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# XIII International Symposium on the Chemistry of Natural Compounds

## 第十三届天然化合物化学国际研讨会

October 16–19, 2019, Shanghai



**Hosted by:**

**Shanghai Institute of Materia Medica, Chinese Academy of Sciences (SIMM, CAS)**

**Xinjiang Technical Institute of Physics and Chemistry, Chinese Academy of Sciences (XTIPC, CAS)**

**Organized by:**

**Central Asian Drug Discovery and Development Center of Chinese Academy of Sciences (CAM, CAS)**

**Institute of Chemistry of Plant Substances, the Academy of Sciences of Uzbekistan (ICPS, AS RUz)**

**Anadolu University of Turkey (AUT)**

# XIII International Symposium on the Chemistry of Natural Compounds (ISCNC 2019)

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## **Introduction**

“International Symposium on the Chemistry of Natural Compounds”, serving as a platform for the exchange of the latest advances in natural products research, is a regular (biennial) professional symposium for researchers globally engaged in chemistry of natural compounds. “XIII International Symposium on the Chemistry of Natural Compounds” is to be held in October 16-19, 2019 in Shanghai, China. Experts from various countries and regions including Uzbekistan, Turkey, Tajikistan, Kazakhstan, Cyprus and China have been invited to participate in this symposium. With the aim to strengthen the cooperation between China and countries involved in “the Belt and Road”, it will play a positive role in further promotion of resource sharing, complementarity, mutual benefits and common development, as well as in promoting the modernization of medicinal plant resources in China and even Central Asia.

## **Keywords for the symposium**

The Belt and Road / Natural Compounds / Innovative Drugs

## **Topics for the symposium**

New techniques, theories and methods for chemical research of natural compounds

Discovery of biological activities of natural compounds

Synthesis of natural compounds and their derivatives

Study on new process of natural compounds enrichment

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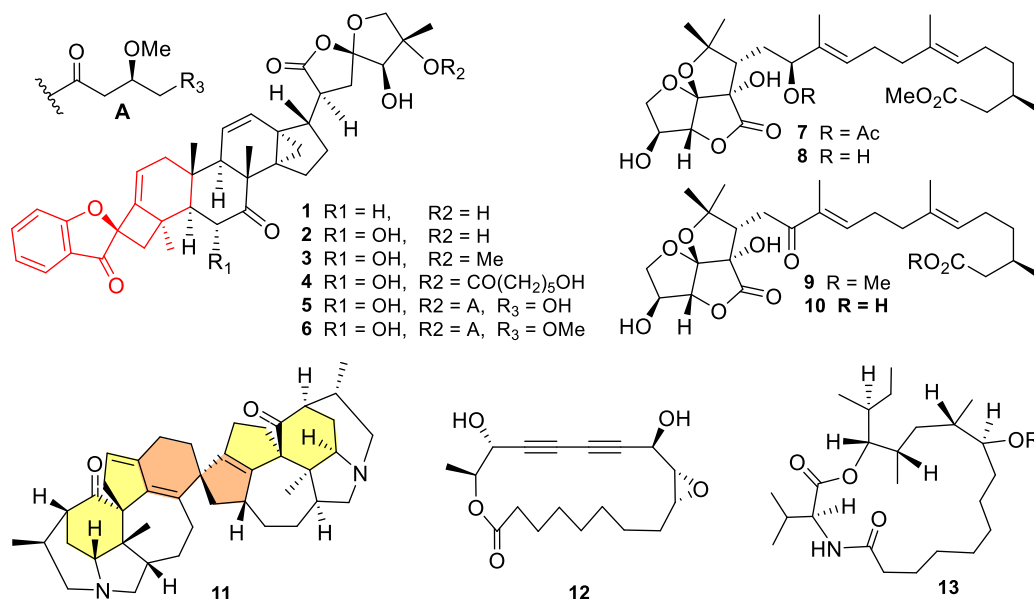
# Plenary Lectures

## DISCOVERY OF STRUCTURALLY AND/OR BIOLOGICALLY SIGNIFICANT COMPOUNDS FROM CHINESE MEDICINAL PLANTS

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Chemical studies on a number of Chinese medicinal plants (including TCM) have led to the discovery of a big array of structurally interesting and/or bioactive components (e. g. **1–13**)<sup>[1-2]</sup>. Bioassays revealed that some compounds exhibited significant biological activities, such as anticancer, immunosuppressive and antimalarial activities. The structure activity relationships of several bioactive compound classes have been studied. Three compounds have been selected as the drug leads and/or candidates for further development. Some interesting compounds have been synthesized.



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## **INNOVATIVE DRUGS RESEARCH BASED ON CHINESE HERBAL MEDICINES**

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Natural Products are an important source of innovative drugs. A lot of important drug molecules, such as morphine, penicillin, aspirin, taxol, artemisinin, etc., were discovered from natural products. From 1981 to 2014, more than one-third of the approved drugs were derived from natural products. To discover lead compounds from traditional Chinese medicine and herbal medicines for drug development, in recent years our group has carried out a systematical investigation on over 200 species of medicinal plants. As a result, a series of natural compounds with diverse structural types have been isolated and identified. A library of natural products from these medicinal plants was constructed, containing more than 8,000 natural products and compositions. Through systematically biological studies, some natural products or their derivatives showed significant antitumor, neuroprotective, and antimicrobial effects. And several active compounds with good pharmaceutical properties had been selected as new drug candidates for further development investigations.

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## ALKALOIDS OF THE RANUNCULACEAE FAMILY PLANTS: CHARACTERISTIC CHEMICAL AND PHARMACUTICAL PROPERTIES OF THE NEW C<sub>20</sub>-DITERPENOID BASES

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A systematic study of Central Asian plants of the *Ranunculaceae* (57 species) and *Asteraceae* (1 species) families led to the isolation of 200 diterpenoid alkaloids, 103 of which were new. C<sub>19</sub>-norditerpenoid bases dominated among the isolates, while C<sub>20</sub>-diterpenoid and C<sub>18</sub>-bisnorditerpenoid bases were less distributed. The new C<sub>20</sub>-diterpenoid alkaloids included the Brunonine, Hetisine, Dihydroatisine, Denudatine, Napelline types, and first representatives of the newly discovered structural types of compounds (acoserine, arkutine, zerakonine, corifine, corifidine, and thalasmine). New C<sub>19</sub>-norditerpenoid and C<sub>18</sub>-bisnorditerpenoid alkaloids related mainly to the aconitine and lycoctonine types.

A methodology chosen by the Laboratory of alkaloid chemistry, ICPS was to study the qualitative and quantitative composition of alkaloids depending on the place of growth and the growing season of the plant, contributing to the constant increase of a structurally diverse alkaloids. For example, the early research of *Delphinium corymbosum* were limited by C<sub>19</sub>-Norditerpenoid alkaloids of lycoctonine type. A study of this plant from other places showed C<sub>20</sub>-diterpenoid alkaloids of denudatine type also, characterized by the presence of a saturated C (16)-C (17) bond instead of an unsaturated one. The validity of the Wiesner's hypothesis on the biosynthesis of lycoctonine alkaloids was proved with detection of lycoctonine, the ancestor of a large group of C<sub>19</sub>-norditerpenoid bases in *D. corymbosum*.

On the other hand, nowadays many unavailable alkaloids became available, and the questions that arose during the procurement of medicinal raw materials found their answers. The availability of a wide range of structurally diverse alkaloids made it possible to conduct a targeted search for highly active substances with curariform, antiarrhythmic, antitumor, and other activities, representing a practical interest as drugs. The dependence of structure-activity, the mechanism of action, and the prospects of their use in practical medicine and biology were determined. Several highly active substances were proposed as chemical tools for biomedical researches and successfully implemented by the French company Latoxan.

A new direction has been discovered in the creation of antiarrhythmic drugs based on diterpenoid alkaloids. A technology for production of allapinin, aclesin and alsumin has been developed. The permission of the Pharmacological Committee, the Ministry of Health of the Republic of Uzbekistan was issued for clinical trials of the antiarrhythmic drug dihydroatisine hydrochloride (quinidine group) that combined the properties of I and IV classes of antiarrhythmics. As a result of many years of research, the technology for a batch obtaining of the drug allapinin, belonging to a small group of antiarrhythmics that do not affect on the blood pressure, from the aerial parts of *Aconitum leucostomum* was developed.

The report will discuss the possible transition of atisine alkaloids to lycotonine type. The first scheme involves the removal of the exomethylene group from the atisine precursor, consistent with Wiesner's hypothesis on the biosynthesis of diterpenoid alkaloids, contrarily, the second one means the exomethylene group preservation during biosynthesis. Chemical and pharmacological properties of new C<sub>20</sub>-diterpenoid alkaloids will also be discussed.

## NEW TECHNIQUES IN TURKISH ROSE OIL RESEARCH

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Rose oil and other rose products are among the most important export commodities in Turkey. Turkey and Bulgaria are forerunners in rose oil production in the World. Rose oil and rose water (Rose hydrosol) are obtained from fresh roses by distillation. Rose concrete is obtained by n-hexane extraction from fresh roses. Rose absolute, on the other hand, is obtained by ethanolic extraction from rose concrete.

This paper gives an account of our own work using Phytosol extraction, Supercritical Fluid extraction, Solid-phase microextraction, Microwave distillation, Head-space trapping and Molecular distillation techniques.

**THE TECHNOLOGIES TO BE TRANSFERRED INTO THE  
MEDICAL PARK FOR PRODUCING OF MEDICINAL SUBSTANCES**

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According to the framework of President Shavkat Mirziyoyev's visit to the People's Republic of China, the two sides discussed the creation of a joint medical technology park for the synthesis of medicinal substances. The open parts of the technologies to be transferred into the medical park for producing the medicinal substances are presented in this talk.



