ISPC-2022

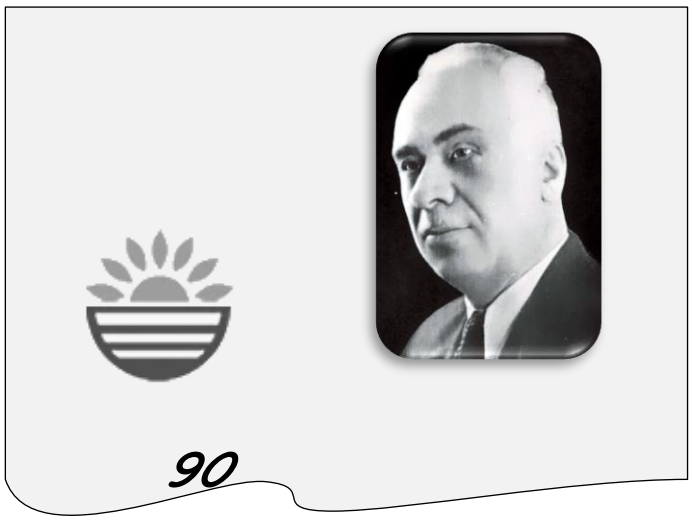
October 1-2, Tbilisi, Georgia

INTERNATIONAL SCIENTIFIC-PRACTICAL CONFERENCE

"Georgian Scientific Pharmacy: Past and Present"

dedicated to TSMU Pharmacochemistry Institute 90th and Academician Iovel Kutateladze 135th anniversary

ABSTRACT BOOK



Organized by:

Tbilisi State Medical University

TSMU I. Kutateladze Institute of Pharmacochemistry

Association of Scientists and Young Pharmacists of Georgia

WELCOME

Dear Colleagues!

The Organizing Committee, has a pleasure and honor to invite you to attend the International Scientific-Practical Conference "Georgian Scientific Pharmacy: Past and Present" dedicated to TSMU Pharmacochemistry Institute 90th and Academician Iovel Kutateladze 135th anniversary (ISPC-2022).

ISPC-2022 has an ambition to bring together a multi-disciplinary group of scientists from Europe and Asia to present and share most recent advances in major areas of pharmaceutical science. We will be glad to see pharmacy experts, medicinal and synthetic chemists, pharmacologists, analysts, and other scientists involved in drug research and development in Georgia – the middle of the ancient Silk Way – historical bridge between Asia and Europe.

The scientific program of ISPC 2022, apart from keynote lectures, oral communications and poster presentations will include Young Researchers Forum and Master Class Workshop "Analytical Challenges in Drug Development: Need in Orthogonal Chromatographic Methods"

We also plan to present a breathtaking and an enthralling social program.

The Organizing Committee thanks you once more for joining and will try to do its best to help you benefit from scientific and social parts of the Conference and carry home good memories of ISPC-2022.

Organizing Committee of the ISPC-2022

CONTENTS

ORGANIZING COMMITTEE

HONORARY CHAIR

Zurab Vadachkoria

CHAIR

Lasha Mskhiladze

CO-CHAIRS

Zurab Orjonikidze
Irina Kvachadze
Sofio Bakhtadze
Zurab Antelidze

MEMBERS

Ether Kemertelidze
Tamar Chikviladze
Dali Berashvili
Aliosha Bakuridze
Davit Chincharadze
Nana Gorgaslidze
Tamaz Murtazashvili
Badri Arziani
Paata Tushurashvili
Karen Mulkijanyan
Meri Alania
Malkhaz Getia
Bela Kikalishvili
Nina Vachnadze
Nana Nadaraia
Vakhtang Barbakadze
Ketevan Mchedlidze
Pavle Iavichi
Giorgi Erkomaishvili

INTERNATIONAL ADVIZORY BOARD

Gunter Bonn, Austria
Athina Geronikaki, Greece
Vladimir Ioffe, Israel
Gary Gellerman, Israel

CONFERENCE SECRETARIAT

Maia Merlani
Sopio Gokadze

GENERAL INFORMATION

Conference Venue

Tbilisi State Medical University, Address: 33 Vazha Pshavela ave, Tbilisi, Georgia

Registration Desk

Conference Material and Name Badges will be distributed at the Regiatration Desk in the University Hall left to main entrance.

Operating hours:

October 1 8:30 – 12:00

Secretariat and Information Desk

The Secretariat and Information Desk will operate in the registration area to provide any information regarding the Scientific Program, Social Events, transportation, lost & found, etc.

Operating hours:

October 1 8:30 – 17:30

October 2 9:30 – 17:00

SCIENTIFIC INFORMATION

For Oral Session Speakers

The session room is provided with LCD projector and laptop computer loaded with MS Office Power Point. Speakers are asked to bring their presentation (either on USB sick or CD) and load it during the break prior to the session. Staff will be available in the session room to assist with the operations.

Alloted time for Plenary Lecture will be 30 min, Oral Presentation -15 min.

For Poster Presentations

The Poster Session will be held in the University hall. Authors are asked to mount posters on boards assigned by Secretariat during the registration. Mounting accessories will be available at the Information Desk.

PROGRAM

OCTOBER 1, SATURDAY	
8:30 – 9:30	**REGISTRATION**
9:30 – 10:30	**OPENING CEREMONY**
	SESSION 1. Co-Chairs: G.Gellerman, V.Barbakadze
10:30 – 11:00	**PL-1**. G. Bonn, *Leopold-Franzens University of Innsbruck, Austria*
11:00 - 11:15	**OP-1**. A. Bakuridze, *Tbilisi State Medical University, Georgia*
11:15 – 11:30	**OP-2**. G. Scriba, *Friedrich Schiller University, Jena, Germany*
11:40 – 12:00	**COFFEE-BREAK**
	SESSION 2. Co-Chairs: V.Ioffe, K.Mulkijanyan
12:00 – 12:30	**PL-2**. A. Geronikaki*, Aristotle University, Thessaloniki, Greece*
12:30 – 12:45	**OP-3.** V. Barbakadze, *Tbilisi State Medical University, Georgia*
12:45 – 13:00	**OP-4.** L. Patsenker, *Ariel University, Israel*
	OP-5. N. Barbakadze, *Tbilisi State Medical University, Georgia*
13:10 – 14:00	**LUNCH**
	SESSION 3. Co-Chairs: A.Geronikaki, N.Imnadze
14:00 – 14:30	**PL-3**. B. Chankvetadze, *Tbilisi State University, Georgia*
14:30 – 14:45	**OP-6**. B.Kikalishvili, *Tbilisi State Medical University, Georgia*
14:45 – 15:00	**OP-7**. A.Hovakimyan, *Sci-Tech Center of Org. & Pharm.Chemistry Nat.Acad.Sci., Yerevan, Armenia*
15:15 – 15:30	**OP-8**. M.Getia, *Tbilisi State Medical University, Georgia*
15:30 – 15:45	**OP-9**. M.Benidze, *Tbilisi State Medical University, Georgia*
15:45 – 16:00	**OP-10**. M.Merlani, *Tbilisi State Medical University, Georgia*
16:00 – 16:30	**COFFEE-BREAK**
	Young Researchers Forum. Co-Chairs: L.Patsenker, M.Merlani
16:30 – 16:40	**SC-1**. N. Todua, *Tbilisi State Medical University, Georgia*
16:40 – 16:50	**SC-2**. T. Korkotadze, *Tbilisi State Medical University, Georgia*
16:50 – 17:00	**SC-3**. G. Moshiashvili, *Tbilisi State Medical University, Georgia*
17:00 – 17:10	**SC-4**. T. Korinteli, *Tbilisi State Medical University, Georgia*
17:10 – 17:20	**SC-5**. G. Jgerenaia, *Tbilisi State Medical University, Georgia*
17:30	**SOCIAL EVENT**

OCTOBER 2, SUNDAY	
	SESSION 4. Co-Chairs: A.Hovakimyan, M.Jokhadze
9:00 – **9:30**	**PL-4**. G. Gellerman, *Ariel University, Israel*
9:30 - **9:45**	**OP-11**. K.Mulkijanyan, *Tbilisi State Medical University, Georgia*
9:45 – **10:00**	**OP-12**. I.Rubashvili, *Tbilisi State University, Georgia*
10:00 -**10:15**	**OP-13**. A. Gruzman, *Bar-Ilan University, Israel*
10:30 – **11:00**	**COFFEE-BREAK**
	MASTER CLASS WORKSHOP
11:00 – **13:10**	MCW part 1 - V. Ioffe, *Teva Pharmaceutical Industries, Ltd., Israel*
13:10 – **14:00**	**LUNCH**
	MASTER CLASS WORKSHOP
14:00 – **16:00**	MCW part 2 - V. Ioffe, *Teva Pharmaceutical Industries, Ltd., Israel*
16:00 – **16:30**	**COFFEE-BREAK**
16:30 – **17:15**	**CLOSING CEREMONY**
17:30	**SOCIAL EVENT**

PLENARY LECTURES

PL 1. NOVEL ADVANCEMENTS IN SEPARATION SCIENCE FOR NATURAL PRODUCT RESEARCH – APPLICATIONS IN PHYTOPHARMACY, PHYTOCOSMETICS AND PHYTONUTRITION

Günther K. Bonn[1,2]

[1] Institute of Analytical Chemistry and Radiochemistry, Leopold-Franzens University of Innsbruck, [2] ADSI - Austrian Drug Screening Institute, Innsbruck, Austria.

Corresponding author e-mail: Guenther.bonn@uibk.ac.at

New approaches in analytical chemistry are increasingly important for natural product research, and innovative advances in separation science enable exploration of inaccessible areas of natural product isolation. Since herbal preparations such as plant extracts often contain multi-component mixtures with hundreds or thousands of small molecules in different concentrations, their separation and analysis is often difficult to perform. Therefore, novel enrichment and purification methods based on advanced solid phase extraction techniques were developed to reduce the complexity of plant extracts while using HPLC for separation, preconcentration and fractionation. The ability to apply these techniques to robotic systems allows for high throughput screening. Significant advances have been made in the development of new stationary phases that can be tailored to a specific application, thus offering endless opportunities to optimize selectivity. A further coupling to high-resolution mass spectrometry facilitates the identification and quantification of active substances in natural products. In addition, the combination of separation science with spectroscopy offers the possibility of combining different technologies in phytopharmacy and food analysis. Near and mid-infrared spectroscopy enable rapid and simultaneous qualitative and quantitative analysis of raw plants and liquid extracts without destruction. In addition, infrared imaging was used to study the distribution of active ingredients in plant materials. All of these approaches offer new strategies for quality control in phytoanalysis and enable deeper insights into the biochemical background of medically relevant issues. In this talk, new approaches in analytical chemistry for various applications in the fields of phytopharmacy, phytocosmetics and phytonutrition will be presented and discussed.

PL 2. PYRAZOLO[4,3-C]PYRIDINE SULFONAMIDES AS CARBONIC ANHYDRASE INHIBITORS: SYNTHESIS, BIOLOGICAL AND IN SILICO STUDIES

Athina Geronikaki

Aristotle University, Thessaloniki, Greece

Corresponding author e-mail: e-mail: geronik@pharm.auth.gr

Carbonic anhydrases (CAs, EC 4.2.1.1) catalyze the essential reaction of CO2 hydration in all living organisms, being actively involved in the regulation of a plethora of patho-/physiological conditions. A series of chromene-based sulfonamides were synthesized and tested as possible CA inhibitors. On the other hand, in microorganisms, the β- and γ- classes are expressed in addition to the α- class, showing substantial structural differences to the human isoforms. In this scenario, not only human but also bacterial CAs are of particular interest as new antibacterial agents with an alternative mechanism of action for fighting the emerging problem of extensive drug resistance afflicting most countries worldwide. Pyrazolo[4,3-c]pyridine sulfonamides were synthesized using methods of organic chemistry. Their inhibitory activity, assessed against the cytosolic human isoforms hCA I and hCA II, the transmembrane hCA IX and XII, and β- and γ-CAs from three different bacterial strains, was evaluated by a stopped-flow CO2 hydrase assay. Several of the investigated derivatives showed interesting inhibition activity towards the cytosolic associate isoforms hCA I and hCA II, as well as the 3β- and 3γ-CAs. Furthermore, computational procedures were used to investigate the binding mode of this class of compounds within the active site of hCA IX. Four compounds (1f, 1g, 1h, and 1k) were more potent than AAZ against hCA I. Furthermore, compound 1f also showed better activity than AAZ against the hCA II isoform. Moreover, ten compounds out of eleven appeared to be very potent against the γ-CA from E.coli, with a Ki much lower than that of the reference drug. Most of the compounds showed better activity than AAZ against hCA I as well as the γ-CA from E.coli and the β-CA from Burkholderia pseudomallei (BpsCAβ). Compounds 1f and 1k showed a good selectivity index against hCA I and hCA XII, while 1b was selective against all 3β-CA isoforms from E.coli, BpsCA, and VhCA and all 3γ-CA isoforms from E.coli, BpsCA, and PgiCA.

PL 3. CURRENT CHALLENGES IN ANALYSIS OF PHARMACEUTICALS WITH THE EMPHASES ON CHIRAL DRUGSECENT RESULTS IN THE INVESTIGATION OF BIOACTIVE PHENOLICS FROM MEDICINAL AND FOOD PLANTS

Bezhan Chankvetadze

Institute of Physical and Analytical Chemistry, School of Exact and Natural Sciences, Iv. Javakhishvili Tbilisi State University

Corresponding author e-mail: bezhan.chankvetadze@tsu.ge

Compounds of pharmaceutical interest are analysed for various purposes. Among them are analytical methods required for drug development, for studies of its quality, for controlling its adequate use, as well as its proper disposal and its environmental impact. Each of these areas have further branches that make pharmaceutical analysis a huge field of research, as well as of scientific and applied impact. The multiplicity of goals related to the analysis of pharmaceuticals leads to the wide variability of matrices these compounds have to be determined in, as well as requires the application of various analytical techniques and detection schemes. This is very challenging and commonly strongly regulated field of mankind´s activity requiring good knowledge and (laboratory) infrastructure.

Currently, the tendency in pharmaceutical industry is shifting from small synthetic molecules to large biopharmaceuticals. This also affects analytical strategies used on the stage of drug development, as well as on the stage of their use. The natural product analysis is also a challenging and rapidly developing area. This presentation shortly summarizes general challenges and trends in the analysis of pharmaceuticals and based on the author´s research experience focusses more on separation of enantiomers of chiral drugs and their enantioselective analysis. In this part, separation methods such as high-performance liquid chromatography [1], capillary electrophoresis [2] and capillary electrochromatography [3] will be shortly overviewed and advantages and disadvantages of these techniques will be highlighted.

References

[1] Chankvetadze, B. Recent trends in preparation, investigation and application of polysaccharide-based chiral stationary phases for separation of enantiomers in high-performance liquid chromatography, Trends in Analytical Chemistry, 122 (2020) 115709

[2] Chankvetadze, B. 2018, Contemporary theory of enantioseparations in capillary electrophoresis, J. Chromatogr. A, 1567, 2-25.

[3] Fanali, S. Chankvetadze, B. History, advancement, bottlenecks and future of chiral capillary electrochromatography, J. Chromatogr. A, 1637 (2021) 461832.25.

PL 4. THERANOSTIC ANTIBODY-DRUG CONJUGATES: NEW FRONTIERS IN DIAGNOSIS AND TREATMENT OF CANCER.

Gary Gellerman

Department of Chemical Sciences, Ariel University, Ariel, 40700, Israel

Corresponding author e-mail: garyg@ariel.ac.il

Antibody-drug conjugates (ADCs) are molecular systems that unlike classic chemotherapy hold the potential to change the nature of cancer treatment. ADCs combine both the advantages of highly specific targeting ability and highly potent killing effect to achieve accurate and efficient eradication of cancer cells. Yet, the visualization of drug release event in "life" by fluorescence monitoring is emerging methodology and can provide a vital info about pharmacokinetics of ADCs. Fluorescent dyes linked to ADCs create theranostic (therapeutic and diagnostic) modalities that afford such a real-time info on the efficacy of drug delivery including quantitative monitoring of drug distribution. To achieve this goal, we equipped an ADCs with a turn-on near-infrared (NIR) dye, sensitive to drug release, and a reference NIR dye. The results suggest that our ratiometric design could be successfully employed for quantitative monitoring of drug release degree and the proposed method is unaffected by the experimental variation, as well as the variation in the mouse response to the administrated conjugate. The future aspects and insights of theranostic ADCs with improving therapeutic index will be discussed.

References

[1] T. Etrych et al. "Targeted Drug Delivery and Theranostic Strategies in Malignant Lymphomas". Cancers 2022, 14, 626.
[2] E. Thankarajan et al. "Antibody guided activatable NIR photosensitizing system for fluorescently monitored photodynamic therapy with reduced side effects" Journal of Controlled Release 2022, 343, 506–517.
[3] E. Thankarajan et al. ''Antibody-guided, dual NIR dye ratiometric drug delivery system for quantification of drug release in-vivo'' ACS Analytical Chemistry 2021, 93, 23, 8265-8272.
[4] D. Poplinger et al. "Ratiometric fluorescence monitoring of antibody-guided drug delivery to cancer cells" Bioconjugate Chemistry 2021, 32, 8, 1641–1651.
[5] L. Patsenker and G. Gellerman, “Fluorescent Reporters for Drug Delivery Monitoring” Israel Journal of Chemistry 2020, 60, 1 – 16.

ORAL PRESENTATIONS

OP 1. FORMULATION AND TECHNOLOGY OF TARGETED DELIVERY AND MODIFIED-RELEASE SYSTEMS

[1]A. Bakuridze, [2]G. Ghibradze, [3]D. Dzidziguri, [2]Z. Vadachkoria

Tbilisi State Medical University: [1]Department of Pharmaceutical Technology; [2]Department of Children and Adolescent Maxillo-Facial Surgery & Surgical Stomatology; [3] Iv.Javakhishvili Tbilisi State University, Tbilisi, Georgia

Corresponding author e-mail: a.bakuridze@tsmu.edu

While using conventional dosage forms, it is hard to avoid change (fluctuation, non-constancy) of the concentration of the active pharmaceutical ingredient (API) in biological fluids. At this time, it is possible to: overdose or conversely, have insufficient effectiveness of the drug; consumption of the medicinal substance in excess amount during use.

After delivering the API into the body, it is actually distributed evenly in all tissues. As a result, only an insignificant part of the active substance 0.001 - 0.01% is provided to the area of damage. The rest of the drug in the best case is wasted, or in the worst case, it causes a toxic effect [1].

Conventional dosage forms are not characterized by selectivity of release and action, so, the drug does not act like an arrow at a specific target, the action of the drug is like a rain. This is what determines the need for new approaches in the field of development of dosage forms

The study aimed to compose the formulations and develop technologies for targeted delivery and modified release dosage forms containing some natural and synthetic active pharmaceutical ingredients.

In order to facilitate the process of taking the tincture of Valerian and Motherwort, to avoid problems with swallowing, as well as negative effects of alcohol, we have developed orodispersible plates, which are solid dosage forms, are applied to the mucous membrane, adsorbed on it, quickly dissolved by saliva and absorbed.

Currently, there are several Aloe formulations on the pharmaceutical market. Studies conducted on various gastric ulcer models in experimental animals have established that the Aloe substance has a pronounced gastroprotective and anti-ulcer effect [5].

Based on biopharmaceutical studies, the composition of Aloe-containing gastro-retentive floating tablets for targeted delivery has been established, and a production technology was developed..

Nowadays the main cause of gastroduodenal diseases is considered to be *Helicobacter pylori* - a bacteria that invades the gastrointestinal (GI) tract and causes ulceric damage in the upper part of the stomach lining or small intestine, which in turn can lead to the development of gastric cancer [2,4].

The so-called "gold standard" of *H.pylori* eradication is triple therapy, which combines two antibiotics (amoxicillin/levofloxacin or clarithromycin/metronidazole) and a proton pump inhibitor (omeprazole/lansoprazole/pantoprazole/rabeprazole). The above medicines are serially manufactured and available in solid dosage forms: tablets and capsules [2,4].

Innovative drug delivery systems such as floating, high and low density, mucoadhesive/bioadhesive, swelling and magnetic systems, ion-exchange resins and nanosystems have been provided to date. Although these systems represent a promising concept for API delivery, they still have a number of drawbacks [2,4].

Foams are of particular interest for targeted API administration in the stomach mucosa as they are light-weight, and, contrary to solid dosage forms, do not precipitate. Instead, they expand in volume and enlarge contact surface, completely covering and penetrating the mucosal membrane [3].

On the basis of "gold standard" ingredients of *H.pylori* eradication, the targeted delivery, modified solid dosage forms - in the form of gastro-retentive, dissolvable and foam forming tablets have been composed.

Vascular hyperplasia of the skin, the so-called hemangioma is the most common congenital and neonatal skin vascular lesion in children. Using ointments, it is possible to deliver the active pharmaceutical ingredient directly to the damaged area, to create its high concentration in the skin, tissues, biological fluids and organs, as well as to avoid negative effects of the primary metabolism of the liver, enzyme system, pH on the API. From this point of view, the local delivery of biologically active natural compounds for the treatment of benign tumors of the skin and subcutaneous blood vessels is relevant.

On the basis of biopharmaceutical studies, formulations of ointments containing growth-regulating thermostable protein complex, salicylic acid and rutin are provided and technologies are developed, their relative diffusion processes and bioavailability in *in vitro* and *ex vivo* tests are investigated.

Bacterial and viral infections of the respiratory system are currently among the most severe challenges. Taking this into account, we have developed a composition of inhalation powder containing Eucalyptus and Thyme essential oil. Particle sizes were determined using a laser diffractometer. It is established that inhalation powders consist of respirable fractions of optimal sizes.

In vitro test studies have established that the delivered inhalation powders are distributed over the entire lung area, which is especially important in the treatment of diseases caused by bacterial and viral infections of the respiratory system.

References

[1] Kulakova, I.I., Lisichkin, G.V., Yakovlev, R.Yu., Selezenev, N.G. 2018. Directional Drug Transport: From Idea to Implementation. Ryazan. 104 p. (In Russian)

[2] Anurag Verma, Juhi Dubey, Rahul Rama Hegde, Vaibhav Rastogi, Pandit J. K. 2016. Helicobacter pylori: past, current and future treatment strategies with gastroretentive drugdelivery systems. Journal of Drug Target. 2016. Dec; 24(10): pp. 897-915.

[3] Dagmara Hoc a, Dorota Haznar-Garbacz b. 2021. Foams as unique drug delivery systems. European Journal of Pharmaceutics and Biopharmaceutics. 167 (2021) 73–82.

[4] Shafika Assaad, Rawan Chaaban, Fida Tannous & Christy Costanian. 2018. Dietary habits and Helicobacter pylori infection: a cross sectional study at a Lebanese hospital BMC Gastroenterology volume 18, Article number: 48 (2018).

[5] Bakuridze A., Berashvili D., Bakuridze L. et al. 2008. Technology of Aloe tablets. Collection of scientific works of Tbilisi State Medical University. pp. 18-20.

OP 2. DEVELOPMENT OF MONOGRAPHS FOR THE INTERNATIONAL PHARMACOPOEIA EXAMPLES AND CHALLENGES

Gerhard K. E. Scriba

Friedrich Schiller University Jena, Institute of Pharmacy, Department of Pharmaceutical/Medicinal Chemistry, Jena, Germany

Corresponding author e-mail: gerhard.scriba@uni-jena.de

The International Pharmacopoeia is a collection of recommended procedures for analysis and specifications for pharmaceutical substances, excipients and finished products, which is published by WHO. It is intended to serve as a reference for any WHO Member State to establish pharmaceutical requirements. The first volume was published in 1951. Since 1975, the International Pharmacopoeia focuses on medicines included in the WHO Model List of Essential Medicines as well as on medicines of major health importance such as medicines for treating malaria, tuberculosis or HIV infections.

The work on The International Pharmacopoeia is carried out in collaboration with members of the WHO Expert Advisory Panel on the International Pharmacopoeia and the WHO Expert Committee on Specification for Pharmaceutical Preparations and with analytical specialists. The process involves consultation with WHO member states medicine regulatory authorities, national medicine quality control laboratories, WHO collaborating centers, standard-setting organizations and manufacturers around the world [1].

The present talk will outline the procedure of the elaboration of monographs and highlight challenges encountered during the development of analytical procedures for the drugs linezolid, tenofovir disoproxil fumarate and dolutegravir. Examples include the identification of the drug substance as well as the determination of drug purity by chromatographic methods including the stereochemical purity.

References

[1] World Health Organization, 2019, Procedure for the elaboration, revision and omission of monographs and other texts for the International Pharmacopoeia, WHO Drug Information, vol. 33, no. 2, 174 – 178, https://apps.who.int/iris/handle/10665/330885.

OP 3. CARBOHYDRATE-BASED BIOPOLYMERS: BIOLOGICALLY ACTIVE POLY[3-(3,4-DIHYDROXYPHENYL)GLYCERIC ACID] FROM MEDICINAL PLANTS OF BORAGINACEAE FAMILY — THE PARADIGM OF A MULTI-TARGET BIOPOLYETHER WITH APPLICATIONS IN CANCER PREVENTION AND TREATMENT

V.Barbakadze, L.Gogilashvili, M.Merlani

Department of Plant Biopolymers and Chemical Modification of Natural Compounds, Tbilisi State Medical University I. Kutateladze Institute of Pharmacochemistry, Tbilisi, Georgia

Corresponding author e-mail: v.barbakadze@tsmu.edu

Water-soluble high-molecular (>1000 kDa) fractions of medicinal plants *Symphytum asperum, S.caucasicum, S.grandiflorum, S.officinale, Anchusa italica, Cynoglossum officinale, Borago officinalis* and *Paracynoglossum imeretinum* (Boraginaceae) were found to be sources of bioactive exotic caffeic acid-derived biopolymer, namely poly[3-(3,4-dihydroxyphenyl)glyceric acid] (PDPGA) that is poly-[oxy-1-carboxy-2-(3,4-dihydroxyphenyl)ethylene] (POCDPE) (Fig. 1). Structure elucidation of PDPGA (POCDPE) was carried out according to data of liquid-state 1H, 13C NMR, APT, 1D NOE, 2D 1H/13C HSQC, 2D DOSY and solid-state 13C NMR spectra of this biopolymer. The assignment of the complete set of resonances signals for POCDPE in the 13C NMR and 1H NMR spectra, based on correlations bet-ween protons and carbon atoms by means of the 2D 1H/13C gHSQCED spectra, was carried out and is listed in Table. The gCOSY spectrum showed a cross peak between the signals at 5.16 and 4.67 ppm, which was consistent with the coupling between H-1 and H-2 of POCDPE. The most carboxyl groups of POCDPE from *A.italica, S.grandiflorum* and *B.officinalis* are methylated (Tab. 1, A, B, C).

Table 1. The signal assignment in the ^{13}C and ^{1}H NMR spectra of POCDPE.

C atom no.	^{13}C chemical shift, δ_C, ppm	^{1}H chemical shift, δ_H, ppm
1'	175.00 (C<u>O</u>O$^-$) 172.00 (C<u>O</u>OCH$_3$) 53.45 (OC<u>H</u>$_3$)	3.8(OC<u>H</u>$_3$)
1	77.48	5.16
2	79.56	4.67
1''	130.71	
2''	116.61	7.16
3''	143.89	
4''	143.00	
5''	117.82	7.06
6''	121.48	7.06

A. POCDPE R=H CH_3,

B. *1R,2R*-POCDPE R=H,CH_3

C. *1S,2S*-POCDPE R=H,CH_3.

The polyoxyethylene chain is the backbone of POCDPE polymeric molecule. Dihydroxyphenyl and carboxyl groups are regular substituents at two carbon atoms in the chain. The hydroxyl groups in positions 3 and 4 of the phenyl ring were unambiguously established. This compound is a representative of a unique class of natural polyethers with a residue of 3-(3,4-dihydroxyphenyl)glyceric acid as the repeating unit. On the other hand POCDPE as a 3,4-dihydroxyphenyl derivative of poly(2,3-glyceric acid ether) also belongs to a rare class of carbohydrate-based biopolymers, namely po-ly(sugar acids). Its basic monomeric moiety, glyceric acid, is a natural three-carbon sugar acid which is an oxidative form of the simplest of all common aldoses, namely glyceraldehyde. In this case poly(2,3-glyceric acid ether) chain constitutes the backbone of this polymeric molecule with 3,4-di-hydroxyphenyl groups as regular substituents in the chain. POCDPE contains two aliphatic chiral car-bon atoms C1 and C2 (Tab. 1, A). As the profiles of the circular dichroism (CD) spectra of POCDPE did not coincide with those of the synthetic enantiomers of the monomers (+)-(2R,3S)-2,3-dihydroxy-3-(3,4-

dihydroxyphenyl)propionic acid and (–)-(2S,3R)-2,3-dihydroxy-3-(3,4-dihydroxyphenyl)propionic acid we excluded the 1R,2S and 1S,2R configurations for chiral atoms C1 and C2 in the repeating unit of POCDPE. Hence, we supposed that C1 and C2 atoms have either 1R,2R (Fig. 2) or 1S,2S (Fig. 3) configurations and consequently the denomination of POCDPE should be either poly[oxy-(1R)-1-carboxy-(2R)-2-(3,4-dihydroxyphenyl)ethylene] (Tab. 1, B) or poly[oxy-(1S)-1-carboxy-(2S)-2-(3,4-dihydroxyphenyl)ethylene] (Tab. 1, C). Ether bonds are found in a wide variety of natural products, mainly secondary metabolites, including lipids, oxiranes, terpenoids, flavonoids, polyketides, and carbohydrate derivatives or aromatic polymer such as lignin. Lignin contains ether links between two aromatic rings or between an aromatic ring and an aliphatic moiety. However, reports concerning biopoly-mers that contain aliphatic ethers as repeating unit were sparse. Within the field of pharmacologi-cally active biopolymers the area of stable polyethers seems rather new and attractive. Natural bio-polymers have been gaining importance since they are already part of living beings, like proteins or polysaccharides, and thus they present higher biocompatibility. Biopolymers may bind to each other, or to phenolics, via either covalent interactions, such as esterification; or non-covalent interactions, such as hydrogen bonds, pi bonds, and electrostatic forces. Both chemical (covalent) or physical (non-covalent) interactions can enhance physicochemical characteristics and therapeutic attributes of phenolics. In POCDPE molecule 3,4-dihydroxyphenyl groups are covalently linked to poly(2,3-glyceric acid ether) chain and contribute therapeutic attributes of phenolics into polymeric molecule. Every repeating structural unit of POCDPE contains three reactive functional groups, two ortho-related phenolic hydroxyl groups and one carboxyl group. Consequently, the polymeric molecule of POCDPE bears many of these functional groups along the polymeric chain. This multifunctionality justifies that POCDPE belongs to several important classes of biopolymers. Moreover, multifunctionality should be a reason of its wide spectrum of biological activities. POCDPE can be promising candidate for many biomedical applications based on their outstanding bioactive characteristics. POCDPE is endowed with intriguing in vitro and in vivo pharmacological properties: anticomplementary, anti-inflammatory, antioxidant, wound-healing and anticancer. POCDPE suppressed the growth and induced death in androgen-dependent (LNCaP) and -independent (22Rv1) human prostate cancer (PCA) cells, with comparatively lesser cytotoxicity towards non-neoplastic human prostate epithelial cells PWR-1E. POCDPE induced apoptotic death by activating caspases, and also strongly decreased androgen receptor and prostate specific antigen (PSA) expression. In 22Rv1 xenograft model male athymic nude mice with 22Rv1 xenografts was administered orally of POCDPE. Plasma analyses revealed that POCDPE administration caused a strong dose-dependent decrease in PSA levels by 87%. Overall, this study identifies POCDPE as a potent agent against PCA without any toxicity.

OP 4. ANTIBODY-GUIDED ACTIVATABLE PHOTODYNAMIC THERAPY

Ebaston Thankarajan[1], Helena Tuchinsky[2], Andrii Bazylevich[1], Leonid Patsenker[1]

[1] Department of Chemical Sciences, the Faculty of Natural Sciences, Ariel University, [2] Department of Molecular Biology, the Faculty of Natural Sciences, Ariel University, Ariel, Israel,

Corresponding author e-mail: leonidpa@ariel.ac.il

Photodynamic therapy (PDT) utilizing an organic dye (photosensitizer) capable of killing cancer cells in the body upon light irradiation is one of the promising non-invasive treatment modalities for many cancers. A known drawback of PDT is a side-effect caused by existing photosensitizers to organs due to insufficient specificity and accidental light exposure of a patient during the delivery of the photosensitizer in the bloodstream.

To overcome this issue, we developed a novel antibody-guided, activatable photosensitizing system, **Ab-mI$_2$XCy-Ac**, where the trastuzumab (Ab) is linked to the non-active (not phototoxic and not fluorescent) dye, **mI$_2$XCy-Ac**, that contains the triggering hydroxyl group protected by acetyl (**Ac**). This targeting, non-photoactive conjugate was shown to be safely (without detectable side-effects) delivered to the targeted tumor, where it is activated by the esterase-mediated acetyl group cleavage and effectively treats the tumor upon NIR light irradiation (Fig.1). It was demonstrated in the Her2 positive BT-474 tumor mouse model that the treatment efficacy of the activatable photosensitizing system is about the same as for the permanently active photosensitizer, **Ab-mI$_2$XCy**, while the side-effects are noticeably reduced.

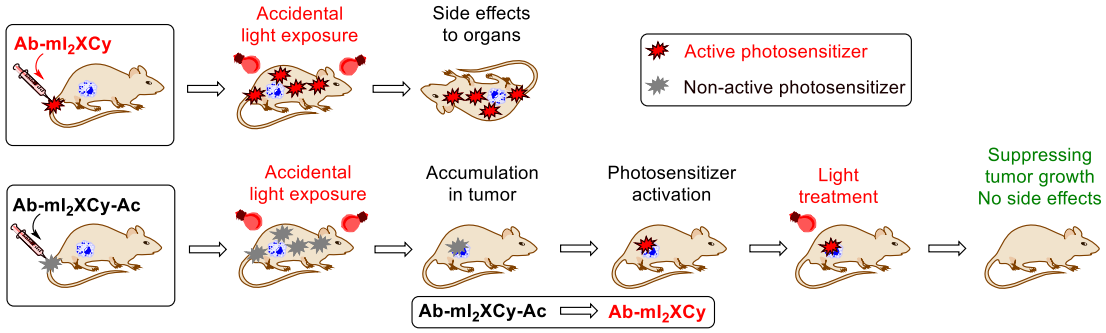


Fig.1. Activation principle of the activatable **Ab-mI$_2$XCy-Ac** photosensitizing system (*A*) and functioning principle of activatable **(Ab-mI$_2$XCy-Ac)** *vs.* non-activatable **(Ab-mI$_2$XCy)** photosensitizers (*B*)

In addition, this activatable system enables near-IR fluorescence monitoring of the photosensitizer activation events. In particular, it provides a way to verify accumulation and activation of the photosensitizer in the tumor and ensure absence of the photosensitizer in the non-treated organs prior to the therapeutic light irradiation.

Thereby, the developed activatable photosensitizer demonstrates a promising approach for designing novel, highly efficient systems for safer photodynamic therapy of different types of cancer. We believe that activatable **mI$_2$XCy-Ac** photosensitizer can be linked to other monoclonal antibodies for broad implementation in targeted anticancer near-**IR PDT**. We hope that the results presented in this work will pave a way for the utilization of antibody-guided activatable photosensitizers to protect patients from accidental light exposure after drug administering.

OP 5. SYNTHESIS AND PHARMACOLOGICAL ACTIVITY OF NITROGEN-CONTAINING 5α-STEROIDS

N. Barbakadze, N. Nadaraia, M. Kakhabrishvili

Tbilisi State Medical University I. Kutateladze Institute of Pharmacochemistry

Corresponding author e-mail: n.barbakadze@tsmu.edu

Steroids, a family of regulatory molecules created throughout the evolution process of living organisms, occupy a distinctive place among the countless natural chemicals. They are widely used in medical practice due to an important function in the physiological and biochemical processes that occur in a live organism.

The investigation of synthetic inhibitors' pharmacological effects on oncological and infectious disease is the ground for the chemical synthesis and rational design of new bioactive molecules.
The creation of new synthetic nitrogen-containing steroid derivatives is now underway. Most of these substances – steroidal amines, oxymes, hydrazones, pyrazolines, pyrazoles, triazoles, exhibit high anti-Alzheimer, antiparkinsonian, antiarrhythmic, antiviral, antimicrobial, antituberculous, cytotoxic, anti-proliferative activities, which are a prerequisite for the creation of new drugs. In order to obtain highly potent pharmacological agents, new schemes of chemical synthesis nitrogen-containing derivatives of steroid are being developed, existing ones are being refined, their structure and biological activity are being studied.

In this regard, the raw material for the synthesis of 5α-steroids, tigogenin, provided by the TSMU Institute of Pharmacochemistry, is important. It is separated from plant *Yucca gloriosa* introduced in Georgia. By modification of its conversion products - pregnenolone and epiandrosterone, we have synthesized a number of amines, oxymes, hydrazones and their numerous derivatives. Among them compounds with fungicidal, antibacterial, anti-inflammatory and antiviral activities have been discovered [1-4].

Nitrogen-containing heterocycles condensed with the steroidal nucleus are also attracting the attention of researchers. It has been established that steroidal azoles are capable to inhibit some enzymes associated with various types of cancer, hence they are considered promising anti-tumor compounds.

We synthesized pyrazolines and triazoles from tigogenin-derived steroidal ketones. Some of these compounds exhibited significant antiviral, antimicrobial, cytotoxic and antitumor activity [3-6].

References

[1] Nadaraia, NSh. Amiranashvili, LSh. Merlani, MI. 2016, Structure-activity relationship of epimeric 3,17-substituted 5α-androstane aminoalcohols, Chemistry of Natural Compounds, vol. 52, no. 5, pp. 961-962.
[2] Sikharulidze, MI. Nadaraia, NSh. Kakhabrishvili, ML. et al. 2010, Synthesis and biological activity of several steroidal oximes, Chemistry of Natural Compounds, vol. 46, no. 3, pp. 493-494.
[3] Nadaraia, NSh. Barbakadze, NN. Kakhabrishvili, ML. et al. 2018, Synthesis and biological activity of several modified 5α-androstanolone derivatives, Chemistry of Natural Compounds, vol. 54, no. 2, 310-314.
[4] Nadaraia, NSh. Amiranashvili, LSh. M. Merlani, MI. et al. 2019, Novel antimicrobial agents' discovery among the steroid derivatives, Steroids, vol. 144, pp. 52-65.
[5] Nadaraia, N.Sh. Kakhabrishvili, ML. Barbakadze, NN. Et. Al. 2018, Synthesis and biological activity of steroidal tigogenin hydrazones and pyrazolines, Chemistry of Natural Compounds, vol. 54, no. 5, pp. 926-929.
[6] Eerlings, R. Barbakadze, N. Nguyen, T.et al. 2022, Small-molecule profiling for steroid receptor activity using a universal steroid receptor reporter assay, Journal of Steroid Biochemistry and Molecular Biology, 217, 106043.

OP 6. STUDY OF SOME PLANTS CULTIVATED IN GEORGIA ON THE CONTENT OF LIPIDS AND ACCOMPANYING BIOLOGICALLY ACTIVE SUBSTANCES

B. Kikalishvili

Tbilisi State Medical University I. Kutateladze Institute of Pharmacochemistry, Tbilisi, Georgia

Corresponding author e-mail: b.kikalishvili@tsmu.edu

Pumpkin (*Cucurbita maxima duch*., Fam. *Cucurbitaceae* and European hazelnut (*Corylus avellana L.(imeretica),* Fam. *Betulaceae*) vegetate in terms of moderate climate. The oil extracted from the plant seeds and fruits contain various biologically active compounds of different classes, carotenoids, phytosterols, flavonoids, vitamins A, E, C, B, fatty acids, micro-elements K, Ca, Se, Mg, Fe, Zn, Cu, P; they are rich in vegetable proteins (up to 40%), essential amino acids. They have versatile pharmacological activities: hepatoprotective, antioxidant, cytotoxic, and antidepressant, and are recommended in the complex treatment of hypertension, atherosclerosis, prostate adenoma, ischemic heart disease, varicose veins, thrombophlebitis, arrhythmia, stroke and heart attack; it helps the healing of ulcers, wounds, and burns, and is efficient to use in preventing diabetes, rheumatism and oncological diseases. These vegetable oils are widely used in cosmetology and dermatology.

