GIBS - 2024

ABSTRACT BOOK

Georgia-Israel Bilateral Symposium on Trends in Drug Discovery & Development

24-25 September 2024
Tbilisi, Georgia

Tbilisi State Medical University
TSMU Institute of Pharmacochemistry
Association of Researchers & Young Pharmacists of Georgia

GIBS - 2024

September 20-25, Tbilisi, Georgia

GEORGIA - ISRAEL BILATERAL SYMPOSIUM
"TRENDS IN DRUG DISCOVERY & DEVELOPMENT"

ABSTRACT BOOK

Organized by:
Tbilisi State Medical University
TSMU I. Kutateladze Institute of Pharmacochemistry
Association of Scientists and Young Pharmacists of Georgia

ISSN:
DOI: https://doi.org/10.52340/2024.26.09

WELCOME MESSAGE

Dear Colleagues!

The Organizing Committee, has a pleasure and honor to greet you at the Georgia - Israel Bilateral Symposium "TRENDS in DRUG DISCOVERY & DEVELOPMENT" (GIBS-2024).

GIBS-2024 has an ambition to bring together a multi-disciplinary group of scientists from Georga and Israel to discuss current trends in one of the most challenging areas of pharmaceutical science – drug discovery and development.

GIBS-2024 will gather pharmacy experts, medicinal and synthetic chemists, pharmacologists, analysts, and other scientists involved in drug research and development in Georgia and Israel.

The scientific program of GIBS-2024, apart from plenary lectures, oral communications and poster presentations will include Young Researchers Forum and Workshop " DRUG FROM LAB TO CLINIC "

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

The Organizing Committee thanks all participants and contributors for joining the GIBS-2024 and will try to do its best to help benefit from both scientific and social parts of the event and carry home good memories of GIBS-2024.

Organizing Committee of the GIBS-2024

ORGANIZING COMMITTEE

HONORARY CHAIR

Irakli Natroshvili

CHAIR

Malkhaz Getia

CO-CHAIRS

Aleksandre Buachidze *Sophia Bakhtadze*

Khatuna Todadze *Rusudan Rukhadze*

Zurab Vadachkoria *Vasil Cheishvili*

MEMBERS

Eter Kemertelidze

Tamar Chikviladze

Dali Berashvili

Aliosha Bakuridze

Davit Chincharadze

Badri Arziani

Nana Gorgaslidze

Tamaz Murtazashvili

Bela Kikalishvili

Zurab Kemoklidze

Lasha Mskhiladze

Karen Mulkijanian

Maia Merlani

Ketevan Mchedlidze

Nanuli Nadaraia

Nana Kavtaradze

Lia Tsiklauri

Liana Nadirashvili

Nina Vachnadze

Pavle Yavich

INTERNATIONAL ADVIZORY BOARD

Gary Gellerman, Israel

Leonid Patsenker, Israel

CONFERENCE SECRETARIAT

Maia Merlani

Sopio Gokadze

CONVENERS

Tbilisi State Medical University

TSMU Institute of Pharmacochemistry

Association of Researchers and Young Pharmacists of Georgia

PARTNER UNVERSITY

Ariel University, Israel

SYMPOSIUM PROGRAM

DAY 1

WORKSHOP: DRUG FROM LAB TO CLINIC

Session 1	
10:00-11:00	Drug Development Lifecycle Overview
11:00-11:15	**Coffee Break**
Session 2	
11:15-12:15	Preclinical pharmacology in GLP-enabling studies and preclinical protocol development:
12:15-13:15	**Lunch Break**
Session 3	
13:15-14:15	Preliminary CRO-directed toxicology studies
14:15-14:30	**Coffee Break**
Session 4:	
14:30-16:00	Case Studies

DAY 2

WORKSHOP: DRUG FROM LAB TO CLINIC

Session 5	
10:00-11:00	Clinical Trials Overview
11:00-11:15	**Coffee Break**
Session 6:	
11:15-12:15	Clinical formulations development and factors that influence small molecule product development
12:15-13:15	**Lunch Break**
Session 7	
13:15-14:15	Clinical Protocols
14:15-14:30	**Coffee Break**
Session 8	
14:30-16:00	Hands-on Exercises and Discussions

DAY 3

SYMPOSIUM: TRENDS IN DRUG DISCOVERY AND DEVELOPMENT

9:00-9:45	**Registration**
10:00- 10:15	Opening ceremony of the Symposium
10:15–11:00	PL 1
11:00-11:15	OP 1
11:15-11:30	OP2
11:30-12:00	**Coffee Break**
12:00-12:45	PL 2
12:45-13:00	OP 3
13:00-13:15	OP 4
13:15-14:15	**Lunch Break**
14:15-14:30	OP 5
14:30-14:45	OP 6
14:45-15:15	Poster Session
15:15 -15:45	**Coffee Break**
15:45-17:00	Poster Session

DAY 4

SYMPOSIUM: TRENDS IN DRUG DISCOVERY AND DEVELOPMENT

9:45-10:15	**Registration**
10:15-11:00	PL 3
11:00-11:15	OP 7
11:15-11:30	OP 8
11:30-12:00	**Coffee Break**
12:00-12:45	PL 4
12:45-13:00	OP 9
13:00-13:15	OP 10
13:15-14:15	**Lunch Break**
14:15-15:15	Young scientist's session
15:30	Closing ceremony

CONTENTS

PLENARY LECTURES

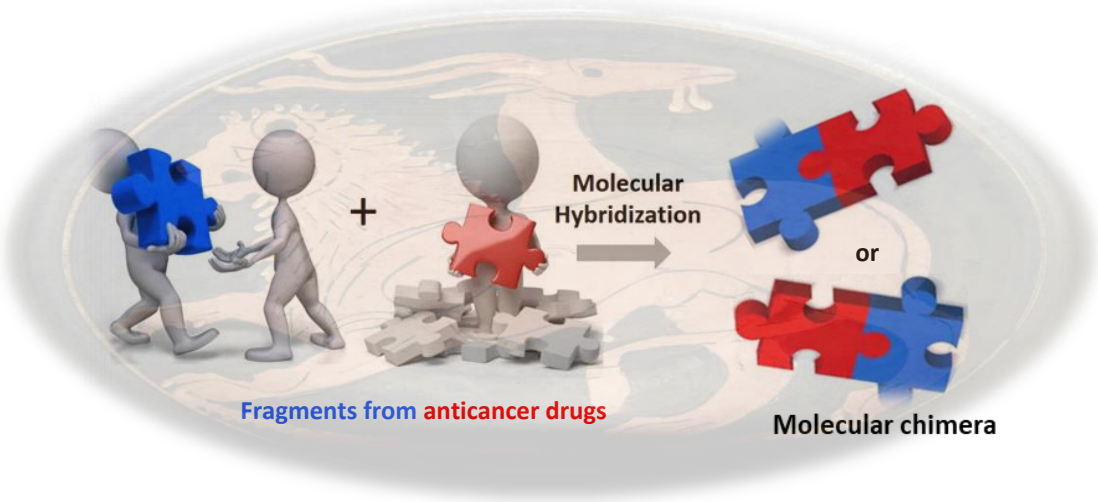
PL 1. DRUG CHIMERISM AS AN EFFECTIVE APPROACH TO DEVELOP POTENT MOLECULAR HYBRIDS (CHIMERS) FOR ANTICANCER THERAPY

Gary Gellerman, Irina Tkachenko and Dipak Walunj

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

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

Modifying existing drugs to enhance their activity and reduce side effects is a major focus of drug development. One promising approach involves creating 'chimeric' small molecules by merging the active parts of known drugs. We developed a new class of structural hybrids between DNA methylating tether monomethyl triazene and Topo II isomerase inhibitors for the treatment of cancer. These chimeras have dual actions. Based on molecular dynamic (MD) simulations, the chimeras exhibit greater binding strength to major grooves in DNA compared to their parent drugs. Furthermore, the DNA intercalating core places the monomethyl triazene portion in an advantageous orientation promoting methylation at the neighboring guanine bases. The mechanism of action is associated with the inhibition of DNA repair in proximity to double-strand breaks (DSB) by guanine methylation. When compared to the Topo II inhibitory drugs, Topo II-DNA methylating chimeras exhibit noticeably higher levels of cytotoxicity, mitochondrial depolarization, cell death, and *in vivo* efficacy. PK, MTD, acute toxicity and other pharmacological parameters will be also discussed. This work underscores the therapeutic potential of the dual-action Topo II-DNA methylating chimeras for cancer treatment.



References

[1] Walunj D. et al.Doxorubizen, a Novel Dual-Action Chimera Demonstrates Superior Efficacy to Doxorubicin in Acute Leukemia, *submitted*

[2] Walunj D. et al.(2021), Targeted methylation facilitates DNA double strand breaks and enhances cancer suppression: A DNA intercalating/methylating dual-action chimera Amonafidazene, Eur. J. Med. Chem. 225113811.

[3] Thankarajan E. et al. (2022). A novel, dual action chimera comprising DNA methylating agent and near-IR xanthene-cyanine photosensitizer for combined anticancer therapy, Photodiagnosis and Photodynamic Therapy, 37, 102722

[4] Walunj D et al. (2021), Expedient synthesis and anticancer evaluation of dual-action 9-anilinoacridine methyl triazene chimeras, Chemical Biology & Drug Design, 97(2), 237-252

[5] Gilad Y. et al. (2017), Discovery of potent molecular chimera (CM358) to treat human metastatic melanoma, Eur. J. Med. Chem. 138, 2017, 602-615.

PL 2. TOWARDS SAFE CANCER TREATMENT: ANTIBODY-GUIDED ACTIVATABLE PHOTODYNAMIC AND SONODYNAMIC THERAPIES

Leonid Patsenker[1], Olga Semenova[1] and Iryna Hovor [1,2]

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

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

Photodynamic (PDT) and sonodynamic (SDT) therapies utilizing an organic dye called sensitizer (**S**) capable of killing abnormal cells in the body upon near-IR light or ultrasound (US) irradiation, respectively, are extremely promising non-invasive treatment modalities for many cancers. A known drawback of PDT and SDT is a side-effect caused by currently available sensitizers to organs due to insufficient specificity and accidental light exposure of a patient during the delivery of the sensitizer in the bloodstream (Fig.1).

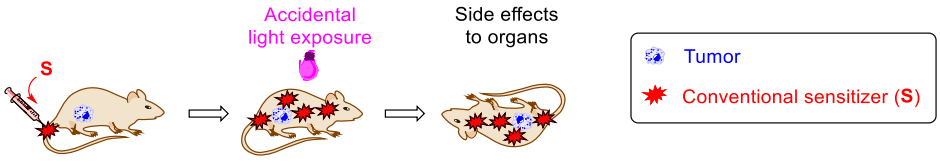


Fig.1. Side effects of PDT and SDT with a conventional (permanently active) sensitizer

Here, we report on a novel approach to overcome this issue (Fig.2). First, sensitizer can be linked to a cancer-specific antibody, providing selective accumulation of sensitizer in the tumor. Secondly, conventional sensitizers (**S**) that generate reactive cytotoxic species upon light or US irradiation are replaced with innovative activatable sensitizers (**S-Tr**), which are inactive upon delivery in the bloodstream but become active in the target abnormal cells due to the cleavage of the triggering group **Tr**. The activation of this sensitizer can be promoted by some substances overexpressed in the tumor, such as esterases or glutathione. Combining targeted antibody-guided delivery and the activatable principle dramatically improves the safety and efficacy of cancer treatment.

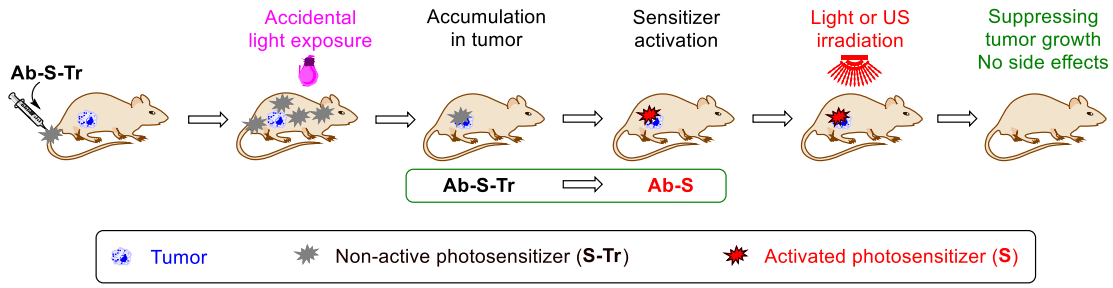


Fig.2. Safe treatment with an antibody-guided activatable sensitizing system, Ab-S-Tr

This approach was demonstrated by the development of a novel antibody-guided, activatable sensitizing system, **Ab-S-Tr**, where the trastuzumab (Ab) is linked to the non-active (not phototoxic, not sonotoxic, and not fluorescent) sensitizer, **S-Tr**, that contains the hydroxyl group “locked” by the triggering group **Tr**. In the mouse xenograft model, this targeting non-active conjugate was shown to be safely (without detectable side-effects) delivered to the targeted tumor, where it is activated and effectively treats the tumor upon irradiation. It was demonstrated in the Her2 positive BT-474 tumor mouse model that the treatment efficacy of the activatable sensitizing system **Ab-S-Tr** is about the same as for the conventional, permanently active sensitizer **Ab-S**, while the side-effects are dramatically reduced.

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

Thereby, the developed activatable sensitizer demonstrates a promising approach for designing novel, highly efficient systems for safer photodynamic and sonodynamic therapy of different types of cancer. Activatable **S-Tr** sensitizers can be linked to other monoclonal antibodies for broad implementation in targeted PDT and SDT applications. The obtained results will pave the way for the utilization of antibody-guided activatable sensitizers to protect patients from accidental light exposure after drug administration.

PL 3. SILVER BIONANOPREPARATIONS: FORMULATION, TECHNOLOGY AND BIOLOGICAL EVALUATION

A.Bakuridze[1], Z. Vadachkoria[2], L. Bakuridze[1]

Tbilisi State Medical University: [1]Department of Pharmaceutical Technology, [2]Department of Children and Adolescent Maxillo-facial Surgery and Surgical Stomatology

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

The great interest in silver nanoparticles is largely due to their unique physicochemical and biological properties, which differ from bulk silver itself [3,6]. In contrast to chemical synthesis, biological synthesis of metallic nanoparticles is an ecological, effective and economical method [1,2]. By incubating silver salt in the presence of a specific plant extract, a nanosilver is formed. Various organic compounds present in the plant may be responsible for reduction, stabilization, packaging processes, resulting in nanoparticles forming [2]. Physico-chemical properties of nanoparticles determine their behavior, biodistribution, safety and efficacy. Therefore, the characterization of silver nanoparticles is important to evaluate the functional aspects of the synthesized particles [4,5]. The development of a sophisticated method of biosynthesis of silver nanoparticles will make it possible to maximize the properties of silver nanoparticles, the full manifestation of which depends on the formation method.

The aim of the research is the biosynthesis of silver nanoparticles, determination of the formulation of the bionanopreparations, development of technology and study of biological activity.

Based on the conducted studies, the biosynthesis of silver nanoparticles using plant extracts containing various biologically active substances has been developed; The influence of exogenous and endogenous factors on the process of silver nanoparticle formation is determined; The optimal conditions for the biosynthesis of silver nanoparticles have been established; Optimum technology for biosynthesis of silver nanoparticles is provided; Characterization of biosynthesized silver nanoparticles using modern instrumental methods of analysis is carried out; The specific biological activity of silver nanoparticles (antibacterial, antitumor) has been determined; Hydrogel films containing antimicrobial silver nanoparticles and flax fiber modified with silver nanoparticles are provided.

The further development of the results of the conducted experimental research will contribute to the serial production and medical practice of the nanotechnology based new generation, highly effective, high-quality and safe antibacterial and antitumor drugs.

References

[1] Galatage TS., Hebalkar SA, Dhobale, et al. (2021), Silver Nanoparticles: Properties, Synthesis, Characterization, Applications and Future Trends. *IntechOpen.* doi:10.5772/intechopen.99173.

[2] Habeeb Rahuman HB, Dhandapani R, Narayanan S, et al. (2022), Medicinal plants mediated the green synthesis of silver nanoparticles and their biomedical applications. *IET Nanobiotechnol*, 16(4):115-144. doi: 10.1049/nbt2.12078.

[3] Liao C, LiY, & Tjong S. (2019). Bactericidal and Cytotoxic Properties of Silver Nanoparticles. *International journal of molecular sciences*, 20(2), 449-449. https://doi.org/10.3390/ijms20020449

[4] Menichetti A., Mavridi-Printezi A, Mordini D & Montalti M. (2023). Effect of Size, Shape and Surface Functionalization on the Antibacterial Activity of Silver Nanoparticles. *Journal of Functional Biomaterials, 14*., no. 5: 244. https://doi.org/10.3390/jfb14050244

[5] Patil R, Chougale A. (2021), Analytical methods for the identification and characterization of silver nanoparticles: A brief review. *Materials Today: Proceedings*. 47. Doi:10.1016/j.matpr.2021.03.384.

[6] Rezvani, Ehsan & Rafferty, Aran & Mcguinness, Cormac & Kennedy, James. (2019). Adverse effects of nanosilver on human health and the environment. *Acta Biomaterialia*. 94. 10.1016/j.actbio.2019.05.042.

PL 4. NEW APPROACHES IN ANALYSIS OF PHARMACEUTICALS FROM THE PLANTS GROWING IN GEORGIA

Malkhaz Getia

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

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

Analytical methods required for analyses and standardization of pharmaceutical of plant origin need continuously development. Medical preparations of a plant origin contain crude extracts with hundreds or thousands of molecules in different concentrations, enriched fractions and rarely individual compound; therefore, their separation and analysis is often complicated. Pharmaceutical analysis of a medical preparations of a plant origin has a huge field of research, as well as of scientific and applied importance. New methods of extraction and purification improve HPLC separation of multimolecular extracts and enriched fractions.

Various new stationary phases can be adopted for separation of the crude extracts, increasing selectivity of new, developed method of analyses pharmaceutical of plant origin. Using to high resolution mass spectrometry, DAD and refractometric detectors facilitates the identification and quantification of active substances in natural products. UV and infrared spectroscopy enable rapid and simultaneous qualitative and quantitative analysis of raw plants and liquid extracts without destruction. All of these approaches give new possibilities for quality control of pharmaceuticals of plant origin.

The lecture summarizes general challenges in the analysis of pharmaceuticals of plant origin and new approaches in pharmaceutical chemistry will be presented and discussed.

ORAL PRESENTATIONS

OP 1. EVALUATION OF PHARMACOGNOSTICAL PROPERTIES AND PHARMACOLOGICAL ACTIVITY OF *ALLIUM SAXATILE* AND *ALLIUM PORTICUM* GROWING IN GEORGIA

G. Jgerenaia[1,2], M. Frederich[2], D. Chincharadze[1], L. Mskhiladze[1]

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

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

Up to 1,233 species are described in the genus Allium, which is included under the Amaryllidaceae family (previously Alliaceae)[1]. Allium species are highly valuable both traditionally and medicinally in the world and in Georgia also. Because of its antifungal, antiseptic, and antibacterial qualities[2]. There are 36 species of allium known to exist in Georgia, including three endemic to the Caucasus and five endemic to the Georgia[3].

The Allium species found in Georgia are abundant in biologically active substances, including saponins, flavonoids, phenolic compounds, sulfuric compounds, and others, according to a bibliographic analysis of the literature. These compounds exhibit a range of biological actions, such as thrombolytic, antiplatelet, antibacterial, nephroprotective, hepatoprotective, antioxidant, and gastroprotective properties[4].

The aim of this experiment was to undertake a phytochemical analysis and pharmacological studies of secondary metabolites in two Allium species, *A. saxatile* and *A. ponticum*, that grow in Georgia. Column chromatography was utilized for obtaining the crude extract as well as four fractions from each plant. The fractions' analgesic, anti-inflammatory, and gastroprotective properties were assessed by using *in vivo* experiments. *In vitro* experiments have been conducted to investigate the cytotoxic, antiprotozoal, and antioxidant activities[5,6]. Lastly, the study assessed the microstructural features of the vegetative and generative organs of *A. saxatile* and *A. ponticum*[7,8].

The UV spectrophotometer has been used to quantify furostanol saponins in the research objects. The quantitative amount of furostanol saponins was evaluated in plant raw materials and crude extracts from study objects. *A. saxatile*'s plant material contained 0.69% furostanol saponin, whereas the crude extract had 37.15%. Furostanol saponins were found in 0.37% of the *A. ponticum* plant material and 11.54% in the crude extract.

The quantitative content of flavonoid astragalin in *A. saxatile* plant material was 0.06% and in crude extract 0.87%. The quantitative content of ferulic acid in *A. ponticum* was 0.004% in plant material and 0.08% in crude extract.

In conclusion, the study examined the quantitative concentration of furostanolic saponins and phenolic components in plant raw material and crude extracts of *A. saxatile* and *A. ponticum*. *In vitro* tests were conducted to determine the cytotoxic and antioxidant properties of these plants. Furthermore, in vivo investigations confirmed the analgesic, gastroprotective, and anti-inflammatory properties of study objects. Several numerical markers were identified during the research, including moisture and total ash content. The data obtained from the studies were utilized to develop a temporary monograph of both species, *A. saxatile* and *A. ponticum*, for standardization purposes.

The identification and isolation of bioactive compounds from *A. saxatile* and *A. ponticum* is a possible expansion of this work, as it could promote the discovery of novel and diverse compounds that may have therapeutic benefits.

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] Bagrationi D. Iadigar Daudi. Edition of Tbilisi University. Republic of Georgia: 1993.

[3] Gagnidze R. Vascular Plants of Georgia a nomenclatural Checklist. Institute of Botany. Tbilisi, Republic of Georgia: 2005.
[4] Jgerenaia G, Frederich M, Mskhiladze L. Phytochemical and Pharmacological Review of Allium Species from Georgia. GEORGIAN Biomed NEWS 2024. https://doi.org/10.52340/GBMN.2024.01.01.76.
[5] Jgerenaia G, Bonnet O, Hamann C, Gviniashvili T, Frédérich M, Augé N, et al. Evaluation of Antioxidant and Cytotoxic Activity of Plants Allium Ponticum and Allium Saxatile, Growing in Georgia. GEORGIAN Biomed NEWS 2023. https://doi.org/10.52340/GBMN.2023.01.01.02.
[6] Jgerenaia G, Sulakvelidze M, Novikova Z, Gogitidze N, Mushkiashvili N, Mulkijanyan K, et al. PHARMACOLOGICAL ASSESSMENT OF CONSTITUENTS OF SPECIES ALLIUM SAXATILE AND ALLIUM PONTICUM GROWING IN GEORGIA. Exp Clin Med Ga 2022. https://doi.org/10.52340/jecm.2022.06.04.
[7] Jgerenaia G, Mchedlidze K, Frederich M, Mskhiladze L. Microstructural features of generative and vegetative organs of Allium ponticum growing in Georgia. GEORGIAN Sci 2022. https://doi.org/10.52340/gs.2022.04.04.32.
[8] Jgerenaia G, Mchedlidze K, Frederich M, Mskhiladze L. Microstructural features of generative and vegetative organs of Allium saxatile growing in Georgia. GEORGIAN Sci 2022. https://doi.org/10.52340/gs.2022.04.04.33.

OP. 2. BIOLOGICALLY ACTIVE PHENOLIC COMPOUNDS OF ASTRAGALUS, PUERARIA, TRIFOLIUM, SALVIA SPECIES SPREAD IN GEORGIA

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

Tbilisi State Medical University, I. Kutateladze Institute of Pharmacochemistry

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

The structural diversity of phenolic substances, the revealed various biological effects and wide distribution in the Plant Kingdom determine the relevance of the study of Georgian flora species on their content. In the I. Kutateladze Institute of Pharmacochemistry 1167 samples of 123 families, 395 genera, 723 species have been analyzed on the content of phenolic substances since the 60s of the last century. As a result, species of promising genera - Astragalus, Pueraria, Trifolium, Salvia and others have been revealed. More than hundred individual compounds were isolated and identified from the studied species; 33 new natural polyphenols were described; biologically active phenolic compounds and substances containing them have been obtained and the effective medicinal remedies have been elaborated on their basis [1]. Among the species distinguished by the content of phenolic compounds were: *Astragalus bungeanus* Boiss., *Astragalus brachycarpus* M. Bieb., *Astragalus falcatus* Lam., *Astragalus galegiformis* Pall., *Pueraria hirsuta* Matsum., *Trifolium arvense* L., *Trifolium hybridum* L., *Salvia gareji* Troitzk.

Purified extracts of *Astragalus bungeanus* and *Astragalus brachycarpus* exposed the leukopoiesis stimulation *in vivo*. They contain polyphenols: cosmosiin, apigenin-7-O-β-D-galactopyranoside, astragalin, tripholin, kaempferol-7-O-α-L-rhamnopyranoside, nicotiflorin, robinin, isoquercitrin, isorhamnetin-3-O-β-D-glucopyranoside (*As. bungeanus*); apigenin, isorhamnetin-3,7-O-β-D-di-glucopyranoside, daidzin, mangiferin (*As. brachycarpus*); these compounds were described for the first time from this species [2].

The content of new oligomeric flavonol glycosides - Falcosides A-E was determined in the active substance of the antiuremic drug “Falronin” obtained from *Astragalus falcatus*. They may have a certain role in the development of the antiuremic effect of the drug. The full structures were established for falcosides C (quercetin-3-O-[β-D-glucopyranosyl(1→3)-α-L-rhamnopyranosyl (1→6)]-β-D-galactopyranosyl-7-O-β-D-glucopyranoside) and D (isoramnetin – 3 – O - [β-D-xylopyranosyl (1→3) -α – L- rhamnopyranosyl (1→6)] – β – D -galactopyranosyl-7-O-α-L-rhamnopyranoside) [3].

The glycosides astragalegoside (isoramnetin-3,4′-O-β-D-diglucoside) and isoastragalegoside (isoramnetin-3,7-O-β-D-diglucoside) isolated from the above-ground parts of *Astragalus galegiformis* exhibited diuretic and hypoazotemic effects, respectively. Flavonoid compounds in this plant are also represented by new hydrophilic glycosides - Flagaloside C (quercetin-3-O-β-D-galactopyranosyl-(6→1)-O-α-L-rhamnopyranosyl-(3→1)-xylopyranoside); Flagaloside D (isoramnetin-3-O-β-D-xylopyranosyl-(2→1)-xylopyranoside) [4].

The crystalline sum of isoflavonoids isolated from the roots of *Pueraria hirsuta* showed hepatoprotective effect *in vivo*. The constituents were determined as daidzein, daidzin, genistin, ononin and new compound - 3’-hydroxydaidzein-7-O-β-D-glucopyranoside [5].

The endemic species *Salvia gareji*, was standout by high content of tannins (25.3%). Luteolin-7-O-β-D-glucuronide, apigenin-7-O-β-D-glucuronide, nepetin, cirsimaritin, epigallocatechin, condensed tannin, rosmarinic and sagerinic acids, salvigenin, salvianic acid A, yunaneic acid F, salvianolic acid A, and its isomer were isolated and identified in high antioxidant activity extracts from the above-ground parts of the plant [6, 7].

The flavonoid-enriched substance from *Trifolium hybridum* with the content of quercetin, isoquercitrin, populnin, and biochanin A-7-O-β-D-glucopyranoside exhibits gonadotropin stimulating effect *in vivo*; that is caused by isoflavone biochanin A -7-O-β-D-glucopyranoside, structurally related to the well-known phytoestrogen – genistein.

The dominant flavonoid (0.9%) hyperin, isolated from the overground parts of *Trifolium arvense*, exhibited hypoazotemic and diuretic actions.

The structures of the isolated compounds were determined by modern spectral methods and by their chemical transformation products' physical-chemical characteristics.

References:

[1] Alania M, Shalashvili K, Sagareishvili T, et al. Phenolic compounds of some plants spread and cultivated in Georgia (2023), Tbilisi, 334 p. [in Georgian]

[2] Sutiashvili M, Getia M, Mshvildadze V. (2024), Chemical components of the aerial parts of *Astragalus brachycarpus* M. Bieb. *Georgian Scientists*, vol.6, No.1, pp.150-152

[3] Alaniya M.D,. Kavtaradze N.Sh, Skhirtladze A.V,. Sutiashvili M.G. (2011), Flavonoid oligosides from Georgian *Astragalus falcatus*. *Chemistry of Natural Compounds*, vol. 47, No.3, pp.377-381

[4] Alaniya M. D, Kavtaradze N. Sh, Bassarello C. et al. (2006), Flavonoid glycosides from *Astragalus galegiformis* leaves. *Chemistry of Natural Compounds*, vol.42, No.6, pp.681-685

[5] Kavtaradze N.Sh, Alaniya M.D, Getia M.Z, et al. Isoflavonoids from roots of Pueraria hirsuta distributed in Georgia and their hepatoprotective activity. (2022), *Chemistry of Natural Compounds*, Vol. 58, No. 1, pp. 27-31

[6] Sagareishvili T, Aneli J. (2010), Preliminary phytochemical analysis of sage species of Georgian flora. Investigation of Georgian Biologically Active Compounds of Plant and Mineral Origin. Collected Scientific Works of I. Kutateladze Institute of Pharmacochemistry, 2(17), pp. 19-25

[7] Sagareishvili T, Alania M, Shalashvili K, Kavtaradze N. (2014), Chemical components of the Caucasus endemic Salvia geradji Troitz. II International Conference "Pharmaceutical Sciences in XXI Century", *Tbilisi State medical University, Collection of Scientific Works*, pp. 120-121

OP 3. THERAPEUTIC POTENTIAL AND CHEMICAL ANALYSIS OF ESSENTIAL OIL FROM GEORGIAN GROWN *ABIES NORDMANNIANA* (STEV.) SPACH

Teona Korkotadze[1,3], Alexis St-Gelais[2], Dali Berashvili[3], Zurab Kemoklidze[1], Vakhtang Mshvildadze[1,4]

[1]Tbilisi State Medical University I.Kutateladze Institute of Pharmacochemistry; [2]Laboratoire PhytoChemia, Inc. Chicoutimi (Québec) Canada; [3]Tbilisi State Medical University Direction of Pharmacognosy and Pharmaceutical Botany; [4]Laboratoire LASEVE, Université du Québec à Chicoutimi

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

Pinaceae is one of the major family [1,2], monoecious evergreen coniferous trees or shrubs. Encompassing 12 genera and over 225 species [3] they are predominantly distributed throughout the temperate regions of the Northern Hemisphere. Within the Caucasus region, three genera of this family are present [4,5]. According to literature sources, approximately 300 essential oils derived from around 2000 plant species hold commercial significance [6].