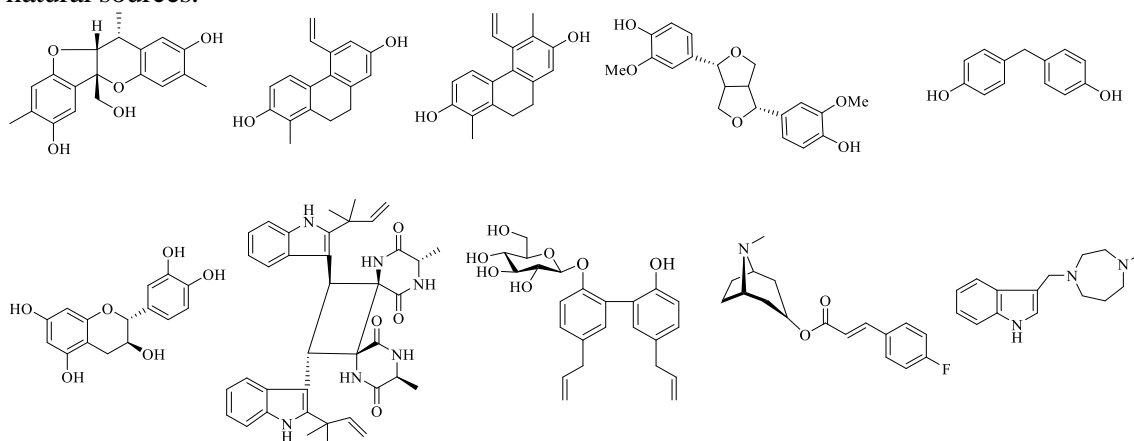
## NATURALLY DERIVED MELATONIN RECEPTORS AGONISTS AND THEIR ANTI-DEPRESSANT EFFECTS

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Depression is a common mental disorder characterized by persistent sadness and helplessness, and at its worst, major depression may lead to suicide. According to WHO estimates, more than 300 million people are suffering from depression worldwide, with an increase of 18% every year. Currently, a series of monoamine-based antidepressants have been developed with the mechanism of inhibiting neurotransmitters' degradation or reuptake, e.g. monoamine oxidase inhibitors (tranylcypromine, phenelzine, isocarboxazid), monoamine reuptake inhibitors (imipramine), selective serotonin reuptake inhibitors (fluoxetine, paroxetine, citalopram), selective noradrenaline reuptake inhibitors (maprotiline, reboxetine, mianserin), selective noradrenaline and serotonin reuptake inhibitors (venlafaxine, trazodone, mirtazapine). Although the present antidepressants are claimed to be effective in treating depression and offer an acceptable therapeutic index, their application is restricted by the drawbacks of obvious side effects and taking effect slowly.

Melatonin receptors including MT<sub>1</sub> and MT<sub>2</sub> subtypes are promising targets for the treatment of depression. Our extensive investigation on *Paeonia veitchii* (Chuanchishao), *Juncus effuses* (Dengxincao), *Uncaria rhynchophylla* (Gouteng), *Magnolia officinalis* (Houpo), *Gastrodia elata* (Tianma), and *Melia toosendan* (Chuanlian) revealed a series of active compounds that could obviously agitate melatonin receptors (MT<sub>1</sub> and MT<sub>2</sub>). This investigation will provide valuable information for searching new anti-depressants from natural sources.



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## **13-YEAR-R&D AND 13-YEAR-POSTMARKETING, A LONG AND RISKY ROAD TO BE A BLOCKBUSTER IN CLINIC**

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Based on the investigation of hydrophilic constituents of *Salvia miltiorrhiza*, magnesium lithospermate B (MLB) and other depsides salts were identified as the most effective components for ameliorating ischemic myocardial injury. Fortunately, MLB is also abundant in the herb even though it is mixed with other salt forms and derivatives. This finding inspired us to use MLB as the key quality control marker for innovative drug of *Salvia miltiorrhiza*, differentiating from other traditional preparation. A quality standard including fingerprinting, as well as preparation process was elaborated to enrich MLB and afforded consistent and identified constituents and controllable quality. Mode of action investigation indicated depsides salts can protect cardiovascular system by selectively modulating L-type calcium current in ventricular myocytes, modulating intracellular calcium concentration in vascular smooth muscle cells, inhibiting migration and proliferation of VSMC, antioxidation, anti-platelet aggregation and anti-inflammation, respectively.

After 13 years R&D, *Salvia Miltiorrhiza* Depsides Salts (SMDS) has been confirmed to be safe and effective for the treatment of patients with coronary artery disease and chronic angina pectoris in multi-center clinical trials. It was licensed by CFDA in 2005. After launching the market, another 13 years passed. Series of post-marketing investigation including Phase IV clinical trial, efficacy and safety in real world and several RCT study of SMDS were conducted to afford more evidence supporting its application in clinic effectively and safely. Till now, more than 20 million patients were benefited from SMDS. A blockbuster with billions of RMB in annual sales is rising.

**Keywords:** *Salvia miltiorrhiza*, depsides salts, cardiovascular disease, microcirculation

## **ALKALOID AKONITINE OF HIGH PURITY FROM TUBER OF *Aconitum jungaricum* AND HPLC METHOD OF ITS ANALYSIS**

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Aconitine alkaloid is widely used in medical practice and in experimental biology as a bioactive for creating a model of cardiac pathology and molecular processes that underlie the generation of the primary impulse in the search for and creation of effective antiarrhythmic drugs. Based on high-purity aconitine, a new homeopathic medicinal product with anti-inflammatory and antiviral effects was created and introduced into medical practice. (Medice Arzneimittel Petter GmbH Germany).

Many companies from different countries produce alkaloid aconitine (Sigma-Aldrich Germany, Merck France, etc.) of various purities (70-98%).

In our country, on the basis of the Pilot Production of our Institute, the batch production of aconitine alkaloid from the tubers of *Aconitum Soongoricum* with the content of the main substance of at least 96% was organized. In the obtained substance, the main impurities are alkaloids 3-dioxiaconitin and 15-dioxiaconitine.

We were able to develop a technology for the production of high purity alkonoid aconitine (99.0-100.0%) from technical aconitine using the column method of purification of a technical product. Brockmann alumina of the III degree of activity was used as the sorbent. A mixture of chloroform and ethyl alcohol was used as the mobile phase. A change in the polarity of the mobile phase (chloroform: ethyl alcohol in a ratio of 100: 0.1-100: 0.5) allowed elution of aconitine alkaloid of high purity (99.0-100.0%) from the column. The purity of the drug was determined by HPLC. At the same time, it was proposed to use a 0.005 M solution of phosphoric acid and acetonitrile in a ratio of 35:65 by volume (at a column temperature of 30 °C) as a mobile phase, on chromatographic columns 250 × 6.4 mm, C-18, particle size 5 μm.

The company “Medice Arzneimittel Petter GmbH” is currently producing a homeopathic medicine Aflubin using the alkaloid aconitine of our production.

**REPOSITIONING AND OPTIMIZING NATURAL PRODUCTS  
GUIDED BY DRUG DESIGN APPROACH**

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With molecular docking and drug design techniques, we repositioned existing drugs, including natural product drugs, for new applications, and optimized existing drugs to improve their bioactivities and bioavailabilities.

## STERIODS AND TRITERPENOIDS IN DRUG DISCOVERY STUDIES

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Natural products having an enormous structural diversity with a wide variety of biological activities are accepted as the main source of drug discovery studies. Among them, squalene as an acyclic triterpene hydrocarbon is produced by all plants and animals. Squalene serves as precursor for the formation of all plant steroids and triterpenoids, including mainly triterpene, cycloartenols, cucurbitacins and the derivatives of cholesterol, cardenolides, bufadienolides, phytosterols, furostanols and spirostanols. Using enzymes or whole-cell systems as catalysts, biotransformation studies performed on the natural compounds led to chemical modification of their structures which resulted in the production of the new promising molecules with interesting biological and pharmacological activities.

Our phytochemical studies focused on the plants of the Flora of Turkey and Cyprus and resulted mainly in the isolation and structure elucidations of the oleanane and ursane-type triterpenic saponins, steroidal saponins, cycloartenol glycosides, cucurbitacins, sterol glycosides and cardenolides. *Primula*, *Cyclamen*, *Caltha*, *Hedera*, *Verbascum* species were found to have oleanane-type saponins. *Astragalus* species were investigated for the cycloartane- and oleanane-type metabolites. The ursane-type saponins were isolated from *Scabiosa* and *Verbascum* species. *Digitalis* species, *Nerium oleander* and *Urginea maritima* were studied for their cardenolide and bufadienolide type glycosides, respectively. A series of sterol glycosides were reported from the *Ajuga salicifolia*. The recent studies are going on the isolation and characterization of cucurbitacins of *Ecballium elaterium*, oleanane-type triterpene saponins of bitter tasting outer seed coat of *Chenopodium quinoa* and ecdysteroids of *Rhaponticum* species.

This presentation will give an overview of the phytochemical studies with special focus on some major classes of plant secondary metabolites emphasising on cycloartenols, triterpene saponins, cucurbitacins and ecdysteroids and the results of the preliminary studies to enhance their pharmacological activities.

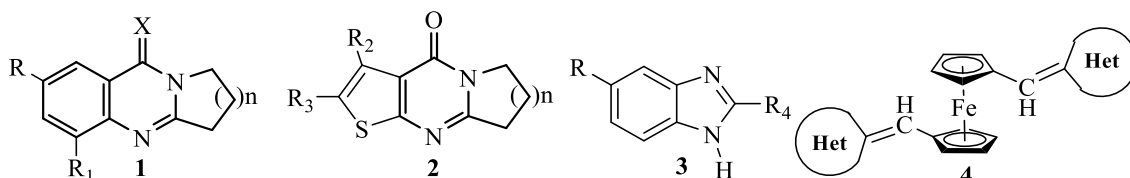
## TRADITIONAL AND MODERN APPROACH TO THE SYNTHESIS AND MODIFICATION OF QUINAZOLINE ALKALOIDS AND THEIR PERSPECTIVE HETEROCYCLIC ANALOGUES

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Many quinazolines are considered an attractive target for medicinal chemists, because they are the scaffold of several potent antitumor drugs. Leading examples are the well-known *erlotinib* and *gefitinib*<sup>[1,2]</sup>. It should be emphasized that, there are among of the new annelated imidazoles and pyrimidines, some highly effective compounds, which were selected by the National Cancer Institute (NCI) for the treatment of different types of human cancer cell lines, also useful lead compounds in the search for powerful dual anticancer-antimicrobial agents. Some benzopyrimidines possessed remarkable broad-spectrum antitumor activity, almost sevenfold and fifteen-fold more active than the known drug 5-fluorouracil (5-FU)<sup>[3,4]</sup>.

In this work, traditional and modern approaches to the synthesis and modification of quinazoline alkaloids (**1**) and their perspective heterocyclic analogues (thienopyrimidines, **2** and benzimidazoles, **3**), also new organometallic alkaloid-ferrocene conjugates (**4**) consisting different EDG (electron donating groups) and EWG (electron withdrawing groups) and fragments will be discussed<sup>[5-7]</sup>:



**1:** R, R<sub>1</sub>=H, Br, NO<sub>2</sub>, NH<sub>2</sub>; X=O, S; **2:** R<sub>2</sub>, R<sub>3</sub>=alkyl, cycloalkyl; **3:** R=Cl, R<sub>4</sub>=alkyl; **4:** Het= residue of deoxyvasicinone and mackinazolinone; n=1-3.

Results of the influence of  $\pi$ -deficient and  $\pi$ -excessive rings, synthesis of the novel potent active compounds, reactions with electrophilic and nucleophilic reagents, and formation of *mono*- and *bis*-cross-coupling (Suzuki coupling), *mono*- and *double* - condensation products from ferrocene (di) carbaldehydes will be highlighted.

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## NATURAL PRODUCT-INSPIRED DRUG PROFILING

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Natural products continue to be a rich source for drug discovery, but the tactics the natural product chemists used are rather limited and remain nearly stagnant for years. Here we present a few strategies from medicinal chemists' toolbox using natural products as a start point by repositioning several well-known natural products from their traditional usages to new therapeutical indications coupled by structural optimization and molecular target engineering. Specifically, we have focused on the drug design based on tanshinones, the lipophilic components of the traditional Chinese herbal medicine *Salvia miltiorrhiza* Bunge. More broad structural modification and various drug design strategies were incorporated, leading to several series of compounds showing significant in vitro antiproliferative effects against cancer cell lines. Drug profiling and chemical biology studies were then conducted.

