantage of the existing synthesis is the average yields of pyrano[3,2-c]chromenes (50-60%). The aim of the work is to develop an effective method for the synthesis of potentially biologically active derivatives of pyrano[3,2-c]chromenes. Commercial reagents (Aldrich, Acros, NevaReaktiv) were used without further purification. Reactions were monitored by TLC (ethyl acetate/hexane (1/1, v/v), visualization in UV light). The NMR spectra of the ob-

tained compounds were recorded on Bruker Avance III (¹H - 400 MHz, ¹³C - 100 MHz) and were calibrated to the solvent signal (DMSO-d₆). Mass spectra of substances (ESI) were recorded on Bruker micrOTOF spectrometer. The melting points of the compounds were measured by the capillary method and were not corrected. The previously studied reaction of electron-deficient 3-vinylchromones, namely ethyl(4-oxo-4H-chromen-3-yl)acrylates, with cyanoacetamide leads to a mixture of products due to the ability of cyanoacetamide to enter into cyclization with both amide and nitrile groups. The replacement of cyanoacetamide by cyanoacetic ester in this synthesis made it possible to get rid of the side reaction of the formation of chromeno[4,3-b]pyridines, thus increasing the selectivity of the process. The synthesis was carried out in ethanol at 80°C and catalysis with a highly basic non-nucleophilic solvent (1,8-diazabicyclo[5.4.0]undec-7-ene, DBU), yields of new derivatives of pyrano[3,2-c]chromenes amounted to 75-87%. The substrate stability of this synthesis was tested on a number of 3-vinylchromones (18 representatives) containing various substituents (CH₃, F, Cl, Br, NO₂, OH, CH₃O) in positions 6-8 of the ring. In the course of the work, an effective method for the synthesis of pyrano[3,2-c]chromene derivatives based on the reaction of 3-vinylchromones with cyanoacetic ester was developed. The synthesis is characterized by high selectivity (yields up to 87%), mild conditions (ethanol, 80°C), easy isolation (crystallization from the reaction mass after acidification), and high substrate resistance to the introduction of various substituents into the chromon.

UDC: 582:547.9:616.858

BACTERIAL MELANIN AS A POSSIBLE THERAPEUTIC AGENT IN THE TREATMENT OF PARKINSON'S DISEASEDanielyan M.H.¹, Pogosyan M.V.¹, Avetisyan Z.A.¹, Khachatryan V.P.¹, Nebogova K.A.¹, Karapetyan K.V.¹¹Orbeli Institute of Physiology NAS RA, Yerevan, ArmeniaCorresponding author e-mail: margaritadanielyan76@gmail.com**Keywords:** Parkinson's disease, bacterial melanin, neurons, substantia nigra pars compacta.

Parkinson's disease (PD) is a slowly progressive chronic disease that primarily affects the motor system. Most motor symptoms are caused by damage of dopaminergic neurons in the substantia nigra pars compacta (SNc).

The aim of this work was to study the effect of bacterial melanin (BM) on the morphofunctional state of SNc using rotenone model of PD. Studies were carried out on SNc of intact rats, on a PD model 4 weeks after rotenone injection and on a PD model with BM injection for 4 weeks. Morphohistochemical studies were carried out by the method for detecting the activity of Ca²⁺-dependent acid phosphatase, developed by Meliksetyan I.B. Behavioral tests were carried out using a Rotometer. Neuronal death and SNc depigmentation are noted with rotenone intoxication of the brain, and abrupt morphological changes in intracellular structures occur, which indicates metabolic and morphological disorders. The affected nerve cells undergo

pronounced atrophy, significant changes in the cytoplasm and nucleus occur in the cells. Behavioural tests have shown that animals display a form of behaviour inherent in PD. With the introduction of BM, positive changes in the structural properties of neurons are observed in SNc in comparison with the model of PD. The morphological picture of neurons is close to normal, the shape and size of the cells are preserved. In the cytoplasm of cells, an increase in phosphatase activity is observed, which indicates the activation of metabolic processes. The data obtained allow us to conclude that BM shows neuroprotective activity, accelerating the compensatory recovery in the central nervous system against the background of developing neurodegenerative changes inherent in PD. In the future, additional studies are needed to decipher the mechanisms of the effect of BM in order to create new-generation drugs based on it for the prevention and treatment of PD.

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UDC: 615.32:615.9

CURCUMIN PROTECTS AGAINST ROTENONE-INDUCED NEUROTOXICITY

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Keywords: *curcumin, rotenone, neurodegenerative diseases.*

Rotenone is involved in the degeneration of dopaminergic neurons, and curcumin may prevent or effectively slow the progression of Parkinson's disease (PD). Previous research has shown that the naturally occurring phenolic compound curcumin can reduce inflammation and oxidation, making it a potential therapeutic agent for neurodegenerative diseases. The present study involves investigation of rotenone-induced histological changes in the brain area, hippocampus using Nissl staining af-

ter 35 day of subcutaneous injection of rotenone in adult male rats. We sought to determine whether curcumin could protect against rotenone-induced dopaminergic neurotoxicity in a rat model by in vivo electrical recording from Substantia nigra pars compacta (SNc). Curcumin treatment significantly improved electrical activity of neurons in the SNc of rotenone-induced PD model rats. The pattern of histological alterations corresponds with electrophysiological manifestations.

UDC: 615.276:668.523

THE COMPARATIVE INVESTIGATION OF ANTI-PAIN AND ANTI-INFLAMMATORY EFFECTS OF ORIGANUM VULGARIS ESSENTIAL OIL AND BETA-CARYOPHYLLENE

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Keywords: *Oregano essential oil, GC-MS analysis, β -Caryophyllene, vegetation periods, analgesic activity.*

The Oregano belongs to the Lamiaceae family. Its herb is known as a valuable source of essential oil, the main bioactive substances of which are different types of terpenoids, particularly phytocannabinoids with expressed anti-pain activity. Oregano, which grows in the highlands of Armenia (OVA), differs in the composition of essential oil compared to Oregano in several European countries. The present research aimed to study the dynamic changes in the qualitative and quantitative composition of the essential oil and phytocannabinoids β -caryophyllene of local oregano in different vegetation periods. Essential oil, rich with β -caryophyllene and its oxide is a raw material for the pharmacological industry and, in particular, for the development of analgesic remedies. The herb of *O. vulgare* was harvested from the region of Gegharkunik and served as an investigation material in 2020 June-August. The identification of β -caryophyl-

lene in the essential oil was carried out by gas chromatography mass-spectrometry method. Formalin and hot plate tests in pain-like behavior in mice were used. The results of the gas chromatography revealed that the quantity of β -Caryophyllene was dynamically changed during pre-blossoming, blossoming, and fruiting periods. The maximal content of β -caryophyllene and β -caryophyllene oxide in OVA essential oil was revealed in the period of blossoming (8.18% and 13.36%, correspondently). In the formalin test, 4% OVA essential oil solution (3.5 mg/mouse, intra peritoneal) exerts significant antinociceptive and anti-inflammatory effects ($P = 0.003$). Pure β -caryophyllene shows a weaker effect, which may be related to the "entourage effect" of essential oil's different components, particularly β -caryophyllene oxide. The wild oregano herb of Armenian highlands, harvested in the blossoming period may be considered a valuable source for developing pain-relieving preparations.

UDC: 615.12:614.27:33

THE PERSPECTIVE OF IMPLEMENTING GOOD DISTRIBUTION PRACTICE (GDP) IN THE PHARMACEUTICAL CUSTOMS WAREHOUSE OF "F.HOFFMANN-LA ROCHE AG" LTD*Dugashvili N¹, Chanturia Z¹, Kvizhinadze N.¹, Bugianishvili M.¹, Tsomaia I.¹**¹Department of Social and Clinical Pharmacy, Tbilisi State Medical University**Corresponding author e-mail: n.dughashvili@tsmu.edu***Keywords:** *GDP, CAPA, standards.*

“Good Distribution Practice” refers to the entities engaged in the pharmaceutical business to the minimum standards that must be observed in order to maintain the quality and integrity of the pharmaceutical product until the end point of destination. The purpose of the study is to conduct an audit / internal inspection at the F.HOFFMANN-LA ROCHE AG Ltd customs pharmaceutical warehouse and to evaluate the prospects for the introduction of “Good Distribution Practice” (GDP). “F.HOFFMANN-LA ROCHE AG” Ltd to detect possible non-compliance with the requirements of the “Good Distribution Practice (GDP)” through internal inspection at the customs warehouse;

- Assess the level of staff knowledge through internal questionnaires;

- Define corrective and preventive measures to eliminate the identified inconsistencies.

Company “F.HOFFMANN-LA ROCHE AG” Ltd. Documentation valid in the customs pharmaceutical warehouse; Internal audit to determine compliance with the requirements and standards

of Good Distribution Practice. As F.HOFFMANN-LA ROCHE AG Ltd. revealed during the internal inspection of the customs pharmaceutical warehouse, the standards of “Good Distribution Practice” (GDP) are more or less taken into account. The recommendations in the World Health Organization guidelines for the storage of temperature-sensitive products are followed. This is due to the head office of the company “F.HOFFMANN-LA ROCHE AG” (Switzerland, Basel), as well as its official representation in Georgia. Particular attention is paid to the detailed documentation of processes, record-keeping and registration, so that in case of non-compliance, its traceability is possible. “F.HOFFMANN-LA ROCHE AG” Customs Pharmaceutical Warehouse visits the internal audit from the head office once in 3 years, the purpose of which is to identify possible discrepancies for further improvement. It is important to plan corrective and preventive measures (CAPA). This confirms the prospect for F.HOFFMANN-LA ROCHE AG to fully implement the Good Distribution Practices standard and meet the requirements.

UDC: 615.322:582(479.25)

THE PHARMACOGNOSTIC ANALYSIS OF FERULA RIGIDA L. HERB HARVESTED IN ARMENIAN FLORA*Ghazaryan A.M.¹, Dumanyan K.H.¹, Danielyan L.V.², Hovhannisyan H.G.², Chichoyan N.B.¹**¹Department of Pharmacognosy, Yerevan State Medical University after Mkhitar Heratsi, Yerevan, Armenia**² Scientific and Production Center “Armbiotechnology” NAS RA, Yerevan, Armenia**E-mail: arshaluysghazaryan@gmail.com***Keywords:** *Ferula rigida L., essential oil, alcoholic extract, GC-MS, stimulating activity.*

Ferula rigida is a perennial herb of the Belifera family. The areal part of the plant is used in traditional medicine of Iran and India. The species of *Ferula rigida* is found in Armenia. The plant *Ferula rigida* evoke significant populations in Byurakan. The aim of this study is evaluation of phytochemical contain of essential oil and biostimulating activity metanolic extract of the herb *Ferula rigidula*, growing in Armenia. The raw material of *Ferula rigida* was collected from Byurakan in the flowering stage. The primary processing and drying of a raw material was carried out by WHO instructions. The aerial parts were extracted by hydro-distillation method. The composition of the essential oil isolated from dried herb was carried out by GC-MS method. The examination of essential oil of *Ferula rigida* grown in Byurakan was carried out in the Analytical laboratory “FDA Laboratory” LLC. Microbiological analysis were carried out in the laboratory of lactic acid bacteria of Scientific and Production Center

“Armbiotechnology” NAS. The probiotic bacteria were isolated from normal human microbiota. The effect of the dry alcoholic extract of the plant was tested on the growth of probiotic lactic acid bacteria *Lactobacillus acidophilus* and *Lactobacillus helveticus* in LAPTg medium. GC-MS analysis of essential oil showed that the composition of *Ferula* herb essential oil consisted of 15 compounds. The most important were monoterpenes (53%). The major components were geraniol (16.12%), menthene (13.14%), menthone (8.14%), cineole (5.56%), humulene (3.89%), β -caryophyllene (2.6%). The results of microbiological analysis showed that the raw alcohol extract has a stimulating effect on the growth of lactic acid bacteria.

Thus, the results of the pharmacognostic study of the areal part of *Ferula* plant showed that the raw material of *Ferula rigida* species growing in Armenia can be promising in medicine due to the content of bioactive substances and stimulating growth of the gut LABs.

UDC: 615.322:579

PHYTOCHEMICAL ANALYSIS AND STIMULATING EFFECT ON THE GROWTH OF PROBIOTICS OF THE ALCOHOL EXTRACT OF THE HERB CHAEROPHYLLUM BULBOSUM L. RA

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Keywords: *Chervil- Chaerophyllum bulbosum L., biological activity, pharmacognostic analysis, amino acids, lactic acid bacteria.*

Chervil- *Chaerophyllum bulbosum L.* is a herb of Umbelliferae family and widely spread in Shirak, Lori, Tavush, Aragatsotn, Gegharquniq, Vayots Dzor, Syuniq, Yerevan marzes. In Armenia from ancient times have been used a number of wildly growing plants, of which is tuber bulbous-rooted. According to the dictionary of medicinal plants names (Revazova L.V., Musaelyan M.S.) the plant is known as "Shushan-banjar, Keghakaros, Pshvik, Berkraterev, Ghmie". There are 40 species of bulbous-rooted chervil, of which in Armenia are met the ramsonal (*Cherophyllum bulbosum*) and gilded (*Cherophyllum aureum*) sorts. The pharmacognostic analysis and stimulating growth activity of plant bulbous-rooted chervil growing in Armenia. The qualitative and quantitative analysis of amino acids composition of the 50% alcohol extract of raw material was carried out using the amino acid analyzer "Shimadzu Nexeria X2". Microbiological analysis

was performed in LAPTg medium. Bacterial growth stimulation was assessed by OD 600 measured on a 1500 UV-visible spectrophotometer. The probiotic bacteria isolated from the of normal human microbiota was used. The effect of dry alcoholic extract of the herb was tested on the growth of probiotic lactic acid bacteria *Lactobacillus acidophilus* and *Lactobacillus helveticus* in vitro. Analysis of the composition of a 50% alcohol extract of *Chaerophyllum bulbosum L.* showed the presence of essential and conditionally essential amino acids in the plant raw material. The alcoholic extract of raw material *Chaerophyllum bulbosum L.* besides other components also contains substances specifically stimulating growth of the probiotic LABs. It was revealed that the alcoholic extract of raw material *Chaerophyllum bulbosum L.* contains essential and conditionally essential amino acids. *Chaerophyllum bulbosum* collected from Aparan, in addition to its nutritional value, may be of interest as a medicine.