Genus Abies Mill. encompasses approximately 40 species, predominantly distributed throughout the temperate zones of Eurasia and America. In Georgia and Caucasus, only one species of this genus is present [4]. Research suggests that the ethereal extract derived from Abies Nordmanniana (Stev.) Spach cones displays moderate antibacterial activity against Pseudomonas aeruginosa and Escherichia coli strains [7]. Furthermore, Abies species (Abies cilicica subsp. cilicica) have exhibited wound healing properties [5]. Investigations conducted on 13 species of genus Abies, including Abies nordmanniana, have unveiled their antibacterial, antifungal, and antiviral attributes [8,9].

The needles of *Abies nordmanniana* (Stev.) Spach collected in Georgia (Kartli floristic area, 2024 year).

Essential oils were hydro-distilled for two hours using a glass Clevenger-type apparatus. The study of the chemical composition of the essential oil, including the quantitative content and the qualitative analysis of the compounds was performed by Gas Chromatography (Agilent technologies 7890B) - Mass Spectrometry (Agilent Technologies 5977A MSD) and GC-FID (Flame ionization detector). Mass spectra were obtained in scan mode (70 eV). Two different chromatographic columns were used: DB-5 and DB-Wax.

The oxygen radical absorption capacity assay (ORAC test) [10] and human skin fibroblast (WS1) [11]. were used to assess the antioxidant activity of essential oils. It was established that the study sample's inhibitory concentration 50 (IC_{50}), which prevents 50 % of the oxidation of 2',7'-dichlorofluorescein (DCFH), was reached. The pharmaceutical reference was trolox and etoposide were used as pharmaceutical references. The anti-inflammatory effect was assessed by measuring the suppression of nitric oxide (NO) generation. N-l-nitro-L-arginine methyl ester hydrochloride (L-NAME) was utilized as positive control [12].

In the needles of essential oil from *Abies nordmanniana*, more than 100 compounds were detected. The major constituent was characterised as pinene.

The essential oil of *Abies nordmanniana* exhibited high anti-inflammatory activity. It revealed moderate antioxidant activity in the ORAC test and *in vitro* assay using WS-1 cells. The essential oil showed weak cytotoxic activity against DLD-1 cells without toxicity against WS-1 cells. Additionally, it demonstrated low antibacterial activity against *E. coli* and *S. aureus*.

The study of essential oil from *Abies nordmanniana* revealed a complex chemical composition with over 100 detected compounds, with pinene identified as the major constituent. The essential oil exhibited significant biological activities, including high anti-inflammatory properties and moderate antioxidant activity, as evidenced by the ORAC test and in vitro assays using WS-1 cells. Furthermore, the essential oil demonstrated selective cytotoxicity, showing weak effects against DLD-1 cells while being non-toxic to WS-1 cells. However, its antibacterial activity was relatively low against *E. coli* and *S. aureus*.

References

[1] Ioannou E, Koutsaviti A, Tzakou O, Roussis V. (2014), The genus Pinus: a comparative study on the needle essential oil composition of 46 pine species. *Phytochem Rev*., vol. 13, no. 4. pp. 741-768.
[2] Sarvmeili N, Jafarian-Dehkordi A, Zolfaghari B. (2016), Cytotoxic effects of Pinus eldarica essential oil and extracts on HeLa and MCF-7 cell lines. *Res Pharm Sci*., vol. 11, no. 6. pp. 476- 483.
[3] Simpson MG. (2010), Evolution and Diversity of Woody and Seed Plants. In: *Plant Systematics*. Elsevier, pp. 129-162.
[4] Georgia flora. Vol I. science. 1987.
[5] Tumen I, Akkol EK, Süntar I, Keleş H. (2011), Wound repair and anti-inflammatory potential of essential oils from cones of Pinaceae: Preclinical experimental research in animal models. *J Ethnopharmacol*, vol. 137, no. 3. pp. 1215-1220.
[6] Park C, Woo H, Park MJ. (2023), Development of Pinaceae and Cupressaceae Essential Oils from Forest Waste in South Korea. *Plants*, vol. 12, no. 19. pp. 3409.
[7] Eryılmaz M, Tosun A, Tümen İ. (2016), Antimicrobial Activity of Some Species from Pinaceae and Cupressaceae. *Turk J Pharm Sci*., vol. 13, no. 1. pp. 77-83.
[8] Mahmutović-Dizdarević I, Žujo B. (2023), Genus Abies Mill. (Pinaceae) as the source of plant antimicrobials: A Review. *Rad Šumar Fak Univ U Sarajevu*, vol. 53, no 1. pp. 56-69.
[9] Öztürk Pulatoğlu A, Güney K, Çeter T, Yilmaz ES. (2023), Chemical Composition of Essential Oils Obtained from Abies taxa in Türkiye and Investigation of Antimicrobial Activities. *Kastamonu Üniversitesi Orman Fakültesi Derg*, vol. 23, no. 1. pp. 31-46.
[10] Legault J, Girard-Lalancette K, Dufour D, Pichette A. (2013), Antioxidant Potential of Bark Extracts from Boreal Forest Conifers. *Antioxidants*, vol. 2, no. 3. pp. 77-89.
[11] Grenier A, Legault J, Pichette A, Jean L, Bélanger A, Pouliot R. (2021), Antioxidant, Anti-Inflammatory, and Anti-Aging Potential of a Kalmia angustifolia Extract and Identification of Some Major Compounds. *Antioxidants*, vol. 10, no. 9. p. 1373.
[12] Coté H, Boucher MA, Pichette A, Legault J. (2017), Anti-Inflammatory, Antioxidant, Antibiotic, and Cytotoxic Activities of Tanacetum vulgare L. Essential Oil and Its Constituents. *Medicines*, vol. 4, no. 34. pp. 1-9

OP 4. ANTIMICROBIAL ACTIVITY OF POLYETHERS FROM PLANTS OF BORAGINACEA FAMILY AND THEIR SYNTHETIC ANALOGUES

Maia Merlani[1], Lela Amiranashvili[1], Lali Gogilashvili[1], Vakhtang Barbakadze[1], Athina Geronikaki[2]

[1] Tbilisi State Medical University I.Kutateladze Institute of Pharmacochemistry, Department of Plant Biopolymers and Chemical Modification of Natural Compounds; [2] Aristotle University of Thessaloniki School of Health, Department of Pharmacy,

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

Extracts from the plants of the Boraginaceae family, are known for centuries to be used in folk medicine of many Eastern and Asian countries for treatment of various diseases [1]. In recent years the mucilaginous water extracts of medicinal plants of *Symphytum asperum (SA), S.caucasicumn (SC), S.grandiflorum (SG), S.officinale(SO), Anchusa italica (AI), Cynoglossum officinale (CO), Borago officinalis (BO) and Paracynoglosum imeretinum (PI)* (Boraginaceae family) were fractionated by ultrafiltration on membrane filters with cut of value of 1000 kDa. According to data of different techniques of NMR spectroscopy the main chemical constituent of high molecular fractions (HMFs) from above mentioned plants was found to be caffeic acid-derived polymer, namely poly[3-(3,4-dihydroxyphenyl)glyceric acid] (PDHPGA) (Fig.1, **1**). The most carboxylic groups of PDHPGA from *A.italica, S.grandiflorum* and *B.officinalis* appeared to be methylated (Fig.1, **2**)[2]. Enzymatic synthesis of analogues of PMDHPO using lipase from *Candida rugosa* yielded oligomer with a degree of polymerization up to 5. Antibacterial assessment of natural polyethers from different species of Boraginaceae family SA, SC, SG, AI, CO, and synthetic oligomer - PMDHPO, reveals that only the synthetic analogue exhibits a promising antimicrobial activity against pathogenic strains *S.aureus* ATCC 25923 and *E.coli* ATCC 25922 with the minimum inhibitory concentration (MIC) being 100 µg/mL [2].

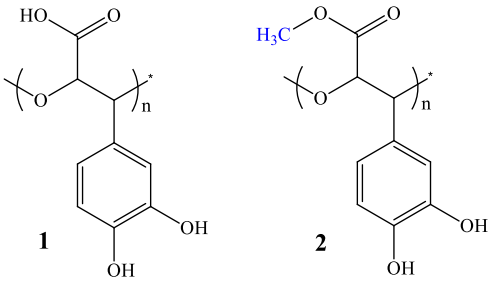


Fig. 1. Poly[3-(3,4-dihydroxyphenyl)glyceric acid] (PDHPGA) (1) and poly[2-methoxycarbonyl-3-(3,4-dihydroxyphenyl)oxirane] (PMDHPO) (2)

Biopolymers from *SA, SC, SG, AI, CO*, and *BO* were tested for their antibacterial activities against a panel of six bacterial species, including *Staphylococcus aureus, Escherichia coli,* and *Pseudomonas aeruginosa*, using a microdilution method for the determination of the MIC and minimal bactericidal concentrations (MBC). The activities of these polymers were moderate to low, with MICs in range of 0.75–6.00 mg/mL and MBCs of 1.00–9.00 mg/mL. These biopolymers were tested against resistant strains of the mentioned bacteria. The best activity was observed against res. *P.aeruginosa*, expressed by biopolymers from *BO* and *SG* stems (MIC/MBC at 0.75 mg/mL). The latter showed better activity against methicillin-resistant *Staphylococcus aureus* (MRSA) and res. *E. coli*, with MIC 1.00 mg/mL and 0.75 mg/mL, respectively, than the biopolymers from the materials of the two other plants. The order of activity against resistant strains can be presented as follows: MRSA > res*. P. aeruginosa* > res. *E. coli.* All biopolymers were also evaluated for their antifungal activities against six fungal species. Biopolymers exhibited better antifungal activities compared to antibacterial activities, with MICs in the range of 0.37–6.00 mg/mL and MFCs of 0.75–9.00 mg/mL. The best activity was observed for

biopolymers from BO stems, with MIC/MFC at 0.37–1.00 mg/mL and 0.75–1.5 mg/L, respectively, followed by those from SG stems. It should be mentioned that biopolymers from *SC* and *AI* roots showed antifungal activities against all six fungi, while those from *CO* stems and *SA* showed antifungal activities
against four fungi and one fungus, respectively, in contrast to the antibacterial activity. In general, the order of activity can be presented as: *BO* stems > *SG* stems > *SC* roots > *AI* roots > *CO* stems > *SA* roots. The best activity among all tested biopolymers was found for the biopolymer from *BO* stems against *Trichoderma viride*, *Penicillium funicolosum*, *Penicillium verrucosum var. cyclopium*, and *Candida albicans* (MIC 0.37 mg/mL). The same good activity was shown by biopolymers from *SG* stems against *Aspergillus fumigatus* and *T.viride*, which was half as active
as ketoconazole, the reference drug. It should be mentioned that biopolymers from all plant material except for *CO* stems were more potent than ketoconazole against *T. viride*. The most sensitive fungus to these biopolymers appeared to be *T. viride,* while *P. funiculosum* was the most resistant, followed by *P.verrucosum var. cyclopium*. It should be noticed that, in general, sugar-based catechol-containing biopolymers demonstrated quite good activity against *C. albicans in comparison to other strains except T.viride.* Antimicrobial studies revealed that PDHPGA from *BO* and *SG* stems showed the best antibacterial as well antifungal activities [3].
The reason of this difference compared to PDHPGA from *SA, SC* and *CO* may be the methylation of the carboxylic moieties of these polymers. The same tendency was observed regarding the synthetic oligomeric analogue of PMDHPO, which was the only polymer showing antimicrobial activities against some pathogenic strains at the concentrations that were used [2].

References

[1] Dresler S., Szymczak G.; Wojcik,M. (2017) Comparison of some secondary metabolite content in the seventeen species of the Boraginaceae family. *Pharm. Biol.* 55, pp. 691–695.

[2] Merlani M, Scheibel DM, Barbakadze V et al. (2022) Enzymatic synthesis and antimicrobial activity of oligomer analogues of medicinal biopolymers from comfrey and their species of the Boraginaceae Family. *Pharmaceutics*, v.14, N.1, 115.

[3] Barbakadze V., Merlani M., Gogilashvili L et al.. (2023) Antimicrobial Activity of Catechol-Containing Biopolymer Poly[3-(3,4-dihydroxyphenyl)glyceric Acid] from Different Medicinal Plants of Boraginaceae Family. *Antibiotics,* 12, 285.

OP 5. BIOLOGICAL ACTIVITY OF FOUR DAPHNE L. SPECIES NATIVE TO GEORGIA

Giorgi Moshiashvili[1], Vakhtang Mshvildadze[1], Nino Tabatadze[2], Zurab Kemoklidze[1]

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

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

The genus Daphne contains around 100 species of evergreen or deciduous shrubs up to 1.5 meters tall with white, yellow or pink aromatic flowers and red, yellow or black drupaceous fruits. The genus belongs to the Thymelaeaceae family and is well know for being toxic. Daphne species are widely distributed across Europe, Asia and North Africa [1]. The Georgian flora contains eight species of Daphne: *D. mezereum* L., *D. pontica* L., *D. albowiana* Woronow ex Pobed., *D. glomerata* Lam., *D. caucasica* Pall., *D. axilliflora* (Keissl.) Pobed. *D. transcaucasica* Pobed. and *D. pseudosericea* Pobed. Among these *D. axilliflora* (Keissl.) Pobed. and *D. pseudosericea* Pobed. are endemic to the Caucasus [2].

Species of this genus have been used in traditional medicine in various countries and regions, such as China, Tibet, Japan, Korea, the Middle East, the Balkans and Pakistan. Traditionally they are used for the treatment of gonorrhoea, skin diseases, various aches, different types of cancer, malaria and inflammations. Over 25 species have already been studied and have demonstrated that extracts, fractions and compounds isolated from different Daphne species show significant antimicrobial, antioxidant, cytotoxic, antiviral and a number of other biological effects [3 – 7].

We have studied four species of Daphne - *D. glomerata*, *D. pontica*, *D. axilliflora* and *D. albowiana*, all four native to Georgia, on their biological activity and potential medical application. Extracts of various polarity and multiple fractions were obtained from the combined leaves and stems of all four species. Their cytotoxic, anti-inflammatory and antioxidant antimicrobial activities were tested *in vitro*. Cytotoxicity was tested using the Resazurine and Hoechst tests on A549 (lung carcinoma), DLD-1 (colorectal adenocarcinoma) and WS-1 (normal fibroblasts) cell lines. Antioxidant activity was evaluated using DCFH-DA and ORAC assays. Measurement of anti-inflammatory activity was conducted by nitrite quantification using RAW 264.7 (murine macrophages) cells (NO inhibition %).

Table 1. Antioxidant, anti-inflammatory and cytotoxic activity of selected extracts and fractions of *D. glomerata*, *D. pontica*, *D. axilliflora* and *D. albowiana*.

	Resazurine test IC50 µg/ml			Hoechst test IC50 µg/ml		
Samples	**A-549**	**DLD-1**	**WS-1**	**A-549**	**DLD-1**	**WS-1**
D. glomerata MeOH extract	12 ± 0,2	>200	>200	14 ± 3	181 ± 2	>200
D. glomerata enriched fraction	<1,563	196 ± 3	>200	<1,563	138 ± 5	>200
D. pontica MeOH extract	3,4 ± 0,4	>200	>200	1,8 ± 0,4	>200	>200
D. pontica enriched fraction	<0,781	>200	>200	<0,781	>200	>200
Etoposide (µM)	33 ± 4	36±5	>50	3,2±0,4	8±2	>50

Samples	**DCFH-DA test IC_{50} µg/ml**	**ORAC µmol TE/mg**	**NO inhibition %**
D. glomerata MeOH extract	1,6 ± 0,6	2,98 ± 0,41	90
D. pontica MeOH extract	3,1 ± 0,8	1,58 ± 0,11	86
D. albowiana MeOH extract	3,5 ± 2	2,02 ± 0,11	83
D. axilliflora EtAc fraction	0,1 ± 0,01	11,78 ± 2,1	100
Quercetin	0,12 ± 0,04	20,9 ± 2,52	-
L-NAME	-	-	59

As can be seen in table 1 fractions with high and specific cytotoxic activity against A549 (lung carcinoma) cells were obtained from methanol extracts of *D. glomerata* and *D. pontica*. *D. axilliflora*

has shown a particularly high antioxidant and anti-inflammatory activities. Thus, these species are worthy of further inquiry and could serve as a source of new potential medications.

References

[1] Halda JJ. (1998). Some taxonomic problems in the genus Daphne L. Acta Musei Richnoviensis Sect. Nat. vol. 5, pp133- 160

[2] Flora of Georgia IX, 50 – 60 “Metsniereba” 1984

[3] Sovrlić M., Manojlovic N. (2017). Plants from The Genus Daphne: A Review of its Traditional Uses, Phytochemistry, Biological and Pharmacological Activity. Serbian Journal of Experimental and Clinical Research, pp. 69 - 80

[4] Dar M. Y., Ara T., Akbar S. (2019), A New Prenylated Coumarin from Daphne oleoides and its Cytotoxic Activity, Chemistry of Natural Compounds, Vol. 55, No. 1, January

[5] Wen-Juan Du, Xiao-Lin Yang, Zi-Jing Song, Jiao-Ying Wang, Wen-Jun Zhang, Xin He, Run-Qi Zhang, Chun-Feng Zhang, Fei Li, Chun-Hao Yu, Chong-ZhiWang and Chun-Su Yuan. (2016)Antitumor activity of total flavonoids from Daphne genkwa in colorectal cancer, Phytotherapy Research, vol. 30, pp. 323–330

[6] Manojlović NT, Mašković PZ, Vasiljević PJ, Jelić RM., Jusković MŽ, Sovrlić M & Radojković M. (2012). HPLC Analysis, antimicrobial and antioxidant activities of Daphne cneorum L. Hemijska industrija, vol.66(5), pp. 709-716

[7] Ren-Fen Ma, Hu Liu, Xue-Chun Zhao, Peipei Shan, Ping Sun, Jun-Juan Xue, Guodong Wei, Hua Zhang, (2023) Meroterpenoids from Daphne genkwa shows promising in vitro antitumor activity via inhibiting PI3K/Akt/mTOR signaling pathway in A549 cells, Bioorganic Chemistry, vol. 140

OP 6. THE ROLE OF ANIMAL WELFARE POLICY IN DRUG DISCOVERY AND DEVELOPMENT

Karen Mulkijanyan [1,2]

[1]Tbilisi State Medical University, I.Kutateladze Institute of Pharmacochemistry; [2]Georgian Association for Laboratory Animal Science

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

Proper ethical care and use of laboratory animals are critical in the drug discovery and development process. Laboratory animals play a crucial role in preclinical testing, where they are used to evaluate the safety, efficacy, and pharmacokinetics of new drug candidates. High standards in animal welfare and ethical use ensure the reliability and reproducibility of experimental results, which are critical for advancing promising therapies from the laboratory to clinical trials.

We aimed to examine the legislative aspects of biomedical research in Georgia, with particular emphasis on the humane care and use of laboratory animals and their importance in drug development from the perspective of international cooperation. Comparisons were made between regulatory frameworks in the USA, EU, and Georgia.

International policies guiding laboratory animal care, including the Public Health Service (PHS) Policy on Humane Care and Use of Laboratory Animals [1] (OLAW NIH 2002) and Directive 2010/63/EU of the European Parliament on the protection of animals used for scientific purposes, set the framework for international standards in laboratory animal welfare.

In the USA, organizations such as the NIH Office of Laboratory Animal Welfare, AALAS, and AAALAC, along with policies like the Animal Welfare Act [2] and PHS Policy, ensure i.) compliance to international standards such as the "Guide for the Care and Use of Laboratory Animals" [3] and ii.) supervision of all animal experiments. In the EU, animal research is regulated by Directive 2010/63/EU [4], along with bodies like FELASA and EARA. Georgia, however, lacks comprehensive legislative and regulatory support.

Significant challenges in Georgia include the absence of such legislative frameworks and rules, insufficient facilities and equipment in the majority of institutions performing animal experimentation, and a lack of institutional and public support. The aforementioned obstacles impede participation in international research, obtaining funding, and publishing in high-impact journals.

There is also a lack of public knowledge of the benefits of animal research, as well as insufficient organizational support and financing. The absence of a legislative framework, as well as noncompliance with globally accepted standards, make international collaborations, securing research funding, and publishing reputable results challenging.

To address these challenges, strategies at both international and local levels are proposed. Internationally, it is suggested to invite foreign specialists for training and assist local researchers with internships abroad, while locally, collaborating with ministries and institutional authorities to update legislation and unify policies on animal care is recommended. Establishing temporary IACUCs and engaging in workshops and collaborative efforts with international organizations like ICLAS and FELASA are crucial steps [5].

Currently, the Georgian institutions conducting animal research are tasked with ensuring that all personnel involved in animal care are aware of their responsibilities and that all activities comply with applicable laws and regulations. Programs are established to maintain high standards of animal care and use, with oversight by IACUCs and the Georgian Association for Laboratory Animal Science (GALAS) being a primary entity in this field [6].

Without robust legislative frameworks and compliance with international standards, research in drug discovery can face significant hurdles. The credibility of data can be compromised, leading to challenges in obtaining regulatory approvals and funding. Furthermore, international collaboration and publication in high-impact journals can be severely affected, hindering scientific progress.

Therefore, the establishment of strong legislative and regulatory support for animal research in Georgia, along with the alignment of local practices with international standards to improve the credibility and impact of the research and the enhancement of public awareness and organizational backing, is crucial for the integration of Georgian scientists into the global drug discovery and development ecosystem.

References

[1] Public Health Service policy on humane care and use of laboratory animals. (2015). *National Institutes of Health. Office of Laboratory Animal Welfare*. https://olaw.nih.gov/policies-laws/phs-policy.htm

[2] Animal Welfare Act. (1966), *United States Department of Agriculture.* https://www.govinfo.gov/content/pkg/COMPS-10262/pdf/COMPS-10262.pdf

[3] National Research Council. (2011). Guide for the care and use of laboratory animals (8th ed.). *National Academies Press*. https://doi.org/10.17226/12910

[4] European Parliament and Council of the European Union. (2010). Directive 2010/63/EU on the protection of animals used for scientific purposes. *Official Journal of the European Union*, L276, 33-79. https://eur-lex.europa.eu/legal-content/EN/TXT/?uri=CELEX:32010L0063

[5] Mulkijanyan K, Chitiashvili L, Ramishviili M, Megralishvili N. (2021), Biomedical research regulation challenges in countries in transition: Georgian experience. *European Scientific Journal, ESJ, 17(18), 41*. https://doi.org/10.19044/esj.2021.v17n18p41

[6] Mulkijanyan K, Ramishvili M, Chitiashvili L. (2023), Implementing the Directive 2010/63/EU in the Absence of National Legislation*. Proceedings of the 1st Central-East European Laboratory Animal Science Congress In: Physiol. Res.* 72: P1-P22 https://www.biomed.cas.cz/physiolres/2023/5_23.htm

OP 7. ORAL DELIVERY SYSTEMS FOR PHYTOBIOACTIVE INGREDIENTS FROM GEORGIAN FLORA

L. Tsiklauri [1], A. Bernkop-Schnürch[2], E. Allémann[3]

[1]Tbilisi State Medical University, I.Kutateladze Institute of Pharmacochemistry, [2] University of Innsbruck, Institute of Pharmacy, [3] University of Geneva, School of Pharmaceutical Sciences

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

Phytochemicals are well assessed and verified for their broad pharmacological effectiveness in various pathologies. Despite that, poor solubility, permeation, stability and poor active efflux mechanism result in limited *therapeutic effect*. Therefore, employment of innovative technologies to overcome the physicochemical and pharmacokinetic limitation of phytochemicals improved the bioavailability and even efficacy of the bioactivities [1].

Liposomes - lipid-based nanocarriers are effectual carriers for the transportation of phytochemicals with enhanced curative effects through amelioration their restrictions. They have become widely applied in the pharmaceutical industry because of their biocompatibility, controllable physicochemical profile, atoxic behaviour and capability to encapsulate both hydrophilic and lipophilic drugs [2].

Employment of thiolated polymers (thiomers) – class of polymers bearing thiol substructures, might resolve these problems. The effectiveness and profound advantages of *thiomer based drug delivery systems* have been established in *numerous* studies. Due the existence of thiol groups in already well-established polymeric excipients permeation-enhancing and efflux pump - reversible inhibiting properties are strongly improved [3].

Kaempferol 3–O-β-D-robinobiosil–7–O-α-L-ramno-piranosid (Robinin) - the active substance of original drug “Flaronin” and sum of four indoline alkaloids (Vingerbine) with cardio-stimulatory and pronounced anti-arrhythmic properties have been obtained at the I. Kutateladze Institute of Pharmacochemistry, TSMU. Robinin was obtained from *Astragalus falcatus Lam.* in the Direction of Phenolic compounds and Vingerbine was isolated from the above-ground parts of *Vinca herbaceae Waldst et Kit* in the Direction of Alkaloids [4-5]. Both plants are distributed in Georgia. “Flaronin” in the form of tablets is proposed in the complex therapy of chronic renal failure [5]. In previous studies we reported the involvement of efflux transporters such as *P-glycoprotein* in the intestinal absorption of each component [6-7].

The present investigation focuses on the evaluation of suitability of thiomer/lipid-based systems for delivery bioactive compounds from Georgian plants.

In this study were used various lipids (DPPC - 1,2-dipalmitoyl-sn-glycero-3-phosphocholine, DSPC -1,2-distearoyl-sn-glycero-3-phosphocholine, DSPG - Anionic 1,2-distearoyl-sn-glycero-3-phosphoglycerol, Cholesterol) for preparation nanosized liposomes and thiolated polymers: chitosan-glutathione (Ch-GSH), Polyacrylic acid – glutathione (PAA-GSH) and glutathione (GSH) alone. Statistical–analysis was performed using Student’s test with $p<0.05$ as the minimal level of significance.

Different lipids in different formulations and ratios were used for the preparation Robinin entrapped nanoliposomes. The systems were prepared by thin film evaporation method. The optimal liposomal composition was selected after by evaluation of particle size, size distribution, encapsulation efficiency and drug release profile.

In our experiments PAA-GSH produced a higher permeation-enhancing effect on absorptive transport of Vingerbine constituent alkaloids in Caco-2 cell lines (Fig.1). An intracellular accumulation of ajmaline type alkaloids was not influenced by Ch-GSH; the addition of GSH resulted in slightly improved intracellular accumulation only one of Vingerbine constituent alkaloids.

In conclusion, the designed nanoliposomes may be a suitable carrier for the delivery of poorly soluble bioactive flavonoid Robinin, and Polyacrylic acid – glutathione conjugate can efficiently improve the oral bioavailability of crude alkaloids.

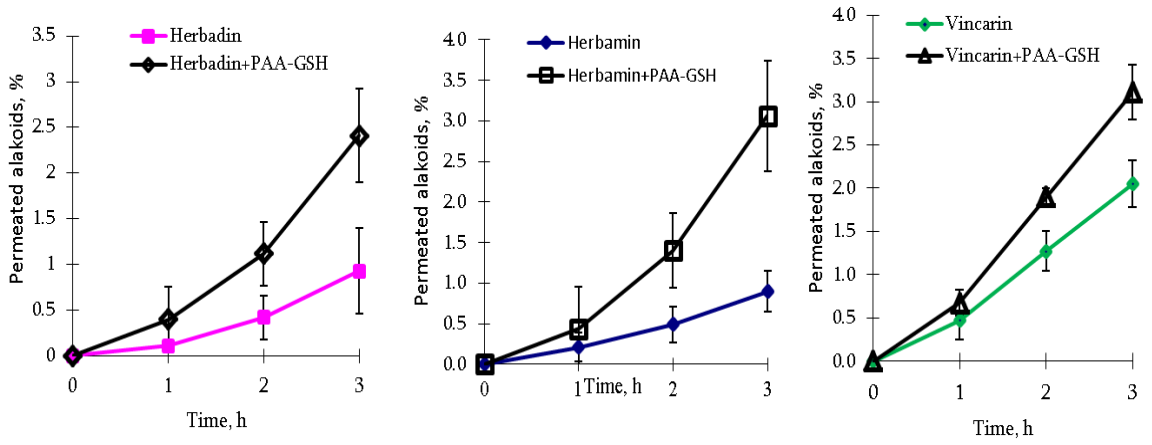


Fig.1. Influence of PAA-GSH conjugate on absorptive transport of Vingerbine constituent alkaloids in Caco-2 cells.

References

[1] Dubey S. K., Parab S., Achalla V. P. K., Narwaria A., Sharma S., Jaswanth Gowda B. H., Kesharwani P. (2022), Microparticulate and nanotechnology mediated drug delivery system for the delivery of herbal extracts, J. Biomater. Sci. Polym. Ed., 33(12), pp.1531–1554.

[2] Cheng X., Yan H., Pang,S., Ya M., Qiu F., Qin P., Zeng C., Lu Y. (2022), Liposomes as Multifunctional Nano-Carriers for Medicinal Natural Products. Frontiers in chemistry, 10, 963004.

[3] Veider F., Haddadzadegan S., Sanchez Armengol E., Laffleur F., Kali G., Bernkop-Schnürch A. (2024), Inhibition of P-glycoprotein-mediated efflux by thiolated cyclodextrins. Carbohydr. Polym., 327, 121648

[4] Chkhikvadze G. V., Vatchnadze V. J., Gambashidze N. B., Gvishiani E. F., Mudzhiri L. S. Reception Method of anti-arrhythmic substance, Pat. N 834964 A61 K 35/78. 1981.

[5] Alania M., Kemertelidze E., Kavtaradze N. Hypoazotemic remedy from the leaves of Pueraria hirsuta Matsum. (2014), National Intellectual Property Center of Georgia – Sakpatenti P. 6199.

[6] Tsiklauri L., Vachnadze V., Bernkop-Schnurch A. (2023), The permeability and efflux of Vinca alkaloids in a CACO-2 cell model, Georgian Scientists, 5(2), pp.220–228.

[7] Tsiklauri L., An G., Alania M., Kemertelidze E., E. Morris M. (2023). Interactions of bioflavonoid robinin with efflux transporters: p-glycoprotein and breast cancer resistance protein, Georgian Scientists, 5(2), pp.234–252.

[1] Tsiklauri L., An G., Alania M., Kemertelidze E., E. Morris M. (2023). Interactions of bioflavonoid robinin with efflux transporters: p-glycoprotein and breast cancer resistance protein, Georgian Scientists, 5(2), pp.234–252.