**Keywords:** Drug discovery; *Salvia miltiorrhiza*; Antiproliferative effects; Tanshinones; Tumor growth; Structural elucidation.

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## TROPANE ALKALOID DERIVATIVES AND THEIR BIOLOGICAL ACTIVITY

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Tropane alkaloids are found mainly in 14 genera plants of the family Solanaceae. They are also discovered in some plants of families Convolvulaceae, Erytroxy-laceae, Euphorbiaceae, Agaricaceae, Proteaceae, and others. The basis of their structure lies in heterocyclic skeleton nortropane (8-Aza-[3,2,1] of bicyclooctane), characterized by a bicyclic system, embodying a condensed piperidine and pyrrolidine ring.

We studied on the alkaloid content of some previously unexplored species of plants of the genus *Convolvulus*, growing in Central Asia. Different organs of plants in different periods of vegetation and from different places of growth were studied. The results showed that most species were characterized by a low content of alkaloids (0.01-0.62%), with the exception of three species: *C. subhirsutus*, *C. krauseanus*, *C. erinaceus*. The studies selected 42 individual alkaloid, among which 22 were new for the latest set construction, 6 new alkaloids were bimolecular. Tropane alkaloids of plants of the genus *Convolvulus* were close to each other in structure. Simple reactions were carried out for mutual transformations and transitions between them, with the purpose of finding active compounds in this series held convolvine reactions with alkyl halides and the related derivatives (iodmethylate, brommethylate, bromhexylate, brommethylate, N-benzyl convolvine), as well as alkaloid derivatives of convolvine with aliphatic and aromatic anhydrides of acids.

The results showed that alkaloids from *Convolvulus*, the most active compound, adminaudit life time of mice were bis-derived convolvine (60.8%), convolamine (54.8%), N-chloroacetyl convolvine (50.5%), N-benzyl convolvine (50.5%). Besides, convolvine and its derivatives had high immunomodulating and anti-inflammatory activity. Convolvine and convolamine had a selective effect on gram-negative and gram-positive bacteria and *Candida* fungi. Both alkaloids gave MIC in gram-positive *Staphylococci* - 5%, and for *Streptococci* - 10%, MIC gram-negative bacteria *E. coli* and *Ps. aeruginosa* were 5% for both alkaloids, and MIC for *C. albicans* – 2.5% solution of convolvine and 5% solution of convolamine. Studies of cytotoxicity demonstrated that alkaloids of N-benzyl convolvine and N-chloroacetyl convolvine showed the greatest activity on cultures of cancer cells HeLa and Hep-2 at a concentration of 10  $\mu\text{g/mL}$ . The percentage of suppression of HeLa cells by N-benzyl convolvine was 35%. N-benzyl convolvine showed selective activity against cancer cells of the larynx, 81.6% suppression of cells ner-2, and showed low cytotoxicity against healthy cells to fibroblasts and hepatocytes. Thus, in comparison with colchicine and antineoplastic drugs of Cisplatin-Vinblastine Teva and Richter, which at a concentration of 10  $\mu\text{g/mL}$  cause nearly 100% cell death of fibroblasts and hepatocytes, the alkaloid N-benzyl convolvine inhibited only 39% of the cells of fibroblasts and 42% of the cells hepatocytes. Summarizing all the above, we can conclude that the alkaloids of the tropane series have not yet exhausted themselves, and from this class of substances we can expect the creation of new drugs for medicine in the future.



## INTEGRATED STUDY OF MAIN BIOACTIVE COMPOUNDS IN STIGMAS OF *Crocus sativus* L. ECOFORMS BY <sup>1</sup>H NMR SPECTROSCOPY AND GC-MS

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*Crocus sativus* L. is a perennial tuberous plant from the subfamily Corocoideae of the family Iridaceae (Iris). Saffron is the dried stigma of *C. sativus* L. which is the most expensive spice in the world. This plant is cultivated and exported in only few countries, mainly in Iran, India, Greece, Afghanistan, Morocco, China, Azerbaijan, Spain and Italy. It has broad use in the food industry as an additive for coloring and flavoring foods. Saffron is also employed as a drug in traditional medicine. The typical color, taste and aroma of saffron are caused by the crocins, responsible for the strong coloring capacity, picrocrocin, the glucosylated monoterpene precursor of safranal, conferring the bitter taste, and safranal, a monoterpene aldehyde derived from the chemical or enzymatic dehydration of picrocrocin during saffron handling, drying and storage, which gives rise to its characteristic odor and aroma.

Currently, on the basis of special value and widespread use of *C. sativus* L., work on its cultivation was launched for the first time in Uzbekistan. It is known that the qualitative and quantitative compositions of secondary metabolites in plants can vary depending on the place of growth and the growing season. In this regard, we began studies on the phytochemical composition of the *C. sativus* L. population introduced in Uzbekistan. The aim of this work was a quantitative evaluation of major components of stigmas of four ecoforms of *C. sativus* by <sup>1</sup>H NMR spectroscopy and by GC-MS.

The chemical constituents of extracts in DMSO-d<sub>6</sub> were identified by comparison of the chemical shifts of compounds with the literature data. Quantitative <sup>1</sup>H NMR analysis was performed by the internal standard method. In the samples of stigmas, crocin and picrocrocin were identified and quantified. The content of safranal and composition of the volatile components of hexane extracts of stigmas were studied by GC-MS. The quantitative <sup>1</sup>H NMR spectroscopy analysis of the stigmas of four ecoforms of *C. sativus* revealed the content of crocin and picrocrocin in ecoforms of Azerbaijan 31.1 and 3.3%, of Holland 36.9 and 9.3%, of Syrdarya 35.5 and 3.3%, and of Uzbekistan 53.0 and 9.5%, respectively. While the content of safranal in hexane extracts of stigmas of Holland, Syrdarya and Uzbekistan ecoforms were 24.7, 20.9 and 8.8%, respectively.

The analysis showed a difference in the quantitative composition of main bioactive compounds in stigmas of *C. sativus* L. cultivated in Uzbekistan, apparently depending on the soil-climatic and environmental conditions of the growing place.

### ACKNOWLEDGEMENTS

This work was supported by the Program for Applied and Fundamental Scientific Research of the Uzbekistan Academy of Sciences under the Grants BV-A-QX-2018-23 and VA-FA-F-6-010.

## STUDY ON THE PREPARATION TECHNOLOGY AND PHARMACOLOGICAL ACTION OF HYPOGLYCEMIC EXTRACTION FROM SEED OF *Nigella Glandulifera* Freyn

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Diabetes Mellitus (DM) is a series of metabolic disorders, caused by absolute or relative insufficiency of insulin secretion and reduced sensitivity of target tissue cells to insulin. Clinical data show that the incidence of patients with diabetic nephropathy (DN) is up to 47.66%, with a history of DM for 10 to 20 years, and the lesions show progressive development, which can result in the emergence of end-stage renal failure after 5 to 10 years. Up to now, many kinds of Chinese Herbs progress in prevention and treatment of DN. Three main plants in this genus showed antidiabetic effect in many reports. *N. glandulifera* is included in each edition of the Pharmacopoeia of the P. R. China, and is believed to have antidiabetic effect. This study was to reveal whether hypoglycemic extraction from it also affects DN.

The results of screening in vitro showed that the EtoAc fraction of the seeds has some effect on inhibiting Aldose Reductase. After comparing with different extraction methods, microwave-assisted extraction was selected, and the extraction conditions of effective part were optimized using response surface methodology (RSM) by evaluating indicated markers of extraction yield, antidiabetic activities (PTP-1B and AR), and antioxidant activity (ABTS and DPPH). The optimal extraction method was found as below: solid-to-liquid ratio 1:20 g/mL, ethanol concentration 70%, extraction time 35.00 min, and extraction temperature 66 °C. The extraction was obtained with a yield of 16.82%, activity against PTP1B and AR with IC<sub>50</sub> values of 4.74 μg/mL, and 69.97 μg/mL, antioxidant activity against DPPH and ABTS with IC<sub>50</sub> values of 75.96 μg/mL and 39.78 μg/mL, respectively. After purification by AB-8 resin, fingerprint of NGE was established, and the main chemical compounds were identified by UHPLC-Q-Orbitrap

-HRMS as one alkaloid, four flavonoid glycosides, seven phenolic compounds, ten triterpenoid saponins, and three oleanolic acid analogues, some of them shown AR inhibitory effects and antioxidant activity. From the fingerprint, 30 common peaks were found in the extraction obtained by different extract conditions, and spectrum - effect relationship of the extractions of NGE and AR showed 19 correlations between peaks and the inhibition of AR were more than 0.6, indicating that they had synergistic effect.

The results of pharmacological effects of NGE in 12 weeks db/db mice showed that compared with model, NGE can significantly relieve the weekly body weight loss and decrease fasting blood glucose, glycated hemoglobin, urea, urinary N-acetyl-β-D-glucosaminidase (NAG) activity and the lipid profiles such as TC, TG, in serum. It also improved GTT of mice especially in low dosage group. Antioxidant and AR inhibition effects were also observed by testing MDA, SOD, GSH and sorbitol.

### ACKNOWLEDGEMENTS

The work were supported by the West Light Foundation (Grant No. 2018-YDYLT - 001) and Central Asian Drug Discovery and Development Center of CAS.

## **NEW LIGAND BINDING DOMAIN ON PPAR PROTEIN AND ITS METABOLIC REGULATION FUNCTION**

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Pan-peroxisome proliferator-activated receptors (PPAR) agonists have long been desired as therapeutic drugs against metabolic syndrome. However, limited efficacy and undesirable adverse effects have hindered the development of PPAR agonists. In this study, we found a new LBD on PPAR $\alpha$  and PPAR $\gamma$ . Natural compound, bavachinin from *Psoralea corylifolia*, can bind to the new LBD as a PPAR agonist and synergize with synthetic PPAR- $\alpha$  agonists (such as fenofibrate) and PPAR - $\gamma$  agonists (such as rosiglitazone) on PPAR transcriptional activities, and glucose and TG lowering effects *in vivo*. Bavachinin exhibited properties desired for an anti-diabetic PPAR-target agonist without weight gain and hepatotoxicity. To our knowledge, it is the first time to find the synergistic effects between PPAR agonists by activating the alternate binding site, which might increase efficiency and decrease toxicity of the market drugs with a lower-dosage.