UDC: 615.32:577.17+616.98:578.834.1

THE SOME FEATURES OF PHARMACOLOGICAL STUDIES OF GEOMIN FORTE AS ANTIOXIDANT IN POST COVID-19 TREATMENT

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Keywords: *pharmacological, geomin forte, Covid-19, treatment.*

The aim of the study was to investigate and analyze the properties and prospects for the use of zeolite with Geomin Forte in the treatment of Covid and post-Covid-19 diseases. Antioxidants are substances that the human body constantly needs to keep it in a normal state, that is, to maintain the necessary balance between free oxidative radicals and the antioxidant forces. Vitamin E increases the non-specific resistance of the organism and tocopherol stimulates its own anti-inflammatory activity by activating the synthesis of cytokines. Vitamin E's action is to stimulate the reproduction of immune cells, systems that must multiply rapidly when encountering a source of potential disease. In the body, this process is called mitogenesis. The pharmacodynamic effects of tocopherol are synergistic when combined with vitamins C and A. Retinol promotes the formation of immune cells (guard cells) that line the airways and gastrointestinal tract and act as a natural barrier against infection. Medicine will increase the body's ability to adapt to a changing environment, since in many cases it is very difficult to protect the population from the effects of a negative factor (including ionizing radiation, natural

disasters, etc.), according clinical results of the study, Geomin Forte can be used for poisoning (as the best sorbent for food, infections, occupational poisoning, chronic metal poisoning and chronic radiation exposure) and also, in intervention of the functional state of the immune system overload, in Covid and Post-Covid condition, as well as an aid in allergic diseases. The mineral zeolite (clinoptilolite) developed by us, activated clinoptilolite 500 mg "Geomin Forte", is characterized by an antioxidant effect. In contrast to conventional antioxidants, it stimulates the body's own antioxidant system and is a directly acting redox active ingredient. Its natural activated mineral zeolite (clinoptilolite) acts directly on the cell membrane as an electron donating surfactant. According clinical study results, Geomin Forte has 200 times more antioxidant effects, than vitamins C and E. So accordingly, study results, Geomin Forte is used in combination with antioxidant therapy as part of the standard treatment of the following diseases: Covid and post-covid condition, as well as in accelerated aging process, endocrine pathologies, atherosclerosis and coronary heart disease, hypertension, stroke and rheumatism.

UDC: 615.012:579

ANTIBIOTIC ADJUVANTS – A BOOMING STRATEGY TO UNLOCK BACTERIAL RESISTANCE

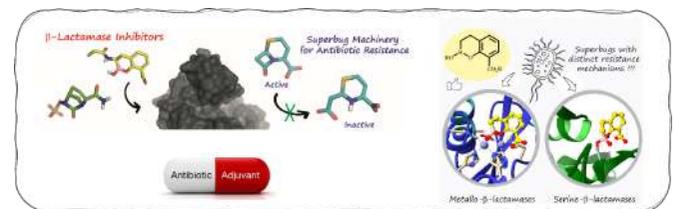
González-Bello C.

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Corresponding author e-mail: concepcion.gonzalez.bello@usc.es**Keywords:** antibiotic adjuvants, bacterial resistance.

After many years of success in the battle against infectious diseases, we are now losing ground in this fight with the worldwide increasing appearance of “superbugs”, which are resistant to most antibiotics in clinical use. Hence, there is great interest in the development of alternative therapies, the identification of unexplored bacterial targets, and the discovery of new strategies for the treatment of infections that are resistant to current antibiotics. A booming and successful strategy that is currently being exploited is the use of an ‘antibiotic adjuvant’ in combination with an antibiotic. These compounds are also named ‘resis-

tance breakers’ or ‘antibiotic potentiators’ and they have little or no antibiotic activity but co-administered with the antibiotic they either (i) block the main bacterial resistance mechanisms or (ii) enhance the antimicrobial action of the drug. Therefore, this approach enables us to prolong the lifespan of the life-saving drugs already in clinical use. Examples of efficient combination therapies *in vitro* and *in vivo* will be discussed, specifically the most recent results in the development of β -lactamase inhibitors.



UDC: 577.112.3

EVALUATION OF NEW PROPERTIES OF SOME NOVEL NON – PROTEIN AMINO ACIDSGrigoryan S.H.¹, Dheryan L.G.¹, Amroyan E.A.¹, Balyan L.S.¹¹Department of Pharmacology, Yerevan State Medical University, ArmeniaCorresponding author e-mail: grigoryanona89@mail.ru**Keywords:** amino acids, cytotoxicity, markers of inflammation.

The goal of achieving anti-inflammatory efficacy with the fewest possible adverse effects through inhibition of COX enzyme is still being investigated in order to develop drugs with safe profiles. Evaluation of the anti-inflammatory and antinociceptive effects of NPAA-34, NPAA-35, NPAA-36, NPAA-38 amino acids at a dose of 10mg/kg in the experimental models of the rats' ear acute inflammation induced by xylene and the “tail-flick” test of nociception assessment, shows that from four amino acids NPAA-34 and NPAA-36 exhibits more expressive antiinflammatory and analgesic activity. This became a subject of more detailed studies – investigation of NPAA-34' and NPAA-36' cytotoxicity, as well as their action on different markers of inflammation. Flow cytometry method results showed, that NPAA-34 and NPAA-36 amino acids are free of cytotoxic effect in case of 500 μ M concentration. The quantitative determination of MDA, under the effect of 10mg/kg dosage of studied amino acids, showed that these compounds prevent accumulation of malondialdehyde – end product of lipids peroxidation in the

inflammatory area, pointing out their antioxidant activity. The derived results confirm that the anti-inflammatory effect of the mentioned compounds, besides their ability to inhibit the COX, could be mediated by their antioxidant properties as well.

The study of NPAA-34 and NPAA-36 effect on the release IL-10 and IL-6 showed that, unlike well known arylpropionic acid derivative NSAIDs, they do not decrease the level of IL-10 and consequently do not increase the quantity of IL-6 in the result of which they do not cover the progress of anti-inflammatory effect due to COX inhibition. Moreover, the studied compounds do not contribute to the release of TNF- α , whereby, some researchers explain the irritative effect of arylpropionic acid derivatives on the gastrointestinal tract mucosa due to the blockage of cyclooxygenase.

Thus, the conducted research forms the basis to propose non-protein amino acids which are new synthetic derivatives of arylpropionic acids, as an perspective source for creation of new non-steroidal anti-inflammatory drugs.

UDC: 579.2:616.5-002.3-08

THE ROLE OF POLYAMINES IN THE REGENERATIVE PROCESS OF EXPERIMENTALLY INDUCED SKIN AEROBIC-PURULENT WOUNDS

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Keywords: polyamine, wound, ornithine decarboxylase, bacteria, fungi, Armenicum, DFMO.

Aliphatic polyamines (putrescine, spermine, spermidine) are organic polycations that play an important role in wound healing by stimulating several cellular mechanisms. In a human skin wound sample, the activity of the enzyme ornithine decarboxylase (ODC), which regulates the rate of polyamine synthesis, rapidly increases along the wound edges and leads to the activation of the polyamine synthesis cascade. Under the influence of polyamines, some signaling systems are also activated in wounds, which are the main pathways for the release of cellular mechanisms, and thanks to them, the healing process begins in wounds. For example, spermine induces the synthesis of urokinase-type plasminogen (uPA), the binding of which to the corresponding receptor (uPAR) at the wound margins releases the uPA/uPAR signaling system, which is the main driver of keratinocyte migration. Eukaryotic cell proliferation depends on precise modification of the eukaryotic initiation factor 5A1 (eIF-5A1), in which spermidine plays an indispensable role. Polyamines also regulate the immune response (spermidine affects the response of CD8+ T cells).

However, in addition to the significant functions performed by polyamines in the human body, polyamines are also necessary for the normal growth and development of fungi and bacteria. Small amounts of some microorganisms have a positive effect on the healing of wounds, and their increase, on the contrary, leads to the violation of the normal course of wound healing. At the initial stage of wound formation, the wound cavity is populated by commensals, then colonization changes over time, gram-positive microorganisms appear in the wound, but in deeper wounds, the microflora can contain both aerobic and anaerobic representatives. Some causative agents of purulent skin diseases, such as *Cl.sporogenes*, *E.coli*, and *Proteus Vulgaris*, carry out an active exchange of polyamines, and the polyamines synthesized by them in the wound microflora can lead to an excess of the latter. In wounds, fungal microflora can coex-

ist with bacterial microflora and contribute to the growth and spread of bacteria. The most frequently isolated fungi from the wound exudate belong to the genera *Candida* and *Trichosporon*, but the pathogenic microflora may also include representatives of *Cladosporidium*, *Pneumocystis*, *Microsporium*, and many other genera that carry out an active exchange of polyamines. The presence of *Pneumocystis carinii* and other fungi in wounds can cause an excess of polyamines.

On the other hand, many studies show that excess ODC and polyamines increase the risk of skin cancer. True, the oncogenic properties of polyamines have not yet been fully disclosed, but it is believed that their large amount in skin wounds causes not only epidermal proliferation but also the activation of stromal cells of the underlying layer, which strongly promotes oncogenesis in the skin. From the foregoing, it follows that the suppression of polyamine synthesis by pathogenic microflora during wound healing can contribute to both rapid healing and the prevention of skin cancer.

In our study, we present studies of inhibition of polyamine synthesis by wound microflora for rapid wound healing and prevention of subsequent cancer. The medicinal mixture “Armenicum/Eflornithine” is a mixture of the drug “Armenicum” and difluoro-methyl ornithine (DFMO). Cell culture exposure of α -difluoro-methyl ornithine (DFMO), an inhibitor of ornithine decarboxylase (ODC), results in almost complete elimination of putrescine and spermidine and arrest of cell proliferation while having little effect on spermine levels, leaving a cytostatic rather than cytotoxic effect. “Armenicum”, by activating the synthesis of fibronectin, promotes the synthesis of type I and III collagens at an early stage of the local inflammatory process, which are then transformed into collagen fibrils. An increase in the amount of fibronectin, in turn, suppresses eNOS and also reduces the cytotoxic effect of high levels of NO. Thus, it can be assumed that the medicinal mixture “Armenicum/DFMO” should be used for wound healing.

UDC: 616-091.8:616.893

APOPTOSIS AS A NEW TARGET FOR DRUG DEVELOPMENT FOR TREATMENT OF NEURODEGENERATIVE DISEASESHovhannisyan A.A.¹, Navasardyan G.A.²¹Department of Pathological Anatomy, Yerevan, State Medical University, Yerevan, Armenia²Department of Pathophysiology, Yerevan State Medical University, Yerevan ArmeniaCorresponding author e-mail: armanhovhannisyan1997.doc@gmail.com**Keywords:** *apoptosis, neurogenesis, phorbol-12-myristate 13-acetate.*

Development of new medications for treatment of dementia and cerebrovascular diseases is important issue and purpose of modern neuroscience. There are still uncovered mechanisms in pathogenesis of development and progression of dementia and cerebrovascular diseases which makes more difficult the process of treatment of diseases. Current pharmaceutical tools aren't possessing enough effectivity for treatment of brain diseases without neurological deficit. Crosslinking of several mechanisms in pathogenesis of cerebrovascular diseases and dementia makes more difficult to find out general pathway for neuronal survival, but opens new targets for actions of medications for intermediate solutions of treatment of specific neurological disease.

Purpose of research was to find out effect of action of PKC activator phorbol-12-myristate 13-acetate on activation of pro-apoptotic mechanisms and decrease of neural stem cell marker NeuN in brain during experiment. In a model of high fat diet was shown the effect of action of apoptosis activator on differentiation rate of neural stem cells and changes of specific

pro-apoptotic markers.

Experiments were carried out on 40 white male rats (n=10). Animals were kept in general vivarium states with free access of daily feeding. Model of high fat diet was developed by feeding animals according to current protocols 20% carbohydrate, 20% protein and 60% fat in daily food. Phorbol-12-myristate 13-acetate was injected by 5mg/kg dosage. All procedures were carried out under anesthesia (injection of 40mg/kg Nembutal). Markers were detected by ELISA. Statistics was performed by SPSS 21.0 program.

Results have shown that BAX increased by 27.1% 40% and 55.2% on 40th, 60th and 90th days, while Bcl-2 modifying factor increased by 36.3% on 90th day (p<0.001). Therefore NeuN decreased by 29.1%, 44% and 56% during experiment (p<0.05)

Activation of pro-apoptotic mechanisms and its indirect mechanisms of action on processes of neurogenesis and shrinkage of differentiation of neural stem cells gives some hope that furthermore research will reveal mechanisms which would be effective to be targeted by pharmaceutical tools for stimulation of healthy neurogenesis and neural differentiation in brain

UDC: 615.21:616.899-092.9

INFLUENCE OF INJECTION OF N-IGF-1 FRAGMENT ON EXPRESSION OF SEVERAL ANTI-APOPTOTIC PROTEINS IN RATS BRAIN DURING MODEL OF VASCULAR DEMENTIAHovhannisyan A.A.¹, Navasardyan G.A.²¹Department of Pathological Anatomy, Yerevan, State Medical University, Yerevan, Armenia²Department of Pathophysiology, Yerevan State Medical University, Yerevan ArmeniaCorresponding author e-mail: armanhovhannisyan1997.doc@gmail.com**Keywords:** *dementia, Gly-Pro-Glu, oxidative stress.*

Wide range of risk factors are involved in development and progression of cerebrovascular diseases. Low quality daily food ratio and increased ability of aggregation of thrombocytes are increasing risk of development and progression of cerebrovascular disease in parallel permanent hypercholesterolemia. Hypercholesterolemia and apoE ε4 allele are increasing risk of dementia and post-stroke brain damage with furthermore development of neurological deficit

Purpose of research was to find out the influence of injection of N terminal IGF-1 fragment (Gly-Pro-Glu) on expression of several anti-apoptotic proteins in rats brain during experimental model of post-stroke dementia via ligation of a. carotis interna pars cerebralis. Point of interest of research were current proteins as well as XIAP, CCS co-chaperone for SOD1 enzyme and NeuN as a marker for neural stem cells.

Experiments were carried out on 48 white male rats (n=12). Animals were kept in general vivarium states with free access of daily feeding. Model of dementia was developed by ligation of a. carotis interna pars cerebralis. N-IGF-1 (Gly-Pro-Glu) was

injected by 5mg/kg dosage. All procedures were carried out under anesthesia (injection of 40mg/kg Nembutal). Markers were detected by ELISA. Statistics was performed by SPSS 21.0 program.

Results are marking that XIAP protein increased by 23% on 90th day, while CCS protein increased by 19.2%, 27% and 34% on 40th, 60th and 90th days (p<0.01). Therefore NeuN increased by 21%, 33.25% and 38% during experiment (p<0.001)

Experimental peptides are possessing properties of stimulation of neurogenesis in brain during neurodegenerative and cerebrovascular disease. But few of them are demonstrating power of action of direct anti-apoptotic mechanisms and action on proteins which are responsible for prevention of oxidative stress in brain. From this point of view this experiment illuminates only one of sides of action of experimental drug candidate molecules for treatment of selected disease and furthermore research hopefully will open new horizons of understanding of action of neurogenesis stimulatory molecule and differentiation regulatory molecule in combined medical pill for clinical use.