YOUNG RESEARCHERS' FORUM

YR 1. PREVALENCE AND TENDENCIES OF FOOD SUPPLEMENTS IN GEORGIA

Z. Jugeli, E. Pruidze

Tbilisi State Medical University, Department of Social and Clinical Pharmacy

e-mail: Zukliki1997@gmail.com

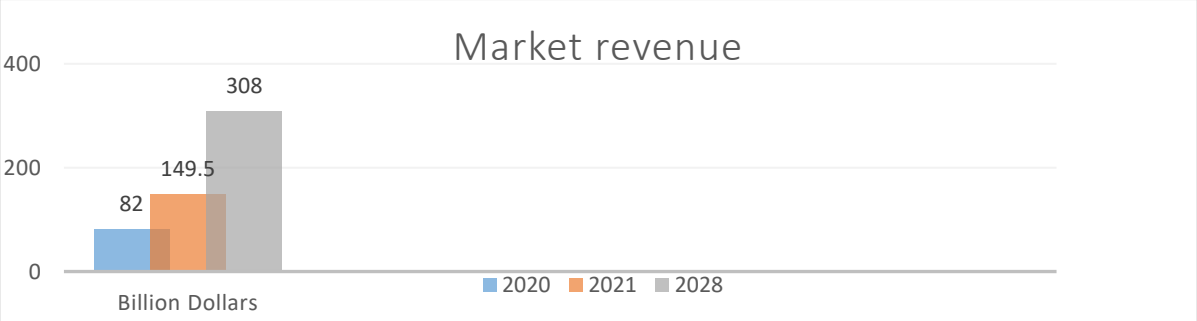
A balanced diet and intake of appropriate micro-macro elements are required to promote human health and well-being. It is precisely through nutritional supplements that restoring the disturbed nutritional balance more easily and improving our health is possible. Dietary supplements are a broad category that includes vitamins, minerals, herbs, amino-fatty acids, and more. They can be used both separately and in combination.

People take nutritional supplements for various reasons, but the most common factors are ensuring proper nutrition, reducing the risk of age-related diseases, and boosting immun system. The market for nutritional supplements is constantly growing, and at the same time, the importance of their quality assurance and the challenges related to this issue are also increasing.

Therefore, it became necessary to develop global standards and new regulations for food additives. The safety and efficacy of food additives is a major challenge in this field. It is a pressing issue for regulatory bodies and healthcare professionals.

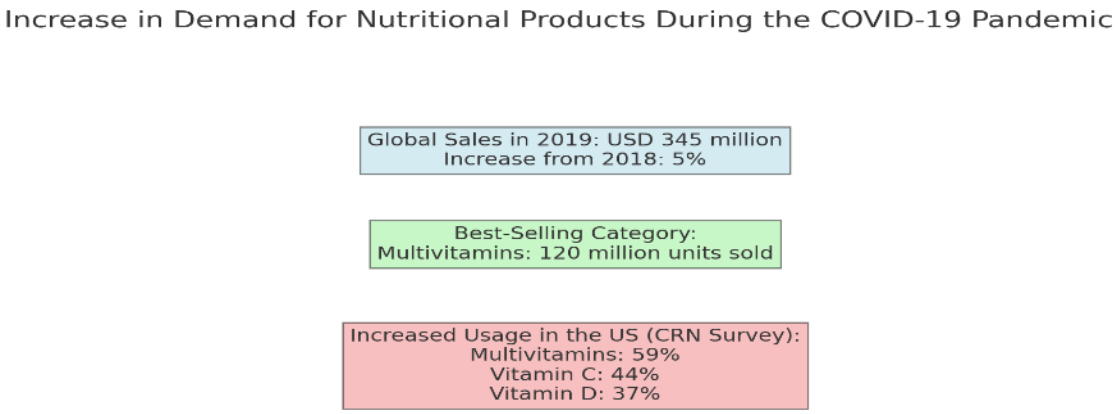
Aim and Objectives: Numerous scientific studies have demonstrated both the positive and negative effects of dietary supplements, including some that are potentially harmful. Given the widespread global interest in this topic, it is important to review the status of dietary supplements before and during the current healthcare crisis. This review aims to summarize the existing evidence on how dietary supplements impact the economy, their regulation, and market trends.

Globally, the dietary supplements market size grew from USD 82 billion to USD 149.50 billion in 2021 and is expected to reach USD 308 billion in 2028. Annual growth rate 8.90%



First, we present an overview of dietary supplements, covering the legislative and regulatory frameworks in the USA, the EU, China, Canada, and Georgia. We then discuss the prevalence and effectiveness of dietary supplements, as well as their side effects and interaction with prescripted medication. Furthermore, we examine the structure and size of the dietary supplement market in key producing and importing countries, global market trends, and the impact of the COVID-19 pandemic on market growth. Finally, we discuss the profiles of dietary supplement users.

Demand for nutritional supplements has increased significantly in the US during the COVID-19 pandemic. In 2019, global sales reached $345 million, a 5% increase over 2018, and multivitamins remained the best-selling category, with nearly 120 million units sold. A Council for Responsible Nutrition (CRN) study found that among US residents aged 18 to 35 (47% men and 39% women), consumption of multivitamins, vitamin C, and vitamin D increased by 59%, 44%, and 37%.



After reviewing rich literature on the subject we used gathered information for our study.

Following the purpose of the research, based on the literature study and analysis, we developed a quantitative questionnaire consisting of 17 questions. Participation was voluntary, their constitutional rights were protected during the survey.

The first part included questions of a demographic nature, and the second was related specifically to the use of food additives in Georgia. The questionnaire was filled out through the online platform, Google Form.

References:

[1] Djaoudene O, Romano A, Bradai YD, Zebiri F, Ouchene A, Yousfi Y, Amrane-Abider M, Sahraoui-Remini Y, Madani K. A Global Overview of Dietary Supplements: Regulation, Market Trends, Usage during the COVID-19 Pandemic, and Health Effects. *Nutrients*. 2023; 15(15):3320. https://doi.org/10.3390/nu15153320

[2] Lordan, R. Dietary Supplements and Nutraceuticals Market Growth during the Coronavirus Pandemic—Implications for Consumers and Regulatory Oversight. *PharmaNutrition* 2021, 18, 2020–2022. https://doi.org/10.1016/j.phanu.2021.100282

YR 2. CHEMICAL AND PHARMACOLOGICAL EVALUATION OF *ANGELICA ADZHARICA* - GEORGIAN ENDEMIC SPECIES

Mariam Nersezashvili[1], Sopio Gokadze[1], Anna Bozhadze[1], Paata Tushurashvili[2], Manana Maisashvili[1]

Tbilisi State Medical University: [1] Direction of Pharmacognosy and Pharmaceutical Botany, [2] Department of Biochemistry

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

Angelica L. is a well-known and widely distributed genus of the Apiaceae family, comprising approximately 60 to 90 species [1]. Species from *Angelica* family are known as the "female ginseng" and are used to treat amenorrhea, dysmenorrhea, menopausal disorders, hypertension, anemia, and vascular dystonia. Various species of the genus *Angelica* are considered official medicinal agents in many countries [2].

In Georgia, the genus Angelica comprises four species, from which *Angelica adzharica* M. Pimenov is endemic to Georgia and is found exclusively in Adjara, in the mid-mountain, upper-mountain, and subalpine zones, on forest edges, and grassy slopes at altitudes of 900-1900 meters above sea level [3]. Literature data on the chemical composition and biological activity of *A. adzharica* is scarce. In addition, the plant was included in the Red Book in 2007 as an endangered species and is also mentioned among the rare and disappearing species in the Regional Development Strategy of the Autonomous Republic of Adjara for 2010-2014 [4, 5].

Preliminary phytochemical studies have determined the presence of biologically active substances, especially coumarins and other volatiles (Table 1).

Table 1. Chemical composition of *A. adzharica* MeOH extract

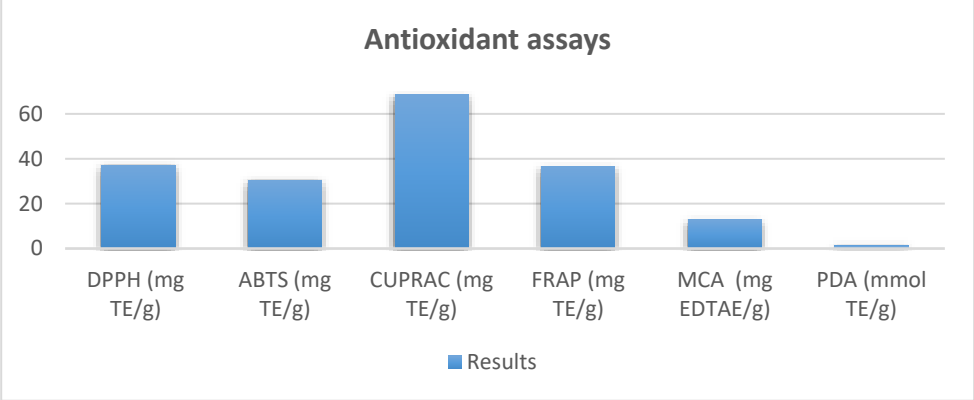
Compound	Retention time
p-Cymen-8-ol	6.58
Myrtenal	6.70
Thiophene, 2,5-dihydro-	6.78
Berbenone	6.80
5-Hydroxymethylfurfural	6.82
Thymol	7.29
Psoralene	10.80
Scopoletin (β-Methylesculetin)	11.40
Umbelliferone	10.81
Xanthyletin	12.03
Osthol	12.18

In addition, *A. adzharica* MeOH extract showed important antioxidant and enzymatic activity (Table 2, Fig. 1).

Table 2. Enzyme inhibitory activity of *A. adzharica* MeOH extract

Assay	ACHE (mg GALAE/g)	BCHE (mg GALAE/g)	Tyrosinase (mg KAE/g)	α-amilase (mg ACAE/g)	α-glucosidase (mg ACAE/g)
Enzyme inhibitory effect	2.33±0.18	1.96±0.17	37.63±2.32	0.66±0.02	0.68±0.01

*Definitions: GALAE - Galantamine equivalents, KAE - Kojic acid equivalent, ACAE – Acarbose equivalent



*Definitions: TE – Trolox equivalent; EDTAE - ethylenediaminetetraacetic acid equivalent

Fig. 1. Antioxidant activity of *A. adzharica* MeOH extract

The genus Angelica, particularly *Angelica adzharica* M. Pimenov, holds significant medicinal value. In Georgia, *A. adzharica* is endemic and thrives in the specific ecological niches of Adjara, yet it faces the threat of extinction, as noted in the Red Book and regional conservation strategies. Preliminary phytochemical analyses reveal a rich composition of biologically active substances in *A. adzharica*. The MeOH extract demonstrates substantial antioxidant and enzymatic activities, highlighting its potential for medicinal use. These findings underscore the need for continued research into the chemical properties and biological effects of *A. adzharica*. Such research is crucial not only for validating its traditional uses but also for exploring its potential integration into modern medical practice. Furthermore, efforts to cultivate and preserve this endemic species are essential for its conservation and sustainable utilization.

References

[1] Batiha GE-S. Shaheen HM, Elhawary EA et al. (2022), "Phytochemical Constituents, Folk Medicinal Uses, and Biological Activities of Genus Angelica: A Review," *Molecules*, vol. 28, no. 1, p. 267, doi: 10.3390/molecules28010267.

[2] Younis IY, El-Hawary SS, Eldahshan OA ET AL. (2021), "Green synthesis of magnesium nanoparticles mediated from Rosa floribunda charisma extract and its antioxidant, antiaging and antibiofilm activities," *Sci. Rep*., vol. 11, no. 1, p. 16868, doi: 10.1038/s41598-021-96377-6.

[3] Chen J, Li H, Wang D, et al. (2008), "Determination of sucrose in radix Angelicae sinensis by HPLC-ELSD," *Mod Chin Med*, no. 10, pp. 19–20, 2008.

[4] Davlianidze M, Gviniashvili T, Jinjolia-Imnadze L, and Jugheli T. (2018) Nomenclatural Checklist of Flora of Georgia.

[5] Gagnidze, R. & Manvelidze, Z. 2014. Angelica adzharica. The IUCN Red List of Threatened Species 2014: e.T199897A2617957. doi:10.2305/IUCN.UK.2014-1.RLTS.T199897A2617957.en.

YR 3.SEASONAL VARIATION OF BIOACTIVE ALKALOID CONTENTS IN MAHONIA AQUIFOLIUM (PURSH) NUTT.

N. Todua[2], D. Chincharadze[2], N. Vachnadze[1].

Tbilisi State Medical University: [1] I. Kutateladze Institute of Pharmacochemistry; [2] Direction of Pharmacognosy and Pharmaceutical Botany

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

Mahonia aquifolium (Pursh) Nutt belongs to the Berberidaceae family, native to East Asia, North and Central America. As is known, isoquinoline alkaloids that are part of Mahonia species exhibit antibacterial, antifungal, cytotoxic, anti-inflammatory, and many other activities. Species of this plant are widely used in folk and traditional Chinese medicine to treat dysentery, tuberculosis, pharyngolaryngitis, eczema, and other skin diseases [1].

he purpose of our study was to analyse the qualitative and quantitative content of total alkaloids in the aerial parts of the *M. aquifolium* introduced in Georgia during the various vegetation seasons.

To study the seasonal dynamics of accumulation of the sum of alkaloids, samples (aerial parts of the plant: leaves, stems, perennial branches) were collected: **I** - at the beginning of the growing season, **II** - in the flowering phase, **III** - in the fruiting phase and **IV** - at the end of the growing season. The extraction of alkaloids was carried out with chloroform after preliminary alkalization, using the method of exhaustive extraction. The completeness of the extraction was checked by reaction with Dragendorff's reagent. After purification from extractive impurities with 10% H_2SO_4 the acidic fractions were basified with 25% NH_4OH to a pH of 9-10 and simultaneously extracted with an organic solvent. The dry residue, brought to a constant weight, was weighed on analytical scales. Preliminary qualitative analysis was carried out by TLC method in the presence of witnesses in the systems $CHCl_3$-CH_3OH (4:1), (9:1), BAW (10:1:3); on $Silicagel_{254}$ plates, Merck; with Dragendorff`s reagent as the detector.

As a result of a qualitative analysis of the amounts of alkaloids, it was established that all identified bases are classified as isoquinoline bases. According to a quantitative analysis of the yield of the total amount of alkaloids, considering the growing season, calculated on air dried material, they can be arranged in the following sequence: 1,4% (II) > 1,15% (IV) > 1% (I)> 0,76% (III)

Based on the spectral methods of analysis (GC/MS and HPLC/MS) of the isolated sums, the content of alkaloids was determined as a percentage of the total amount of bases in terms of absolutely dry raw materials. As a result, some differences from previously published data in foreign periodicals were identified in the chemical composition of M*. Aquifolium* introduced in Georgia.

Thus, in phase **I**, pharmacologically active alkaloids were identified - norisocorydine, sinomenine, and lirinine [2-4]. **II** – isocorydine, sinomenine, and isoboldine [5-6]. **III** - isocorydine, sinomenine. **IV** – glaucine, isocorydine, sinomenine, isoboldine, and lirinine [7]. Sinomenine, norisocorydine and lirinine were identified for the first time in the chemical composition of the species M. *Aquifolium* introduced in Georgia, which attracts attention and provides prerequisites for further research work in this direction.

The sums obtained from samples collected at the beginning of the growing season - flowering were assessed as positive for antiproliferative (human keratinocytes of the HaCaT line) and showed pronounced cytotoxic activity against ALD-1 cell lines; DLD-1 and WS-1 according to the methods of Hoeste and Resazurin in the presence of Etoposide.

References

[1] 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, pp. 668–683 https://doi.org/10.1016/j.jep.2015.09.013

[2] E S, Shang ZC, Qin S-h, et al. (2022), A Systematic Method for the Identification of Aporphine Alkaloid Constituents in Sabia schumanniana Diels Using UHPLC-Q-Exactive Orbitrap/Mass Spectrometry. Molecules. 27(21):7643. https://doi.org/10.3390/molecules27217643

[3] Wei Z., Chen J, Zuo F, et al. (2022), Traditional Chinese Medicine has great potential as candidate drugs for lung cancer: A review. Journal of ethnopharmacology, 115748, vol.300, 115748, https://doi.org/10.1016/j.jep.2022.115748.

[4] Nasrullah AA., Zahari A, Mohamad J & Awang K. (2013), Antiplasmodial Alkaloids from the Bark of Cryptocarya nigra (Lauraceae). Molecules, 18, 8009 - 8017. https://doi.org/10.3390/molecules18078009

[5] Zhou Q, Zhang Q, Liao L, et al..(2024), Isocorydine Exerts Anticancer Activity by Disrupting the Energy Metabolism and Filamentous Actin Structures of Oral Squamous Carcinoma Cells. Curr Issues Mol Biol. 46(1):650-662. ; https://doi.org/10.3390/cimb46010042

[6] Li Y, Zeng RJ, Chen JZ, et al. (2015), Pharmacokinetics and metabolism study of isoboldine, a major bioactive component from Radix Linderae in male rats by UPLC-MS/MS. J Ethnopharmacol.;171:154-60. https://doi.org/10.1016/j.jep.2015.05.042

[7] Cowan DC, Smith AD, Thomson NC. (2014). Chapter 16 - Drugs that act on the respiratory tract. (2014), Chapter 16 - Drugs that act on the respiratory tract. Side Effects of Drugs Annual, Elsevier, vol. 35, pp. 309-326, https://doi.org/10.1016/B978-0-444-62635-6.00016-4.

POSTER PRESENTATIONS

PP 1. POLYGLYCERIC ACID-BASED MULTICATECHOL-CONTAINED BIOPOLYMERS: POLY[3-(3,4-DIHYDROXYPHENYL)GLYCERIC ACID] FROM MEDICINAL PLANTS OF BORAGINACEAE FAMILY WITH THERAPEUTIC EFFICACY

L. Amiranashvili, L. Gogilashvili, M. Merlani, V. Barbakadze

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

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

The main chemical constituent of high molecular (>500 kDa) water-soluble preparations from Symphytum asperum, S.caucasicum, S.officinale, S.grandiflorum, Anchusa italica, Cynoglossum officinale, Paracynoglossum imeretinum and Borago officinalis (Boraginaceae) was found to be poly[oxy-1-carboxy-2-(3,4-dihydroxyphenyl)ethylene] that is poly[3-(3,4-dihydroxyphenyl)glyceric acid] (**PDPGA**) according to data of liquid-state ^{1}H, ^{13}C NMR, 2D $^{1}H/^{13}C$ HSQC, 2D DOSY and solid-state ^{13}C NMR spectra [1-7] (Fig. 1).

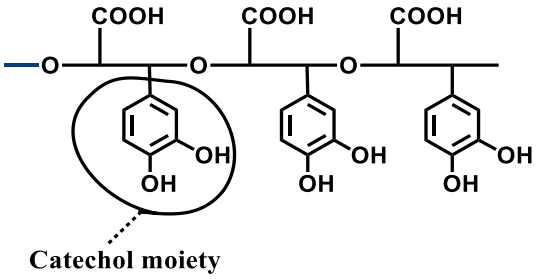


Fig. 1. Poly[oxy-1-carboxy-2-(3,4-dihydroxyphenyl)ethylene] that is poly[3-(3,4-dihydroxyphenyl)glyceric acid] (**PDPGA**).

The polyoxyethylene (polyethylene glycol) (PEG) chain is the backbone of this biopolymer with a residue of 3-(3,4-dihydroxyphenyl)glyceric acid as the repeating unit. 3,4-Dihydroxyphenyl (catechol) and carboxyl groups are regular substituents at two carbon atoms in the chain. Its basic monomeric moiety glyceric acid is an oxidative form of the simplest of all common aldoses glyceraldehyde. **PDPGA** represents a new class of natural polyethers. **PDPGA** as a multicatechol-functionalized poly(2,3-glyceric acid ether) belongs to a rare class of polyglyceric acid-based numerous catechol-contained biopolymer as well. Poly(2,3-glyceric acid ether) chain is the backbone of this polymer and catechol moieties are regular substituents at carbon atoms in the chain. **PDPGA** did not find in the following species of Boraginaceae family: Echium rubrum, Lithospermum officinale, Aegonychon purpurocaeruleum, Asperugo procumbens, Myosotis arvencis**,** Myosotis micrantha. One of the main chemical constituent of high molecular (>500 kDa) water-soluble preparation (HMP) from Onosma sericea (Boraginaceae) was found to be novel p-coumaric acid-derived biopolymer, namely poly[oxy-1-carboxy-2-(4-hydroxyphenyl)ethylene], that is poly[3-(4-hydroxyphenyl)glyceric acid]. Besides, the data also reveal in HMP of O. sericea the presence of complex pectin type polysaccharide. Every repeating trifunctional structural unit of **PDPGA** contains two phenolic hydroxyl groups in ortho-position and one carboxyl group. Multifunctionality of **PDPGA** should be a reason of its wide spectrum of biological activities. **PDPGA** exhibited anticomplementary, antioxidant, antimicrobial, antiinflammatory, burn, wound healing and anticancer activities. **PDPGA suppressed** the growth and induced death of prostate cancer (PCA) cells. **PDPGA** induced apoptotic death by activating caspases, strongly decreased androgen receptor and prostate specific antigen (PSA) expression. **PDPGA** administration caused a strong dose-dependent decrease in PSA levels by 87%. Overall, this study identifies **PDPGA** as a potent agent against PCA without any toxicity [8]. Catechol-containing **PDPGA** due to its ability to donate protons or electrons showed strong antioxidant activity. **PDPGA** demonstrates moderate antimicrobial properties due to the abundant catechol groups, which can denature bacterial proteins and damage bacterial cell membranes [9].

PDPGA has also been shown to exhibit pro-oxidant activities under certain culture conditions. **PDPGA** due to oxidation of catechol groups into quinones can be generated various types of reactive oxygene species (ROS) such as superoxide anion ($O_2^{\bullet-}$), hydrogen peroxide (H_2O_2), singlet oxygen ($^1O_2$), and hydroxyl radical (•OH) during oxidizing conditions such as autoxidation, chemical-induced oxidation, and metal ion-mediated oxidation. H_2O_2 is not a very potent disinfectant. The hematin (HEM), a porphyrin derivative that contains an Fe^{3+} ion enhance antimicrobial property of catechol. Fe^{3+} can convert the generated H_2O_2 to •OH via a Fenton-like reaction process. •OH and $^1O_2$ are highly reactive and strong oxidant with remarkable antimicrobial properties. Besides, H_2O_2 also can be converted to more reactive oxidant such as HOCl [e.g. hypochlorite (OCl^-)] by myeloperoxidase enzyme stored inside neutrophils. The resulting reactive species are the strongest antimicrobial oxidants in neutrophils. The anticomplementary activity of **PDPGA** is apparently related to its phenolic nature and can be explained by the formation of catechol unit–protein complexes capable of blocking complement convertases and besides inhibits xanthine oxidase and NADPH oxidase which are responsible for generation of ROS. Catechol moieties of **PDPGA** have potent to induce production of cytoprotective proteins and consequently have a protective role against diseases, such as inflammation and cancer.

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. Compnd.,* vol. 45, no. 1, pp. 6-10.

[3] Barbakadze V., Gogilashvili L., Amiranashvili L., 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 L., 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. 115-121.

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

[6] Barbakadze V., Gogilashvili L., Amiranashvili L., 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.

[7] Barbakadze V., Gogilashvili L.,.Amiranashvili L. et al. (2022) Biologically Active Sugar-Based Biopolyet her Poly[3-(3,4-Dihydroxyphenyl)Glyceric Acid] from the Stems and Roots of *Paracynoglossum imeretinum* (Kusn.) M.Pop. *Bull. Georg. Natl. Acad. Sci.*, vol.16, no. 3, pp. 110-115.

[8] Shrotriya S., Gagan D., Ramasamy K., et al. (2012), Poly[3-(3,4-dihydroxyphenyl)glyceric acid] from Comfrey exerts anti-cancer efficacy against human prostate cancer via targeting androgen receptor, cell cycle arrest and apoptosis. *Carcinogenesis*, vol. 33, no. 8, pp.1572-1580.

[9] Barbakadze V., Merlani M., Gogilashvili L. et al. (2023) Antimicrobial Activity of Catechol-Containing Biopolymer Poly[3-(3,4-dihydroxyphenyl)glyceric Acid] from Different Medicinal Plants of Boraginaceae Family. *Antibiotics,* vol. 12, Article no. 285.

PP 2. SYNTHESIS OF POTENTIAL BIOLOGICALLY ACTIVE STEROIDAL HYDRAZONES

N. Barbakadze, N. Nadaraia, M. Kakhabrishvili, T. Kvaratskhelia

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

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

Steroids play an important role in physiological processes in living organisms, they are characterized by high and versatile biological activity.

The search for new biologically active molecules among steroid compounds, their structural modification is still relevant and is connected with time-consuming work in the field of organic synthesis. The researchers' interest in steroids is related to their special biological and pharmacological effects on the body.

Steroid drugs, obtained by semisynthesis of compounds of plant origin, are widely used in medical practice as remedies. The universal biological activity of compounds of the androstane, pregnane, estrane series, including hydrazones and oximes, indicates that they can become key starting points for the development of new drugs [1,2].

We have synthesized numerous derivatives of 5α-steroids by several-step modification of tigogenin, a steroidal aglycon obtained from the introduced plant in Georgia, "*Yucca Gloriosa*". The *in vitro* study of the compounds showed that it is interesting to continue the work in this direction. They are characterized by significant antiviral, cytotoxic, antibacterial, antimycotic, antitumor activity [3,4].

The synthesis of new derivatives of steroids with different structures and the results of their pharmacological studies on structure-activity correlation will enrich the possibility of creating libraries of potential therapeutic agents. Rapid and efficient screening of these libraries helps identify lead compounds for new drug development.

The work was financially supported by the Shota Rustaveli National Science Foundation of Georgia (SRNSF) (Grant FR-23-1931 „Synthesis of potential biologically active nitrogen-containing 5α-steroids by modification of tigogenin”).

References

[1] Mistry Sh. Singh AK. (2022), Synthesis and in vitro antimicrobial activity of new steroidal hydrazone derivatives, *Future Journal of Pharmaceutical Sciences,* vol. 8, no. 7, pp. 1-10.

[2] Jabeen M. Choudhry M.I. Miana GA. Rahman KM. Rashid U. Khan H. Arshia A. Sadiq. (2018) Synthesis, pharmacological evaluation and docking studies of progesterone and testosterone derivatives as anticancer agents, *Steroids*, vol. 136, pp. 22-31.

[3] Eerlings R. Barbakadze N. Nguyen T. Nadaraia N. Smeets E. Moris L. handle F. Kharraz S.E. Devlies W. Voet A. Dehaen W. ClaessensF. Helsen Ch. (2022) Small-molecule profiling for steroid receptor activity using a universal steroid receptor reporter assay, *Journal of Steroid Biochemistry and Molecular Biology,* vol. 217, pp. 106043.

[4] Merlani M. Nadaraia N. Barbakadze N. Amiranashvili L. Kakhabrishvili M. Petrou A. Carević T. Glamočlija J. Geronikaki A. (2024) Steroidal hydrazones as antimicrobial agents: biological evaluation and molecular docking studies, *SAR and QSAR in Environmental Research,* vol. 35, no. 2, pp. 137-155.

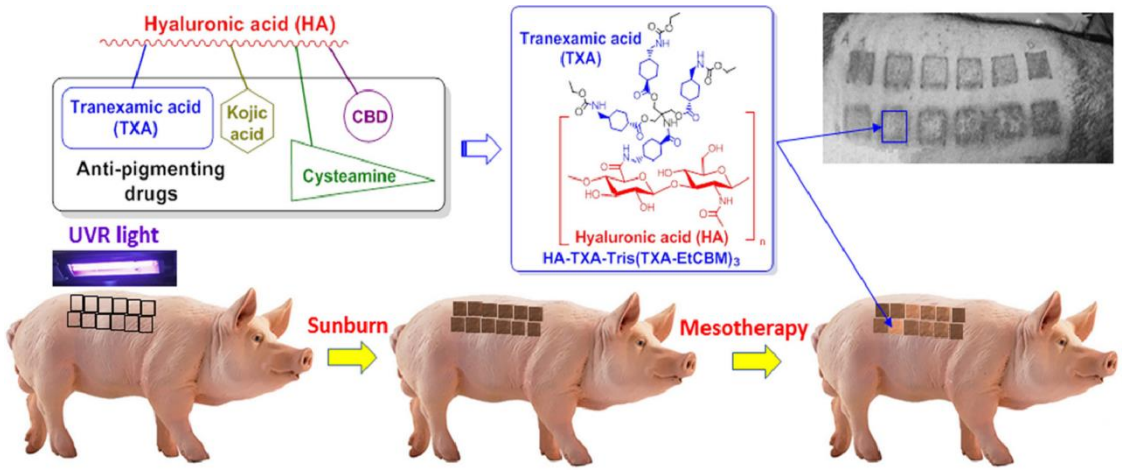
PP 3. DRUG CONJUGATES CONTAINING HYALURONIC ACID TO TREAT SKIN HYPERPIGMENTATION

Andrii Bazylevich [a] and Sarit Aviel-Ronen [b,c]

[a] Department of Chemical Sciences, Ariel University, Ariel 40700, Israel; [b] Adelson School of Medicine, Ariel University, Ariel 40700, Israel; [c] Sheba Medical Center, Tel-Hashomer, Ramat Gan, Israel

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

Hyperpigmentation is frequently treated with drug combination therapy. However, the lack of sufficient activity of combined drugs frequently limits the success of treatment. In order to enhance the therapeutic efficacy of drug combination therapy, we created and examined multiple conjugates that consisted of both homogeneous and heterogeneous anti-pigmenting medications attached to a hyaluronic acid (HA) carrier via unique biodegradable linkers. In hydrolytic media, the drug release profile of these HA-drug conjugates was measurable. When applied via mesotherapy to pig models that had been exposed to UV light and developed pigmentation, the majority of the tested conjugates showed better depigmentation than the corresponding controls. Of these, the dendron-like conjugate NH_2-TXA-Tris-TXA-$(EtCMB)_3$, which solely contains tranexamic acid (TXA), outperformed its equimolar mixture of HA and TXA (control) in terms of depigmenting the swine skin. These findings support the use of HA as a delivery platform for the treatment of a variety of skin disorders and highlight the significance of conjugation depigmenting agents to HA for enhancing the efficacy of treatment.