N-Hexane extraction was used to obtain the total neutral lipids (NL) of a yellow color and oily consistency with the yield of 40% and 60%, respectively, from young pumpkin and European hazelnut seeds growing in West Georgia. The physical and chemical indices of the above-mentioned oils are given in Table 1.

Table 1.

N	Physical-chemical indicators	*Cucurbita maxima duch.*	*Corylus avellana*
1	Refraction index	1,471	1,460
2	Density	0,910	0,940
3	Acid value (KOH)	0,7	1,1
4	Iodine value	106	108
5	Saponification number	191	200

Color reactions, R_f values and tracking standards were used to identify the following classes in the sum of neutral lipids: hydrocarbons, triglycerides, fatty acids, and sterins.

High-performance liquid chromatography was used to identify the following fatty acids: in *C. maxima* duch. oil: dodecane 0.2%, tetradecane 0.3%, octadecane 5.5%, hexadecane 9.07%, 9-octadecane 28.1%, 9.12, octadecadiene 40.2%, octadecantriene 12.1%, eicosane 2.0%, docasane 1.2%, and in *C. avellana* oil: dodecane 0.10%, tetradecane 0.10%, hexadecane 5.1%, octadecane 1.65%, 9-octadecane 80.61%, 9.12, octadecadiene 14.28%, 9,12,15-octadecantriene 0.12%, eicosane 0.18%, docasane 0.10%, and tetracosane 0.11%.

The carotenoids content in total NLs in studied objects were 2.8 mg% and 1.1 mg%, respectively, and that of vitamin C was 0.11% and 0.16%, respectively.

The following amino acids were found in pumpkin and European hazelnut seeds: phenylalanine, methionine, alanine, serine, asparagine, lysine, histidine, proline, glycine, cysteine, valine.

Total polar lipids with the yield of 3.2% for pumpkin seeds and 1.2% for European hazelnut seeds were obtained from the extraction waste after the obtaining of NLs.

The following substances were identified and quantified in the sums of polar lipids: in pumpkin seeds: lysophosphatidylcholine-6.85% phosphatidylinositol 17.0%, phosphatidylcholine-46.5%, phosphatidylethanolamine-10.6%, N-acylisophosphatidylethanolamine-9.6%, and N-acylphosphatidylethanolamine-9.13%, and in hazelnut: lysophosphatidylcholine-5.4%,

lysophosphatidylethanolamine-12.2%, phosphatidylcholine-39.6%, phosphatidylethanolamine-27.6%, and N-acylphosphatidylethanolamine- 3.12%.

The characteristics of vegetable lipids derived from the study objects encourage the creation of inexpensive and effective therapeutic and prophylactic remedies which may be used in medicine and perfumery on the basis of local raw materials.

Reference

[1] B. Kikalishvili, D. Zurabashvili, D. Turabelidze, J. Aneli, L. Shanidze . Georgian Medical NEWS. 2014 N9 (234). pp.138- 141. Content of fatty acids in pumpkin seed oil (Cucurbitae Maxima Duch), cultivated in Georgia.
[2] B. Kikalishvili, N. Gorgaslidze, D. Zurabashvili, Ts. Sulakvelidze, M. Malania, D. Turabelidze. Georgian Medical News 2017, №5 (226) pp.74-79. A study of the lipids of the fruits of European hazelnut (Corylus avellana L) growing in Georgia.
[3] British Pharmacopoeia, vol. V; London: The Stationery Office. 2017, pp. 202-203.

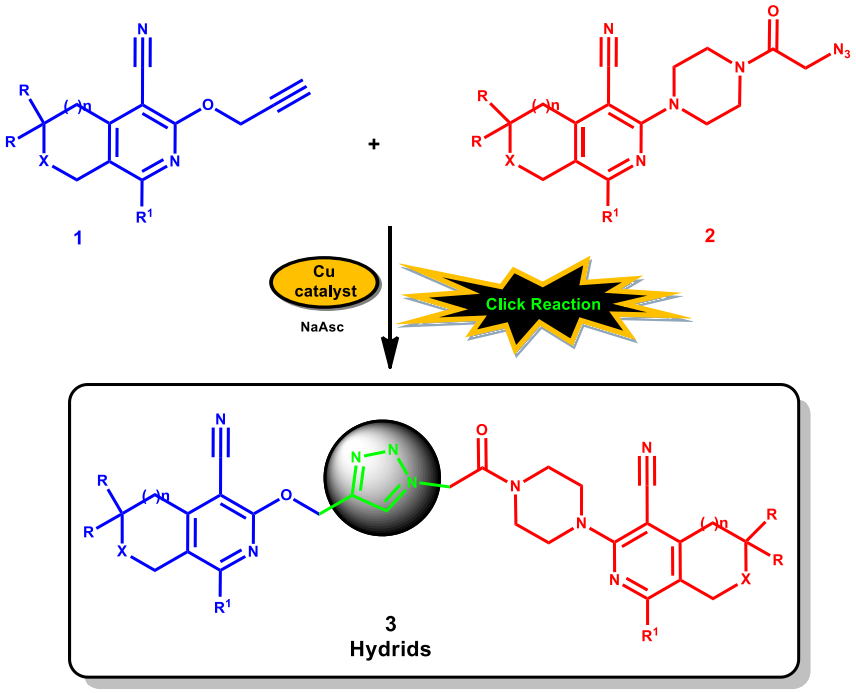
OP 7. SYNTHESIS OF HYBRID COMPOUNDS LINKED TO 1,2,3- OR 1,2,4-TRIAZOLE RING AND THEIR ANTICONVULSANT ACTIVITY

Sirakanyan S.N.[1], Hovakimyan A.A.[1], Geronikaki A.[2], Hakobyan E.K.[1], Yegoryan H.A.[1]

[1]Scientific Technological Center of Organic and Pharmaceutical Chemistry of National Academy of Science of RA, Yerevan, Armenia; [2]Department of Pharmaceutical Chemistry, School of Pharmacy, Aristotle University, Thessaloniki, Greece

Corresponding author e-mail: aaa.h.87@mail.ru

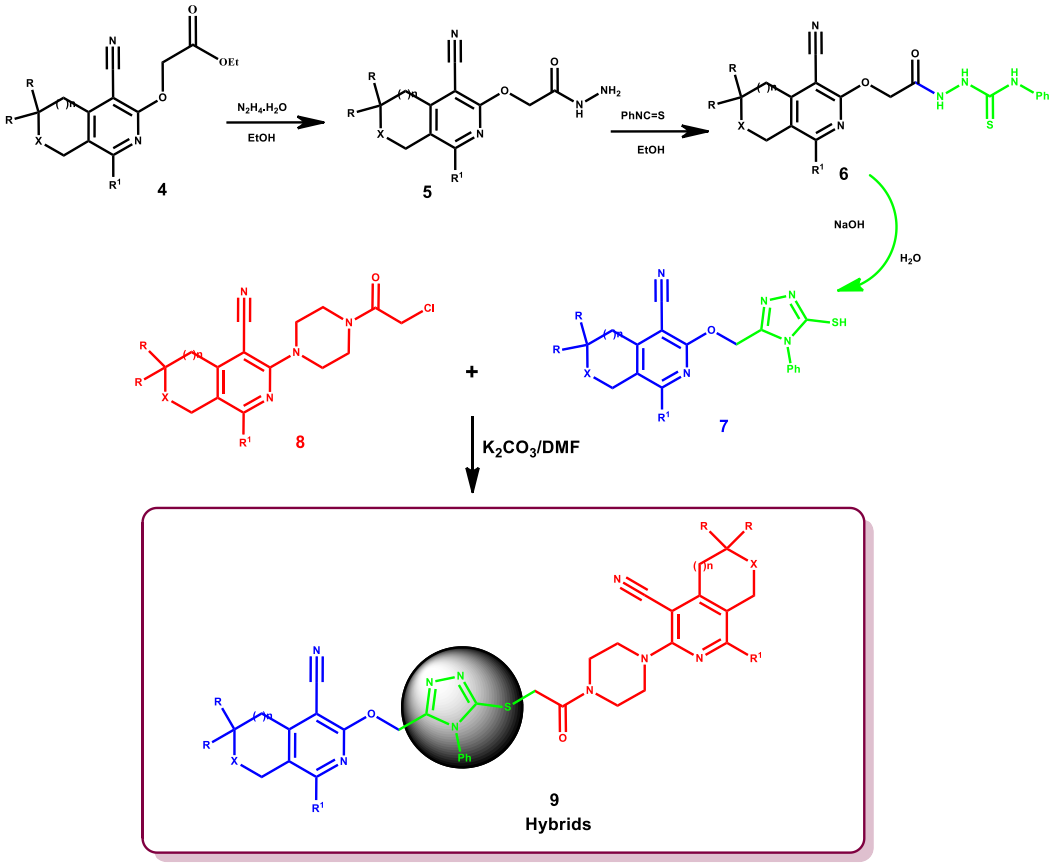
Among the nitrogen containing heterocycles the triazole ring is an important moiety and has received considerable attention in the design and synthesis of bioactive compounds. There are numerous papers on the pharmacological profiles of triazoles indicating that their derivatives represent interesting substrates in medicinal and pharmaceutical chemistry [1, 2]. In this study, a new class of 1,2,3- and 1,2,4-triazole linked hybrid compounds was synthesized. A click synthesis: Cu-catalyzed azide-alkyne cycloaddition (CuAAC) reaction, was used to afford 1,2,3-triazoles according to Scheme 1 [3].



1–**3**. X = CH_2, O; n = 0, 1; R = H, Me; R^1 = alkyl, aryl.

Scheme 1. Synthesis of disubstituted 1,2,3-triazoles 3.

From a biological point of view, it is interesting to synthesize similar hybrids linked by 1,2,4-triazole ring. For this purpose, a special methodology was developed by us. Thus, by the short refluxing of compounds **4** with hydrazine hydrate in ethanol the relevant acetohydrazides **5** were obtained. The reaction of the latter with phenyl thiocyanate led to the formation of compounds **6**, which further were cyclized under the action of sodium hydroxide to the aimed 5-mercapto-4-phenyl-4*H*-1,2,4-triazoles **7**. Further, the synthesized triazoles **7** were alkylated with different alkyl halides **8** under basic conditions thus obtaining 1,2,4-triazoles **9** (Scheme 2).



4–**9**. X = CH_2, O; n = 0, 1; R = H, Me; R^1 = alkyl, aryl.

Scheme 2. Synthesis of disubstituted 1,2,4-triazoles 9.

Preliminary biological studies have shown that these hybrids **3** and **9** exhibit pronounced anticonvulsant activity.

The work was supported by the Science Committee of RA, in the frames of the research project № 20TTWS-1D009.

References

[1] Agalave, SG.; Maujan, SR.; Pore, V.S. 2011, Click chemistry: 1,2,3-triazoles as pharmacophores, *Chem. Asian J.*, vol. 6, no. 10, pp. 2696-2718.

[2] Maddila, S.; Pagadala, R.; Jonnalagadda, SB. 2013, 1,2,4-Triazoles: A review of synthetic approaches and the biological activity, *Lett. Org. Chem.,* vol. 10, no. 10, pp. 693-714.

[3] Sirakanyan, SN.; Ghochikyan, TV.; Spinelli, D.; Galstyan, AS.; Geronikaki, A.; Samvelyan, MA.; Hakobyan, EK.; Hovakimyan, AA. 2022, Synthesis of novel 1,2,3-triazole-based hybrids *via* click reaction, *Arkivoc,* part ii, pp. 7-21.

OP 8. DEVELOPMENT OF METHODS OF SEPARATION AND ANALYSIS OF SOME PLANTS GROWING IN GEORGIA

M. Getia, G. Moshiashvili

Tbilisi State Medical University I. Kutateladze Institute of Pharmacochemistry, Dept.of Pharmaceutical Analysis and Standardization. Tbilisi, Georgia,

Corresponding author e-mail: m.getia@tsmu.edu

The methods of analysis of biologically active extracts and enriched fractions of plant origin are steadily evolving, with new techniques and approaches proposed and developed every year. Their separation efficiency and selectivity are of paramount importance.

Improvement of analytical methods of well-defined model mixtures is very important because, they sometimes do not describe convince in respect to practical use and applicability.

At the department of pharmaceutical analysis and standardization of TSMU I.K. Institute of Pharmacochemistry, using the different techniques of chromatographic analysis (GC-MS, LC-MS, LC-prep.) various chemical groups were characterized: Essential oils, free fatty acids, Polypenolic compounds, alkaloids, Cyclooctanes and terpene glycosides [1-18].

This presents the role of various analytical techniques and their corresponding analytical methods in the analysis of biological active extracts and enriched fractions derived from the species growing or cultivated in Georgia: *Prunus domestica* L., *Armeniaca vulgaris* Lam., *Cichorium intibus* L., *Sambucus nigra* L., *Sambucus ebulus* L., *Juglans* regia L., *Laurus nobilis* L., *Zea mays* L., *Vitis vinifera* L., *Triticum sp*., *Eriobotrya japonica* Lindl., *Persica vulgaris* Mill., *Humulus lupulus* L., *Thymus tiflisiensis* Klokov & Des.-Shost., *Thymus collinus* M.Bieb., *Salvia verticillate* L., *Salvia glutinosa* L., *Salvia sclarea* L., *Rosa* x *gallica* L., *Rosa* x *damascene* Mill., *Astragalus falcatus* Lam., *Pueraria hirsute* (Thunb.) Matsum., *Senecio vernalis* Waldst. & Kit., *Yucca gloriosa* L., *Daphne glomerata* Lam., *Daphne pontica* L., *Rhododendron ungernii* Trautv., *Rhododendron ponticum* L., *Ononis arvensis* L., *Anchusa italica* Retz., *Symhytum asperum* Lepech., *Aconitum orientale* Mill., *Aconitum nasutum* Fisch. ex Reichenb., *Vinca herbacea* Waldst. & Kit., *Vinca minor* L., *Peganum harmala* L., *Chelidonium majus* L., *Mahonia aquifolium* Nutss., *Delphinium flexuosum* Bieb., *Teucrium nuchense* K.Koch) Rech.f., *Hypericum perforatum* L., *Ruscus colchicus* L., *Cupressus sempervirens* L., *Equisetum arvense* L., *Borago officinalis* L.

The use of modern, simple, and reproducible analytical methods for their detection and determination of quality is a step forward in modern pharmacy.

References

[1] Kikalishvili B., Sulakvelidze Ts., Getia M., Malania M., Turabelidze D., Study of Lipids and Some Biologically Active Compounds from theSeeds of Apricot Growing in Georgia. Acta Scientific Pharmacology, 2021, 2,9. p. 24-27

[2] Kikalishvili B., Sulakvelidze Ts., Malania M., Getia M. Turabelidze D. Characterization of fatty acids in some plants growing in Georgia. International Journal of Pharmacognosy and Phytochemistry, 2020; 9(5): 1331-1333; https://www.phytojournal.com/archives/2020/vol9issue5/PartS/9-5-150-321.pdf

[3] KIKALISHVILI BELA, TS. SULAKVELIDZE, GETIA M., MALANIA M., TURABELIDZE D. STUDY OF LIPIDS AND SOME BIOLOGICALLY ACTIVE COMPOUNDS OF THE FLOWERS SAMBUCUS NIGRAGROWING IN GEORGIA. Experimental andclinical Medicine, 2022. vol.1. DOI: https://doi.org/10.52340/jecm.2022.716

[4] Kikalishvili B., Sulakvelidze TS., Getia M., Malania M., Turabelidze D. Study of lipids and some biologically active compounds of Sambucus ebulus L. spread in Georgia, Journal of Pharmacognosy and Phytochemistry; 2022, 11(4): 33-35

[5] Kikalishvili B., Sulakvelidze Ts., Malania M., Getia M., Turabelidze D. Study of Lipids from Fruits of Some Plants Growing in Georgia. International Journal of Pharmacy and Pharmaceutical Research, 2020 Vol.:19, Issue:4. P. 502-508

[6] Kikalishvili B., Sulakvelidze Ts., Malania M., Getia M., Turabelidze D. STUDY OF LIPIDS AND SOME BIOLOGICAL COMPOUNDS OF VITIS VINIFERA AND TRITICUM SP.GROWING IN GEORGIA, International Journal of Pharmacy and Pharmaceutical Research, 2020 Vol.:19, Issue:4. P. 502-508.

[7] Gorgaslidze N., Kikalishvili B., Sulakvelidze Ts., Malania M., Turabelidze D. The lipid composition of some plants growing in Georgia. 6th International Conference and Exhibition on Materials Science and Chemistry. May 17-18, 2018 | Rome, Italy

[8] Kikalishvili B., Sulakvelidze Ts., Getia M., Malania M., Turabelidze D., Study of Lipid Constituent of the Cones of Humulus lupulus Growing in Georgia, International Journal of Pharmacy and Pharmaceutical Research. 2020 Vol.:20, Issue:1, p. 122-126

[9] Moshiashvili G., Pichette A., Legault J., Mshvildadze V. Chemical Composition and Cytotoxic Activity of Daphne glomerata and D. Pontica. Chemistry of Natural Compounds volume 58, pages329–331

[10] Getia M., Korkotadze T., Moshiashvili G., Tabatadze N., Legault J., Mshvildadze V. Study of the composition and cytotoxicity of essential oils of the aerial parts of Thymus tiflisiensis and Thymus collinus growing in Georgia. Chemistry of Natural Compounds, 2022, (5). *In press*

[11] Korkotadze T., Berashvili D., Mshvildadze V., Getia M., Bakuridze A. GENUS SALVIA L. STUDY OFSOME SPECIES, GROWING IN GEORGIA, CHEMICAL COMPOSITION AND ANTIOXIDANT ACTIVITY EXPERIMENTAL & CLINICAL MEDICINE GEORGIA, NO.1 (2021): ISSUE 5-6

[12] Puladze M., Mulkijanyan K., Gogitidze N., Sulakvelidze M., Novikova Zh., Mushkiashvili N., Getia M., Frédérich M., Mickalad A.M., Franck Th., Mskhiladze L. Phytochemical and pharmacological studyof Rosaxgallica L. Georgian cultivar essential oil productionwaste GSC Biological and Pharmaceutical Sciences, 2022, 19(03), 213-222

[13] Aleksidze N., Mchedlidze K., Getia M., Mulkijanyan K., Frédérich M., Mskhiladze L., Pharmacognostic, phytochemical and pharmacological aspects of Rosa x damascena Herrm. Georgian cultivar, GSC Biological and Pharmaceutical Sciences, 2021, 16(01), 001-010.

[14] Alania M., Sutiashvili M., Skhirtladze A., Getia M. CHEMICAL COMPONENTS FROM STEMS ASTRAGALUSFALCATUS, GROWING IN GEORGIA. Georgian Medical News, 2021, (312):180-183

[15] Alaniya M. D., Sutiashvili M. G., Skhirtladze A. V., Getiya M. Z. Cycloartane Glycosides from Astragalus falcatus of the Flora of Georgia. Chemistry of Natural Compounds, 2021,Vol. 57, p.887–890

[16] Kavtaradze N. Sh., Alaniya M. D., Getia M. Z., Gogitidze N. M., Mushkiashvili N. I., Mulkijanyan K. G., Mskhiladze L. V., Kemertelidze E. P. Isoflavonoids from Roots of Pueraria hirsuta Distributed in Georgia and their Hepatoprotective Activity. Chemistryof Natural Compounds, 2022 Vol.58, p. 27–31

[17] Getia M., Korinteli T., Vachnadze N. Study of alkaloids of Senecio vernalis grown in Georgia, International Scientific Conference “Green Medications – By Green Technologies – For Healthy Life”, 27-28 September, 2019, Tbilisi, Georgia

[18] Benidze M. M., Skhirtladze A. V., Getia M. Z., Kemertelidze E. P. Chemical Constituents of Yuccagloriosa Flowers. Chemistry of Natural Compounds, 2022. Vol.58, No.1, January

OP 9. NEW CHEMICAL COMPONENTS OF YUCCA GLORIOSAL.FLOWERS

M. Benidze, M.Getia, E. Kemertelidze

[1] Tbilisi State Medical University I. Kutateladze Institute of Pharmacochemistry, Tbilisi, Georgia

Corresponding author e-mail: m.benidze@tsmu.edu

The chemical composition of *Yucca gloriosa* L. has been subject of our research for many years. The steroidal sapogenin- tigogenin from the plant leaves was recognized as an economical raw material for synthesizing steroidal hormone preparations. Plantations of Yucca gloriosa were cultivated in Eastern Georgia on an area of 150 ha to ensure a supply of tigogenin from plant raw material. Seventy compounds of various chemical classes, including 22 new compounds, were isolated and identified from vegetative organs of *Y. gloriosa*. The proposed fungicidal preparation "Gloriofucin" that consisted mainly of spirostanol glycosides was prepared from the total glycosides of dried leaves on the lower tier of the living plant [1].

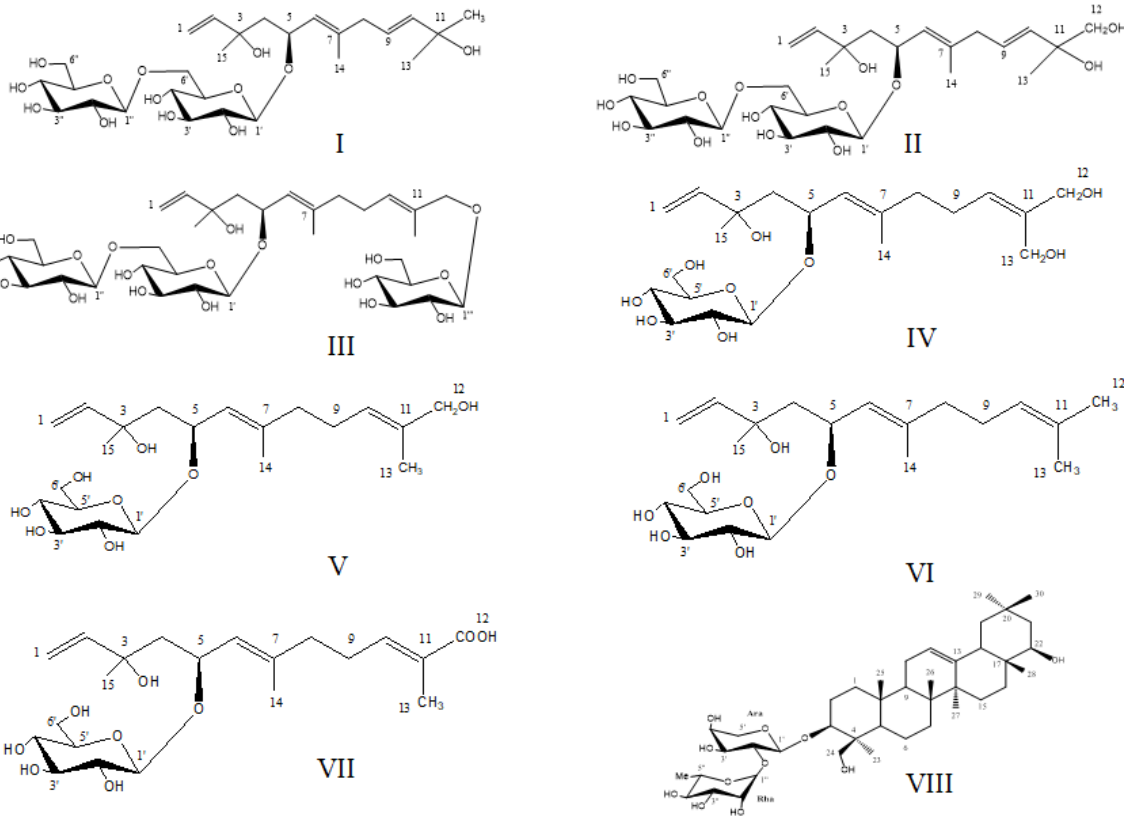
Yucca flowers abundantly twice per year, in spring and in autumn, developing one inflorescence in the first year and then 3-4 inflorescences. The flowering period lasts 20-25 day, after which the flowers dry and fall as unused waste. The effective growth and development stimulator for agricultural crops "Aleksin" was developed from total steroidal glycosides of flowers. Pre-sowing seed treatment or spraying of saplings with low concentration of aqueous solutions of Aleksin produce 20-30% increases in the yields of some agricultural crop capacity.

Recently, six spirostanol, two furostanol glycosides, three flavonoids and three phenolic carboxylic acids were isolated and identified from the flowers [1].

In continuation of study of the chemical composition of *Y. gloriosa* flowers they were extracted with 70% MeOH.The organic extract was removed in vacuo and the aqueous liquid was purified of lipophilic substances by $CHCL_3$. Purified aqueous phase was eluted on a Diaion HP-20 column with 60% and 80% MeOH. MeOH eluates were applied to Sephadex LH-20 and Silicagel columns chromatographyration. Using HPLC there were isolated 7 (1-7) sesquiterpene and 1 (8) triterpene glycosides. Chemical structures of the compounds were established by physical-chemical data and modern spectral methods of analysis such as one- and two-dimensional NMR (^1H,^{13}C, HSQC, HMBC, COSY) and mass-spectrometry (ESI-MS). Spectral data were indicative sesquiterpene glycosides of nerolidol-type [2] and triterpene glycoside derivative of soyasapogenol B [3].

Isolated glycosides were characterized as:

1. (1E,3S,5R,6E,9E)-5-O-β-DGlcp(1→6)-O-β-D–Glcp-3,5,11-trihydroxy-3,7,11-trimethyldodeca -1,6,9-triene.
2. (1E,3S,5R,6E,9E)-5-O-β-D-Glcp(1→6)-O-β-D–Glcp-3,5,11,12-tetrahydroxy-3,7,11-trimethyldodeca-1,6,9-triene.
3. (1E,3S,5R,6E,10E)-(12-O-β-D –Glcp)-5-O-β-D-Glcp-(1→6)-O-β-D- Glcp- 3,5,12-trihydroxy-3,7,11-trimethyldodeca-1,6,10-triene.
4. (1E,3S,5R,6E,10E)-5-O-β-D- Glcp-3,5,12,13-tetrahydroxy-3,7-dimethyldodeca – 1,6,10-triene.
5. (1E,3S,5R,6E,10E)-5-O-β-D-Glcp-3,5,12-trihydroxy-3,7,13-trimethyldodeca-1,6,10- triene.
6. (1E,3S,5R,6E,10E)-5-O-β-D–Glcp-3,5-dihydroxy-3,7,12,13-tetramethyldodeca-1,6,10-triene.
7. (1E,3S,5R,6E,10E)-5-O-β-D-Glcp-3,5-dihydroxy-12-carbonyl-3,7,13-trimethyldodeca -1,6,10-triene.
8. Soyasapogenol B – 3-O -α-L-rhamnopyranosyl-(1→2)-O-α-L-arabinopyranoside.



All of them are new compounds and new class for the genus *Yucca*.

References

[1] Kemertelidze E.P.,Benidze M.M., Skhirtladze A.V., et al. 2018. Synthesis of steroidal hormonal preparations from tigogenin of Yucca gloriosa L. introduced in Georgia and study chemical composition of the plant. Georgian National Academy of Sciences, Tbilisi, , 230p. (in Russian)

[2] Yang M.C., Kim S.M., Lee K.H., Kim K.H., Lee K.R. 2007. A new sesquiterpene glycoside from the aerial parts of Saussurea triangulate. Molecules, vol.12, no.10, p. 2270 -2276.

[3] Kemertelidze E.P., Skhitladze A.V., Ganzera M. 2017. Steroidal and triterpenoid glycosides from roots of Digitalis ciliata. Chemistry of Natural Compounds, vol. 53, no. 3, p. 492 – 496.

OP 10. OLIGOMER ANALOGUES OF BIOPOLYMERS FROM COMFREY AND OTHER SPECIES OF THE BORAGINACEAE FAMILY: SYNTHESIS AND BIOLOGICAL ACTIVITY

M. Merlani[1], D. M. Scheibel[2], I. Gitsov[2], L. Amiranashvili[1]

[1] Tbilisi State Medical University I. Kutateladze Institute of Pharmacochemistry, Tbilisi, Georgia; [2]Department of Chemistry, ESF, State University of New York, Syracuse, USA;

Corresponding author email: m.merlani@tsmu.edu

Synthetic approach to the synthesis of oligomer analogues of natural biopolymers **1** and **2** (Fig.1), isolated from high molecular fractions (HMF) of the roots and stems of different species of Boraginaceae family: *Symphytum officinale* (SO), *Symphytum asperum* (SA), *Symphytum caucasicum* (SC), *Symphytum grandiflorum* (SG), *A. italica* (AI), *Cynoglossum officinale* (CO), and *Borago officinalis* (BO), involves classical cationic and enzymatic polymerization.

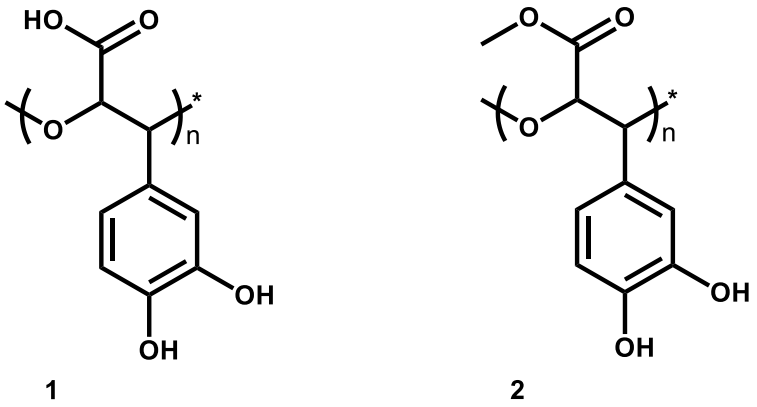
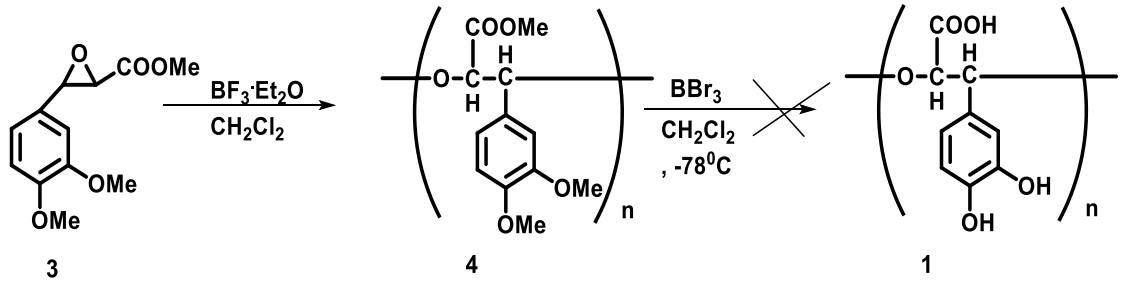


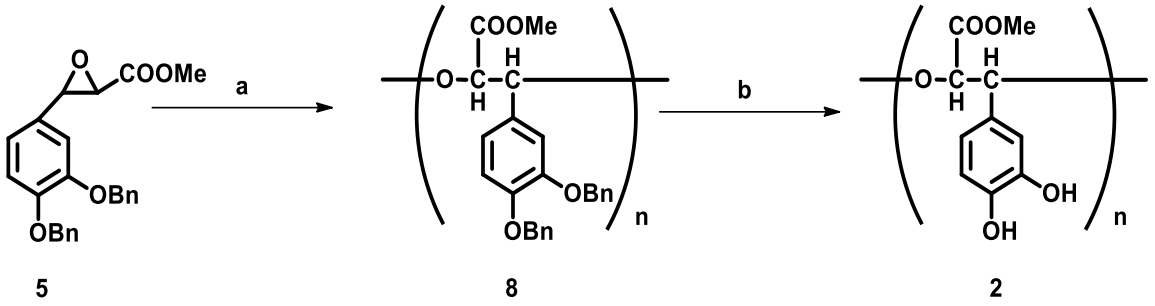
Figure 1. Poly[3-(3,4-dihydroxyphenyl)glyceric acid] (PDHPGA) 1 and poly[2-methoxycarbonyl-3(3,4-dihydroxyphenyl)-oxyrane] (PMDHPO) 2



Scheme 1. Cationic ring opening polymerization of MDMPO

Attempts to provide enzymatic polymerization of synthesized 2-methoxycarbonyl-3-(3,4-dibenzyloxyphenyl)-oxirane (MDBPO) 5, 2-benzyloxycarbonyl-3-(3,4-dibenzyloxyphenyl)oxirane (BDBPO) 6, 2-t-butyloxycarbonyl-3-(3,4-dibenzyloxyphenyl)oxirane (TBDBPO) 7 under mild and more environmentally-friendly conditions using lipases from three different sources - Candida rugosa (C. rugosa), porcine pancreatic PPL-II and Penicillium camemberti (P. camemberti) leads to formation of oligomer analogues of PDHPGA just in case of MDBPO 5. It was found that lipase from C. rugosa was the most efficient in inducing the ring-opening polymerization of MDBPO. The reactions with BDBPO and TBDBPO did not show any trace of polymer, most probably due to the steric hindrance by the

benzyloxy- and t-butyloxy groups. Catalytic debenzylation of PMDBPO 8 using H2 on Pd/C yielded the synthetic analogue of PMDHPO 2 at 80% yield and without loss in molecular mass (Scheme 2).



5 8 2

Scheme 2. Enzymatic polymerization of MDBPO and modification of the polymer: (a) *C. rugosa* lipase, toluene, 80 °C, 7 days; (b) Pd/C, H_2, THF/EtOH.

Antibacterial assessment of natural polyethers from different species of Boraginaceae family: SO, SA, SC, SG, AI, CO, BO and synthetic polymer PMDHPO, reveals that only the synthetic analogue PMDHPO **2** exhibits a promising antimicrobial activity against pathogenic strains *S.aureus* ATCC 25923 and *E.coli* ATCC 25922 the minimum inhibitory concentration (MIC) of 100 μg/mL (Table 1)

Table 1. Antibacterial activity reported in terms of MIC against bacterial strains grown as planktonic cell cultivation on MHB.

Strains	PMDHPO MIC (μg/mL)
S. aureus ATCC 25923	100
E. coli ATCC 25922	100
P. aeruginosa ATCC 15442	No Activity
E. faecalis ATCC 29212	No Activity

OP 11 PHARMACOLOGICAL SCREENING OF NATURAL COMPOUNDS: RESULTS AND CHALLENGES

Karen Mulkijanyan

Tbilisi State Medical University I. Kutateladze Institute of Pharmacochemistry, Tbilisi, Georgia

Corresponding author e-mail: k.mulkijanyani@tsmu.edu

For ages, medications have been discovered by the random testing of natural products (mostly from plant parts) on humans. Later drug candidates from natural sources have been firstly assessed on animals and then in humans, and this process of screening compounds in biological systems is known under the term phenotypic or physiological screening. Here we report the generalized results of our studies on preliminary pharmacological efficacy of natural products and compounds from plant and mineral sources obtained at the Institute of Pharmacochemistry that were carried out during past decades.

In total, up 350 samples of plant secondary metabolites were screened for pharmacological activity. The generalized data of the study is represented in Fig.1 and Fig.2.

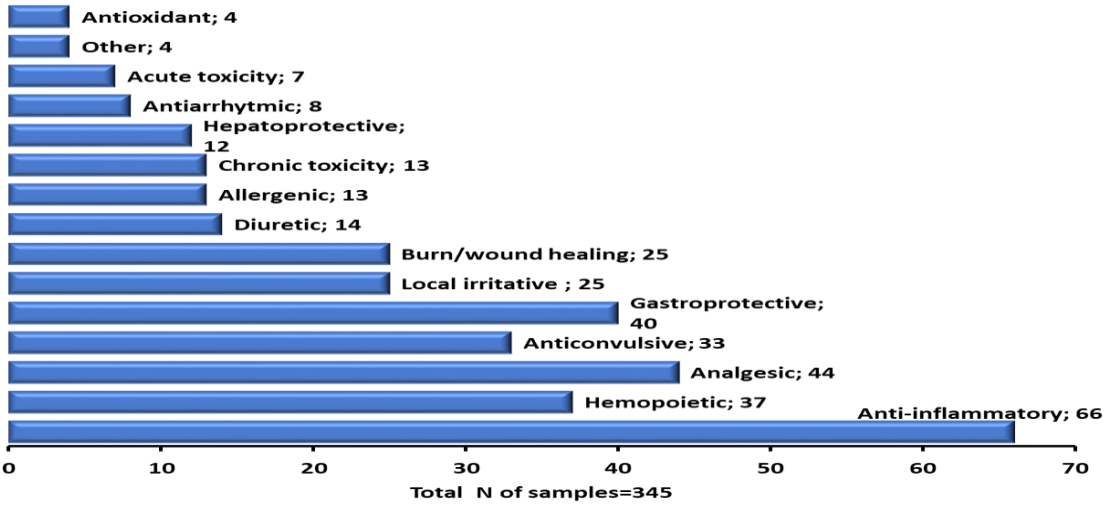


Fig.1. Activity targeted screening of natural products/compounds obtained at the Institute of Pharmacochemistry

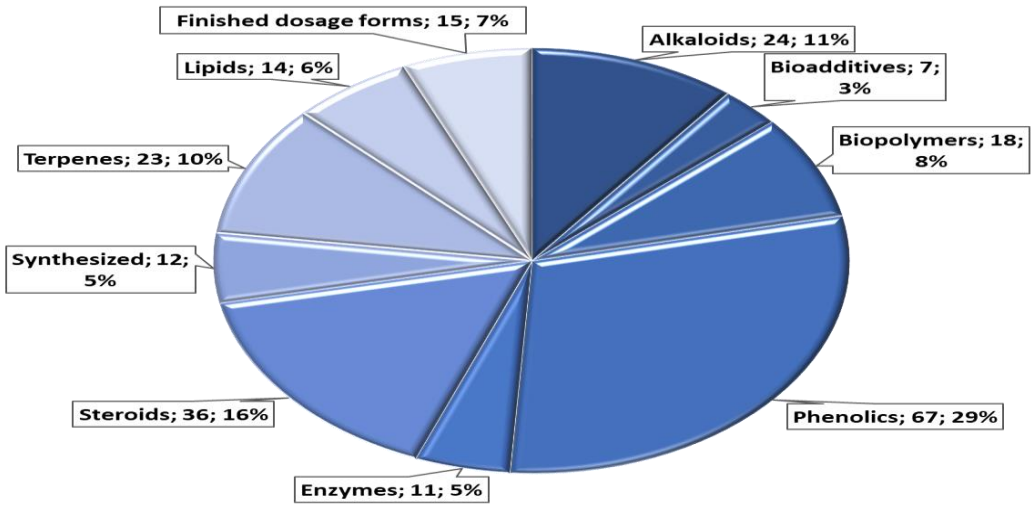


Fig.2. Major groups of products subjected to activity targeted screening.

As mentioned above, *in vivo* trials are most commonly used to evaluate medication effectiveness, major pharmacokinetic characteristics, and one of the most significant parameters in the drug development process - preclinical toxicity, which entails the use of a large number of animals that in turn is obviously very expensive and often involves ethical issues. At the same time safety tests (especially, general toxicity) are required by national and international regulatory agencies for further clinical trials. Despite the undisputable importance of aforementioned, several features of animal models, specifically the quality of animal-based studies, are increasingly being scrutinized for informational and ethical reasons (9.3 mln animals were used for research and testing only in the EU in 2017) and continue to be a source of debates [1]. Thus, improving the standards for both basic and preclinical research has been considered a top priority for drug development.

Nowadays the 3Rs (Replacement, Reduction, Refinement) declared in the "Directive 2010/63 / EU on the protection of animals used for scientific purposes" that has been adopted by the EU Parliament, became a leading guide in preclinical research. 3R compliant models (predictive computational tools and robotic high-throughput screening; imaging systems in cancer research; organ-on-a-chip systems and 3D printed organoids with multiple cell types in toxicological studies, etc) are focused on achieving the reduction in animal numbers used in *in vivo* experiments. As well, the synergy between *in silico*-, *in vitro* and *in vivo* methods is highly appreciated.

In conclusion, it should be mentioned that despite growing number of scientific questions solved through alternative methods, the use of animals in preclinical research is still irreplaceable (convincingly confirmed during the COVID-19 outbreak) and remain necessary in the foreseeable future.