## CHEMICAL COMPOSITIONS OF THE SEEDS OF *Lepidium sativum*

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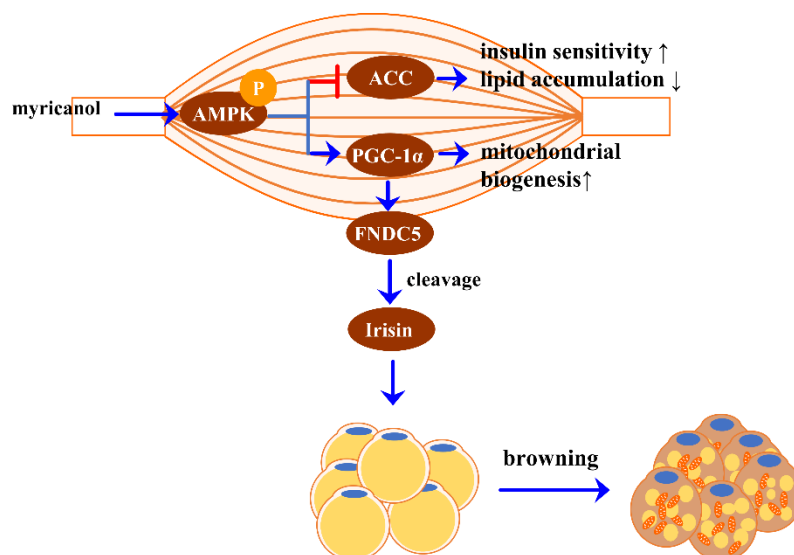
The seeds of *Lepidium sativum* L. is called Jia Du Xing Cai Zi which has been used in traditional Uygur medicine for the treatment of intestinal worms and constipation. HPLC-DAD analysis for the ethanol extract of *L. sativum* revealed sinapic acid derivatives, flavonoids and aliphatic esters to be the major components. Guided by LC-MS/MS guided isolation, five new sinapic acid derivatives were isolated and identified from the seeds of *L. sativum*.

## MYRICANOL MODULATES SKELETAL MUSCLE-ADIPOSE CROSSTALK TO ALLEVIATE HIGH FAT DIET-INDUCED OBESITY AND INSULIN RESISTANCE

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Skeletal muscle is the predominant site for glucose disposal and fatty acid consumption. Emerging evidences have indicated the crosstalk between adipose and skeletal muscle is critical in maintaining insulin sensitivity and lipid homeostasis. The current study was designed to investigate whether myricanol (MY) improves insulin sensitivity and alleviates adiposity through modulating skeletal muscle-adipose crosstalk. MY was found to increase mitochondrial quantity and function through activating AMP-activated protein kinase, resulting in reduced lipid accumulation and enhanced insulin-stimulated glucose uptake, in PA-treated C2C12 myoblasts. Furthermore, MY stimulated irisin production and secretion from myotubes to reduce lipid content in 3T3-L1 adipocytes. In high fat diet-fed mice, MY treatment alleviated adiposity and insulin resistance through enhancing lipid utilization and irisin production in skeletal muscle, and subsequently browning of inguinal fat. Taken together, our results implicated that MY modulates skeletal muscle-adipose crosstalk, to alleviate adiposity, improve insulin sensitivity, and stimulate browning of adipose tissue. MY might be a potential candidate for treating insulin resistance and obesity.



### ACKNOWLEDGEMENTS

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## NEW TERMICIDE AGENT AND METHOD OF ITS PRODUCTION

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One of the most serious problems in Uzbekistan is the *Anacanthotermes turkestanicus* Jacobs and the *A. ahngeranium* Jacobs termites, which cause enormous damage to buildings and structures, including historical monuments of Bukhara, Samarkand and Khiva, which have a worldwide cultural value.

Currently, insecticides are used against termites in foreign and domestic practice of contact action, for example, natural pyrethrins and their synthetic pyrethroid analogues (pyrethrin I, pyrethrin II, jasmolin I, jasmolin II, permethrin, tetramethrin, allethrin, deltamethrin and others) give a temporary effect, since they do not lead to the complete death of a colony of termites, including the Queen. In this regard, there is a need to develop new methods and means of controlling termites using toxic food lures intestinal prolonged action.

As a result of our researches it was established that sesquiterpene lactone cumambrine A ( $8\alpha$ -acetoxy- $9\alpha$ -hydroxy- $1\alpha,5\alpha,6\beta,7\alpha$ (H)-guai-3,11(13)-dien-6,12-olide) showed high termicide activity. It was experimentally revealed that use of high concentrations, for example, 0.01% solution, due to complete death of termites in 1 and 2 days. At concentration of 0.002-0.005% the 100% death of termites was observed on the 8<sup>th</sup> day. At a concentration of 0.001% the total of termites' death was observed on day 10.

The results showed that the proposed agent cumambrine A has high termicide activity in low concentrations, which led to 100% death of termites. By varying of the concentration of sesquiterpene lactone cumambrine A in food lure, this agent may be the basis for creating of new effective termicide preparation with enteric-prolonged action<sup>[1]</sup>.

The source of cumambrine A is the aerial part of endemic plant of Central Asia - *Handellia trichophylla* (Schrenk) Heimerl.

We have developed a new industrially applicable method for its production from the plant *Handellia trichophylla*, which allowed to simplify the process of producing, to increase its safety and the yield of the target product<sup>[1]</sup>.

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## MEDICINAL PLANTS OF TAJIKISTAN: CHEMISTRY AND BIOLOGICAL ACTIVITY

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Tajikistan is a small country located in Central Asia. The high-mountain ecosystems of Tajikistan have been regarded as biodiversity hotspots with around 5500 species of higher plants recorded in Tajikistan and about 15% endemics [1].

*Prangos pabularia*, one of the most known species of the genus in Tajikistan, possesses many medicinal properties and has been used in traditional medicine in several cases. Our investigation, reports on the isolation, structure elucidation of 20 pure compounds and essential oil with potent antidiabetic activity. The new coumarin - yuganin A showed the best anti-vitiligo effect on the proliferation of B16 melanoma cells. The essential oil induced a PTP-1B enzymatic inhibition with IC<sub>50</sub> value 0.06 ± 0.01 μg/mL (p < 0.02) which was 25 times more than the positive control [2,3].

The 50% EtOH extract of *Geranium collinum* underground part led to isolation of 10 pure major biologically active compounds. Based on molecular docking analysis and *in vitro* evaluations, we conclude that polyphenolic constituents are likely responsible for the inhibition of PTP-1B and α-glucosidase. Our investigations suggest the development of herbal formulations based on the root parts of *G. collinum* growing in Tajikistan [4].

The aerial parts of eight *Artemisia* species including *A. annua*, *A. vachanica*, *A. vulgaris*, *A. makrocephala*, *A. leucotricha*, *A. dracunculus*, *A. absinthium*, and *A. scoparia* were studied by their assessments of artemisinin. Content of artemisinin ranged between 0.07-0.45% in dry weight of *Artemisia* species. *A. vachanica* was found to be a novel plant source of artemisinin and the essential oil showed strong antimicrobial activity [5,6].

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## TERPENES FROM ETHNOMEDICINAL PLANTS IN THE WEST PART OF CHINA AND CENTRAL ASIA

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Ethnomedicinal plants are a rich source to search for lead compounds for drugs. Central Asian countries, possess abundant ethnomedicinal plant resources which are classic herbs in ethnomedicines. Investigations on ethnomedicinal plants in the west part of China and Central Asia resulted in the discovery of novel terpenes [1-8]. Moreover, bioactive screening and structural modification based on natural bioactive terpenes were applied [8-11], and some lead compounds or potential candidates for the lead compound were obtained.

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**DO ALL ROADS LEAD TO ROME?  
EXPLORING THE METABOLIC PHENOTYPES TO EXPLAIN  
THE SAME ANTI-HYPERTENSIVE EFFECT ACHIEVED BY FIVE  
UNCARIA SPECIES**

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The sourcing of plants from multiple botanical origins is a common phenomenon in traditional Chinese medicines. *Uncaria* Stem with Hooks (UHs) is approved for use based on five botanical origins in the Chinese Pharmacopoeia (2015 Edition). It is commonly used for treating hypertension, even though the plants have thoroughly different chromatographic fingerprints based on our previous study. However, their hypotensive effects and metabolic phenotypes in spontaneously hypertensive rats (SHRs), until now, has remained unknown. In the present study, SHRs were orally administered five aqueous extracts (4 g crude drug/kg) prepared from the different UHs over a six-week period. Systolic blood pressure (SP) was measured every week and urine was collected after SP measurement. Untargeted metabonomics using UPLC coupled with a LTQ-Orbitrap mass spectrometer was performed. Bidirectional orthogonal projection to latent structures-discriminant analysis (O2PLS-DA), Student's t test, and correlation analysis were used for pattern recognition and the selection of significant metabolites. The results showed that a similar and prolonged reduction of SP was observed in each of the groups given the five different UHs, while the metabolic profiles were perturbed slightly compared with that of SHR. Following further analysis, it was interesting to note that a few common, different components were observed within the five groups which might promoted the similar antihypertensive effect in spite of the distinct metabolic pathways due to their different alkaloids composition. It promoted the mechanism of the phenomenon "different origins, same effect" of UHs.

**Keywords:** *Uncaria* Stem with Hooks, multiple botanical origins, spontaneously hypertensive rats, metabonomics, indole alkaloids

**SITE-SPECIFIC MODIFICATION OF VANCOMYCIN FOR  
ENHANCED ANTIBACTERIAL ACTIVITY AGAINST DRUG-  
RESISTANT BACTERIA**

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Herein, we employed several modification strategies for development of novel vancomycin derivatives, including extra sugar modification, lipid modification, sulfonium modification, metal chelate modification, etc. The resulted vancomycin derivatives promote the interaction with the cell-wall peptidoglycan of drug-resistant bacteria, enhance the permeability of cell membrane, and increase the activity of anti-vancomycin resistant bacteria by more than 1000 times. Pharmacokinetic and safety evaluation showed that carbohydrate modification played an important role in regulating the pharmacokinetics of glycopeptide antibiotics.

## AROMATIC-TURMERONE FROM *Curcuma longa* L. ATTENUATES LPS-INDUCED NEUROINFLAMMATION AND CONSEQUENT MEMORY IMPAIRMENT

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*Curcuma longa* (turmeric) is a folk medicine in South and Southeast Asia, which has been widely used to alleviate chronic inflammation. Aromatic-turmerone is one of the main components abundant in turmeric essential oil. However, little information is available from controlled studies regarding its biological activities and underlying molecular mechanisms against chronic inflammation in the brain. In the current study, we employed a classical LPS model to study the effect and mechanism of aromatic-turmerone on neuroinflammation.

The effects of aromatic-turmerone were studied in LPS-treated mice and BV2 cells. The cognitive function assays, protein analyses, and histological examination were performed. Oral administration of aromatic-turmerone could reverse LPS-induced memory disturbance and normalize glucose intake and metabolism in the brains of mice. Moreover, aromatic-turmerone significantly limited brain damage, through inhibiting the activation of microglia and generation of inflammatory cytokines. Further study in vitro revealed that aromatic-turmerone targeted Toll-like receptor 4 mediated downstream signaling, and lowered the release of inflammatory mediators.

These observations indicate that aromatic-turmerone is effective in preventing brain damage caused by neuroinflammation and may be useful in the treatment of neuronal inflammatory diseases.