UDC: 615.21:616.899-092.9

CHANGES OF NEUROGENESIS MARKERS AND RESOLVIN DERIVATIVES IN WHITE RATS' BRAIN DURING DEMENTIA LIKE STATE UNDER INJECTION OF FORSKOLIN

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Keywords: *resolving neurogenesis, nestin.*

Despite the rising interest against new viral and bacterial stains which are endangering safer life in the world and eventually concluding to development of pandemics, the other groups of diseases are still near us. Non-infectious diseases are possessing properties of statistical growth and automatically it leads to progression of mortality and morbidity in whole spectrum of disease statistics. There are specific mechanisms which are associated with stimulation of expression of anti-inflammatory cytokines in brain as well as IL-10 and SDF1 α for supporting brain against cytotoxic effects of oxidative stress and each of mechanisms possess a role of general pathway for action of medications.

Purpose of research was to find out changes of influence of injection of forskolin on changes of levels of specific neurogenesis markers as well as Nestin Vimentin and NeuN during high fat diet induced dementia like state in brain. cAMP dependent pathways are still effective and modern from scientific and practical side of view to be stimulated by specific designated medications for treatment of mild dementia.

Experiments were carried out on 32 white male rats (n=8). Animals were kept in general vivarium states with free access of daily feeding. Model of high fat diet was developed by feeding animals according to current protocols 20% carbohydrate, 20% protein and 60% fat in daily food. Forskolin was injected by 5mg/kg dosage. All procedures were carried out under anesthesia (injection of 40mg/kg Nembutal). Statistics was performed by SPSS 21.0 program.

Results have shown that Nestin increased by 28% 42.2% and 53% on 40th, 60th and 90th days, while Vimentin increased by 31.4% on 90th day (p<0.001). Therefore NeuN increased by 25%, 41.3% and 57% during experiment (p<0.02).

Stimulation of neurogenesis is important part of treatment of dementia, although there are still no serious medications which would allow to boost and control this process in brain, while there are various mechanisms, crosslinking of which finally will conclude to developed medical pill in clinical use. Action on cAMP dependent pathway is faster and direct pathway and possesses for some hope for development of intermediate solution for drug development in area of treatment of dementia.

UDC: 615.28:613.287.58:579

PROBIOTIC POTENTIAL OF ARMENIAN FUNCTIONAL SOUR MILK BEVERAGE "NARINE"

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Keywords: *Lactobacillus helveticus, sour milk Narine, probiotic, antibacterial activity.*

Fermented milk beverage "Narine" was invented by Professor Levon Yerzinkyan in Institute of Microbiology NAS RA in 1964 intended for curing and prophylaxis of gut disorders and substitute/supplement of human breast milk. Despite of up to 60 years wide use in dozens of countries "Narine" remains poorly investigated.

For cultivation of the starter culture skimmed milk and LAPTg media were used. Standard methods for assessing growth and fermentation rate, proteolytic activity, sensitivity to sodium chloride and bile salts, antibacterial activity, auto- and co-aggregation and adhesion to solvents, ribosomal 16S RNA and *rpoA* genes sequencing were used.

According Berge's manual and ribosomal 16S RNA and *rpoA* genes sequencing data (GenBank accession no. HQ379170 and HQ379179 respectively) the starter of "Narine" was identified as *Lactobacillus helveticus* instead of formerly considered *Lactobacillus acidophilus*. The identified strain was deposited

in the Microbial Depository Center (MDC) of RA as *L. helveticus* MDC9602. The latter possesses resistance to 2-4% sodium chloride, hydrogen chloride around pH 1 and 0.3% bile salts. It has high adhesion and co-aggregation ability. Supernatant of *L. helveticus* strongly inhibits the growth of *E. coli*, *S. aureus* and *C. albicans*. Treatment of supernatant by proteases dramatically decreases the antibacterial activity, which means that the main antibacterial substance is of protein nature. MDC9602 is growing better in the milk rather than in the known microbiological media. It is able to ferment milk within 4-5 hours and can acidify the milk up to 350 °T, shows higher exoprotease activity compared to other strains of *L. helveticus*.

The starter of Narine identified as *L. helveticus* expresses probiotic and adaptive properties, such as antibacterial effect, growth rate, the ability to resist to physical and chemical stresses (pH, bile, oxidative, and osmotic factors), the adhesion and aggregation. Thus *L. helveticus* MDC9602 can serve as an efficient strain complementing the list of worldwide known probiotics.

PHARMACOKINETIC DETERMINANTS AND DRUG-BIOLOGICAL ACTIVE SUPPLEMENTS INTERACTIONS

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Pharmacokinetics, sometimes described as what the body does to a drug, refers to the movement of drug into, through, and out of the body—the time course of its absorption, distribution, metabolism and excretion. Currently, it is generally accepted that a change in only individual pharmacokinetic characteristics can lead to clinically significant changes in effect. Such pharmacokinetic characteristics are commonly called “pharmacokinetic determinants”.

One of the first “pharmacokinetic determinate” was identified for antibiotics, it was proved that only a change in the total content of the active ingredient in the blood can lead to a change in the severity of the effect of antibiotics. Insignificant (less than 30%) changes in the rate of absorption or elimination of antibiotics did not cause statistically significant changes in their effect.

In recent years, due to the craze of the use for dietary supplements, which often contain extracts of medicinal plants, an important the importance of studying the effect of herbal medicines on the pharmacokinetics and pharmacodynamics of drugs with a narrow therapeutic range, such as warfarin, theophylline, etc. As example it is interesting to discuss the results of the comparative study of the effects of extracts of *R. rosea* and *H. perforatum* on the pharmacokinetics of theophylline and warfarin in rats for precise identification the pharmacokinetic determinate of this drugs.

Whilst there was little alteration in the pharmacokinetics of theophylline when administered in the presence of SHR-5, concomitant treatment with extracts of *H. perforatum* leads to a significant decrease in the concentration of theophylline in the blood of treated animals. Thus, total clearance and the apparent volume of distribution of theophylline increased 5-6 fold in the presence of *H. perforatum*, presumably occasioned by the activation of liver enzymes, consequently reducing the therapeutic effect of theophylline. In contrast, these parameters were little changed when *R. rosea* was co-administered with theophylline.

Warfarin is a widely used oral anticoagulant but its use necessitates a tight control on dosage. This drug is easily metabolised in the organism by cytochrome P450, and a number of studies have demonstrated significant pharmacokinetic/ pharmacodynamic interactions between herbal products and warfarin. Such interactions are of particular concern when perturbations to the absorption, metabolism, or protein-binding capabilities are suspected. Since warfarin has a relatively high elimination half-life, the anticoagulant effect of the drug can be increased dramatically by such interactions. Comparison of these profiles reveals that the concentration of warfarin in the blood of animals treated with SHR-5 was slightly higher than in the control animals during the first 8 h following administration and prior to the concentration peak. The maximum concentration of warfarin in the blood of animals treated with SHR-5 was also higher than in the controls. However, following the attainment of peak concentration, the pattern changed within the interval 12 to 24 h after drug administration such that the concentration of warfarin in the blood of rats treated with SHR-5 was slightly lower than that in control animals. After 24 h, the differences in mean concentration values of warfarin between the two groups were not statistically significant.

Moreover, the values of the main pharmacokinetic parameters of warfarin, were not significantly different between the control animals and those treated with SHR-5.

Since the difference in the maximum concentrations of warfarin between animals that had been treated with RRE and those that had not was (only 25%), the risk of compromising the safety and efficacy of warfarin by the concomitant administration of SHR-5 would not appear to be critical. The hypothesis that simultaneous treatment with the two drugs would have no influence on the pharmacological effects of warfarin is supported by the results obtained with respect to Prothrombin time (PT) measurements. The differences in mean PT_{max} values and the areas under the effect-time curve were not statistically significantly different between animals treated with SHR-5 and untreated animals.

UDC: 615.322:582

THE STUDY OF MINERAL COMPOSITION OF RAW MATERIAL (RHIZOMATA CUM RADICIBUS) OF VALERIANA CARDIOLA L.

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Keywords: *Valeriana cardiola L., thermal emission photometric analysis, macroelements, microelements, ecological safety.*

The study of mineral elements makes possible to evaluate the presence of essential and conditional essential elements in each herbal raw materials collected from different climatic conditions, as well as the ecological safety of the raw materials. *Valeriana cardiola L.* species is interesting from this point of view. This species does not grow in Armenia, it is grown in some mountainous regions of Armenia. The study of the mineral composition of the rhizome and roots of the *Valeriana cardiola L.* species grown in Armenia. The raw material of *Valeriana cardiola L.* roots (*Rhizomata cum radicibus Valerianae cardiola L.*) cultivated from Zovuni and Aparan collected in the second half of September was served as a material for the research. In the framework of the merchandizing analysis, the determination of total ash was performed in the analytical test sample according to the 13th Russian Pharmacopeia. The determination of macro and microelements in the ash was carried out at the Institute of Geological Sciences of the National Academy of Sciences of the

RA by using the DFS-8 device and the method of thermal emission photometric analysis. The results of the research showed, that the total ash content in the samples of the raw materials of *Valeriana cardiola L.* collected from different regions of Armenia (Zovuni, Aparan) was no more than 14%, which did not exceed the index set by the 13th Russian Pharmacopeia. According to the analysis of the results, a high content of macro-, micro- and ultra-microelements was observed in the raw materials. The content of mineral elements in the raw materials collected from Aparan prevailed over the indices of the raw materials collected from Zovuni. Lead was not found in the raw material of *Valeriana cardiola L.* cultivated in the Kotayk and Aragatsotn regions. It proved about the ecological safety of the latter and, in general, the minimal heavy metal contamination of *Valeriana cardiola L.* acclimatized in these regions. The collected raw materials of *Valeriana cardiola L.* species acclimatized in different regions of Armenia are raw source of vital elements for the organism and ecologically clean.

UDC: 547.7

THE STRUCTURE ACTIVITY RELATIONSHIP OF ISOINDOLE DERIVATIVES AND THEIR INTERACTIONS WITH THE TARGET

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Keywords: *isoindole derivatives, SAR, docking, acetylcholine receptors, antinociceptive activity.*

Isoindole derivatives have shown high antinociceptive activity according to our previous studies tested in the tail-flick method. The mechanism of antinociceptive activity was not determined. The molecules' structure and deep research of cholinergic receptors were the main reason to find out structure activity relationship of isoindole derivatives (GH-3, GH-9, GH-10) and possible involvement of N-Acetyl Choline receptor into the antinociceptive activity. The purpose of this study was to prove N-Acetyl Choline receptor involvement into isoindole derivatives antinociceptive activity and determine possible interactions with the active center.

All the tested derivatives were synthesized in STCOPC. The docking of compounds was performed using the computer program GOLD. The molecule of the protein used in the study was taken from Protein Data Bank (RCSB protein databank PDB code 2XYT). The best cluster conformations and scores were

pertained and visually studied by using Computer Visualization Pymol program.

The docking studies have shown that all the compounds bind with the target in the active center as their internal ligand. All three compounds (GH-3, GH-9, GH-10) interact with the active center forming hydrogen and hydrophobic interactions. The highest affinity towards the active center has shown the GH-10 compound, which can be explained by the ability to make more hydrophobic interactions in the active center than remaining compounds, which can be explained by containing isopropyl group in the molecule.

The study confirmed that all 3 compounds can bind to the target in the active center. The antinociceptive activity is related to the alkyl group's ability to form hydrophobic interactions, which is the most expressed in compound GH-10. Thus, the tested isoindole derivatives are new prospective molecules to develop new antinociceptive medications.

UDC: 615.322:616-092.4/9

IMPACT OF STEVIOSIDE ON INDICES OF THE FUNCTIONAL RECOVERY OF RAT'S INJURED SCIATIC NERVE*Isoyan A.S.¹, Avetisyan L.G.¹, Simonyan K.V.¹, Chavushyan V.A.¹, Hovhannisyan L.E.²*¹*Orbeli Institute of Physiology NAS RA, Yerevan, Armenia*²*Davtyan Institute of Hydroponics Problems NAS RA, Yerevan, Armenia**Corresponding author e-mail: isoyanarmin@gmail.com***Keywords:** *stevioside, injured nerve, functional recovery.*

We investigated the quality indices and productivity of *Stevia rebaudiana*, a valuable technical culture grown in the hydroponic conditions. Steviosides in *Stevia* have high pharmaceutical potential. These findings point to the presence of improved targeted pharmacologically active food products in Armenia, as well as the possibility of producing multifunctional phytopreparations from the endemic materials.

The aim of this study was to evaluate the efficiency of stevioside from *Stevia* on the degree of sensomotor functional recovery of rat's injured sciatic nerve.

Excess fructose consumption increase the vulnerability of peripheral nerve to traumatic injury. In condition of fructose-induced diabetes we evaluate the effects of *i/m* injection of stevioside after sciatic nerve crush-injury on the sensomotor recovery of the damaged limb and a restoration of the electrophysiological

parameters of responses of motoneurons of spinal cord to stimulation of the distal part of the injured sciatic nerve.

In condition of metabolic disorder after crush-injury stevioside causes a rapid recovery of the sensomotor function of the damaged limb. Stevioside caused an increase in variety of responses of ipsilateral motoneurons, with predominant excitatory reactions and lack of share of nonreactive neurons in ipsilateral units. The protective process of stevioside is achieved by increasing the intensity of responses, redistribution of shares and increasing the variety of responses, contributing to greater integration of neurons into functional chains.

Generally, in condition of sciatic nerve crush-injury of high fructose-diet rats stevioside from Armenian *Stevia* is able to amplify positive adaptive changes of nervous system and enhance functional recovery.

UDC: 615.272:616-092.9

COMPARATIVE STUDY OF EMPAGLIFLOZIN IN POST-INFARCTION CHRONIC HEART FAILURE IN NORMOGLYCEMIC RATS*Ivkin D.Y.¹, Okovityi S.V.¹, Kulikov A.N.²*¹*Saint Petersburg State Chemical and Pharmaceutical University, Saint Petersburg, Russia*²*Pavlov First Saint Petersburg State Medical University, Saint Petersburg, Russia**Corresponding author e-mail: dmitry.ivkin@pharminnotech.com***Keywords:** *chronic heart failure, empagliflozin, fosinopril, bisoprolol, spironolactone.*

Numerous pleiotropic effects of the sodium glucose cotransporter type 2 inhibitor empagliflozin are of interest. Experimental study of the effectiveness of empagliflozin in the treatment of CHF in normoglycemia.