References

[1] Bazylevich A et al. (2024), Hyaluronic acid drug conjugates for the treatment of skin hyperpigmentation, *J. Mol. Structure*, 1297(2), 2024, 136972.

PP 4. ESSENTIAL OILS AS PENETRATION ENHANCERS FOR TRANSDERMAL DELIVERY OF DICLOFENAC SODIUM

N. Bregvadze[1], G. Mikaia[1], L. Ebralidze[1], L. Kodanovi [2]

[1] Tbilisi State Medical University, Faculty of Pharmacy, Department of Pharmaceutical Technology; [2] Batumi Botanical Garden

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

Diclofenac sodium is a non-steroidal anti-inflammatory drug that exhibits anti-inflammatory, analgesic, and antipyretic activities. This medication is used to treat various aches and pains, including joint problems such as rheumatoid arthritis, osteoarthritis, sprains, strains in muscles and ligaments, back pain, gout, and ankylosing spondylitis. Diclofenac sodium inhibits cyclooxygenase, which converts arachidonic acid released from the cell membrane into prostaglandins. When administered orally, various side effects can occur, such as epigastric discomfort, and there is a high risk of gastrointestinal toxicity due to first-pass metabolism (diclofenac sodium has a two-hour half-life). Currently, transdermal analgesics are extensively used in pain management [2,3,4].

Transdermal delivery systems provide systemic therapeutic effects through the skin microcirculation and are designed to deliver an effective therapeutic amount of the drug. These systems aim to enhance bioavailability and prolong the duration of action, thereby minimizing the frequency of dosing, reducing side effects, and maintaining drug plasma levels. Transdermal delivery systems are often more convenient for self-administration compared to injections, which improves patient compliance. Thus, for the treatment of many conditions, transdermal delivery systems are safer and more effective than oral and injectable options [2,4].

To enhance skin permeability, penetration enhancers are employed, which alter the barrier function of the stratum corneum and improve drug flux. These enhancers can be derived from both natural and synthetic sources, including azones, pyrrolidones, surfactants, and essential oils. Essential oils are aromatic compounds extracted from natural sources, primarily plants, and are widely used in the pharmaceutical, cosmetic, and food industries [5,6].

Penetration enhancers contain active anti-inflammatory compounds that exert their effects through various mechanisms. The anti-inflammatory mechanisms of essential oils include reducing levels of reactive oxygen species (ROS) and nitrogen species while increasing the levels of antioxidant enzymes. Treatment with essential oils decreases the expression of pro-inflammatory cytokines and mediators, neutralizes excess ROS, alleviates tissue edema, and accelerates wound healing [7,8,9].

Studies have shown that essential oils such as eucalyptus, peppermint, clove, turpentine, cinnamon, and cedar can effectively serve as penetration enhancers to improve the transdermal permeability of diclofenac sodium [1,10]. Essential oils reduce the barrier function of the stratum corneum without causing damage to skin cells. They have been successfully used to enhance the transdermal delivery of hydrophobic anti-inflammatory drugs, including diclofenac sodium [6,10].

Therefore, the unique properties of essential oils allow them to be utilized as adjuncts in transdermal delivery systems, serving as anti-inflammatory and permeation-enhancing agents. This area requires further investigation and clarification.

This study aims to explore the penetration properties of essential oils in transporting diclofenac sodium through the skin into systemic circulation via transdermal delivery systems.

To achieve this goal, the following task has been outlined: Determining the formulation and evaluation of a transdermal patch of pure diclofenac, and with essential oils.

Based on data from the literature, we selected the following essential oils as the subjects of the study, which have anti-inflammatory activity as well as provide enhanced permeability: eucalyptus oil, peppermint oil, clove oil, turpentine oil, cinnamon oil, and cedar oil.

In in vitro experiments using Francis diffusion cells, it has been established that all essential oils increase the diffusion of diclofenac sodium into the membrane compared to the permeability of pure diclofenac sodium within the range of 10-30%, the ability of essential oils to enhance permeability is likely significant dependent on their volatility and the magnitude of the generated pressure.

References

[1] Alhasso B, Ghori MU, Conway BR. (2022), Systematic Review on the Effectiveness of Essential and Carrier Oils as Skin Penetration Enhancers in Pharmaceutical Formulations. *Scientia Pharmaceutica*. 90(1):14.

[2] Hendradi, E, Rahayuningtyas, E, & Erawati , T. . (2023). The Effect of Polymers Ratio Carboxymethyl Chitosan, Polyvinyl Pyrolidone K-30, and Ethyl Cellulose N22 on Physico-Chemical Characteristics and Drug Release from Matrix Type Diclofenac Potassium Patch. *Jurnal Farmasi Dan Ilmu Kefarmasian Indonesia*, 10(1), 54–61.

[3] Abdullah, H.M, Farooq, M, Adnan, S. et al. Development and evaluation of reservoir transdermal polymeric patches for controlled delivery of diclofenac sodium. Polym. Bull. 80, 6793–6818 (2023).

[4] Khoerunnisa, F, Yolanda, Y.D, Nurhayati, M, et al. (2023), pH-responsive chitosan/poly (vinyl pyrrolidone) based hydrogel composites: Antibacterial properties and release kinetics of diclofenac sodium. *Journal of Drug Delivery Science and Technology.*

[5] Samiullah Jan SU, Gul R, Jalaludin S, & Asmathullah (2020), Formulation and Evaluation of Transdermal Patches of Pseudoephedrine HCl. *International Journal of Applied Pharmaceutics*.

[6] Tuntiyasawasdikul S, & Sripanidkulchai B. (2022), Development and clinical trials on anti-inflammatory effect of transdermal patch containing a combination of Kaempferia parviflora and Curcuma longa extracts. *Journal of Drug Delivery Science and Technology*.

[7] Zhao Q, Zhu L, Wang S et al. (2022). Molecular mechanism of the anti-inflammatory effects of plant essential oils: A systematic review. *Journal of ethnopharmacology*, 115829 .

[8] Çalışkan, UK, & Karakuş MM. (2020). Essential Oils as Skin Permeation Boosters and Their Predicted Effect Mechanisms.

[9] Marrelli M, Amodeo V, Perri MR et al.. (2020). Essential Oils and Bioactive Components against Arthritis: A Novel Perspective on Their Therapeutic Potential. *Plants*, 9.

[10] Barão Paixão VL, & Freire de Carvalho J. (2021). Essential oil therapy in rheumatic diseases: A systematic review. *Complementary therapies in clinical practice*, 43, 101391

[11] Xu Y, Zhao M, Cao J, et al. (2023). Applications and recent advances in transdermal drug delivery systems for the treatment of rheumatoid arthritis. *Acta Pharmaceutica Sinica*. B, 13, 4417 - 4441.

PP 5. FOR STUDYING THE ISSUE OF DIETARY SUPPLEMENT CONSUMPTION TRENDS IN GEORGIA

L. Dateshidze[1], D. Berashvili[1], N. Todua[3]

[1] Department of Pharmaceutical Botany, Tbilisi State Medical University, Georgia, [2] Department of Marketing, School of Economics and Business, Ivane Javakhishvili Tbilisi State University, Georgia

Corresponding author e-mail: lali.dateshidze@tsmu.edu

The increase in the use of dietary supplements (DS) is a characteristic trend of the last decades. Interest in DSs dates back to the 1970s, and in 2021, the global market size was estimated at USD 149.50 billion. By 2028, the size is expected to reach USD 308 billion, and the annual growth rate will be 8.90%. [1]

According to the Law of Georgia on Medicines and Pharmaceutical Activities (LGMPA), a biologically active supplement (BAS) is considered a means of maintaining physiological conditions. Unlike medicines, their authorization is voluntary; it is not mandatory for a manufacturer or importer, and the submission for approval depends only on their initiative. [2,5] Supplements not registered as pharmaceutical products are regulated under the competence of the Ministry of Agriculture and Food of Georgia, the National Food Agency, whose guiding legal document is the Resolution of the Government of Georgia No. 360 of July 12, 2022.[3]

To study the DSs available on the local market, the National Food Agency database was used as the primary source of information. Since enrollment of the first item in this register (from May 2023 to January 13, 2024) 2,381 items of food supplements were registered. [4] Specific information was searched for each supplement (2381 items) to get the target data. The obtained data were processed and grouped by DSs composition and functional purpose of their usage. [6]

The study revealed that 2381 items of DSs from 44 countries have been submitted for consumption in the local market. The vast majority (up to 99%) of the DSs range is imported. The five leading countries in the product range are the United Kingdom, the USA, Poland, Germany, and Italy. The research confirmed DS domestic production's low (1%) rate. The segmentation by the content of DSs shows that the most significant parts presented on the market are combined, the ingredients of which can be vitamins, mineral substances, amino acids, proteins, fatty acids, enzymes, and various biogenic compounds. Regarding the possible risks related to containing multiple ingredients in the product, it is advisable to develop measures to avoid risks. According to functional segmentation, most DSs presented on the market justify their primary purpose - maintenance of physiological processes. [6]

To study the whole picture of trends in DS consumption, the next consistent step has been dedicated to finding factors (variables) affecting DS consumption. As a result of studying the scientific reference, 22 relevant variables were selected, and 15 experts were interviewed face-to-face for their ranking. The variable rated as the most important by each expert was given 1 point, the next variable 2, and so on. The ranking of the average values of all 15 experts according to the variables is presented in Tab.1.

Table 1. Ranking of variables determining DS consumption according to the survey of experts.

#	Variable/expert	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	Aver.
X1	Acceptance	6	3	6	4	2	5	5	5	3	2	1	2	4	1	3	**3.47**
X2	Perceived usefulness	4	2	5	1	8	1	9	1	16	3	3	3	5	5	1	**4.47**
X3	Awareness	1	1	14	13	4	7	1	4	1	1	2	1	20	3	2	**5.00**
X4	Percieved credibility	7	6	4	11	22	2	12	3	4	18	6	5	6	7	4	**7.80**
X5	Perceived information quality	2	4	13	3	1	13	15	12	2	16	4	6	19	6	14	**8.67**
X6	Attitude towards use	10	7	3	20	8	3	18	2	18	4	7	8	8	2	18	**9.07**
X7	Engagement	9	8	15	12	3	9	11	6	8	5	8	9	13	8	17	**9.40**
X8	Usage behavior	5	10	16	5	5	4	19	8	10	13	11	11	14	14	16	**10.73**
X9	Perceived ease of use	8	5	7	19	14	19	7	13	5	17	5	4	7	18	15	**10.87**
X10	Perceived behavioral beliefs	19	17	2	15	13	8	20	7	6	7	17	17	18	4	7	**11.80**
X11	Behavioral intention	17	9	19	18	10	6	21	11	9	6	9	10	9	15	13	**12.13**

X12	Perceived stimulus factor	18	16	1	9	21	11	10	9	7	20	18	18	11	11	5	**12.33**
X13	Perceived utilitarian value	21	14	8	6	16	12	13	10	13	10	15	13	15	12	11	**12.60**
X14	Perceived attachment	12	15	12	7	11	17	14	14	14	9	14	15	21	10	10	**13.00**
X15	Perceived self-efficacy	16	18	10	16	18	21	3	18	11	8	19	22	1	16	8	**13.67**
X16	Perceived severity	15	20	9	14	12	15	4	20	12	14	20	19	17	9	9	**13.93**
X17	Perceived ecological motives	11	19	18	2	15	22	2	17	17	12	22	21	2	17	19	**14.40**
X18	E-WOM	22	12	11	17	9	10	22	16	20	19	12	12	10	13	20	**15.00**
X19	Perceived resistance	13	11	20	8	20	20	17	15	15	15	16	16	16	20	6	**15.20**
X20	Perceived monetary value	20	13	21	22	6	18	8	21	19	21	13	14	12	19	12	**15.93**
X21	Perceived normative beliefs	14	21	17	10	19	16	6	19	21	11	21	20	3	21	22	**16.07**
X22	Perceived risk	3	22	22	21	17	14	16	22	22	22	10	7	22	22	21	**17.53**

Based on highly rated variables given in Table 1, it is planned to develop a survey questionnaire for users' profile research and assess the whole picture of the local trends in DS consumption.

References

[1] Total Dietary Supplements Market Size Worldwide from 2016 to 2028. (2023). Dietary supplements market size worldwide 2028 forecast | Statista

[2] LAW OF GEORGIA ON MEDICINES AND PHARMACEUTICAL ACTIVITIES. Parliament of Georgia Issued 17.04.1997. https://matsne.gov.ge/en/document/view/29836?publication=30

[3] Resolution No. 360 of 2022 of Georgian Government onTechnical Regulation on Food Supplements. https://faolex.fao.org/docs/pdf/geo212860.pdf.

[4] LEPL National Food Agency of Georgia. Register of food supplements. https://nfa.gov.ge/Ge/Page/sasursato%20danamatebi

[5] Dateshidze L,. Berashvili D, Todua N. (2023), Review of Dietary Supplement Regulation. *Georgian Biomedical News*. vol.1. Issue 4. https://www.gbmn.org/copy-of-article-1-23-52

[6] Dateshidze L,. Berashvili D, Todua N. (2024), The Market for Dietary Supplements in Georgia: Trends of Development. *Georgian Biomedical News*. Vol. 2. issue 1.

PP 6. RISK ANALYSIS OF PHARMACEUTICAL LOGISTICS

N. Dughashvili, T. Khuchua, T. Chanturia, N. Kvizhinadze, N. Nikuradze

Tbilisi State Medical University, Faculty of Pharmacy

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

Pharmaceutical logistics plays a key role in various dimensions of healthcare supply chain management. At its core, it serves to ensure the safety and health of the patient in the timely and reliable supply of medicines. In addition, pharmaceutical logistics plays a critical role in the distribution process in meeting quality assurance standards and regulatory requirements. Logistics risk management is one of the most important elements of business management, which allows to achieve stability and uninterrupted production processes in the company. When identifying the risks, it is necessary to objectively analyze the risks and select the most effective methods of influencing them.

Determining the level of logistical risks of the Georgian pharmaceutical enterprise "GM Pharmaceuticals" and analyzing the results using the FMEA method. The FMEA method involves analyzing the impact of a non-conforming condition on the quality, safety and efficacy of the product, risk to the patient or compliance.

Risk Ranking (RPN)

RISK LEVEL (S *O *D)	
low/unimportant	1-128
medium/important	144-405
high/critical	441 - 1000

Based on the results of the conducted research, the main risks related to the pharmaceutical logistics of the pharmaceutical enterprise "GM Pharmaceuticals" were identified:

1. Qualification of the supplier (RPN 105) and personnel (RPN 112): the risks emphasize the fact that the company does not fully evaluate the supplier, does not invest in staff training, does not conduct internal audits regularly;

2. The risks posed by natural disasters (RPN 72) and technological failures (RPN 90) emphasize the importance of developing strategies.

3.Risks associated with temperature-controlled trucks (RPN 210), active containers (RPN 175) and passive containers (RPN 112) highlight the neglect of temperature integrity and equipment validation;

4. Sea Shipping and Customs Processes: The challenges of order documentation (RPN 128), visual inspection (RPN 112) and customs procedures (to RPN 405) highlight the complexity and potential vulnerabilities of international logistics;

5. Warehouse management: Risks during order receipt and processing (RPN 16 and RPN 210) emphasize the need for reliable IT infrastructure and thorough order processing procedures.

References:

[1] Alsaidalani R, Elmadhoun B. Quality Risk Management in Pharmaceutical Manufacrturing Operations: Case Study for sterilie product filling and final product handing stage. 2022;
[2] ICH guideline Q9 on quality risk management. 2015;
[3] Drozdov PA – Logisticts basics. 2015

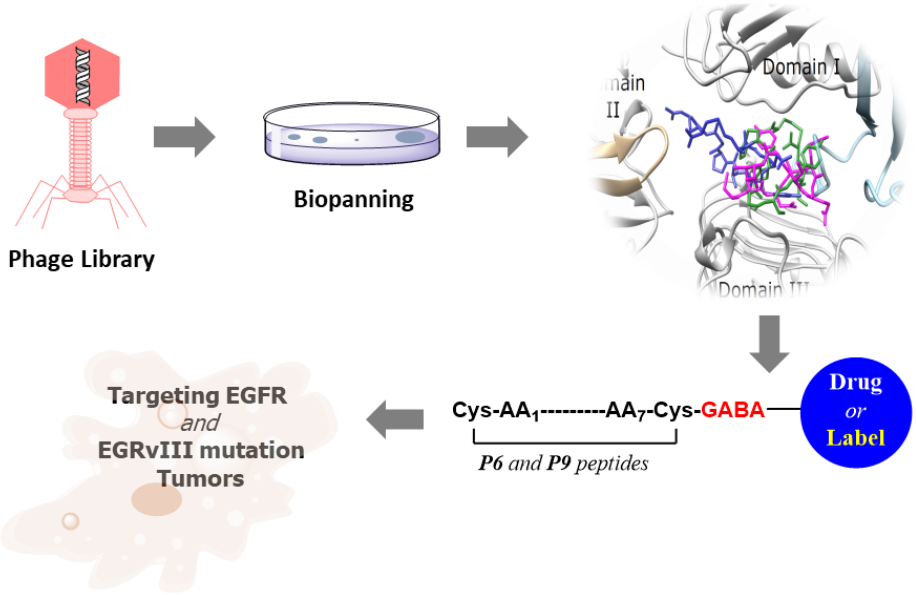
PP 7. DRUG DELIVERY USING NOVEL CYCLIC PEPTIDES THAT TARGET THE EGFR AND EGRVIII MUTATION

Olga Furman [a], Dror Tobi [b], Andrii Bazylevich [a] and Bat Chen R. Lubin [c,d]

Ariel University: [a] Department of Chemical Sciences; [b] Department of Molecular Biology, [c] Department of Chemical Engineering, Biotechnology and Materials; [d] Agriculture and Oenology Department, Eastern Regional R&D Center, Ariel 40700, Israel

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

With selective chemotherapy, the epidermal growth factor–epidermal growth factor receptor (EGF–EGFR) pathway has taken center stage. Most patients experience drug resistance even though they initially respond well to these medications. Thus, novel therapeutic modalities are required. Our goal in this work was to identify a novel short cyclic peptides that are specific to EGFR and may be utilized for targeted drug delivery. The EGFRvIII mutation-expressing cells were among the three EGFR-expressing cells to which phage display peptide technology and biopanning were applied. Next-generation sequencing (NGS) was used to sequence the peptide inserts after extracting DNA from the internalized phage. Confocal microscopy and peptide docking were used to confirm the findings. Two peptides, P6 and P9 displayed high specificity for glioblastoma and non-small cell lung cancer (NSCLC), respectively. Camptothecin (CPT) was chemically coupled to these peptides. When compared to free CPT, the conjugates were more cytotoxic to EGFR+ve cells. According to our findings, a new cyclic peptide can be used to deliver drugs specifically to cells that overexpress the EGFR and EGFRvIII mutation.



References

[1] Furman O et al. (*2022),* Novel cyclic peptides for targeting EGFR and EGRvIII mutation for drug delivery, Pharmaceutics, *14(7), 1505-1523.*

PP 8. SIMULTANEOUS DETERMINATION OF ARIPIPRAZOLE AND ALPRAZOLAM BY LC/MS/MS IN BIOLOGICAL FLUIDS

N. Imnadze, N. Lekishvili, Z. Kikvadze, T. Papashvili

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

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

One of the important and actual problem of study for analytical toxicology, nowadays is the development and optimization of various physical and chemical methods analysis for determination of narcotic and psychotropic drugs in biological material. [1,2]

From the chemical-toxicological direction, two medicinal products: aripiprazole and alprazolam are the objects of such particular interest. The main indication of both is schizophrenia, and they are also prescribed for other psychotic disorders. [3,4]

A number of therapeutic advantages lead to the high frequency of prescribing these drugs by physicians. Despite the periodic monitoring of drug safety data, there are literature data about intoxication and even death from overdose with aripiprazole and alprazolam. [5]

In this regards, aripiprazole and alprazolam are interesting objects of research from the analytical toxicology point of view. Respectively, the main task of our research was to optimization and the development of methods of chemical-toxicological analysis of simultaneous determination aripiprazole and alprazolam.

For faced goal achievement, was studied the several conditions of liquid-liquid and solid-phase extraction from biological material. Based on the conducted studies, we recommend the following optimal solvent combination for aripiprazole and alprazolam liquid-liquid extraction: chloroform-cyclohexane (1:1 (vol/vol)), with ER=91.5% for aripiprazole, and ER=86.7% for alprazolam. Cartridge Octadecyl LC 18 (97.8-100.09%) was effective for separation of these two substances: aripiprazole and alprazolam during solid-phase extraction.

Was studied a method of LC/MS/MS for the qualitative and quantitative determination of aripiprazole and alprazolam in biological fluids, as an individually, as simultaneously, where the retention time of aripiprazole and alprazolam is 1.02 min and 2.00 min, respectively (Fig. 1), and the quantitative analysis of calibration curve (C=20 ng/ml - 60 ng/mL) was linear R2 =0.9957.

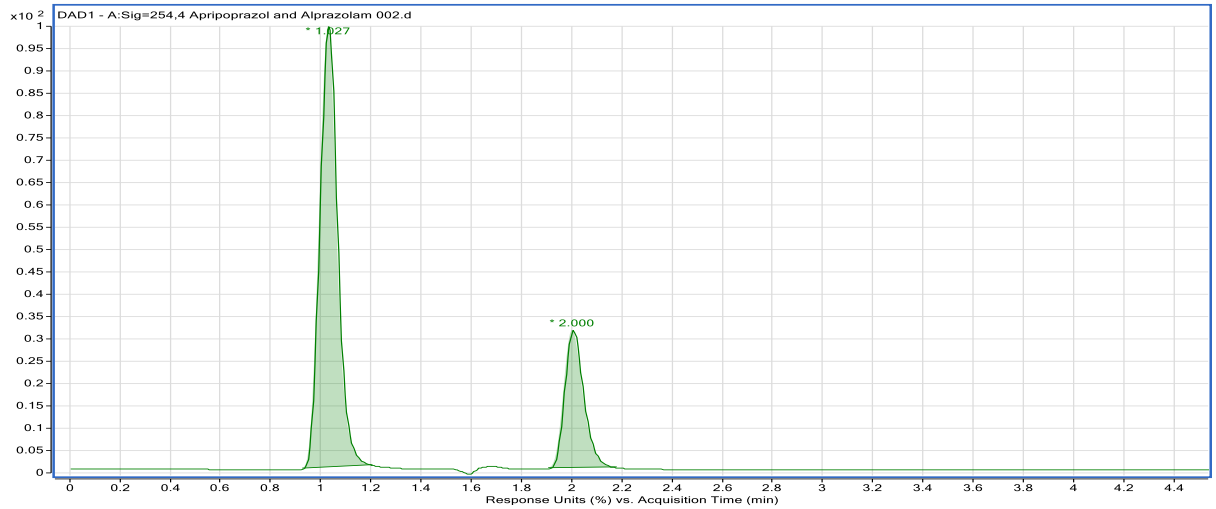


Fig. 1. Aripiprazole and Alprazolam chromatogram of simultaneous determination in biological fluids

Proposed optimized methods of analysis will allow to relevant analytical laboratories, do the determination of individual substances, or the simultaneous determination of aripiprazole and alprazolam in biological fluids.

References

[1] Marszalek D., Goldnik A. , Pawinski T., et al. (2017), Simultaneous Assay of Aripiprazole and its Active Metabolite in Serum By Hplc. *Acta Pol Pharm*. 74(2):405-411.

[2] Huang HC, Liu CH, Lan TH. et al. (2007), Detection and quantification of aripiprazole and its metabolite, dehydroaripiprazole, by gas chromatography-mass spectrometry in blood samples of psychiatric patients. *J Chromatogr B Analyt Technol Biomed Life Sci*. Sep 1;856(1-2):57-61.

[3] Spagnoli C, Rizzi S, Salerno GG et al. (2021), Pharmacological Treatment of Severe Breathing Abnormalities in a Case of HNRNPU Epileptic Encephalopathy. Case Reports. *Mol Syndromol.* 12(2):101-105. doi: 10.1159/000512566.

[4] Argo TR, Carnaham RM, Perry PJ. (2004), Aripiprazole, a novel atypical antipsychotic drug. *Pharmacotherapy* 24:212–228.

[5] Bowles TM, Levin GM. (2003), Aripiprazole: A new atypical antipsychotic drug. *Ann Pharmacother* 37:687–694.

PP 9. FORMULATION, TECHNOLOGY, AND BIOPHARMACEUTICAL EVALUATION OF GINKGO CREAM

Tamar Inashvili

Tbilisi State Medical University Faculty of Pharmacy, Student of the Master's Program in Pharmaceutical and Cosmetic Technologies, , Georgia

Corresponding author e-mail: tamar.inashvili27@gmail.com

In the modern world, the demand for cosmetic products is increasing daily, which is caused by the deterioration of environmental conditions, the impact of polluted air on the skin, as well as various physical or chemical factors, etc. Consequently, there is an increased demand for facial skin care products. It's noteworthy that today, among the cosmetic products used for facial skin care and protection, products containing plant-based biologically active substances are of particular interest due to their broad spectrum of action. Of interest is the dry extract obtained from ginkgo leaves, which is rich in biologically active substances, containing more than 70 types of flavonoids, which provides a wide range of actions, such as antioxidant activity through free radical binding, as well as protecting the skin from environmental stress factors, acting as an anti-inflammatory agent, and also improving skin structure. Among facial skin care products, preference is given to microsponges and cream containing them.

The aim of the research was to determine the formulation of a cream containing ginkgo microsponges and develop its technology. Based on the conducted biopharmaceutical studies, optimal formulations of ginkgo microsponges and their containing cream have been determined, and preparation technologies have been developed. The proposed cream is of the o/w emulsion type.

In terms of quality indicators: homogeneity, pH, colloidal and thermal stability, spreadability and viscosity, the proposed ginkgo cream meets the general requirements of the Pharmacopoeia for semisolid dosage forms. The diffusion profile of the active pharmaceutical ingredient (API) – naringenin, from the ginkgo cream has been studied in vitro using Franz diffusion cells.

The stability of the proposed ginkgo cream has been studied under normal storage conditions. It has been established that the developed formulation maintains optimal quality indicators throughout the entire observation period.

References

[1] Radwa MA. (2020), Drug Delivery from Microsponges: A Review Article. *Rec. Pharm. Biomed. Sci*. 5 (3), 21-27, p. 22.

[2] Jyoti and Kumar Sandeep. (2018), Innovative and novel strategy: Microsponges for topical drug delivery, *Journal of Drug Delivery & Therapeutics.* pg. 29-31

[3] Maqbool MA, Mishra MK, Pathak S. et al. (2017), Semi solid dosage forms manufacturing: tools, critical process parameters, strategies, optimization and recent advances, *Indo American Journal of Pharmaceutical Research*, pg. 883.
[4] Zhao, LJ, Liu W, Xiong S. Het al. (2018), Determination of Total Flavonoids Contents and Antioxidant Activity of *Ginkgo biloba* Leaf by Near-Infrared Reflectance Method. *Int. Journal of Analytical chemistry*, *2018*, 8195784.
[5] Sekar M, Sivalinggam P, Mahmad A. (2017). Formulation and Evaluation of Novel Antiaging Cream Containing Rambutan Fruits Extract. *IJPSR*, Vol. 8(3): 1056-1065.
[6] Ozawa Y, Watanabe Y, Ando D, et al. (2021). Advanced Formulation Design for Topical Creams Assisted with Vibrational Spectroscopic Imaging. *Chemical & pharmaceutical bulletin, 69 3*, 271-277.

PP 10. FORMULATION OPTIMIZATION AND IN VITRO EVALUATION OF BENTONITE-BASED THIXOTROPIC GEL FOR NASAL ADMINISTRATION

A. Janezashvili, L. Tsiklauri

I. Kutateladze Institute of Pharmacochemistry, TSMU, Tbilisi, Georgia,

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

The intranasal route of drug delivery is broadly used for the medication of nasal cavity disorders. An Accurate examination of formulation aspects is critical as neither of its components should irritate the nasal mucosa. In order to prevent irritation, the pH of the formula supposed to be within a range of 4.5 to 6.5; additionally, it leads to attain effective drug absorption and hinder pathogenic bacterial growth in the nasal passage. Moreover, *consistency* of the *composition* has significant influence on *spray* characteristics of the *formulations* and nasal drug *absorption. Higher viscidity* expands the exposure time with nasal mucosa, consequently increasing the time for permeation; but very high viscosity can decrease the drug penetration rate across the mucus layer [1-4].

Citric acid (CA) - a tricarboxylic acid - is extensively used in pharmaceutical formulations as pH adjuster or antioxidant due to its biocompatibility, remarkable physicochemical properties and environmentally friendly chemistry [2,5].

The objective of the present study is to optimize the nasal gel formulation employing Georgian bentonite clay and aqueous extract of *Matricaria chamomilla* L. and investigate the influence of composition on formulation properties.

Different samples were formulated by combining varied proportions of the same ingredients: Tikha – Ascane (TA)- preparation obtained from Georgian bentonite clay from the deposit of Askana (Ozurgeti region) and water extract of aerial parts of *Matricaria chamomilla* L cultivated in Georgia [6,7]. The pH of the formulations was modified by citric acid. After the determination physicochemical properties, viscosity and spray pattern, in vitro release study of chamomile extract (ChE) from different formulations compared to ChE. The analyses were performed *by* high-performance liquid chromatography (*HPLC*) *with* UV detection. Fourier transform infrared spectroscopy (*FTIR*) was used to investigate the structural interactions between TA and ChE in the systems.