**Keywords:** Aromatic-turmerone; LPS; Memory impairments; Neuroinflammation; Toll-like receptor

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## **BENEFICIAL EFFECTS OF SAFFRON (*Crocus sativus* L.) IN OCULAR DISEASES**

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*Crocus sativus* L. from Iridaceae family is a pricy plant in the world's trade. The stigmas of saffron flowers are known as a dye and spice since ancient times. Traditionally, dried stigmas, saffron, are also used as a medicine in the treatment of different diseases such as antihypertensive, antitussive, anticonvulsant, antigenotoxic and antioxidant, cytotoxic effects, anxiolytic aphrodisiac, antinociceptive, antidepressant, antiinflammatory, and relaxant activity. Macular degeneration is the main cause for elderly persons' oculars and carotenoids delay and help the treatment of mild and moderate macular degeneration. Saffron contains different classes of compounds which are mainly terpenoids, carotenoids, and phenolics. Crocins, crocetins, and picrocrosin are major chemicals of saffron. In the last decade, many pharmaceutical products used for retinal deformations and age-related macular degeneration contain carotenoids as active constituents. This chapter summarizes the carotenoid derivatives of saffron and discusses their beneficial effects on the oculars diseases.

## OBTAINING OF RECOMBINANT PROTEINS IN THE *Bombyx mori* EXPRESSION SYSTEM

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At present one of the most efficient expression systems that allows obtaining of biologically active recombinant proteins with correct post-translational modifications is the baculovirus / insect cell expression system <sup>[1-4]</sup>. To obtain of biologically active recombinant proteins, we used the recombinant baculoviruses derived from the nuclear polyhedrosis virus of *Bombyx mori* (silkworm). The virus was highly specific, infecting only one type of insect - silkworm, and was safe for humans and farm animals. In this expression system we obtained the GFP (Green Fluorescent Protein),  $\beta$ -Galactosidase, MIS (Mullerian inhibiting substance), and Pres2-S region (34 kDa) of the surface antigen of Hepatitis B virus (HBV) containing three antigenic determinants. These recombinant proteins were obtained not only in *Bombyx mori* cell culture, but also in silkworm larvae. The silkworm larvae does not require sterile facilities and large-scale cultivation in flasks or culture bags, and increases its body weight  $10^4$  fold within 25 days, from 0.5 mg at hatching to 5 g at the 5th age, by eating only 20-25 g of mulberry leaves <sup>[1, 2]</sup>. We have studied the expression level of the recombinant proteins in different breeds of silkworm. For this purpose, the four domestic breeds of silkworm larvae were infected with recombinant baculoviruses encoding the target proteins. The amount of synthesized proteins were determined by fluorescence microscopy, X-Gal assay, ELISA and standard SDS PAGE methods. Based on the obtained data for the first time a breed of *Bombyx mori* larvae – Marvarid, which produced a high level of recombinant proteins, was determined. Studies showed that silkworm larvae could serve as a promising, economical, and safe source for obtaining of biologically active recombinant proteins.

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**INVESTIGATION OF SEVERAL *Heracleum* AND *Angelica* SPECIES FROM BULGARIA FOR CHEMICAL PROFILE, ANTIOXIDANT ACTIVITY AND INHIBITORY PROPERTIES AGAINST ACETYLCHOLINESTERASE AND  $\alpha$ -AMYLASE ENZYMES**

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In this study, aromatic profiles of *H. verticillatum* leaves, fruits and roots were found to be quite different. Octyl acetate (44.8%), octyl 2-methyl butyrate (20.8%) and octyl isobutyrate (13.1%) in fruit,  $\beta$ -caryophyllene (32.3%) in the leaf and  $\alpha$ -pinene (41.6%) in the root oils were the main constituents. In *H. sibiricum* fruit oil octyl acetate (49.2%) and octanol (36.2%) were the main constituents while in the leaf and root essential oils, methyl eugenol (25.7% and 38.4%) and elemicin (20.8% and 18.8%) were identified as the main compounds. The fruit oils of *H. angustisectum* were found to be rich in phenyl propanoid compounds 4-vinyl guaiacol (55.3%) and methyl eugenol (12.9%). In the leaves, *cis*-isoelemicin accounted for 66.6% of the oil. Methyl eugenol (63.6%) and elemicin (19.4%) were identified as the main compounds in the root oil. The fruit oil of *Angelica panicii* was rich with  $\beta$ -phellandrene (69.1%), while the leaf oil contained germacrene D (9.7%),  $\delta$ -cadinene (6.6%), caryophyllene oxide (6.1%) and the root oil contained kessane (9.6%), elemol (9.8%), and  $\gamma$ -cadinol (5.3%) as main compounds.

The methanol and hexane extracts as well as the oils of *Heracleum* and *Angelica* leaves, fruits and roots were investigated. In hexane extracts, quantification of furanocoumarins was performed by <sup>1</sup>H-NMR. Pimpinellin was found to be the main component in roots of all studied species. Bergapten and imperatorin were the major compounds in fruits of *H. sibiricum* and *H. verticillatum*, respectively, while byakangelicol dominated in *H. angustisectum* and *H. ternatum* fruits. In methanol extracts, luteolin/campherol glucoside, diglucoside, rutinoid, dideoxyglucoside, isorhamnetin and its glucoside and diglucoside, apigenin glucoside and glucuronide, quercetin rhamnosyl glucoside, cumaroylquinic acid, quercetin glucoside, hydroxycoumarin, dihydroxycoumarin acetate, 5-dicaffeoylquinic and 5-feruloylquinic acids were detected.

The leaf and fruit extracts of *H. angustisectum* demonstrated the highest DPPH radical scavenging activity and TEAC (IC<sub>50</sub> 0.58 mg/mL and 1.83 mM, respectively). The root extracts of *H. verticillatum* and *H. angustisectum* were found to be the most effective against acetylcholinesterase (IC<sub>50</sub> 0.30 and 0.34 mg/mL, respectively). The studied extracts were inactive or demonstrated a weak inhibitory effect (%Inh. up to 32) towards  $\alpha$ -amylase. However, *H. verticillatum* leaf oil showed moderate inhibitory effect (42 %).

#### ACKNOWLEDGEMENTS

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## STUDY ON THE CHEMICAL COMPOSITIONS AND BIOLOGICAL ACTIVITIES OF ESSENTIAL OILS FROM SEVERAL AROMATIC PLANTS ENDEMIC IN XINJIANG

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Xinjiang is located in the interior of Eurasian continent and far from the ocean. Xinjiang's special geographical environment and climate have bred unique plant resources in arid zones, which contain abundant aromatic medicinal plant resources. Aromatic plants are widely used in traditional Chinese medicines, which have wide spectrum of biological activities such as anti-bacterial, anti-inflammatory and neurobeneficial effects. In this research several endemic aromatic plants *Schizonepeta tenuifolia* (Benth.) Briq, *Foeniculum vulgare* Mill. and four *Mentha* L. species were investigated chemically and biologically. The chemical compositions of essential oil isolated from the aerial parts of *Schizonepeta tenuifolia* (Benth.) Briq were characterized by GC-Q-TOF-MS analysis. The oxygenated monoterpenes D-menthone (51.87%) and pulegone (30.93%) were found to be the predominated components of essential oil. The major constituents were screened in silico by molecular docking against *Staphylococcus aureus* tyrosyl-tRNA synthetase (TyrRS) that played an essential role in controlling bacterial protein synthesis. Moreover, the main active compounds were isolated by the combing high speed counter-current chromatography (HSCCC) and preparative Capillary-Gas Chromatography (pc GC). Respond surface method (RSM) was applied to optimize the extracting essential oil from *Foeniculum vulgare* Mill. seeds by supercritical carbon dioxide extraction method. Based on single factor test, the influence factors of extraction temperature, extraction time and extraction pressure were evaluated using Box-Behnken central composite design method. The chemical composition and biological activity of the essential oils from *M. haplocalyx* Briq, *M. asiatica*, *M. spicata* and *M. pulegium* collected in Xinjiang were investigated. GC-MS method was applied to analyze the chemical compositions of essential oils. In terms of the biological activity of the essential oils, the antioxidant and antibacterial properties of the samples were screened. From the results we found that, essential oils from the four *Mentha* L. species possessed antioxidant and antibacterial properties in different degrees.

**Keywords:** Essential oil; aromatic plants; chemical composition; GC-MS; preparative gas chromatography

### ACKNOWLEDGEMENTS

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## DESIGN, SYNTHESIS AND BIOACTIVITY EVALUATION OF MULTI-TARGETED TETRAHYDROPROTOBERBERINE DERIVATIVES (THPBS)

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Tetrahydroprotoberberines (THPBs) belong to a class of tetrahydroisoquinoline alkaloids with multiple bioactivities derived mainly from Chinese medicinal herbs. An effective and rapid method for the microwave-assisted preparation of the key intermediate for the total synthesis of THPBs including *l*-stepholidine (*l*-SPD) was developed. A series of new THPB derivatives were designed, synthesized, and tested for their binding affinity towards dopamine (D1 and D2) and serotonin (5-HT1A and 5-HT2A) receptors. Many of the THPB compounds exhibited high binding affinity and activity at the dopamine D1 receptor, as well as high selectivity for the D1 receptor over the D2, 5-HT1A, and 5-HT2A receptors. On the basis of the pharmacophore model of the marketed drug silodosin, THPBs were modified by introducing an indole segment into their core scaffolds. In calcium assays, 7 compounds displayed excellent antagonistic activities against  $\alpha_{1A}$ -ARs, with  $IC_{50}$  less than 250 nM. In the functional assay using isolated rat tissues, compound (S)-27 inhibited norepinephrine-induced urethra smooth muscle contraction potently, without inhibiting the aortic contraction, displaying a better tissue selectivity than the marketed drug silodosin. Additional results of preliminary safety studies and pharmacokinetics studies indicated the potential druggability for compound (S)-27 which is a promising lead for the development of selective  $\alpha_{1A}$ -AR antagonists for the treatment of Benign Prostatic Hyperplasia (BPH).



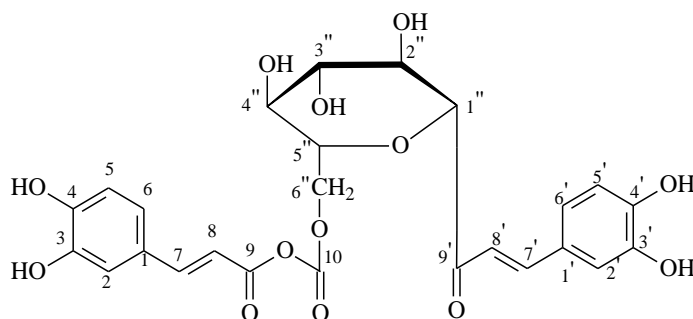
A NOVEL PHENOL GLYCOSIDE FROM *Pulicaria gnaphalodes***K. A. Eshbakova<sup>1\*</sup>, B. D. Komilov<sup>1</sup>, H. A. Aisa<sup>2</sup>**

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The continuing studies of the chemical composition of *Pulicaria gnaphalodes* led to the isolation of a new phenol glycoside, Punalozid with the molecular formula  $C_{25}H_{17}O_{13}$ , from n-butanol fraction by PHPLC methods. Structure of the Punalozid was established on the basis of the analysis of the data of  $^1H$ , and  $^{13}C$  NMR spectra, as well as the DEPT, HSQC, and HMBC experiments.