CHF in 50 rats was modeled as a result of permanent ligation of the left coronary artery, 10 rats managed to perform a sham operation. A month later, under the control of an echocardiographic study, the operated animals were randomized into 5 densities of groups of 10 animals: groups that did not receive, treatment groups that received empagliflozin, fosinopril, bisoprolol and spironolactone, respectively, as monotherapy. After 3 months of therapy, the analysis of echocardiography, daily diuresis, and duration of treadmill running was carried out. Empagliflozin resulted in slower progression of left ventricle (LV)-dysfunction in untreated animals showing marked exercise tolerance compared to reference disease in rats; moreover, no lethal origin has been found. The data of this study suggest that the use of empagliflozin in normoglycemic rats with CHF, as well

as other main means of treating CHF, causes the development of pathological remodeling of the LV. The latter expression occurred in a progredient increase in LV dimensions (its end-diastolic size and, especially, end-systolic volume) and a decrease in its contractility (decrease in ejection frequency (EF) and fractional shortening (FS)), which were increases in untreated animals. In the groups of animals that received empagliflozin, fosinopril and spironolactone, no changes were detected. An exception was the animals treated with bisoprolol - they continued the frequency of FS and EF and the magnitude of mitral valve exclusion systolic exclusion (MAPSE), which can be interpreted as a result of the direct cardiodepressive effect of bisoprolol. Animals of the same group did not show the increase in body weight observed in all other groups. the reason turned out to be a relatively high dose of drugs (10mg/kg), although the latter was chosen based on the results of earlier experimental studies. Empagliflozin improves exercise tolerance in normoglycemic rats with experimental CHF, outperforming reference CHF prosecutions in this regard.

UDC: 615.35:616.12-008.46-092.9

SGLT2 INHIBITOR EMPAGLIFLOZIN IMPROVES EXERCISE TOLERANCE IN NORMOGLYCEMIC RATS WITH POST-INFARCTION CHRONIC HEART FAILURE

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Keywords: *chronic heart failure, empagliflozin, fosinopril, bisoprolol, spironolactone.*

The multiple effects of the sodium-glucose cotransporter type 2 inhibitors empagliflozin, including natriuretic effect, reduced osmotic diuresis due to glucosuria, and reduced afterload due to the importance of high blood pressure, have led to suggestions for the applicability of empagliflozin for the chronic heart failure (CHF) treatment when carbohydrate metabolism is excluded. Experimental study of the empagliflozin effectiveness in the treatment of CHF in normoglycemia. CHF in 50 rats was modeled as a result of permanent left coronary artery ligation, 10 rats managed to perform a sham operation. A month later, under the echocardiographic study control, the operated animals were randomized into 5 densities groups of 10 animals: groups that did not receive, treatment groups that received empagliflozin, fosinopril, bisoprolol and spironolactone, respectively, as monotherapy; the control group consisted of 10 rats with sham surgery. After 3 months of therapy, the analysis of echocardiography, daily diuresis, and duration of treadmill running was carried out. Empagliflozin resulted in slower progression of left ventricle (LV)-dysfunction in untreated animals showing marked exercise tolerance compared to reference disease in rats; moreover, no lethal origin has been found. The study data suggest that the use of empagliflozin in normoglycemic rats with CHF, as well as other main means of treating CHF, causes

the development of pathological remodeling of the LV. The latter expression occurred in a progredient increase in LV dimensions (its end-diastolic size and, especially, end-systolic volume) and a decrease in its contractility (decrease in ejection frequency (EF) and fractional shortening (FS)), which were increases in untreated animals. In the groups of animals that received empagliflozin, fosinopril and spironolactone, no changes were detected. An exception was the animals treated with bisoprolol - they continued the frequency of FS and EF and the magnitude of mitral valve exclusion systolic exclusion (MAPSE), which can be interpreted as a result of the direct cardiodepressive effect of bisoprolol. Animals of the same group did not show the increase in body weight observed in all other groups. The reason of turned out to be a relatively high dose of drugs (10 mg/kg), although the latter was chosen based on the results of earlier experimental studies. The most obvious of the observed cases of a positive experimental study of empagliflozin during CHF is the diuretic effect, which was convincingly confirmed in our experiment, however, the severity of the urinary effect follows the statement of moderate, observed with that in animals treated with spironolactone. The sodium-glucose cotransporter type 2 inhibitor empagliflozin improves exercise tolerance in normoglycemic rats with experimental CHF, outperforming reference CHF prosecutions in this regard.

UDC: 615.32:582:577.2

SELENIUM: THE VITAL ANTIOXIDANT

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Keywords: *Selenium, selenoproteins, biological activity, dimethyl selenide, redox titration.*

Selenium is an essential trace element which fulfils important functions in the organism and is obtained from dietary sources like oat, sunflower, chicken meat, eggs, etc. Its deficit may cause various disorders, but an overdose can also cause poisoning, because of dimethyl selenide formation in organism. The biological activity of selenium is mainly connected with its antioxidant properties, as it is an essential part of antioxidant enzymes i.e. selenocysteine, glutathione peroxidase, thioredoxin reductase and selenoproteins. Disturbances of oxidant balance have been found to be involved in the pathogenesis of diverse illnesses. Selenium administration has proved to be effective against diverse conditions. However, the narrow therapeutic window of selenium, makes the choice of selenium a complex issue. Divergent forms of selenium are still being studied, including inorgan-

ic and organic compounds and selenium nanoparticles. However, the main source of selenium still remains food.

The purpose of the study is to show how the concentration of selenium varies through dietary sources obtained from different regions of Armenia depending on the difference of selenium concentration in soil. During the analysis of soil for selenium concentration the redox titration was used. During the titration potassium permanganate oxidizes selenous acid to selenic acid. The excess of permanganate is titrated using Mohr's salt solution in presence of Na_2HPO_4 , which prevents the liberation of MnO_2 . It was confirmed that selenium concentration varies through different regions of Armenia which affects the Se content in food. Based on broad literature study we obtain that Selenium is biologically important element. The Se content of food varies considerably according to its concentration in soil obtained from different regions of Armenia.

UDC: 615.21:577.1:616-092.9

ISCHEMIC BRAIN PROTECTION BY PYRIMIDINE NUCLEOTIDES IN RATS*Khachatryan M.S.¹, Topchyan H.V.², Dheryan L.G.³*¹*Department of Pharmacy, Yerevan State Medical University, Yerevan, Armenia*²*Department of Drug Technology, Yerevan State Medical University, Yerevan, Armenia*³*Department of Pharmacology, Yerevan State Medical University, Yerevan, Armenia**Corresponding author e-mail: milena_s85@mail.ru***Keywords:** *cerebral ischemia, pyrimidine nucleotides, anxiety, memory disorders, discoordination.*

Pyrimidine nucleotides activating the structural phospholipids biosynthesis in the neuronal membranes appear a wide range of biological activity, including stimulation of cerebral metabolism and circulation. Based on above it was studied the effects of uridine 5-triphosphate and cytidine 5-monophosphate combination on cerebral blood microcirculation, neurobehavioral consequences and morphological changes of brain tissue after local ischemia in rats.

Experiments have been carried out on inbred, albino rats. Acute cerebral blood flow disorder was induced by unilateral occlusion of common carotid artery (CCA). Local cerebral ischemia was induced by middle cerebral artery occlusion (MCAO). Local cerebral blood flow was registered by laser Doppler flowmetry. Blood pressure and heart rates were monitored by tail-cuff method. Rats behavioural changes after MCAO were evaluated in elevated plus maze (EPM), passive avoidance and rota-rod

tests. Hystopathological analysis were performed by Nissl's staining method.

Conducted experiments evident that investigated nucleotides combination lead to improvement of ischemic brain blood supply in rats with unilateral CCA ligation without any changes from animals' arterial blood flow and heart rate. Under the condition of local cerebral ischemia prevention of anxiety-like behavior, memory loss and motor coordination disorders were observed in the nucleotide treated rats compared to control group. Hystopathological analysis of brain tissue in nucleotides injected rats after MCAO demonstrates reduced number of dystrophic neurons, decreased processes of karyolysis compared with control groups. Thus, obtained data concerning to the cerebrovascular activity and neuroprotective properties of 5-triphosphate and cytidine 5-monophosphate indicate that pyrimidine nucleotides molecules could be served as potential source for development of new drugs for ischemic brain protection.

UDC: 615.322

STANDARTIZATION ISSUES OF HOP CONES*Khaliullina A.S., Aliullina L.A., Morgatskaya O.V., Shakirova D.Kh.**Kazan (Volga region) Federal University, Kazan, Russia**Corresponding author e-mail: anela_90@mail.ru***Keywords:** *Humulus lupulus, standartization, prenylated flavonoids, bitter acids.*

Humulus lupulus L. – herbaceous perennial vine, belonging to Cannabaceae family. To date, hop cones are recognized as official herbs. Hop cones have a rich phytochemical profile and contain essential oil, prenylated flavonoids and bitter acids, which are responsible for the antimicrobial activity. The definition is the hop cones content of biologically active substances – essential oil and flavonoids in terms of rutin – in according of the State Pharmacopoeia of the Russian Federation of the XIV edition. The purpose of the study is the experimental evaluation of official pharmacopoeial methods of hop cones (*Strobili Humuli lupuli*) quality. The object of the study was used hop cones, which were prepared in the Botanical Garden KFU. Morphological and microscopical indicators and impurities of hop cones are consistent with requirements of regulatory and technical documentation – State Pharmacopoeia of the Russian Federation of the XIV edition. Hop cones are blended and fractionated. The content of the essential oil was measured by method 1 in according of GPM 1.5.3.0010.15 of the State Pharmacopoeia of the XIV edition. Also quality assessment of hop cones was carried out

on the flavonoids in terms of rutin by differential spectrophotometry in according of GPM 2.5.0046.15 of the State Pharmacopoeia of the XIV edition.

Essential oil content in hop cones was 2.7±0.3%; flavonoids content was 0.41±0.2%. These indicators of hop cones quality are consistent with requirements of regulatory and technical documentation – part “Quantitative content” of State Pharmacopoeia of the Russian Federation of the XIV edition. The absorption of aliquot of extract from hop cones after adding aluminium solution is consistent with the main spectral characteristics of flavonoids. In this case, the observed bathochromic shift of the long wavelength bands of flavonoids: I band – at a wavelength from 300 nm to 319 nm; II band – at a wavelength from 372 nm to 477 nm. To date, the main biologically active substances of hop cones are prenylated flavonoids and bitter acids. But the bitter acids content is not normalized in according of GPM 2.5.0046.15 of the State Pharmacopoeia of the XIV edition. In that regard, standartization of hop cones (especially the development of antimicrobial drugs from hop cones) requires a pharmacognostic informed revision.

UDC: 616.2:504:613.1(479.25)

CONTAMINATION OF THE ENVIRONMENT AND RESPIRATORY MORBIDITY IN CERTAIN MARZES OF ARMENIA

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Keywords: *environment, pollution, morbidity.*

The share of non-communicable diseases is growing and, as a dominant health problem, is closely linked to sustainable development issues. Nowadays, the attention of specialists is focused on the complex impact of rapidly growing chemical pollution of the environment, due to numerous factors that shape human health. The priority is explained by the increase in both quantitative and qualitative emissions of chemicals, with an increase in the number of global, so-called “eternal” pollutants. This group includes organochlorine pesticides (OCPs), the use of which is also closely associated with environmental pollution by synthetic surfactants (SS), being a part of various pesticide preparations. Some OCPs are included in the group of endocrine-disrupting chemicals that have the ability to disrupt the hormonal balance, suppress the immune system, and increase susceptibility to various diseases, including respiratory diseases.

Purpose of study is to investigate the possible impact of some pollutants on the respiratory diseases prevalence in cer-

tain marzes of Armenia. OCPs and SS were determined in the environmental objects (surface waters, soil) and agricultural plant products of certain regions of Armenia (Kotayk, Lori, Gegharkunik marzes) by chromatographic, spectrophotometric methods. The analysis of data on respiratory morbidity (total, asthma) was carried out based on official statistical reports. The average chronological indicators were calculated for different population groups for dynamic pattern of disease prevalence. Asthma prevalence rates were analyzed separately as considered environmental-related disease. Despite some multidirectional nature of the results obtained, the data for respiratory morbidity to a certain extent correlated with the status of the environment in the studied regions.

The results obtained confirm the need of further research to study the possible adverse effects of environmental pollution on the morbidity, conduct a comparative analysis clarifying their role in morbidity patterns, particularly with regard to respiratory morbidity.

UDC: 615.12:614.27(479.22)

REVIEW ON GOVERNANCE OF COMMUNITY PHARMACIES IN GEORGIA

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Keywords: *social and clinical pharmacy, governance of community.*

The pharmaceutical industry is one of the country's major private employers. According to information accessible to the LEPL Regulation Agency for Medical and Pharmaceutical Activities, 3255 pharmacists with higher pharmaceutical education are now working as responsible person for pharmaceutical activity in pharmacies in Georgia. Government of Georgia or an administrative act of a state government body based on law, which independently carries out political, state, social, educational, cultural and other public activities under state control; it is also a separate organization from state government bodies, established under a normative act of a supreme executive body of an autonomous republic, which independently carries out social, educational, cultural and other public activities under state control). An authorized pharmacy is subject to regulatory control, and its operation is only permitted after receiving specific permission. Apart from the pharmaceutical products specified in the authorized pharmacy permit (s), it is permitted to store and sell (supply) voluntarily unregistered complementary medicines, biologically active additives and paramedics, dental and medical supplies, sickness and baby care products, baby food and baby

hygiene products, tampons and other similar products, food intended for a specific contingent, cosmetics, hygiene and perfumed goods, eyeglasses, packaged drinking water (including mineral water), and medical disinfectants.

The aim of the topic is to determine the place and priority of pharmacy for the state; analyze the Georgian Law and regulation. To find out how flexible the national pharmacy policy is in Georgia, a survey of the law and regulation and real pharmacy market was conducted. All distributors of pharmaceutical products have the obligation to submit a mandatory notification, if they have a reasonable suspicion that the pharmaceutical product has no right of entry to the Georgian market, is falsified, faulty, inappropriate or expired. In such a situation, at the same time, the seller is required to suspend the sale of a suspect pharmaceutical product. The agency investigates the information provided by the seller and, if the suspicion is not verified, notifies the seller within a reasonable time frame. However, if it is determined that a series of pharmaceutical goods have no right of access to the Georgian market, are falsified, faulty, inappropriate, or expired, the agency shall supervise the withdrawal of the pharmaceutical product from the wholesale and retail sales networks.

UDC: 615.12:614.27+616.379-008.64(479.22)

PHARMACISTS'S ROLE IN DIABETES MANAGEMENT IN GEORGIA*Kvizhinadze N., Dugashvili N., Dughashvili A., Putkaradze Z.,
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Diabetes is a chronic disease, which improper treatment causes the vital complications and adversely affects the patient's quality of life. Therefore, it is important to mobilize all medical staff, on the one hand, to timely diagnose the patient and on the other hand to adequately manage it throughout the treatment cycle, which will allow us to avoid possible complications caused by the disease and improve the patient's quality of life. First of all, we studied the recommendations and guidelines in Georgia in the management of patients with diabetes and the issues of involvement of various specialists in this process. In the second stage, through specially prepared questionnaires, we interviewed diabetic patients and pharmacists working in pharmacy networks in different cities of Georgia. 68 pharmacists (mean age +/- SD 30 +/- 7.6) participated in the study, 97% were female. We also interviewed 67 patients with diabetes (mean age +/- SD 40 +/- 10.5), 78% were female. 48% of pa-

tients surveyed are insulin-dependent only, and 4% use both insulin and oral anti-diabetic drugs. 89% of patients mentioned, that they rarely use the services of a pharmacist regarding diabetes and prefer to consult an endocrinologist, however, more than 50% of patients refused treatment due to financial factors, which posed some threat to his health. Most patients use the services of a pharmacist several times a week, although they do not receive complete information about possible complications of the disease. A large proportion of 85% of pharmacists wish to take special diabetes management courses in order to improve their skills and be actively involved in the management of patients with diabetes. The role and importance of the pharmacist in the treatment of Diabetics in Georgia is not yet clearly defined. Georgian guidelines do not clearly describe the role and functions of a pharmacist, which is reflected in the results of the study.