Obtained results. The pH for the optimised formulations was found to be within a range of 5.5±0.17-6±0.095, thus mucosal irritation would not be expected since pH values are appropriate for nasal products. All samples have exhibited thixotropic behaviour, with the degree of thixotropy depending on the bentonite concentration and the presence of CA. At room temperature selected samples

exhibited suitable viscosity and rheological properties. In the presence of CA, the viscosity of the samples increased and sustained release of active ingredients was observed (Fig.1). The addition of ChE resulted in the decrease-of viscosity. Small expand in the formulation consistency was detected after 30 days of storage. Correlations between the composition and spraying area were established; presence of CA and increasing the concentration of TA caused decreases in mean spraying area with no change in the ovality (Fig.2). FTIR analysis results confirmed the presence of ChE in the systems. Microscopic examination showed the uniformity of samples. The chromatographic data, obtained from HPLC, *revealed similar qualitative* fingerprint in all *formulations.*

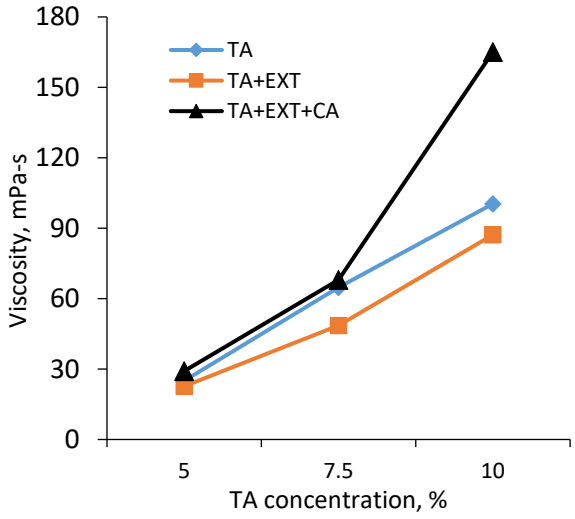


Fig. 1. Influence of composition on viscosities of bentonite based nasal formulations

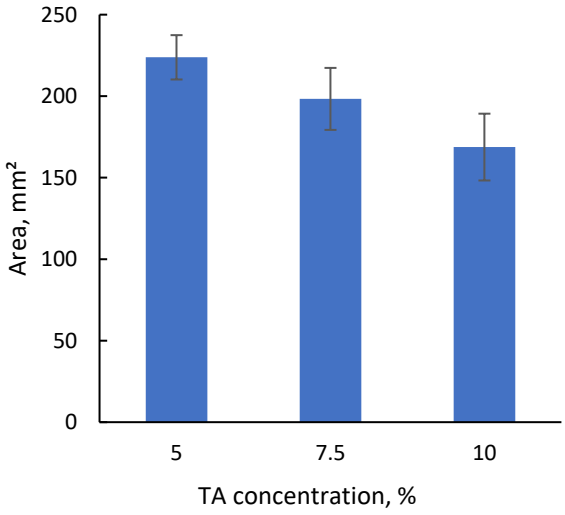


Fig.2. Influence of bentonite concentration on spray pattern area of nasal formulations

In conclusion, the concentration variation of TA and the presence of CA in gel composition employing Georgian bentonite clay and ChE showed an effect on the properties of the nasal formulations in terms of viscosity, thixotropy, spray pattern and release profile.

References

[1] Hariharan A, Tran SD. (2023), Localized Drug Delivery Systems: An Update on Treatment Options for Head and Neck Squamous Cell Carcinomas, Pharmaceutics, 15(7):1844.

[2] Lambros M, Tran TH, Fei Q, Nicolaou M. Citric Acid: A Multifunctional Pharmaceutical Excipient. Pharmaceutics. 2022;14(5):972. Published 2022 Apr 30. doi:10.3390/pharmaceutics14050972.

[3] Atar, Y., Karaketir, S., Aydogdu, I., Sari, H., Bircan, H. S., Uyar, Y., Ekincioglu, E., Karaketir, S. G., Atac, E., & Berkiten, G. (2022), Comparison of Isotonic Seawater Nasal Spray Containing Chamomile Liquid Extract and Other Isotonic Seawater Nasal Washing Solutions for Allergic Rhinitis, The Annals of otology, rhinology, and laryngology, 131(4), pp.427–434.

[4] Sailer MM, Köllmer M, Masson B, et al. (2023), Nasal residence time and rheological properties of a new bentonite-based thixotropic gel emulsion nasal spray - AM-301. Drug Dev Ind Pharm., 49(1), pp.103-114.

[5] Książek E. (2024), "Citric Acid: Properties, Microbial Production, and Applications in Industries" Molecules 29, no. 1: 22

[6] Kutateladze I.G. (1955), Tikha-ascane for medical purpose. "Gruzmedgiz". Tbilisi, 39 p (in Russian).

[7] Tsiklauri L, Tsagareishvili G. (2011), Gastroenterological and dermatological soft drug formulations containing Georgian bentonite clay preparation – Thicha-ascanae. Tbilisi. “Universal”, 89 p (ISBN 978-9941-17-458-2) (in Georgian).

PP 11. STUDY OF SECONDARY METABOLITES OF HIMALAYAN CEDAR (*CEDRUS DEODARA*) INTRODUCED IN GEORGIA

Malkhaz Jokhadze [1], Sopio Gokadze [1,3], Tekla Baratashvili [1] , Anna Bozhadze [1], Lali Zardiashvili

Tbilisi State Medical University [1] Department of Pharmaceutical Botany; [2] Department of Pharmacognosy; [3]Scientific Research and Practical Skills Laboratory

Corresponding author e-mail: s.gokadze@tsmu.edu

The pine family is wealthy with plants which are producing essential oils and secondary metabolites , they and are used in aromatherapy, phytotherapy, and cosmetology. [1]

The aim of our research was to study the secondary metabolites of the species *Cedrus deodara*, cultivated in Georgia, belonging to the pine family and the cedar genus.

Researchers and practitioners extensively utilize the essential oil of Himalayan cedar in medicine, cosmetology, perfumery, and various household applications. [2]

Using modern instrumental methods of research (GC-MS; LC-MS/DAD) it was confirmed that the essential oil of Himalayan cedar (*Cedrus deodara*) cultivated in Georgia contains a diverse array of compounds - 46 individual substances were identified including β-Myrcene, α-Pinene, (+-)-α-terpineol, γ-Cadinene, Geranylgeranyl Alcohol (Fig.1)

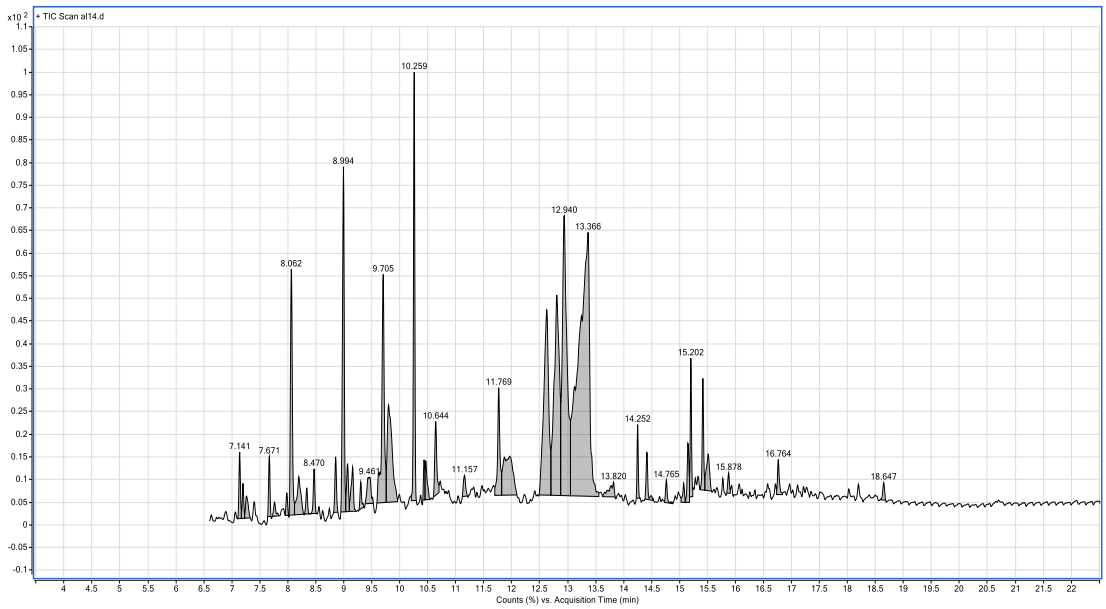


Fig. 2. GC-MS Chromatogram of *Cedrus deodara* essential oil.

Microscopic analysis revealed several diagnostic features characteristic of this species. The epidermal cells of Himalayan cedar are radial in structure. The stomata are found in the depths. The mesophyll, composed of resin storage and wrinkled parenchyma, is located underneath the hypodermis. (Fig. 2)

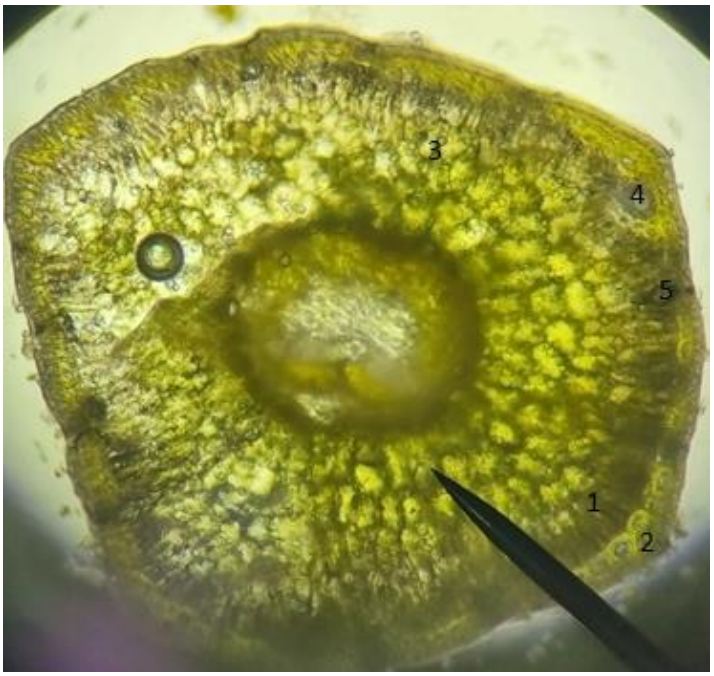


Fig. 1. 1.Hypoderm, 2.Epiderm, 3. Parenchyma 4. Resin canals, 5. Stoma

Antioxidant properties of the essential oil obtained from cedar cultivated in Georgia were assessed by DPPH method.

References

[1] Bisht A., Jain S., Misra A., Dwivedi J., Paliwal S., Sharma S. (2021), *Cedrus deodara* (Roxb. Ex D. Don) G. Don : A Review of Traditional Use, Phytochemichal Composition and Pharmacology.

[2] Pathak H., Pathania S., Metha Sh., Sharma R. (2023), Cedrus Deodara (Roxb.) : A Review on the Recent Update on its Pharmacological and Phytochemical Profile.

PP 12. TOXICOLOGICAL ANALYSIS OF CARBAMAZEPINE IN BIOLOGICAL SAMPLES BY BY LIQUID CHROMATOGRAPHY TANDEM MASS SPECTROMETRY

Koba Sivsivadze[1] , Tamaz Murtazashvili[1] , Tsisia Mchedlidze[2] , Mariam Tatanashvili [1]

Tbilisi State Medical University [1] Department of Pharmaceutical and Toxicological Chemistry; [2] Department of Pharmaceutical Botany

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

Carbamazepine (CBZ) has been originally discovered in 1953 and was first marketed in the UK in 1962 for the treatment of trigeminal neuralgia. This drug is now considered one of the oldest and most common anticonvulsant and moodstabilizing agent, approved for a wide range of diseases such as epilepsy, bipolar disorder, attention deficit hyperactivity disorder, schizophrenia, phantomlimb syndrome, complex regional pain syndrome and others. It is particularly effective in treatment of partial and generalized tonic-clonic seizures, whilst it has lower efficacy in patients with absence or myoclonic seizures [1].

CBZ is metabolized in the liver, primarily by CYP3A4, to the pharmacologically active metabolite carbamazepine-10,11-epoxide, which is further degraded to carbamazepine-10,11-dihydroxide [2].

The aim of our research was to optimize the methods of toxicological analysis of carbamazepine in biological samples. Research objects were postmortem bloods and urines. To achieve the goal, we set the following tasks: Optimization of isolation of CBZ from biological objects, choosing the parameters for sample preparation and development of conditions for liquid chromatographic mass-spectrometric (LC-MS/MS) methods for CBZ analysis in biological samples.

Methods: LC–MS/MS with electrospray ionization (ESI) was conducted on an Agilent 1290 LC system containing a microdegasser and high-performance autosampler, which was connected to a 6460 Triple Quad LC/MS tandem MS instrument (Agilent). The used column was a Zorbax Eclipse, stationary phase - C18 (100 x 3.2 mm, 3.8 µm) and the column temperature was set at 30°C. The mobile phases consisting of 0.1 % water solution of formic acid (A) and 0.1 % acetonitrile solution of formic acid (B) with gradient elution. The LC conditions were as follows: injection volume, 5 µl; flow rate 0.8 ml/min; elution mode, gradient with (A) and (B) from 90 % A/10 % B to 90 % B over. The total run time was 4.2min. The ionisation mode was Electrospray positive (ES+). Instrument parameters were optimized to achieve the best sensitivity and were set as follows: drying gas temperature 275 °C, drying gas flow 5 L/min, nebulizer pressure 45 PSI (0.31 MPa), sheath gas temperature 320 °C, sheath gas flow 11 L/min, capillary entrance voltage 4000 V, nozzle voltage 1000 V. The dwell time was 25 ms. Quantitation was conducted using the multiple reaction monitoring (MRM) mode using ion transitions, m/z: 267.2→192, 237.2→179 and 237.2→165; fragmentor voltage and collision energy were 100 and 30, 32 and 35 (V). Data acquisition, peak integration, and calculations were performed on an Agilent MassHunter computer workstation.

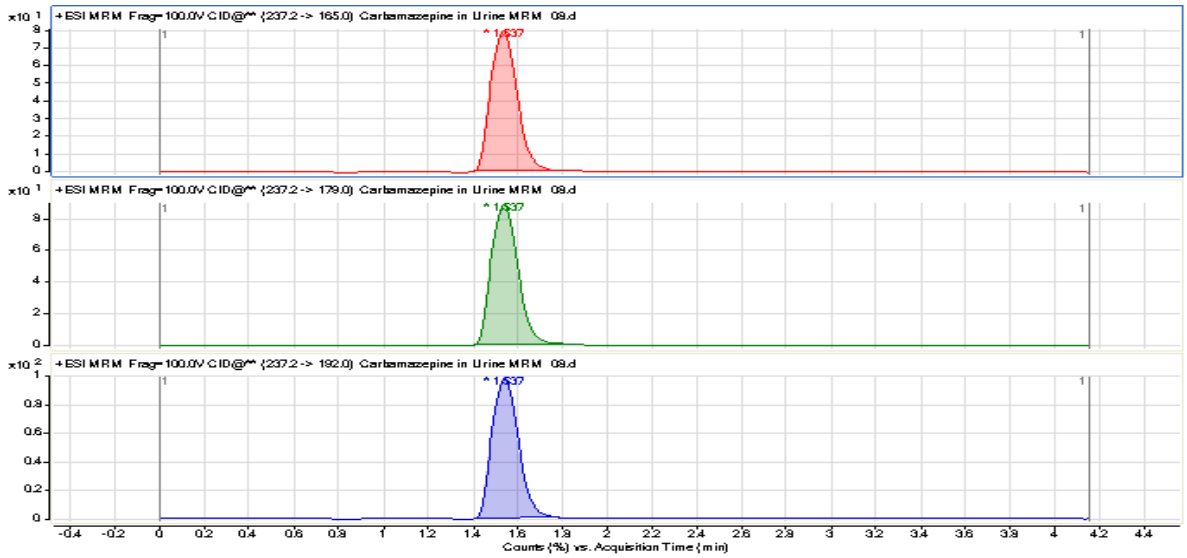


Fig 1. LC-MS/MS chromatogram of carbamazepine in blood

Results: The best extraction of target compounds were achieved by the solvent system with the following composition: ethyl acetate: dichloromethane: heptane: propanol (55:35:7:3).

The Method validation was completed for the following categories: linearity, limit of detection, limit of quantification, accuracy and imprecision, extraction efficiency and matrix effect.

The applied chromatographic method ensured the elution of the target compound within 2 minutes and produced peaks of acceptable symmetry. Selectivity of the method was achieved by a combination of retention time of precursor and 3 product ions. Figure 1 shows the MRM chromatogram obtained after the analysis.

The precisions of the method were 1.3–3.2 % for blood and 1.2– 3.8 % for urine. The accuracies of the method were 98–104 % for blood and 97–104 %for urine. All accuracies and precisions were acceptable. The LODs were 1.5–1.2 ng/mL, and LOQs were 8.4– 6.9 ng/mL for blood and urine. The blank samples used after the investigation of carryover did not show any relevant peaks. The extraction recoveries were in the range of 72-89 % and 80-99 % at three concentrations for blood and urine, respectively.

Conclusions: These methods have high sensitivity and good selectivity, which is suitable for the detection of carbamazepine and its metabolite in blood and urine samples, and can be used for carbamazepine-related routine forensic identifications. The method has been successfully verified using authentic case samples.

References

[1] Tolou-Ghamari Z, Zare M, Habibabadi JM, et al. (2013), A quick review of carbamazepine pharmacokinetics in epilepsy from 1953 to 2012. J Res Med Sci 2013;18:S81-5.

[2] Ferreira et al. (2014), Liquid chromatographic assay based on microextraction by packed sorbent for therapeutic drug monitoring of carbamazepine, lamotrigine, oxcarbazepine, phenobarbital, phenytoin and the active metabolites carbamazepine-10,11-epoxide and licarbazepine. J. Chromatogr. B.

PP 13. NEW DATA ABOUT CHEMICAL COMPOSITION OF FRUITS OF DIGITALIS CILIATA TRAUTV.

E. Kemertelidze[1], V. Nebieridze[1], A. Skhirtladze[2], M. Benidze[1], N. Sakvarelidze[1]

[1]TSMU I.Kutateladze Institute of Pharmacochemistry; [2]I. Javakhishvili Tbilisi State University

Corresponding author e-mail: e.kemertelidze@tsmu.edu

Cardiac glycosides – cardenolides are one of the most important class of biologically active plant metabolites. A special place among them is occupied by the species of the genus Digitalis, which have been successfully used in medicine for more than two centuries. The genus Digitalis includes 36 species, among them *Digitalis ciliata Trautv*. – endemic of the Caucasus is widespread in the mountainous region of the Caucasus 1200 -2000 m height above sea level and creates large natural resources. *D.ciliata* is the rich plant of this genus and contains up to 4% cardenolides, which are the products of genins characteristic for the genus *Digitalis* – digitoxigenin, gitoxigenin, digoxigenin, gitaloxigenin and diginatigenin. The plant is the subject of our long-time research. Preparations made from it – Digicilen in ampoules and Digicil in tablets were successfully used in medicine. *D. ciliata* is considered as a source of digitoxin and acetyldigitoxin. The seeds of the plant represent the industrial raw material of irreplaceable biochemical reagent- digitonin. The method of digitonin production is patented in England, Germany and Switzerland [1].

We continued the study of the plant. The spirostanol, furostanol, pregnane, cardenolide and triterpen glycosides obtained from the fruits were identified. Four of them are new substances:

Substance 1 – furostanol glycoside with chemical structure - (25R)-26-O-β-D-Glcp- 5α-furostan-2α,3β,22α,26-tetraol 3-O – [β-D-Glcp-(1→4)-O-β-D- Galp] [2].

Substance 2 – pregnane glycoside – 12α,20α-epoxy-3β-hydroxy-14β,17α-pregn-5-en-11,15-dion 3-O-[β-D-Glcp(1→4)-O-β-D-Glcp (1→4)-O-β-D-Dgtp]. Diginigenin product glycoside was isolalated from D.ciliata for the first time [2].

Substance 3 – pregnane glycoside with chemical structure – pregnan-3β,14β-diol-15,20-dion 3-O-β-D-Glcp (1→4)-[O-β-D-AcDgtp (1→4)-O-β-D-Dgtp(1→4)-O –β –D –Glcp [3].

Substance 4 – triterpene glycoside of soyasapogenol B with chemical structure – olean- 12 -en, 3β,22β,24 triol 3-O-α-L-Rhap (1→4) – [O-β- D- Xylp(1→2)]-O-β-D- Galp(1→2)-O-β-D-Glcp, named as digitoside D [3].

The structures of the substances were established using one- and two- dimensional NMR (^{1}H, ^{13}C, HSQC, HMBC and COSY) and mass-spectroscopy (ESI/MS).

Steroidal glycosides obtained from the seeds of *Digitalis ciliata* show an antiproliferative effect against MCF-7, HT-29 and A 549 cancer cells. The obtained results reflect the perspective of their possible use in medicine [2].

References:

[1] Kemertelidze EP., (1977), Chemical investigation of *Digitalis ciliata*. Tbilisi, "Mecniereba", (in Russian) 171p;

[2] Perrone A., Capasso A., Festa M., et al. (2012), Antiproliferative steroidal glycosides from *Digitalis ciliata*. *Fitoterapia*, v.83, p.554-562;

[3] Nebieridze V., Skhirtladze A., Benidze M. et al. (2023), C_{21} and triterpene glycosides from pericarp of Digitalis ciliata. *Chemistry of Natural Compounds*, v. 59, N 2, p.309-313.

PP 14. ALKALOIDS OF AERIAL PARTS OF *CONSOLIDA ORIENTALIS*, COMMON IN GEORGIA

L.G. Kintsurashvili

Tbilisi State Medical University Iovel Kutateladze Institute of Pharmacochemistry, Tbilisi, Georgia

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

For centuries, species of the genus Consolida (fam. *Helleboraceae*) have been extensively utilized for their extremely high ornamental and medicinal values. Phytochemical investigations of Consolida species have revealed the presence of multiple active ingredients, including diterpenoid alkaloids. These chemical constituents are of great research significance due to their novel structures and broad biological activities. The genus Consolida is composed of approximately 50 species. Consolida plants are mainly distributed in drought regions in southern Europe, northern Africa, and western Asia [1]. By four species of Consolida are represented in the flora of Georgia [2]. In Turkey, China, and some other countries and regions, especially the Mediterranean and western Asia, various Consolida species have been extensively employed as herbal medicines for hundreds of years to treat multiple kinds of diseases, such as traumatic injury, rheumatism, sciatica, enteritis, stomach ache, ringworm, scabies and other skin diseases. In addition, Consolida plants can also be used externally against body lice [3,4]. According to literature data, 126 alkaloids (C-18, C-19 and C-20) have been identified from the Consolida genus, where the C-19 type base of lycaconitine can be considered a characteristic and representative compound of the Consolida genus [5]. In order to obtain pharmacologically active alkaloids, it was advisable to search for new sources among the Consolida species distributed in Georgia.

The aim of the research was to study the aerial organs of *Consolida orientalis* (J. Gay) Schrödinger, common in Georgia, for the content of alkaloids. *C. orientalis* in flowering phase was collected in Vashlijvari area (Georgia).

We have obtained alkaloid sums by two methods: I- classical method (air-dried aerial parts of *C. orientalis* were alkalized with a 5% sodium carbonate solution and extracted with chloroform), II - extraction with soluent system: methanol-acetic acid-water (70:3:27) (the acidic -water extract was alkalinized with sodium carbonate to pH 9 under cooling condition and the alkaloids were extracted with chloroform). After dehydration with anhydrous sodium sulfate, the tertiary sum of diterpene alkaloids were dried using a rotary evaporator. The yield of the sum of alkaloids obtained from the first method was 0.38%, and by the second method was 0,42%. To obtain individual bases from the sums we have used: different solubility of alkaloids in organic solvents, the method of obtaining salts, division according to basicity. Phytochemical study of above-mentioned plant was performed with GC/MS and TLC analysis to determine qualitatively and quantitatively content. TLC conditions: Silicagel 254, Merck; Mobile phases: I-II - chloroform-methanol (6:1; 4:1); detection –Dragendorff reagent. In comparison with reference standards, it was determined, that identified compounds were diterpene alkaloids [5].

It was found that the sums of bases obtained by two methods are identical in terms of the qualitative composition of alkaloids and contain diterpene bases: delcozine, gigactonine, lycoctonine. In sum I (classical method), delcozine dominates, and in sum II (extraction with soluent system: methanol-acetic acid-water (70:3:27) lycoctonine dominates.

According to the results of the study: the alkaloid content of *C. orientalis* (J. Gay) Schrödinger, common in Georgia, was studied for the first time. The diterpene base delcozine was dominant in the sum obtained from aerial parts of *C. orientalis*, using the first method, while lycoctonine- was dominant in the sum obtained by the second method.

References:

[1] Hajdú, P. Forgo. Löffler B, Hohmann J.(2005), Diterpene and norditerpene alkaloids from Consolida orientalis, *Biochemical Systematics and Ecology*. Vol.33, Issue 10, pp. 1081-1085

[2] Gagnidze R. (2005),Vascular plants of Georgia a nomenclatural checklist. Tbilisi.: *"Universal"*, pp.33-34

[3] Xu TF, Liu S, Meng LL et al.. (2016), Bioactive heterocyclic alkaloids with diterpene structure isolated from traditional Chinese medicines, *J. Chromatogr. B*., vol. 1026, pp. 56–66.

[4] Meriçli LF, Fi, Meriçli AH,, Ulubelen A et al. (2001), Norditerpenoid and Diterpenoid Alkaloids from Turkish Consolida orientalis, *J. Nat. Prod*. Vol.64, no 6, pp. 787–789

[5] Liu F, Yang C.H, Liang J.Y, Liu J.H. (2012), Advances in the studies on the pharmacologicalactivities and toxicities of C19 diterpenoid alkaloids, *Strait Pharm. J.*vol.24, pp. 1–5.

PP 15. STUDY OF ALKALOIDS CONTAINING FRACTIONS ISOLATED FROM *DELPHINIUM FLEXUOSUM* BIEB., *PEGANUM HARMALA* L. AND *MAHONIA JAPONICA* (THUNB.) DC.

Lali Kintsurashvili, Tamar Suladze, Nino Kachlishvili, Nina Vachnadze.

TSMU, I. Kutateladze Institute of Pharmacochemistry;

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

Among the biologically active compounds, alkaloids play an essential role; they demonstrate a broad spectrum of pharmacological activities and are characterized by their cytotoxic, anti-inflammatory, sedative, antioxidant, and anti-arrhythmic activities.

The purpose of our research was to study the alkaloid content in plants distributed and introduced in the territory of Georgia and to evaluate their pharmacological activity [1–4].

Delphinium flexuosum Bieb., *Peganum harmala* L. and *Mahonia japonica* (Thunb.)DC. were selected for the study.

The chemical substances of alkaloids were obtained from the aerial parts of plants by liquid-liquid extraction. Air-dried powdered material was submitted to pre-extraction by hexane for degreasing. The raw materials were then dried and extracted with ethyl alcohol. Alcohol extracts of alkaloids were combined, concentrated on a vacuum evaporator, treated with a 10% H_2SO_4 solution, acidified with a 25% ammonia solution and alkaloids extracted with chloroform. The combined chloroform extracts were washed with distilled water, dehydrated with anhydrous sodium sulfate, filtered and the resulting filtrate was subjected to concentration in a vacuum evaporator to produce a dry residue.

As a result, the total alkaloid substances were obtained, and their phytochemical, antioxidant and anti-inflammatory activities were studied.

Total alkaloid content analysis was conducted using TLC (Silicagel 254 plate. Merck) with a chloroform-methanol solvent system (4:1; 6:1; 9:1) and the detection was facilitated by Dragendorff`s reagent. Additionally, modern instrumental methods such as GC/MS and HPLC/MS were employed, along with appropriate controls. The identified bases were categorized as alkaloids belonging to the diterpenes, chinasoline and isoquinoline groups.

It was established that methyllycaconitine and lycoctonine predominate in the substances isolated from D. flexuosum. Peganine and vasicinone - in the substances isolated from P. harmala The quaternary bases: jatrorrhizine, magnoflorine and berberine - in the substances isolated from M. japonica.

The mentioned substances were evaluated for their antioxidant activity by the ORAC method and the anti-inflammatory effect was measured by the quantitative determination of nitrite.

The total alkaloid substances isolated from D. flexuosum and M. japonica showed moderate antioxidant activity, whereas P. harmala showed weak antioxidant activity. It was found that the total alkaloid substances isolated from D. flexuosum and P. harmala exhibit moderate anti-inflammatory activities, and the substances isolated from M. japonica exhibit weak anti-inflammatory activity.

References

[1] Chen S, Meng L, Fatma M, et al. (2020) Review of Compounds and Pharmacological Effects of Delphinium. *Journal of Chemistry*. doi:10.1155/2020/9375619].

[2] Faridi B, Zello A, Touati D, et al. (2014). Toxicite aigue et activite anti-inflammatoire des grains de Delphinium staphysagria. *Phytotherapie*. no. 12, pp. 175–180.

[3] Vachnadze V, Kintsurashvili l, Vachnadze N et al (2017). Some alkaloid-containing plants grown and introduced in Georgia and their biological activities. *J. EXPERIMENTAL & MEDICINE* no. 3. pp. 31-36.

[4] Rolle J, Asante DO, Kok-Fong LL, et al. (2021), Jatrorrhizine: a review of its pharmacological effects. *J Pharm Pharmacol.* Vol. 73, no. 6, pp. 709-719.

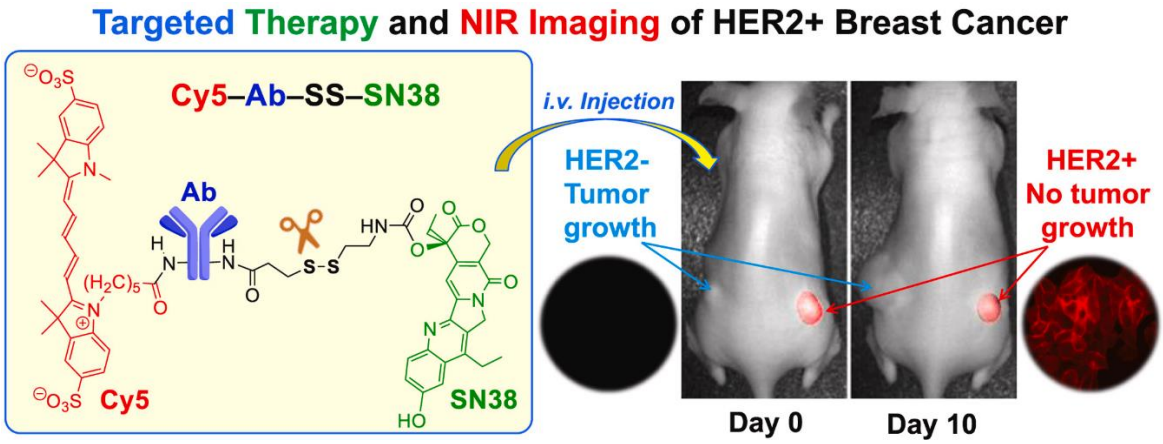
PP 16. THERANOSTIC TRASTUZUMAB–SN38 CONJUGATE SYNTHESIS AND BIOLOGICAL ASSESSMENT FOR NEAR-IR FLUORESCENCE IMAGING AND TARGETED THERAPY OF HER2+ BREAST CANCER

Dmytro Kobzev and Gary Gellerman

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

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

In this work, we describe the synthesis, design, and biological assessment of a novel theranostic antibody drug conjugate (ADC), Cy5-Ab-SS-SN38, comprising SN38, a bioactive metabolite of the anticancer medication irinotecan, and the HER2-specific antibody trastuzumab (Ab) coupled to the near infrared (NIR) pentamethine cyanine dye Cy5. SN38 is attached to an antibody through a glutathione-responsive disulfide carbamate linker. The created ADC showed no effect on HER2- but specific accumulation and nanomolar anti-breast cancer activity on HER2-positive (HER2+) cell lines. According to in vivo studies, trastuzumab alone or in combination with SN38 had significantly lower anticancer potency than the ADC, which demonstrated good targeting ability for HER2+ tumors. The HER2+ tumor showed specific accumulation and reduction in the side-by-side HER2+/HER2-xenograft at a dose of 10 mg/kg, while the HER2-counterpart did not show any accumulation or growth inhibition. As a result of the study's successful implementation of the self-immolative disulfide linker, its application to other antibodies for targeted anticancer therapy has expanded.