Based on the spectral characteristics, it was found that the substance had the following structure for Punalozid - 3,4-dihydroxy-*O*-caffeoyl-9'-10-glucopyranosyl-carboxy.



**DEVELOPMENT OF AN INNOVATIVE DRUG DERIVED FROM  
THE CLASSIC PRESCRIPTION OF BAIHE-ZHIMU DECOCTION  
THAT AMELIORATES DEPRESSIVE DISEASE**

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Baihe-Zhimu decoction, consisting of two herbs, Baihe (*Lilii Bulbus*) and Zhimu (*Anemarrhenae Rhizoma*), is a classic Chinese medicine formula, which was initially recorded in *Jingui Yaolue*, a famous work of TCM written by the famous Chinese physician Zhongjing Zhang more than 1,800 years ago. It has been used to treat the affect-mind dissatisfaction, spirit of trance and inability of self-control in ancient China, which exhibits similar symptoms to depression. Our investigation observed that anti-depressive compounds were accurately determined in the brain after oral administration of Baihe-Zhimu decoction. Then, we obtained the related derivatives with new structures after chemical modification that are completely different from the internationally marketed drugs. Previous pharmacological studies have demonstrated that these derivatives have antidepressant effects on various animal models, including acute and chronic animal models. Moreover, our results showed that the administration of these derivatives enhanced the excitability of cerebral cortex neurons and promoted the release of inter-synaptic glutamate neurotransmitters, etc.

## PHYTOCHEMICAL PROFILES AND BIOLOGICAL ACTIVITIES OF ENDEMIC MEDICINAL PLANTS FROM KAZAKHSTAN

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The traditionally natural products have played an important role in developing of natural product chemistry which continues to expand to exciting new frontiers of great importance in medicine. Over six thousand kinds of plants grow in Kazakhstan, among which more than 720 are endemic ones. These natural plant resources have been efficiently used in the treatments for a variety of diseases in Kazakh traditional medicine. We focused our attention on study of the bioactive chemical constituents of endemic medicinal plants such as *Ikonnikovia kaufmaniana*, *Artemisia heptapotamica*, *Daphne altaica* and *Limonium michelsonii* Lincz.

The flowering plants of *I. kaufmaniana* and *A. heptapotamica* Poljak were collected in July, 2018, from Almaty region of Kazakhstan. Phytochemical profiles from ethyl acetate extract of *I. kaufmanniana* were quantified by HPLC-ESI MS/MS. Isolation and structural identification processes of *I. kaufmaniana* revealed phenolic compounds: dihydroflavanonol, flavonol, isoflavone and flavanol skeletons and most compounds were further screened for their antioxidant capacities (DPPH, ORAC, and hydroxyl radicals), including a DNA damage protection ability and their efficacies were found to differ by their functionality and skeleton. Phytochemical investigation of *A. heptapotamica* resulted in one new dimeric and two monomeric sesquiterpene lactones, together with 10 known compounds including three dimers, four guaianolides and three *seco*-guaianolides. The structures of new compounds were mainly achieved by extensive analysis of MS, 1D and 2D NMR spectroscopic data, and ECD spectrum. All isolates were evaluated for their inhibitory activities against activation of NF- $\kappa$ B induced by lipopolysaccharides (LPS) on a model based on the THP1-Dual cells.

## SEARCHING FOR ANTIDOTES TO ALKALOID NEUROTOXINS AMONGST DITERPENOID ALKALOIDS AND ANTIARRHYTHMIC DRUGS

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Plant species of the genera *Aconitum*, *Delphinium*, and *Veratrum* containing alkaloid neurotoxins, are widespread in nature, popular in folk medicine in different countries, and therefore can cause poisoning to people and animals. The general toxic effects of the alkaloid neurotoxins aconitine, veratridine and their derivatives are associated with the activation of voltage-gated Na<sup>+</sup>-channels, modulation of the neurotransmitters norepinephrine and acetylcholine, as well as their receptors, increasing peroxidation of lipids and the induction of apoptosis in heart, liver, brain and other cells. To date, there are no effective medications for the treatment of alkaloid neurotoxin poisoning. The conventional treatment includes amiodarone, magnesia and lidocaine (in ventricular dysrhythmias), and atropine (in sinus bradycardia). Recent studies have shown that the puffer fish neurotoxin tetrodotoxin (TTX), an activator of Na<sup>+</sup>-channels, eliminates the effects of aconitine, veratrin and batrachotoxin (BTX, alkaloid neurotoxin from the skin glands of the *Phylllobates* frog). But, TTX can not be used as antidote because of its neurotoxicity.

We have studied 73 diterpenoid alkaloids of aconitine, lycocotonine, lappaconitine, heteratisine, napelline and denudatine types, and their modifications, as well as antiarrhythmic drugs of I-IV classes. Neurointoxication in mice was induced by intravenous administration of an absolutely lethal dose of aconitine (200 µg/kg). The most active in suppression of neurointoxication and prevention the death of mice poisoned with aconitine were 14-*O*-benzoyltalatisamine, 1-*O*-benzoylnapelline, lappaconitine, 6-*O*-benzoylheteratisine. ED<sub>50</sub> of them were 6.6, 3.0, 0.48, and 0.25 mg/kg, and the breadth of the therapeutic (antidote) effect (LD<sub>50</sub>/ED<sub>50</sub>) were 18.5, 45, 32.3, and 86.0, respectively. III class antiarrhythmic drug amiodarone, a blocker of “slow” Ca<sup>2+</sup>-channels, at doses of 50-100 mg/kg i.p. reduced the intensity of aconitine intoxication (200 µg/kg). Verapamil, IV class antiarrhythmic, at a dose of 75 mg/kg i.v. strengthened the toxic effects of a non-lethal dose of aconitine (100 µg/kg), that led to 100% death of animals. Lidocaine, IV class antiarrhythmic drug, at doses of 10-50 mg/kg did not show antidote effect. Ethacyzin (group I C drug, “fast” Na<sup>+</sup>-channels blocker) at doses of 50-70 mg/kg prolonged the latent period of the animal death and increased their survival up to 60-80%.

Structural analysis of the most active antidote alkaloids shows the presence of a number of functional groups that are potentially capable to form electrostatic and hydrogen bonds with amino acids making an active centre of neurotoxines receptors, as well as relatively small sizes and a rigid frame of molecules. In general, as a recommendation for the further searching for antidotes to neurotoxins among alkaloids, it can be noted that such a search should be carried out among monoaromatic substituted alcohols.

# Oral Presentations

## STRUCTURAL MODIFICATION OF ALEPTEROLIC ACID FOR ANTI-CANCER DRUG DISCOVERY

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*Aleuritopteris argentea* (S.G. Gmél.) Fée, also known as *Cheilanthes argentea* (S.G. Gmél.) Kunze, is a fern plant widely distributed in Asia<sup>[1]</sup>. This fern characteristically grows on limestone joints and wall joints with good drainage. It was alleged that the extract of the plant can promote blood circulation, regulate menstruation and prevent cancer, but scientific reports on its chemical constituents and exact mechanism are limited. Pioneer investigation on *A. argentea* by Hiroyuki Ageta *et al* isolated alepterolic acid as the major metabolite. In continuation of our research on medicinal ferns, recently we have obtained grams of alepterolic acid from *A. argentea*, which enabled the structural modification and subsequent activity evaluation.

It is obviously noticed that 15-carboxy group and 3-hydroxyl group of alepterolic acid, like those two groups in ursolic acid and betulinic acid<sup>[2]</sup>, are prone for easy structural modification, we thus initiated our preparation of derivatives by incorporation of amino moiety to 15-carboxyl group of alepterolic acid. More than 30 compounds were prepared and characterized by NMR, HRMS and HPLC. Biologically evaluation of anticancer potency showed that the newly semi-synthesized compounds exhibited better activity as compared to alepterolic acid itself. In the study of apoptotic mechanism of the best hit, it was found that compound induced apoptosis in Hela cancer cells via a mitochondria-dependent endogenous pathway. These findings encouraged the preparation of additional target compounds by click chemistry.

**Keywords:** *Alepterolic acid*, structural modification, semi-synthesis

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## APPLICATION OF EGG-YOLK SIALYLGLYCOPEPTIDE IN CELL-SURFACE GLYCAN EDITING AND IMAGING

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Oligosaccharides isolated from natural resources provide carbohydrate substances for biological studies. A homogeneous sialylglycopeptide (SGP) extracted from chicken egg yolks carries a native biantennary N-glycoform, which is useful for glycopeptide synthesis and protein glyco-remodeling. Our group has developed an efficient and optimized procedure to isolate the SGP from egg yolks rapidly. Herein, we report the application of SGP in cell-surface glycan editing and imaging. Glycan editing offers multiple opportunities to study the functional roles of glycans during internalization, receptor dimerization, cell-cell communication, etc. For cell-surface glycan editing, first we deglycosylated the cell-surface glycoproteins using EndoF<sub>3</sub> endoglycosidase, and then chemoenzymatic transglycosylation with mutant EndoF<sub>3</sub> D165A and N-glycan oxazolines derived from SGP to assemble the well-defined glycoform onto cell surface.

Moreover, azido modification on sialyl terminal of the SGP enables late-stage labeling with fluorescent probes by click reaction. This leads to a cell surface glycan imaging. Combined with receptor-specific antibody, tagged with another fluorescent label, allows protein-specific glycan visualization by FRET technology. This approach facilitates protein-specific glycan detection and also opens a new avenue for functional study of glycans during various cellular processes and cancer diseases.

Based on this method, we established a triple-color FRET method to explore the intracellular destiny of Her2-specific glycans during internalization. Time-lapse monitoring of Her2-specific glycans labelled with multiple fluorescent probes elucidated the mechanism of intracellular glycan catabolism. We observed sequential turning off the fluorescent probes attached on antibody, fucose and sialic acid. These results indicate that glycans catabolize bidirectionally following the receptor degradation. To our perspective, this mechanism will help us to better understand the rationale behind glycosylation of drug receptors.

**COMPONENTS OF THE PLANT *Haplophyllum griffithianum*. THE  
STRUCTURE OF THE NEW ALKALOID GRIFFININE**

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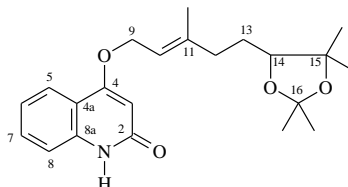
Currently, preparations based on natural compounds of plant origin remain to be one of the effective agents in the treatment of cardiovascular, gastrointestinal, oncological diseases, as well as diseases of the liver, kidneys, etc. Chemists show interest in quinoline alkaloids for the diversity of their structural and the possibility on solving interesting and significant scientific and practical problems. In this work, studies were carried out on *Haplophyllum griffithianum* Boiss. (Rutaceae) plant, collected from the two vicinity of Nilu village and Khondiz, of Surxondaryo District, Uzbekistan.