UDC: 615.12:614.27(479.22)

GEORGIAN PHARMACEUTICAL MARKET AND SPECIFICS OF PRICE REGULATION*Kvizhinadze N., Dughashvili N., Sulashvili N., Shashiashvili N.
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Georgia's pharmaceutical sector is import-oriented. Both imported finished medicines and substances are imported into the sales network in the name of products manufactured in Georgia. The prices of medicines, as well as all imported goods, are sensitive to the exchange rate of the GEL, with a decrease in prices. The study includes analysis of Georgia and world drug price policy and development of appropriate recommendations, taking into account the political and economic situation. Discussion analysis, in-depth interviews with respondents, questions with industry experts were conducted to obtain information. The research design includes an overview of documents (secondary analysis of data from various sources and surveys, analysis of information from a public source). In order to identify the factors hindering the formulation of the drug policy, a thorough research of the Georgian pharmaceutical market is needed. The study allowed us to evaluate the physical and financial access

of the population to pharmaceutical products. When conducting a drug pricing policy, it is important to study pricing based on the data obtained. Interventions need to be planned, where appropriate, including the use of the World Health Organization's first price regulation mechanism - price regulation-supply-chain and distribution. The implementation of this mechanism is very simple from a technical point of view, as the implementation of this policy requires only information on medication prices and sales data. It would be justified to use the fifth mechanism provided by the World Health Organization to promote the use of generic medicines, which aims to increase the consumption of available generic medicines compared to expensive original, branded pharmaceuticals and thus reduce the cost of medicines. Introducing this mechanism and encouraging the use of generic medicines, including doctors, will in the future help the population access to medicines financially and reduce the financial burden of medical expenses.

UDC: 615.2:616.83/85

NOVEL SELECTIVE BIFUNCTIONAL ANALOGS OF VANOXERINE AS POTENTIAL DRUGS FOR NEURODEGENERATIVE DISORDERS

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Keywords: *vanoxerine, neurodegenerative disorders, dopaminergic neurons.*

Vanoxerine, or GBR12909, is one of the most selective and affinity ligands for the dopamine transporter. It is this feature that makes it possible to consider the chemical structure of GBR12909 as a basis for the development of new biologically active molecules with therapeutic potential in neurodegenerative diseases. Previously, our research team succeeded in synthesizing a new universal analogue of GBR12909, suitable for modification with fluorophores and pharmacophores. Thus, a new fluorescent analogue of GBR12909 with BODIPY-acid was accumulated selectively in dopaminergic neurons via the dopamine transporter. This fact allowed us to develop a new method for selective imaging of living dopaminergic neurons.

The aim of this work was to develop new bifunctional analogs of GBR12909 with antioxidant and anti-inflammatory effects.

Monoethylfumaric acid, activating the endogenous antioxidant system Nrf2/Keap1, and sulindac (drug with anti-inflammatory effect) were chosen as pharmacophore groups for modifying the universal analogue of GBR12909. These pharmacophores were attached to the distal amino group of the universal analogue GBR12909.

Bifunctional analogue with monoethylfumaric acid demonstrated protective antioxidant properties under conditions of oxidative stress in a model of peroxidation, as well as activation of the Nrf2 antioxidative factor in cells SHSY-5Y. The analog of GBR12909 with sulindac demonstrated anti-inflammatory activity, which was assessed by the level of nitric oxide (II) in microglial cells BV-2.

The experiments carried out for the first time demonstrated the potential of similar GBR12909 analogs for the creation of new drug compounds.

UDC: 615.22:616-092.4/9

ALPHA-2 ADRENOBLOCKERS CEASE INCREASED OXIDATION OF PLASMA PROTEINS AND ANXIETY OF RATS CAUSED BY CHRONIC NOISE EXPOSURE

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Keywords: *sympathetic nervous system, beditin, mesedin, noise, anxiety.*

Noise is one of the environmental factors, which is considered as a powerful stressor for the organism. Generally, the acoustic stress affects the behavior and physiological state of humans and animals.

The goal of this study is to investigate the relationship between chronic noise exposure and the effects of adrenergic alpha-2 receptor antagonists, beditin and mesedin, on the anxiety and oxidation of plasma proteins and fibrinogen in rats. The experiments were carried out on non-linear albino male rats, divided into four groups (six animals in each): 1. Healthy controls 2. Exposed to noise of a level 91 dB(A), eight hours daily, during

7, 30 and 60 days; 3. Injected with 2 mg/kg of beditin (2-(2-amino-4-thiazolyl)-1,4-benzodioxane hydrochloride); 4. Injected with 10 mg/kg mesedin (2-(2-methyl-amino-thiozoly)-1,4-benzodioxane hydrochloride). For evaluating the cognitive impairment, the Any-maze test was applied. The level of carbonylation of proteins was assessed by reaction with 2,4-dinitrophenylhydrazine, spectrophotometrically. Chronic noise decreased locomotor activity and increased anxiety and oxidation of plasma protein and fibrinogen. Intensity of these changes was dependent on the duration of noise exposure. The Alpha-2 adreno-blockers alleviate oxidative modification of plasma proteins and reduce the cognitive impairment caused by chronic exposure to noise.

UDC: 541

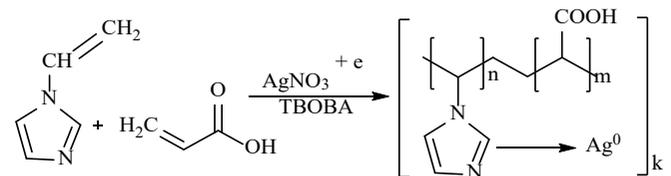
ELECTROSYNTHESIS OF SILVER METALS NANOCOMPOSITES IN A COPOLYMER MATRIX OF VINYLIMIDAZOL (VIM) AND ACRYLIC ACID (AA)Margaryan K.S.¹, Sargsyan T.S.², Aslanyan A.S.¹¹Department of Pharmacy, Yerevan State Medical University after M. Heratsi, Yerevan, Armenia²Department of Orthopedic Stomatology, Yerevan State Medical University after M. Heratsi, Yerevan, Armenia

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Keywords: silver metal, nano composition, electron transmission.

The synthesis of new functional thromboresistant non toxic polymer materials with silver nanoparticles can expand the assortment of materials used in pharmacy when creating new drug forms. For the use of nanomaterials in medicine, they must have thrombotic resistance, hydrophilicity, biological activity, biocompatibility, and also have the ability, due to the presence of functional groups, to find to various substances including drugs, and delivery systems of drugs. Among metal nanoparticles, silver nanoparticles exhibit the highest antibacterial and antiviral activity. In this work, we aimed at the synthesizing of silver-containing nanocomposites on pure iron and steel electrodes when combining the process of electrochemical (co) polymerization of VIM and AA with cathodic metal separation. During the electrolysis of aqueous or aqueous ethanol solutions of (VIM- is a nontoxic, LD₅₀ > 3500mg/kg) and AA or their mixtures of various ratios in the presence of AgNO₃ (in some cases in the presence of chitosan), in the presence of peroxide type initiator, e.g., 4-trethylperoxy-4-oxobutanoic acid (TBOBA) the

electroreduction potential of which is close to the potentials of cathodic metal evolution -06-1.2V. The composition and structure of nanocomposites is confirmed by UV, IR spectroscopy, X-ray diffraction analysis, transmission electron microscopy, thermogravimetric method, etc. An intense band at 1710 cm⁻¹ in the spectra points to the fact that carboxyl group of the acrylic acid in the co-polymers is not ionized. The number of not ionized carboxyl group (-COOH) in the nanocomposites decreased, and a new absorption band at 1578 cm⁻¹ appeared, which is characteristic of stretching vibrations of the carboxylate-anion (-COO⁻). In addition, in polymer of metal nanoparticles characteristic is the planes of the crystalline phase of zero-valent silver. The silver content in nanocomposite films is 7,6-9,3% according to atomic absorption spectroscopy. They represent moderately polydisperse crystalline forms sized 2-10nm. The data obtained indicate that a nanocomposite of the following structure is formed:



UDC: 616.62-002:616.98:578.834.1

COVID-19 ASSOCIATED INCRUSTING CYSTITIS

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Keywords: Incrusting cystitis, COVID-19, en-block resection.

The COVID-19 pandemic has become a test for the global healthcare system. The most frequent complication of the disease is bilateral viral pneumonia, which leads to respiratory failure in many patients. Regarding respiratory infections, Covid-19 is multisystem disease and can lead to damage to almost any human organ. The organs of the urinary system are no exception.

Purpose of the study is to present relatively rare bladder complication in a patient with COVID-19-incrusting cystitis, which may be encountered by urologists, internists and infectious disease doctors in the treatment of patients.

Patient aged 76 was hospitalized in the urological department with complaints of frequent and painful urination, blood

in the urine. Within 3 months before hospitalization, the patient was treated in the infectious diseases department. During the hospitalization in the urology department, multislice computed tomography of the urinary tract was performed, according to which calcifications were determined along the wall of the bladder. The patient underwent en-block resection and vaporization of the altered bladder mucosa.

In this clinical case, incrusting cystitis, in our opinion, can be considered as a complication of a new coronavirus infection. Its pathogenetic basis is probably the affinity of SARS-COV-2 to ACE-2 receptors in the urothelium.

The presented clinical case indicates the need for a multidisciplinary approach to the treatment and rehabilitation of patients who have undergone a new coronavirus infection.

UDC: 615.12:614.2+615.45:616-053.2

PROSPECTS FOR POST-MARKETING STUDIES OF THE EFFECTIVENESS OF DRUGS (BY THE EXAMPLE OF PHARMACOTHERAPY OF CHILDREN WITH COVID-19)

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Keywords: COVID-19, children, drugs.

COVID-19 pandemic caused by the severe acute respiratory syndrome coronavirus SARS-CoV-2, today is one of the indicators of the effectiveness of public health systems of modern states. According to WHO, from 30.12.2019 to 13.09.2021, the incidence of COVID-19 in children covers 22.6% of the total structure and in 0.6% of cases leads to a fatal outcome of the patient. At the same time, the segment of older adolescents and young people aged 15 to 24 years makes the maximum contribution to the structure of morbidity (14.5%) and mortality (0.4%).

Purpose of the study was to conduct a post-marketing observational assessment of approaches to the treatment of children with COVID-19 under the global clinical practice.

The materials for the study conducted by the content analysis method were the methodological recommendations "Features of clinical manifestations and treatment of the disease caused by a new coronavirus infection (COVID-19) in children" (Russia), "Diagnosis and treatment plan for new coronavirus pneumonia" (China), as well as a group of recommendations for the treatment of COVID-19 (USA).

It is established that the Russian guidelines for children contain umifenovir, lopinavir/ritonavir, ribavirin, favipirovir. Oseltamivir is present in all recommendations with clarification of the possibility of use only in patients infected with the influenza virus. Remdesivir is the only drug approved by the FDA for the treatment of COVID-19 in children. This drug is registered in Russia under three trade names, namely: remdesivir, vekluri, remdeform.

However, in Russian practice its use is not indicated in pediatrics.

In all the recommendations considered, the use of interferon-alpha is recommended in order to reduce the viral load at the initial stages of the disease, relieve symptoms and reduce the duration of pathology.

At present, there is no evidence base to support the use of monoclonal antibodies against SARS-CoV-2 in children hospitalized with COVID-19. However, tocilizumab and sarilumab are recommended for the treatment of cytokine storm in children with COVID-19 in Russia. The FDA additionally recommends the use of baricitinib in combination with remdesivir.

It is worth noting that the Chinese and Russian recommendations pay special attention to the pathogenetic and symptomatic therapy of children, however, there are some differences in dosages. So, in Russia the use of paracetamol at a dose of 60 mg / kg is recommended, in China – 10-15 mg / kg. Also, ibuprofen is used in Russia at a dose of 30 mg / kg, in China – 5-10 mg / kg. It is noteworthy that metamizole sodium and antispasmodics are indicated only in the recommendations of the Russian Federation.

It is worth to pay attention that in all the cases considered, depending on the severity of the patient and concomitant diseases, it is possible to take glucocorticoids, anticoagulants, antibacterial drugs, intravenous immunoglobulins, bronchodilators.

Post-marketing studies of the effectiveness of therapy for children with COVID-19, including taking into account international approaches, represent one of the vectors of improving the drug provision of this segment of patients.

UDC: 615.28:616-08-039.57(479.25)

DISPENSING ANTIMICROBIALS TO OUT-PATIENTS IN ARMENIA

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Keywords: antimicrobial medicines, rational use, pharmacy.

Antimicrobial resistance is now considered to be a global public health challenge, and misuse and overuse of antimicrobials are among the main drivers of it. Dispensing prescription-only antimicrobials without prescription contributes to irrational use of these medicines.

Purpose of the study is to evaluate the situation on dispensing antimicrobials to out-patients in Armenia.

The study was conducted in Armenia. Data on medicines dispensed to out-patients in 30 community pharmacies were collected. The percentage of antimicrobials prescribed by physicians, the percentage of patients, who got antimicrobials without providing a prescription and other related indicators were calculated.

Antimicrobials have consisted 11.3% of all the dispensed

medicines. Only 14.6% antimicrobial medicines were dispensed to patients who had prescriptions. 12.6% of antimicrobial medicines provided without prescription were OTC-medicines; other 87.4% were prescription-only antimicrobials. 58.5% of all dispensed antimicrobials were selected by physicians (information was provided by patients), 10.5% of antimicrobials were advised by pharmacists and almost one third was selected by patients themselves, their family members, etc. More than 90% of the total number of visitors, to whom antimicrobials were dispensed, got them without providing a prescription.

The great majority of prescription-only antimicrobial medicines are dispensed from community pharmacies without prescription. Many antimicrobials are not prescribed by physicians and are for self-medication. That means that many of prescription-only antimicrobials are used in Armenia inappropriately.

UDC: 615.21:615.357

NEUROPROTECTIVE AND CEREBROVASCULAR EFFECTS OF GABA CONJUGATE WITH PROSTAGLANDIN E₂Mirzoyan N.R.^{1*}, Meliksetyan V.S.^{1†}, Hakobyan A.A.¹, Ganshina T.S.², Baghdasaryan M.G.¹, Arakelyan A.M.¹, Gnezdilova A.V.², Gretskaya N.M.³, Bezuglov V.V.³, Mirzoyan R.S.²¹ Clinical Pharmacology Department, Yerevan State Medical University after M. Heratsi, Yerevan, Armenia² V.V. Zakusov Research Institute of Pharmacology, Moscow, Russia³ Shemyakin-Ovchinnikov Institute of Bioorganic Chemistry of Russian Academy of Sciences, Moscow, RussiaCorresponding author e-mail: nanamirzoyan@gmail.com**Keywords:** Brain ischemia, GABA conjugate with prostaglandin E₂, lipofuscin, cerebral blood flow.