References

[1] 2019 report on the statistics on the use of animals for scientific purposes in the Member States of the European Union in 2015-2017. Report from the Commission to the European Parliament and the Council. https://op.europa.eu/s/wCA4

OP 12. NEW GLOBAL CHALLENGES FOR PHARMACEUTICAL MANUFACTURING AND QUALITY CONTROL: GENOTOXIC IMPURITIES - N-NITROSAMINES IN DRUGS

Imeda Rubashvili

Petre Melikishvili Institute of Physical and Organic Chemistry, Ivane Javakhishvili Tbilisi State University

Corresponding author e-mail: imeda.rubashvili@tsu.ge

Food and Drug Administration (FDA) and European Medicines Agency (EMA) in mid of June 2018 became aware of the presence of N-nitrosamine impurity in some commonly prescribed drugs such as blood pressure, antacids, diabetes and smoking cessation medicines. Unacceptable levels of N-nitrosamine impurities have been found in Valsartan tablets, an angiotensin II receptor blocker containing a tetrazole group which was recalled due to the presence of N-nitrosodimethylamine (NDMA) contamination. Further N-nitrosamine impurities namely N-nitrosodiethylamine (NDEA), N-nitrosodiisopropylamine (NDIPA), N-nitrosoethylisopropylamine (NEIPA) and N-nitrosoN-methyl-4-aminobutyric acid (NMBA) were subsequently detected in other drugs belonging to sartans. In late 2019, the FDA issued warnings for NDMA contamination of ranitidine, and in April 2020 requested that all products be removed from sale. In February 2020, some US lots of metformin were found to contain NDMA, which prompted the recall of several extended-release formulations [1-2]. The latest recalls (2022) have centred on Orphenadrine Citrate ER Tablets and Quinapril HCl/Hydrochlorothiazide due to the presence of N-nitroso Orphenadrine and N-nitroso Quinapril, respectively [3].

N-nitrosamines are considered a matter of concern as the ICH M7 (R1)2 guideline classifies them as Class 1 impurities or mutagenic carcinogens and they are categorized as probable carcinogens by the International Agency for Cancer Research (IARC). N-nitrosamine impurities are limited to acceptable excess risk in drug substance and drug product by well accepted the above-mentioned guideline where for the calculation of its limit is used [4].

N-nitrosamines are produced by the reaction of a secondary or tertiary amine with a nitrosating agent. However, secondary amines are the most likely to form nitrosamines. Tertiary amines cannot react directly with a nitrosating agent – they first cleave into secondary amines and then form N-nitrosamines. Nitric oxide, sodium nitrite, dinitrogen tetroxide and nitrous acid are some frequently used nitrosating agents. But, nitrosation can occur even without the presence of these agents. An acidic environment is usually required for nitrosation. However, nitrosation can occur in basic and neutral environment under the presence of catalysts such as aldehydes. The nitrosating agent can be introduced during any stage of the drug manufacturing process. Identifying the source of contamination is thus challenging and may necessitate analysing the entire supply chain. There are some possible scenarios that may result in the introduction of N-nitrosamine impurities: side reactions from drug syntheses, breakdown of unstable drug compounds, contamination from recycled solvents used in manufacturing, improperly cleaned reactors which may leave traces of the nitrosating agent and drug packaging [5].

To ensure drug product quality, manufacturers must properly assess the risk of N-nitrosamine formation in their products and further investigate any potential risks. While product recalls are concerning, this is part of the process to overcome the challenge of N-nitrosamines and work to eliminate them from our drug supply. To protect patients and strengthen the global medicines supply chain, United States Pharmacopeia (USP) is supporting manufacturers and regulators with standards, tools and solutions for testing, assessing risk and understanding potential sources related to N-nitrosamine impurities. FDA requests drug manufacturers to take a fresh look at the formulations of their products from this aspect and recommends examining the addition of antioxidants such as ascorbic acid or alpha-tocopherol to the formulation of medicinal products, especially if the risk assessment does not exclude a possible formation of this type of N-nitrosamines.

N-nitrosamine impurities occur at micro- or nanogram levels. Hence, highly sensitive and specific analytical methods are required for their quantification. The development of analytical methods to determine N-nitrosamines impurities is the challenging task due to very low levels of impurities present in the complex matrices. The developed methods also need to be validated to conform to GMP requirements. Several methods have been published by the FDA to cover NDMA and NDEA in different "sartans". The EMA has indicated the extension of measures to include more N-nitrosamines. Most of the methods used for testing of N-nitrosamines in drug substance and drug product utilize the chromatographic techniques such as RP-LC or GC combined with various detectors such as MS, UV-spectrophotometry or nitrogen chemiluminescence. The three main components of N-nitrosamine assay are: sample preparation, chromatographic separation and MS measurement. The goal of sample preparation is to solubilize all of the target analyte and produce a sample that is suitable for LC-based analysis. The volatility and small molecular size of N-nitrosamines, NDMA in particular, means that extra care is needed. Exposure to the evaporating conditions of standard sample preparation techniques, such as solid-phase extraction or evaporation and reconstitution, can lead to problems with recovery [1-2].

The presence of N-nitrosamines in medicinal products shall be mitigated as much as possible and shall be at or below a limit based on ICH M7(R1) principles for substances of the "cohort of concern" defined in this guideline and calculated considering a lifetime daily exposure. This should be achieved by an appropriate control strategy and by the design or adaptation of the manufacturing processes aiming to prevent formation of and contamination with N-nitrosamines whenever possible. The risk of presence of N-nitrosamines must be evaluated by drug manufacturers. In case of risk, confirmatory testing must be performed. The limit will usually need to be included in the finished product specification. With regard to the analytical methods the limit of quantitation (LOQ) should provide the minimum level at which an analyte can be quantified with acceptable accuracy and precision. If quantitative testing is performed as a routine control, the LOQ should be at or below the limit for the respective N-nitrosamine impurity [4, 6].

References

[1] Shaikh, T. 2020, Nitrosamine Impurities in Pharmaceutical Drugs, *Acta Scientific Pharmaceutical Sciences,* v. 4, no. 6, p. 27.

[2] Kern, R. 2021, Overcome N-nitrosamine analysis challenges with chromatography and mass spectrometry techniques, SCIEX, executive summary, RUO-MKT-03-12830-A. https://sciex.com/content/dam/SCIEX/pdf/documents/webinar-executive-summary-overcome-n-nitrosamine-analysis.pdf.

[3] Sandoz, Inc. Issues Nationwide Recall of 13 Lots of Orphenadrine Citrate 100 mg extended-release tablets due to presence of a nitrosamine impurity. March 22 2022. https://www.fda.gov/safety/recalls-market-withdrawals-safety-alerts/sandoz-inc-issues-nationwide-recall-13-lots-orphenadrine-citrate-100-mg-extended-release-tablets-due.

[4] ICH guideline M7(R1) on assessment and control of DNA reactive (mutagenic) impurities in pharmaceuticals to limit potential carcinogenic risk. 25 August 2015, EMA/CHMP/ICH/83812/2013 Committee for Human Medicinal Products.

[5] Ratanghayra, N. T. 2021, Nitrosamine Impurities – Understanding Risks, Overcoming Challenges, *Technology networks – Drug discovery*. https://www.technologynetworks.com/drug-discovery/articles/nitrosamine-impurities-understanding-risks-overcoming-challenges-349866.

[6] Assessment report: Procedure under Article 5(3) of Regulation EC (No) 726/2004. Nitrosamine impurities in human medicinal products. 25 June 2020 EMA/369136/2020 Committee for Medicinal Products for Human Use (CHMP).

OP 13. DEVELOPMENT OF CHIRAL FLUORINATED ALKYL DERIVATIVES OF RETINAL ANALOG: EMIXUSTAT AS DRUG CANDIDATES FOR THE TREATMENT OF RETINAL DEGENERATIVE DISEASES

Eliav Blum[1], Jianye Zhang[2], Edward Korshin[1], Krzysztof Palczewski [2,3,4] , Arie Gruzman[1]

[1]Department of Chemistry, Faculty of Exact Sciences, Bar-Ilan University, Ramat-Gan, Israel; [2]Department of Ophthalmology, Gavin Herbert Eye Institute; [3]Department of Physiology and Biophysics, and [4]Department of Chemistry, University of California, Irvine, California, USA.

Corresponding author e-mail: gruzmaa@biu.ac.il

The discovery of how a photon is converted into a chemical signal is one of the most important achievements in the field of vision. The understanding of the basic mechanisms of the vision might lead to development of effective drugs against blindness. In majority of the cases, blindness resulting from retinal degeneration that is a critical problem that still does not have a therapeutic solution. However, in recent years significant progress was achieved in understanding the role of all-trans-retinal-(all-*trans*-RAL)-related mechanisms of toxicity in retinal degeneration. A key molecule in this process is the visual chromophore retinal. Several eye diseases are attributed to the abnormal metabolism of retinal in the retina and the retinal pigment epithelium. Also, the accumulation of two toxic retinal derivatives, N-retinylidene-N-retinylethanolamine and the retinal dimer, can damage the retina leading to blindness. RPE65 (Retinal pigment epithelium-specific 65 kDa protein) is one of the central enzymes that regulates the metabolism of retinal and the formation of its toxic metabolites. Its inhibition might decrease the rate of the retina's degeneration by limiting the amount of retinal and its toxic byproducts. Two RPE65 inhibitors, (R)-emixustat and (R)-MB001, were recently developed for this purpose.

We designed, synthesized and biologically evaluated several chiral fluorinated alkyl derivatives of emixustat. Two final compounds (enantiomers) showed significant inhibition of RPE-65 at a 2-fold lower concentration compared with known RPF-65 inhibitor: (R)-MB001, one of the developed compounds caused 100% cell protection under all-trans-retinal treatment and both molecules showed equal potency as racemic emixustat. Such molecules might be used as drug candidates for developing novel treatments against retinal degeneration.

YOUNG RESEARCHERS FORUM

YR 1. ALKALOID CONTAINING PLANT SPECIES OF THE GENUS MAHONIA INTRODUCED IN GEORGIA AND THEIR BIOLOGICAL ACTIVITY

Nika Todua[2], David Chincharadze[2], Nina Vachnadze[1].

[1]TSMU, I. Kutateladze Institute of Pharmacochemistry; [2]TSMU Direction of pharmacognosy and pharmaceutical botany, Tbilisi, Georgia.

Corresponding author e-mail: nika.todua@yahoo.com

Mahonia Nuttall is the second largest genus in the Berberidaceae Torr family. et Grey, which unites 19 genera and about 755 species of alkaloid-bearing plants. Of the 50 species of the Mahonia genus, which is considered to be native to East Asia, North and Central America, 6 species have been introduced on the territory of Georgia: *Mahonia aquifolium* (Pursh) Nutt.; *M. bealei* (Fort.) Carr; *M. fortune* (Lindl. Fedde); *M. japonica* (Thunb.) DC.); *M. lomariifolia* Takeda; *M. wagneri* Join., which until now have not been studied for the presence of biologically active bases[1].

Considering the fact that only a few of Berberidaceae representatives grow in natural conditions on the territory of Georgia, the introduced species of this family are of particular interest. Therefore, the goal of the study was to screen the aforementioned plants in order to identify the most productive alkaloid-bearing species of the genus *Mahonia*.

Phytochemical studies revealed that *M.aquifolium* (Pursh) Nutt., *M. bealei* (Fort.) Carr; *M. japonica* (Thunb.) DC., and *M. wagneri* Join. deserve attention. *M. aquifolium* is the most common on the territory of Georgia, and therefore the most accessible raw material among the above listed species. Investigation of qualitative and quantitative composition of alkaloids, as well as the determination of the authenticity of this plant's raw material based on microstructural features was carried out. Qualitative TLC analysis, in the presence of referent witnesses, allowed to identify biologically and pharmacologically active alkaloids, which were assigned to the protoberberine, aporphine groups of alkaloids: Berberine, Palmatine, Jatrorrhizine, Magnoflorine [2].

Using various liquid-liquid extraction methods, fractions were obtained in which using the HPLC-MS/MS and GC/MS methods the following componds have been identifed: (+)-Corydine ($C_{20}H_{23}NO_4$) - m/z: 341; 326; 310; Norisocorydine ($C_{19}H_{21}NO_4$) – m/z: 327; 312; 29 Quinoline, 8-methoxy-2,4-diphenyl - m/z: 341; 326; 310.

According to research, the main biologically active constituents of all M. aquifolium vegetative organs belong to the isoquinoline alkaloids, which are known for a wide range of pharmacological activities such as antifungal, antiradical, cytotoxic, antioxidant, antihistamine, antimicrobial, hypoglycemic, antipsoriatic, and many others. [3].

References:

[1] Jian-Ming He, Qing Mu. The medicinal uses of the genus Mahonia in traditional Chinese medicine: An ethnopharmacological, phytochemical and pharmacological review. 2015, J. of Ethnopharmacology, , 175, pp. 668–683

[2] Nika Todua, David Chincharadze, Nina Vachnadze. 2022, Experimental And Clinical Medicine Georgia, JECM, 3, pp.1-5. DOI:https://doi.org/10.52340/jecm.2022.03.08

[3] Andra Diana Andreicuț, and all. 2019, Antitumoral and Immunomodulatory Effect of Mahonia aquifolium Extracts, Hindawi Oxidative Medicine and Cellular Longevity, Volume 2019, Article ID 6439021, PP.1-13. https://doi.org/10.1155/2019/6439021

YR 2. CHEMISTRY AND BIOLOGICAL ACTIVITY OF ESSENTIAL OILS OF SOME SPECIES OF LAMIACEAE FAMILY GROWING IN GEORGIA

Teona Korkotadze[1], Vakhtang Mshvildadze[2], Jean Legault[3], Sopio Gokadze[1], Dali Berashvili[1]

Tbilisi State Medical University: [1]Department of Pharmaceutical Botany; [2]I. Kutateladze Institute of Pharmacochemistry, Tbilisi, Georgia; [3] Laboratoire LASEVE, Université du Québec à Chicoutimi, Québec, Canada

Corresponding author e-mail: t.korkotadze@tsmu.edu

Essential oils, among biologically active compounds produced in plants, are one of the most important groups. Due to chemical diversity, their components are characterized by a wide range of pharmacological activity. They play an important role in the metabolic process. They have bactericidal, antiviral, anti-inflammatory, fungicidal activity. Essential oils are laxative, antispasmodic, sedative, hypotensive, secretion enhancer, antioxidant [1 - 4].

The aim of this research is to study chemical composition and to evaluate biological activity of essential oils from the aboveground parts some endemics and cultivar species growing in Georgia that belong to Lamiaceae family: of *Salvia sclarea* L., *S. verticillata* L, *S. glutinosa* L., *Thymus collinus* Bieb., *T. tiflisiensis* Klokov et Des.-Shost, *T. polium* L., and *Teucreum nuchense* K.Koech.

Essential oils were obtained from the research objects by hydrodistillation with a Clevenger type apparatus and constituents were identified by gas chromatography with a mass spectrometry detector. The optimal conditions of the gas chromatography method were selected for different plant genera.

Anticancer, antibacterial, fungicidal, anti-inflammatory, and antioxidant activity of essential oils was evaluated *in vitro* on different cell cultures.

In essential oils of *S. scalrea* aboveground parts 25 components have been identified. Dominant compounds: linalool, α-terpineol, linalyl acetate, geranyl acetate, spathulenol. The essential oil showed interesting anti-inflammatory activity on mouse macrophage-like cell line (RAW 264.7).

In the essential oils of *T. tiflisiensis* Klokov et Des.-Shost aboveground parts 31 components were identified. Dominant compounds: pinene, myrcene, caryophyllene, germacrene, elemene, cadinol.

In the essential oils of *T. collinus* Bieb aboveground parts 29 components were identified. Dominant compound: eucalyptol, ocimene, terpinene. *T. collinus* essential oil reveals interesting antioxidant activity in ORAC (Oxygen Radical Absorbance Capacity) test.

Both tested essential oils exhibited moderate cytotoxicity against colorectal carcinoma (DLD-1) and lung carcinoma (A-549) cell lines [5].

In the essential oils of *T. nuchense* K.Koch aboveground parts 29 components have been identified. Dominants are: 1-octen-3-ol, bourbonene, caryophyllene, germacrene, caryophyllene oxide.

In the essential oils of *T. polium* L aboveground parts 28 components have been identified. Dominants are: pinene, sabinene, (-)-terpinen-4-ol, (E)-β-famesene, germacrene.

Genus *Salvia* two species: 1. Gas chromatographic analysis of essential oils, obtained from leaves and flowers of Salvia *verticillata* L. showed more than 60 substances, of which 6 substances were identified both in leaves and flowers. 2. 21 substances have been described in the essential oil obtained from *S. glutinosa* L. aboveground parts. 8 common substances (farnesane, humulene oxide II, spathulenol, β-bourbonene, linalool, caryophyllene oxide, caryophyllene, D-limonene) were found in the essential oil of both species (*Salvia verticillata* and S. glutinosa). Antioxidant activity was determined using DPPH (1,1-diphenyl-2-picrylhydrazyl). It was determined that the tested samples have high antioxidant activity, the methanolic extract of the aboveground parts of S. glutinosa L. inhibited 93.3% of free radicals; and in the case of S. verticillata L. 93.73% [6].

From the point of view chemical composition and biological activity of essential oils of some species of Lamiaceae family growing in Georgia are quite interesting, Research are continuing to study species of interest to medicine.

References

[1] Asif Hanif M., Nisar S., Samin Khan G., Mushtaq Z., Zubair M.. 2019. Essential Oils Research, Springer Nature Switzerland. M. A. Hanif et al, Chapter 1.

[2] K. Husnu Can baser, Buchbauer G.. 2010. Handbook of essential oils-Science, technology and applications. Tailor and Francis group, USA. Chapter 9, 235-280.

[3] Dhifi W, Bellili S, Jazi S, Bahloul N, Mnif W. 2016. Essential Oils' Chemical Characterization and Investigation of Some Biological Activities: A Critical Review. Medicines (Basel). 3(4):E25.

[4] Lenardão EJ, Savegnago L, Jacob RG, Victoria FN, Martinez DM. 2016, Antinociceptive Effect of Essential Oils and Their Constituents: an Update Review. 27:435–74

[5] Getia M., Korkotadze T., Moshiashvili G., Tabatadze N., Legault J., Mshvildadze V. 2022. Comparative study of essential oils composition and in vitro cytotoxic effects from two species of Thymus L. growing in Georgia (Accepted for publishing)

[6] Korkotadze T., Berashvili D., Mshvildadze V., Getia M., Bakuridze A. 2021. Genus Salvia L. Study of some species, growing in Georgia, chemical composition and antioxidant activity Experimental and clinical medicine. 5-6, P 139-143.

YR 3. ADVANCES AND TRENDS IN THE RESEARCH OF THE GENUS DAPHNE

Giorgi Moshiashvili [1], Vakhtang Mshvildadze [1,2]

[1] Tbilisi State Medical University, I. Kutateladze Institute of Pharmacochemistry, Tbilisi, Georgia; [2] Department of Basic Sciences, University of Quebec, Chicoutimi, Canada

Corresponding author e-mail: g.moshiashvili@tsmu.edu

Daphne is a plant genus belonging to the *Thymeleaceae* family and it contains between 90 and over 100 species of deciduous and evergreen shrubs with fragrant flowers. Some recent studies have suggested this genus to be non-monophyletic. *Daphne* grows across Asia, Europe and parts of North Africa [1 - 4]. The plants in this genus are highly toxic and are notorious for their toxicity in their native habitats. All parts of these plants are poisonous, but the juicy and, often, bright red berries are especially so. Coumarins and diterpenes are the primary causes of the toxicity [5].

Around 15 species of the genus *Daphne* are used in traditional medicine, especially in China and the Middle Eastern. They are used for the treatment of bruises, scrofula, various kinds of cancer, inflammations, common cold, laryngitis, sore throat, diarrhoea, rheumatism, malaria, fever, rheumatism, lumbago infectious wounds and skin diseases. They are used as antitussive and diaphoretic, anthelmintic, diuretic, antitussive, analgesic, abortive and expectorant [6 - 8].

Up until now over 430 secondary metabolites have been isolated and/or identified in this genus. The major groups found in this genus are coumarins, flavonoids, lignans, terpenoids, and several other less common compounds like phenylpropanois, organic acid esters, fatty acids, steroids and alkaloids [6, 7, 9].

Coumarins are among the most abundant secondary metabolites of the genus. Around 60 of them have been identified in *Daphne* so far. These include monomeric, dimeric and trimeric coumarins and their glycosides. Some, such as daphnin, are carachteristic in many species of the genus. Some of these have shown cytotoxic, antioxidant, antimicrobial, anti-inflammatory activities [6, 8].

Terpenoids are the most diverse group of secondary metabolites found in the genus *Daphne*. Out of these diterpenes are the most numerous with over 135 identified so far, of which there are three types - daphnane, tigliane and lathyrane diterpenes. At least several new Daphne diterpenes are described every year. The former can be divided into 6-epoxy daphnane diterpenoids, genkwanines, resiniferonoids and 1-alkyldaphnanes, though some compounds don't fit well into either of these groups. Lathyrane diterpenoids are the most recent addition to the diversity of *Daphne* terpenoids with only 2 identified so far [9, 10]. Around 30 sesquiterpenes and 8 triterpenes have also been identified in *Daphne* [9, 11].

Around 120 flavonoids have been identified in this genus so far. These include flavonols, methoxyflavonoids, bioflavonoids, and their glycosides. *Thymelaeceae*-specific bioflavonoids like daphnodorins, genkwanols, daphnorigins, daphnegiravans and daphnegiralins are characteristic for the genus *Daphne*. The isolated flavonoids have shown the following activities: K+-ATP inhibition, anti-HIV, antifungal, insecticidal, anti-acetylcholinesterase, 12-lypoxygenase and cyclooxygenase inhibitory, NO production inhibition, anti-RSV, antioxidant and angiotensin II formation inhibition [6, 7, 12, 13].

Almost 40 lignans are known from *Daphne* so far with the furofuran-type lignans being the most common in the genus. Other lignans include the furan-, dibenzylbutane-, dibenzylbutyrolactol-type, and dibenzylbutyrolactone-type, several secolignans, one neolignan and one dilignan. A few of these lignans possess anti-inflammatory, anti-HIV and cytotoxic activities [6, 7, 14].

The main focus of the biological investigation of the genus *Daphne* has been on its effect on various cancer cell lines. A large portion of the studied species has shown some form of cytotoxic activity. Different species have been active against HBL-100 (breast cancer), A549 (lung carcinoma), HeLa

(cervical cancer), K562 (myelogenous leukemia), U937 (monoblastic leukemia), Ag.8 (mouse myeloma), Eca-109 (human oesophageal squamous cell carcinoma), AGS (gastric carcinoma), SMMC-7721 (hepatoma) and other cell lines. The spectrum of cytotoxic activity is expanding with new research. Other identified activities common among the Daphne species include antioxidant, antiviral (especially anti-HIV) and antimicrobial, including antituberculotic[9, 12, 14 - 18].

Due to its array of biological effects and diverse chemical composition, *Daphne* and the various compounds that are derived from it have a great potential in the treatment of inflammations, viral and bacterial infections, and especially cancer.

References

[1] Halda JJ., 1998, Some taxonomic problems in the genus Daphne L. Acta Musei Richnoviensis Sect. Nat. vol. 5, pp. 133- 160

[2] Plant Name Details for Daphne L., The International Plant Names Index https://www.ipni.org/n/30024583-2

[3] Beaumont, A J et al., 2009, Gnidia (Thymelaeaceae) is not monophyletic: taxonomic implications for Thymelaeoideae and a partial new generic taxonomy for Gnidia, Botanical Journal of the Linnean Society, vol. 160 , no. 4, pp. 402–417

[4] Lee SY, et al., 2021, Molecular phylogenetic analyses based on the complete plastid genomes and nuclear sequences reveal Daphne to be non-monophyletic as current circumscription. Plant Divers, vol. 2, no. 44, pp. 279-289

[5] Lewis RA., 1998, "Daphne", Lewis' Dictionary of Toxicology, Lewis Publishers, pp. 346–347

[6] Xu, WC., Shen, J.-G., Jiang, J.-Q. 2011, Phytochemical and Biological Studies of the Plants from the Genus Daphne, Chemistry & Biodiversity, vol. 8, no. 7, pp. 1215–1233

[7] Miroslav M., Nedeljko T., 2016, Plants from the genus Daphne: A review of its traditional uses, phytochemistry, biological and pharmacological activity Manojlović Department of Pharmacy, Faculty of Medical Sciences, University of Kragujevac, Serbia,

[8] Agnihotri S. et al., 2010, An overview on anti-inflammatory properties and chemoprofiles of plants used in traditional medicine. Indian Journal of Natural Products and Resources, vol. 1, pp. 150-167

[9] Nie, Y.-W. et al.; 2021, Phytochemistry and Pharmacological Activities of the Diterpenoids from the Genus Daphne. Molecules, vol. 26, pp. 6598.

[10] Minh, N.V. et al., 2018, Genkwalathins A and B, new lathyrane-type diterpenes from Daphne genkwa, Natural Product Research, vol. 32, pp. 1782–1790

[11] Huang SZ., et al. 2022, Hexahydroazulene-2(1H)-one Sesquiterpenoids with Bridged Cyclobutane, Oxetane, and Tetrahydrofuran Rings from the Stems of Daphne papyracea with α-Glycosidase Inhibitory Activity. J Nat Prod., vol. 85(1), pp. 3-14

[12] Lin H., 2012, A new flavonoid from Daphne feddei and its anti-HIV-1 activity, Asian Journal of Chemistry , vol. 24, no. 11, pp. 5391-5392

[13] Bai Z., et al. Characteristic biflavonoids from Daphne kiusiana var. atrocaulis (Rehd.) F. Maekawa. Nat Prod Res. 2022 vol.11, pp. 1-8

[14] Wang L. et al., 2010, Lignans from Daphne feddei Levl. var and their cytotoxicity, Asian Journal of Chemistry, vol. 22, no. 10, pp.8162-8166

[15] Hedayati LM., et al , 2011, A New Diterpene Extracted from Daphne Mucronata, Effects on Human K562 and CCRF-CEM, Cell Journal of Cancer Therapy, vol. 2, pp. 71-75

[16] Amirghofran Z., Miri R., Javidnia K., Davoodi M., 2001 Study of cytotoxic activity of Daphne mucronata Royle grown in Iran, Iranian Journal of Medical Sciences, vol. 26, pp. 146-151

[17] Nikahd M., et al. 2022, Phytochemical analysis of Daphne pontica L. stems with their pro-apoptotic properties against DU-145 and LNCaP prostate cancer cells, Daru, vol. 30, no 1, pp. 85-101

[18] Manojlović NT., et al. 2012, HPLC Analysis, antimicrobial and antioxidant activities of Daphne cneorum L. Hemijska industrija. vol. 66, no. 5, pp.709-716

YR 4. DEVELOPMENT OF GELS FOR THE TREATMENT OF MUSCULOSKELETAL DISORDERS FROM NATIVE AND MODIFIED BROMELAIN

T. Korinteli[1], N. Gorgaslidze[2], L. Nadirashvili[1], G. Erkomaishvili[1]

[1]Tbilisi State Medical University: I. Kutateladze Institute of Pharmacochemistry, Department of Phytochemistry;
[2]Department of Social and Clinical Pharmacy, Tbilisi, Georgia

Corresponding author e-mail: t.korinteli@tsmu.edu

Musculoskeletal disorders (MSDs) are one of the primary reasons people seek medical care worldwide [1]. A plant derived proteolytic enzyme bromelain, found in almost all parts of the Pineapple plant (*Ananas comosus* L. Merr.), is currently used in the treatment of musculoskeletal disorders [2,3]. Chemical modification reactions have been carried out to improve the physical, chemical and pharmacological properties of bromelain and to reduce its side effects [4,5,6]. The topical administration of drugs, including enzyme-based drugs, in order to achieve optimal cutaneous and percutaneous drug delivery has recently gained an importance and gels, among the other semi-solid dosage forms, have multiple advantages [7,8].

The study aimed to develop native and modified bromelain containing gels for the treatment of musculoskeletal disorders, with more stability and fewer side effects than the available medications for MSDs treatment.

Firstly, the chemical modification of bromelain with dextran aldehyde was performed and the degree of bonding was about 70%. Gels from native and modified bromelain oil-based and aqueous phases were prepared, native and modified bromelain were introduced into the oil phase, to protect the enzymes from interaction with water. Carbopol 940 was chosen as a gel base.

To characterize the prepared gels, tests, required by the USP, were caried out. The proteolytic activity determination method was used for quantitative analysis [9]. Proteolytic activity of native and modified bromelain gels was 144.5 PU/g and 147.08 PU/g, respectively. Light microscopy showed the gel base, native bromelain and modified bromelain containing gels to be uniform and no large inclusions were observed within them. Based on the conducted rheological studies, it can be concluded that the research samples represent dispersed systems with elastic-plastic properties. Their viscosity varied within the limits of 572-15223 cp. The results demonstrated that the gels' bioaccessibility was within the norm. Spreadability is considered an important factor in patient compliance with treatment and in the prepared base and gels this factor was satisfactory in topical application. The pH of all the formulations indicates that they are acceptable to avoid the risk of irritation upon application to the skin. The base and gels also showed high thermal and colloidal stability.

Considering the results of the conducted tests, we can conclude, that the goal of this work was successfully fulfilled.

References

[1] Musculoskeletal conditions. 2021. WHO https://www.who.int/news-room/fact-sheets/detail/musculoskeletal-conditions
[2] Rathnavelu V., Alitheen N., Sohila S. et al. 2016. Potential role of bromelain in clinical and therapeutic applications (Review). Biomedical reports, 5(3), 283–288.
[3] Chakraborty, A. J., Mitra, S., Tallei, T. E., et al. 2021. Bromelain a Potential Bioactive Compound: A Comprehensive Overview. from a Pharmacological Perspective. Life, 11(4), 317.
[4] Nwagu TN, Ugwuodo CJ. 2019. Stabilizing bromelain for therapeutic applications by adsorption immobilization on spores of probiotic Bacillus. Int J Biol Macromol. 15;127:406–14.
[5] Xue Y, Wu CY, Branford-White CJ, et al. 2010. Chemical modification of stem bromelain with anhydride groups to enhance its stability and catalytic activity. Journal of Molecular Catalysis B, Enzymatic. 3–4(63):188–93.

[6] Brito AMM, Oliveira V, Icimoto MY, Nantes-Cardoso IL. Collagenase Activity of Bromelain Immobilized at Gold Nanoparticle Interfaces for Therapeutic Applications. Pharmaceutics. 2021 Jul 27;13(8):1143.
[7] Billah R, Mondal M, Somoal S, et al. 2019. Enzyme-Responsive Hydrogels. In book: Cellulose-Based Superabsorbent Hydrogels pp.309-330
[8] Rathod H, Mehta D. 2015. A Review on Pharmaceutical Gel. International Journal of Pharmaceutical Sciences. Oct 1; 1:33–47.
[9] Kaverzneva E.D. 1971. Standard method for determining proteolytic activity for complex protease preparations. Appl. Biochem. And microbiol. 7(2), 225-228 (In Russian).

YR 5. PHYTOCHEMICAL STUDY OF SECONDARY METABOLITES OF PLANTS OF THE GENUS ALLIUM, GROWING IN GEORGIA AND DETERMINATION OF THEIR BIOLOGICAL ACTIVITY

Giorgi Jgerenaia[1,3], Natela Gogitidze[2], Nadezhda Mushkiashvili[2], Michel Frederich[3], Lasha Mskhiladze[1]

Tbilisi State Medical University: [1]Department of Pharmacognosy, Direction of Pharmacognosy and pharmaceutical Botany, Faculty of Pharmacy; [2] Department of Preclinical Pharmacological Research, I. Kutateladze Institute of Pharmacochemistry, Tbilisi, Georgia; [3]Laboratory of Pharmacognosy, Center of Interdisciplinary Research on Medicines (CIRM), University of Liège, Belgium.

Corresponding author e-mail g.jgerenaia@tsmu.edu

The genus *Allium* belongs to the former family Alliaceae (now included in Amaryllidaceae). This genus involves up to 1233 species [1]. Plants of the genus *Allium* have a long history of traditional uses worldwide. The story of Allium cultivation starts over 4000 years ago in ancient Egypt [2]. Allium species are widely used in Georgian traditional medicine as antifungal, antiseptic and antibacterial remedy [3,4]. 36 species of genus Allium are described in Georgia. Among them 5 species are endemic of Georgia and 2 of Caucasus region [5].

The aim of this project was the phytochemical study of secondary metabolites of species of the genus Allium, namely *A. saxatile* and *A. ponticum* growing in Georgia. To obtain crude extract of these plants, powdered plants were extracted with 80% EtOH, using an ultrasonic water bath heated at 50˚C. Dried extracts of each plant were subjected to Diaion HP-20 column chromatography. The mobile phase was H_2O-MeOH in gradient condition (100:0; 50:50; 0:100 v/v) and EtOAc to give 4 enriched fractions of each plant (A.S.F1_H_2O; A.S.F2_MeOH-50%; A.S.F3_MeOH-100%; A.S.F4_EtOAc; A.P.F1_H_2O; A.P.F2_MeOH-50%; A.P.F3_MeOH-100%; A.P.F4_EtOAc).

Analgesic, anti-inflammatory and gastroprotective activity of the aforementioned fractions were evaluated in rodents using “Hot plate”, carrageenan induced paw edema, and ethanol induced ulcer assays, respectively [6].

A. saxatile total extract reveals analgesic activity reaching its maximum at 60 min after the administration. Differently, *A. ponticum* total extract revealed faster onset but shorter duration of action. Similar tendency was observed when studying the efficacy of fractions obtained from total extracts. The fact that A.S.F3 fraction has even higher activity than total extract, allows to conclude that this fraction contains compound(s) responsible for analgesic effect. In ethanol induced ulcer model, only crude extract of *A. saxatile* has moderate gastroprotective effect (Table 1).

Table 1. Pharmacological assessment of total extracts and fractions of A. *saxatile* and *A. ponticum*

Extracts & fractions (50 mg/kg i.p.)	Effect (%) vs corresponding control groups			
	analgesic		anti-inflammatory	gastroprotective
	at 30’	at 60’		
Allium saxatile	55.2	70.3	63.5	37.3
A.s. F2	44.3	58.1	21.4	22.2
A.s. F3	64.6	80.4	59.5	0
Allium ponticum	105.6	81.3	32.7	-15
A.p. F2	56.1	37.4	n/d	n/d
A.p. F3	58.9	39.9	n/d	n/d

Moreover, the crude extract of *A. ponticum* revealed ulcerogenic properties increasing the ulcer index over one in control animals. Assessment of anti-inflammatory activity revealed a notable efficacy of A.S.tot and A.P.tot extracts (63.5% and 32.7%, respectively). Similarly to analgesic assay, 100% methanolic fraction (A.S.F3) showed the pronounced activity.

The obtained results will contribute to the phytochemistry of *Allium* species already studied and give a strong background for further investigation of active fractions to isolate the individual compounds responsible for the detected activity.

References

[1] Allium L. in GBIF Secretariat. 2021. GBIF Backbone Taxonomy. Checklist dataset https://doi.org/10.15468/39omei accessed via GBIF.org on 2022-06-01. n.d.
[2] Rahman K. Historical Perspective on Garlic and Cardiovascular Disease. J Nutr 2001;131:977S-979S. https://doi.org/10.1093/jn/131.3.977S.
[3] Bagrationi D. 1993. Iadigar Daudi. Edition of Tbilisi University. Republic of Georgia:.
[4] Panaskerteli-Tsitsishvili Z. 1978. Karabadini. Tbilisi, Republic of Georgia: Sabchota Sakartvelo;.
[5] Gagnidze R. 2005. Vascular Plants of Georgia a nomenclatural Checklist. Institute of Botany. Tbilisi, Republic of Georgia:
[6] Jgerenaia G. et al. 2022, Pharmacological Assessment of Constituents of Species Allium saxatile and Allium ponticum Growing in Georgia. *J.Experimental and clinical medicine* v.4, pp.25-33.

POSTER PRESENTATIONS

PP 1. BIOLOGICALLY ACTIVE FLAVONOIDS OF SOME PLANTS OF GEORGIAN FLORA

M. Alania, T. Sagareishvili, K. Shalashvili, N. Kavtaradze, M. Sutiashvili

Tbilisi State Medical University I. Kutateladze Institute of Pharmacochemistry, Tbilisi, Georgia

Corresponding author e-mail:m.alania@tsmu.edu

Long – term studying of plants spread and cultivated in Georgian flora revealed species with significant content of phenolic compounds. The deep investigation of some prospective species was carrying out for the purpose of their use in medicine. Among them were: *Astragalus falcatus* Lam., *Astragalus bungeanus* Boriss., *Salvia garedji* Troitzk., *Rhododendron ponticum* L., *Pueraria hirsuta* (Thunb.) Matsum.

Individual flavonoids and other phenolic compounds were isolated and identified: 7,2'-dihydroxy-3',4'-dimethoxyisoflavan (isomucronulatol), liquiritigenin (*Astragalus falcatus*) [1]; cosmosiin, apigenin-7-O-β-D-galactopyranoside, astragalin, trifolin, kaempferol-7-O-α-L-rhamnopyranoside, nicotiflorin, robinin, isorhamnetin-3-O-β-D-glucopyranoside (*Astragalus bungeanus*); yunnaneic acid E, yunnaneic acid F, salvianolic acid A and its isomer, rosmarinic acid, luteolin-7-O-β-D-glucuronide, apigenin-7-O-β-D-glucuronide, nepetin, nepetin-7-O-β-D-glucuronide, hispidulin, salvigenin, cirsimaritrin (*Salvia garedji*) [2]; quercetin-3-O-β-D-rhamnopyranoside, delphinidin-3-O-β-D-rhamnopyranoside, delphinidin, leucocyanidin (*Rhododendron ponticum*); 3'-hydroxi-daidzein-7-O-β-D-glucoside, daidzin, daidzein, ononin and genistin (*Pueraria hirsuta*) [3].

Apigenin-7-O-β-D-galactopyranoside, kaempferol-7-O-α-L-rhamnopyranoside, nicotiflorin, robinin, isorhamnetin-3-O-β-D-glucopyranoside and isomucronulatol, liquiritigenin respectively were described from *Astragalus bungeanus* Boriss. and *Astragalus falcatus* Lam. for the first time. 3'-hydroxi-daidzein-7-O-β-D-glucoside turned up structurally new substance (Fig. 1).

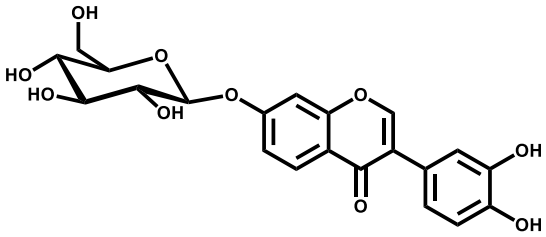


Figure.1. 3'-hydroxi-daidzein-7-O-β-D-glucoside

Chemical structures of isolated compounds were identified using physical and chemical properties, investigation of chemical transformation products, and spectral (UV, IR, NMR, HPLC-MS) data.

Extractive substances reveal specific biological activities. According to the Department of Preclinical Pharmacological Research of the I. Kutateladze Institute of Pharmacochemistry, flavonoid extracts from *Astragalus bungeanus* and *Rhododendron ponticum* stimulate leukopoiesis in vivo studies.

Salvia garedji aqueous, alcohol and acetone extracts increase the cellular antioxidant activity of WS1 cell line (normal human skin fibroblasts).

Total isoflavones from *Pueraria hirsuta* roots abolish the hepatotoxic effect of carbon tetrachloride in a mouse model of acute liver injury caused by CCl_4, reducing animal mortality by 95% and normalizing the length of nembutal-induced sleep [3].

References

[1] Sutiashvili M. G., Alaniya M. D., Skhirtladze A. V. et al. 2022, Chemical Constituents of Stems of *Astragalus falcatus* Growing in Georgia, *Chemistry of Natural Compounds*, vol. 58, No 2, pp. 337–338

[2] Sagareishvili T., Shalashvili K. 2019, Flavonoids of *Salvia garedji* and *Trifolium canescens*, International Scientific Conference "*Green Medications – By Green Technologies - For Healty Life*", 27-28 September, Tbilisi, Georgia
[3] Kavtaradze N., Alaniya M., Getia M. et al. 2022, Isoflavonoids from Roots of *Pueraria hirsuta* Distributed in Georgia and their Hepatoprotective Activity, *Chemistry of Natural Compounds*, vol. 58, No 1, pp. 27-31

PP 2. BIOLOGICALLY ACTIVE POLY[3-(3,4-DIHYDROXYPHENYL)GLYCERIC ACID] FROM THE STEMS OF *PARACYNOGLOSSUM IMERETINUM* (KUSN.) M.POP. (BORAGENACEAE)

L. Amiranashvili, V. Barbakadze, L. Gogilashvili

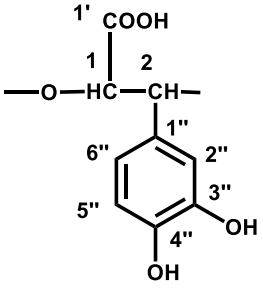
Tbilisi State Medical University I. Kutateladze Institute of Pharmacochemistry, Tbilisi, Georgia

Corresponding author e-mail:l.amiranashvili@tsmu.edu

The main chemical constituent of high-molecular water-soluble mucilage preparations from *Symphytum asperum, S.caucasicum, S.officinale, S.grandiflorum, Anchusa italica, Cynoglossum officinale* and *Borago officinalis* (Boraginaceae) was found to be a biologically active caffeic acid-derived polymer poly[oxy-1-carboxy-2-(3,4-dihydroxyphenyl)ethylene] or poly[3-(3,4-dihydroxyphenyl)glyceric acid] **(PDPGA**) [1-6].