By GC-MS analysis, the major components in petroleum ether fraction of *H. griffithianum*, collected from Nilu, were identified and main components from the aerial part were Seselin (28.97 %), Hexadecanoic acid (12.39 %), Linolenic acid (11.99 %), Methyl linolenate (5.29 %), 6-methyl-5-nitro-7-azaindole (4.78%). In petroleum ether fraction of flowers, major components were 5 (4H)-Isoxazolone, 3-phenyl-4-(phenylmethyl)- (38.95%), Seselin (2H, 8H-Benzo [1, 2-b: 3, 4-b'] dipyrans-2-one, 8, 8-dimethyl) (28.96 %). Main components of the extracts of the plant from Khondiz (petroleum ether fraction of H.g-1ex) were Dodecanoic acid (20.47), Tetradecanoic acid (19.60%), n-Hexadecanoic acid (10.08%), Phytol (8.24%), and that of H.g-2ex were 9, 12, 15-Octadecatrienoic acid, methyl ester, (Z,Z,Z)- (15.28), Tetradecanoic acid (13.99%), 9,12-Octadecadienoic acid, methyl ester, (E,E)-(11.88), 9-Octadecenoic acid (Z)-, methyl ester (7.97).

Chemical investigation on *H. griffithianum* collected from Khondiz yielded 6 compounds, dubinine, dictamnine, skimmianine, evoxine, folimine, griffinine from the exact of the aerial part, and 2 compounds, dictamnine, skimmianine from the root exact.

Chemical investigation on *H. griffithianum* collected from Nilu, led to the isolation of 14 compounds from the exact of the aerial part, identified to be dubinine (H.g-1), dictamnine (H.g-2), skimmianine (H.g-3), dubinidine (H.g-4), dubamine (H.g-5), evoxine (H.g-6), N-methylhaplofoline (H.g-7), flindersine (H.g-8), folimine (H.g-9), griffithine (H.g-10), gerphytine (H.g-11), gerphytinine (H.g-12), griffinine (H.g-13) and 1,8-Dihydro-8,8-dimethylpyrano [2,3] quinolin-2-one (H.g-14), wherein, griffinine (H.g-13) was a new compound. 4 compounds, dictamnine, skimmianine, folimine, and griffinine were obtained from the roots exact of this material.

The structure of a new compound - griffinine (H.g-13) was established on the basis spectral data (IR, <sup>1</sup>H, <sup>13</sup>C NMR and 2D, HETCOR-140, HMBC, and COSY). Griffinine showed the growth inhibition of human mantle cell lymphoma (MINO) 56.93%, CCRF-CEM 62.15%, MV-4-11 52.56%, RL952 and KLE cells at 20  $\mu$ M.





## **STRESS DEGRADATION STUDIES ON RIVAROXABAN AND DEVELOPMENT OF A VALIDATED STABILITY INDICATING HPLC METHOD**

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A validated stability indicating high-performance liquid chromatography coupled methods were developed to analyze Rivaroxaban and its degradation products. Forced degradation studies under stress conditions were carried out in order to establish its stability profile. Stress conditions recommended by the international conference on harmonization (ICH) including oxidative, photolytic, thermal, acidic, and basic hydrolysis were applied. Rivaroxaban showed susceptible to acid and base hydrolytic stress conditions. Rivoroxaban is a common process-related impurity (PRI) of many active pharmaceuticals. In this study, a reverse phase high performance liquid chromatography (RP-HPLC) method coupled with ultraviolet (UV) detection was developed for simultaneous determination and quantitation of these impurities. The method was further validated with respect to specificity, linearity, limit of detection (LOD), limit of quantitation (LOQ), accuracy, recovery, precision and robustness. The developed HPLC method for the related substances and assay determination of rivaroxaban can be used to evaluate the quality of regular production samples.

## DETERMINATION OF GENOTOXIC IMPURITIES IN ARIPRAZOLE AND BREXPIRAZOLE

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Sensitive methods for the determination of genotoxic impurities (GIs), namely 1-Bromo-4-chlorobutane (A), 1,4-dibromobutane (B), 1,4-dichlorobutane (C), 7-(4-bromobutoxy)-3,4-dihydro quinolin-2(1H)-one (D), 7-(4-chlorobutoxy)-3,4-dihydro quinolin-2(1H)-one (E), 7-(4-chlorobutoxy)-1H-quinolin-2-one (F) and 7-(4-bromobutoxy)-1H-quinolin-2-one (G) in aripiprazole (Ar) and brexpiprazole (Br) have been developed using hyphenated techniques. A, B and C were determined by GC-MS, while D, E, F and G were determined by LC-MS. These techniques have been selected based on the structural alerts (SAs), sensitivity, and stability of GI under study. All the developed methods were validated as per International Council for Harmonization (ICH) guidelines. The quantitation limit was found to be 50.0 ppm and the linearity ranged from 5.0 to 100.0 ppm for all the two methods. The correlation coefficient values were found to be 0.99. The recoveries ranged from 70 to 130% signifying the good accuracy of the developed methods.

## AN EFFICIENT METHOD FOR THE SYNTHESIS OF CANNABIDIOL

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(-)-Cannabidiol ((-)-CBD), which is the major non psychotropic cannabinoid in most cannabis preparations, such as hashish and marijuana, is approved for the treatment of seizures associated with Lennox-Gastaut syndrome and Dravet syndrome in patients 2 years of age and older, by the United States Food and Drug Administration (U.S. FDA) on June, 2018. Starting from phloroglucinol, a key intermediate (-)-CBD-2OBoc-OTf is efficiently and regioselectively prepared and further undergoes Negishi cross-coupling to obtain (-)-CBD, and these approaches have no impurity such as Abnormal CBD derivatives, THC- derivatives and double alkylation derivatives. This method allowed an efficient five-step synthesis of (-)-CBD from commercially available materials, phloroglucinol in 28% yield on grams scale by Negishi cross-coupling reaction.

# Posters and Publications

## CHANGES IN LIPID METABOLISM IN PATIENTS WITH CHRONIC KIDNEY DISEASE

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Hyperlipidemia is a frequent accompanying sign of kidney disease, in some cases even reflecting the degree of activity of renal process. Unfortunately, almost always the presence of lipid metabolism disorders in the renal patient worsens the prognosis, both due to the acceleration of nephrosclerosis, and due to the acceleration of atherosclerosis and development of cardiovascular complications.

**Objective.** To study the blood lipid spectrum in patients with chronic kidney disease (CKD), depending on the presence or absence of stenotic vascular lesions.

**Materials and Methods.** A prospective study was conducted in 23 patients (3 men, 20 women) with CKD of stages I – III, aged 48-75 years, an average age – 61.5 (10.45)  $\pm$  2.34 years (M (SD)  $\pm$  m, where M is the mean value, SD is the standard deviation, m is the standard error of the average value), who were treated in the Department of Internal Diseases of the Tashkent city clinical hospital No. 5. The diagnosis of CKD and the stage of the disease were established in accordance with the classification NKF-KDOQI (2003, modification 2013). A specially developed “registration card of patient with chronic kidney disease” (Patent RUz) was filled in for each patient. Glomerular filtration rate (GFR) was determined using CKD-EPI and MDRD formulas. Lipid spectrum of blood serum was studied on the basis of determination of fasting levels of total cholesterol (CS), triglycerides and CS of high (HDLP) and low density lipoproteins (LDLP). Stenotic changes in the vessels were determined using Ultrasound Doppler of brachiocephalic trunk and kidneys vessels. The control group included 10 healthy individuals (10 women), comparable in age.

**Results.** In patients with CKD, GFR averaged 79.74 (10.3)  $\pm$  2.32 mL / min/1.73 m<sup>2</sup>. Arterial hypertension was diagnosed in 92.3% of cases. Among all patients with CKD, chronic pyelonephritis was diagnosed in 5 (21.7%) patients, type 2 diabetes mellitus in 6 (26%), chronic rheumatic heart disease in 1 (4.34%) patient. In 15 (65.2%) patients, dyslipidemia was observed in the form of increase in total CS, triglycerides, HDLP cholesterol in 2.2 times, in comparison with control values. In this case, the severity of dyslipidemia did not depend on the degree of stenotic vascular lesions, which may be associated with the administration of lipid-lowering agents in patients with a high risk of cardiovascular diseases.

**Conclusions.** Dyslipidemia is closely related to the progression of CKD. Its effect is due to both atherosclerotic lesions of renal and other vessels, and direct nephrotoxic action of lipids. Detection of the initial manifestations of lipid metabolism disorders in patients with CKD allowed identifying high risk groups with poor outcome in CKD, and timely prescribing therapy to prevent the development of cardiovascular complications.

## ANTINEOPLASTIC ACTIVITY COLCHAMINOLE (K-19) IN COMPARISON WITH TAXOL AND ETOPOSIDE

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Preparation K-19 named colchaminol has been studied at National institute of a cancer of the USA (NCI) on the panel from 60 tumors of the person *in vitro* that has revealed its high cytotoxic activity. After studying *in vivo* on animals with tumors this preparation has been selected for further preclinic researches

**The work purpose.** A comparative estimation of "acute" toxicity and antineoplastic activity *in vivo* new derivative colchamine K-19.

**Materials and methods.** Studying is executed on 347 mice of line Balb/c of both sexes and SHK healthy and with intertwined tumors AKATOL, AKATON and Sarcoma S180. K-19 for 2-3 days after subinoculation tumors entered to mice intraperitoneal daily 10-was multiple in single doses 40, 35 and 30 mg/kg, comparison preparations taxol and etoposide in known therapeutic doses. An estimation of results spent by standard criteria: LD<sub>5</sub> (MPD) and LD<sub>50</sub>, TGI and life span increase (LSI). Authentic considered distinctions at  $p < 0.05$ .

**Results.** K-19 has appeared low-toxic for mice (MPD=210 mg/kg, LD<sub>50</sub>=350 mg/kg) and highly active on 3 tumors AKATON, AKATON and Sarcoma S180, TGI =91-100%, including on life expectancy increase on strain AKATON with LSI=258% ( $p < 0.05$ ). In comparison with taxol and etoposide, K-19 has appeared on 5-10% more effectively on TGI and on 40-140 % on LSI.

**The conclusion.** New derivative colchamine K-19 differ lower toxicity compared with taxol and etoposide and high antineoplastic activity that allows considering its perspective for advancement in clinic. It can be useful for treatment of solid tumors at parenteral introduction, and a skin cancer at external application.

## ANTINEOPLASTIC ACTIVITY OF NEW PREPARATION COLCHAMINOLE (K-19) ON SUBINOCULATION TUMOURS OF RATS

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In National Cancer center of Uzbekistan studying cytotoxic activity on the panel of tumours of the person at National institute of a cancer of the USA (NCI) in vitro is studied. For preparation K-19 named colchamine, parametres of "sharp" toxicity and antineoplastic activity in vivo on mice are revealed. K-19 has appeared pure toxic for mice ( $LD_{50}=350$  mg/kg) and highly active on 3 tumors. In the present work studying colchamine on tumours of rats is presented.