References

[1] Kobzev D et al. (2023), Synthesis and biological evaluation of theranostic Trastuzumab–SN38 conjugate for Near-IR fluorescence imaging and targeted therapy of HER2+ breast cancer, *Eur. J. Med. Chem,* 252, 115298.

[2] Su Z et al. (2021), Antibody–drug conjugates: Recent advances in linker chemistry, *Acta Pharmaceutica Sinica B,* 11(12), 3889-3907.

PP 17. DETERMINATION OF OLIGOSACCHARIDES IN "OLIGOPHOS" CONCENTRATE

L. Kunchulia-Gurashvili[1], N. Imnadze[1], D. Kazarov[2], N. Zazashvili[2], N. Chichakua[2]

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

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

The scientific researches of recent years show, the big relevance of the detection of biologically active phyto-compounds in cereal crops for their future pharmacotherapeutic use.

Such a great interest in this domain was caused by a global challenge as the danger of constant emergence of resistant microbes when using chemical-therapeutic drugs. On the other hand, despite the high therapeutic efficiency of synthetic drugs, compared to natural biologically active drugs, they are more toxicity, while phytopreparations in most cases do not show such features. [2,3]

Maize (Zea Mays), compared to other cereal crops, is distinguished by a wide range of biologically active substances content and higher productivity. Maize is native to Mexico, it is an integral part of the country's biological and cultural heritage. There are 250 types of corn on the entire continent of North America, and only in Mexico 59.[1,4]

Depending on the color of the corn kernels, the following types of corn are known: blue, purple, black, yellow, red, blue and other colors. They are called pigmented corn and are used in industry and especially in food industry for a variety of purposes.[1]

The aim of our research was the identification of oligosaccharides in the "Oligophos" concentrate by the Gas Chromatography - Mass Spectrometry method and the development of the iodometric titration method for determination of their total concentration.

"Oligophos" concentrate (food supplement) - obtained by hydrolysis of corn grains. Its reception technology is patented and is the intellectual property of the Biorational Technology Research Center (BrTRC). "Oligophos" concentrate contains a wide range of biologically active phytocompounds present in corn kernels. The standard of the entrepreneurial entity (MST-201946895-001-2019) was created on it.

Table 1. The results of determining the total concentration of oligosaccharides in "Oligophos" concentrate

№	"Oligophos" concentrate batch #	0.1 M iodine solution (in mL)	total concentration of oligosaccharides		Validation
			in %	in mg/mL	
1	010523-052027	0.9	0.9	9	R^2 =0.9954
2	020523-052027	1.1	1.0	10	
3	030623-060227	1.3	1.28	13	(N ≥0.995)
4	040623-062027	0.9	0.89	9.0	
5	050723-072027	1.1	1.0	1.0	
6	060923-092027	1.4	1.4	14	
					CV=0.2%
					(N ≤ 2%)

During the study had been identified three dominant oligosaccharides were in the "Oligophos" concentrate by gas chromatography - mass spectrometry method of determination. There are 1,4,3,6,-dihydro-α-d-glucopyranose with a retention time- 9.74 min.; β-d-glucopyranose with a retention time -10.38 min and α-d-glucopyranoside (1), 0- α-d-glucopyranosyl(2), β -d-fructofuranosyl (3) with a retention time of 12.0 min.

Had been determined the total concentration of oligosaccharides in the extract of "Oligophos" by the developed method of iodometric titration, on 6 batches of the test samples. The results of the analysis are presented in Tab.1.

Thusly, had been identified three dominant oligosaccharides were in the "Oligophos" concentrate by gas chromatography - mass spectrometry method of determination.

Was also developed an iodometric method for determining the total concentration of oligosaccharides in the "Oligophos" concentrate.

The method is reliable, linear (R^2 *=0,9954*). The proportional dependence of the total concentration of oligosaccharides on the used mL of 0.1 M iodine solution is in the concentration frames of 5 mg/mL - 20 mg/ml (interval value of the total concentration of oligosaccharides).

The coefficient variability *CV*=0.2% (N ≤ 2%) fully meets the requirements of validation.

References

[1] Guzzon, F.; Arandia Rios, L.W.; Caviedes Cepeda, G.M.; Céspedes Polo, M.; Chavez Cabrera, A.; Muriel Figueroa, J.; Medina Hoyos, A.E.; Jara Calvo, T.W.; Molnar, T.L.; Narro León, L.A.; et al. Conservation and Use of Latin American Maize Diversity: Pillar of Nutrition Security and Cultural Heritage of Humanity. Agronomy 2021, 11, 172.

[2] Muteeb G., Rehman M.T., Shahwan M., Aatif M. Origin of Antibiotics and Antibiotic Resistance, and Their Impacts on Drug Development: A Narrative Review. Pharmaceuticals (Basel). 2023 Nov 15;16(11):1615.

[3] Nwozo, Sarah; Effiong, Magdalene; Aja, Patrick; Awuchi, Chinaza. (2023). Antioxidant, phytochemical, and therapeutic properties of medicinal plants: a review. International Journal of 2022;11(6):1579-1582.

[4] Sánchez-Nuño Y.A., Zermeño-Ruiz M., Vázquez-Paulino O.D., Nuño K., Villarruel-López A. Bioactive Compounds from Pigmented Corn (Zea mays L.) and Their Effect on Health. Biomolecules. 2024 Mar 12;14(3):338.

PP 18. ROSEHIP ORAL MUCOADHESIVE FILMS FORMULATION AND TECHNOLOGY

N. Kurdiani[1], N. Tsagareishvili[1], S. Marabian[1], K. Chichua[2]

[1]Tbilisi State Medical University, Department of Pharmaceutical Technology, [2]European University, Faculty of Dentistry

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

One of the most frequent diseases is inflammation in the oral cavity. Among them, stomatitis is the leading cause of inflammation of the mucous membranes. The most efficient form of treatment in this process is local and systemic forms. Oral films are perceived as the most effective and rational forms, it adheres to the mucous membrane, which ensures a much higher pharmacological effect[1,2,3].

Based on theoretical and experimental studies, rosehip oral mucoadhesive films (rosehip oil-2g, acyclovir-1g, sodium KMC-2g, sodium alginate-0.5g, polysorbate-80 – 2g, glycerin-3g, aqueous chamomile extract-up to 100g) and the technology were developed, which has prolonged, antiseptic, antiviral, and anti-inflammatory effects. Additionally, its standardization indicators were also studied: organoleptic characteristics - a film color is yellow, it is homogeneous and does not contain mechanical inclusions and air bubbles; Dimensions - 1±0.021cm ×1cm±0.1cm ×0.146±0.01; pH: 7.2; Adhesion test: the film sticks to the finger when pressed with a (wet) thumb; Bendability test - satisfactory (folding 50 times); Air permeability - 98.987g/m2h; loss in mass - 8.5%; moisture absorption rate-8%; Strength - 28.1±1.26 N/m2 ×105.

The release of the substance is determined using Franz diffusion cells. Quantification of the active substance-acyclovir was done by spectrophotometric method at 255 nm wavelength, full release time – 120mn

References

[1] Ahuja A, Khar RK, Ali J. (1997)Mucoadhesive drug delivery systems, *Drug Development and Industrial Pharmacy,* 23:489–515

[2] Albrecht K, Zirm EJ, Palmberger TF, Schlocker W, Bernkop-Schnurch A. (2006), Preparation of thiomer microparticles and *in vitro* evaluation of parameters influencing their mucoadhesive properties Drug Development and Industrial Pharmacy, 32:1149–57 th

[3] Bruschi, M. L.; Freitas, O. (2005), Oral bioadhesive drug delivery systems. *Drug Development and Industrial Pharmacy*, v.31, n.3, p.293-310.

PP 19. BIOLOGICALLY ACTIVE EXTRACTS FROM THE BUDS OF *POPULUS EUPHRATICA* OLIV. GROWING IN GEORGIA

T. Kvaratskhelia[1], M. Jokhadze[1], J. Kuchukhidze[1], J. Legault[2]

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

Corresponding author e-mail: tkvaratskhelia93@gmail.com

Populus euphratica Oliv. is a species of tree native to Georgia that belongs to the genus *Populus* L.,which contains around 40 species found in Europe and Asia. Species of the genus *Populus* L. are widely used in traditional medicine for their astringent, anti-inflammatory, antirheumatic and antiseptic properties [1-7]. Medications produced from *Populus* species are very extensive, because of a wide range of pharmacological and physiological actions [8]. *Populus* species contain mainly polyphenolic compounds [9-11].

The aim of the study was the assessment of biological activities (cytotoxic, antioxidant, anti-inflammatory) of aqueous and ethanolic extracts from the buds of *Populus euphratica*.

The cytotoxicity of the aforementioned extracts was evaluated *in vitro* on A-549 (lung carcinoma), DLD-1 (intestinal adenocarcinoma), WS1 (human fibroblasts) cell lines and the results (Table 1) show that aqueous extracts possess an activity [12].

Results of the antioxidant and anti-inflammatory activity tests are shown in table 2. As can be observed both extracts exhibit a high antioxidant and anti-inflammatory activity.

Table 1. Cytotoxic activity of the aqueous and ethanolic extracts of the buds of *P. euphratica*

Samples	Resazurine µg/ml			Hoechst µg/ml		
	A-549	DLD-1	WS-1	A-549	DLD-1	WS-1
Aqueous extr.	91 ± 14	103 ± 16	>200	135 ± 43	86 ± 16	>200
EtOH extr.	10,0 ± 0,3	11 ± 1	5 ± 1	17 ± 2	18 ± 2	41 ± 14
Etoposide	3,3 ± 0,2 µM	2,9 ± 0,4 µM	>50 µM	4,4 ± 0,7 µM	2,1 ± 0,5 µM	>50 µM

Table 2. Antioxidant and anti-inflammatory activities of the aqueous and ethanolic extracts of the buds of *P. euphratica*

Samples	Antioxidant Cellular	Anti-inflammatory		ORAC					
	IC_{50} antioxidant µg/ml	IC_{50} anti-inflammatory µg/ml	NO % inhibition µg/ml	µmol Trolox / ml		µmol Trolox / mg		µmol Trolox / µmol	
Aqueous extr.	0,28 ± 0,04	14 ± 4	60% 20 µg/ml	64.79	± 10,78	**4.05**	**± 0,67**		
EtOH extr.	0,117 ± 0,004	2,3 ± 0,2	73% 5 µg/ml	56.63	± 17,57	**3.54**	**± 1,10**		
Trolox	0,018 ± 0,003	L-NAME 250 µM	56 ± 3%	21.79	± 2,78	21.79	± 2,78	**4.36**	**± 0,56**
Quercetin	0,16 ± 0,05	L-NAME 1 mM	81 ± 3%	115.81	± 21,10	115.81	± 21,10	**23.16**	**± 4,22**

References

[1] 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.

[2] 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.

[3] 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.

[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] 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
[6] 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.
[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 20. FORMULATION AND TECHNOLOGY OF DUALLER-G INHALATION LIPOSPHERES

M. Kveselava, L. Bakuridze T. Tchumburidze

Tbilisi State Medical University: Department of pharmaceutical technology, Department of Social and Clinical Pharmacy

Corresponding author e-mail: m.kveselava17@gmail.com

Currently, allergic diseases are considered one of the most common chronic conditions worldwide. In recent years, the incidence of allergic diseases has increased significantly, affecting approximately 20% of the global population. Among the first-line medications for treating allergic diseases are antihistamines, which have several side effects and can lead to the development of resistance with prolonged use, posing a major problem for individuals who use these medications long-term [4]. To reduce side effects and to deliver the drug specifically to the target site, nanoparticles are widely used today. Delivery systems based on nanoparticles offer an alternative and effective approach in the treatment process. Lipospheres are among the most extensively studied nanoparticles, with advantages such as high drug stability, the ability to control particle size, a large capacity for drug loading, controlled release, and non-toxic nature of the carrier, among others [1]. Dualler-G is a combined drug that contains second-generation antihistamine ingredients—Quifenadine and Sequifenadine. The combination of these active pharmaceutical ingredients creates a synergy, resulting in the drug's effect being three times greater than that of the individual components at the same doses. However, when administered orally in tablet form, the drug is adversely affected by both stomach acid and liver enzymes. The drug's bioavailability decreases with oral administration, which reduces its effectiveness [1,5]. Inhalation drug forms have several advantages over oral forms, especially when targeted delivery to a specific area of the respiratory system is required. Inhalation drug forms ensure that the drug bypasses initial metabolism in the liver, preventing the action of gastrointestinal enzymes on the active pharmaceutical ingredient, increasing drug bioavailability, and ultimately leading to improved pharmacological effects [2,3]. Based on literature data and experimental studies, an initial development of 10 formulations of Dualler-G inhalation lipospheres was carried out. Subsequently, two formulations were selected based on scanning electron microscopy. Three additional formulations were prepared based on these, two of which exhibited greater powderiness and flowabillity. Therefore, in the next stage, these two formulations were tested using an Andersen cascade impactor to determine the distribution of particles in the respiratory system. As a result, it was found that the powder was unevenly distributed across different regions of the respiratory system, indicating the need to improve the quality of dispersion.

References:

[1] Kumar A, Jain UK, Patel AI. (2021). Formulation Development and Evaluation of Liposphere of Poor Water Soluble Drug for Hyperlipidemia. *Journal of Drug Delivery and Therapeutics*, 11, 23-30.

[2] Yue L, Zhang X, Zhao C et al. (2023). Inhaled drug delivery: Past, present, and future. *Nano Today*. Vol.52;

[3] Patra M, Swain MP, Patnaik M. (2016). Excipients and its variation in pharmaceutical aerosol formulation: a review. *Innovat International Journal Of Medical & Pharmaceutical Sciences*, 1(1), 4–8

[4] Chen N, Zhang S, Javeed A, et al. (2023), Structures and Anti-Allergic Activities of Natural Products from Marine Organisms. *Marine Drugs.* 21(3):152.

[5] Tchumburidze T, Alavidze N, Chikviladze T et al. (2018), Study of effectiveness of combined antiallergic drug Dualler-G. *Journal of Pharmacy and Pharmacology,* vol.6, 629-632.

PP 21. STUDY OF PHYSICOCHEMICAL CHARACTERISTICS OF A LYOPHILISATE OF PAPAIN LIPOSOMES

D. Lagazidze, M. Orjonikidze, L. Nadirashvili

Tbilisi State Medical University I. Kutateladze Institute of Pharmacochemistry

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

Papain is a sum of enzymes obtained from the latex of immature fruits of Carica papaya, its quality and biological activity are determined by its proteolytic activity. It is used as a medicinal and cosmetic agent, although certain side effects, allergenicity, inactivation in biofluids and other negative factors limit its use. Recent publications confirm that the development of a new, nano-sized, liposomal, less toxic dosage forms of papain is highly relevant. Liposomes are nano-sized vesicles based on phospholipids. They are biocompatible and can protect the encapsulated drug from physiological degradation and at the same time provide selective delivery of the drug, reduce its side effects, therefore increase the maximum tolerated dose and improve the therapeutic effect [1,2].

The aim of the research is to develop a liposomal form of papain and to reduce or remove its irritating effect and allergenicity with the help of liposomal containers. For this purpose, it is necessary to evaluate the quality of the physicochemical indicators of the model samples that are obtained.

The object of research was papain (Nanning Pangbo Biological Engineering Co., Ltd); Auxiliary substances and reagents: soy lecithin (L-α-Lecithin Soybean, Merck, Germany), cholesterol (cholesterol, Sigma), L-cysteine (Merck, Germany), Sephadex-G-50 (Sigma Aldrich), casein (Carl Roth).

Research methods: lipid membrane hydration and ultrasound treatment [3] and the drying of liposomes via lyophilization [4] were used to obtain liposomes. Morphology of liposomes - by electron microscopy, and average diameter and zeta - potential by dynamic light scattering spectroscopy method. The proteolytic activity of native papain was determined on a casein substrate by Anson's method [5]. Separation of incorporated and free papain was performed by gel filtration (Sephadex-G-50).

Results of the study, their interpretation and conclusions: within the framework of the study, a lyophilizate of papain liposomes was obtained based on naturally occurring phospholipids - soy lecithin and cholesterol, and the morphology and size of the vesicles were determined by an electron microscope (X 40,000) using the negative contrast method. Papain liposomes had a spherical shape. The average diameter fell in the range of 50-500 nm, and was 192.6 nm, polydispersity index (PDI) - 0.308, zeta-potential: (-36.3 ± 4.7 mV). Incorporation index of the active component into liposomes - 70-80%. Quantitative evaluation of the proteolytic activity of papain liposomes was carried out using the modified Anson method. In order to increase the accuracy and reliability of liposomal papain enzyme activity determination, a modified method was validated [6]. Validation of the spectrophotometric method included determination of specificity, linearity, accuracy and analytical range. The obtained relative standard deviation was $\Delta X = 0.2769\%$ and the relative error was $\varepsilon = 1.87\%$.

Conclusion: Thus, on the basis of experimental studies, the quality-determining physico-chemical indicators of papain liposomal lyophilisate, which we developed, have been established.

References

[1] Lima CSA, Varca JPRO, Nogueira KM et al. (2020), Semi-Solid Pharmaceutical Formulations for the Delivery of Papain Nanoparticles. *Pharmaceutics*, 12(12):1170; doi:10.3390/pharmaceutics12121170.

[2] Sapkota R, Munt DJ, Kincaid AE, & Dash AK. (2023), Liposomes and transferosomes in the delivery of papain for the treatment of keloids and hypertrophic scars. *PLoS One*, 18(12): e 0290224; doi: 10.1371/journal.pone.0290224.

[3] Gregoriadis G. (2019), Liposome technology; doi:10.1201/9781420005875

[4] Lagazidze D., Orjonikidze M., Tsagareishvili G., Nadirashvili L., Erkomaishvili G. (2020), Development of technologies and formulations of Carica Papaya protease liposomes; *The Ii International Scientific-Practical Internet-Conference Modern Pharmacy – Science And Practice*; Kutaisi,Georgia.

[5] 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.

[6] Validation of analytical procedures: Text and methodology - International Conference on Harmonisation. ICH-Q2" (R1), Geneva, 2005.

PP 22. PHYLOGENETIC DIAGNOSTIC CHARACTERISTICS OF THE MICROSTRUCTURE OF SOME *RUBUS* L. SPECIES SPREAD IN GEORGIA

K. Mchedlidze [1], J. Aneli [1], N. Gergauli [2]

[1] Tbilisi State Medical University, I.Kutateladze Institute of Pharmacochemistry, Department of Pharmacobotany; [2] Tbilisi state medical university, faculty of pharmacy , Tbilisi 0186, Georgia.

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

The qualitative and quantitative study of biologically active substances, as well as systematic, including the use of anatomical methods, made it possible to use, along with official species, many species of the nearby Georgian flora with healing properties. In this regard, researchers are particularly interested in endemic plants of the local flora.

Based on the relevance, the anatomical structure of the above-ground vegetative organs of the *Rubus* endemic species of Georgia - *R. cyri* Juz., the endemic species of the Caucasus - *R. carthalinicus* Juz., and *R. idaeus* L. have been studied. The following uniformity of microstructural features of phylogenetically related species has been established: Above-ground vegetative organs of the species are covered with rosette-based, star-shaped trichomes (Fig. 1-A);

Single-celled, with conical and spherical glandular hairs (Fig. 1-B); In the tissue covering the organs with the axis, encyclocyclic, and in the leaf, the parasitic type of stoma apparatus is differentiated (Fig. 1-C,D); Organs with a species axis are characterized by a transitory bundle system, and the vascular bundle itself is characterized by a vascular-fibrous collateral structure (Fig. 1-F).

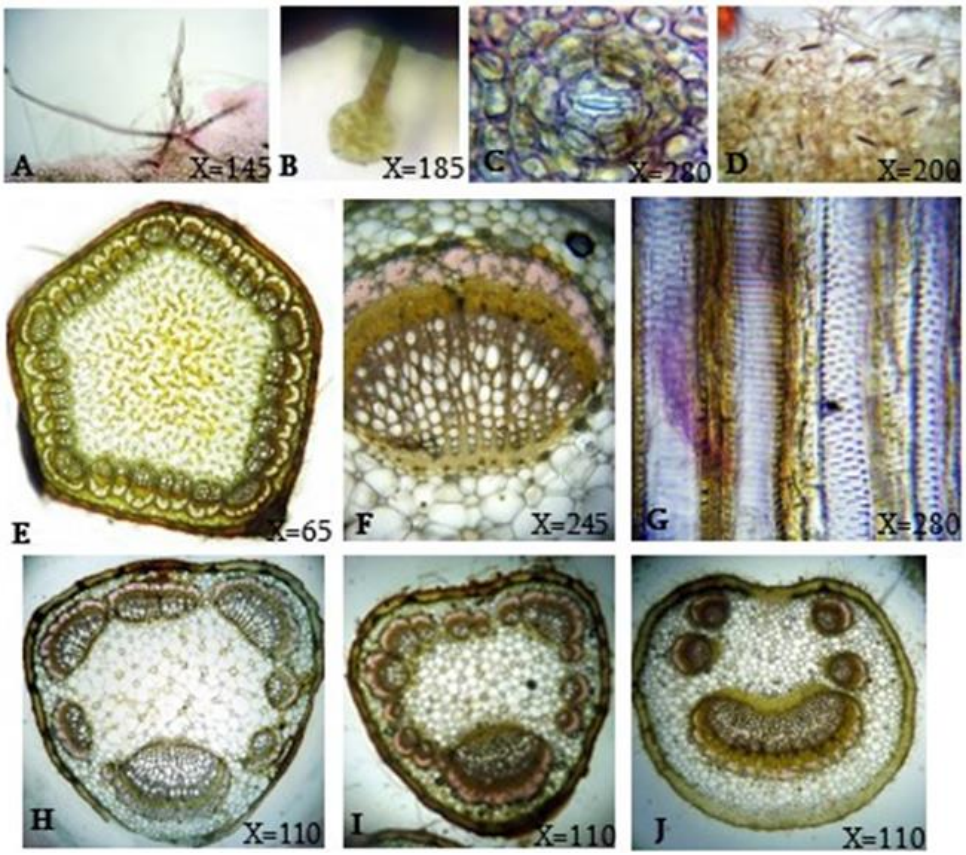


Fig. 1. Phylogenetic diagnostic features of the microstructure of *R. cyri, R. carthalinicus and R. idaeus* species: A. A star-shaped hair with a rosette base; B. Spheroidal glandular hair; C. encyclocyclic and D. parasitic type of stoma; E. Panorama of the geminate, hetero-disjunctive, monocyclic structure of conductive

tissue; F. Collateral vascular bundle; G. view of thickening of the inner membrane of tracheal tissues; H. *R. cyri*, I. *R. carthalinicus* and J.*R. idaeus* Panorama of leaf stalk.

Among the species, the geminate (pair), hetero-disjunctive (non-homogeneous mijrilconoval), monocyclic structure of the interarticular conductive tissue is expressed (Fig. 1-E) [1]. alternately porous and spiral thickening of the inner membrane of tracheal tissues has been detected (Fig. 1-G); Also, easy, indirect perforate of the perforation plate. In the tracheal tissue of the wood of the species, correctly directed, homocellular radial rays are differentiated. The leaf of the studied species has a bifacial shape, hypostomatic, dorsoventral structure, while the spine has an almost uniform structure.

The taxonomic separation of the studied species is conditioned by the consideration of the number and disposition of vascular bundles in the stalk of the mesopetiole zone of the leaf (Fig. 1-H, I, J), as well as by specifying the number of radial rays between the bundles in the epidermis of the shoot and the number of radial rays in the internodes.

References

[1] Aneli NA. (1969), Anatomical structure of the internode as a diagnostic sign. Chemistry and biology of active substances of medicinal plants of Georgia, publ. "Science", pp. 148-167

PP 23. PROTECTIVE EFFECTS OF COLD-PRESSED OIL FROM HAZELNUT (*CORYLUS AVELLANA* L.) GROWING IN GEORGIA.

Karen Mulkijanyan[1] , Natela Gogitidze[1], Nadezhda Mushkiashvili[1], Marine Sulakvelidze[1], Tsisana Sulakvelidze[2]

Tbilisi State Medical University I.Kutateladze Institute of Pharmacochemistry: [1]Department of Preclinical Pharmacological research; [2]Department of Phytochemistry

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

Hazelnut oil, which is derived from the seeds of Corylus avellana L. (family Betulaceae), is becoming more and more popular because of its diverse benefitial effects [1]. Cold-pressed hazelnut oil (CPHO) comprising hydrocarbons, triglycerides, fatty acids, and sterols was obtained from the C. avellana L. using Wartmann WM-1402 OP Electric Oil Press with a yield of 40%. GC qualitative and quantitative analysis of fatty acids revealed the following composition: tetradecanoic acid 0.04%, hexadecanoic acid 7.89%, 9.12 octadecanoic acid 60.44%, 9.12 octadecatrienoic acid 26.7%, and octadecanoic acid 3.13%. carotenoids (4.73 mg%) and vitamin E (16.5 mg%) were also found.

Hepato- and gastroprotective effects of the CPHO were assessed in in-vivo experiments in rodents. All experimental protocols were submitted to and authorized by the TSMU Ethical Committee on Animal Research (Approval #AP-64-2024).

The hepatoprotective effect of CPHO was studied in a CCl_4-induced liver injury model [2] (pentobarbital-induced sleep potentiation). CPHO was administered orally in a volume of 0.2 ml for 3 days. 1 hour after the third administration, and also on the second day, CCl_4 was injected subcutaneously in the same mice at a dose of 1 ml/kg (diluted 1:1 with olive oil). Then we continued to administer the drug for another 7 days (10 oral administrations in total). The control (intact) group received only olive oil, and the negative control animals - only CCl_4, at the same dose. On days 3 and 10 of the trial, the hepatoprotective effect of CPHO was evaluated by pentobarbital sodium (45 mg/kg, i.p.)-induced sleep duration in the background of CCl_4-depressed liver enzyme activity and the number of surviving mice. The lethal effect within 10% was observed in all groups except the control (Table 1).

Table 1. Hepatprotective effects of CPHO in pentobarbital-induced sleep potentiation assay in mice

	Sample/dose				
	Control	CCl_4 (3 d) 1 ml/kg	CCl_4+CPHO (3 d) 1 ml/kg +0.1 ml	CCl_4 (10 d) 1 ml/kg	CCl_4+CPHO (10 d) 1ml/kg +0.1 ml
Mortality (%)	0	10	10	10	10
Sleeping time (min)	9.6	14.9	8.8	21.5	10.6
Effect (%)			115.5		91.2

Gastroprotective effect of the CPHO was assessed using ethanol-induced gastric ulcer model in mice [3]. White mice (22-28 g total 24 animals, 8 per group) were used in the experiment. 24 hours before the start of the experiment, the animals were in deprivation mode (deprived of food, water ad libitum). After 24 hours, experimental group animals were orally given CPHO at a dose of 0.1 or 0.2 ml per animal. Mice of the control group received 0.1 olive oil. After 1 hour, all mice received the ulcerogenic factor - 96% ethanol at a dose of 0.1 ml/20 g. 1 hour after ethanol consumption, animals were killed with ether. Ulcerative disorders were assessed by means of the macroscopic ulcer index (MUI) according to the following scale: no lesion = 0; single point lesions (n<10) = 1; multiple (n≥10) punctate (n≥10) or short (≤4 mm) linear hemorrhagic lesions = 2; Long (>4 mm) linear hemorrhagic lesions = 3; Continuous linear hemorrhagic lesions along the entire length of the glandular part of the stomach = 4. The gastroprotective effect was calculated by the formula: E=(MUIc-MUIe)/(MUIc)*100%, where MUIc and MUIe refer to average MUI in control and experimental group, respectively.

Oral administration of 0.1 ml of CPHO/animal resulted in a 20% gastroprotective effect, which rose to 27% when the dosage was doubled (Fig. 1 a, b).