Within our ongoing search for biologically active caffeic acid-derived polymers in plant species belonging to different genera of the Boraginaceae family, the isolation and structure elucidation of a main chemical constituent of water-soluble high-molecular mucilage fraction (Mr>500 kDa) from *Paracynoglossum imeretinum* stems (**HMP-PS)** was carried out. According to data of UV, IR, liquid-state ^{1}H, ^{13}C NMR, gCOSY and 2D heteronuclear $^{1}H/^{13}C$ gHSQCED experiments, the main structural element of HMP-PS by analogy of HMFs from *S.asperum, S.caucasicum, S.officinale, S.grandiflorum*, *A.italica, B.officinallis and C.officinale* was found to be a regularly substituted polyoxyethylene, poly[3-(3,4-dihydroxyphenyl)glyceric acid] or poly[oxy-1-carboxy-2-(3,4-dihydroxyphenyl)ethylene] **(PDPGA)** (Tab. 1).

Table 1. The signal assignment in the 13C and 1H NMR spectra of PDPGA from P.imeretinum

The repeating unit of PDPGA	C atom no.	^{13}C chemical shift, δ_C, ppm	^{1}H chemical shift, δ_H, ppm
	1'	175.0	
	1	77.5	5.7
	2	79.6	5.1
	1''	130.7	
	2''	116.6	7.6
	3''	143.9	
	4''	143.0	
	5''	117.8	7.5
	6''	121.5	7.4

References :

[1] Barbakadze, V. Kemertelidze, E. Targamadze, I. et al. 2005, "Poly[3-(3,4-dihydroxyphenyl)glyceric acid], a new biologically active polymer from *Symphytum asperum* Lepech. and *S.caucasicum* Bieb. (Boraginaceae)" *Molecules,* vol. 10, no. 9, pp. 1135-1144.
[2] Barbakadze, V. Van den Berg, A.J.J. Beukelman, C.J. et al. 2009, "Poly[3-(3,4-dihydroxyphenyl)glyceric acid] from *Symphytum officinale* roots and its biological activity*". Chem. Nat. Compds.,* vol. 45, no. 1, pp. 6-10
[3] Barbakadze, V. Gogilashvili, L. Amiranashvili, et al. 2010, "Poly[3-(3,4-dihydroxyphenyl)glyceric acid] from *Anchusa italica* roots" *Nat. Prod. Commun.,* vol.5, no. 7, pp. 1091-1095.

[4] Gokadze, S. Gogilashvili, L. Amiranashvili, et al. 2017, "Investigation of water-soluble high molecular preparation of *Symphytum grandiflorum* DC (Boraginaceae)". *Bull. Georg. Natl. Acad. Sci.,* vol. 11, no. 1, pp.1091-1095

[5] Gogilashvili, L. Amiranashvili, L. Merlani, et. al. 2020, "Poly[3-(3,4-Dihydroxyphenyl)Glyceric Acid] from Cynoglossum officinale L. (Boraginaceae)". *Bull. Georg. Natl. Acad. Sci.* vol. 14, no. 1, pp. 108-113

[6] V. Barbakadze, L. Gogilashvili, L. Amiranashvili et al. 2021, "Carbohydrate-Based Biopolymers: Biologically Active Poly[3-(3,4-Dihydroxyphenyl)Glyceric Acid] from *Borago officinalis "Bull. Georg. Natl. Acad. Sci.* vol. 15, no 4, pp. 140-145.

PP 3. SYNTHESIS OF POLYCYCLIC-ORGANOMETALLIC CONJUGATES: N-(α-METALLOCENYL) ALKYLATED PRODUCTS FOR PHARMACOLOGICAL PURPOSES

Kh. Barbakadze[1], G. Lekishvili[1], B. Arziani[1], D. Zurabishvili[2], N. Lekishvili[2]

[1]Tbilisi State Medical University, Faculty of Pharmacy, Department of Medical Chemistry; [2]Ivane Javakhishvili Tbilisi State University, Faculty of Exact and Natural Sciences, Tbilisi, Georgia

Corresponding author e-mail: kh.barbakadze@tsmu.edu

The synthetic possibilities of the α-metallocenylalkylation reactions of O- and N-nucleophiles are conditioned, first of all, by the availability of the appropriate organometallic component and the high stability of α-ferrocenyl carbocations, which is due to the presence of an electron-donating ferrocenyl fragment on the α-position of the cationic center.

N-alkylation reaction of nitrogen-containing immunotropic and membranotropic alicyclic nucleophiles with α-hydroxy(alkyl)ferrocenes in two-phase system consisted of an organic solvent (dichloroethane, chloroform) and 45-70% aqueous solution of acids HX (X = BF_4^-, ClO_4^-) was studied. Reactions efficiently proceed predominantly at the organic-inorganic interface. In the aqueous region of the process, the protonation of the polar hydroxyl group of the organometallic substrate becomes favorable. The highly acidic environment (pH -7 ÷ -9) on the surface of the phase separation promotes the formation of a thermodynamically stable α-ferrocenylalkyl carbocation in the *in situ* active form. The non-polar part of the formed intermediate (ferrocene core) remains in the organic phase, which causes effective interaction of the carbenium center with the corresponding nucleophilic reagent. At the same time, when using the mentioned systems, transformations typical for ferrocenyl carbocations (dimerization, rearrangement, polymerization, etc.) and oxidation of ferrocenyl alkylated products are practically excluded.

The composition and structure of the synthesized new hybrid derivatives − N-(α-ferrocenylalkyl)-perchlorates and amines were determined by the IR, UV, nuclear magnetic resonance (^1H, ^{13}C), and mass spectroscopic analysis methods.

New biologically active compounds containing simultaneously ferrocenyl and alicyclic fragment obtained as a result of targeted synthesis present interesting objects for further investigations in terms of both as theoretical, e. g., for study the mutual influence between chemical structure and biological activity, and in a practical point of view, including medicine, various branches of industry, technology, as well as the direction of search of the new medicaments with the broad spectrum of pharmacological activity.

References

[1] Michael D., Mingos P., Crabtree, R.H. Ed., Comprehensive Organometallic Chemistry III from Fundamentals to Applications. Elsevier Science, 2007.

[2] Artsimovich N., Galushina T., Fadeeva T. 2000, Adamantanes – Medicines of XXI Century, Intern. J. Immunorehabilitation, vol. 2, no. 54, pp. 54-60.

[3] El-Emam A.A., Alrashood K.A., Al-Omar M.A., Al-Tamimi A.S. 2012, Synthesis and antimicrobial activity of N'-heteroarylidene-1-adamantylcarbohydrazides and (±)-2-(1-adamantyl)-4-acetyl-5-5-(4-substituted pheyl-3-isoxazolyl)-1,3,4-oxadiazolines, Molecules, vol. 17, pp. 3475–3483.

PP 4. 5α-PREGNANOLONE HYDRAZONES. SYNTHESIS AND CYTOTOXIC ACTIVITY

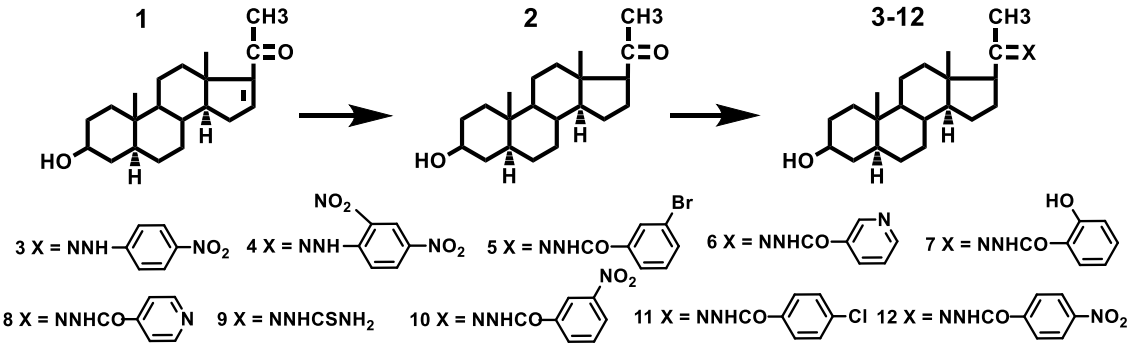
M. Kakhabrishvili, N. Barbakadze

Tbilisi State Medical University I. Kutateladze Institute of Pharmacochemistry, Tbilisi, Georgia

Corresponding author e-mail: n.barbakadze@tsmu.edu

Steroidal hydrazones exhibit broad spectra of biological activity, including cytotoxic, anabolic, anti-ovulatory, antituberculosis, antiparasitic, and fungicidal activity [1–3].A number of nitrogen-containing compounds were obtained using a condensation reaction to investigate structure-chemical reactivity and structure-biological activity relationships in the search for potential biologically active steroids within ketone of the 5α-pregnane serie. Starting steroidal ketone **2** was synthesized on the basis of a convenient domestic raw material – tigogenin, isolated from plant *Yucca gloriosa* introduced in Georgia.

Acetic acid catalyzed condensation reactions were carried out in ethanol using various reagents with pharmacophores features – arylhydrazides, arylhydrazines and thiosemicarbazide.



Scheme. Synthesis of hydrazones of 5α-pregnanolone

The structure of the synthesized compounds **3-12** was proved by ^{1}H-, ^{13}C NMR and mass spectral data. The cytotoxic activity of **3–9** was studied *in vitro* against lung carcinoma (A-549), colorectal adenocarcinoma (DLD-1), and normal skin fibroblast cell lines (WS-1) as compared to etoposide [4]. The results indicated that only p-nitrophenylhydrazone **3** of all tested compounds was of further interest because its activity against lung carcinoma was comparable to that of etoposide (IC50 18 ± 2 and 14 ± 2, respectively), in contrast to the other compounds.

As it turned out, the presence of a 3β-hydroxy group and a C-20 p-nitrophenylhydrazone (hydrazone **3**) appeared most important for manifestation of cytotoxic activity in the series of synthesized 5α-pregnanolone hydrazones **3–8**. Previously, a similar enhancement of the effect against A-549 and DLD-1 was observed for 5α-pregn-16-en-3β-ol-20-one p-nitrophenylhydrazone [4]. Thus, this moiety was definitive for cytotoxic activity in this series.

References

[1] Verma, G. Marella, A. Shaquiquzzaman, et al. 2014, A Review exploring biological activities of hydrazones, Journal of Pharmacy and Bioallied Sciences, vol. 6, no. 2, pp. 69-80.

[2] Mohareb RM. Al-Omran F. 2012, Reaction of Pregnenolone with cyanoacetylhdrazine: Novel synthesis of hydrazide-hydrazone, pyrazole, pyridine, thiazole, thiophene derivatives and their cytotoxicity evaluations, Steroids, vol. 77, pp. 1551-1559.

[3] Visbal, G. San-Blas, G. Maldonado, A. et al. 2011, Synthesis, in vitro antifungal activity and mechanism of action of four sterol hydrazine analogues against the dimorphic fungus Paracoccidioides brasiliensis, Steroids, vol. 76, pp. 1069-1081.
[4] Nadaraia, NSh. Kakhabrishvili, ML. Barbakadze, NN. et al. 2018, Synthesis and biological activity of steroidal tigogenin hydrazones and pyrazolines, Chemistry of Natural Compounds, vol. 54, no. 5, pp. 926-929.

PP 5. DETERMINATION OF BIOLOGICALLY ACTIVE COMPOUNDS IN GRAPEVINE SHOOTS

N. Bokuchava[1], M. Tatanashvili[1], T. Murtazashvili[1], P.Tushurashvili[2], K. Sivsivadze[1]

Tbilisi State Medical University: [1] Department of Pharmaceutical and Toxicological Chemistry; [2] Department of Biochemistry, Tbilisi, Georgia, Tbilisi, Georgia

Corresponding author e-mail: n.bokuchava@tsmu.edu

According to the data of World Health Organization (WHO), the majority of the population prefers natural remedies. Regardless of the high pharmacological activity of synthetic mono- and combined chemical medicines, plant raw materials continue to be a promising source of new drugs [4, 8].

Plant raw material contains various biologically active substances, such as alkaloids, polyphenols, cardiac glycosides, tannins. Polyphenols are an important group among them, which are actively used for the treatment and prevention of different diseases [1,5].

Based on the above mentioned, it is relevant to conduct complex phytochemical research and estimate biological activities of plants growing on the territory of Georgia, in order to develop new medicinal drugs in the future.

It is especially important to study various products derived from grapevine growing on the territory of Georgia, to obtain total and individual biologically active substances, standardize and determine their effectiveness. Raw materials of grapevine origin contain compounds of various groups with medicinal properties, including organic acids (tartaric, malic, citric acid), macro- and microelements (calcium, magnesium, sodium, iron, manganese, phosphorus, sulfur, zinc), vitamins (ascorbic acid, vitamin A), cellulose, phenolic compounds (anthocyanides, gallic acid, catechins, epicatechins, kaempferol, myricetin, rutin, quercetin, ellagic acid, caffeic acid, resveratrol) [6, 7].

It is worth noting the fact that the raw material (shoots) of grapevine contains a significant amount of polyphenols, which are actively used both in human diet and for the treatment and prevention of various diseases due to antioxidant, anti-inflammatory, antitumor effects [2, 3].

The aim of the present study was to study the content of biologically active compounds in the extract obtained from the grapevine shoots, the resource-saving raw material of grapevine, in order to use them further.

Saferavi grapevine shoots were collected in Kakheti, in the village of Alvani (Akhmeta Municipality), in the month of June 2021. 10 g of chopped grapevine shoots were transferred to a 250 ml flask and 100 ml (1:10 ratio) of 50% ethyl alcohol was added. Extraction process was performed for 30 minutes at 70°C, obtained extract was filtered through membrane filter.

Phytochemical studies of the obtained shoots extract were carried out on the basis of the Departments of Pharmaceutical and Toxicological Chemistry, Pharmacognosy and Pharmaceutical Botany of Tbilisi State Medical University; Department of Chemical and Narcotic research of the Levan Samkharauli National Forensics Bureau.

Qualitative-quantitative analysis of biologically active compound was carried out by liquid chromatography using the tandem mass spectrometric (LC-MS/MS) method under the following conditions: system: A2 : B2 = 70:30; A2- 0.1% formic acid: acetonitrile B2- 0.1% formic acid: water.

Stationary phase - C18, column temperature - 30°C, collision energy 22 eV, positive ionization (ESI^+), multi reaction monitoring mode (MRM), solvent flow rate - 0.8 ml/min. The results are presented on below chromatograms (Figure 1.)

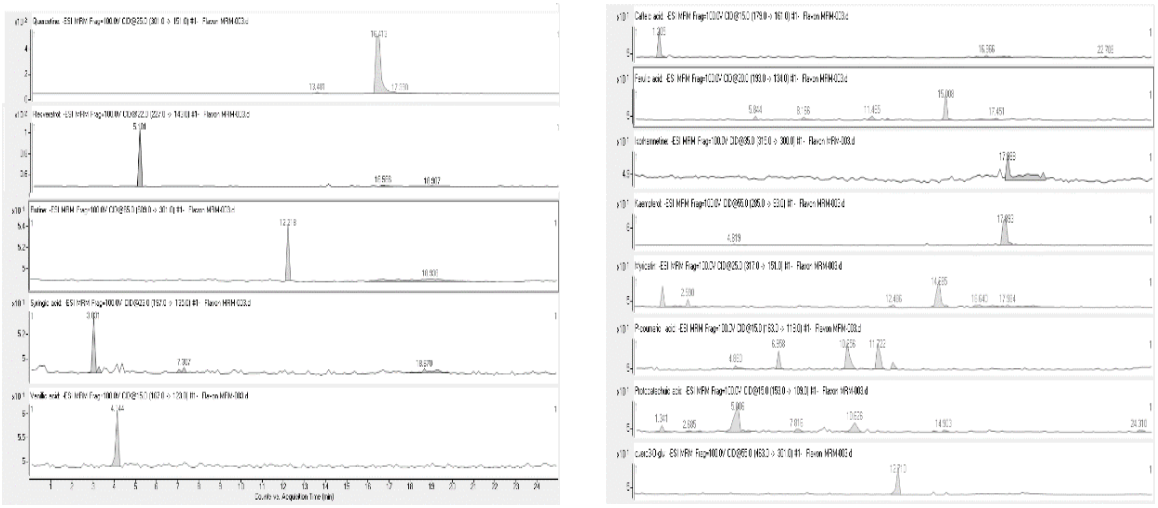


Fig.1. LC-MS/MS - MRM chromatogram of some phenolic compounds in grapevine shoot extract

As a result of the experiment, the content of various biologically active compounds was determined in the extract obtained from the grapevine shoots, such as Caffeic acid, Ferulic acid, Isorhamnetin, Kaempferol, Myricetin, P-coumaric acid, Protocatechuic acid, Quercetine, Resveratrol, Rutine, vanillic asid.

Therefore, from the scientific and practical perspective, it is relevant to conduct fundamental phytochemical and in vitro pharmacological, modern research, in order to develop optimal methods of deriving and study of biologically active compounds in plant materials of grapevine.

References

[1] Bakuridze A., Berashvili D., 2016. Basics of preparing medicinal herbal plant materials, National Center for Education Quality Development, Tbilisi
[2] Cory H., Passarelli S., Szeto J., Tamez M., Mattei J., 2018 Sep 21, The Role of Polyphenols in Human Health and Food Systems: A Mini-Review, Front Nutr. 2018; 5: 87.
[3] Da-Cheng H., 2019, Genomics and Evolution of Medicinal Plants, Ranunculales Medicinal Plants Biodiversity, Chemodiversity and Pharmacotherapy, Pages 1-33
[4] Eristavi L., 2005 Pharmacognosy, publishing house "Messenger of Georgia" Tbilisi
[5] Kuchukhidze J., Jokhadze M., 2012. "Botany" (medicinal plants), publishing house "Formati"
[6] Mandic A. I., Bilas S. M., detkovic G. S., M. J., danadanovic-Brunet & Vesna T. Tumbas, Polyphenolic Composition and Antioxidant Activities of Grape Seed Extract, International Journal of Food Properties, 11:4, 713-726
[7] Salem A., Saltana H., Chemical Composition Of Pulp, Seed And Peel Of Red Grape From Libya, GJSR Journal. Vol. 3(2), pp. 6-11
[8] Sharma G. N., Dave R., Sanadya J., Sharma P., Sharma K. K. 2010 Apr-Jun, Various types and management of breast cancer: an overview, J Adv Pharm Technol Res.; 1(2): 109–126.

PP 6. RISK MANAGEMENT IN THE DISTRIBUTION OF PHARMACEUTICAL PRODUCTS

N. Dughashvili, N. Kvizhinadze, Z. Chanturia, M. Murjikneli, N. Nikuradze

Tbilisi State Medical University, Department of Social and Clinical Pharmacy

Corresponding author e-mail: n.dughashvili@tsmu.edu

The implementation of GDP standards ensures that the quality and integrity of the drug is maintained throughout the supply chain[1,2]. In current study we aimed to determine what risks pharmaceutical product distributors are facing. In particular, the algorithm (block-schemes) for the development of pharmaceutical warehouse operations has been compiled in accordance with the GDP of "good distribution practice"[1] and temperature risk management in pharmaceutical supply chain was assessed by FMEA method [2].;The study was carried out in the pharmaceutical warehouse/depot of Esemo-Pharmina LLC, a clinical trial management organization using following research methods: logical modeling, information retrieval, processing and analysis based on the FMEA method [2].

Based on the FMEA analysis, we calculated the risk priority number. As a result, it was determined that the highest risk score at this stage is 21, since RPN in the interval 8-64 is considered a minor deviation and there is a very small probability of risk detection, in this case it does not require significant correction. In order to alleviate or eliminate minor deviations, which were observed during the research, it is necessary to improve the technical and software, as well as periodic training of all persons involved in the process. It is necessary to inform the persons involved in the process during transportation and warehousing at the customs regarding the specifics of the product, so that there is no violation of the temperature regime and the products are unusable. Although the process is performed by highly trained personnel, human errors can occur and significantly affect the process, so the protocol must be clearly drawn up to minimize unwanted consequences and avoid errors.

References:

[1] Quality risk management during pharmaceutical "good distribution practices" – A plausible solution. Bulletin of Faculty of Pharmacy, Cairo University. Volume 56, Issue 1, June 2018, Pages 18-25.

[2] FMEA RPN – risk priority number, calculation and evaluation. John Hartwell, July 1, 2022.

PP 7. POLYVINYL ALCOHOL-POLYETHYLENE GLYCOL-LACTIC ACID HYDROGELS FOR DRUGS CONTROLLED RELEASE

N.Durgaryan, N.Miraqyan

Yerevan State University, Yerevan, Armenia

Corresponding author e-mail: n.durgaryan@ysu.am

Poly(vinyl alcohol) (PVA) is successfully used for different biomedical applications [1]. It's well known the importance of hydrophile-hydrophobic balance on the properties of this systems. This work provides the synthesis of polyethylene glycol – polylactic acid copolymer and polylactic acid by stannum octannoate Sn(Oct)2 catalyst. Polylactic acid obtained by the same method was insoluble in water and not comfortable for hydrogel synthesis. On the base of obtained copolymer different composites hydrogels with PVA were prepared by freeze - fraw method [2,3] . After four cycles the swelling coefficient of 75% was determined for the composites on the base of 20% PVA. It was established that the composites with 20% PVA content were not show enough mechanical strength when used for dexamethasone delivery. The more comfortable composition was found 54.7 vol% PVA, 4.2 vol% copolymer for 0.4 vol% dexametasone content. Drug realese was established using phosphate buffer pH 7.4 (0.1M KH2P04 and 0.1 M NaOH), at constant temperature 37oC. UV-VIS absorption method was used to determine the drug concentration at λ=241 nm. Comparative study of PVA-

dexamethasone and PVA-copolymer-dexamethasone systems shows sustained release in the case of copolymer: after 6 days the drug content released from composite composed 50% of the drug released from PVA hydrogel.

References

[1] Jiang S, Liu S, Feng W. PVA hydrogel properties for biomedical application. J Mech Behav Biomed Mater. 2011 Oct;4(7):1228-33. doi: 10.1016/j.jmbbm.2011.04.005. Epub 2011 Apr 19. PMID: 21783131.
[2] Yokoyama, F., Masada, I., Shimamura, K., Ikawa, T., Monobe, K. Morphology and structure of highly elastic poly (vinyl alcohol) hydrogel prepared by repeated freezing-and-melting. Colloid and Polymer Science 264.7 (1986): 595-601.
[3] Hassan, C. M., Peppas, N. A. Structure and morphology of freeze/thawed PVA hydrogels. Macromolecules 33.7 (2000): 2472-2479.

PP 8. ANALGESIC ACTIVITIES OF PLANT SECONDARY METABOLITES

Natela Gogitidze[1], Nadezhda Mushkiashvili[2], Zhana Novikova[3], Marine Sulakvelidze[2]

[1] Tbilisi State Medical University I. Kutateladze Institute of Pharmcochemistry, Department of Preclinical Pharmacological Research, Tbilisi, Georgia

Corresponding author e-mail: n.gogitidze@tsmu.edu

Conducting a comprehensive study of the activity of a potential drug substance in animal experiments is the main part of preclinical trials of a pharmacological study. To date, the study of new drugs with analgesic activity occupies ~24% of the total number of studies in the world [1]. The main standard operating procedure for measuring the threshold of acute pain sensitivity and the potential analgesic effect of the studied pharmacological drugs in response to thermal stimulation is the “Hot plate” test, the basis for the study of analgesic activity, which is used to identify analgesically active compounds that suppress somatically superficial pain, and acute pain. The Hot plate approach has an advantage over other methods of thermal stimulation, such as the “Tail flick”, in that it can be repeated in the same animals over a short period of time (2-3 h) without producing tissue injury. Here we present the generalized results of our recent studies of the analgesic activity of herbal extracts and their purified fractions containing main classes of plant secondary metabolites: flavonoids, terpenes, steroids, and alkaloids. Surprisingly, the literature data on the analgesic activity of flavonoids turned out to be much less than we expected, so we paid special attention to this particular group (Fig.1).

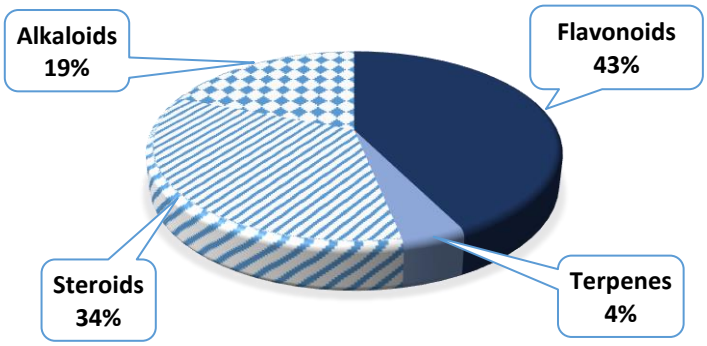


Figure.1. Distribution of plants secondary metabolites screened for analgesic activity.

In total, 47 samples from 18 plant species have been investigated using “Hot plate” model in mice and 31% of them exhibited more than 50% increase in latency period, including six samples (4 flavonoids and 2 alkaloids) with analgesic effect above 100% (Tab.1).

Table 1. Comparative analgesic potency of screened secondary metabolites

Metabolites	N of samples	N of samples with analgesic effect			
		mild (< 30 %)	average (30-50 %)	strong (>50%)	hyperalgesia
Alkaloids	9	1	3	5	-
Flavonoids	20	3	7	10	-
Steroids	16	6	5	1	4
Terpenes	2	-	2	-	-

References

[1] Rauf, A., Jehan, N., Ahmad, Z., & Mubarak, M. S. (2017). Analgesic Potential of Extracts and Derived Natural Products from Medicinal Plants. *In (Ed.), Pain Relief - From Analgesics to Alternative Therapies. IntechOpen, 339-351*

PP 9. PHYTOCHEMICAL STUDY OF LAVENDER CULTIVATED IN GEORGIA

M. Jokhadze, S. Gokadze, L. Zardiashvili, M.Maisashvili, K. Kirkitadze

Tbilisi State Medical University, Scientific research and practical skills laboratory, Tbilisi, Georgia

Corresponding author e-mail: S.Gokadze@tsmu.edu

Lavender *(Lavandula spica),* plant- native to the Mediterranean region. belongs to the family Labiatae /Lamiaceae [3]. Nowadays lavender is cultivated all over the globe (in Bulgaria, France, Spain, Great Britain, China, Australia, and the United States of America) [4], due to its extensive use in perfumery, cosmetics, aromatherapy, traditional and modern medicine [1] In recent years, the cultivation of lavender has also begun in Georgia, prompting the necessity for a phytochemical investigation of native lavender varietals. The current study aimed to characterize some pharmacobotanical and phytochemical features of lavender Georgian cultivar. Commodity analyses of leaves and flowers were done in accordance with State Pharmacopeia. Microscopic analysis of lavender leaves was performed using light microscopy. Qualitative analysis of lavender essential oil was carried out using GC-MS and TLC methods. In addition, the antioxidant potency of has been evaluated by DPPH assay.

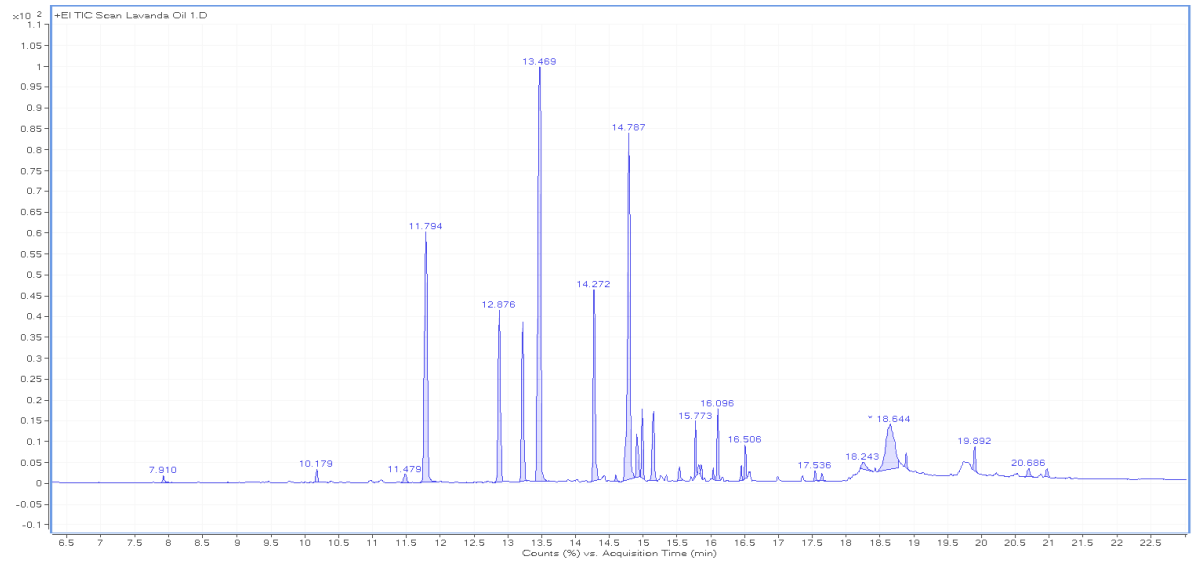


Figure 1. GS-MS chromatogram of of Lavender methanolic extract

Humidity and total ash of the raw material were determined by commodity analysis and appeared, respectively, 11% and 6%. Microscopic study of lavender leaves revealed the following diagnostic signs: diacytic stomata, essential oil containing glandular trichomes and stellar villi. Dominating chemical constituens: linalool acetate; linalool; geranyl acetate; cineole and caryophyllene oxide, have been identified by TLC analysis. GC-MS of lavender leaves and flowers methanolic extract revealed 45

dominant individuals: lavender acetate, β linalool, camphor, geraniol, linalyl acetate, o-cymene, eucalyptol (cineole), iα-terpineol, geraniol (Fig.1). The antioxidant capacity of *L.spica* in DPPH assay expressed as IC_{50} was 263.14 μg/ml [2].

The obtained results allow concluding that Georgian lavender cultivar is a suitable raw material for the industrial production of lavender essential oil and other bioactive products.

References :

[1] Catherine J. Chu and Kathi J. Kemper. 2001. Lavender (Lavandula spp.) The Center for Holistic Pediatric Education and Research.
[2] Choukairi Z., Hazzaz T., Ferrandez M.J., Fechtali T. 2020. The cytotoxic activity of Salvia officinalis L. and Rosmarinus officinalis L. Leaves extracts on human glioblastoma cell line and their antioxidant effect. Journal of Complementary and Integrative Medicine, Volume 17 Issue 4,
[3] Giray F. H. 2019. An Analysis of World Lavender Oil Markets and Lessons for Turkey . Journal of Essential oil bearing Plants,volume 21,issue 6,page 1612-1623.
[4] Wells R., Truong F., Adal A.M et al. 2018. Lavandula Essential Oils: A Current Review of Applications in Medicinal, Food, and Cosmetic Industries of Lavender . Natural Product Communications, 2018 Vol. 13 No. 10 page 1403 – 1417

PP 10. DETERMINATION OF NITROFURAN METABOLITES IN MEAT BY LIQUID CHROMATOGRAPHY WITH DDODE-ARRAY DETECTOR

Davit Gotsiridze [2], Qetevan Baramidze [1], Tamar Chikviladze [2]

[1]Globaltest testing laboratory, [2] Tbilisi State Medical University ,Department of pharmacy and toxicology Tbilisi, Georgia

Corresponding author e-mail: davit.gotsiridze@gmpgeo.com

For the analysis of four metabolites of nitrofurans in meat - furazolidone, furaltadone, nitrofurazone and nitrofurantoin - a liquid chromatographic method using a diode detector was used. The method complies with the requirements of European Commission Resolution 2002/657 / EC. [1]

The sample was extracted by ethyl acetate, liquid-by-liquid extraction method, cleaning by solid phase extraction on a silica gel column, after sample hydrolysis and derivatization with 2-nitrobenzaldehyde.

The validation of the method was conducted following the European Union criteria for the analysis of veterinary drug residues in foods. [2,3] The decision limits (CCα) were 0.16-0.34 μg/kg, and the detection capabilities (CCβ) 0.20-0.41 μg/ kg.

The advantage of the method is that with relatively less financial costs it is possible to determine the amount less than the minimum working limit for nitrofuran metabolites set by the EU (MRPL Minimum Required Performance Limit 1 μg /kg) and the method is in financial terms, available to developing countries [4,5,6]

References

[1] Commission Decision (2002): Commission Decision 2002/657/EC of 12 August 2002 implementing Coun-cil directive 96/23/EC concerning the performance of analytical methods and the interpretation of results. Official Journal of the European Communities, L221, 8–36.
[2] Chang, G. R.; Chen, H. S.; Lin, F. Y. 2016. Analysis of banned veterinary drugs and herbicide residues in shellfish by liquid chromatography-tandem mass spectrometry (LC/MS/MS) and gas chromatography-tandem mass spectrometry (GC/MS/MS). Mar. Pollut. Bull. 113, 579– 584
[3] Li, J.; Ren, X.; Diao, Y.; et.al. 2018. Multiclass analysis of 25 veterinary drugs in milk by ultra-high performance liquid chromatography-tandem mass spectrometry. Food Chem. 257, 259–264,
[4] Gotsiridze D, Baramidze K , Chikviladze T, Otarashvili T. Nitrofurans and their metabolites in food; (2022) J. Experimental and Clinical Medicine, Georgia. No.4

[5] Gotsiridze D., Baramidze K., Chikviladze T.,et al. Development And Validation Of Liquid Chromatographic MethodFor The Determination Of Nitrofuran Residues In Fish Samples. 2020. Collection of Scientific Works. Vol 54 (42-45)
[6] Gotsiridze D., Baramidze K., Chikviladze T. et al. 2022. Development and validation of liquid chromatographic methodfor the determination nitrofuran residues in honey. Collection of Scientific Works. Vol 55 (60-63)

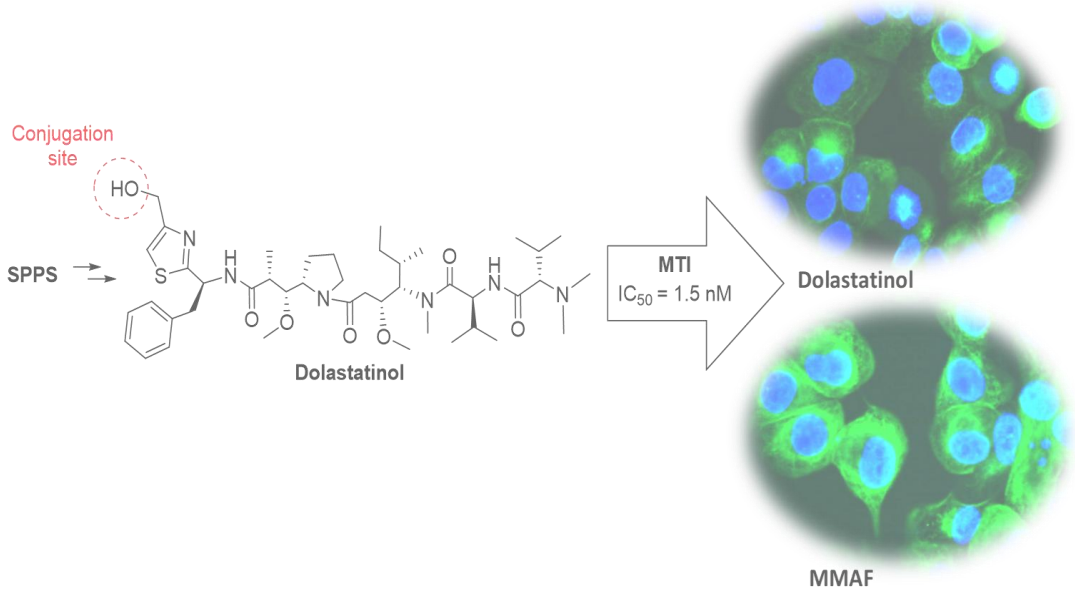
PP 11. SPOC SYNTHESIS OF LINKER-DOLASTATIN 10 DERIVATIVES FOR ANTIBODY DRIVEN TARGETED DRUG DELIVERY.

Hodaya Gutman, Akash Panja, Lena Tuchinsky

Department of Chemical Sciences, Ariel University, Ariel, Israel;

Corresponding author e-mail: akash@ariel.ac.il

This work describes the development of targeted drug delivery (TDD) tools to treat cancer. One possibility to overcome the side effects of chemotherapy is delivering the drugs by specific carriers that target mainly cancer cells. As a toxic payload we develop a dolastatinol, the derivative of sub-nanomolar microtubule toxin – DOLASTATIN 10. It differs from the parent peptide by methylene hydroxyl tether at C-terminus and synthesized by solid phase peptide synthesis (SPPS) on 2-chlorotrityl chloride resin utilizing a pH-triggering self-immolative monosuccinate linker. The introduction of the C-terminus hydroxyl methylene functionality preserves the anticancer properties of the parent dolastatin 10, including strong suppression of the cell proliferation, migration, high cytotoxicity. Our research establishes a new facile route toward the further development of C-terminus modified dolastatin-10-based microtubule inhibitors for antibody-driven targeted anticancer treatment.



References

[1] [H. Gutman et al. ''Discovery of Dolastatinol: A Synthetic Analog of Dolastatin 10 and Low Nanomolar Inhibitor of Tubulin Polymerization'' ACS Medicinal Chemistry Letters 2021 12 (10), 1596-1604. DOI: 10.1021/acsmedchemlett.1c00432

PP 12. GAS CHROMATOGRAPHY-MASS SPECTROMETRIC DETERMINATION OF VENLAFAXIN IN BIOLOGICAL FLUIDS

N. Laziashvili[1], N. Imnadze[1], M. Jalaghania[1]

[1]Tbilisi State Medical University, Department of Pharmaceutical and Toxicological Chemistry, Tbilisi, Georgia

Corresponding author e-mail: n.imnadze@tsmu.edu

In recent years, the global situation in the world provoked the permanent increase in mental disorders in our society, which also has led the increased prescription of antidepressants [1].

Antidepressants used for the treatment of depressive disorders [2] are often the cause of acute and fatal poisonings, therefore, today, antidepressants represent one of the most interesting classes from the point of view of chemical-toxicological research.

Often, antidepressants and analgesic agents such as venlafaxine and tramadol are prescribed simultaneously. The combination of these two drugs in some cases causes of induction of different types of manias and frequently intoxications [3].

Therefore, the development of methods for confirmatory determination of Venlafaxine is an important task for analytical toxicology. Interest duplicates, as in Georgia Tramadol is attributed to narcotic drugs.

Thus, the aim of this study was to choose the optimal liquid-liquid extraction method of Venlafaxin isolation from human urine. Blank urine samples (#10) spiked with venlafaxine concentrations of 500 ng/mL. To achieve the designed goal the various conditions of liquid-liquid extraction have been studied. The results shown that system: Cyclohexane gives ER=94.2% and effectively can be used for Venlafaxine extraction from biological material.The GC-MS study of the substance was done in following conditions: equipment - Agilent 7000 Triple Quad, 30m×250µm×0.25µm Elite 5-MS column. The injector temperature was 250°C, the owen temperature was progammed at 60°C-300°C, the source ionization EI - 70 ev. Helium with flow rate 1 ml/min was used as mobile phase, the scanning regime was TIC. Chromatographic period 15 min.