The problem of pharmacotherapy of cerebrovascular diseases remains one of the most important areas of research.

The neuroprotective and cerebrovascular effects of endogenously bioactive lipid N-arachidonoyl-GABA putative COX-2 metabolite-GABA conjugate with prostaglandin E₂ (PGE₂-GABA) were studied by evaluation of lipofuscin levels under the condition of permanent focal brain ischemia and cerebral circulation under the condition of global transient ischemia.

The study has been implemented using the models of occlusion of left middle cerebral artery (MCAO) and global transient ischemia of the brain. The methods of local blood flow registration by laser flowmeter and quantitative measurement of lipofuscin by fluorescence spectroscopy were used.

PGE₂-GABA showed significant neuroprotective and cerebrovascular effects in global and focal cerebral ischemia. In the MCAO model PGE₂-GABA at dose of 2 mg/kg/day admin-istered i/p for 6 or 12 days prevented excessive accumulation of lipofuscin in both brain hemispheres in rats with MCAO. The cerebrovascular effect of PGE₂-GABA exceeded the activity of N-arachidonoyl-GABA, PGE₂ and nimodipine. The difference between the others substances is statistically significant ($p \leq 0.05$). PGE₂-GABA, unlike PGE₂ and nimodipine, increase the cerebral blood flow in rats with global transient brain ischemia and has no influence on the intact animals. This effect of PGE₂-GABA has been blocked by bicuculline, acting via GABA_A-receptors of the brain vessels. Bicuculline has no impact on the cerebrovascular activity of nimodipine. Apparently, the GABAergic vascular system of the brain is involved in the mechanisms of the cerebrovascular and neuroprotective action of the compound.PGE₂-GABA-AA-GABA putative COX-2 metabolite improves cerebral circulation and prevents lipofuscin accumulation during cerebral ischemia. Neuroprotective and cerebrovascular activity of PGE₂-GABA indicates the need for further development of this area of research.

UDC: 615.27

N-ARACHIDONOYL-GABA - A NEW ENDOGENOUS NEUROPROTECTORMirzoyan R.S.^{1*}, Ganshina T.S.¹, Gnezdilova A.V.¹, Kurdyumov I.N.¹, Arakelyan A.M.², Meliksetyan V.S.^{2†}, Gretskaya N.M.³, Bezuglov V.V.³, Mirzoyan N.R.²¹ V.V. Zakusov Research Institute of Pharmacology, Moscow, Russia.² Yerevan State Medical University after M. Heratsi, Yerevan, Armenia.³ Institute of Bioorganic Chemistry. MM. Shemyakin and Yu.A. Ovchinnikov RAS, Moscow, RussiaCorresponding author e-mail: cerebropharm@mail.ru**Keywords:** N-arachidonoyl-GABA, endogenous neuroprotector, global transient and local permanent cerebral ischemia, hemorrhagic brain damage, combined disorders of cerebral and coronary circulation, brain morphology, lipofuscin.

A comprehensive study revealed the neuroprotective properties of neurolipin N-arachidonoyl-GABA (GABA conjugate with arachidonic acid), synthesized in the laboratory of oxylipins of the Institute of Bioorganic Chemistry, Russian Academy of Sciences. It should be noted that neurolipin is of natural origin, as it was found in the brain tissue of cattle and in the brain tissue of mice.

N-arachidonoyl-GABA was found to be able to improve blood supply to the brain in conditions of global transient ischemia, hemorrhagic brain damage, and combined vascular damage to the brain and heart, while in intact animals it did not increase cerebral circulation. It has been established that N-arachidonoyl-GABA prevents the development of structural damage and an increase in the level of lipofuscin in the brain tissue under conditions of local permanent cerebral ischemia. It is important to emphasize that N-arachidonoyl-GABA also has an antiaggregatory effect. Therefore, the inclusion of an amino acid in the

neurolipin structure transforms the aggregate activity of arachidonic acid into a diametrically opposite effect.

The ability of N-arachidonoyl-GABA, as well as known cerebrovascular drugs (picamilon and mexidol) to demonstrate cerebrovascular activity only under conditions of experimental pathology, is characteristic of compounds with a GABA_A-ergic mechanism of action. Indeed, the cerebrovascular activity of N-arachidonoyl-GABA is not manifested against the background of the action of bicucullin. Therefore, we believe that the presence of an inhibitory amino acid in the structure of neurolipin plays a decisive role in the implementation of the neuroprotective activity of N-arachidonoyl-GABA. As is known, GABA plays a multi-circuit role (adrenergic, neurotransmitter, non-neuronal) in the regulation of cerebral circulation.

Thus, the natural compound N-arachidonoyl-GABA, which has pronounced cerebrovascular properties in cerebral ischemia and hemorrhage, prevents platelet aggregation, as well as the development of structural damage and an increase in the level of lipofuscin in ischemic brain tissue, is an endogenous vascular neuroprotective factor.

UDC: 616.33/34:615.12

A STUDY OF PHARMACEUTICAL CARE DURING GASTROINTESTINAL SYMPTOMS

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Keywords: *Pharmaceutical care, gastrointestinal symptoms, algorithms.*

Some of the most common reasons to visit the pharmacy for self-medication are minor gastrointestinal disorders, such as diarrhea, constipation, heartburn, and flatulence. The literature proves that the main tool for management self-medication during gastrointestinal symptoms is pharmaceutical care.

The aim of the study was to evaluate pharmaceutical care during gastrointestinal symptoms in Republic of Armenia (RA), highlighting the existing problems and to develop possible ways to improve them.

A cross-sectional study was carried out from March 2018 to November 2019 on the basis of an anonymous questionnaire.

During the research, the most frequently self-medicated symptoms were specified. Disorders of the gastrointestinal system occupy the second place (25%). According to the results

of the survey, the majority of consumers use over-the-counter (OTC) drugs without consulting a specialist for minor gastrointestinal disorders, which is quite worrying. Most of the pharmacists (44%) don't inquire about the nature of the complaint before dispensing the drug, and only 18% provide information about the side effects of the given drug, and 45% about the method of use. It becomes clear that only 20% of the consumers were satisfied with the answers of the pharmacy employees regarding the OTC drugs used for gastrointestinal symptoms. It is also important to note that in case of the given symptoms, the pharmacy employees offered a number of drugs that are registered in RA as prescription drugs.

It can be assumed that it is necessary to improve the quality of professional continuous education of pharmacy employees in the direction of pharmaceutical care, as well as to develop pharmaceutical care algorithms for the gastrointestinal symptoms.

UDC: 615.276

TOXICOMETRY PARAMETERS OF SOME NON-STEROIDAL ANTI-INFLAMMATORY COMPOUNDS

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Keywords: *anti-inflammatory compounds, toxicometric parameters, hazard class.*

Non-steroidal drugs, especially propionic acid derivatives, are widely used as analgesics, anti-inflammatory and antipyretic drugs. However, their long-term use caused serious side effects. Therefore, the development of new drugs with high efficacy and low side effects remains an important area of modern medicine. Evaluation of non-steroidal anti-inflammatory compound's toxicometric parameters. The experiments were carried out according to generally accepted toxicological methods. S (-)-2-amino-3 - (4'-fluoro) phenyl propanoic acid was tested at doses of 1000, 1300, 1600 mg/kg, and 3-propyl-5-thioxo-1, 2, 4-triazole-1-yl]- α -alanine at doses of 1000, 1600, 2000 mg/kg with single oral administration to rats. During the observed period integral indicators were evaluated: behavior, feed and water consumption, body weight gain, etc. A macroscopic study of internal organs was carried out. Single median lethal dose (LD_{50}) was calculated by the Litchfield-Wilcoxon method modified by

Prozorovsky. The hazard class for oral toxicity was assessed in accordance with regulatory documents. The clinical picture of acute poisoning with S (-)-2-amino-3-(4'-fluoro) phenylpropanoic acid was manifested by lethargy of animals, apathy for food and water, pain and tactile irritants. The death of animals occurred during the first two days. The absolutely lethal (DL_{100}) dose for rats was 1600 mg/kg, the maximum tolerated (DL_0) dose was 1000 mg/kg and the median lethal dose was 1300 ± 102 mg/kg. Macroscopic examination of dead animals revealed hyperemia and hemorrhages of internal organs, areas of necrosis in the stomach. The clinical picture of intoxication with 3-propyl-5-thioxo-1, 2, 4-triazol-1-yl]- α -alanine is not pronounced. There were no deaths of rats. The LD_{50} of the drug is at a level of more than 2000 mg/kg. The experimental rats gained weight evenly and did not differ from the control ones. 3-propyl-5-thioxo-1, 2, 4-triazol-1-yl]- α -alanine and S (-)-2-amino-3-(4'-fluoro) phenyl propanoic acid in acute oral toxicity are assigned to the 3rd hazard class (moderately dangerous).

EVALUATION OF THE LOCAL IRRITANT EFFECT OF "YUBIVAX" OINTMENTPoghosyan S.B.¹, Akopyan K.A.², Ter-Zaqaryan S.H.¹, Keshishyan A.A.³, Kurazyan M.A.¹¹Laboratory of Environmental Hygiene and Toxicology of SRC, Yerevan State Medical University, Yerevan, RA²Department of Maxillofacial Surgery, Yerevan State Medical University, Yerevan, RA³Laboratory of Neurobiology of COBRAIN center, Yerevan State Medical University, Yerevan, RACorresponding author e-mail: spoghosyan9@gmail.com**Keywords:** burn wounds, ointment "Yubivax", local irritant effect.

The local irritant effect on the skin was evaluated on rats with multiple (20) applications of "Yubivax" ointment with an exposure of 4 hours. The observation period is 20 days. One of the topical problems of medicine is research of new effective ways of treatment of burn wounds. YSMU employees have created a complex ointment named "Yubivaks" with the following ingredients in various proportions: sea-buckthorn oil, bees wax, propolis, clove oil. Each of the ingredients has multipurpose biological activity. Assessment of the local-irritating effect of the ointment "Yubivax". After contact, skin condition, the thickness, the presence of hyperemia, erythema and edema were taken into account. The irritant effect of the ointment on the mucous membranes was evaluated on rabbits. A single dose of native ointment was injected into the conjunctival sac of one eye. The opposite one served as control. Within 14 days, daily monitor-

ing of the condition of the cornea and mucous membranes was carried out. The criterion for irritation was hyperemia, increased vascular pattern of the eyeball, lacrimation, swelling, partial eversion of the eyelids, clouding of the cornea. The impact of "Yubivax" on the skin of rats did not cause visible disorders: erythema, edema, necrosis, and thickness of skin folds. The irritating effect of the ointment is not expressed. When assessing the effect of the ointment on the mucous membranes when injected into the conjunctival sac of the eye, hyperemia and profuse lacrimation are observed with a gradual decrease that disappeared by the end of the second day of observation, which indicates a slightly irritating effect on the mucous membranes of the eyes. "Yubivax" ointment does not have a local irritating effect on skin and has a slightly irritating effect on the mucous membranes. The use of "Yubivax" from the position of local irritant action can be safe.

EMPAGLIFLOZIN AND ORNITHINE ASPARTATE ALLEVIATE NEUROMUSCULAR JOINT DYSFUNCTION IN A MURINE MODEL OF NON-ALCOHOLIC STEATOHEPATITISPrikhodko V.A.¹, Sysoev Y.I.², Okovityi S.V.¹¹Saint Petersburg State Chemical and Pharmaceutical University, Saint Petersburg, Russia²N.P. Bechtereva Institute of the Human Brain of the Russian Academy of Sciences, Saint Petersburg, RussiaCorresponding author e-mail: veronika.prikhodko@pharminnotech.com**Keywords:** non-alcoholic steatohepatitis, empagliflozin, ornithine aspartate, neuromuscular joint function, electromyography.

Non-alcoholic steatohepatitis (NASH) has multiple extrahepatic complications, possibly including the impairment of neuromuscular joint function. Empagliflozin (EMPA) and L-ornithine L-aspartate (LOLA) have therapeutic value for NASH, but their effects on neuromuscular activity are not known.

The study was performed to test whether EMPA and/or LOLA would have a beneficial effect on neuromuscular joint dysfunction induced by experimental NASH.

100 male C57Bl/6 mice were randomized into 4 groups: (1) Intact (n = 10; 0.9% NaCl p/o qd); (2) Control (n = 30; NASH + 0.9% NaCl p/o qd); (3) LOLA (n = 30; NASH + 1.5 g·kg b.w.⁻¹ LOLA p/o qd); (4) EMPA (n = 30; NASH + 10 mg·kg b.w.⁻¹ EMPA p/o qd). NASH was induced over 3 months using a combined diet/chemical model. M-waves were registered in the left *m. gastrocnemius* (MG) and right *m. biceps brachii* (MBB) following electrical

stimulation (0.1 ms, 1-10 mA in increments of 1 mA) of the left *n. ischiadicus* and right *n. musculocutaneus*, respectively, using a Neuro-MEP-8 8-channel system with Neuro-MEP.NETω 3.7.3.7 software.

In the Control group, peak M-wave amplitudes and onset currents were decreased in the MG (p<0.01 and p<0.05 vs. Intact), and peak latencies were increased (p<0.05 vs. Intact) in the MBB. EMPA increased peak latencies in the MG, and reduced peak latencies in both MG and MBB (p<0.01 vs. Control for all). LOLA reduced peak latencies in both MG and MBB (p<0.01 vs. Control for both). No changes in peak currents were observed in either MG or MBB.

Experimental NASH was associated with neuromuscular joint dysfunction, possibly caused by peripheral neuropathy. EMPA and LOLA were able to restore some of the M-wave parameters in upper and lower extremity muscles, indicating improved neuromuscular activity.