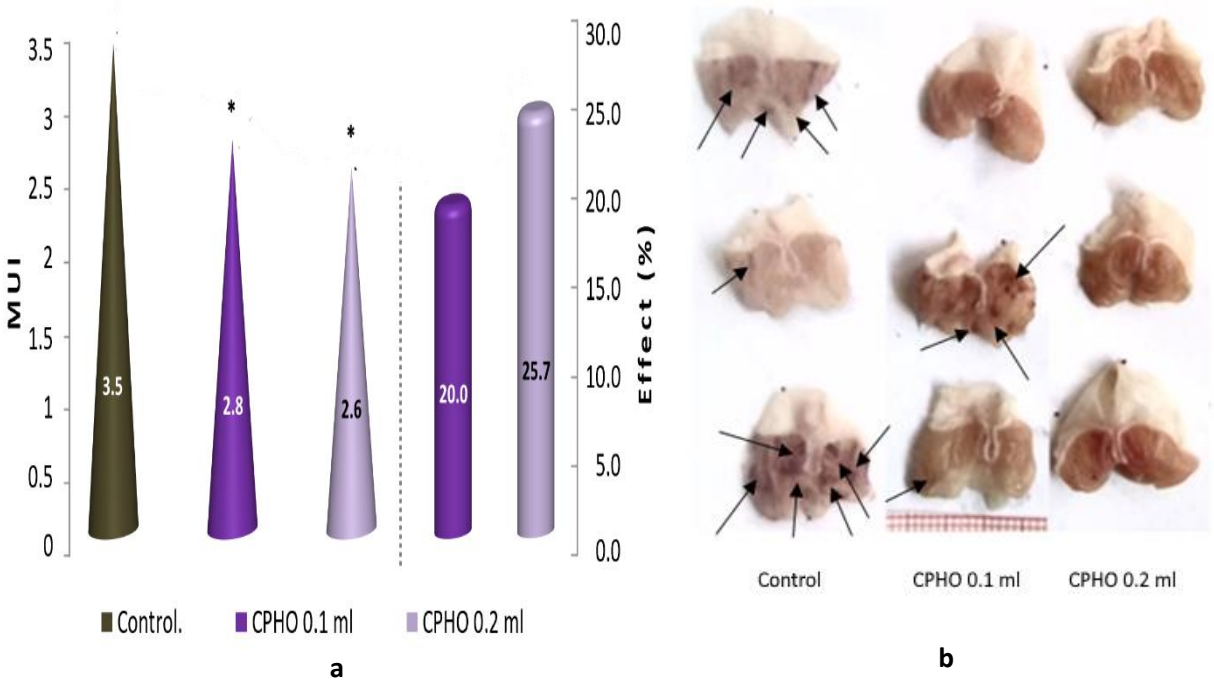


Fig. 1. Gastroprotective action of CPHO. Arrows indicate hyperemic areas. * - p<0.05 vs control

Based on the obtained results, we can conclude that the oil of the hazelnut (*Corylus avellana* L.) fruit has a moderate gastroprotective, but pronounced hepatoprotective activity, dramatically reducing CCl_4-induced liver damage. It is worth noting that the hepatoprotective effect is manifested in case of both weak and strong liver function disorders.

References

[1] Topkafa M, Ayyildiz HF, Kara H. (2019). Hazelnut (*Corylus avellana*) Oil. In: Ramadan M. (eds) Fruit Oils: Chemistry and Functionality. Springer, Cham. https://doi.org/10.1007/978-3-030-12473-1_10

[2] He H, Li X, Yu H, et al. (2019). Gastroprotective effect of araloside A on ethanol- and aspirin-induced gastric ulcer in mice: involvement of H(+)/K(+)-ATPase and mitochondrial-mediated signaling pathway. J. Nat. Med. 73 (2), 339–352. doi:10.1007/s11418-018-1256-0

[3] Kim JW, Kim CS, Hu Z. et al. (2012). Enhancement of pentobarbital-induced sleep by apigenin through chloride ion channel activation. Arch. Pharm. Res. 35, 367–373 (2012). https://doi.org/10.1007/s12272-012-0218-4.

PP 24. INFLUENCE OF CURCUMINE, QUERCETIN AND MENTHOL ON THE PROTEOLYTIC ACTIVITY OF PAPAIN

L.Nadirashvili , N.Chaganava

Tbilisi State Medical University I. Kutateladze Institute of Pharmacochemistry

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

The aim of the study described here, was investigation of the influence of three active compounds, namely quercetin, curcumin, and menthol, on the proteolytic activity of papain. These compounds have been shown to have potential wound healing properties due to their anti-inflammatory, antioxidant, and anti-coagulant effects. Polyphenolic compounds, such as quercetin, and curcumin possess potent anti-inflammatory and antioxidant properties, which are important for efficient wound healing [1-3]. Menthol has been found to promote skin wound healing by modulating the antioxidant system and inflammatory response, as well as stimulating epithelialization [4].

Papain enzymes are commonly used in wound care for debridement, the initial step in the repair of chronic wounds. To enhance the action of papain, it is often combined with other active agents. Papain enzymes demonstrate strong anti-inflammatory activity, which works in conjunction with vitamins A, C, and E to inhibit inflammation [5].

In the present study, the proteolytic activities of papain mixtures with curcumin, quercetin, and menthol of different mass ratios varied from 1:0.5 to 1:3 were determined using Anson's method, based on the incubation of the enzyme under strictly defined conditions with the casein substrate and spectrophotometric evaluation of the equivalent amount of tyrosine released as a result of proteolytic activity [6].

Among the tested ratios, the highest percentage of proteolytic activity 113.5%, was observed in the papain:curcumin ratio of 1:1.5. These results suggest that curcumin may have a positive influence on papain's proteolytic activity and could be a potential candidate for inclusion in natural wound debridement formulations containing papain.

References:

[1] Irfan F, Jameel F, Khan I, Aslam R, Faisi S, Salim A, (2022), "Role of quercetin and rutin in enhancing the therapeutic potential of mesenchymal stem cells for cold induced burn wounds." Regenerative Therapy, vol. 21, pp. 225-238.

[2] Kant V, Gopal A, Pathak NN, Kumar P, Tandan SK, Kumar D, (2014), "Antioxidant and anti-inflammatory potential of curcumin accelerated the cutaneous wound healing in streptozotocin-induced diabetic rats." International Immunology, vol.20, pp. 322-330.

[3] Kumari A, Raina N, Wahi A, Goh KW, Sharma P, Nagpal R, Jain A, Ming C, Gupta M, (2022), "Wound-healing effects of curcumin and its nanoformulations: A comprehensive review." Pharmaceutics, vol.14, p. 2288.

[4] Rozza AL, Bessera P, Vierira AJ, Souza EO, Hussni CA, Martines E, Nobrega RH, Pellizini CH, (2021), "The use of menthol in skin wound healing anti-inflammatory potential, antioxidant defense system stimulation and increased epithelialization." *Pharmaceutics,* vol. 13, p.1902.

[5] Wijaia DP, Herlina, Fetri NA, Mardiuanto, Maksusanti, Fernando, (2020), "Preparation, characterization and wound healing activity of papaya lives extracts on spray gel." *Trad. Med. J,* vol. 25(2), pp. 105-109.

[6] 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.

PP 25. Determination of Formulation of Sphagnum rubellum Wilson Sticks and Development of Technology

K. Natobidze [1], N. Kushashvili [1], I. Tsurtsumia [3], I. Matchutadze [2]

[1] Tbilisi State Medical University, Department of Pharmaceutical Technology; [2]Batumi Shota Rustaveli State University, Department of Biology

Corresponding author e-mail: Ketevan.natobidze@gamil.com

The best way to protect the human body from microorganisms is therapeutic or prophylactic antimicrobial agents enriched with components of natural origin [6]. Medicines developed using natural ingredients are safe in action and are characterized by fewer side effects [4, 5].

Kolkheti plain is rich in sphagnum peatlands, where 9 species of sphagnum are common. The use of sphagnum in medicine has a centuries-old history. Sphagnum, also known as peat moss, has been known in folk medicine since the 11 th century. Today, scientists consider sphagnum as a source of many biologically active substances that have pronounced antibacterial, antiviral and antifungal activity [4,5].

Among the medicinal forms sticks have a number of advantages: they act on the skin and mucous membrane at a local place, it is possible to simultaneously include biologically active components of different physical-chemical nature in the base of the stick, the cosmetic stick remains as a thin layer on the skin or mucous membrane for a long time. On the surface, therefore, the pharmacological effect is long-lasting, it is portable to carry, convenient to use, hygiene, economy and long shelf life have been achieved by special packaging . Although there are medicinal stick for various purposes, the assortment of medicinal stick produced by pharmaceutical companies with natural components is quite limited [2,3,6].

Based on the above, the aim of the research was *Sphagnum rubellum* Wilson of the genus *Sphagnum L*. in the peatland of Imnat. - Research of the antibacterial activity of the species, determination of the formulation of sticks containing it, development of technology and assessment of quality indicators.

Thickened extract of *S. rubellum* Wilson. and investigational compositions of sticks with antibacterial activity were studied using physicochemical, biopharmaceutical and technological research methods: [1,6].

It was determined that the methanolic extract of the *S. rubellum* Wilson has a pronounced antibacterial effect against: *Pseudomonas aeruginosa* 2532, *Proteus vulgaris* 8, *Klebsiella pneumonie* 29, *E. coli* 30, *Shigella flexneri, Salmonella typhimurium, Staphylococcus aureus* 106431 - strains;

Based on biopharmaceutical studies, 11 research compositions of antibacterial sticks have been developed, based on the study of quality indicators, the optimal formulation has been identified with the following composition, wt.%: *S.rubellum* Wilson thick extract - 15.0; Paraffin-7.0; Spermaceti-13.0; Emulsion wax-13.0; Vaseline-12.0; Castor oil-30.0; Jojoba oil-8.0; Twin-80-2.0.

The technological scheme and technological process of *S.rubellum* Wilson – sticks with antibacterial action have been developed; The material balance of the technological process was drawn up and the technical and economic indicators were calculated: technological solution Ꞑ=95.8%; Technological expenditure E=4.2%, spending coefficient Ks=1.04.

The quality indicators of *S.rubellum* Wilson-antibacterial sticks have been studied: uniformity, hydrogen indicators, pH; Firmness and plasticity, the ability to apply and cover the skin. Based on the conducted research, the results meet the requirements for antibacterial sticks [1,7].

References

[1] Aleshnikova K. Yu. 2021 .Development of the composition, technology of medicinal stikc containing eucalimine. Thesis. Moscow. 143p

[2] Baki G., Kenneth S. A., .2019. Introduction to Cosmetic Formulation and Technology. University of Toledo, College of Pharmacy and Pharmaceutical Sciences. P. 287, 320;
[3] K. Natobidze, M. Gasanova,..2022. Design, Formulation and Biological Assessment of Antibacterial Medical Sticks. International Scientific-practical Conference „Georgian Scientific Pharmacy and Present“. ISPC-2022 (1-2 October, Tbilisi. Georgia);
[4] Natela Tetemadze, Izolda Matchutadze.2023. Comparative description of Sphagnum austinii and S. Papillosum of the genus Sphagnum species of Kolkheti plain; Georgian Scientists. Vol. 5 Issue 2.172-177;
[5] N. Tetemadze. 2021. Morphological-anatomical study of sphagnum species of Kolkheti percolation peatlands, conservation and wise use. Doctoral thesis, Batumi;
[6] Nesteruk T., Polovko N., Kovalova T., Bevz N., Kukhtenko H. 2021. Development of technolojy and determination of the content of biologically active compounds in the medical stick with extracts of medicinal vegetable raw materials. National University of Pharmacy.
[7] State Pharmacopoeia of the Russian Federation 14th ed. OFS. 1.4.1.0028.18 .Medicinal Sticks. - M., 2018 - V.2.;

PP 26. PHARMACEUTICAL CARE IN A SORE THROAT MANAGEMENT

N. Nemsitsveridze, T. Iamanidze, T. Zarkua, L. Tomadze

Tbilisi StateMedical University, Department of Social and Clinical Pharmacy

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

Overview: Diseases of the upper respiratory tract are one of the most frequent reasons for referral to the pharmacy. Causes of sore throat may vary, but the most common are laryngitis and pharyngitis. Both are different types of inflammation, observed in children, adolescents and adults, especially in the winter months. Most often it's caused by viral or bacterial infections, which can progress acutely or in chronic way. Such patients often go to the pharmacy for the purpose of self-medication or due to a doctor's prescription. In case when patients do not have a doctor's prescription, they need qualified pharmaceutical care.

The aim of the study: The aim of the research paper was to develop a care plan that a clinical pharmacist could use for patients with sore throat, based on the example of a specific patient. A 30-year-old woman consulted a pharmacist for a hoarseness of voice and a dry cough. She is a teacher and often has to strain her voice. Other signs, worth noting, are the change of voice, discomfort, dryness and pain in the throat and the loss of voice. The temperature is normal, thus, according to the pharmacist, the patient's condition looks like acute laryngitis, a farther consultation with a doctor is recommended to clarify the diagnosis. In order to improve current condition, it is possible to use the drug Isla Moos. As part of the care plan, the pharmacist recommends taking warm liquids (hot tea with lemon, warm milk). He also explains to the patient that during this period it is better to avoid smoking cigarettes, avoid consuming drinks that are too hot or too cold, to refrain from straining the voice and trying to put less strain on the vocal cords, spicy and sour food should also be avoided. The pharmacist also warns the patient to immediately consult the doctor in case the condition does not improve within 3 days. As it turned out later, the patient was satisfied with the pharmaceutical service, checked the diagnosis with the doctor, who approved the pharmacist's advice. The doctor farther consulted with the pharmacist and only added one the drug Doritricin.

Results: We believe that the clinical pharmacist plays an important role in the implementation of the pharmaceutical care plan. By being in constant communication and consulting with the doctors, a pharmacist can provide qualified assistance to the patients in the selection of medication and monitoring of their condition.

PP 27. PROBLEMS OF ACHONDROPLASIA IN GEORGIA

N. Nikuradze, G. Kanteladze, N, Dughashvili, N. Kvizhinadze, T. Zarkua

[1]Tbilisi State Medical University, Department Social and Clinical Pharmacy; [2]„Aversi“ pharmacy

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

Background: In 2022-23, the parents of 21 teenagers with achondroplasia, together with their children, requested help for 16 months: designation of achondroplasia in the list of rare diseases, the introduction of the only treatment medicine VOXZOGO (vosoritide) [1], development of treatment schemes, financing of medical services and treatment.

The aim and task of the research was to research of this problem: with the surrounding statistical data, regulatory/normative acts, communication with specialists and parents of patients, and facts available to us. With desk and field studies, cause-and-effect explanations of the obtained results, and correlations of the conclusions.

Any disease with frequency in the population less than 1 per 2,000 inhabitants is considered rare, is life-threatening, and causes limited abilities; It is characterized by a chronic, often severe course and needs multidisciplinary management. 80% of diseases are genetic, or chronic, and 20% are caused by infectious agents, allergens, chemical substances, or radiation [2].

Nowadays, there are about 40 pathologies among "rare diseases" in Georgia. Achondroplasia has been on this list since September 2023. 24 patients are registered. According to international statistics, it occurs in 1 in 15,000 to 40,000 newborns with gene mutations. Visually, they are short, adult men are on average 131 sm, and adult women - 124 cm. They have a medium-sized torso, short arms and legs, a large head with a prominent forehead, and intelligence is generally normal. Other health problems are also often expected: ear infections, and hearing loss with speech impediment. Sleep apnea, spine, and skeletal changes. The legs bend, lordosis and kyphosis. Vertebral deformities cause severe back pain, and hydrocephalus is a rare but serious complication. [2]

Achondroplasia can be diagnosed by ultrasound examination of the embryo. Also, examination of the amniotic fluid of the pregnant woman for the detection of mutation in the FGFR3 gene. Achondroplasia treatment was symptomatic for many years. From 2021, the FDA and the EMA have approved VOXZOGO (vosoritide) in an accelerated manner. According to WHO international studies, in children older than two years who received VOXZOGO, the linear growth rate increased to 6.3-7.8 centimeters, compared to untreated children with achondroplasia of the same age and gender. [3]

According to the latest, 14 rare diseases are financed by the state, including achondroplasia from May 2022. Concentrating certain services and competent medical personnel, their further training, creation of a protocol, implementation with WHO, and adaptation to the existing resources of the country are provided. Agreement with the company "Biomarin" supplying the main medicinal medicine, vozoritide, import/supply of vozoritide, and all other necessary medicines. Iashvili Clinic and Western Georgia Medical Center were selected for treatment. Injections were performed in stages from 4 to 11 patients. (There are a total of 21 teenagers of different ages). Currently, there is significant support for ensuring the quality of health care for children suffering from achondroplasia, both in the world and in our country, and parallel with the annual progress, there are still some challenges, both in the organizational and the medical part. The fact that VOXZOGO-vozoritide is still in the process of pharmacoepidemiological research and the limit of the treatment effect is not fully determined indicates this.

References:

[1] https://www.ema.europa.eu/en/medicines/human/EPAR/voxzogo
[2] https://medlineplus.gov/ency/article/001577.htm
[3] Dauber A, Zhang A, Kanakatti Shankar R et al. (2024), Vosoritide treatment for children with hypochondroplasia: a phase 2 trial. *EClinicalMedicine, 71, 102591.*

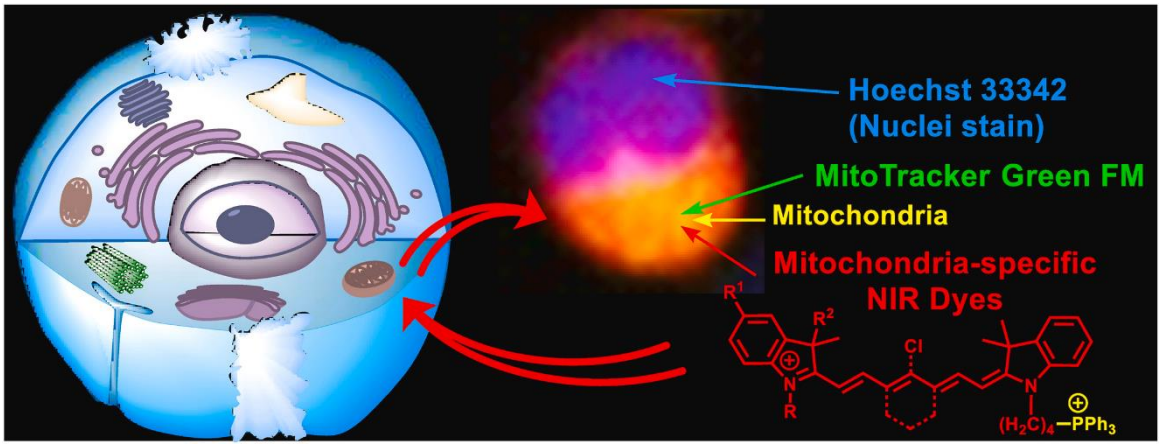
PP 28. DUAL SPECIFIC MITOCHONDRIA TARGETING DRUG DELIVERY SYSTEM

Arpita Panda, and Arjun V. Prakash

Ariel University, Ariel, Israel

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

Targeted drug delivery (TDD) that uses anticancer drug, increases the efficacy and specificity of drug delivery to abnormal cells reducing the off-target toxicity, and thereby improves quality of medical treatment. TDD systems additionally equipped with a permanently fluorescent or turn-on switchable fluorescent dye enable real-time monitoring of drug delivery and drug release, respectively, which is extremely important for controlled cancer treatment. The near infrared (NIR) dyes absorbing and emitting within 650–900 nm spectral region is advantageous for monitoring in the body due to deeper light penetration, reduced photodamage to tissue, and minimal interference with background autofluorescence of biomolecules. Essential and very desirable targets for drug delivery inside the cells are mitochondria, which play a principal role in programmed cell death. In order to target mitochondria, we have synthesized novel fluorescent NIR cyanine dyes incorporating triphenylphosphine (TPP+) group. The specificity of these dyes to mitochondria was evidenced by fluorescence imaging in the example of SKBR3 (HER2 positive) and MDAMB231 (HER2 negative) breast cancer cell lines. Furthermore, recently we have designed new NIR dyes with primary hydroxyl group for anticancer drug (as prodrug) conjugation to study real time monitoring of drug delivery and release. As well to increase dual specificity of the scaffold anion group is attached for antibody conjugation for successful delivery of our prodrug into mitochondria of desired cancer cells.



References

[1] Panda A, Kobzev D, Bazylevich A, Gellerman G, Patsenker L, (2023), Synthesis and evaluation of novel mitochondria-specific near-IR stains based on triphenylphosphonium-heptamethine cyanines, *Dyes and Pigments*, 219, , 111648.

[2] Huang H, Huang D, Li M, et al. (2020), NIR aza-pentamethine dyes as photosensitizers for photodynamic therapy, *Dyes and Pigments*, 177, 108284.

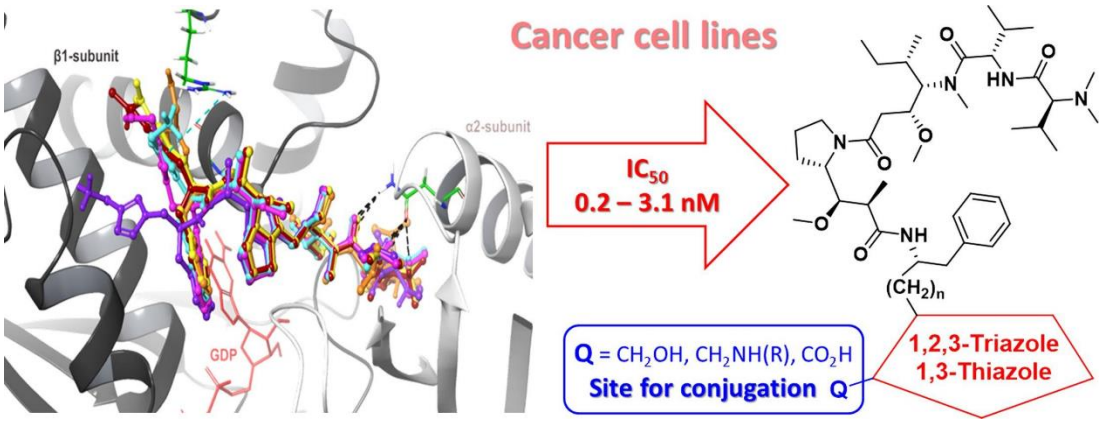
PP 29. NEW DOLASTATIN 10 ANALOGS' SYNTHESIS AND ANTICANCER QUALITIES: FIVE-MEMBERED HETEROCYCLIC RINGS WITH A LINKABLE GROUP AT THE C-TERMINUS

Akash Panja [a], Vipin Sharma [b], Pousali Mitra [a], Chen Drori [a,b]

Ariel University: [a] Department of Chemical Sciences; [b] Department of Chemical Engineering, Ariel 40700, Israel;

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

Dolastatin 10 (Dol-10), a pentapeptide derived naturally from marine sources, is thought to be one of the most effective antimitotic agents discovered to date. However, Dol-10's inability to conjugate chemically limits the viability of using it in targeted medication therapy. This restriction has raised the possibility that the derivatives' conjugation to drug carriers like antibodies could be made possible by the parent molecule's chemical structure. We created and synthesized a number of novel Dol-10 analogs with a modified C-terminus by first using docking studies. DA-1, among the synthesized pentapeptides, showed the highest potency in prostate cancer (PC-3) cells, eliciting apoptosis (IC_{50} 0.2 ± 0.1 nm) and cell cycle arrest at the mitotic stage. These new Dol-10 derivatives, in our opinion, offer a fresh and simple path toward the creation of C-terminus modified Dol-10-based microtubule inhibitors, advancing the field of targeted anticancer therapy.



References

[1] Panja A et al. (2024), Synthesis and anticancer properties of novel dolastatin 10 analogs featuring five-membered heterocyclic rings with a linkable group at the C-terminus, *Dyes and Pigments*, 228, 112232.

[2] Gutman H et al. Discovery of Dolastatinol: A Synthetic Analog of Dolastatin 10 and Low Nanomolar Inhibitor of Tubulin Polymerization, *ACS Med Chem Lett*, 12(10), 2021,1596–1604.

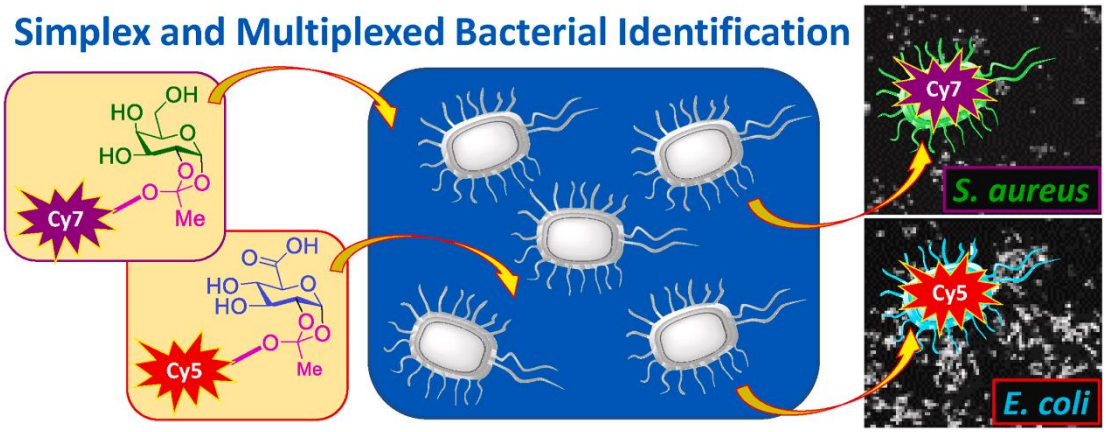
PP 30. CYANINE-SACCHARIDE HYBRIDS FOR THE DIAGNOSIS OF BACTERIA: MOVING TOWARD MULTIPLEXED ASSAYS

Olga Semenova[a], Dmytro Kobzev[a], Israel Alshanski[b,c] and Leonid Patsenker[a]

[a]Department of Chemical Sciences, Ariel Un., Ariel, Israel, 40700, Israel; [b] The Institute of Chemistry and Center of Nanotechnology, The Hebrew Un. of Jerusalem. Jerusalem, 91904, Israel; [c] BactoByte, Ltd., Jerusalem, Israel

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

A popular method for identifying and detecting bacteria is the fluorescence-based enzymatic assay, which uses an enzyme-specific bacterial substrate stained with a fluorogenic ("off-on") dye. Fluorogenic dyes, however, are restricted to a few classes of organic fluorophores, and among their many shortcomings, these dyes frequently exhibit inadequate brightness. We created new fluorescently labelled bacterial enzyme substrates with the goal of increasing the range of effective tools for enzymatic bacterial identification assays, such as high-throughput multiplexed analyses. In these substrates, the traditional (non-fluorogenic) dyes of the Cy5 and Cy7 series are conjugated to an enzyme-specific saccharide via an orthoester bond for the first time. As demonstrated by the conjugates' ability to produce a robust and consistent fluorescence signal inside target bacteria, such as Escherichia coli, Staphylococcus aureus, and Klebsiella pneumoniae, these conjugates allow for the selective identification of bacteria. The suggested method, which entails labeling enzyme substrates with intensely bright dyes that emit light at different wavelengths, opens the door to the development of fluorescent arrays for multiplexed diagnostics of bacteria.



References

[1] Semenova O et al. (2024), Cyanine-saccharide conjugates for bacterial diagnostics: Towards multiplexed assays, *Dyes and Pigments*, 228, 112232.

[2] Jia Z et al. (2021), Multiplexed detection and differentiation of bacterial enzymes and bacteria by color-encoded sensor hydrogels, *Bioact. Mater*, 6(12), 4286-4300.

PP 31. IMPLEMENTATION OF PHYTOCHEMICALS IN ENDODONTIC PRACTICE

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

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

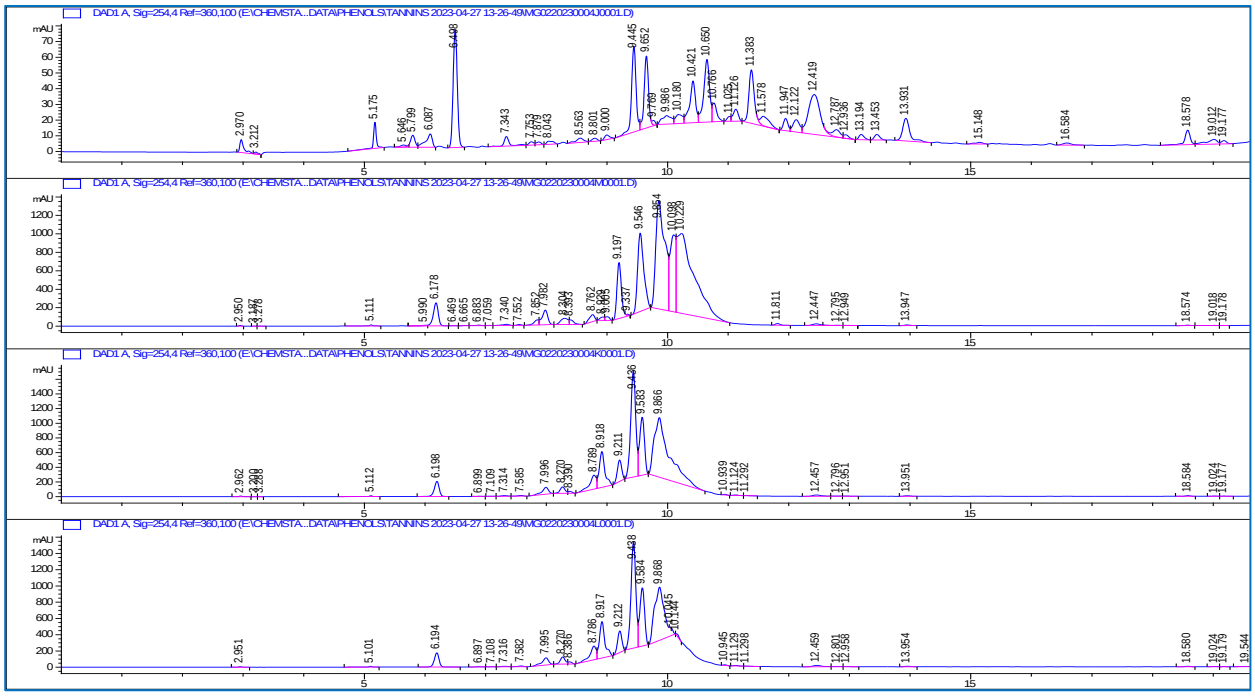
Corresponding author e-mail: Nizharadzenatia@yahoo.com

Endodontics is the most important part of Dentistry. The main goal of endodontic treatment is decontamination of root canal system with chemical substances. Despite the scientific progress and rapid developed on this field, persistent infection is still the main challenge in clinical endodontics. Nowadays the most popular irrigation system, like sodium hypochlorite (NAOCL) is not effective against the most pathogenic microbe - Enterococcus faecalis. For this reason, the issue for searching for alternatives, more effective and biologically compatible substances is still relevant. That's why, we start our research, to find and implement new effective, cheap, non-toxic antimicrobial irrigation solution in endodontic practice. Literature suggests that biologically active compounds, secondary metabolites of plants exhibit wide range of antibacterial and anti-inflammation properties.

From wide range of Georgian Flora the plant *Cotinus coggygria* Scop. (family Anacardiaceae) due to high level of phytochemicals- polyphenol composition is characterized with exceptional biological activity we are interested in. At TSMU Iovel Kutateladze Institute of Pharmacochemistry the chemistry, biology of cultivated in Shirak plant was studied and the rich polyphenolic composition of *C. coggygria* Scop. leaves has been confirmed. Gallic acid, methyl gallate, dimethyl digallane, trimethyl trigallate, tetragalloyl glucose, pentagalloyl glucose, myricetin 3-0-B-D-galactopyranoside, myricetin 3-0-a-rhamnopyranoside were isolated. The presence of high-molecular compounds: hexa-, hepta-, and octagalloyl glucose, pentagalloyl glucose in crude polyphenols is also confirmed.