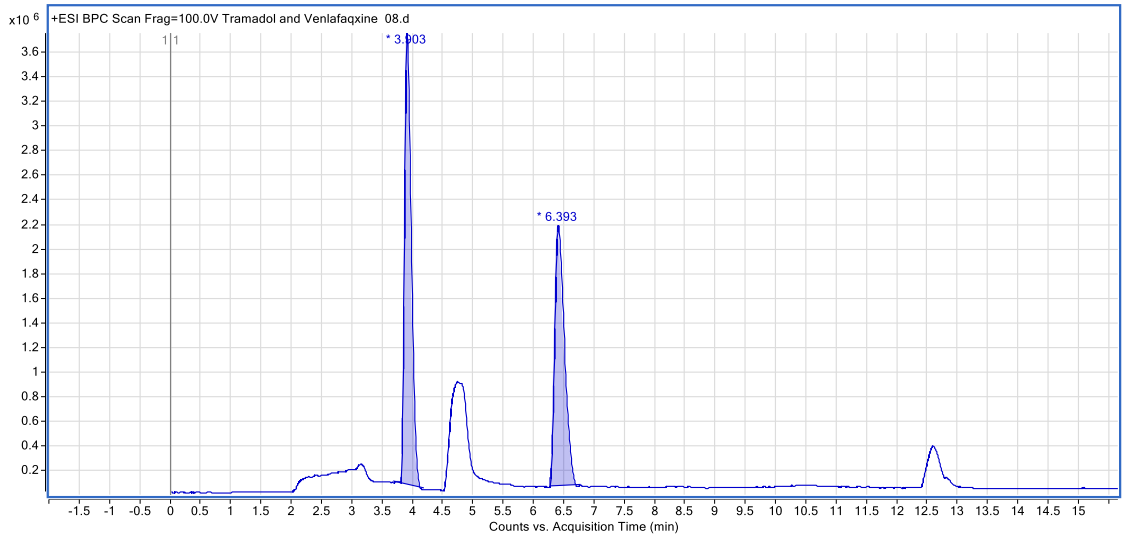


Figure 1. GC-MS chromatogram of Venlafaxine (retention time =3.9 min) and Tramadol (retention time =6.39 min)

The described conditions of GC-MS method give opportunity to thin symmetric peak of Venlafaxine at 3.9 min, meanwhile tramadol retention time in same conditions is 6.39 min.

Developed sensitive and selective GC-MS method gives opportunity as for individual identification of venlafaxine in biological fluids, as for its simultaneous determination with tramadol.

References:

[1] Ng C, Sarris J, Singh A, Bousman C, et al. 2013, Pharmacogenetic polymorphisms and response to escitalopram and venlafaxine over 8 weeks in major depression. *Hum Psychopharmacol.* Sep;28(5):516-22.

[2] Suwała J, Machowska M, Wiela-Hojeńska A. 2019, Venlafaxine pharmacogenetics: a comprehensive review. *Pharmacogenomics.* Jul; 20(11):829-845

[3] Cipriani A, Furukawa TA, Salanti G. 2018, Comparative efficacy and acceptability of 21 antidepressant drugs for the acute treatment of adults with major depressive disorder: a systematic review and network meta-analysis. *Lancet.* 391:1357–1366.

PP 13. DEVELOPMENT OF POLYMER-CLAY BASED HYDROGEL FORMULATION FOR ESSENTIAL OIL FROM MATRICARIA CHAMOMILA, CULTIVATED IN GEORGIA

A. Janezashvili[1,2], L. Tsiklauri[1]

[1]Tbilisi State Medical University I. Kutateladze Institute of Pharmacochemistry, [2] Tbilisi State Medical University, Tbilisi, Georgia,

Corresponding author e-mail: ani.janezashvili@icloud.com

Polymer-clay hybrid materials find their broad application in drug delivery systems due to the improved technological (rheology, drug incorporation efficiency and controlled release ability) characteristics and integrate the properties of each component, such as swelling, water uptake, bioadhesion [1].Georgian bentonite clay preparation – Tikha-Ascane, investigated and developed at the I. Kutateladze Institute of Pharmacochemistry, is approved for the curative and pharmaceutical applications by national public health authorities [2, 3]. The phytoremedies are introduced and used in medicinal practice due to their natural action on the body, fewer side effects and wide range of pharmacological activities; these properties are determined by the geographical area of distribution, environmental factors, methods of collection and processing of herbal row materials [4].

Matricaria chamomilla L. is one of the popular medicinal plants from the Asteraceae family commonly used in folk and conventional medicine. Essential oil (EO) is presented in varying amounts in almost all parts of herb. The content and chemical composition of EO is different and determined by genetic and environmental factors. Due to its distinguished biological activity, chamomile EO is extensively used in ointments, gels, capsules, suppositories and solutions for the treatment of several diseases [4].

The objective of the present study was to develop a hydrogel formulation for EO extracted from *Matricaria chamomilla* L. cultivated in Georgia using polymer-bentonite clay hybrid material.

In this study polymer-clay complex was synthesized using domestic bentonite clay (Tikha-ascane) from Ascana deposit; the polymeric matrix of the composites consists of polyacrylic acid (Carbopol 940). The intercalation of Tikha-ascane in the polymer structure was confirmed by infrared spectroscopy.

EO was extracted from air-dried aerial parts of *M.chamomilla* harvested in the beginning of June in western Georgia. EO was evaluated by thin-layer and gas chromatography coupled with mass spectrometry (GC-MS) methods. It was found out that the chemical composition of essential oil obtained by hydrodistillation is consistent with data reported in the literature [4]. The extraction yield of EO from air-dried material was 0.3%; the major constituents were α-bisabolol oxide (44.17%), α-bisabolol oxide B (13.62%), β-farnesene (12.51%), bisabolone oxide A (9.39%), spathulenol (2.5) and chamazulene (1.71%).

The hydrogels were prepared by addition of 1% of EO to Tikha-ascane - Carbopol 940 composite and their organoleptic properties, moisture content, pH, uniformity, spreadability, viscosity, rheological parameters, thermal and colloidal stabilities have been determined. The optimized formulation was homogeneous, with high stability and good rheological properties and complied with requirements for semisolid dosage forms. Qualitative and quantitative evaluation of essential oil in hydrogels showed

similar chromatographic profile for the tested samples and the presence of constituents of chamomile EO; the content of active component in formulations was in the range of 0.97-1.15% (in relation to bisabolol oxide A).

References

[1] Meirelles, LMA., Raffin, FN. 2017, Clay and Polymer-Based Composites Applied to Drug Release: A Scientific and Technological Prospection, J Pharm Pharm Sci., vol.20, pp.115-134.
[2] Kutateladze I. 1955, Ticha-Ascanae for medical purposes. Tb., Gruzmedgiz, 40 p.
[3] Tsiklauri, L., Dadeshidze, I., Tsagareishvili, G. 1994, The Rheological Studies of Ticha-Ascanae Suspension and Ointments with Sea-Buckthorn Oil on Its Basis, Bull. Georgian Acad. Sci., vol. 150, no. 2, pp. 262-265.
[4] Stanojevic, LP., Marjanovic-Balaban, ZR., Kalaba, VD., et al. 2016, Chemical Composition, Antioxidant and Antimicrobial Activity of Chamomile Flowers Essential Oil (Matricaria chamomilla L.), J. Essent. Oil-Bear. Plants, vol. 20, no. 6, pp. 1557-1569.

PP 14. SYNTHESIS OF SOME CONDENSED HETEROCYCLIC SYSTEM CONTAINING π-ELECTRONDEFICIENT AND π-ELECTRONPREFICIENT NUCLEI

B. Arziani, I. Jinikashvili

Tbilisi State Medical University, Tbilisi, Georgia

Corresponding author e-mail: i.jinikashvili@tsmu.edu

Synthesis-type researches that are focused on merging of two or several heterocycles in a single system are topical and prospective. In our case the interest towards these studies is heightened by the fact that there takes place conjugation of π–electon-deficit and π–excess-electron heterocycles, which to a certain extent keep their autonomy, and as a result reaction centers of diametrally opposite nature, one of them easily participates in electrophilic, while second one – in nucleophilic substitution reaction, are originated in one molecule. This fact drastically increases a number of products obtained in the research process and rises the probability of successful goal-oriented synthesis of biologically active compounds. Condensed heterocyclic compounds, in which indole fragment is annelated with heterocycles containing two nitrogen atoms, present a new polyheterocyclic systems. In order to create medicinal preparations of some pharmacological action we deemed topical to develop an convenient preparative method that will make it possible to synthesize targeted heterocyclic systems aimed to study of their structure, chemical properties and biological activity. From this perspective, development of convenient preparatory methods for their synthesis, study of structure and reaction capacity sparks definite interest.

Heterocycles (pyridazine, pyrazine, phthalazine) conjugated with phthalazines, create in them structural basis for very important natural or synthesized biologicall active compounds and health aids. Indole is a key structural fragment of series of alcaloids, antibiotics and medications [1-3]. The list of those biologically active compounds and medications that are based on phthalazine cycle is impressive, as well. Phthalazine-hydrazines are characterized by persistent hypotensive activity, and insignificant toxicity that is the most important [4]. Some phenylphthalazides have high tuberculostatic activity.

We offer a convenient preparative method for the synthesis of the key aminophtalazine from 1,4-dichloro-5-nitrophtalazine. By redusing the diazonium salt of 5-aminophtalazine to the corresponding hydrazine and condensing the latter with pyruvic acid ethyl ester, a mixture of pyruvic acid ethyl ester phthalhydrazone was synthesized [2]. A convenient preparative method for the synthesis of 1H-pyrrolo-[3,2-h]-phthalazine was processed.

References

[1] M. Suman, B.Vijayabhaskar, V.K.Syam Kumar, & B.Venkateswara. 2017, “One-pot Three-component green synthesis of novel dihydrophthalazine-1,4-diones”. J. of General Chemistry, vol.87, p.2039-2044.

[2] Z. Malinovski, E. Fornal, B.Sierocinska, R.Czeczko, M. Nowak. 2016. "Synthesis of 4-alkylsulfanylphtalazin-1(2H)-ones via palladium catalyzed sulfanylation of substituted 4-bromophtalazin-1(2H)-ones". Tetrahedron, vol.72, Issue 49, p.7942-7951.
[3] C.Lim, S.Kim, B.Lee & others. 2012, "4-Arylphtalazin-1(2H)-one derivaties as potent antagonists of the melanin concentrating hormone receptor 1(MCH-R1), vol.22, Issue1, p.427-430.
[4] M.Khalil, A.Berghot and A. Gouda. 2011. "Desing, synthesis and antibacterial activity of new phthalazinedione derivatives". J. of the Serbian Chemical Society. vol. 76, no. 3, p. 329-339.

PP 15. TRITERPENE GLYCOSIDES FROM BUPLEURUM WITTMANNII STEV. AND BUPLEURUM ROTUNDIFOLIUM L.

Zurab Kemoklidze, Zhana Novikova, Marine Sulakvelidze

Tbilisi State Medical University I. Kutateladze Institute of Pharmacochemistry, Tbilisi, Georgia

Corresponding author e-mail: z.kemoklidze@tsmu.edu

Bupleurum falkatum. from Apiaceae (Japanese name - Saiko) family has been used in Japanese and Chinese folk medicine since ancient times to treat rheumatism and other diseases. Two species common in Georgia – *B.Wittmannii* Stev. (Caucasian annual endemic) and *B.rotundifolium* L., were investigated on the content of triterpene saponins and an optimal conditions to obtain the maximal yield of triterpene glycosides has been developed. It was established that *B.Wittmannii* Stev. contains 3.4%, whereas *B. rotundifolium* L. -3.7% of triterpene glycosides. Among the triterpene glycosides obtained from aboveground organs, the oleanolic type saponins - saikosaponin A and saikosaponin C have been identified.

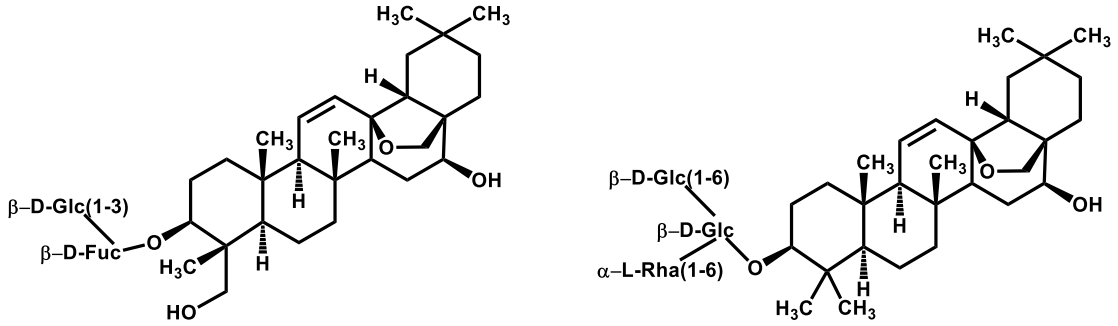


Figure 1. Saikosaponin A (left) and Saikosaponin C (right)

Crude triterpene glycosides obtained from the aerial parts of *B.rotundifolium* (BUP-2) and *B. Wittmannii* Stev. (BUP-3) have been tested in carrageenan-induced edema model in rodents. It was established that both of investigated products exhibit pronounced anti-inflammatory effects (Fig.2). Interestingly, the effective dose of triterpene glycosides from *B. Wittmannii* Stev. appeared to be four times higher than that of *B.rotundifolium* – 100 mg/kg and 25 mg/kg, respectively.

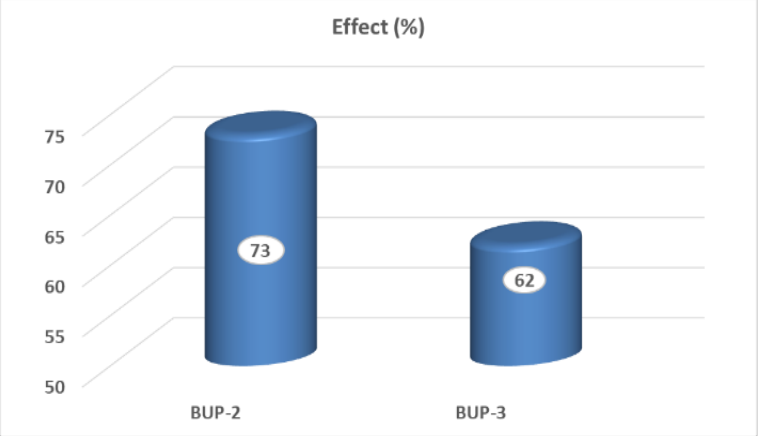


Figure 2. Antiinflammatory effect of triterpene glycosides of *B.rotundifolium* (BUP-2) and *B.Wittmannii* Stev. (BUP-3)

The obtained results correlate with data published by Yamamoto [1]. The structure activity relationship of saikosaponins was fundamentally studied by Abe et al., who attributed activity to presence of the CH_2OH radical in position 24 [2].

References

[1] M.Yamamoto, A. Kumugai and Y.Yamara. Structure and actions of saikosaponins isolated from *Bupleurum falkatum* L. I. Anti-inflammatory action of saikosaponins. Arzneimittelforschung. 1975; vol.25(7):1021-3.
[2] H. Abe et all. The effects of saikosaponins on biological membrane. Planta medica,1978; vol.34: 287-290.

PP 16. FATTY ACIDS AND SOME BIOLOGICALLY ACTIVE COMPOUNDS OF THE SEEDS OF ARMENIACA VULGARIS MILL. AND PERSICA VULGARIS MILL. SPREAD IN GEORGIA

B. Kikalishvili, Ts. Sulakvelidze, M. Malania, D. Turabelidze

Tbilisi State Medical University I. Kutateladze Institute of Pharmacochemistry, Georgia, Tbilisi 0159, P. Sarajishvili St. 36

E-mail: b.kikalishvili@tsmu.edu

The families of apricot (*Armeniaca vulgaris Mill.*) and peach (*Persica vulgaris Mill.*) are *Rosaceae* timber plants. Their cultivars are well adapted to moderate climate.

The fruits of both plants are rich in various biologically active substances. Apricot and peach seeds contain fat, sterins, folic acid, catechins, flavonoids, organic acids, carotenoids, K, A, E, C, P and B group vitamins, glycoside amygdalin. In medicine, apricot seeds and air-dry fruits are used to treat vitamin deficiency, anemia, and cardiovascular and digestive diseases. Its oil has hepatoprotective, antibacterial, antiviral and cytostatic activities. It is used in pharmacy, dermatology and cosmetology. Peach oil is used in medicine to treat dermatitis, burns, eczema, anemia, gastritis, vitamin deficiency, as well as in cosmetology as a smoothening and anti-inflammatory agent.

Sums of neutral lipids (NL) from seeds of apricot and peach of a yellow color and oily consistence, with yields of 28% and 35%, respectively are obtained by extracting with N-hexane at a room temperature and following thickening at 60°C with a vacuum-rotary apparatus. The physical-chemical parameters of the above-mentioned oils are given in Table 1.

Neutral lipids were divided by thin-layer chromatographic method on a Silica gel F254 (20 cm × 20 cm, Merck, Darmstadt, Germany) plate. Detection was done with iodine vapor and 30% sulfuric acid, color

reactions, Rf values, and witnesses. The main classes included in NL were identified: hydrocarbons, triglycerides, fatty acids, and sterins.

Table 1. Physical-chemical parameters of the oil from the seeds of *A.vulgaris Mill. and P.vulgaris Mill.*

No	Physical-chemical indicators	Value	
		Armeniaca vulgaris Mill	**Persica vulgaris Mill**.
1	Refraction index	1,464	1,468
2	Density	0,910	0,912
3	Acid value (KOH)	1,1	0,4
4	Iodine value	96	102

Saturated, mono- and poly-unsaturated fatty acids were identified in some of NLs by Gas Chromatography combined with Mass Spectrometry. The following acids were identified: hexadecane 6.09%, hexadecene 1.68%, octadecane 2.25%, 9-octadecene 74.09%, eicosane 0.27%, eicosene 0.66%, tetracosane 0.13% and hexacosane 0.09% in *Armeniaca vulgaris Mill.* oil, and tetradecane 55%, hexadecane 6,74%, octadecane 7,50%, octadecene 8%, 9; 12 octadecadiene 8,50%, 9;12;15 octadecatriene 9%, eicosane 12,09%, dokosane 13,01% in *Persica vulgaris Mill*. oil.

Carotenoids in the obtained NLs were determined quantitatively by using a spectrometric method in 451 nm wavelength, at 4.7 mg% and 3.3 mg%, respectively.

The presence of amino acids in 80% alcohol solution of apricot and peach seeds is established qualitatively, in particular, histidine, asparagine, serine, alanine, valine, and phenylalanine in apricot seeds and lysine, asparagine, glycine, serine, valine, and phenylalanine in peach seeds.

The vegetable oils obtained from the study object are rich in fatty acids and various biologically active compounds making it possible to develop inexpensive and efficient therapeutic and prophylactic drug with the local raw materials, which can be practical applied in medicine and perfumery.

References

[1] Gagnidze R. 2005, Vascular plants of Georgia, *a nomenclatural checklist*. Tbilisi, pp. 96-97.

[2] Guclu K., Altun M., Ozyurek M., Karademir S.E., Apak R., 2006, Antioxidant capacity of fresh, sun- and sulphited-dried Malatya apricot (Prunus armeniaca) assayed by CUPRAC, ABTS/TEAC and folin methods, *Int J Food Sci Technol*. 41(1), pp. R.76-85.

[3] Kikalishvili, Sulakvelidze Ts., Malania M., Getia M., Turabelidze D., 2020 Characterization of fatty acids in some plants growing in Georgia. *International Journal of Pharmacognosy and Phytochemistry*, 9(5): pp.1331-1333.

[4] *British Pharmacopoeia*, vol. V; London: The Stationery Office. 2017, pp. 202-203.

PP 17. KNOWLEDGE, ATTITUDES AND PRACTICES OF PHARMACISTS ABOUT PHARMACOVIGILANCE IN GEORGIA

Z. Kikvadze[1], T. Tchumburidze[1], N. Imnadze[2], G. Tsertsvadze[2]

Tbilisi State Medical University: [1]Department of Social and Clinical Pharmacy; [2]Department of Pharmaceutical and Toxicological Chemistry, Tbilisi, Georgia

zurab.kikvadze@gepha.com

Today, society should fight with different types of dangers associated with healthcare, environmental pollution, global warming, etc.

But today, when challenges of the world are absolutely new and life style became different, the most important to create and develop the safe and effective treatment against the sever diseases, and of course along with this, increased role of pharmacovigilance (PV).

The side effect monitoring and risk management system become vitally important and needs well established plan, that should be followed by any professional in the healthcare system [1].

Pharmacists, the healthcare team members with complete drug therapy knowledge, have a significant role in PV activities. The pharmacists working in pharmacies and in hospitals, in particular, clinical pharmacists with an excellent clinical background are more likely to report adverse reactions (ADRs) because of their regular interaction with the physicians and other health team members in addition because to access to patients' medical records [2].

There is a strong relationship between ADR reporting and healthcare professionals' knowledge, attitude, and practice (KAP) [3].

Studies have demonstrated that streamlining KAP concerning PV is vital in detailing methodologies to encourage ADR reporting. Certain studies have been conducted in Georgia, namely in pharmacies of pharmaceutical company Gepha.

A self-administered 30-item questionnaire was used to investigate the KAP of pharmacists working in JSC Gepha's pharmacies towards ADR reporting and PV, including the factors that discourage ADR reporting. The survey was created using previously published local and international studies as a guide. At this stage the study was conducted only in Tbilisi.

Of 250 pharmacists selected, 238 completed the questionnaire. The pharmacists' knowledge of pharmacovigilance and reporting of adverse drug reactions was poor even the existance of PV department in company. Only 25.1% correctly defined pharmacovigilance and 20% knew about obligation of transfer of such information. The attitudes of the pharmacists to pharmacovigilance was positive: 76% believed that pharmacovigilance (PV) study needed to be enforced in the pharmacy curriculum. 72.5% said that they need and would like to practice PV reporting, if they will get the appropriate training in this field. Pharmacists usually depended mostly on drug information leaflets to update their knowledge on adverse drug reactions.

Based on our study we can conclude that there is very low level of knowledge regarding the pharmacovigilance, but in same time the readiness of the pharmacists to be involved in training programmes is relatively high.

Therefore, should be introduced for practising pharmacists to improve their knowledge, skills and encourage their active participation in post marketing study of drugs.

Same time Educational system and Regulatory authorities need to reinforce the knowledge and importance of reporting of drug adverse reactions and try to implement pharmacovigilance policies in the Georgian healthcare system.

References

[1] Kikvadze Z., Gagua N., Tchumburidze T., Imnadze N. 2020, Importance of Pharmacovigilance in Assurance of the Safety of COVID -19 Vaccination. Collection of scientific works XLXIV. pp. 103-105

[2] Hadi MA, Neoh CF , Zin RM, Elrggal M, Cheema E. 2017, Pharmacovigilance: pharmacists' perspective on spontaneous adverse drug reaction reporting. Integr. Pharm. Res. Pract., 6 (2017), pp. 91-98

[3] Ibrahim DM , Shawki MA , . Solayman MH, Sabri, NA. 2021, Pharmacovigilance education to healthcare professionals: Will it affect their performance in reporting adverse drug reactions? Int. J. Clin. Pract., 75 (11)

PP 18. BREAST CANCER PHOTOIMMUNOTHERAPEUTIC TREATMENTWITH NOVEL ANTIBODY-GUIDED IODINATED PHOTOSENSITIZER

Dmytro Kobzev [1,2], Olga Semenova[1,2], Anatoliy Tatarets[2], Leonid Patsenker[1]

[1]Department of Chemical Sciences, the Faculty of Natural Sciences, Ariel University, Ariel, Israel. [2]State Scientific Institution "Institute for Single Crystals" of the NAS of Ukraine, Ukraine.

Corresponding author e-mail: dmytrok@ariel.ac.il

Photoimmunotherapy (PIT) is one of the promising cancer treatment methods, which synergistically combines two different modalities, immunotherapy and photodynamic therapy (PDT). While PDT utilizes an organic dye termed photosensitizer (**PS**) that upon light exposure generates cytotoxic species killing cancer cells, immunotherapy is based on modulation of the immune system with certain compounds such as antibodies (**Ab**) including the FDA-approved humanized monoclonal antibody trastuzumab (Herceptin™) which is widely used for immunotherapy of breast cancer. Antibody can be utilized also as a carrier for specific delivery of photosensitizer to targeted cancer cells in PDT. Arming of a photosensitizer with a tumor-specific antibody to yield a **PS–Ab** conjugate affords its selective delivery to cancer cells, which increases treatment efficacy and reduces side effects to healthy organs.

Herein we introduce a photoimmunotherapeutic method based on the newly synthesized, highly water-soluble diiodinated heptamethine cyanine photosensitizer, **2ICy7**, absorbing and emitting in the near-IR spectral range conjugate and linked to trastuzumab. This **2ICy7-Ab** conjugate is investigated in the xenograft mouse model to suppress tumor growth *versus* the non-iodinated **Cy7–Ab** conjugate (Fig. 1*A*). The only immunotherapeutic effect (1.4-fold tumor growth suppression) is observed for **Cy7–Ab** and **2ICy7–Ab** in the dark and for the light-irradiated **Cy7–Ab**, while the synergistic impact of PDT (5.4-fold tumor growth suppression) is obtained upon light irradiation with **2ICy7-Ab** (Fig. 1*B*). In addition, these Dye–Ab conjugates provide a well-detectable fluorescent signal in the body that enables real-time monitoring of their delivery and accumulation, which is important to recognize the optimal time for light irradiation and thus improves the precision and safety of the treatment.

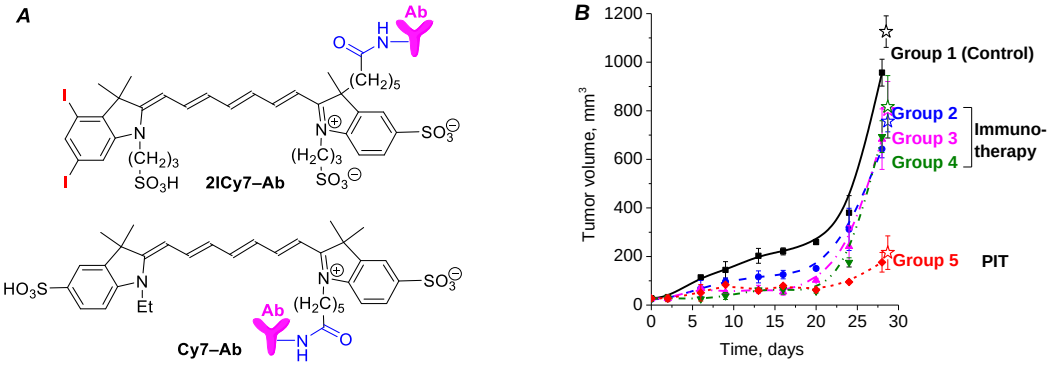


Figure 1. (***A***) Chemical structures of the **2Cy7–Ab** and **Cy7–Ab** conjugates and (***B***) tumor growth curves of BT-474 human breast cancer tumor bearing mice: control (group 1), monitored after a single IV administering of 100 µg (0.5 mg/mL) of **Cy7–Ab**, when kept in the dark (group 2) or exposed to NIR light (730 nm LED, 63 J/cm^2) for 15 min (group 3), and **2ICy7–Ab**, when kept in the dark (group 4) or exposed to the same NIR light dose (group 5).

We anticipate that conjugation of **2ICy7** or other cyanine-based photosensitizers of a similar structure with a wide range of antibodies can help to develop efficient tools for the photoimmunotherapeutic treatment of different types of cancer.

PP 19. CHEMICAL MODIFICATION OF BROMELAIN WITH DEXTRAN ALDEHYDE FOR ITS THERAPEUTIC USE IN MUSCULOSKELETAL DISORDERS

T. Korinteli[1], N. Gorgaslidze[2], L. Nadirashvili[1], G. Erkomaishvili[1]

Tbilisi State Medical University: [1]Iovel Kutateladze Institute of Pharmacochemistry, Department of Phytochemistry; [2]Department of Social and Clinical Pharmacy, Tbilisi, Georgia

Corresponding author e-mail: t.korinteli@tsmu.edu

Musculoskeletal disorders (MSDs) are one of the most important medical issues we face today, due to humanity's modern sedentary lifestyle [1]. Because of the multiple side effects of nonsteroidal anti-inflammatory drugs, search for new remedies and selection of the best dosage forms remains one of the major challenges of modern medicine [2]. The proteolytic enzyme bromelain derived from the stems of the pineapple plant (*Ananas comosus*) has a wide range of therapeutic activity and is characterized by minor side effects [3]. Among its activities are a strong anti-inflammatory and an analgesic effects [4]. Proteolytic enzymes of plant origin sometimes cause allergic reactions and their chemical modification is one of the most efficient ways of reducing such a side effect [5].

The goal of this research was to create a more stable and less allergic form of bromelain by means of chemical modification. The modification was carried out with a water-soluble, biocompatible and biodegradable natural polysaccharide – dextran, oxidized to dextran aldehyde. As shown in Fig.1 A, after gel filtration of native bromelain only one fraction-peak was obtained, whereas after gel filtration of modified bromelain with dextran aldehyde revealed two fraction-peaks (Fig.1, B).

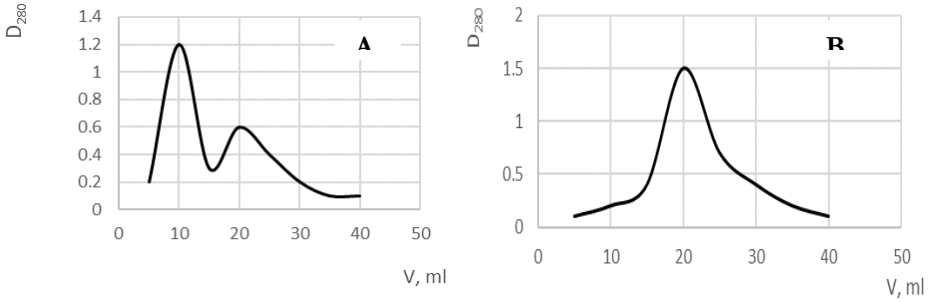


Figure 1. Gel-filtration of native bromelain (1) and) modified bromelain by dextran aldehyde (2) on Sephadex G-75,UV spectrum.on sephadex G-75, UV spectrum.

From Fig 1,B. it is clear that the chemical modification of bromelain with dextran aldehyde took place, and the degree of bonding was about 70%. Judging from the obtained results and comparing them with published data [3] we suggest that modified bromelain may have greater potential in medicinal application for musculoskeletal disorders than the available native bromelain.

References

[1] Musculoskeletal conditions. 2021. WHO https://www.who.int/news-room/fact-sheets/detail/musculoskeletal-conditions
[2] Teslim O, Afolabi J. 2014, Side Effects of Non-Steroidal Anti-Inflammatory Drugs: The Experience of Patients with Musculoskeletal Disorders. American Journal of Health Research. Jan 1;2:106.
[3] Rathnavelu V., Alitheen N., Sohila S., Kanagesan S and Ramesh R. 2016, Potential role of bromelain in clinical and therapeutic applications (Review). Biomedical reports, 5(3), 283–288.
[4] Akhtar N., Naseer R., Farooqi A., Aziz W & Nazir M. 2004 Oral enzyme combination versus diclofenac in the treatment of osteoarthritis of the knee – a double-blind prospective randomized study. Clinical Rheumatology, 23(5), 410-5.
[5] Bencharitiwong R., Kleij H., Koppelman S., Nowak-Węgrzyn A. 2015, Effect of chemical modifications on allergenic potency of peanut proteins. Allergy and asthma proceedings, 36(3), 185–191.

PP 20. STUDY OF THE ANTIOXIDANT ACTIVITY OF 3-HYDROXYPYRIDINE DERIVATIVES: "DILOX" 125 MG TABLETS, "ENERGY" GELATIN CAPSULES AND PROSPECTS OF THEIR USE IN MEDICINE

L. Kunchulia-Gurashvili [1], N. Zazashvili [2], M. Chukhua[1], M. Tchikaidze [2], T. Otarashvili [1]

[1] Tbilisi State Medical University Department of Pharmaceutical and Toxicological Chemistry; [2] Biorational Technologies Research Center., Tbilisi, Georgia

Corresponding author e-mail: l.kunchulia@tsmu.edu

Pyridine belongs to the number of bioactive molecules. It still maintains a leading position in the global pharmaceutical market, which is due to the design of the original structure of its molecule [1].

Lately, the synthetic drugs of 3-hydroxypyridine have attracted the special attention of scientists, they were found to have high antioxidant activity and the ability to modulate biochemical processes in the experiment, as a result of which a new direction, under the name of biocorrectors, has appeared.

In recent years, the Department of Pharmaceutical and Toxicological Chemistry of TSMU has been studying the antioxidant efficiency of medicinal preparations. In particular, the antioxidant activity of Mexidol-2-ethyl-6-methyl 3 hydroxy pyridine succinate has been determined [2]. As it is known, it is recognized as an evaluation marker of the antioxidant activity of drugs.

Modern lifestyle, as well as various exogenous adverse factors, for example, toxic ecological environment, from endogenous factors, stress, and diseases of various genesis result in oxidative stress. Currently, another dangerous pandemic caused by the Covid-19 virus, which is also characterized by the development of oxidative stress [3], has been added to our reality. During the oxidative stress in the biosystem, intensive generation of free radicals commences, causing damage to cell macromolecules: lipids, proteins, and especially nucleic acids, which play an important role in the development of a wide range of diseases [4].

The purpose of our study was to determine the antioxidant activity of 125 mg tablets of the Georgian generic drug "Dilox" (Aversipharma) and gelatin capsules of the original drug "Energy" (50 mg of Endocyte, "Biotecsi"). Gelatin capsules of "Energy" represent a multicomponent heterosystem. Physicochemical properties of "Biotecsi", as well as its chemical composition, were studied using the chromatographic mass-spectrometric method. Dominant compounds are hydroxy pyridine and alkyl derivatives: 2-methyl-3-hydroxy-pyridine, 2,6-dimethylpyridinol, 2-methyl-6-ethylhydroxypyridinol, and simple alkyl derivatives of pyridine, 2-methyl, and 6-ethyl pyridine compounds [5], therefore it was important to determine the antioxidant activity of this drug. Antioxidant "Mexidol" 125 mg tablets was chosen as reference drug. Antioxidant potential was assessed in DPPH assay [2].

Thus, our research subjects: Gelatin capsules of "Energy" were found to have a high antioxidant activity of 55.5%. Dilox 125 mg tablets had 47.2%. The antioxidant activity of both study drugs exceeds the antioxidant potential of the antioxidant test drug Mexidol.

Therefore, it is feasible to use Georgian generic drug "Dilox" 125 mg tablets (Aversipharma) and gelatin capsules of the original herbal drug "Energy" (Biotecsi) for the purposes of combined therapy in patients infected with Covid-19 and viruses in general, in order to reduce the adverse effects caused by oxidative stress through prevention and timely avoidance of its accompanying complications.

Reference

[1] Manjusha C. Nevase, Reshma D. et al. (2018) Review On Various Molecule Activity, Biological Activity & Chemical Activity Of Pyridine. EJPMR, (11), 184-192. ISSN 2394-3211

[2] Gurashvili-Kunchulia L., Zazashvili N., Imnadze N. et al. (2021), "Study of Antioxidant Activity of "Endocite" 100 mg soft capsules and "Proptoplasma" 5% and 10% Solution for Injection in future Perspectives of their use as a "Biocorrectors". TSMU, Collection of Scientific Works, Vol. 55, pp. 63-65

[3] Shchulkin A., Filimonova A.(2020), The role of free-radical oxidation, hypoxia and their corrections in the pathogenesis of Covid-19. M. Therapy N5(39) pp. 187-194. DOI:
[4] https://dx.doi.org/10.18565/therapy.2020.5.187-194
[5] Halliwell, B. Gutteridge, J.M.C. (2015) Free Radicals in Biology and Medicine. 5th Edition, Oxford University Press, New York. http://dx.doi.org/10.1093/acprof:oso/9780198717478.001.0001
[6] Kunchulia L., Makharadze R., Mindiashvili N., et al (2012), study of chemical-physical characteristics of the preparation DAS. TSMU, Collection of Scientific Works, XLVI, pp. 53-55.

PP 21. BIOLOGICAL ACTIVE COMPOUNDS FROM THE BUDS OF *POPULUS TREMULA* L. GROWING IN GEORGIA

T. Kvaratshkelia[1], J. Legault[3], J. Kuchukhidze[1]

Tbilisi State Medical University: [1]Department of pharmacognosy and botany; [2] Department of fundamental sciences University of Quebec at Chicoutimi, Canada

E-mail: tkvaratskhelia93@gmail.com

Populus tremula L. (Salicaceae) is tree growing in deciduous forests of Georgia. The genus *Populus* L. contains more than 40 species widespread in Europe and Asia. The species of *Populus* have a long history in traditional medicine, with uses in many areas. In traditional medicine is also used the bark of the members of Gen. *Populus*, which was assigned with astringent, anti-inflammatory, anti-rheumatic and antiseptic properties [1-7]. The medical applications of Populus buds' products are very extensive, because of a wide range of pharmacological and physiological actions [8]. Phytochemical investigations of Populus species have shown that they contain mainly polyphenolic compounds and terpenoids [9-11].

The aim of the study was simultaneous determination of compounds extracted by solvents of different polarities from buds of *Populus tremula* and evaluation of their cytotoxic activity *in vitro*. About 50 compounds present in hexane extract from buds of *P. tremula* in amounts of not less than 0.1% of TIC. The components of hexane extract represent aromatic compounds, sesquiterpene hydrocarbons and sesquiterpenoids.

The first group contains the aromatic compounds - benzyl alcohol, 2- phenylethanol, eugenol, 2-hydroxybenzaldehyde, methyl acetophenone, and ethyl benzoate. The second group is formed by sesquiterpene hydrocarbons and sesquiterpenoids. Among sesquiterpenoids in buds' tertiary bicyclic alcohols of azulene type structure are prevailed. The third group is formed by esters of cinnamic acid.

Ethyl acetate extract constituents can also be divided into several groups. One of them consists of polyols. The main fraction of the ethyl acetate extract consists of acidic compounds of aliphatic and aromatic series. The former is represented by saturated and unsaturated mono-, dicarboxylic and hydroxycarboxylic acids. Aromatic acids are represented by two groups of compounds. One of them includes benzoic, 4-hydroxybenzoic, and 4- hydroxyphenyl acetic acids. The other one is formed by cinnamic acid and its derivatives. The cytotoxicity of hexane and ethyl acetate extracts of the buds of *P. tremula* was evaluated *in vitro* on A-549 (lung carcinoma), DLD-1 (intestinal adenocarcinoma), WS-1 (human fibroblasts) cell lines and the results (Table 1) reveal specific activity of aforesaid extracts [12].