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BIOEQUIVALENCE STUDY OF PARACETAMOL 0.5 TABLETS REGISTERED IN RA BY THE BIOWAIVER METHOD

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Keywords: *biowaiver, paracetamol tablets, dissolution profile.*

According to the normative documents of WHO and FDA, for some generic drugs *in vivo* bioequivalence studies can be replaced by the study of comparative *in vitro* dissolution profiles by the “biowaiver” procedure. It only applicable for BCS Class I compounds, if the substance immediate release and Class III drug substance, if the test product and reference product display very rapid *in vitro* dissolution characteristics under the defined conditions. The purpose of this study was to compare dissolution profiles of paracetamol 0.5 tablets registered in the RA according to the biowaiver procedure. In this study, we compared the *in vitro* dissolution profiles of two paracetamol 0.5 tablet formulations manufactured by Pharmstandard and Sopharma. Comparison of dissolution profiles was carried out according to WHO Guidance (75rpm, 37±0.5°C, dissolution media volume was 900ml). All dissolution studies were performed using USP Apparatus 2. Dissolution media were buffer solutions:

hydrochloric acid solution (pH 1.2), acetate buffer solution (pH 4.5) and phosphate buffer solution (pH 6.8) prepared according to USP XXX. The sampling was carried out at 5, 10, 15, 20, 30 and 45 min for the dissolution profile. Quantitative detection has been performed using UV-VIS spectrophotometer at 243 wave length. The obtained data indicate that two formulation paracetamol 0.5 tablets were rapidly dissolved (≥85% of the labeled amount of drug in 30 minutes) in all three-dissolution media. The percent relative standard deviation (% RSD) for all time points fulfills all requirements (≤20% for 15 min, ≤10% for other time points), so results are valid. Moreover, both tablets (manufactured by the pharmaceutical companies Pharmstandard and Sopharma) have high solubility. Based on obtained data, we can conclude that the similarity of dissolution profile of paracetamol tablets manufactured by Pharmstandard and Sopharma has been demonstrated due to very rapid dissolving of tablets.

UDC: 615.322:615.451.16

DETERMINATION OF RUMEX CRISPUS SEEDS AND ROOT EXTRACTS BY USING MODERN METHODS OF ANALYSES

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Keywords: *Rumex crispus, seed, root, extract, chromatography.*

This study was carried out to investigate qualitative-quantitative composition of organic compounds of extracts of the roots and seeds of Rumex crispus. The infusion or decoction of R. crispus is commonly used in folk medicines for the treatment of internal bleeding and vascular diseases. By this reason, the separation of bioactive compounds from different organs of Rumex crispus and their quantitative and qualitative analysis are necessary to demonstrate the effectiveness of bioactive compounds in order to verify the accuracy of traditional methods. The work was conducted by three steps: a) quantitative and qualitative analysis of extracts from various organs of Rumex crispus using the modern methods of physicochemical analysis, b) separation of fatty oils from seeds of Rumex crispus, qualitative and quantitative analysis of fatty acids contained in that oil and de-

termination of their structure, c) isolation and characterization of individual compounds from alcoholic extract of roots of Rumex crispus and determination of their structure. The Fatty oils from seeds of Rumex crispus have been obtained by Soxhlet extraction method. The qualitative analysis of fatty acids in fatty oils were performed using gas-liquid chromatography method (“vet 800”). It was confirmed that the following fatty acids exist in fatty oils separated from seeds of Rumex crispus: lauric acid, palmitic acid, cis-, trans- oleic acid, stearic acid.

A method for obtaining fatty oils from seeds of Rumex crispus has been developed, which ensured separation of the maximum amount of fatty oils from a raw material. Due to the low boiling point of methylene chloride, the solvent was removed under mild temperature conditions. This condition is very important for the activity of biologically active substances in fatty oils.

DETERMINATION OF OPTIMAL DOSAGE FORM FOR DENTAL PREPARATIONS

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Corresponding author e-mail: fadeeva@bsu.edu.ru**Keywords:** *gels, gel bases, gingivitis, periodontal diseases.*

The development of new dosage forms for the treatment of dental diseases is relevant now. The medicinal data showed that the most common inflammatory disease of the oral cavity is gingivitis (more than 62%). There is a lot of dosage forms used for treating of this disease, which contain anti-inflammatory agents. The aim of the study was to choose the best dosage form for treating gingivitis.

During the experiment it was estimated that gels are the most common dosage forms (44.4%). Gels have many advantages such as easily applying, good adhesive properties, significantly prolonging the effect of the drug. There was established that the most common bases for gels are cellulose esters, polyethylenglycols, carbopol.

At present, the prevalence of periodontal diseases has increased dramatically and has acquired the significance of both a general medical and social problem. This group of diseases is caused by factors such as: violation of oral hygiene, frequent consumption of carbohydrate food, which leads to the formation of dental plaque, improper setting of orthodontic (mouth guards, braces and plates for bite correction) and dental prostheses (prostheses, tooth crowns), decreased secretion saliva, traumatic injuries. In addition to these factors, chronic diseases play an important role: hypertension, diabetes mellitus, obesity, atherosclerosis and its complications. The risk group also includes: smoking, stress, gastrointestinal diseases, and lack of vitamins. The cause of periodontal disease is the formation of microbial plaque, which is an accumulation of bacteria that cause demineralization of the enamel and lead to inflammatory diseases of the gums and destruction of the structure of the teeth. The microbial plaque is formed by anaerobic and gram-negative microorganisms: *Streptococcus sanguinis*, *Streptococcus oralis*, *Streptococcus mitis*, *Fusobacterium*, *Actinomyces*, *Fusobacterium nucleatum*, *Prevotella intermedia* and *Capnocytophaga*.

Periodontal diseases are an extensive group, including: gingivitis, stomatitis, periodontitis, parodontosis. Gingivitis is the initial stage of paradontium, which is characterized by gingival inflammation caused by the adverse effects of microbial plaque. The second stage of paradontium is stomatitis, in which ulcers form on the oral mucosa. Progressive destruction of the normal structure of tooth foundation characterizes the inflammatory disease periodontitis. The final stage of paradontium is parodontosis, in which periodontal tissues (gums, muscle ligaments, bone tissue) are destroyed and the necks of the teeth are exposed. The number of the population suffering from chronic in-

flammatory diseases of periodontal tissues is about 98%.

Studies have shown that gingivitis is the most common, it accounts for about 62% of all pathologies, so treatment in the early stages and prevention of further development is relevant and necessary. In modern periodontology, the priority is conservative treatment, which has a sparing effect on periodontal tissues, affects microorganisms and leads to their destruction.

Thus, it is necessary to elaborate new dosage forms for treating of gingivitis as the most common periodontal disease.

The aim of the study was to choose the best dosage form for treating gingivitis.

Standard economic and marketing techniques were used to study the market for dental drugs.

A review of the pharmaceutical market of drugs for the treatment of periodontal diseases was carried out. The most common dosage form is gels, which account for about 44.4% of the entire range of dosage forms, then in terms of prevalence - topical solutions - about 26%, pastes - 18.5%, sprays - 7.4%, dental powders - 3.7%. Gels have many advantages over other dental dosage forms: they are easily applied to the surface of the oral mucosa, adhere well to it, and provide long-term contact with the treated surface, significantly prolonging the effect of the drug.

As known, the composition of gels includes: active ingredients, gel bases and excipients. The analysis of data on groups of excipients used for gels bases was carried out. Thus, most often, polyethylene glycol - 6000 is used in the compositions of dental gels - 30%, 26% carbopol; hydroxyethyl cellulose (HEC) and hydroxypropyl methylcellulose (HPMC) are found in gels in 11% of drugs. Other gel bases make up 14%. These include: methylcellulose (MC), polypropylene glycol, carboxymethylcellulose (CMC).

As a result of the research, it was found that the most promising dosage forms for use in dentistry application are gels. Gels have a number of undeniable advantages: gels are easily applied to mucous membranes, show good adhesion and allow prolonged release of the drug from the gel base.

The polymers that are most often used for the manufacture of gels have been identified. There was established that the most common bases for gels are cellulose esters, polyethylenglycols, carbopol-containing. The results obtained will form the basis for further research on the development of the composition and technology of dental gel for the treatment of inflammatory diseases of the oral cavity.

UDC: 616.831-005-092.4:577.1

IN SILICO, IN VIVO PERMEABILITY EVALUATION OF PEPTIDE COMPOUNDS THROUGH THE BLOOD-BRAIN BARRIER

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Keywords: BBB permeability, docking, dipeptides, HPLC, cerebrospinal fluid.

Previous study had shown the central analgesic characteristics of the recently synthesized peptide compounds in the "Tail-Flick" test, indicating the presence of spinal mechanisms of antinociceptive activity. Although the processes of their possible penetration into the BBB were not clarified. Our research focused on evaluation of potential permeation paths and the purpose of this study was to prove *in silico* and *in vivo* permeability of aforementioned compounds through the blood-brain barrier. Drug-like properties and physicochemical constants of peptides were calculated using the SWISSADME website. Through Cbligand.org/BBB/ website, the calculation of the BBB penetration index was also carried out. Afterwards, the docking of compounds was performed using the computer program Autodock_vina_1_1_2_wi32. In order to detect the quantity of the compound in the cerebrospinal fluid, a reverse phase HPLC

analysis with UM detection was performed. All compounds match to Lipinski's rule, except for a few deviations, that have a quite big molecular weight. BBB permeability index is negative for all compounds (BBB-), and it may be assumed because of the high results of TPSA. The MCT1 transporter was selected as a prospective target transporter for docking experiments because the compounds have a free carboxyl group. Docking study discover that dipeptide with tryptophan residue has highest affinity and it was used for *in vivo* studies. Following injection of the corresponding compound into the rats, HPLC analysis showed that the retention time of the substance ranges 1.977-2.063 min and the concentration in the cerebrospinal fluid is around 0.0198 mg/ml. The determination of compounds in the cerebrospinal fluid of rat evidence that they penetrate the BBB, however passive transport does not work for those compounds. They require a certain carrier system to be transported through BBB, which can be MCT1.

UDC: 615.45:616.36-092.4/.9

STUDY OF THE HEPATOTROPIC EFFECTS OF THE EXTRACT OF CÍSTUS SALVIIFÓLIUS ON THE MODEL OF NON-ALCOHOLIC FATTY LIVER DISEASE

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Keywords: Non-alcoholic fatty liver disease, Cistus extract, Cistus salviifólius.

Non-alcoholic fatty liver disease (NAFLD) is an independent nosological unit that combines clinical and morphological changes in the liver: steatosis, NASH, fibrosis and cirrhosis. NAFLD is closely associated with obesity, especially abdominal, metabolic life syndrome (MS), which significantly increases cardiometabolic risk and leads to disease morbidity, prognosis, and disease duration.

The study was performed to investigate the comparative efficacy of the tested drug tablets containing 18% Cistus extract (in 2 doses) in comparison with the reference drug Ursosan® (in a therapeutic dose) when administered intragastrically to male mice in a model of NAFLD induced by intraperitoneal weekly administration 5% oil solution of carbon tetrachloride against the background of a high-fat diet.

The study was carried out on 125 inbred C57BL/6 male mice weighing 16–18 g. The mice were divided into 5 groups: group 1 – Intact (n=25), group 2 - CCl4 + high-fat diet (NAFLD) (n=25), group 3 - NAFLD + tablets with Cistus extract dose 1 (n=25), group 4 - NAFLD + tablets with Cistus extract dose 2 (n=25), group 5 - NAFLD + Ursosan® (n=25). Tablets containing Cistus extract and Ursosan® were administered to animals daily (1 time per day) intragastrically in the form of suspensions for 90 days.

Based on the data obtained, it was found that dietary supplement tablets containing 18% Cistus extract have a pronounced effectiveness in NAFLD.

It was found that tablets containing 18% Cistus extract have a pronounced dose-dependent hepatotropic (hepatoprotective) effect, comparable, and in some cases superior (including the effect on the hard end point) of the reference drug Ursosan®.

UDC: 615.214.2:577.1:612

SIGMA1R CHAPERONE DEPENDENT NEUROPROTECTION. PHYSIOLOGY AND PHARMACOLOGY

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Corresponding author e-mail: seredeninpharm@mail.ru**Keywords:** *fabomotizole, Sigma 1R, anxiolytic, neuroprotection, cytoprotection.*

Sigma-1 receptor (Sigma1R) is an endoplasmic reticulum (ER) resident ligand-dependent chaperone. Sigma1R is predominantly expressed in mitochondria-associated membranes (MAMs) where it modulates protein folding, Ca²⁺ flux into mitochondria, and ER stress sensors. Under ER stress or ligand activation, Sigma1R is able to translocate into plasma and nuclear membranes within cholesterol-rich lipid microdomains and regulate the functional activity of target ion channels, receptors and enzymes.

Purpose of the study is to determine the involvement of Sigma1R chaperone in the mechanisms of formation of emotional stress reactions, anxiolytic and neuroprotective action of fabomotizole.

With a set of in vitro and in vivo methods evaluate indexes

of the mechanisms of cytoprotection and pharmacodynamics of fabomotizole.

The response to emotional stress was been found to be consistent with Sigma1R activation. Ligand properties of fabomotizole to Sigma1R, its ability to induce translocation of Sigma1R from ER towards plasma and nuclear membranes, and the dependence of fabomotizole anxiolytic effects on Sigma1R were proved. We revealed neuroprotective properties of fabomotizole dependent on the interaction with Sigma1R in an experimental model of Parkinson's disease. The cyto- and neuroprotective properties of fabomotizole were established in the modeling of hypoxic, ischemic and other injuries *in vitro* and *in vivo*.

Sigma1R is a new pharmacological target for neuroprotective and anxiolytic action. Fabomotizole along with its anxiolytic effect has neuroprotective properties.

UDC: 615.12:614.27(479.25)

MAINTAINING THE PACKAGE INTEGRITY OF MEDICINES AT COMMUNITY PHARMACIES IN ARMENIA

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Corresponding author e-mail: sevikyan@mail.ru**Keywords:** *package integrity, medicines dispensing, pharmacists.*

Labeling is an integral part of medicines information. However, sometimes pharmacists do not maintain the package integrity of medicines when dispensing products to patients at community pharmacies. As the results patients can have problems with access to the medicines labeling and the Patient Package Inserts information.

The objective of this work was to study the pharmacists' attitude to maintaining the package integrity of medicines when dispensing products to patients.

Survey was conducted in all the regions of Armenia. Questionnaire was developed and distributed. 348 community pharmacists participated in the study. The results were analyzed with the SPSS statistical software.

71.6% of respondents reported that they practice dispensing medicines after splitting original pack. The majority (91.7%) of pharmacists consider that this practice is not appropriate. Opinion of professionals on appropriateness of splitting original

pack depends on their work experience: all the specialists with a work experience from 16 to 25 years and more than 36 years suppose that splitting original pack is not an appropriate practice ($p = 0.048$). 77.9% of professionals reported that they are not comfortable with dispensing medicines without an original pack. 62.6% of professionals suppose that premises for dispensing are not meet sanitary standards necessary for dealing with medicines repackaging. 60.6% of respondents noted that medicines are dispensed without patient information, 58.9% believe that splitting original pack can affect the quality of the dispensing medicines.

The majority of community pharmacists not always are maintaining the package integrity of medicines when dispensing products to patients and most of them consider the current practice of dispensing medicines after splitting manufacturer's original pack to be is not appropriate. The majority of respondents point out certain reasons supporting their opinion.