Exclusively for our study with patented technology the unique formula of purified CCPE (*C.coggygria* polyphenol extracts) was developed at laboratory of Institute. On basis of extract different concentrations of solutions were prepared and sterile endodontic irrigation solution was formulated.

The objective of this research was to evaluate the antimicrobial potential of plant CCPE on resistant strains of endo pathogens. Beside microbiological research for safe and efficient implementation of CCPE in contemporary endodontic practice we have studied novel extract solution in aspects of safety, cytotoxicity, compatibility with other endodontic materials, with respect of "Iatrogenic Esthetic Endodontics". The new revealed cutting-edge information about phytochemicals_ polyphenolic extract is encouraging.



HPLC /UV spectra of CCPE

For now, we are making ex vivo research. In this study we are harvesting pathological microbes from infected endodont of teeth, and study antimicrobial activity of CCPE solutions on identified pathogens.

References:

[1] M. Mamaladze N. Nizharadze T. Shavadze K. Shalashvili. Cultivated in Georgia Cotinus coggygria Scop's Trimli's leaves extract: Study in dentistry. Proceedings of the 1st International Conference on Medicine, Public Health and Biological Science (MPHBS-2016), CASRP Publishing, Tehran, Iran, 18-19 September 2016. Doi:doi.org/10.18869/MPHBS.2016.173

[2] Natia Nizharadze, Marine Mamaladze, Ketevan Shalashvili, Tamar Shavadze. "NOVEL HERBAL PREPARATION AS A PROSPECTIVE ANTIMICROBIAL ENDODONTIC IRRIGANT". Abstract Book ISPC-2022, 2022, Vol.1, NO.1, 86-87. DOI: doi.org/10.52340/gsp

[3] Tamar Shavadze, Natia Nizharadze, Marine Mamaladze "ASSESSMENT OF SMOKE TREE EXTRACT SAFETY FOR ITS FURTHER APPLICATION IN DENTAL PRACTICE", Abstract Book ISPC-2022, 2022, Vol.1, NO.1, 94-95. DOI:10.52340/gsp

[4] Nizharadze N., Shavadze T., Mamaladze M., Shalashvili K. Antimicrobial screening of cotinus coggyggria scop leaves extract for its application in endodontics. Experimental and Clinical Medicine (JECM), 2022, # 8, 9-14. Doi:10.52340/jecm.2022.08.01

[5] Tamar Shavadze, Natia Nizharadze, Marina Mamaladze, Ketevan Shalashvili, Marine Sulakvelidze, Zhana Novikova, Karen Mulkijanyan, Eteri Kemertelidze. Comparative safety study of the phenolic constituents of smokebush (Cotinus coggygria) leaves. Georgian Biomedical New, 2023, Vol. 1, Issue 2, 59-63. ISSN (Online): 2720-8796. DOI:10.52340/GBMN.2023.01.01.14.

PP 32. PHYTOCHEMICAL PROFILES AND MICROSTRUCTURAL FEATURES OF SELECTED PRIMULA L. SPECIES GROWN IN GEORGIA

Nino Sukhishvili[1], Ketevan Mchedlidze[2]

Tbilisi State Medical University I. Kutateladze Institute of Pharmacochemistry : [1]Department of preclinical Pharmacological Research; [2]Department of Pharmacobotany

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

Creating new medicine is a priority in modern healthcare. The world's foremost nations are dedicated to developing new medicinal products derived from plant raw materials that are effective, safe, high-quality, and affordable for patients. Georgia's flora boasts a wealth of diverse medicinal plant materials, offering promising prospects for creating herbal remedies.

There are 22 species of Primula in Georgia, 12 of which are endemic to the Caucasus, and two, *Primula abchasica* and *Primula saguramica,* to Georgia [1-3].

The study aimed to determine phytochemical profile and microstructural features study and determination of microstructural features of selected Primula L. species grown in Georgia: *Primula macrocalyx* Bunge, *Primula woronowii* Losinsk. – endemic of the Caucasus and *Primula saguramica* Gavr.- endemic of Georgia.

Morphological research on experimental samples was carried out using standard laboratory methods adopted in microtechnology. Preliminary investigation of phytochemicals was carried out using thin layer chromatography (TLC). The system $CHCl_3$:CH_3OH:H_2O(26:14:3) was employed for screening secondary metabolites.

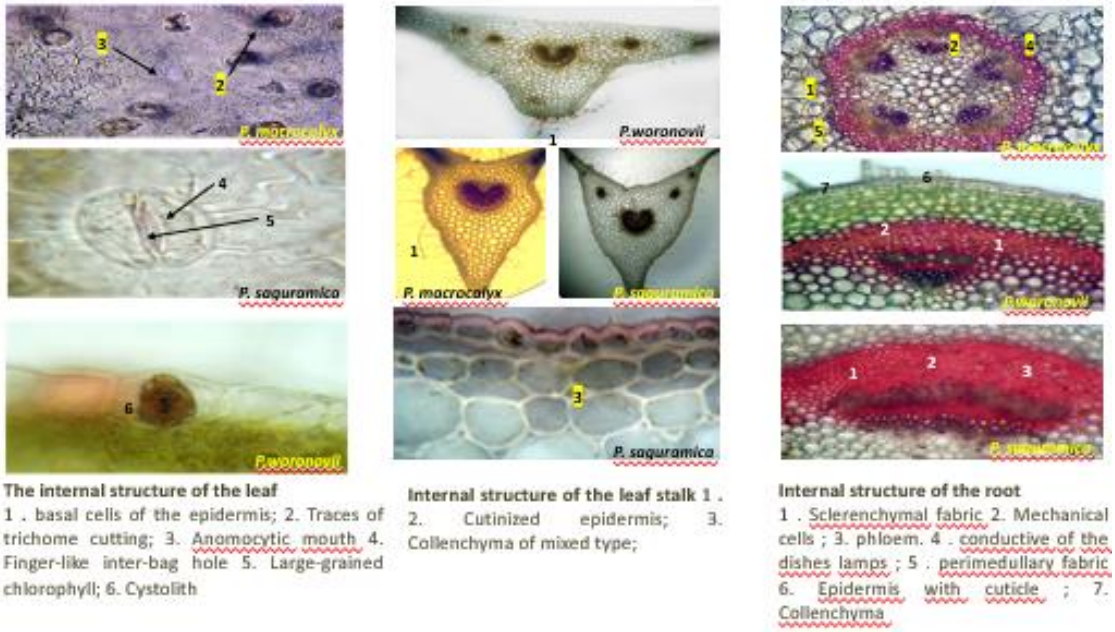
Phytochemical investigation revealed the domination of flavonoids and triterpene glycosides in all studied samples (Tab.1). Rutin served as the reference standard at a concentration of 1 mg/ml, while samples were prepared at 20 mg/ml. Before chromatography, the silica gel plate was conditioned in the chromatography tank for approximately 2 hours.

Table 1. Phytochemical profiles of samples

Plant	Fractions	flavonoids	triterpene saponins	Alkaloids	Tannins	Cardiac glycosides
P. macrocalyx	Lyo	√	√	-	-	-
	H_2O	-	√	-	-	-
	MeOH 50%	√	√	-	-	-
	MeOH 100%	√	√	-	-	-
P. woronovii	Lyo	√	√	-	-	-
	H_2O	-	-	-	-	-
	MeOH 50%	√	√	-	-	-
	MeOH 100%	√	√	-	-	-
P. saguramica	Lyo	√	√	-	-	-
	H_2O	-	-	-	-	-
	MeOH 50%	√	√	-	-	-
	MeOH 100%	√	√	-	-	-

Common and distinguishing features of all three species were identified (Fig.1). The basal cells of the upper and lower epidermis of the leaves of *P. woronowii, P. macrocalyx,* and *P. saguramica* are non-stitched, curvilinear, and curved-walled; also, a chaotically arranged stomata apparatus differentiated into a simple, anomocytic type is typical for all three species, and the presence of a cystolith in the cells of the upper epidermis of *P. woronowii* leaf is observed. In all three species of petiole xylem, there are large, oval-shaped openings surrounded by mechanical-type cells. Small-caliber spaces in *P. woronowii* and *P. saguramica* are arranged longitudinally, while in *P. macrocalyx*, they are arranged asymmetrically with differentiated spherical lumens. Th. e cross-section of the axial organs of the flower is oval or spherical in outline; the flower stem, but not the stalk, is characterized by the

obliteration of medullary cells; *P. saguramica* collenchyma is of a mixed type, while *P. woronowii* and *P. macrocalyx* have lamellar collenchyma. Endodermal cells of *P. saguramica* have clearly expressed Casparian strips, but in the *P. woronowii* and *P. macrocalyx* endoderm, they are less apparent; the central cylinder of *P. woronowii* and *P. macrocalyx* is pentarcular, while *P. saguramica* tends to have a multi-beam xylem structure. In all species, the cells of the central tissue of the crown petals are exceptionally thin-walled, isocytic, and surrounded by dense epidermal tissue; their transitional tissue is incomplete; only the lumens of the conducting vessels of the xylem are visible [4].



The internal structure of the leaf
1 . basal cells of the epidermis; 2. Traces of trichome cutting; 3. Anomocytic mouth 4. Finger-like inter-bag hole 5. Large-grained chlorophyll; 6. Cystolith

Internal structure of the leaf stalk 1 . 2. Cutinized epidermis; 3. Collenchyma of mixed type;

Internal structure of the root
1 . Sclerenchymal fabric 2. Mechanical cells ; 3. phloem. 4 . conductive of the dishes lamps ; 5 . perimedullary fabric 6. Epidermis with cuticle ; 7. Collenchyma

Fig. 1. Microstructural characteristics of the leaf, leaf stalk and root of selected Primula L. species

Conclusion: The results indicate that analyzing microstructural characteristics helps identify both shared and distinctive features among species. Furthermore, the presence of flavonoids and triterpene saponins suggests potential pharmacological benefits, including antioxidant, anti-inflammatory, and cytotoxic effects.

References

[1] Revaz Gagnidze R. (2005) Vascular plants of Georgia a nomenclatural checklist, " Universal" publishing house." p. 121-122.
[2] Flora of Georgia. T. _ X. Publishing House II, " Science," Tbilisi 1985 1985, p. 43-68.
[3] Nomenclature List of flora Georgia, publishing house "Universal" 2018, pp. 215-216.
[4] Microstructural Features of Primula worownoii Losinsk., Primula macrocalyx Bunge. and Primula saguramica Gavr. from Georgian Flora. Nino Sukhishvili, Ketevan Mchedlidze, Karen Mulkijanyan and Lasha Mskhiladze DOI: 10.52340/GBMN.2023.01.01.17

PP 33. PHARMACOGNOSTICAL STUDY OF *PINUS ELDARICA* MEDW. GROWING IN GEORGIA

Mariam Tatanashvili [1], Teona Korkotadze [2], Nino Tskhvediani[3] , Irina Kapetivadze[4] , Nino Gogiashvili

Tbilisi State Medical University: [1] Department of Pharmaceutical and Toxicological Chemistry; [2] *I.*Kutateladze institute of Pharmacochemistry, Direction Of Terpene Compounds; [3] *Department of Physics, Biophysics, Biomechanics and Informational Technologies;* [4] *Department of Physical Rehabilitation Policy and Strategic Management*

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

The Pinaceae family is among the largest conifer families . Various therapeutic properties are known for species from this family. They are valued not only in medicine but also in cosmetology, aromatherapy, and perfumery due to their properties. [1]

Our study aimed to explore the medical uses of the Pinus species growing in Georgia, as both its needles and wood are known for their distinctive chemical compositions and pharmacological actions.

We were capable of to figure out the anatomical structure of Pinus eldarica. Furthermore, a variety of raw material quality indicators were established.

Thirty-three components were identified in the essential oil which was obtained from the pine cones using gas chromatography-mass spectrometry (GC-MS). (Fig.1)

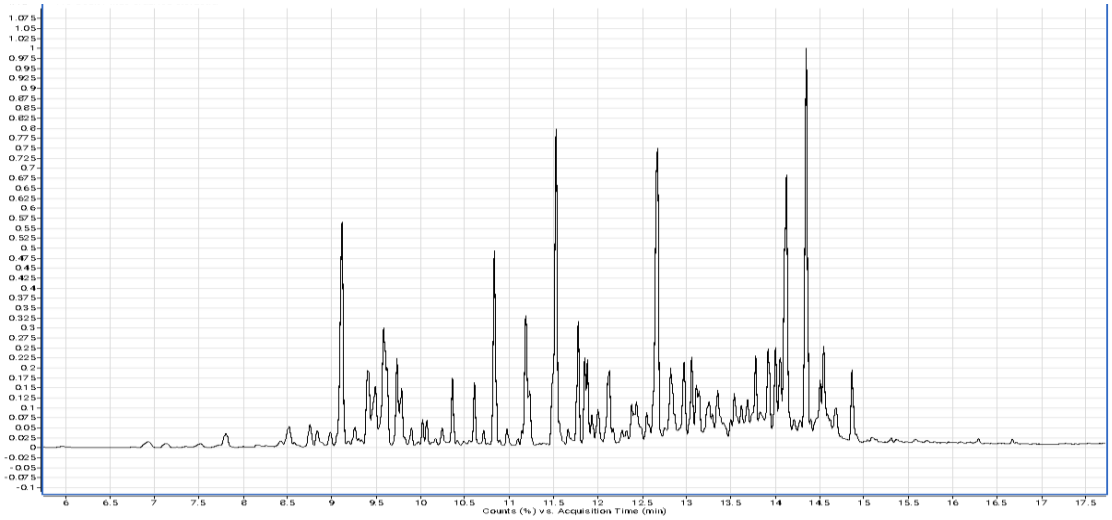


Fig.1. GC-MS of *Pinus eldarica* Medw essential oil.

Additionally, the methanolic extract of Pinus eldarica. needles exhibited moderate antioxidant activity, with an IC50 value of 4.166 mg/ml.

The following quality indicators were found through analysis: total ash 3% and moisture content 5.6%

References

[1] Ali B. Essential oils used in aromatherapy: A systemic review // Asian Pacific Journal of Tropical Biomedicine. 2015. № 8 (5). С. 601–611.

PP 34. DEVELOPMENT OF CLINICAL PHARMACY IN GEORGIA

T. Tchumburidze[1], N. Nemsitsveridze[1], T. Chikviladze[2], L. Tomadze[1], I. Tomadze[1]

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

Corresponding author e-mail:T.tchumburidze@tsmu.edu

This year marks five years since the establishment of clinical pharmacy as a specialty, which allows us to analyze the past period.

The process was not easy, because the main challenges were the lack of tradition, the skeptical attitude of both the medical specialists and the regulators of the education system. Which was natural, as with all new directions and ideas.

Which led to the need to overcome many obstacles, and today we can express our gratitude to all those specialists - pharmacists and doctors, the leadership of the medical university, who supported us on this difficult path.

The first step was to establish a clinical pharmacy course at the Department of Social Pharmacy of TSSU, to create an appropriate program and manuals.

The next important step was the recognition of clinical pharmacy as a specialty by the Ministry of Education, which made it possible to establish a master's program and further accreditation.[1]

As a result of overcoming the past stages, today we have a situation where 50 specialists have completed the master's course in clinical pharmacy, and this number is growing.

In the future, the demand for such specialists will increase from advanced clinics, which creates a good perspective for further rapid development of clinical pharmacy in our country.

References

[1] About the accreditation of the clinical pharmacy master's educational program of the Tbilisi State Medical University. (2017), National Center For Educational Quality Enhancement https://eqe.ge/ka/decisions/7048/show

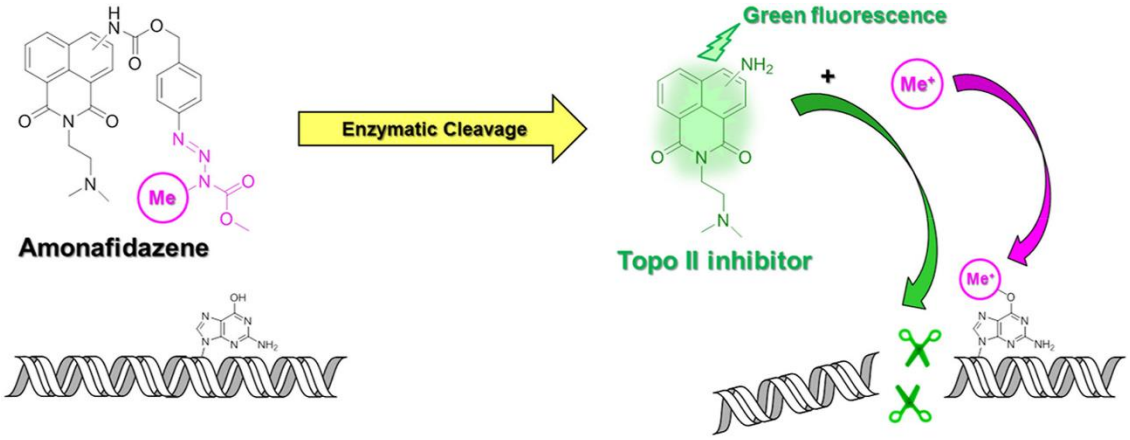
PP 35. THE DUAL-ACTION CHIMERA AMONAFIDAZENE WITH INTERCALATION AND METHYLATION PROPERTIES

Iryna Tkachenko and Dipak Walunj

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

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

A DNA intercalating agent Amonafide interferes with topoisomerase 2 (Topo II) activity and prevents re-ligation of DNA strands, leading to double-strand breaks (DSB). If DSB repair fails, cells stop dividing and eventually die. In a search of approaches to enhance the anti-cancer activities of Topo II inhibitors, we hypothesized that introducing additional damage in proximity to the DSB may suppress DNA repair and enhance cancer cell killing. Chimeric compound containing Amonafide was synthesized and subjected to comprehensive biological evaluation. The presence of the methylating moiety in Amonafidazene enhanced the formation of double-strand DNA breaks (DSBs) and impeded DNA repair processes. Cell viability assays confirmed that Amonafidazene exhibited superior anticancer activity compared to Amonafide. We utilized the fluorescent properties of chimera Amonafidazene to develop a ''photo-switchable'' reporting system to monitor the prodrug activation. We found that the chimera accumulated and was activated at the tumor sites specifically and demonstrated significantly stronger tumor-suppressing activities compared to Amonafide. This study provides a promising strategy for developing chimeric molecules with improved anti-cancer properties, potentially applicable to other topoisomerase inhibitors



References

[1] Walunj D et al. (2021), Targeted methylation facilitates DNA double strand breaks and enhances cancer suppression: A DNA intercalating/methylating dual-action chimera Amonafidazene, *Eur. J. Med. Chem.* 225, 113811.

[2] Gilad Y et al. (2017), Discovery of potent molecular chimera (CM358) to treat human metastatic melanoma, *Eur. J. Med. Chem*. 138, 602-615.

PP 36. FORMULATION, TECHNOLOGY AND BIOPHARMACEUTICAL EVALUATION OF HESPERIDIN CREAM

N. Tsagareishvili[1], A. Bakuridze[1], N. Kurdiani[1], G. Mikaia[1], N. Baliashvili[1]

[1]Tbilisi State Medical University, Department of Pharmaceutical Technology

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

Hesperidin is one of the main bioflavonoids of citrus, which is obtained from the so-called residue of citrus processing: from secondary raw materials - citrus peel. It is characterized by antioxidant, anti-inflammatory, hypolipidemic, vasoprotective and anticarcinogenic affect[1,2,3,4,5,6]. That is why its use as an active ingredient for pharmaceutical and cosmetic products is an actual issue.

The purpose of our research was the development of the hesperidin cream formulation, its technology and biopharmaceutical evaluation of the obtained product.

Based on biopharmaceutical studies, hesperidin cream formulation was proposed with the following composition: Vaseline oil 8.0 g, lanolin 1.5 g, beeswax 2.0 g, stearin 4.0 g, cetyl palmitate 2.0 g, propylene glycol 5.0 g, glycerin 4.0 g, borax 0. 2 g, glyceryl monostearate 3.0 g, hesperidin 0.5 g, citrus flavoring 0.1 g, distilled water for 100 g q.s.

A technological flow char was developed for the hesperidin cream production, and its consists of the following stages: preparation of initial ingredients and materials, preparation of the base (preparation of the oily phase – dissolution of hesperidin and borax, preparation of the waxy phase), mixing, homogenization, standardization, filling, packaging and labeling.

The gravimetric method was used for determination of hesperidin cream's osmotic activity and it was revealed that the developed cream has an average osmotic activity, which can be considered as satisfactory due to the time of its active use.

Also, was determined the quercetin release level from the developed cream, using agar plates by diffusion method and was established that the active substance is released from the prepared hesperidin cream equally, therefore the active ingredientsrelease level is the similar and proceeds dynamically.

The structural-mechanical and rheological characteristics of hesperidin cream were studied. The following product's quality indicators were determined: uniformity, pH, viscosity, colloidal and thermal stability. Base on done study was determined that the proposed cream formulation meets the general requirements for cosmetic creams and can be used as a protective and anti-wrinkle product, to apply on the skin around eyes.

References

[1] Ratz-Lyko A., Arct J., Majewski S., Pytkowska K. (2015), Influence of polyphenols on the physiological processes in the skin. *Phytother. Res,* 29:509–517. doi: 10.1002/ptr.5289.

[2] Chanet A., Milenkovic D., Manach C., et al. (2012), Citrus Flavanones: What Is Their Role in Cardiovascular Protection? *J. Agric. Food Chem*. 60:8809–8822. doi: 10.1021/jf300669s.

[3] Garg A., Garg S., Zaneveld L.J.D., Singla A.K. (2001), Chemistry and pharmacology of the citrus bioflavonoid *Hsd. Phytother. Res.* 15:655–669. doi: 10.1002/ptr.1074.

[4] Heim K.E., Tagliaferro A.R., Bobilya D.J. (2002), Flavonoid antioxidants: Chemistry, metabolism and structure-activity relationships*. J. Nutr. Biochem.* 13:572–584. doi: 10.1016/S0955-2863(02)00208-5.

[5] Roohbakhsh A., Parhiz H., Soltani F., et al. (2014), Molecular mechanisms behind the biological effects of hesperidin and hesperetin for prevention of cancer and cardiovascular diseases. *Life Sci.*, 124:67–74. doi: 10.1016/j.lfs.2014.12.030

[6] Jovanovic S.V., Steenken S., Tosic M., et al. (1994), Flavonoids as antioxidants. *J. Am. Chem. Soc.* 116, 4846–4851. doi: 10.1021/ja00090a032.

PP 37. DITHRANOL AS A CHEMICAL AND BIOLOGICAL MARKER FOR THE QUANTIFICATION OF "PSORANTRONE C"

D. Turabelidze[1], M. Getia[2], Ts. Sulakvelidze[1], M. Malania[1], B. Kikalishvili[1]

Tbilisi State Medical University I. Kutateladze Institute of Pharmacochemistry; [1] Department of Phytochemistry ;[2] Department of Pharmaceutical Analysis and Standartisation,

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

"Psorantron C" is an ointment containing dithranol (1,8-dihydroxy-9-anthrone) and salicylic acid as active ingredients and it stops the uncontrolled division of cells in tissues affected by psoriasis. It is an original medication developed at the TSMU I. Kutateladze Institute of Pharmacochemistry. The main active component of the ointment is dithranol. Dithranol was selected as chemical and biological marker for the development of a method for quantification of the ointment. HPLC separation was performed on an Eclipse plus C-18 column (250mm x 4.6mm, 5µm) with a solvent system of acetonitrile – water (60:40) under isocratic conditions, UV detection was performed at 354 nm. The dependence of the concentration of solutions on the peak area by the provided method. The dependence of the concentration of solutions on the peak area is linear $R^2 = 0.999$. Method Standard Deviation (SD) ≤1% and Relative Standard Deviation (RSD) ≤1.5% [1;2]. The method provided is accurate, sensitive and reproducible; which can be successfully used for the quantification of Psorantrone C ointment [3;4].

References

[1] Nair PA, Badri T. Psoriasis. 2023. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing;
[2] Gamret AC, Price A, Fertig RM, Lev-Tov H, Nichols AJ. (2018), Complementary and Alternative Medicine Therapies for Psoriasis: A Systematic Review. JAMA Dermatol, vol. 154, no. 11, pp.1330-1337.
[3] Benezeder T, Painsi C, Patra V, Dey S, Holcmann M., Lange-Asschenfeldt B, Sibilia M, Wolf P. (2020), Dithranol targets keratinocytes, their crosstalk with neutrophils and inhibits the IL-36 inflammatory loop in psoriasis. ELife vol. 9, pp. 56991
[4] Sulakvelidze Ts., Malania M., Kikalishvili B., Turabelidze D.. (2010), Standardization of anti-psoriasis ointment with keratolytic action. Study of biologically active substances of plant and mineral origin of Georgia, collection of scientific works, vol. 2, pp. 170. (in Georgian).

PP 38. ON THE PROBLEM OF OBTAINING SUNSCREENS.

P. Yavich [1], M. Kakhetelidze [1], B.Kikalishvili [1], M. Puladze [1], L. Mskhiladze [2]

Tbilisi State Medical University: [1]I. Kutateladze University Institute of Pharmacochemistry, [2]Faculty of Pharmacy Direction of Pharmacognosy and Pharmaceutical Botany Department of Pharmacognosy,

**Corresponding author e-mail l.mskhiladze@tsmu.edu*

The spectrum of solar radiation, reaching the Earth,consists of 6.8% ultraviolet (UV), 38.9% visible (VL) and 54.3% near-infrared (IR). UV is divided into UVA (320–380 nm), UVB (280–320 nm) and UVC (100–280 nm). While UVB exposure is primarily limited by the epidermis, UVA penetrates more deeply and can affect the cellular and extracellular structures of the dermis. UVC is the most harmful and is adsorbed by the ozone layer. Skin exposure to UV radiation is the main cause of melanoma, non-melanoma skin cancer, basal cell and plane cell carcinoma. Actinic keratosis, burns , premature aging of the skin and a number of other skin diseases are possible [1]. Exposure to IR radiation causes inflamed erythema with potential transformation into squamous cell carcinoma or Merkel cell carcinoma, thermal burns, urticaria, skin wrinkles [2]. Visible VL radiation can cause erythema, urticaria, hyperpigmentation, photodermatoses [3]. The protective effect of cosmetic sunscreens is based on the creation of sunscreens that have absorption, reflection or scattering effects. Synthetic organic substances, oxybenzone and its analogues, exhibit a protective effect only in the UVA and UVB zones of action, and have a large number of side effects [4]. Therefore, creams, containing natural products of plant, animal and mineral origin with minor side effects are preferred [5-8]. The development of sunscreen compositions was carried out using almond, pumpkin, apricot and hazelnut oils, obtained using technologies developed at the Institute of Pharmacochemistry, in a concentration range of 3-15%. The SPF value of the oils is at an acceptable level for protection against solar radiation in the UVA and UVA region actions. Based on our data, perlite (produced in Georgia) was used to increase the range of protective action, due to which the protection spectrum was increased to 1000 nm. But it, like other mineral components, has a certain photoreactivity, which can reduce the antioxidant effect of the cream [9,10]. Considering the ability of EGCG and other catechins in dry extract from green tea leaves to neutralize radicals, it was used in creams, and its concentration was selected based on these data [9,11].

References:

[1] Neale RE, Lucas RM, Byrne SN et. al., (2023), „The effects of exposure to solar radiation on human health “, *Photochem Photobiol Sci*., pp. 1–37.

[2] Horton L, Brady J, Kincaid C. M, et. al., (2023), “The effects of infrared radiation on the human skin”, *Photodermatology Photoimmunology and Photomedicine*, 39(6), pp.1-7.

[3] Austin E, Geisler AN, Nguyen J et. al., (2021), “Visible Light Part I. Properties and Cutaneous Effects of Visible Light “, J. Am Acad Dermatol, 84(5), pp. 1219–1231.

[4] Ballestín SS, Bartolomé MJ, (2023), “Toxicity of Different Chemical Components in Sun Cream Filters and Their Impact on Human Health: A Review”, *Applied Sciences*, 13(2), p.712.

[5] Yavich PA, Kakhetelidze MB, Kikalishvili BY et. al., (2024), “Concept for creating sunscreen cosmetics. Review. Part 2. Chemical substances used as sunscreens. Features of action of natural organic acids”, Georgian *Scientists*, Vol. 6 Issue 2, pp. 162-176.

[6] Yavich PA, Kakhetelidze MB, Kikalishvili BY, Mskhiladze LV. (2024), „Natural Phenolic Compounds – Protection from Solar Radiation”, *XII International Scientific Conference., The Modern Vector of The Development of Science*. *Philadelphia. USA*, pp.131-132.

[7] Yavich PA, Kakhetelidze MB, Kikalishvili BY, Mskhiladze LV. (2023), “Concept for creating sunscreen cosmetics. Review. Part 1. Influence of solar irradiation spectrum”**,** *Georgian Scientists*, Vol. 5 Issue 4, pp.272-284.

[8] Yavich PA, Kakhetelidze MB, Kikalishvili BY, Mskhiladze LV. (2024), “Concept for creating sunscreen cosmetics. Review. Part 3. Inorganic substances used as sunscreens*”, Materials 1st International Scientific and Practical Conference Proceedings of the 1st International scientific and practical conference, “Industry*

4.0: modern directions of the Pharmaceutical industry" dedicated to the 95 th anniversary of I. M. Pertsev, pp. 66-71.

[9] Lan A, Lui Y, Zuo J, et. al., (2023), "Methodology to Reach Full Spectral Photo-Protection by Selecting the Best Combination of Physical Filters and Antioxidants", *Cosmetics*, 10(1),1.

[10] Churadze LI, Chagelishvili VA, Kakhetelidze MB, et. al., (2021), "Development of sunscreen using mineral and plant resources of Georgia", *Electronic scientific & practical journal «Modern scientific researches and innovations»*, № 11(127), pp.1-11.

[11] Waingeh NC, Mignolet E, Herent M-F, et. al., (2022), "The Catechins Profile of Green Tea Extracts Affects the Antioxidant Activity and Degradation of Catechins in DHA-Rich Oil," *Antioxidants* (Basel), 11(9), 1844.

AUTHORS INDEX


PER TRADITIONES AD FUTURUM
ASYPG