Table 1. Cytotoxic activity of the hexane and ethyl acetate extracts of the buds of *P. tremula*

Samples	Resazurine			Hoechst		
	A-549 µg/ml	DLD-1 µg/ml	WS-1 µg/ml	A-549 µg/ml	DLD-1 µg/ml	WS-1 µg/ml
Hexane extract	43 ± 1	30 ± 3	57 ± 7	35 ± 3	28 ± 4	71 ± 8
Et.Ac. extract	103 ± 10	81 ± 2	138 ± 11	67 ± 9	50 ± 2	118 ± 30
Etoposide	14.1 ± 2.4	5.9 ± 1.2	20.6 ± 9.4	1.3 ± 0.2	1.3 ± 0.2	18.2 ± 0.8

References

[1] Stanescu, U.; Hancianu, M.; Cioanca, O.; Aprotosoaie, A.C.; Miron, A. Medicinal Plants From A to Z, revised and added, 3rd ed.; Polirom: Ia¸si, Romania, 2018; ISBN 978-973-46-7240-0.
[2] Kuete Victor, Seo Ean-Jeong, Krusche Benjamin et al. Cytotoxicity and Pharmacogenomics of Medicinal Plants from Traditional Korean Medicine. Evid Based Complement Alternat Med. 2013; 2013: 341724
[3] Scaysbrook T., Greenaway W., and Whatley F. R. (1992), Relation of "antimicrobial" compounds present in poplar bud exudates to disease resistance by poplars. Z. Naturforsch. 47c, 197-200.
[4] Hancianu, M.; Stanescu, U.; Aprotosoaie, C. Pharmaceutical, Pharmacological and Clinical Bases of Phytotherapy; "Gr. T. Popa": Ia¸si, Romania, 2008; Volume 3, ISBN 978-973-7682-68-0.
[5] Royer, M.; Houde, R.; Viano, Y.; Stevanovic, T. Non-wood Forest Products Based on Extractives-A New Opportunity for the Canadian Forest Industry Part 1: Hardwood Forest Species. J. Food Res. 2012, 1, 8.
[6] Bouchard, M. Identification D'utilisations pour le Bouleau à Papier et Le peuplier Faux-Tremble; Enseignement Supérieur, Recherche, Science et Technologie: Quebec, QC, Canada, 2013; pp. 1–45.
[7] Stanescu, U.; Hancianu, M.; Cioanca, O.; Aprotosoaie, A.C.; Miron, A. Medicinal Plants From A to Z, revised and added, 3rd ed.; Polirom: Ia¸si, Romania, 2018; ISBN 978-973-46-7240-0.
[8] Chi, Y.S.; Jong, H.G.; Son, K.H.; Chang, H.W.; Kang, S.S.; Kim, H.P. Effects of naturally occurring prenylated flavonoids on enzymes metabolizing arachidonic acid: Cyclooxygenases and lipoxygenases. Biochem. Pharmacol. 2001, 62, 1185–1191.
[9] Greenaway,W.; May, J.; Scaysbrook, T.; Whatley, F.R. Identification by gas chromatography-mass spectrometry of 150 compounds in propolis. Z. Nat. Sect. C J. Biosci. 1991, 46, 111–121.
[10] Greenaway, W. Compositions of Bud and Leaf Exudates of Some Populus Species Compared. Z. Nat. C 1992, 47, 329–334.
[11] Jerkovic, I.; Mastelic, J. Volatile compounds from leaf-buds of Populus nigra L. (Salicaceae). Phytochemistry 2003, 63, 109–113
[12] O'Brien, J., Wilson, I., Orton, T., Pognan, F., 2000. Investigation of the Alamar Blue (resazurin) fluorescent dye for the assessment of mammalian cell cytotoxicity. Eur. J. Biochem. 267, 5421–5426

PP 22. DEVELOPMENT OF THE COMPOSITION AND TECHNOLOGY OF AN OINTMENT OF "PS 551", A PURIFIED FRACTION OF "FATSIFLOGIN"

D. Lagazidze, M. Orjonikidze, Z. Kemoklidze

Tbilisi State Medical Univercity, I. Kutateladze Institute of Pharmacochemistry, Tbilisi, Georgia

Corresponding author e-mail: d.lagazidze@tsmu.edu

Rheumatoid arthritis affects 0.5-1% of the world's population [1]. Treatment involves the alleviation of symptoms using anti-inflammatory steroidal and non-steroidal drugs. An alternative to the synthetic anti-inflammatory drugs are medicinal products of plant origin, whose mild, less toxic action determines the growing trend of their use in medicine [2].

The aim of this study was the development of the technology and composition for a soft dosage form of "PS 551", a purified fraction of "Fatsiflogin" with a total content of triterpene saponins of 97% [3]. The latter is an anti-rheumatic, anti-inflammatory and analgesic medication derived from the air-dried leaves of *Fatsia japonica* (fam. *Araliaceae*), an ornamental Japanese plant cultivated on the Black sea coast of Georgia.

The study was based on pharmacopoeial physico-chemical and technological analysis methods [4,5]. Model ointments were made by a standard pharmaceutical technology, taking into account the properties of the main substances and constituents. Based on the quantitative analysis method of determination of "Fatsiflogin" [6], an HPLC quantitative analysis method was developed for the determination of the marker glycoside "Facioside D" in the ointment and dialysate. The dynamics of active substance release was studied by dialysis and direct diffusion methods in distilled water and an isotonic saline solution at +32 ± 2°C [7]. Structural-mechanical properties were measured on a rotary viscometer (with LVDV-IT). The data were processed statistically.

Ointments are complexes of medicinal substances with base-carriers, which provide optimal consistency and determine the speed and completeness of the release and absorption of medicinal substances. Consistency determines rheological parameters such as viscosity, elasticity, plasticity and thixotropy. Based on this, the design of the conducted research meant the selection of the base of the ointment and the preparation of model samples based on it, and the determination of the quality of the obtained samples at the next stage.

In order to select the base of the ointment, 7 compositions of base-carriers containing vaseline, bentonite, glycerine, polyethylene glycol, distilled monoglyceride, cocoa fat, white wax, water, vaseline oil and other ointment base ingredients allowed by the pharmacopoeia were prepared, into which the purified fraction of Fatsiflogin PS- 551 was introduced by the appropriate method in the amount of 5%. Physical-chemical indicators were studied in freshly prepared samples and after 14-days of storage at room temperature.

Experimental data confirmed the homogeneity of all freshly prepared samples. During the 14-day storage, no visual changes were detected in the samples prepared on vaseline, bentonite and emulsion bases. Accordingly, further studies were continued on the mentioned samples. Experiments under critical conditions confirmed the stability of samples prepared only on emulsion and bentonite bases. In order to select the optimal composition, the rheological characteristics of model ointments prepared on emulsion and bentonite bases were studied.

Both compositions of ointments are characterized by a reverse relation of shear speed and dynamic viscosity, which ensures the appropriate consistency and the ability to restore the structure after deformation and distribute evenly when applied to the surface. The dynamics of the release of the active substance was studied in vitro using the dialysis method and the direct diffusion method in a Petri dish - in direct contact with the dialysis medium. The results of the study show the prolonged

nature of fatsioside release from the bentonite base. As for the ointment prepared on the emulsion base, after 4 hours the content of Fatsiflogin in the dialysate by direct diffusion and dialysis methods was on average 50-55% and 32-35%, respectively.

On the basis various physical-chemical, bio-pharmaceutical and technological studies, a soft emulsion-based dosage form was developed for “PS 551”, a purified triterpene saponin fraction of an anti-rheumatic, anti-inflammatory and analgesic pharmaceutical medication "Fatsiflogin". The parameters and norms determining the quality of the ointment were established.

References

[1] Flynn J.A.; Choi M. J.; Wooster L. D., 2013, Oxford American Handbook of Clinical Medicine. OUP USA. p. 400.
[2] Long L., Soeken K., Erns E., 2001, Herbal medicines for the treatment of osteoarthritis: A systematic review,Rheumatology, vol. 40, pp. 779-793.
[3] Kemertelidze E., Kemoklidze Z., Dekanosidze G., Bereznyakova A., 2001. Terpene glycosides of Fatsia japonica cultivated in Georgia and their pharmacological properties, Chemical and Pharmaceutical Journal, vol. 35, no. 8,
[4] European Pharmacopoeia (Ph. Eur.) 10th Edition
[5] State Pharmacopoeia of Georgia, 2003, vol. 1 and 2, Tbilisi
[6] Getia M., Mshvildadze V., Pichette A., Dekanosidze G., Kemoklidze Z., 2017, Development of Analitycal Procedure for the Quantification of “Fatsiflogin”, Journal of Pharmacy, vol. 7,no. 3 pp. 96-99.
[7] Olejnik A., et al., 2012,“Active Compounds Release from Semisolid Dosage Forms,” J. Pharmaceutical Sciences. vol. 101, no. 11, pp. 4032–4045

PP 23. PROSPECTS OF USE OF PREPARATIONS CONTAINING MINERALS IN COSMETOLOGY

T. Masiukovichi, K. Natobidze, E. Mosidze, I. Tsurtsumia

Tbilisi State Medical University, Department of Pharmaceutical Technology, Tbilisi, Georgia

Corresponding author e-mail: tatia.masiukovich@yahoo.com

Unlike vitamins and herbal components, the benefits of using minerals for cosmetic purposes for the skin is largely ignored and the products containing them are rarely used. That is why determining the prospects of using their containing soft medicinal forms in cosmetic practice, is one of the urgent problems for modern medicine and cosmetology [6].

Potassium and sodium [4] are dominant intracellular and extracellular electrolytes and osmolytes, that maintain the cell membrane potential.

Calcium not only contributes to hemostasis, but is also the main regulator of epithelization. The right combination of calcium and magnesium improves restoring of the skin barrier [6].

There are known two main consumer products containing magnesium: talc (magnesium silicate) and magnesium sulfate. Talc is most often found in baby powders. Talc is also found in colored cosmetic powders and antifungal agents.

In the United States, the FDA recognizes 3 zinc-containing compounds: zinc acetate (0.1–2%), zinc carbonate (0.2–2%) and zinc oxide (1–25%), as safe and effective skin protection products [6].

Colored cosmetic products containing iron oxide have been used on the skin since ancient times. Analysis of iron content in the epidermis of exposed (from the sun) and protected (from the sun) skin showed significantly higher free iron content in the epidermis of exposed skin [6].

The use of copper compounds is related to their known antibacterial, antifungal and antiviral activity [2]. A cosmetic company has created a bimineral complex consisting of copper and zinc, which has anti-

inflammatory action [3,5]. The gel containing the bimineral complex improved the tone, color, and texture of the skin, and significantly reduced the dark coloration and wrinkles around the eyes.

Oral administration of selenium in mice reduced inflammation induced by UV light, pigmentation, hyperkeratosis, and carcinogenesis. In the United States of America, preparations containing selenium sulfide are used for the treatment of dandruff and seborrheic dermatitis [7].

Peloids occupy a special place among the mineral deposits of Georgia. They are widespread in the territory of Georgia, in particular in the Adjara region [1].

Sulfide silt peloids are characterized by bactericidal, adsorptive, anti-inflammatory, antioxidant, analgesic properties. Sulfide silt peloids contain minerals, micro- and macroelements - potassium, calcium, silicon, copper, iron, boron, bromine, iodine, etc.

The purpose of the research was to determine the formulation and develop the technology of the hydrogel containing the sulfide silt peloid of Niphi Lake of the Adjara region.

Using a plasma atomic emission spectrometer, the spectrum of micro- and macroelements was studied in the sulfide silt peloid of Niphi Lake of the Adjara region. The content of essential and non-essential elements (Mg, Si, S, Fe, P, Ca, K, Na, Cu, Zn and others) was established, which play an important role in the human body.

In order to select the base-carrier of the gel, we mainly used hydrophilic gel formers: carbopol, sodium alginate, xanthan gum, carboxymethylcellulose, methylcellulose and maltodextrin. Based on the conducted studies, carboxymethylcellulose have been selected as the optimal gel former agent.

The physical-chemical and technological characteristics of the hydrogel compositions of Niphi Lake have been studied (uniformity, structure, pH, colloidal stability, thermal stability).

The structural-mechanical properties of the hydrogel containing the sulfide silt peloid of Niphi Lake have been studied. It has been determined that the rheological characteristics of the hydrogel are within the optimal values for soft dosage forms.

On the basis of the biopharmaceutical studies, the formulation for the hydrogel containing the sulfide silt peloid of Niphi Lake is provided and the preparation technology is developed.

References

[1] Masiukovichi, T., Bakuridze, A., Murtazashvili, T., 2016, Research of sulfide silt peloids widespread in Adjara region on the content of minerals by X-ray phase analysis method, Bulletin of the National Academy of Sciences of Georgia, Chemistry Series, vol. 42 #4 (2016), pp. 541-545.
[2] Borkow, G. and Gabbay, J. Copper, 2009, An ancient remedy returning to fight microbial, fungal and viral infections. Cur Chem Biol. 3, pp. 272–278.
[3] Chantalat, J., Bruning, E., Liu, J. C. and Sun, Y. 2010, Biomimetic signaling technology generated by a bimineral complex reduces signs of photoaging in the eye area. J. Am. Acad. Dermatol. 62 (3 Suppl 1), AB60 (2010).
[4] Higdon, J. and Drake, V. J. 2012, Potassium. An Evidence- Based Approach to Vitamins and Mineral, 2nd edn. pp. 196–223. Georg Thieme Verlag, Stuttgart, Germany.
[5] Kaur, S., Lyte, P., Garay, M., et al. Galvanic zinc–copper microparticles produce electrical
[6] stimulation that reduces the inflammatory and immune responses in skin. Arch. Dermatol.
[7] Res. 303, 551–562 (2011).
[8] Polefka, T. G., Bianchini, R. J. and Shapiro, S. 2012, Interaction of mineral salts with the skin: a literature survey. International Journal of Cosmetic Science, 2012, 34, pp. 416–423.
[9] Sengupta, A., Lichti, U.F., Carlson, B.A., et al. 2010, Selenoproteins are essential for proper Keratinocyte function and skin development. PLoS 5, e12249 (2010).

PP 24. ALKALOIDS FROM *DELPHINIUM* FLEXUOSUM BIEB. GROWING IN GEORGIA AND MICROSTRUCTUAL CHARACTERISTICS OF ITS VEGETATIVE ORGANS

Ketevan Mchedlidze, Lali Kintsurashvili, Manana Churadze, Jemal Aneli

Tbilisi State Medical University I. Kutateladze Institute of Phamacochemistry, Tbilisi, Georgia

Corresponding author e-mail: k.mchedlidze@tsmu.edu

The genus *Delphinium* L. is rich in diterpene alkaloids, which exhibit a pronounced curare-like, anti-tumor, anti-inflammatory, analgesic, antidote and insecticidal action. The content of diterpene alkaloids in the aboveground and underground vegetative organs of Delphinium flexuosum Bieb., a promising medicinal plant of the flora of Georgia, and diagnostic features of the internal structure were studied in order to determine the identity of the experimental raw material.

GC / MS peripheral analysis revealed that the dominant alkaloid obtained from the vegetative organs of the plant is the pharmacologically active methyllicaconitine. Other alkaloids have been identified as anthranoillocytonine, delcosine, lycotonine. As well, the underground organs contain also zongorine, delectine and norzongoramine.

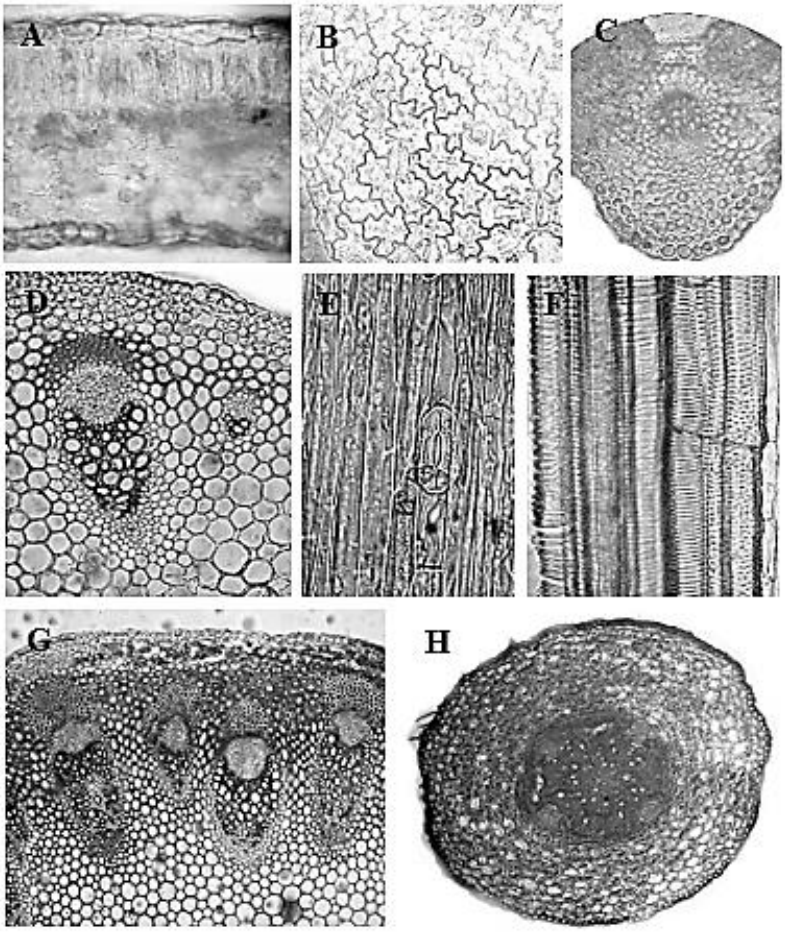


Figure 1. Microstructure of the vegetative organs of *D. flexuosum*. **A**. dorsoventral mesophyll of the leaf; **B**. curved cells of the leaf epidermis, stomata; **C**. main leaf vein, reverse-collateral vascular cone; **D**. leaf petiole and **G**. stem axillary, mechanical, root tissues and open-collateral conductive cones; **E**. stem has rounded, linear and straight-walled basal cells and anomocytic stomata of the stem; **F.** Thickening of the spiral-reticular sheath of the stem vessels; H. polar wood of the root

A set of diagnostic features of the internal structure of *D. flexuosum* was determined using the methods adopted in microtechnics (Fig. 1). The leaf of *D. flexuosum* is bifacial, hypostomatic and has dorsoventral structure. It is very rarely covered with long conical trichomes, the underlying cells of the lower and upper epidermis of the leaf are non-wrinkled and curved. The differential stomatal apparatus in leaf-covering tissue is anomocytic. Stomata are lenticular, and structure of the stomata is chaotic, in terms of the reciprocal location of the locking cells. The leaf pulp is differentiated into open, reverse-collateral conductive cones. The aboveground organs of D. flexuosum are characterized by an orderly aligned structural elements of the epidermal tissue, with linear and straight-walled stem cells and orderly arranged anomocytic stomata. Collenchymal and fibrous cells of the mechanical type and open-collateral type conducting cones with a thickening of the spiral and reticular membrane are actively reflected in the organs of the plant axis. The conductive tissue of the root system of D. flexuosum contains a number of polar rays of the wood with differentiated stepwise, spiral and ring-shaped tracheal elements.

PP 25. MODERN APPROACHES IN THE TREATMENT OF SICKLE CELL DISEASE

N. Merkviladze, N.Jakhutasvili, E.Tsitsilashvili, M.Papava

Tbilisi State Medical University, Department of Biochemistry

Corresponding author e-mail: n.merkviladze@tsmu.edu

Sickle cell disease (SCD) is a group of inherited heterogeneous red blood cell disorders in which HbS predominates [2,7]. SCD affects more than 3 million worldwide. [6] The characteristic mutation at the sixth codon of the beta-globin gene causes a substitution of valine for glutamic acid, resulting in an abnormal hemoglobin tetramer HbS with poor solubility. The polymerization of deoxygenated HbS is central to vaso-occlusive phenomena, that is followed by secondary processes including inflammation, hemolysis, anemia, vasculopathy, and oxidative stress affecting many organs [6].

Complications can be grouped into 4 categories: acute and chronic pain, cardiopulmonary, central nervous system and kidney damage [6]. Life expectancy of patients with SCD is reduced by more than 2 decades compared to the general population [1,2] We reviewed the current data on the available treatments that can prevent complications and lengthen the lives of those who have this condition.

Current management strategies include prophylactic penicillin and immunizations to decrease the occurrence of infections, hydroxyurea (a disease-modifying agent), blood transfusions (for symptomatic acute anemia, stroke management, preoperative optimization), and bone marrow transplant [7]. Emerging drug therapies target the various mechanisms underlying SCD. One approach to therapy is reduction of reactive oxygen species by blockade of cellular adhesion, inhibition of hemoglobin S polymerization, and antioxidants. Several drugs are being studied both alone and in combination with hydroxyurea, as combination therapies offer the best prospects for optimizing disease outcomes. Gene editing (*e.g.*, CRISPR/Cas9) is also among promising new approaches [8,9]

Table 1. Major FDA-approved therapies for the treatment of SCD (According to A. M. Brandow and R. I. Liem)

Drug and FDA approval	Mechanism of action	Dosing	Common adverse effects
Hydroxyurea	↑ Fetal Hb via temporary arrest of hematopoiesis and stress erythropoiesis ↓ Inflammation through ↓ in WBC and platelets ↓ Adhesion molecule expression ↑ Nitric oxide production	Usual starting dose 20 mg/kg/day Dose escalate to maximum tolerated dose (~ 30–35 mg/kg/day) Alternatively, dose escalate to absolute Alternatively, dose escalate to absolute neutrophil count of 1500–2000/μL	Neutropenia (13%) Thrombocytopenia (7%) Nausea (3%)
l-glutamine	↑ NAD redox potential in sickle red blood cells Protects red blood cells from oxidative stress	Dose by weight < 30 kg—1 packet (5 g) BID 30–65 kg—2 packets (10 g) BID > 65 kg—3 packets (15 g) BID May take with or without hydroxyurea	Constipation (21%) Nausea (19%) Abdominal pain (17%) Headache (18%) Cough (16%)
Crizanlizumab	Binds to P-selectin Blocks interactions with ligands, including P-selectin glycoprotein ligand 1	5 mg/kg/dose IV on weeks 0, 2 and every 4 weeks thereafter May take with or without hydroxyurea	Infusion-related adverse events (< 10%) Nausea (18%) Arthralgia (18%) Back pain (15%)Fever (11%)
Voxelotor	Allosteric modifier of hemoglobin to stabilize oxygenated state ↓ Sickle Hb polymerization ↓ Hemolysis	1500 mg po daily May take with or without hydroxyurea	Headache (26%) Diarrhea (20%) Nausea (17%) Abdominal pain (19%) Skin rash (14%) Fever (12%) Fatigue (14%)

New approvals are expected to continue the research process.

References:

[1] Sachdev, VA, Douglas RR, Thein SL. 2021,Cardiovascular Complications of Sickle Cell Disease, Trends Cardiovasc Med. 31(3): 187–193. doi:10.1016/j.tcm.2020.02.002.

[2] Williams, TN. 2016, Sickle Cell Disease in Sub-Saharan Africa, Hematol Oncol Clin North Am. 01; 30(2): 343–358. doi:10.1016/j.hoc.2015.11.005.

[3] Gardner K, Douiri A, Drasar E, Allman M, et al. 2016, Survival in adults with sickle cell disease in a high-income setting. *Blood.* 128(10):1436–8. [PubMed: 27439910]

[4] Elmariah H, Garrett ME, De Castro LM, et al. 2014, Factors associated with survival in a contemporary adult sickle cell disease cohort. Am J Hematol. 89(5):530–5.

[5] Ali MA, Asrar A, Chaudry H, AimanW 2020,et.al Efficacy and safety of recently approved drugs for sickle cell disease: areview of clinical trials. Experimental Hematology 92:11−18

[6] Brandow A. M. Liem R. I. Advances in the diagnosis and treatment of sickle cell disease, 2022, Journal of Hematology & Oncology 15:20

[7] Onimoe G., Rotz S. Sickle cell disease: A primary care update, 2020 Clevelend Clinic Journal Of Medecine vol. 87

[8] Odame I. Jain D. Sickle cell disease: Progress made & challenges ahead,2020 Indian J Med Res 151, June 2020, pp 505-508
[9] Salinas Cisneros, Thein L. Recent Advances in the Treatment of Sickle Cell Disease, 2020 Frontiers in Physiology doi: 10.3389/fphys.2020.00435

PP 26. GREEN SYNTHESIS OF SILVER NANOPARTICLES AND EVALUATION OF THEIR BIOLOGICAL ACTIVITY

E. Mosidze, L. Ebralidze, L. Bakuridze, A. Bozhadze, A. Bakuridze

Tbilisi State Medical University

Corresponding author e-mail: ekaterine.mosidze@yahoo.com

Nanotechnology is a new field of scientific research that has been very well known over the last few decades [1]. Nanoparticles are attracting the attention of researchers in various fields due to their extraordinary properties. A bulk material has constant physical properties regardless of their size and shape, but at the nanoscale, the size, morphological substructure of the substance, and shape are the major contributing factors for changing their biological, chemical, and physical properties. Because at the nanoscale, the materials behave differently and they emerge with few novel characters in themselves [2].

Metal nanoparticles have size-related properties that are significantly different from bulk materials. These unique properties are giving them the potential for applications in medicine, catalysis, optics, cosmetics, renewable energy, microelectronics, medical imaging, environmental restoration, and biomedical equipment [3]. Of the wide range of metal nanoparticles, silver nanoparticles (AgNPs) are the most popular due to their unique physical, chemical, and biological properties when compared to their macro-scale equivalents [4]. The effect of silver nanoparticles against various pathogens and other benefits are already well known in medicine. AgNPs can be used in medicine for antimicrobial and antitumor therapy. They exhibit antiviral effect and they were found to be able to combat even SARS-CoV-2 virus [5,6].

According to modern data, the most promising approach to obtain silver nanoparticles is Green Synthesis. Research around this topic focuses on the development of an efficient and environmentally friendly method for the synthesis of metal nanoparticles using green chemistry. The Biosynthesis of silver nanoparticles has several advantages over chemical and physical methods. First of all, it is very simple, effective, eco-friendly and inexpensive way due to using bio-resources that serve as a reducing, as well as stabilizing and capping agent [7], doesn't need to provide additional means for this purpose. Procedure doesn't not require high temperature and pressure. It is a non-toxic method due to small or zero consumption of hazardous materials on the surface of nanomaterials. The process is characterized by low energy costs [8]. In addition, biosynthesized nanoparticles are primarily biocompatible and can be used in biomedical applications. In scientific literature biosynthesis of silver nanoparticles is described using plants, bacteria, fungi, and algae [9].

For biosynthesis of silver nanoparticles we used methanolic extracts of Gentiana septemfida, Erysimum contractum and Chelidonium majus. Obtained nanoparticles were evaluated for antibacterial and fungicidal activities against Gram-negative Escherichia coli, Gram-positive Staphylococcus aureus and Candida albicans. Also, their cytotoxic effects were evaluated on human lung carcinoma A-549, colon adenocarcinoma DLD-1, and healthy human skin fibroblasts WS1 cell lines.

The results have shown that synthesized silver nanoparticles have antibacterial, antifungal and

cytotoxic effects at different level for each type, though highest biological activity was exhibited

by AgNPs biosynthesized using methanolic extract of Erysimum contractum.

For sum up we can conclude that biosynthesis of silver nanoparticles is definitely simple, cost effective, eco-friendly method and obtained nanoparticles have potential to be used as antibacterial, antifungal and cytotoxic agents.

References

[1] Hulla J. et al 2015, Nanotechnology: History and future. Human & Experimental Toxicology.:1318-1321.
[2] Chouhan N., 2018. Silver Nanoparticles: Synthesis, Characterization and Applications. 10.5772/intechopen.75611. 3.
[3] Harish K.K, et al. 2018, Metallic Nanoparticle: A Review. Biomed J Sci &Tech Res 4(2). BJSTR.MS.ID.001011. DOI: 10.26717/ BJSTR.2018.04.001011.
[4] Zhang XF et al. 2016, Silver Nanoparticles: Synthesis, Characterization, Properties, Applications, and Therapeutic Approaches. Int J Mol Sci.;17(9):1534. Published 2016 Sep 13. doi:10.3390/ijms17091534
[5] Balagna C. et al, 2020, Virucidal effect against coronavirus SARS-CoV-2 of a silver nanocluster/silica composite sputtered coating; Open Ceramics 1
[6] Allawadhi, P. et al, 2021. Silver nanoparticle based multifunctional approach for combating COVID-19. Sensors International, 2, 100101 - 100101.
[7] Siddiqi, K.S., et al. 2018; A review on biosynthesis of silver nanoparticles and their biocidal properties. J Nanobiotechnol 16, 14 . https://doi.org/10.1186/s12951-018-0334-5
[8] Sujata P. et al. 2015; Green synthesis, characterization of gold and silver nanoparticles and their potential application for cancer therapeutics; Materials Science and Engineering C 53, 298–309
[9] [9] Zubair A.R. et al. 2020; Green Chemistry Synthesis of Silver Nanoparticles and Their Potential Anticancer Effects; Cancers 12, 855; doi:10.3390/cancers12040855

PP 27. DEVELOPMENT AND VALIDATION OF A RAPID LC-MS/MS METHOD FOR THE DETECTION OF AB-CHMINACA AND AB-FUBINACA IN PLASMA

M. Murtazashvili[1], M. Jokhadze[2], T. Chikviladze[1], T. Murtazashvili[1], P. Tushurashvili[3]

Tbilisi State Medical University: [1] Department of Pharmaceutical and Toxicological Chemistry,[2]Direction of Pharmacognosy and Pharmaceutical Botany; [3]Department of Biochemistry, Tbilisi, Georgia

Corresponding author e-mail: M.jokhadze@tsmu.edu

Synthetic cannabinoid receptor agonists are a group of substances designed as legal alternatives for cannabis that mimic the psychoactive effects of tetrahydrocannabinol by binding to cannabinoid receptors type 1 (CB1) and 2 (CB2). They are the largest group of new psychoactive substances monitored by the European Monitoring Centre for Drugs and Drug Addiction (EMCDDA). In October 2020, the EMCDDA reported that at least 207 synthetic cannabinoids had appeared in the drug market since 2008 [4].

Their shorter duration of action may increase the risk of dependency, and their effects are more pronounced than those of marijuana: elevated mood, relaxation, sensory perception changes, confusion, paranoia, and hallucinations, among others. Some adverse effects include tachycardia, agitation, vomiting, seizures, hyperglycemia, hypokalemia, stroke, myocardial infarction, acute kidney injury, and/or death [2].

Biological matrices may help detect drug intake and associate consumption to the clinical symptoms/signs and toxicity, although this is very challenging. On the one hand, the development and validation of analytical methods are always a step behind the appearance of new substances [3].

AB-CHMINACA and AB-FUBINACA are some of the new generations of cannabinoid compounds developed as marijuana substitutes and have been risk-assessed by the EMCDDA [1].

The aim of the present work is the development and validation of a target LC-MS/MS method for the detection of AB-CHMINACA and AB-FUBINACA in plasma and its application to forensic cases. The

plasma samples were prepared using solid-phase extraction (OASIS HLB 3 cc, 60 mg). The Chromatographic separation and detection were achieved using an Agilent Technologies 1290 liquid chromatograph coupled to a 6460-triple quad mass spectrometer with an electrospray source. Separation was performed on Zorbax Eclipse plus C18 (100×3.0 mm, 1.8 µm) column. The mobile phases consisting of 0.1 % water solution of formic acid: 0.1 % acetonitrile solution of formic acid with gradient elation. Sample volume -5 µl, flow rate - 0.8 mL/min. The MS was operated in positive ESI mode and the analysis was operated in multiple reactions monitoring acquisition mode: m/z 356.7→311.2, m/z 356.7→241.0, m/z 356.7→144.8 (AB-CHMINACA); m/z 368.7→323.4, m/z 368.7→252.3, m/z 368.7→108.7 (AB-FUBINACA);

The method validation was carried out using drugfree human plasma samples spiked with analytes. The following parameters were evaluated for the validation of method for the analysis synthetic cannabinoids: selectivity, specificity, linearity, limit of quantitation, limit of detection, within- and between-day precision, accuracy, matrix effects and extraction recovery.

Linearity for all analytes was established along the range of 0.8–75 ng/mL (r>0.99). Both intraday and interday accuracy and precision data were all within acceptable limits ±15% RSD. Recovery ranged from 86.7% to 92.7% with an average of 94% and matrix effects were less than 15% for most compounds. The limits of detection were in the range of 2.3-2.7 ng/mL.

References

[1] EMCDDA. Europol EMCDDA–Europol 2011. Annual Report on the Implementation of Council Decision 2005/387/JHA; EMCDDA: Lisbon, Portugal.
[2] Cooper, Z.D. 2016. Adverse Effects of Synthetic Cannabinoids: Management of Acute Toxicity and Withdrawal. Curr. Psychiatry Rep., 18, 52.
[3] Franz, F., Jechle, H., Angerer, V., 2018. Synthetic cannabinoids in hair—Pragmatic approach for method updates, compound prevalences and concentration ranges in authentic hair samples. Anal. Chim. Acta, 1006, 61–73.
[4] Navarro-Tapia E., Codina J., Villanueva-Blasco V. 2022 Detection of the Synthetic Cannabinoids AB-CHMINACA, ADB-CHMINACA, MDMB-CHMICA, and 5F-MDMB-PINACA in Biological Matrices: A Systematic Review. Biology 2022, 11, 796.

PP 28. SYNTHESIS AND ANTIVIRAL ACTIVITY OF SOME MODIFIED EPIANDROSTERONE HYDRAZONES

N. Nadaraia

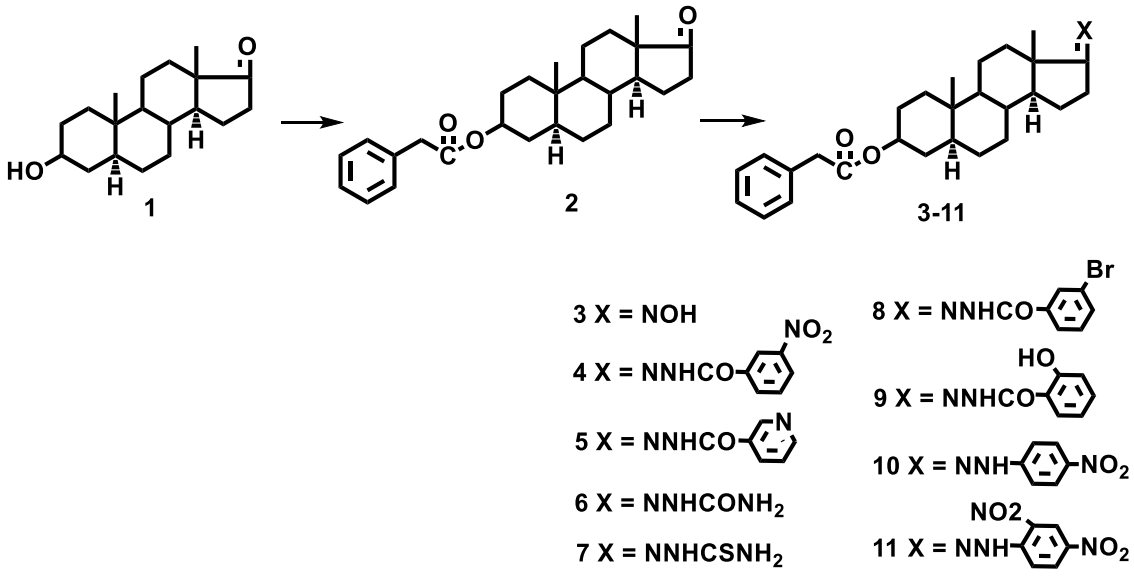
TSMU I. Kutateladze Institute of Pharmacochemistry, Tbilisi, Georgia

Corresponding author e-mail: n.nadaraia@tsmu.edu

Steroidal oximes, carbazones and hydrazones attract attention do to their high pharmacological activity, such as antituberculosis, antibacterial, antiviral, antifungal, anti-inflammatory, antitumor activity [1,2].

Transformation into ester derivatives is a common method of structural modification of steroids. Addition of an ester into the steroid core affects the biological activity.

In continuation of the research on the synthesis new biologically active steroids and the study structure–activity relationship, esterification of epiandrosterone **1** by using of phenylacetic acid chloride [3] into compound **2** and condensation reactions of the latest with hydroxylamine, m-nitrobenzoic, m-bromobenzoic, salicylic, nicotinic acid hydrazides, 2,4-dinitrophenyl-, p-nitrophenylhydrazines, semi- and thiosemicarbazides were carried out. Corresponding hydrazones **3-11** were synthesized.



Scheme. Synthesis of hydrazones of modified epiandrosterone

The structures of **3-11** were confirmed using IR, NMR, and mass spectra.

Screening for specific antiviral activity of hydrazones **3-11** was performed by the National Institute of Allergy and Infectious Diseases at the University of Utah (USA). The results showed that hydrazone **4** has a high, compounds **5,10** - moderate antiviral activity against Polio virus (cell culture Vero 76, strain Type 3, WM-3). Against Sarscorona virus (Vero 76 cell culture, Urbani strain) hydrazones **4, 5** showed weak activity. With respect to Rift Valley fever virus (Vero 76 cell culture, strain MP-12) and Takaribe virus (Vero cell culture, TRVL-11573 strain) only compound **5** has weak activity.

For exhibition of antiviral activity in the series of hydrazones of esterified steroids **3-11** the presence of m-nitrobenzoylhydrazone fragment at the C-17 position of the 5α-androstane ring (hydrazone **4**) is more convenient.

References

[1] Gan, C. Cui, J. Su, S. Lin, Q. Jia, L. Fan, L. Huang, Y. 2014, Synthesis and antiproliferative activity of some steroidal thiosemicarbazones, semicarbazones and hydrazones, Steroids, vol. 87, pp. 99-107.

[2] Nadaraia, NSh. Onashvili, EO. Kakhabrishvili, ML. Barbakadze, NN. Silla, B. Pichette, A. 2016, Synthesis and antiviral activity of several N-containing 5α-steroids, Chemistry of Natural Compounds, vol. 52, no.5, pp. 853-855.

[3] Nadaraia, NSh. Barbakadze, NN. Kakhabrishvili, ML. Sylla, B. Pichette, A. Makhmudov, US. 2018, Synthesis and biological activity of several modified 5α-androstanolone derivatives, Chemistry of Natural Compounds, vol. 54, no. 2, pp. 310-314.

PP 29. DESIGN, FORMULATION AND BIOLOGICAL ASSESSMENT OF ANTIBACTERIAL MEDICAL STICKS

K. Natobidze, M. Gasanova, I. Tsurtsumia, M. Tatanashvili

Tbilisi State Medical University, Department of Pharmaceutical Technology

Corresponding author e-mail: ketevan.natobidze@gmail.com

Substantial problem faced by modern population is protection/treatment of the skin and mucous surfaces from environmental pollution that seems unachievable without antibacterial cosmetic products [3]. Among actively/frequently used modern cosmetic products, cosmetic sticks that can be applied to a particular/local area of the skin and mucous membranes are most preferable. Core of the

medical sticks can be filled simultaneously with biologically active components of varying physical and chemical nature. As cosmetic sticks remains on the surface of the skin and mucous membranes as thin film for a long time, consequently, its pharmacological effect is also persisting. In addition, it is user-friendly, easy to carry and due to its unique packaging format (case, stick, felt-tip pen etc.) - hygienic, economic, and with a long shelf-life [1,6]. It should also be noted that, as selection of medical cosmetic sticks in the modern pharmacies is scarce, study/development of the recipe of medical cosmetic sticks and development/production of cosmetic sticks of various purposes using modern technologies is one of the relevant issues.

Aim of the research was to determine formulation and develop technology for antibacterial cosmetic sticks using natural biologically active and auxiliary substances: sage dry extract, sage essential oil, grapefruit dry extract, citrus essential oil, clay "keda," paraffin, vaseline, vaseline oil, castor oil, cocoa butter, peach oil, almond oil, emulsion wax, beeswax, lanolin, sunflower oil, and permaceti [5,7,8, 9].

Out of nine medical stick compositions developed in accordance with reviewed literature and on the basis of pharmaceutical study, we selected an optimal stick formulation (for 10 sticks each) as follows: 3.5 g; paraffin 3.0 g; castor oil 15.0 g; cocoa butter 3.0 g; emulsion wax 6.0 g; beeswax 3.0 g; lanolin 3.0 g; sage dry extract 3.0 g; sage essential oil 0,015 mg.

On the basis of technological studies, technological scheme and technological process of antibacterial sticks have been developed, material balance of the technological process of making sticks was drawn up, and technical and economic indicators have been determined; (technological outcome Ꝑ=97,78%; technological expenditure E= 2,22%; spending coefficient Ks= 1,022);

We studied indicators of good quality such as: homogeneity, pH, firmness, plasticity, spreadability, coverage, osmotic activity [1]. Research results meet standard requirements for sticks [1,2,4];

Active pharmaceutical ingredients (mixture of sage essential oil and dry extract) proved to have high antibacterial activity against Streptococcus pyogenes, Escherichia coli, Salmonella typhimurium, Klebsiella pneumoniae, Proteus vulgaris, Shigella flexneri, Enterococcus faecalis and Staphylococcus aureus.

Reference:

[1] Aleshnikova K. Yu. 2021 "Development of the composition, technology of medicinal pencils containing eucalimine". Thesis. Moscow. 143p. (in Russian);
[2] State Pharmacopoeia of the Russian Federation 14th ed. OFS. 1.4.1.0028.18 "Medicinal Sticks". - M., 2018 - V.2. – p. 2014-2016. (in Russian);
[3] Dribnokhod Yu.Yu. 2019 "Cosmetology". Rostov-on-Donuy Phoenix.p. 392-404. (in Russian);
[4] Veretennikova M. A. 2016 "Development of the composition, technology and quality assessment of medicinal sticks with acyclovir and phytocomposition." dissertation .Volgograd, 119p. (in Russian);
[5] Hernandez E.I. and etc, . 2020 "New cosmetology". /Cosmetics /. FROM . 554. (in Russian);
[6] Baki G., Kenneth S. A., .2015. "Introduction to Cosmetic Formulation and Technology". University of Toledo, College of Pharmacy and Pharmaceutical Sciences. P. 287, 320;
[7] Ghorbani A., Esmaeilizadeh M., 2017. Complement Med., "Pharmacological properties of Salvia officinalis and its components". 2017 Jan13; 7(4):433-440. doi: 10.1016/ j.jtcme.2016.12. 014. Collection 2017 Oct;
[8] Yashaswini P., 2018. " Antimicrobial Properties of Orange (Citrus reticulata var. Kinnow) Peel Extracts against Pathogenic Bacteria". International Journal of Current Microbiology and Applied Sciences ISSN: 2319-7706 Volume 7 Number 03 (2018). 737-746;
[9] Raganathan V., 2019. "Development and evaluation of punica granatum fruit based herbal lipstick" / V. Raganathan, C.X. Pyng, P. Sri // International Journal of Research in Pharmaceutical Sciences - Volume 10, Issue 2 - 29 April . p. 1430-1434.