UDC: 615.451.16+615.322

INVESTIGATION OF PHARMACOLOGICAL ACTIVITY OF SOUR CHERRY (*P. CERASUS*) ETHANOL EXTRACT AND THE DEVELOPMENT OF FREEZE-DRYING TECHNOLOGY FOR CHERRY FRUITS

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Keywords: *Sour cherry, anthocyanins, freeze-drying, anti-inflammatory activity.*

It's prominent that natural sources in the development of safer pharmacological agents remain an important way for the creation and design of new medicines. Taking into account the reach content of polyphenolic substances, anthocyanins, particularly cyanidin, cyanidin-3-rutinoside, cyanidin-3-glucoside, cyanidin-3-sophoroside, cyanidin-3-glucosyl rutinoside in sour cherry and their content up to the environmental factors such as temperature, light and highness gave a basis for investigation of the active substances and pharmacological activity of freeze-dried sour cherry of Armenian flora.

Experiments were carried out on white inbred male rats, weighing 180-220g. Anti-inflammatory activity was evaluated by xylene induced inflammation method using 70% ethanol extract of sour cherry injected intraperitoneally (i/p) at a dose 500

mg/kg. The content of anthocyanins was determined in freeze-dried sour cherry by spectrophotometric analysis.

Experimental data evidence that freeze-drying leads to the increase of anthocyanins content about 1.8 fold compared with 70% ethanol extract of sour cherry fruits.

It was obtained that i/p injection of 70% ethanol fruit extract accompanied by anti-inflammatory action decreases the rats inflamed ear's weight by 59,3% compared with the control group.

Thus, obtained results concerning the anti-inflammatory activity of sour cherry extract and the high content of anthocyanins in freeze-dried products compared with ethanol extract can serve as a milestone for the development of a new dosage form based on freeze-drying technology due to rich natural, effective agent for correction of pathologies accompanied with inflammation.

UDC: 615.322:616.82-092.9

PLASTICITY OF RAT'S ENTORRHINAL CORTEX INDUCED BY FRUCTOSE OVERLOAD AND GALANTAMINE TREATMENT

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Keywords: *entorhinal cortex, fructose, Galantamine, plasticity.*

The fructose containing beverages intensive use in humans causes clinical symptoms of the metabolic syndrome (MetS). MetS affects the cholinergic transmission and cognitive functions. Galantamine, a centrally acting acetylcholinesterase inhibitor, has been shown to improve significant aspects of MetS pathophysiology, such as inflammation and insulin-resistance. Fructose overload in experimental animals has been associated with insulin-resistance, neuroinflammation and dementia. We supposed galantamine could be beneficial in treating neuronal cholinergic disorders in fructose-induced MetS.

The aim of this study was to evaluate the synaptic plasticity (and related biomarkers) of cholinergic neuronal chain in rats in the fructose-induced MetS and galantamine therapy.

The Fructose group rats received a 50% aqueous solution of dietary fructose instead of drinking water for 9 weeks. The Fructose+Galantamine group rats received fructose for 9 weeks and Galantamine (Nivaline, 0.25 mg/kg/day) injected intramuscularly from the 6-th to 9-th weeks. After 9 weeks the spike activity of

the entorhinal cortex single neurons was extracellularly recorded *in vivo* during high-frequency stimulation (tetanization) of the cholinergic basal nucleus (NB).

Singleunit recording and analysis in real time before stimulation (background activity), poststimulation and tetanization revealed degenerative changes in short-term plasticity in the Fructose group, expressed in drastically decrease of the percentage share and excitation strength during tetanization time in the cortical neurons responses to high-frequency stimulation of NB. Galantamine resulted in: i) increase in the portion of post-stimulus excitatory responses (significantly above normal) without excitation strength restoration during tetanization time; ii) a significant increase in the portion and strength of inhibitory responses during tetanization time.

Galantamine caused an increase of the percentage share and strength of the tetanic depression – posttetanic potentiation combination, contributing to greater integration of cortical neurons into cholinergic chains and enhancing homeostatic plasticity in fructose overload.

UDC: 615.21

CORRECTION OF EXPERIMENTAL CEREBRAL CIRCULATION DISORDERS AND THEIR BEHAVIORAL OUTCOMES BY MESEDINTananyan A.G.¹, Baykov A.V.¹, Ayvazyan A.H.¹¹Department of Pharmacology, Yerevan State Medical University, Yerevan, ArmeniaCorresponding author e-mail: adamyanhovsepyan@mail.ru**Keywords:** mesedin, ischemia, behavior.

Carried out investigation revealed mesedin neuroprotective properties on the brain tissue conditioned by acute ischemic disorders, which are first reason of disability and the second reason of mortality all over the world. Mesedin is an α -adrenoblocker with antihypoxant and antiaggregant activities synthesized in the Scientific Technological Center of Organic and Pharmaceutical Chemistry NAS RA. The study of the effect of mesedin under condition of cerebral circulation disorder induced by ligation of rCCA revealed the ability (10mg/kg and 25mg/kg) to recover the impaired local cerebral circulation almost to its baseline level, without notable changes in the systemic arterial pressure. It was obtained, that the antihypoxic property of mesedin in ischemic conditions caused by rCCA ligation is manifested by significantly prevention the increase in the level of MDA, as well as the quantities of aldehyde- and ketone-dinitrophenylhydrazones of neutral character, also aldehyde- and ketone-dinitrophenylhydrazones of basic character. Studies of mesedin on the behavioral changes and memory caused by the left MCA ligation showed that mesedin prevents the mentioned shifts caused by local ischemia. The experiments performed in

the EPM test showed that mesedin (10mg/kg) on the 6th and especially on the 12th day of MCA ligation weakens the anxiety development caused by the ischemic disorders and decreases the motor activity fall which is expressed more distinctly at a later date of ischemia. At the same period of ischemia, experiments performed in the "Rota-Rod Treadmill" test recorded correction of the rats' motor coordination impairments, which had statistically verifiable character in all studied phases of ischemia. In case of long term administration of the drug, the loss of memory was completely prevented in all animals tested in passive avoidance test. Neuroprotective effect of the drug was confirmed by morphological studies which testify that mesedin mitigates structural alterations caused by the ligation of the left middle cerebral artery. All of this demonstrates that the use of mesedin as a potential medicine for correction of cerebral ischemic disorders is justified, since along with its property to improve the cerebral blood flow, to prevent the development of structural changes and neurobehavioral impairments caused by brain local ischemia, this compound mitigates the aggressive action of oxidative stress, protecting the brain tissue from consequences of hypoxia.

UDC: 615.22

THE ASSESSMENT OF FLOWABILITY AND COMPRESSIBILITY OF VALSARTAN

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Angiotensin II receptor blockers (ARB), in particular valsartan, are widely used for the treatment of arterial hypertension (AH). This active pharmaceutical ingredient (API) has proved high safety and efficacy in the treatment of hypertension. Therefore, the research of the technological properties of API valsartan for the further development of a solid dosage form is a relevant topic.

The assessment of flowability and compressibility of API valsartan, according to pharmacopoeial criteria (flowability and bulk density) and the calculated values of the Carr index (CI) and Hausner index (IH).

API valsartan (Zhuhai Rundu Pharmaceutical Co., China). Equipment: analytical balance SARTOGOSM CE224-C with an accuracy of 0.1 mg, Russia; granulate flow tester ERWEKA GT, Germany; tapped density tester ERWEKA SVM 221, Germany

(equipment of GMP training-center of Center for Collective Use of SPCPU). Methodology: State Pharmacopoeia of the Russian Federation XIV edition, volume 2.

The flowability was 0.0 s/100 g, without stirring. The value of bulk density before compaction ($D\alpha$) was 0.44 g/ml, after compaction (Dc) – 0.73 g/ml. Due to the values $D\alpha$ and Dc , the values of CI and IH were calculated – 1.66 and 39.73%, respectively.

The value of the API flowability is rated as unsatisfactory. The closer values of $D\alpha$ and Dc , the smaller CI and the closer IH to unity led to the better flowability and compressibility of API. Based on the obtained experimental and calculated data, the technological properties of valsartan (flowability and compressibility), that are key for further tableting, are assessed as unsatisfactory. Therefore, it is important to select appropriate excipients and technological scheme for the further development of valsartan tablets.

UDC: 615.214.32:547.9

MECHANISMS OF ANTIDEPRESSANT ACTIVITY OF SMALL PEPTIDE-LIKE TRKB LIGAND

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Keywords: dipeptide TrkB ligand, antidepressant, AKT/BAD activation, unpredictable chronic mild stress.

Current data indicate the importance of BDNF/TrkB pathway for depression pathophysiology and significance of TrkB as a valuable target for antidepressants. Orally available dipeptide GSB-106, resembling the part of BDNF loop 4, has been developed at the Zakusov Institute of Pharmacology. The compound exerts a trophic effect, up-regulates the TrkB phosphorylation, downstream signaling pathways and shows the antidepressant effect in the behavioral tests.

Purpose of the study was to examine the cell survival-promoting activity *in vitro* and the potential antidepressant-like effects of GSB-106.

Experiments were conducted in SH-SY5Y cells in serum-free conditions. Antidepressant-like effect of GSB-106 administration (1 mg/kg, 26 days, *per os*) was evaluated in unpredictable chronic mild stress model (UCMS). The levels of BDNF, Akt, BAD

proteins, TrkB site-specific phosphorylation were assayed by Western blot.

GSB-106 decreased amount of cells in early and late apoptosis, elicited the increase of BAD^{pSer136} and AKT^{pSer473} under serum-free conditions. In mice exposed to UCMS, chronic GSB-106 treatments decreased the immobilization by 2.9 folds (Porsolt's test). GSB-106 restored a decrease in BDNF level induced by the UCMS in prefrontal cortex and hippocampus; activated a TrkB^{Y706/707} phosphorylation in prefrontal cortex; induced an increase of TrkB^{Y816} phosphorylation in prefrontal cortex and hippocampus.

The study revealed that the survival of serum-deprived SH-SY5Y was dependent solely on the presence of GSB-106. GSB-106 treatment during continuous UCMS resulted in a BDNF increase and induction of TrkB^{Y706/707} and TrkB^{Y816}, in this way mimicking the pattern attributed for the most of the conventional antidepressants.

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OFF-LABEL USE OF MEDICINES IN CHILDREN IN ARMENIA

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Keywords: off-label, children, medicines prescribing.

The lack of suitable medicine formulations for children is a global challenge that leads to the situation that medicines are often prescribed to them off-label.

The purpose of this work was to evaluate a practice of off-label prescribing to children in outpatient care in Armenia.

Data on medicines prescribing were collected from 293 pediatricians and family physicians in Primary Health Care settings from all regions of Armenia. Medicines prescribed for 879 children aged 0-17 years were studied. Off-label medicine use was identified by comparing actual prescribing and information from the Summary of Product Characteristics.

114 (6.3%) out of 1817 totally prescribed medicines were prescribed off-label. 32.5% of all off-label prescriptions were off-label contraindications, 19.3% - off-label age, 17.5% - off-label method of administration, 8.8% - off-label dosing, 7.9% -

off-label indications, 7.0% - off-label pharmaceutical form, 7.0% - absence of pediatric information. Medicines most commonly prescribed off-label were Vitamin C (ascorbic acid) in solid pharmaceutical form (21.9%), Linkus syrup (17.5%) and Salbutamol, tablets (13.2%). Solid pharmaceutical forms of Vitamin C and Salbutamol were off-label prescribed to some patients despite other pharmaceutical forms of these medicines, which are authorised for use in children, are available in the pharmaceutical market of Armenia.

Off-label prescribing to children in Primary Health Care settings is observed in Armenia. In some cases off-label use could be avoided and more appropriate pharmaceutical forms could be prescribed. It seems that education of physicians in the area of medicines information would be beneficial for improving situation with safety of medicines use.

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THE TREATMENT OF PARAGANGLIOMA-PHEOCHROMOCYTOMA OF THE ORGAN OF ZUCKERKANDL CASE REPORTVarzhapetyan A.¹, Chitchyan A.^{2*}¹"Astghik" Medical Center, Department of endocrine surgery, Yerevan, Armenia²Yerevan State Medical University after M. Heratsii, Department of pharmacology, Yerevan ArmeniaCorresponding author e-mail: alisaruda@mail.ru**Keywords:** organ of Zuckerkandl, paraganglioma, pheochromocytoma, neuroendocrine tumors.

Pheochromocytoma (PCC) and paraganglioma (PGL) of the organ of Zuckerkandl (OZ) are rare neuroendocrine tumors with the classic symptomatic triad of tachycardia, headache, and profuse sweating. To confirm the diagnosis of PCC and PGL, increased plasma and urine concentrations of metanephrines are determined. A computed tomography is the most reliable diagnostic test method, and magnetic resonance imaging may be done. The main treatment of PCC and PGL is divided into medicinal, surgical, and auxiliary tumor treatments.

The patient was admitted to the surgical department with complications of abdominal and lumbar pain, general weakness. He has suffered from an aggressive form of arterial hypertension. There has been an increase in blood glucose levels be-

tween 17 and 22 mmol/L, which is difficult to control with insulin injections only.

The tumor was removed through the median laparotomy access. The course of postoperative period was uneventful. Starting from the second day after the surgery and in the following months, blood pressure did not rise, and blood glucose levels returned to normal.

To avoid postoperative complications, 1-14 days prior to surgery, patients should be given appropriate α - and β -blockers, calcium channel blockers; which ensure increased circulating blood volume achieved by saline infusion; after 6 months, 1 year, annual tumor imaging is also required. Postoperative treatment of PCC and PGL of the OZ is the main most effective treatment, it is necessary to identify and take measures to combat metastases in time.

UDC: 615.1:614.27

GXP COMPLIANCE SYSTEMS IN THE PHARMACEUTICAL INDUSTRYZhamharyan L.G.¹¹National Institute of Health named after academician S. Avdalbekyan, Yerevan, ArmeniaCorresponding author e-mail: zhamharyan@mail.ru**Keywords:** GxP system, risk assessment, validation.

GxP is a set of regulations and quality standards intended to ensure the quality & integrity of the data used to make product-related safety decisions along with different stages lifecycle of product development, production, testing, etc., with a wide range of compliance-related activities like Good Manufacturing Practices (GMP), Good Laboratory Practices (GLP), Good Clinical Practices (GCP), and others, with product specific requirements. GxP systems compliance based on risk management principles of ICH Q9 as presented by the following: Initial Assessment, Identification of functions with Impact on Patient Safety, Product Quality, and Data integrity; Perform Functional Risk Assessments and Identify Controls; Implement and verify appropriate testing and controls; and Review risks and monitor controls. GxP software validation is an essential requirement for compliance with the FDA, EMA, MHRA and ISO 13485. All

computerized systems used within a clinical trial should be subject to processes that confirm that the specified requirements of a computerized system are consistently fulfilled and that the system is fit for purpose. Validation should ensure accuracy, reliability and consistent intended performance, from design until decommissioning of the system. Validation activities (test cases as per traceability matrix) shall be preplanned and documented (IQ/OQ/PQ). The data integrity maintenance and protection of the rights of trial participants, computerized systems, used in clinical trials, the security requirements are applied to prevent unauthorized access and accidental or deliberate data changes and maintain blinding of the treatment allocation, data entry. Validation of a system maintained throughout the full life cycle. Periodic system reviews shall be conducted to assess and document whether the system can still be considered to be in a validated state, required for revalidation.