PP 30. Collaboration of doctor and pharmacist in the treatment of varicose veins

N. Nemsitsveridze[1], E. Ivanishvili[1], T. Mokhevishvili[2], T.Zarkua[1]

[1]Tbilisi State Medical University, Department of Social and Clinical Pharmacy; [2] N.Bokhua Cardiovascular Center Tbilisi, Georgia

Corresponding author e-mail: n.nemsitsveridze@tsmu.edu

Chronic varicose veins is a common disease. Its prevalence ranges from 10% to 30% in the world, most of the cases have been recorded in developed and industrialized countries [1]. Varicose veins often cause serious health problems [2, 4]. Patients complain of pain or cramping as well as general fatigue, burning, tingling or heaviness in the legs [3]. The number of cases increases with age. The most affected age group is 40-80 years [6]. Genes play a major role in the development of varicose veins [5]. Profession, age, gender, obesity can be the reason for the development of varicose veins. Often, patients avoid visiting the doctor and engage in self-treatment, go to the pharmacy and buy the medicine, which is the precise reason why the pharmacist should provide qualified pharmaceutical care in order to avoid the unfortunate consequences of incorrect treatment.

The present study aimed to analyze the collaboration of a clinical pharmacist and a physician in the pharmacotherapy. There was a discussion on the topic of diagnosis of varicose veins in patients of different gender, age, selection of the optimal medications for treatments by joint decision, taking into account their effectiveness, safety, side effects, possible interactions with other drugs, and fees. During the research process, observation and focusing on details took place. Only those with venous varicose were the subject of the investigation. Research has shown that a collaboration between clinical pharmacist and a physician positively impacts the treatment process. We have found that in many cases, patients with varicose veins have other concomitant diseases, therefore they need individual consultation on taking medicine, the choice of the particular dosage form and determination of the prescribed dosage. All aforesaid can be done perfectly by the clinical pharmacist, thus saving doctor's time. The study confirmed the previously existed opinion that in the case of varicose veins drugs belonging to the third group, i.e. over-the-counter drugs are mainly used. If there is another pathology along with varicose veins, in this case the treatment includes the second group or prescription drugs.

References:

[1] C. Michael Gibson, M.S., Callam MJ. 1994. Varicose veins epidemiology and demographics; "Epidemiology of varicose veins". Br J Surg. 81 (2): 167–73.

[2] Papadakis MA, 2022. et al. eds. Varicose veins. In: Current Medical Diagnosis & Treatment. 61st ed. McGraw Hill; 2022. Accessed Nov. 17, 2021.

[3] Debra Jaliman, 2021. MD .Varicose Veins and Spider Veins: Symptoms and Treatment; Medically Reviewed on November 15,

[4] I Lin, F., Zhang, S., Sun, Y., Ren, S., Liu, P. 2015.The Top 9 Varicose Vein Risk Factors; The Management of Varicose Veins. Int Surg, p. 185-189.

[5] Fukaya E, Flores AM, Lindholm D, et al. 2018. Clinical and Genetic Determinants of Varicose Veins. Circulation; 138(25):2869-2880.

PP 31. PHARMACOGNOSTIC EVALUATION OF SELECTED GEORGIAN PLANTS OF THE APIACEAE FAMILY

M. Nersezashvili[1], D. Berashvili[1], Ł. Kulinowski[2], K.Skalicka-Woźniak[2], I. Korona-Głowniak[3]

[1] Tbilisi State Medical Univerisity Direction of Pharmacognosy and Pharmaceutical Botany, Tbilisi, Georgia; Medical University of Lublin: [2]Department of Natural Products Chemistry, [3]Chair and Department of Pharmaceutical Microbiology, Lublin, Poland

Corresponding author e-mail: mariam.nersezashvili@tsmu.edu

Approximately 7.1% of species of rich and diverse Georgian flora are Georgian endemics [2]. According to the Royal Kew Garden, there are 12 plant families that demonstrate a higher than normal percentage of species with medicinal use. Apiaceae family is placed 6th on this list with 15% of plants counted as medicinal species and coumarins are considered mainly responsible for therapeutic properties [4]. Except coumarins, plants from the Apiaceae family contain flavonoids, essential oils, triterpene saponins and, sometimes, alkaloids. These compounds possess anti-coagulant, antibacterial, antifungal, antiviral, antioxidant, hypotensive, anti-helminthic, spasmolytic, sedative, anti-fever, and cytotoxic activity [3]. The increasing incidence of health problems caused by drug-resistant pathogenic microbes and fungi has evoked the interest in development of new therapeutic modalities for treating a myriad of diseases [1]. Coumarins have evolved as a potentially interesting and still unexplored molecular framework for drug discovery and hence are of clinical significance. Recent data regarding the phytochemistry and bioactivity of the various species of the Apiaceae family highlights the significance of studying Georgian endemics, which are expected to have an important pharmaceutical value. Available data regarding the Georgian endemic plants of the Apiaceae family are limited and outdated, in addition, most endemic species are not studied yet.

The aim of our research is to perform detailed phytochemical analyses and to study the bioactivity of selected Georgian endemic species. For that purpose, optimal methods for extraction, purification and isolation of bioactive compounds from *Seseli foliosum* (Sommier&Levier)Manden.), *Angelica adjarica* M.Pimen *and Heracleum sosnowskyi* I.Manden. were developed. 20 g of each *S. foliosum* root and seed*, A. adjarica* rhizome *and H. sosnowskyi* root and seed were trice extracted with 200 ml methanol at room temperature for 30 minutes in the ultrasonic water bath. Extracts were filtered through the filter paper and vacuum dried. Identification of the extracted compounds by the HPLC/LC-HRMS/MS technique is ongoing. Though, we already can describe the possible molecular formula of some compounds.

Table 1. The molecular formula of extracted compounds

Extract type	Compound	Formula	$[M+H]^+$ (*m/z*)	Fragment ions (*m/z*)
S.f.r/S.f.s	Coumarin 1/2	$C_{14}H_{10}O_3$	227.0705/04	199.0598/88 171.0761/67 143.0847/44 128.0615/14
A.a.rh	Coumarin 3	$C_{15}H_{16}O_5$	277.1081	259.0977 205.0500
H.s.r	Coumarin 4	$C_{13}H_{10}O_5$	247.0595	232.0361 217.0125 189.0173
H.s.s	Coumarin 5	$C_{12}H_6O_5$	231.0283	218.0207 203.0337 188.0105 175.0388

The crude methanolic extracts of selected plants were checked against gram-positive (*S. aureus; B. subtilitis; M. luteus; S. epidermidis; E. fecealis; B. cereus*) and gram-negative (*S. typhimurium; K.*

preumoniaea; P. mirabilis; E. coli; P. aeruginosa) bacterial strains and fungi (*Candida parapsilosis; C. albicans; C. glabrata*). Extracts showed bactericidal activity against gram-possitive bacterial strains. *S. foliosum* root extract was active against M. luteus (MIC=125 µg), while seed extract was active against *S. aureus* and *S. epidermidis* (MIC=125 µg). Seseli seeds and Angelica rhizome showed fungistatic activity against *C. glabrata*.

The Apiaceae plants are considered as a potentially rich source of bioactive chemicals that should be explored for their potential medicinal use due to their diversity, huge metabolic capacity, and ready availability. To the best of our knowledge, this is the first case of HPLC/LC-HRMS/MS identification and antimicrobial evaluation of chemicals from Georgian endemic Apiaceae species, hence the current study may have significant scientific potential.

References

[1] Cordell, GA.; Colvard, M.D. 2012, Natural products and traditional medicine – turning on a paradigm, *Journal of Natural Products*, vol. 3, no. 75, pp. 514–525
[2] Davlianidze, M., Gviniashvili, T., Mukbaniani M., Jinjolia-Imnadze, L., Jugheli, T. 2018
[3] Gagnidze R. 2005, Vascular plants of Georgia, a nomenclatural checklist. Tbilisi, pp. 96-97.
[4] Mohammad S. A.; Mohammad R. 2016, Joharchi Ethnobotanical knowledge of Apiaceae family in Iran: A review, *Avicenna Journal of Phytomedicine*, vol. 6, no. 6, pp. 621-635,
[5] Willis, K.J. (ed.) 2017. State of the World's Plants 2017. Report. Royal Botanic Gardens, Kew.

PP 32. THE PHARMACIST'S ROLE IN IMPROVING THE QUALITY OF MEDICAL SERVICES

N.Nikuradze, N.Kvizhinadze, N.Nemsitsveridze, M.Bartia

Department of Social and Clinical Pharmacy

Corresponding author e-mail: nestan.nikuradze@tsmu.edu

The study aimed to discuss and evaluate the activities of the medical representative of the pharmaceutical company with a medical purpose in relation to the quality of health care. In the activities of the medical representative of the pharmaceutical company "World Medicine", the assessment of managerial (non-marketing) aspects from the company's business portfolio, during the personal sales of promotional drugs - anti-urticaria second generation antihistamines.

Analysis of drug assortment for the treatment of chronic form of urticaria, retrospective Pareto study, ranked tables, marketing moves and qualitative-quantitative indicators of "business portfolio", interviewing doctor allergists, evaluation of information activities of the medical representative with doctors were used during the study.

As a result, the following picture was obtained. Out of 100 employees of "World medicine", 85 are medical representatives. Promotional medicines of "World Medicine" hold 10% of the group by trade name, which is 17% in total. Basically, there are pharmaceutical products of 30 trade names of 5 active substances, the market value of which is 10-45 GEL. These are: desloratadine-11 position, fexofenadine-6, levocetirizine-9, cetirizine-1 position and bilastin-nixar (brand) - a relatively new formula of the second generation. It is the most demanded, non-competitive, effective position in the treatment of urticaria (43%), despite the high price (45-50 GEL), it holds a relatively non-competitive position. Next comes our promotion positions: Eslotin, Leylin, and finally Letran.

The market is saturated with foreign (79%) and Georgian medicines (21%). According to the opinion of allergists, Eslotin has the highest ranking ratio of promotional medicines 10/5, Leylin 10/3, Letran 10/2.

The data for sales intensification was divided as follows: personal selling 30%, advertising 27%, sales promotion 20%, direct marketing 13%, public relations 10%. The impact (multiplicity) of the visits made by the medical representative is directly proportional to the dynamics of the sale.

For the majority of doctors (48%), are graduate doctor or pharmacist, age of 25-35 years. 62% of respondents believe that 1-2 visits of a representative during a month is much more effective. 78% get information about new medicine from a medical representative.

The analysis showed how the doctor reacts the competence and integration of pharmacists in their work, to what extent will the prohibition of communication between doctors and medical representatives affect and who will be negatively affected? The answer is - pharmaceutical company - 62%, health care quality - 38%. Namely: the visit of a medical representative is of a commercial nature, it forces the doctor to violate professional ethics, their activity is often to prescribe more expensive drugs for the patient, it wastes the doctor's time, interferes with his normal work.

To our knowledge this is the first study that, based on the theoretical and practical (field) data of a multi-faceted research, their study and comparison, recognizes and positively evaluates the activities of medical representatives, their integration in the health care of the population, in terms of providing new reliable and effective medicines.

PP 33. NOVEL HERBAL PREPARATION AS A PROSPECTIVE ANTIMICROBIAL ENDODONTIC IRRIGANT

Natia Nizharadze[1], Marine Mamaladze[1], Ketevan Shalashvili[2], Tamar Shavadze[1]

[1]Tbilisi State Medical University Department of Odontology, [2] Tbilisi State Medical University I. Kutateladze Institute of Pharmcochemistry, Tbilisi, Georgia

Corresponding author e-mail: Nizharadzenatia@yahoo.com

At present, endodontic failure remains the most urgent problem of contemporary endodontics. The main reason for the complication of endodontic treatment is the retention of pathogenic microbe *Enterococcus faecalis* inside the root canal system after endodontic treatment. In the era of advances in endodontics, dentists still face challenges in the decontamination of canals, as *E. faecalis* is resistant to the most widely used, "rated" canal disinfection agents. Therefore, in modern endodontic practice, the issue of finding an effective antimicrobial solution for the root canal system irrigation is still relevant.

On the other side, the world pharmacy is becoming increasingly focused on natural drugs. Taking this tendency into consideration, the development and application of novel herbal antibacterial medicines is demanded for the successful management of persistent endodontic infection. According to the literary data, compounds obtained from the plant *Cotinus coggygria* Scop. (family Anacardiaceae) are claimed to have diverse biological activity, including antibacterial activity against a wide range of microorganims. The foregoing predetermined the choice of the object for our investigation.

The study aimed to assess the antimicrobial efficacy of *C. coggygria* Scop. extract water solutions against *E. faecalis*.

At TSMU Iovel Kutateladze Institute of Pharmacochemistry unique formulation from the cultivated in Georgia *C. coggygria* Scop. leaves – polyphenols enriched extract has been developed. Later its aqueous solutions of various concentrations (2%, 5%, 10% and 15%) were prepared as endodontic irrigation solutions exclusively for our study. A microbiological study of polyphenol extract aqueous solutions against endodontic pathogens (*Streptococcus spp*. and *Enterococcus spp*.) was conducted at the Laboratory of General Microbiology of Eliava Bacteriophage Analytical Diagnostic Center.

The result of *in vitro* studies seems encouraging as 2% extract was found to be most effective against *Streptococcus spp*, while extract 10% solutions were observed to be most effective against *E. faecalis*.

The revealed high antibacterial activity suggests that aqueous solutions of *C. coggygria* Scop. extract could be used successfully in endodontic therapy. The *in vivo* investigation is now underway to endorse this unique herbal formulation as an alternate antibacterial endodontic irrigant.

PP 34. DEVELOPMENT OF A LIPOSOMAL DOSAGE FORM OF PAPAIN

M. Orjonikidze, D. Lagazidze

Tbilisi State Medical University, I. Kutateladze Institute of Pharmacochemistry, Tbilisi, Georgia

Corresponding author e-mail: m.orjonikidze.tsmu.edu

The difficulties of using proteolytic enzymes in enzyme therapy are related to a number of their side effects: toxicity, allergenicity, vulnerability and inactivation of the enzyme in biological fluids. The present research is devoted to the development of a liposomal dosage form of Papain, a complex of proteolytic enzymes from the latex of unripe fruits of papaya (*Carica papaya*).

The aim of the research was the development of an effective and less toxic liposomal form of Papain, which would expand the area of pharmacological implementation of these enzymes.

The object of research - Papain (Nanning Pangbo Biological Engineering Co., Ltd), excipients and reagents: soy phosphatidylcholine, D-glucose cholesterol, α--tocopherol acetate, L-cysteine, Sephadex-G-50 (Sigma Aldrich), casein (Carl Roth).

The methods used the study were the lipid membrane hydration method and the ultrasound treatment method (Thin-Film Method) [1]; the proteolytic activity of natural papain and liposomal papain were determined on a casein substrate by the Anson's modified method [2]; the average diameter of nanoparticles was assessed by dynamic light scattering spectroscopy; the quality of encapsulation was measured by gel chromatography.

In the first stage of the research, excipients were selected according to their physical-chemical and functional purpose. Soy phosphatidylcholine and cholesterol were used as the main components of the liposomal membrane, α-tocopherol was used as an antioxidant.

In total, 5 liposomal compositions with different ratios of papain and phospholipids were designed using the lipid membrane hydration method. The optimal ration was papain / soy phosphatidylcholine / cholesterol / α -tocopherol (1: 10: 2: 0.03). The average diameter of the obtained liposomes ranged from 400 to 840 nm, with a polydispersity index of 0.52 to 0.96. In order to give the obtained liposomal dispersion a dosage form, glucose (30% of the mass of lecithin) was added and the mass was treated with 43 kHz ultrasound for 15-60 minutes. Effective reduction of particle size was achieved as a result of a 45-minute ultrasonic treatment. Their average diameter was - 192.6 nm, the polydispersity index - 0.308, and the zeta-potential was (-36.3 mV).

"Liposome incorporated" and "free" papain were separated by gel-chromatography: gel - Sephadex G-50, eluent - purified water; elution speed 0.5 ml/min. Preliminary studies investigated gel filtration of natural papain and free liposomes under the same conditions. Quantification of papain was carried out using spectrophotometry at a wavelength of 280 nm. The release time of liposomal papain (7-12 minutes) coincides with the release time of control liposomes, and free papain (20-25 minutes). Incorporation efficiency was 70-75%.

References

[1] Šturm L, Poklar Ulrih N. 2021. Basic Methods for Preparation of Liposomes and Studying Their Interactions with Different Compounds, with the Emphasis on Polyphenols. Int J Mol Sci. 22(12):6547. doi: 10.3390/ijms22126547

[2] Kaverzneva E., 1971, Standard method for determining proteolytic activity for complex preparations of proteases. Appl. Biochem. and microbiology, vol. 7, no. 2, pp. 225-228. (In Russian)

PP 35. HIGHLY SPECIFIC AND HIGHLY BRIGHT NEAR-IR MITOCHONDRIA STAINS

Arpita Panda[1], Dmytro Kobzev[1,2], Leonid Patsenker[1]

[1]Department of Chemical Sciences, the Faculty of Natural Sciences, Ariel University, Ariel, 40700, Israel,

[2]SSI "Institute for Single Crystals" of the National Academy of Sciences of Ukraine, Kharkiv, Ukraine

Corresponding author e-mail: pandar@ariel.ac.il

Due to multiple functions in cell life, mitochondria are considered a highly desirable target in cancer treatment and imaging. Damage of the mitochondrial DNA leads to cancer cells killing. The inner mitochondrial membrane of normal healthy mammalian cells has a strong negative potential that even more increases in cancer cells. This effect can be utilized for the development of mitochondria-specific dyes that obviously must be positively charged. Up to now, several mitochondria-specific, positively charged dyes have been developed for visualization of mitochondria and real-time monitoring of treatment responses upon chemo- and photodynamic therapies [1]. These dyes suffer, however, from insufficient selectivity and a poor brightness within the near-IR spectral region, which limits their clinical applications.

Herein, we developed a series of the new near-IR dyes, **mCy1, mCy3**–**mCy5**, and **ICy7-TPP** that contain triphenylphosphonium (TPP^+) group, **TPP-dyes** (Fig.1), and evaluate their specificities to mitochondria and brightnesses as compared to the previously introduced mitochondrial tracker **Cy-TPP** [1]. This work was done in the example of the fixed and live human breast cancer cell line SK-BR-3 (HER2-positive) and an epithelial, triple-negative human breast cancer cell line MDA-MB-231 (HER2-negative).

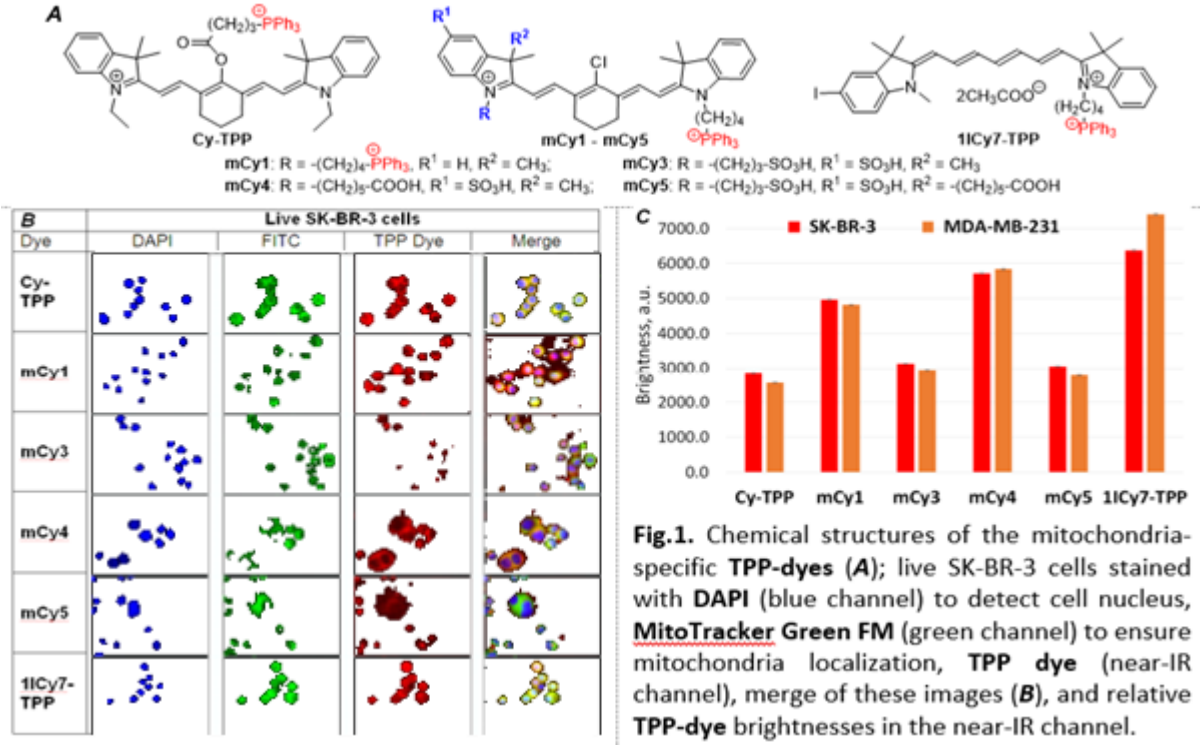


Fig.1. Chemical structures of the mitochondria-specific **TPP-dyes** (***A***); live SK-BR-3 cells stained with **DAPI** (blue channel) to detect cell nucleus, **MitoTracker Green FM** (green channel) to ensure mitochondria localization, **TPP dye** (near-IR channel), merge of these images (***B***), and relative **TPP-dye** brightnesses in the near-IR channel.

We found that the dyes **mCy1**, **mCy4**, and especially **1ICy7-TPP** stain mitochondria of both cell lines more efficiently than the previously reported dye **Cy-TPP**

Reference:

[1] Ning, J., et al. 2017, Mitochondria targeting and near - infrared fluorescence imaging of a novel heptamethine cyanine anticancer agent, *Mol. Med. Rep.*, vol. 15, no. 6, pp. 3761-3766.

PP 36. DOLASTATINOL 10 DERIVATIVES AS HIGHLY POTENT MICROTUBULE INHIBITORS FOR TARGETED DRUG DELIVERY

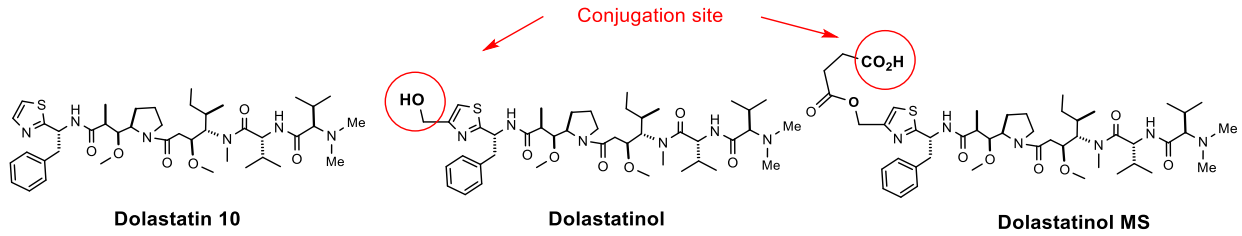
Hodaya Gutman, Akash Panja, Helena Tuchinsky and Gary Gellerman

Department of Chemical Sciences, Ariel University, Ariel, 40700, Israel

Corresponding author e-mail: hodayago@ariel.ac.il; akash@ariel.ac.il; garyg@ariel.ac.il

Dolastatin 10 (Dol-10) is a marine pentapeptide discovered from the mollusk *Dolabella auricularia* in the Indian Ocean. Dol-10 has attracted a lot of interest in recent years since it can efficiently trigger apoptosis destabilizing microtubules in tumor cells at sub-nanomolar concentrations, and it has been turned into drug candidate for treatment several specific lymphomas. Dol-10 was found to be very toxic to a variety of tumor cells in vitro, including L1210 leukemia cells (IC_{50} = 0.03 nM), small cell lung cancer (SCLC) NCI-H69 cells (IC_{50} = 0.059 nM), human prostate cancer DU-145 cells (IC_{50} = 0.5 nM), and in A549 non-small cell lung cancer (NSCLC) lung cancer cells (IC_{50} = 1.3 nM) among others. Clinical research based on Dol-10 core structure has made significant progress thanks to the rise of antibody-drug conjugates (ADCs). Auristatins (Dol-10 derivatives) are the most well-known payloads used in ADCs. As of September 2021, the FDA had approved 11 ADCs, eight of which have been approved since 2017, and monomethyl auristatins (MMAE and MMAF) are used as payloads in five of them.

Our group has discovered Dolastatinol, a novel cytotoxic Dol-10 derivative by our unique and simple solid phase peptide synthesis (SPPS) method bypassing time and effort-intensive liquid phase synthesis. Dolastatinol shows nanomolar toxicity in a battery of breast cancer cell lines. Among them, Dolastatinol almost completely eradicated hard-to-treat triple negative breast cancer cell line MDA-MB-231 (IC_{50} = 1.54 nM), and two HER2+ breast cancer cell lines BT474 (IC_{50} = 2.3 nM) and SKBR3 (IC_{50} = 0.95 nM).



The modified C-terminus of Dolastatinol and Dolatatinol MS can be used for linker strategy, ready for antibody conjugation. The conjugation of Dolastatinol to antibody is in process in our lab.

References

[1] Hodaya Gutman, Andrii Bazylevich, Chandrashekhar Prasad, et. Al. 2021, 'Discovery of Dolastatinol: A Synthetic Analog of Dolastatin 10 and Low Nanomolar Inhibitor of Tubulin Polymerization', ACS Medicinal Chemistry Letters, 12 (10), 1596-1604

PP 37. PHARMACEUTICAL FORMULATION AND TECHNOLOGY OF APIGENIN ORODISPERSIBLE TABLETS AND IT'S ANTIHYPERTENSIVE POTENTIAL.

N. Papiashvili[1], L. Bakuridze[1], L. Ebralidze[1], T. Zarkua[3], N. Gongadze[2]

Tbilisi State Medical University: [1]Department of Pharmaceutical Technology; [2]Department of Medical Pharmacology; [3]Departments of Social and Clinical Pharmacy.

Corresponding author e-mail: nika.papiashvili1991@gmail.com

Plant origin phenolcarbonic compounds belonging to flavonoids may produce soluble epoxide hydrolase (sEH) inhibitory activity preventing the conversion [2] of vasodilatory agents-epoxyeicosatrienoic acids (EETs) to less active dihydroxyeicosatrienoic acids (DHETs).

In our previous study [3] phenolcarbonic agent Luteolin obtained from domestic plant *Perilla Nankinensis* Decne.

In hypertensive Wistar rats i.p. administration during two weeks caused marked hypotensive action by reduction arterial pressure (-25-30 mm Hg) associated with slowing of cardiac rhythm and increased baroreflex sensitivity.

From solid oral dosage forms, orodispersible tablets (ODT) are convenient to use, as they disperse and dissolve in the oral cavity without taking water. Most often, disintegration of ODT in saliva does not exceed 10-30 seconds. They can be taken not only by patients with impaired swallowing, but also travelling people who do not have direct access to water while taking the medicine. Taking fast-dissolving ODT is also proper for the elderly and bedridden patients who have difficulty taking the drug orally due to impaired swallowing.

ODT that dissolve quickly in the mouth are especially important for patients with arterial hypertension.

Based on literary data and preliminary pharmacological studies, it has been revealed that the biologically active substance of plant origin - Apigenin, has the ability to inhibit soluble epoxide hydrolase.

The purpose of this study was to determine the composition of Apigenin ODT and develop its pharmaceutical formulation and technology for achieving rapid and prolonged antihypertensive action.

The objects of the research were the active pharmaceutical ingredient (API) - Apigenin series N:H452212321, company Dalian launcher fine chemical co. (China), Prosolv SMCC HD90 series N: H951056, company JRS Pharma (Germany), Collidon 30 series N:31255368E0, company BASF (Germany), Mannitol series N:H361210021, company Dalian launcher fine chemical co. (China), Sodium Starch Glycolate, series N:H324560054, company Dalian launcher fine chemical co. (China), Sodium Stearyl Fumarate (Spain)

The residual moisture content of the API was determined using an automatic moisture analyzer (MS-70) at 105^0C.

To evaluate the fractional composition and the morphological characteristics (size, shape, surface relief) of the powder, we used the method of Direct Optical Microscopy with visible light. The samples are examined on the microscope Axio Observer.Z1 Carl Zeiss (Germany) and on the lens A-Plan 10x/0.25 Ph 1, the particle sizes of the powder of the research substance are measured. Determination of dispersion was carried out by means of sieving analysis.

The flowability of API was determined by measuring the powder flow rate and the angle of inclination using the device ERWEKA GTB (Germany). The angle of repose was determined by using protractor, which is the angle between the cone formed from the friable material and the horizontal plane. The bulk density of the API was determined using device ERWEKA SVM 223 (Germany). Crushing strength

parameter of ODT was measured using ERWEKA TBH 125 (Germany) testers. Friability was determined using TAR 220 ERWEKA (Germany) following USP Pharmacopoeia (reference of the USP pharmacopoeia), rotational frequency at 20 rpm for 5 minutes. Wetting time, water absorption capacity and dispersibility were investigated in in vitro tests using methods described in the literature [1,5].

To prepare apigenin ODT, we used a model formulation of ODT selected by artificial intelligence, which is a ready-made composition containing various active pharmaceutical ingredients (%): Proslv SMCC HD90 - 47.5, mannitol - 45.0, collidon 30 – 6.5 and stearyl fumarate sodium 1.0.

On the basis of conducted biopharmaceutical studies, the Apigenin ODT formulation is provided and the technology of preparation is developed by melting method.

Apigenin ODT were evaluated for the following pharmacotechnological parameters: uniformity of dosage, mechanical strength, wettability, disintegration, solubility and stability. According to the quality indicators, the tablets provided meet the requirements of the current European Pharmacopoeia (Ph. Eur. 10). The use of superdisintegrant - sodium starch glycolate ensures fast disintegration of tablets (21-25 sec.) and 99.8% release of apigenin.

In chronic experiment Apigenin ODT (3-5mg/kg) caused dose-dependent diminution in arterial pressure lasting for about 2-3 hours. It is suggested, that Apigenin ODT can provide rapid and prolonged hypotensive action in different hypertensive states.

References

[1] Blasco A. Torrado G. Peña MÁ. 2020, Formulation and Evaluation of Loperamide HCl Oro Dispersible Tablets, J. pharmaceuticals, vol. 13,no.5, pp. 100.
[2] Fleming J. 2014, The pharmacology of the cytochrome P-450 epoxygenase/soluble epoxide hydrolase axis in vasculature and cardiovascular diseases., J. pharmaceutical reviews. Vol. 66, no.4, p.p 1106-1140
[3] Papiashvili N. Bakuridze K. Ghongadze M. Bakuridze A. Ghongadze N. 2022, Influence of plant origin soluble epoxide hydrolase inhibitors on hemodynamic parameters in hypertensive rats. European J. of clinical pharmacology, vol.78, no. 1, p.p. 38-38
[4] Vivek D., Renu BY., Richa A., Atul KS., 2017, Formulation and evaluation of orally dispersible tablets of Chlorpheniramine maleate by fusion method, J. of Marmara Pharmaceutical vol. 21. pp. 67-77.
[5] Vishali T, Damodharan N. 2020, Orodispersible Tablets: A Review Research, J. Pharmacy and Technology, vol. 13, no. 5, pp. 2522-2529.

PP 38. ANTIMICROBIAL PHOTODYNAMIC THERAPY WITH NOVEL NEAR-IR CYANINE PHOTOSENSITIZERS

Arjun Veliyil Prakash[1], Fares Yazabak[2], Faina Nakonechny[2], Gary Gellerman[1]

[1]Department of Chemical Sciences, the Faculty of Natural Sciences; [2]Department of Chemical Engineering, Ariel University, Ariel, Israel.

Corresponding author e-mail: arjunp@ariel.ac.il

Antimicrobial photodynamic therapy (APDT) has emerged as the efficient treatment modalities in treatment of pathogenic bacterial diseases. The main advantage of this medication is its minimal side effects over conventional chemotherapy and antibiotic therapy. PDT utilizes dye molecules (photosensitizers) that generate various cytotoxic species upon light exposure, and these reactive species kill abnormal cells around. One of the main issues with current photosensitizers is insufficient phototoxicity under the near-infrared (NIR) light irradiation, which is most transparent in the body.

To address this issue, we synthesized novel, NIR-excitable indolenine- (**IR786**), benzothiazole- (**IR2S, IR3S**) and benzoselenazole- (**IR2Se**, and **IR3Se**) based cyclohexene-cyanine dyes containing two and

three heterocyclic groups and investigated them as photosensitizers for eradication of *S. aureus* (Gram positive) and *E. coli* (Gram negative) pathogenic bacteria.

We found that the most phototoxic dyes are the compounds containing two heterocyclic groups, **IR786**, **IR2S**, and **IR2Se**, that almost completely eradicate *S. aureus* at 10 nM concentration (light dose 100 J/cm^2) and *E. coli* at 50 µM concentration (light dose 200 J/cm^2) (Fig.1). The least phototoxic dye is **IR3S**. This dye is as bright as **IR786** but much less phototoxic and can be recommended therefore as a safer fluorescence reporter in biomedical imaging experiments.

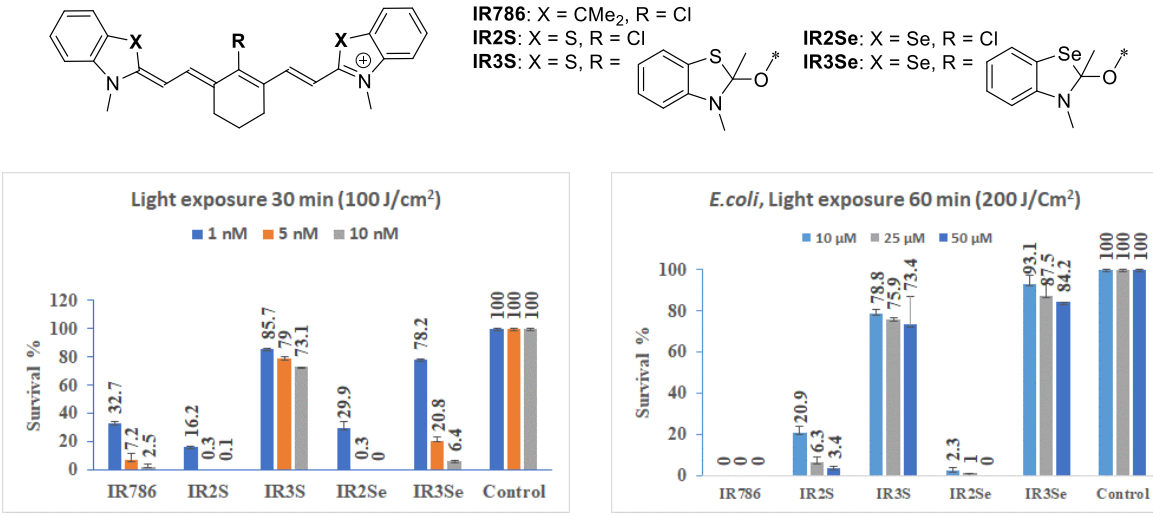


Fig. 1. Phototoxicity. Survival percentage of *S. aureus* (left) and *E. coli* (right) treated with the investigated photosensitizers (1 nM, 5 nM, and 10 nM) upon exposure with 100 J/cm^2 near-IR light dose after dark incubation at 20 °C for 15 min.

We believe that the di-substituted benzoselenazole and benzothiazole cyanines, such as IR2Se and IR2S, can be further exploited for the development of highly-efficient sensitizing systems for photoeradication of many other kinds of abnormal cells.

PP 39. DEVELOPMENT-VALIDATION OF COMBINED METHOD OF ULTRASOUND-ASSISTED EXTRACTION AND ANALYTICAL HPLC PROCEDURES FOR QUANTITATIVE DETERMINATION OF URSOLIC AND OLEANOLIC ACIDS IN APPLE AGRO-INDUSTRIAL WASTE MATERIAL USING ANALYTICAL QUALITY BY DESIGN APPROACH

Imeda Rubashvili, Mzia Tsitsagi, Ketevan Ebralidze, Mariam Chkhaidze, Miranda Khachidze

Iv. Javakhishvili Tbilisi State University P. Melikishvili Institute of Physical and Organic Chemistry, Tbilisi, Georgia

Corresponding author e-mail; imeda.rubashvili@tsu.ge

Apple pomace as a waste material of the apple processing industry containing approximately 25% of the processed apple represents a low-cost and rich source of fruit-derived bioactive compounds with valuable properties including pentacyclic triterpenoids regioisomeric triterpene acids - ursolic acid (UA) and oleanolic acid (OA). These bioactive compounds have attracted a lot of attention due to their unique and strong biological, a wide variety of approved pharmacological activities including anticancer, chemopreventive, hepatoprotective, antiviral, antibacterial, anti-inflammatory, antiatherosclerostic, antidiabetic, antioxidant, immunomodulatory and gastroprotective properties [1]. Due to the wide range of applications in pharmaceutical and nutraceutical industries, these

bioactive compounds have a high commercial value. Therefore, an efficient, selective and high-yield extraction to obtain UA and OA from raw plant materials and quantitative determination of these compounds in the mentioned material and the extracted product using a suitable analytical method has a great significance and practicability.

The aim of this study was to develop and validate a new, effective and reproducible method obtained with a combination of the high-yield and selective stepwise ultrasound-assisted extraction (UAE) procedure and the specific, sensitive and simple analytical HPLC procedure for quantitative determination of UA and OA in the dry extracted product and the apple processing waste material using analytical quality by design approach (AQbD).

The AQbD as a novel approach suggested by current pharmaceutical guidelines is not meant for analytical method development only, but this concept can be implemented to develop a robust analytical method, gives information on risk associated with the method as well as the influencing factor effect on analytical method performance. The AQbD approach is based on the principles of experimental design (DoE) that participated in a systematic thoughtful of the reasonable risk and interaction between the experimental variables [2]. The quality target method profile was defined and several critical attributes were identified. The analytical target profile of the proposed method was fixed based on the established acceptable criteria.

Apple pomace as the apple processing waste material provided by local apple juice and jam manufacturer was dried using the laboratory conditions. The two-stage sequential UAE was carried out in the controlled temperature (25-40^{o}C) conditions under ultrasonication by different ultrasound powers at 25 and 37 kHz. The two stage UAE was performed by adding 5-20 g of the powdered dried sample of the raw material and 50-200 mL of different solvent/ a mixture of solvents in 200 mL extraction vessel equipped with digital temperature controller for 10-40 minutes. After both extraction stages, the crude extract solutions were centrifuged at 4000 rpm and then the obtained supernatants were collected to evaporate by rotary evaporator for removing solvents. The obtained wet powder containing OA and UA was treated, purified and dried by the stepwise clean-up and drying procedure to obtain the extracted dry product [1].

The chromatographic analysis was performed using LC-20AD Prominence Shimadzu HPLC System (Japan) and the column - Agilent SB-C18 4.6×250 mm, 5 µm (USA) with an isocratic elution of mobile phase (MP). The flow rate of MP was 1.0 mL/min; The UV-spectrophotometric detection was performed at the wavelength - 210 nm; The injected volume was 20 µL; The column temperature was maintained at 35°C. The external standard method was used for quantification of UA and OA [1].

The developed method was validated with respect to the following validation parameters: robustness, system suitability test, specificity, linearity-range, precision, accuracy, sensitivity, limits of quantification (LOQ) and detection (LOD).

In order to optimize the selected extraction conditions, to establish the optimal extraction parameters and to study robustness of the analytical procedure, the DoE was used; the quantitative and qualitative critical parameters with two levels (“-”, “0” and “+“) of both UAE and analytical procedures were considered and selected based on risk assessment.

The LOD and LOQ of the analytical procedure were 0.000025 mg/mL and 0.00005 mg/mL for OA 0.000025 mg/mL and 0.000075 mg/mL for UA, respectively. The calibration curve (0.00005-0.5 mg/mL for OA and 0.000075-0.5 mg/mL for UA) is linear and the square of correlation coefficient is more than 0.99 for both analytes. The mean recovery of the combined method is more than 95. %. The purity of the dry extracted product of hesperidin is not less than 89 %.

The research results have been shown that the proposed combined method is validated and can be used for obtain UA and OA as the extracted dry product with high purity. The validated method can be

successfully applied for quantitative estimation of these compounds of the dry raw material as a starting material of the apple juice and jam manufacturer and the extracted dry product.

The research was financially supported by the Shota Rustaveli National Science Foundation within the framework of project #21-4196.

References

[1] Rubashvili, I. et al. 2020, Extraction and analysis of oleanolic acid and ursolic acid from apple processing waste materials using ultrasound-assisted extraction technique combined with high performance liquid chromatography, *Rev. Roum. Chim.,* vol. 65, no. 10, pp. 919–928.

[2] Bhaskaran, NA. et al. 2021, An analytical "quality by design" approach in RP-HPLC method development and validation for reliable and rapid estimation of irinotecan in an injectable formulation, *Acta Pharm.,* vol. 71, no. 1, pp. 57–79.

PP 40. ASSESSMENT OF SMOKE TREE EXTRACT SAFETY FOR ITS FURTHER APPLICATION IN DENTAL PRACTICE

Tamar Shavadze, Natia Nizharadze, Marine Mamaladze

Tbilisi State Medical University Department of Odontology, Tbilisi, Georgia

Corresponding author e-mail: tamoshaa@yahoo.com

The primary aim of endodontic treatment is to remove bacteria from the root canal system. Irrigation of root canal system is considered one of the most important processes for successful root canal disinfection. Endodontic research has always been focused on developing methods or endodontic irrigants that can completely remove the bacteria with minimal side-effects. Although sodium hypochlorite (NaOCl) is most effective and widely/ commonly used in Endodontics, but it is a well-known irritant to periapical tissues. In this sense, the search of alternative natural preparations for the disinfection of root canals remains relevant.

Natural products have generally been thought to be safer than synthetic ones, but given that most of them are complex mixes of organic compounds from various classes, an accurate assessment of their safety is required when offering prospects for innovative treatments.

In acute safety investigations, it should be urged to use as few animals as possible to collect as much scientific information as possible. An estimated LD_{50} value and/or the specification of a dangerous dosage range often provide sufficient information on the acute toxicity of medications for which numerous additional toxicologic data are available.

The goal of our study was to determine safety margins as well as possible irritative and allergenic properties of smoke tree (*Cotinus coggygria*) polyphenols containing extract (**STPE**), that is proposed for oral irrigation.

The experiments were carried out in accordance with the OECD Guidelines for the Testing of Chemicals [1-3]. In addition, the precise determination of **STPE** LD_{50} value was determined using probit-analysis [4].

LD_{50} of **STPE** was determined after intraperitoneal and oral administration in mice and appeared to be 20.5 mg/kg and 266 mg/kg, respectively (Fig.1). **STPE** revealed no local irritating and allergenic properties in corresponding assays.

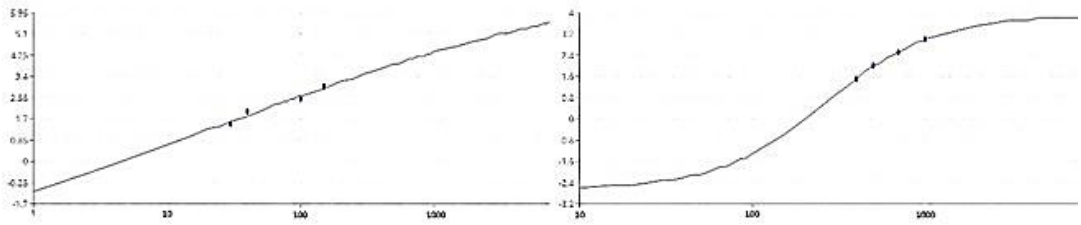


Fig.1. Determination of LD_{50} of STPE in intraperitoneal (left) and oral (right) administration.

Taking into consideration that the suggested maximal concentration of **STPE** as oral irrigant will vary in range between 7 and 14 mg/kg, it can be concluded, that smoke tree extract is safe for the desired application.

References

[1] OECD Guidelines for the Testing of Chemicals, Section 4. Test No. 423: Acute Oral toxicity - Acute Toxic Class Method. https://www.oecd-ilibrary.org/environment/test-no-423-acute-oral-toxicity-acute-toxic-class-method_9789264071001-en

[2] OECD Guidelines for the Testing of Chemicals, Section 4. Test No. 404: Acute Dermal Irritation/Corrosion. https://www.oecd-ilibrary.org/environment/test-no-404-acute-dermal-irritation-corrosion_9789264242678-en

[3] OECD Guidelines for the Testing of Chemicals, Section 4. Test No. 406: Skin Sensitisation. https://www.oecd-ilibrary.org/environment/test-no-406-skin-sensitisation_9789264070660-en

[4] http://14.139.232.166/Probit/probitanalysis.html

PP 41. PHYTOCHEMICAL CHARACTERISATION AND BIOLOGICAL ASSESSMENT OF SECONDARY METABOLITES OF PRIMULA SPECIES GROWING IN GEORGIA

Nino Sukhishvili, Karen Mulkijanyan, Lasha Mskhiladze

Tbilisi State Medical University I. Kutateladze Institute of Pharmacochemistry, Tbilisi, Georgia

Corresponding author e-mail: n.sukhishvili@tsmu.edu

The development of novel medical products from natural resources still remains among top priorities of contemporary pharmacy and medicine, and plant extracts are regarded as one of the most advantageous and promising sources. However, the diverse chemical composition of plants can pose a significant hazard to human health, and exact assessment of plant phytochemical composition and biological properties is of great importance.

The family *Primulaceae* includes 68 genus of plants and approximately 1252 species [1]. In Georgia, this family is represented by 7 genera and 46 species. 22 species of the genus Primula can be found in Georgia, among them 12 are endemics of the Caucasus, and two - endemics of Georgia: *Primula abchasica* and *Primula saguramica* [2].

The aim of the study was the comparative phytochemical analysis the representatives of genus *Primula* growing in Georgia: *P. macrocalyx* Bunge*, P. woronovii* Losinsk and *P. saguramica* Gavr. and primary pharmacological evaluation of secondary metabolites-containing fractions of different polarity obtained from aforesaid plant species.

The whole plant was air-dried, grinded and treated by 80% EtOH followed by condensation and freeze-drying (Lyo.). Further chromatographic separation was done on Diaion HP-20 packed column by water-methanol mixture elution with an ascending gradient of 0-100% [3] (H_20, MeOH 50%, MeOH 100% and EtOAc). As a result, 5 fractions from each plant: P.mac Lyo, P.mac H_20, P.mac MeOH 50%, P.mac MeOH 100%, P.mac EtoAc from *P. macrocalyx*; P.wor Lyo, P.wor H_20, P.wor MeOH 50%, P.wor MeOH 100%,

P.wor EtoAc - from *P. woronowii* and P.sag Lyo, P.sag H_20, P.sag MeOH 50%, P.sag MeOH 100%, P.sag EtoAc from *P. saguramica*.

TLC screening for secondary metabolites revealed the domination of flavonoids and alkaloids (Tab. 1).

Table 1. Results of TLC screening of total extracts and fractions of *P. woronovii, P. macrocalyx and P. saguramica.*

Fractions	*P. macrocalyx*				*P. woronovii*				*P. saguramica*			
	Lyo	H_2O	MeOH 50%	MeOH 100%	Lyo	H_2O	MeOH 50%	MeOH 100%	Lyo	H_2O	MeOH 50%	MeOH 100%
Flavonoids	+	-	+	-	+	-	+	-	+	-	+	-
Alkaloids	-	-	-	+	+	-	-	+	+	-	-	+
Cardiac glycosides	-	-	-	-	-	-	-	-	-	-	-	-
Ascorbic acid	-	+	-	-	-	+	-	-	-	+	-	-

Taking into consideration the results of TLC screening and the literary data, the analgesic and anti-inflammatory potency of total extracts from each plant and corresponding fractions were assessed *in vivo* using "Hot plate" and carrageenan-induced inflammation models, respectively (Fig.1). All animal experiments were carried out in accordance with [4, 5] and authorized by the TSMU Ethics Committee on Animal Research (Approval # AP-56-22).

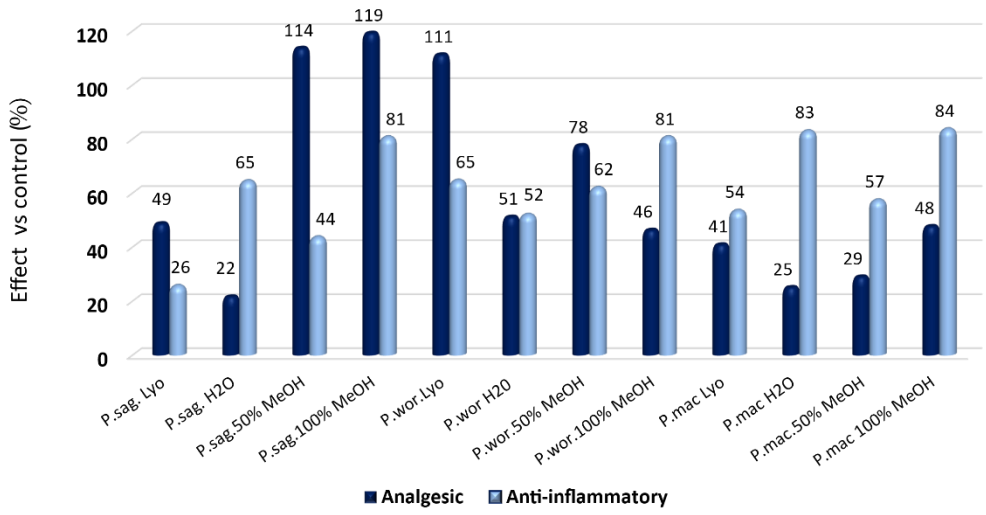


Fig. 1. Pharmacological effects of total extracts and fractions of *P. woronovii, P. macrocalyx and P. saguramica.*

Hence, flavonoids and alkaloids appeared the dominant secondary metabolites in all studied fractions. The results of *in vivo* experiment proved fractions' analgesic and anti-inflammatory potency and the revealed differences in the activity may be determined by flavonoid/alkaloid ratio in particular fractions. It seems reasonable to continue the study of most active fractions in order to isolate and identify individual compounds, responsible for the revealed pharmacological activities.

References

[1] The Plant List. 2013. Version 1.1. Available from http://www.theplantlist.org/Primulaceae

[2] Davlianidze M., Gviniashvili T., Mukbaniani M., Jinjolia-Imnadze L. Jugeli T. Nomenclatural Checklist of Flora Georgia. Ilia Stat University Institute of Botany. Tbilisi, Republic of Georgia: 2018. pp. 296

[3] H. Wagner, S. Bladt, Munich, March 1996, Plant drug analysis, second addition pp. 196

[4] Guide for the Care and Use of Laboratory Animals, 8th Ed. (2011). The National Academies Press, USA.g

[5] Directive 2010/63/EU of the European Parliament and of the Council of 22 September 2010 on the Protection of Animals Used for Scientific Purposes. (2010). Official Journal of the European Union, L 276/34.

PP 42. HPLC DETERMINATION OF CAFFEIC ACID in *Cephalaria gigantea*

N. Tabatadze[1], I. Tsomaia[2], A. Chikovani[1], E. Churgulia[1]

[1] Sokhumi State University Faculty of Natural Sciences, Mathematics, Technology and Pharmacy; [2] Georgian Technical University Department of Pharmacy; Tbilisi, Georgia

Corresponding author e-mail: nino_tabatadze@yahoo.com

Out of 60 species of the genus *Cephalaria*, 12 are found in Georgia, among these *Cephalaria gigantea (Ledeb*.) Bobr. (fam. Dipsacaceae) is a Caucasian endemic plant and is widespread throughout the Caucasus [1]. The presence of alkaloids, flavonoids, phenolcarboxylic acids and triterpene compounds (saponins) was demonstrated in different members of the genus *Cephalaria*. Preliminary phytochemical analysis showed the presence of 0,2 % alkaloids (including gentianine, gentianidine, gentianaine) in the plant's roots [2-6].

By using HPLC method, UV and MS spectra of corresponding standards, 6 phenolic compounds have been identified: chlorogenic acid, caffeic acid, 4,5 di-O-caffeoylquinic acid, 3,5 di-O-caffeoylquinic acid, 3,4 di-O-caffeoylquinic acid and 3,4,5-tri-O-caffeoylquinic acid. These phenolic acids were reported for the first time in *C. gigantea's roots*.

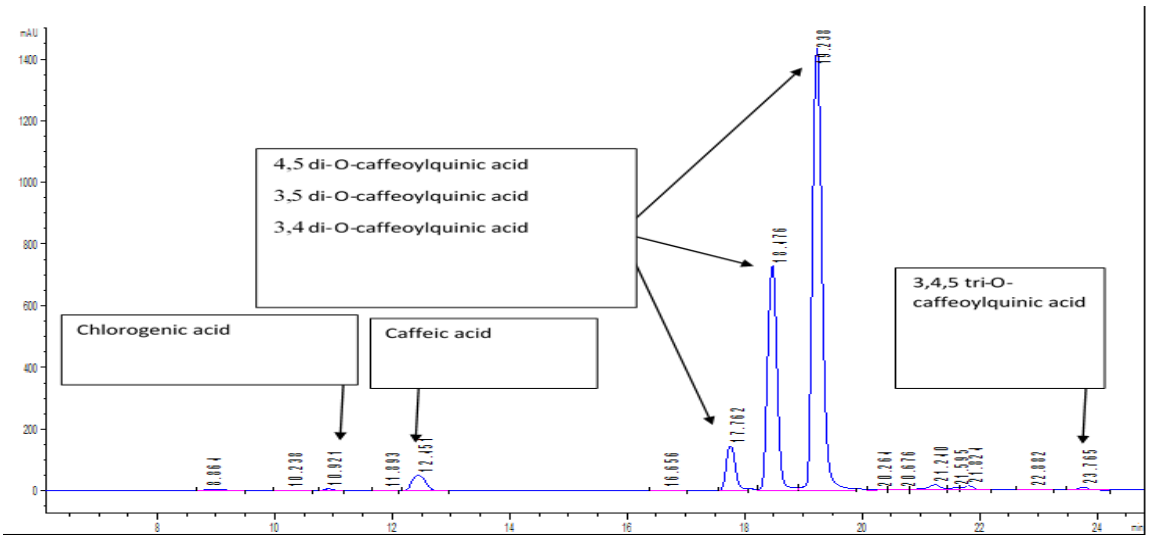


Fig. 1. Phenolic compounds of the roots of *Cephalaria gigantea*

The qualitative and quantitative HPLC analysis was performed on an Agilent 1200 HPLC system (Agilent Technologies, Palo Alto, CA) consisting of a degasser, a quaternary pump, an automatic injector, a temperature-controlled column compartment, a diode array detector (UV detection was performed at 365 nm) and a mass selective detector Agilent G1946 VL model equipped with an ES-APCI source in negative mode on a C18 reversed phase column Kinetex XB-Rp18, 250X4.6mm (Phenomenex), the mobile phase A (H_2O+HCOOH 0.1%) and phase B (Acetonitrile + HCOOH 0.1%) were used in gradient condition (acetonitrile 5% →40%). Flow rate was 1.0 ml/min, injection volume - 10µL and run time - 25mn. The standard stock solutions were prepared by dissolving 1 mg of each standard in MeOH (1 mL), the concentration of the EtOAc fraction sample was 10 mg/mL in MeOH.

The chromatograms reveal the peak areas attributed to caffeic acid. The concentration of caffeic acid in our extract is 0.084 mg/mL. The quantification method is linear, accurate and reproducible R^2=0.9907.

Thus, in the AcOEt phase of *Cephalaria gigantea* roots extract, we have identified the presence of six major phenolic compounds including caffeic acid in a concentration of $8.654*10^{-2}$ mg/mL. This

concentration can be used as a basis in standardization of *Cephalaria* extract in case of its further commercialization.

References:

[1] Ketskhoveli N,. Kharadze A., Gagnidze R. 2001. Flora of Georgia, Caprifoliaceae – Campanulaceae. Tbilisi, Metsniereba, Edition 2, Vol. 13, .

[2] Tabatadze N., Elias R., Faure R., Gerkens P., De Paul-Gillet M. C., Kemertelidze E., Chea A., Ollivier E. 2007, Cytotoxic triterpenoid saponins from the roots of Cephalaria gigantea. Chem. Pharm. Bull. 55(1), 102-105.

[3] Tabatadze N., Mshvildadze V., Elias R., Ollivier E., Faure R., Dekanosidze G., Balansard G., Kemertelidze E. 2003, A new triterpenoid glycosides from the roots of Cephalaria gigantea L. Georgia Chemical Journal 3(2), 158-160.

[4] Gerkens P., Dobson R., Tabatadze N., Mshvildadze V., Elias R., Peulen O. J., Jolois O. M., De Paul-Gillet M. C. 2007, Apoptosis and cytolysis induced by giganteosides and hederacolchisides in HL-60 cells. Anticancer Research, 27, 2529-2534.

[5] Tabatadze N., Vachnadze N., Tabidze B., Getia M., Gogitidze N., Mshvildadze V., Dekanosidze G. 2014, Chemical content and pharmacological active compounds from the roors of Cephalaria gigantea growing in Georgia. Experimental and Clinical medicine, 4, 93-97.

[6] Tabatadze N., Tabidze B, Getia M., Mshvildadze V., Pichette A., Dekanosidze G., Kemertelidze E. 2017, HPLC analysis of an anticonvulsant fraction from the roots of Cephalaria gigantea. Bull. of the Georg. National Academy of Sciences, 11(2), 118-122.

[7]

PP 43. MANAGEMENT OF DRUG DEVELOPMENT LIFE CYCLE OF THE ORIGINAL ANTI-ALLERGIC "DUALLER-G"

I. Tomadze, T. Tchumburidze, N. Dughashvili, E. Tsitsilashvili

Tbilisi State Medical University, Department of Social and Clinical Pharmacy

Corresponding author e-mail: I.tomadze@tsmu.edu

Allergic diseases are the most common chronic conditions lasting throughout the patient's life. They not only cause significant deterioration in the quality of life of patients but also lead to significant absenteeism and reduced productivity, resulting in very high costs for society. Effective and safe treatment of allergic diseases is therefore one of the main challenges 1]

The creation of a new generation anti-allergic drug requires great scientific and labor potential, which only the world's leading companies have, and against this background, Dualler-G, a new generation anti-allergic, extended-spectrum drug created by a Georgian scientist Pr. Tamaz Tchumburidze and registered by the Ministry of Health of Georgia, can be considered a unique achievement. [2]

A broad spectrum anti-allergic drug - Dualler-G is a high-tech product indicated for pollinosis, acute and chronic urticaria, Quincke's angioneurotic edema, hay fever, allergic rhinitis, rhinosinusitis, dermatoses (eczema, neurodermatitis, skin vasculitis, lichen planus, skin itching, etc.), and allergic complications caused by medicinal drugs. Dualler-G does not cause drowsiness, has a rapid (15-30 min) onset and dose depending longlasting (12-24 h) action. Even 2.5 overdose dose not cause side effects.

The conducted research shows that Dualler-G is potentially competitive according to many parameters (drug efficiency, safety, wide spectrum of action, onset and duration of action), but it cannot occupy a suitable place in the pharmaceutical both local and global market, due to the lack of appropriate commercialization activities, as well as the poorly regulated market that hinders development of the life cycle of the drug.

Prospects for the development of Dualler-G medicinal forms - the development and implementation of technological processes of anti-allergic gel and aerosol pharmaceutical preparation, which will have

a targeted effect for the treatment of allergic diseases of the skin and respiratory tract, provide the possibility of achieving the maximum effect with a minimum dose.

References:

[1] Piotr Kuna, Dariusz Jurkiewicz, Magdalena M. Czarnecka-Operacz, et al. 2016. The role and choice criteria of antihistamines in allergy management – expert opinion. Postepy Dermatol Alergol., 33(6).
[2] T. Tchumburidze, N. Alavidze, T. Chikviladze, N. Nemsitsveridze, N. Dugashvili, N. Kvizhinadze and T. Zarkua. 2018. Study of Effectiveness of Combined Antiallergic Drug Dualler-G. Journal of Pharmacy and Pharmacology v.6, pp. 629-632.

PP 44. FORMULATION AND TECHNOLOGY OF POMEGRANATE (*PUNICA GRANATUM* L) SPRAY

A. Poloziani[1], N. Tsagareishvili[1], N. Kurdiani[1], M. Goderdzishvili[2], S. Barbakadze[2]

[1]Tbilisi State Medical University, Department of Pharmaceutical Technology; [2] G. Eliava Institute of Bacteriophages, Microbiology and Virology

Corresponding author e-mail: n.tsagareishvili@tsmu.edu

Based on European Respiratory Society data, because of the upper respiratory tract diseases, 25% of the patients, contact physicians every day [2]. Despite antibiotics' strong efficacy against pathogenic microorganisms, they are also damaging to beneficial bacteria, reducing organism resistance [6,7]. Therefore, one of the most significant tasks for modern pharmaceutical technology is to develop safe and effective medicines, among which are pharmaceutical forms to treat upper respiratory tract infections. In recent years, scientists have paid more attention to the discovery and development of alternative antimicrobial and antibacterial medications. As a result, it is critical and promising to develop plant-derived pharmaceutical formulations that successfully combine the intended pharmacological impact with minimal potential side responses.

It is well known that the peel of a pomegranate is rich in biologically active substances, such as phenolic compounds, vitamins, macro and micronutrients, organic acids, tannins, pectins, etc. [1,4].

We aimed to composite and develop the technology of an antimicrobial and antibacterial phyto-spray recipe using the raw materials rich in phytochemicals [3, 5].

On the basis of a biopharmaceutical investigation, we elaborated the pomegranate (*Punica granatum* L) spray composition consisting of pomegranate peel ethanolic (70%) extract, eucalyptioil, sunflower oil, glycerol, sucrose, methylparaben, calcium sorbate, citric acid, Twin 80, polypropilenglycole, Carbopol, sodium carboxymethylcellulose, and purified water. As well the flow chart of phyto-spray production has been made.

Study of the structural-mechanical and rheological characteristics of the product (homogeneity, pH, viscosity, colloidal and thermostability, the spray content release uniformity) proved that phyto-spray conforms the quality control specifications demanded for given pharmaceutical form.

References:

[1] Hajiyeva S.R, Aliyeva T.I., Abdullayev R.A., Veliyeva Z.T., Isaeva N.M. 2014.Chemical composition of grenades. Baku State University.
[2] Zhelonkin N.N. 2009.Development of the composition and technology of the drug "Spirulina-Spray" for the treatment of diseases of the upper respiratory tract. Dissertation. Pyatigorsk.
[3] Elfalleh W, Hannachi H, Tlili N, Yahia Y, Nasri N and Ferchichi A: Total phenolic content and antioxidant activities of pomegranate peel, seed, leaf and flower. J Med Plants Res. 6:4724–4730. 2012.
[4] Samir Garib oglu Gafizov, Garib Kerim oglu Gafizov 2018 RU. Patent. U2712602C1
[5] Seeram NP, Adams LS, Henning SM, Niu Y, Zhang Y, Nair MG and Heber D: In vitro antiproliferative, apoptotic and antioxidant activities of punicalagin, ellagic acid and a total pomegranate tannin extract are enhanced in combination with other polyphenols as found in pomegranate juice. J Nutr Biochem. 16:360–367. 2005.
[6] Zalepukha S.I. 1973.Antimicrobial properties of plants used for food // Kyiv, Naukova Dumka. 191 p.

[7] Ovaskanen M.L., Torronen R., Koponen J.M. et al. Dietary Intake and Major Food Sources of Polyphenols in Finnish Adults // J. Nutr. – 2008. – Vol. 138, № 3. – P.562 - 566.

PP 45. DEVELOPMENT OF BENTONITE-BASED TOPICAL FORMULATION CONTAINING ROYAL JELLY FROM SHIDA KARTLI REGION OF GEORGIA

L. Tsiklauri

Tbilisi State Medical University I. Kutateladze Institute of Pharmacochemistry, Tbilisi, Georgia

Corresponding author e-mail: l.tsiklauri@tsmu.edu

Clays and particularly bentonites are used in pharmaceutical and cosmetics industry not only as excipients (thickening and emulsifying agent, carriers and releaser of active ingredients, disintegrates, diluent and binder) but also as active components, because of their curative and cosmetic effects [1].

Academician Iovel Kutateladze was the first who suggested application of Georgian bentonite in medicine. From clays of Askana deposit (Georgia) topical preparations “Tikha-Askane” and “Askancol” were proposed by I. Kutateladze Institute of Pharmacochemistry TSMU. Besides versatile therapeutic application, they are also universal base for production of semisolid dosage forms [2, 3].

Royal Jelly (RJ) is one of the most valued and studied bee products used in medicine and cosmetics due to its diverse pharmacological properties. Chemical composition and biological activity of RJ depends on many factors, including constitution and geographical distribution of plants, the harvest time and bee species [4].

The objective of the current study was to develop bentonite-based topical formulation containing RJ from Shida Kartli region of Georgia.

Samples of fresh royal jelly were collected from the hives with colonies of the honeybee species *Apis mellifera caucasia* (Georgian bee) from May to August 2020 and evaluated for the main quality parameters such as water content, 10-hydroxy-2-decenoic acid (10H2DA), pH, acidity.

The samples were prepared by incorporating 3% of RJ into base, developed with combination of Tikha-Ascane aqueous gel and glycerine. The formula of the cream with good consistency, appearance and stability was optimized and selected for further study; the quality specifications - organoleptic properties, pH, acid number, thermal and colloidal stability, uniformity and rheological parameters for chosen formulations were determined. Qualitative and quantitative evaluation of RJ in the cream was performed by infrared spectroscopy and high-performance liquid chromatography. According to the obtained results the incorporation of RJ in the bentonite does not cause qualitative changes of the active substance; the chromatographic profile of the tested formulations displayed identical fingerprints and the existence of 10H2DA in all samples (fresh RJ and RJ cream). The developed cream had appealing appearance with smooth texture and no signs of separation. Viscosity, homogeneity, pH and release profile of RJ from the formulations were acceptable, the content of royal jelly was in the range of 2.93-3.15% (in relation to 10H2DA).

References

[1] Babahoum, N., Ould Hamou, M. 2021, Characterization and purification of Algerian natural bentonite for pharmaceutical and cosmetic applications, BMC Chemistry, vol. 15, no. 1, pp 50.
[2] Kutateladze I. 1955, Ticha - Ascanae for medical purposes. Tb., Gruzmedgiz, 40 p.
[3] Tsiklauri, L., Dadeshidze, I., Tsagareishvili, G. 1998, Study of the Stability and Specific Activity of the Emulsion Containing Sea-Buckthorn (Hippophae rhamnoides L.) Oil and Ticha - Ascanae. Bull. Georgian Acad. Sci., vol. 157, no. 2, pp. 251-253.
[4] Ahmad, S., Campos, MG., Fratini, F. et al. 2020, New Insights into the Biological and Pharmaceutical Properties of Royal Jelly. Int J Mol Sci., vol. 21, no. 2, pp. 382.

PP 46. CYTOTOXIC ACTIVITY OF SOME ALKALOIDS FROM PLANTS SPREAD AND INTRODUCED IN GEORGIA.

L. Kintsurashvili, T. Suladze, N. Todua, N.Vachnadze

TSMU I. Kutateladze Institute of Pharmacochemistry, Tbilisi, Georgia.

Corresponding author e-mail: n.vachnadze@tsmu.edu

Chemotherapy is one of the highly effective methods of treatment, as well as an important component in the complex therapy of oncological diseases. To date, drugs based on biologically active compounds of plant origin, in particular alkaloids, occupy a significant place in cancer chemotherapy. Therefore, the search for new resources of alkaloid-containing plant materials in order to create a new antitumor drug is relevant for modern medicine and pharmacy [1].

Alkaloids from different organs of *Taxus baccata L. (сем. Taxaceae)* and Ephedra *Procera Fisch (сем. Ephedraceae),* and *Mahonia aquifolium* (Pursh) Nutt. *(сем. Berberidaceae)* were obtained by the liquid-liquid extraction method. The dominant consistence of plants is the alkaloids, which belong to the diterpene, acyclic and isoquinoline classes of alkaloids, respectively [2-4].

Cytotoxic activity of these total alkaloids against human lung carcinoma (A-549), human colon adenocarcinoma (DLD-1), and human normal fibroblasts (WS-1) cell lines obtained from ATCC was assessed using the resazurin reduction and Hoechst assays. Etoposide was used as positive control (Tab.1). The study was conducted at the University of Quebec at Chicoutimi Laboratory LASEVE, Canada.

Table 1. *In vitro* cytotoxic activity (expressed in IC_{50}, μg/ml) of total alkaloids vs Etoposide (μM).

Plant	Vegetative organ	Cells line and methods					
		Resazurin			Hoechst		
		A-549	DLD-1	WS-1	A-549	DLD-1	WS-1
E. procera Fisch	Aerial parts	43±3	>200	130±3	36±5	155±11	114±4
Etoposide		27±14	14±2	3,7±0,8	2,0±0,3	1,7±0,3	0,5±0,1
T. baccata L.	Needles	13±14	16±12	79±12	4±5	2±5	>200
Etoposide		2,3±0,2	2,8±0,4	19±3	1,18±0,0	1,0±0	>50
M.aquifolium **(Pursh) Nutt.**	Flowers	25±3	17,8±0,2	9,7±0,9	15±2	13,4±0,4	9 ± 2
	Bark	23±2	23±2	9±1	13±1	15±1	11,7±0,8
	Roots	20±2	20±2	6,4±0,8	8 ± 2	11±1	15,0±0,6
	Seeds	39±6	26±2	14 ± 1	23 ±3	18±2	21±4
Etoposide		13±2	15±2	5,1±05	2,9±0,4	1,5±0,4	0,5±0,2

According to the received data it can be concluded that: the total alkaloids of *Ephedra Procera Fisch.* presented selective activity on A-549, DLD-1 and WS-1. The total alkaloids of *Taxus baccata L.* showed strong activity against A-549, DLD-1 and weak for WS-1. The total alkaloids of *Mahonia aquifolium (*Pursh) Nutt. have shown strong *cytotoxic* activity against A-549, DLD-1, WS-1.

References:

[1] Vachnadze V.Y.; Kintsurashvili L.G.; Suladze T.Sh et al. 2011. Alkaloid-Containing Plants Species of Georgia Flora as Sources of Pharmacologically Active Alkaloids. 2nd International Conference on Organic Chemistry:"Advances In Heterocyclic Chemistry", Tbilisi, Georgia.

[2] He, J.-M., & Mu, Q. 2015. The medicinal uses of the genus Mahonia in traditional Chinese medicine: An ethnopharmacological, phytochemical and pharmacological review. J. of Ethnopharmacology, 175, 668–683.

[3] Wani M., C., Taylor H.L., Wall M. E. et al. Plant Antitumor Agents. Vi. 1997. Isolation and structure of taxol, a novel antileukemic and antitumor agents from *Taxus brevifolia*. J. Am. Chem. Soc., 1.93, 9, 2305-2327.

[4] *Abourashed E.A., El-Alfy A.T., Khan I.A., Walker L.* 2003. Ephedra in perspective — a current review. Phytotherapy Research., 17(7), 703—712.

PP 47. THE USE OF PLANT AND MINERAL RESOURCES OF GEORGIA IN THE CREATION OF COSMETICAL AND COSMECEUTICAL PRODUCTS

P. Yavich, M. Kakhetelidze

Tbilisi State Medical University I. Kutateladze Institute of Pharmacochemistry, Tbilisi, Georgia;

Corresponding author e-mail: p.iavichi@ tsmu.edu

The growing consumer demand for cosmetic products with cosmeceutical elements is mainly due to the desire of the majority of the population to improve their appearance and health status, especially in the presence of skin diseases. They use products in a variety of forms - creams, ointments, sprays, lotions and others. With increasing of awareness of the fewer side effects of herbal products, consumers' demand for herbal cosmetics is becoming a rapidly growing segment worldwide.

It should be noted that cosmeceuticals, which are cosmetic products containing natural ingredients and completely organic beauty products, have become a trend. The consumer appeal of these products and the global demand for herbal cosmetics are expected to increase significantly in the future. At present, most cosmetics manufacturers in developed countries are constantly researching new herbal products and ingredients. Let us consider a number of ingredients, most commonly used in the production of cosmetics.

Oils are sources of fatty acids mainly of plant origin, showing nourishing, antioxidant, antiseptic, conditioning, softening and moisturizing properties, which are one of the most used parts of the base for creams, emulsions, ointments, cosmetic masks, lipsticks and others. For example, olive (Oleum Olivarum), castor (Oleum Ricini), almond (Amygdalus communis L.), corn (Oleum Maydis), grape seeds (vitis vinifera seed oil) and others.

Fats and waxes are ingredients for the production of personal care products and decorative cosmetics. Harder substances, that are resistant to oxidation and microbial attack, are used in the preparation of creams, lotions, ointments, lipsticks. The most used are: Cocum oil (Garcinia indica (Thouars) Choisy), avocado oil (Persea americana Mill.), cocoa butter (Theobroma cacao L.), carnauba wax (Copernicia prunifera (Mill.) HEMoore), candelilla wax (Euphorbia spp.), and others .

Essential oils of Lemon oleum, Aliquam Oleo, Eucalyptus Globulus Leaf Oil and many others, that are used in cosmetic products for their aromatic, antibacterial and antifungal propertyes, are used in a wide range of cosmetic products. Along with them, are used plant extracts in various forms (leaves and shoots of green and black tea, aloe, grape seeds and others), mineral waters - Lugela, Sairme, therapeutic mud - Akhtala, therapeutic sorbents - perlite, bentonites and others, in which are rich flora and mineral resources of Georgia. All these products are used in the development of cosmetics during their creation at the Institute of Pharmacochemistry I. Kutateladze, of Tbilisi State Medical University.

PP 48. SYNTHESIS AND REARRANGEMENT OF 1-AMINO-3-OXO-2,7-NAPHTHYRIDINES

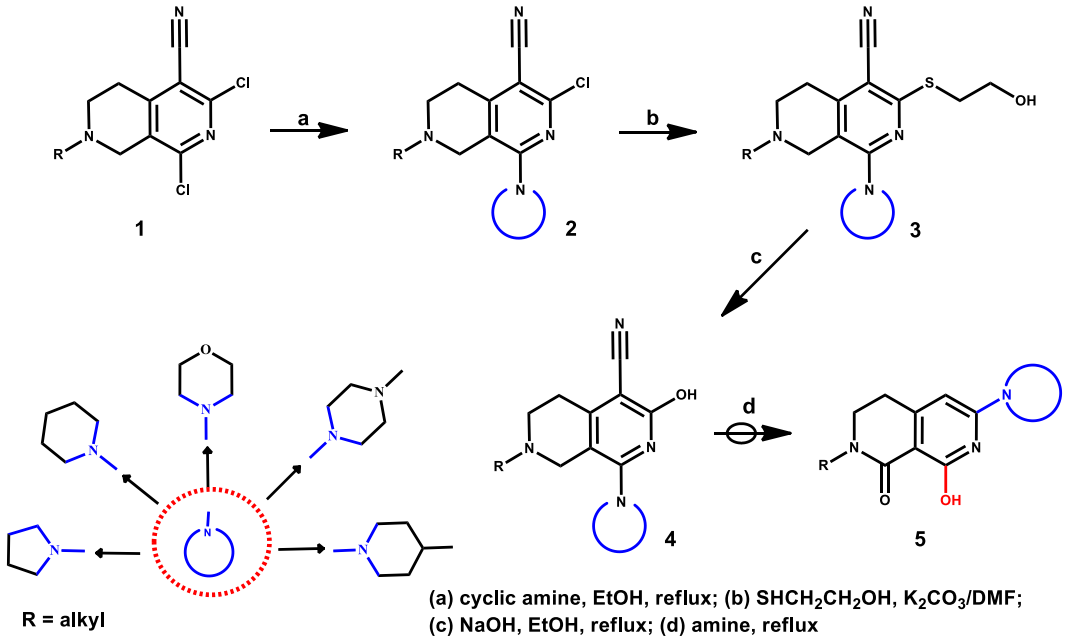
S. Sirakanyan [1], A. Hovakimyan[1], E.Hakobyan [1], H.Yegoryan[1]

[1]Scientific Technological Center of Organic and Pharmaceutical Chemistry of National Academy of Science of RA, Yerevan, Armenia;

Corresponding author e-mail: aaa.h.87@mail.ru

2,7-Naphthyridine derivatives are interesting compounds in the field of heterocyclic chemistry also because of their interesting biological activities, as evidenced by recent reviews [1, 2]. In this line of research, some of our investigations reveled that bicyclic 1,3-dihydroxy-2,7-naphthyridines could show antiarrhythmic activity [3], while tricyclic pyrazolo[3,4-*c*]-2,7-naphthyridines [4] and triazolo[3,4-*a*]-, triazolo[5,1-*a*]-2,7-naphthyridines [5] displayed high neurotropic activity.

Herein we report the synthesis of 1-amino-3-oxo-2,7-naphthyridines **4** as a new scientific direction in the field of chemistry of heterocyclic compounds. For the synthesis as starting compounds 7-alkyl-3-dichloro-5,6,7,8-tetrahydro-2,7-naphthyridine-4-carbonitriles **1** were used. Their reaction with cyclic amines, in mild reaction conditions led to the formation of 1-amino-3-chloro-2,7-naphthyridines **2**. In turn, compounds **2** were reacted with 2-mercaptoethanol giving the corresponding 1-amino-3-[(2-hydroxyethyl)thio]-2,7-naphthyridines **3**. In a following step, compounds **3** under the action of sodium hydroxide in ethanol underwent a Smiles rearrangement leading to the formation of aimed 1-amino-3-oxo-2,7-naphthyridines **4** (Scheme) [6].



Scheme. Synthesis and rearrangement of 1-amino-3-oxo-2,7-naphthyridines 4.

It will be quite promising and interesting to study the new rearrangement discovered by us [7] in the 1-amino-3-oxo-2,7-naphthyridine series **4**. For this purpose, compounds **4** were interacted with some amines having high boiling point ($T_{b.p.}$> 145°C). As a result of the reactions the formation of 1-oxo-8-hydroxy-2,7-naphthyridines **5** was observed, as expected (Scheme).

The work was supported by the Science Committee of RA, in the frames of the research project № 21AG-1D036.

References

[1] Wójcicka, A. 2021, Synthesis and biological activity of 2,7-naphthyridine derivatives: an overview, Curr. Org. Chem., vol. 25, no. 22, pp. 2740-2764.

[2] Litvinov, VP. 2006, Advances in the chemistry of naphthyridines, Adv. Heterocycl. Chem., vol. 91, pp. 189-300.

[3] Paronikyan, EG.; Sirakanyan, SN.; Noravyan, AS.; et.al, 1996, Synthesis and antiarrhythmic activity of 7-benzyl(ethyl)-1-hydroxy-4-carbamoyl-3-oxo-5,6-dihydro-8H-2,7-naphthyridines, Pharm. Chem. J., vol. 30, no. 6, pp. 365-367.

[4] Sirakanyan, SN.; Hakobyan, EK.; Nikoghosyan, AG. et. al. 2018, Synthesis and neurotropic activity of new 7-cyclohexyl-6,7,8,9-tetrahydro-3H-pyrazolo[3,4-c]-2,7-naphthyridine-1,5-diamines, Pharm. Chem. J., vol. 52, no. 2, pp. 108-111.

[5] Sirakanyan, SN.; Tonoyants, NA.; Noravyan, AS.; et al. 2014, Synthesis and neurotropic activity of triazolo[3,4-a]- and triazolo[5,1-a]-2,7-naphthyridines, Pharm. Chem. J., vol. 48, no. 4, pp. 231-234.

[6] Sirakanyan, SN.; Spinelli, D.; Geronikaki, A.; et al. 2022, Synthesis of 1-amino-3-oxo-2,7-naphthyridines via Smiles rearrangement: a new approach in the field of chemistry of heterocyclic compounds, Inter. J. Mol. Sci., vol. 23, no. 11, pp. 5904-5904.

[7] Sirakanyan, SN.; Kartsev, VG.; Spinelli, D.; et al. 2014, On the reactivity of 4-cyano-1,3-dichloro-7-methyl-5,6,7,8-tetrahydro-2,7-naphthyridine with several amines in different experimental conditions: monosubstitution, disubstitution, and a new unexpected rearrangement, *Tetrahedron*, vol. 70, no. 33, pp. 4891-4902.

AUTHORS INDEX

NOTES