**The work purpose.** Comparison of antineoplastic activity of new preparation K-19 on rats with tumoral strains the Sarcoma 45 (S-45) and Walker Carcinosarcoma (W-Cs).

**Materials and methods.** Studying is executed on 78 not purebred rats with intertwined tumors S-45 and W-Cs. K-19 entered to rats for 3-7th day after subinoculation tumors 8-fold or 10-fold is multiple intraperitoneal introduction, in comparison with colchamine, colchicine, cyclophosphan, taxol and etoposide, all preparations were entered in therapeutic doses. An estimation of results spent by standard criteria: tumor growth inhibition (TGI), weight of a body and a spleen of animals. Authentic considered distinctions at  $p<0.05$ .

**Results.** The received results followed that on tumor W-Cs the preparation K-19 suppressed growth of tumors on 98/99 - 98/96 %, colchicine on 32/47 %, colchamine on 35/46 %, taxol on 94/92 % and etoposide on 15/34 %. On S-45 preparation K-19 suppressed growth of tumor on 90/88 %, colchamine on 34/40 % and cyclophosphan on 51/75 %.

**Conclusion.** Studying of preparation K-19 on rats with tumors has revealed its more expressed activity in comparison with initial colchicine, colchamine, cyclophosphan, taxol and etoposide.

Highly active K-19 speaks its complex mechanism of action damaging tumors, and smaller level of by-effects - ability to induction colony-forming uniton spleen (CFUs).

## MODIFICATION OF PEGYLATED CHOLIC ACID INTERMEDIATES FOR USAGE IN GETTING OF STEALTH® LIPOSOMES

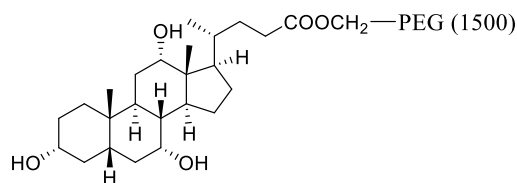
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PEGylation is one of the most successful strategies to improve the delivery of therapeutic molecules such as proteins, macromolecular carriers, small drugs, oligonucleotides, and other biomolecules. PEGylated molecules show increased half-life, decreased plasma clearance, and different biodistribution, in comparison with non-PEGylated counterparts. These features appear to be very useful for therapeutic proteins, since the high stability and very low immunogenicity of PEGylated proteins result in sustained clinical response with minimal dose and less frequent administration. PEGylation of liposomes improves not only the stability and circulation time, but also the 'passive' targeting ability on affected tissues, through a process known as the enhanced permeation retention effect, able to improve the therapeutic effects and reduce the toxicity of encapsulated drug.

The advantages of PEGylation on drug efficacy were exploited also to improve other delivery technologies: a typical example of such application is represented by long-circulating liposomes. Classical conventional liposome consists of an aqueous core entrapped by one or more bilayers composed of natural or synthetic lipids. Liposomes composed of natural phospholipids are biologically inert and weakly immunogenic, and possess low intrinsic toxicity. Drug delivery can be improved either through a change in formulation or by a chemical modification of drug molecule. Innovative drug formulation such as liposomes, microspheres, nanoparticles or other colloidal systems can increase the circulating time by enhancing the stability and decreasing the clearance of the drug. For this goal, we carried out a combination of the PEG (1500) with cholic acid and reported here about conditions of the synthesis of PEG intermediates for their conversion into a range of derivatives.

PEG-1500 (Ferak Berlin; 5 g) was dissolved in 25 mL toluene, and 20 mL toluene were removed by distillation to remove water. Triethylamine (0.1 g; distilled over calcium hydride) was added to the PEG-toluene solution. Cholic acid (0.69 g) was dissolved in 5 mL 1.0 M NaOH in methanol to prepare the salt, and the solvent was then removed by lyophilization. The lyophilate was dissolved in 20 mL anhydrous ethyl ether, to which was added dropwise 2 mL oxalyl chloride. The solvent was removed by rotary evaporation, and the residue resuspended in 20 mL toluene. The PEG and acid chloride solutions were mixed and heated to reflux for 15 min. Cooling to 40 °C resulted in precipitation of the product. Yield was 4 g. The product was purified in three stages. In the first stage product was repeatedly (five times) dissolved in 200 mL acetone (slight warming aids solution) and precipitated by addition to 300 mL anhydrous ethyl ether at 0 °C. TLC on silufol (solvents - methanol : water / 5:1) Rf PEG = 0.26; PEG-ester (Rf = 0.48) and cholic acid (Rf = 0.81). The construction of PEG-liposome intermediates is going on.





## SECONDARY METABOLITES OF THE AERIAL PARTS OF *Lepidolopha komarovii*

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Plants of the genus *Lepidolopha* (Asteraceae family) in the flora of Central Asia are represented by 8 species, of which four species grow in Uzbekistan. One of the widespread plant species of the genus *Lepidolopha* in the flora of Uzbekistan is *Lepidolopha komarovii* - a shrub up to 1 m tall, blooms in June-July, fruit in August-September, grows on rocky slopes, screes in the lower and middle zones of mountains in Tashkent (Pskem and Ugam ranges), Samarkand (Zeravshan range), Surkhandarya (Gissar range) areas.

Chemically this plant is practically not studied, it was only noted that the aerial part of the plant produced sesquiterpene  $\gamma$ -lactones. In this regard, we carried out phytochemical studies of the aerial part of *Lepidolopha komarovii*, collected at the beginning of flowering in the spurs of the Nurata ridge in the vicinity of the village of Ukhum of Jizzakh region.

The chromatographic separation on a column of extractive substances mixture from chloroform, ethyl acetate and *n*-butanol fractions of the 70% alcohol extract from the aerial part of *Lepidolopha komarovii*, resulted in seven substances of phenolic nature: caffeic acid (1), luteolin (2), quercetin (3), luteolin-7-*O*- $\beta$ -D-glucopyranoside (cynoraside) (4), luteolin-3',4'-dimethoxy-7-*O*- $\beta$ -D-glucopyranoside (5), 5,4'-dihydroxy-3,6,7,3'-tetramethoxyflavone (chrysosplenethin) (6), 5-hydroxy-3,3',4',6,7-pentamethoxy flavone (artemethine) (7) and sesquiterpene lactone with guanine-type skeleton of achillin (8). Identification of the isolated compounds was performed on the basis of their spectral data (UV, IR,  $^1\text{H}$  and  $^{13}\text{C}$  NMR) and their comparison with those described in the literature. All identified compounds were isolated for the first time from the aerial parts of *Lepidolopha komarovii*.

## DITERPENOID ALKALOIDS FROM *Aconitum barbatum* var. *puberulum*

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*Aconitum barbatum* var. *puberulum* Ledeb., a herbaceous plant distributed in the northern part of China, as well as in the Siberia region of Mongolia and Russia, has been used as a folk medicine for a long period of time in China to treat stomach-ache, tracheitis, rheumatic arthritis, lymphatic tuberculosis and some other inflammations [1-3]. Phytochemical studies have revealed that *A. barbatum* var. *puberulum* contained 54 compounds including 39 diterpenoid alkaloids [4-6]. During our further investigation for more diterpenoid alkaloids on the whole herb of this plant, two new diterpenoid alkaloids, barpuerudines A (1), barpuerudines D (2), and five known diterpenoid alkaloids, leucostomine A (3), leuconine (4), sepaconitine aminoalcohol (5), lappaconidine (6) and acosanine (7) were isolated (Fig. 1). Compounds 3-7 were isolated from the plant for the first time.

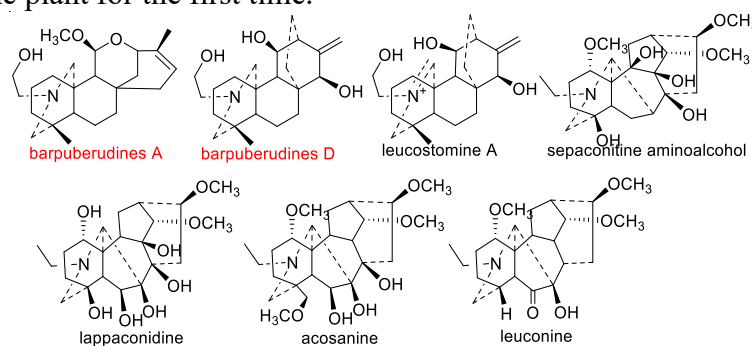


Fig. 1 The structures of compounds 1-7

### ACKNOWLEDGEMENTS

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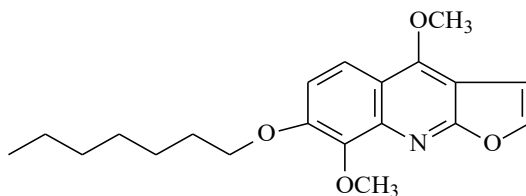
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**ANGUSTININE A NEW ALKALOID FROM *Dictamnus angustifolius*****Z. Ch. Abrayeva, Kh. A. Rasulova**

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The genus *Dictamnus* (fam. Rutaceae) includes five species used as a traditional herbal medicine. Since ancient times, *D. angustifolius* and *D. dasycarpus* have been used in China to treat hives, eczema, jaundice, rheumatism, and other various diseases. Compounds isolated from the genus *Dictamnus* are mainly furoquinoline alkaloids and limonoid triterpenoids. Chemical studies of these *Dictamnus* species showed that some exhibited strong bioactivity and toxicity to tumor cells too. Therefore, chemical and physiological studies of plants of the genus *Dictamnus* are relevant and promising.

We firstly studied the roots of *D. angustifolius*, collected from a new place of growth (Pskom, 2015) during the drying period. The chloroform fraction of the plant *D. angustifolius* was separated on a column, resulting in alkaloids skimmianine,  $\gamma$ -fagarine, haplamine, and base **1**. Based on the IR, NMR spectra, the structure of base **1**, called angustinine, was provided. Angustinine, a new alkaloid, is a heptyl derivative of 4,8-methoxyfuranquinoline.

**1**

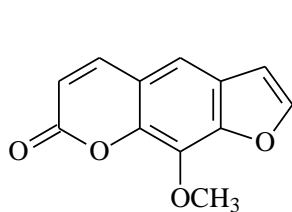
**COMPONENTS FROM *Ruta graveolens*****Z. Ch. Abrayeva, Kh. A. Rasulova, K. K. Turgunov**

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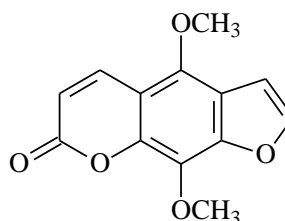
*Ruta graveolens* L. (Rutaceae), a medicinal plant, has strong antifungal activity, antispasmodic and expectorant properties. The antispasmodic property is attributed to the presence of coumarins, as well as essential oils.

Seeds of *Ruta graveolens* were collected in an infield of ICPS and extracted with ethanol. Gasoline, chloroform, ethyl acetate, ethanol and water fractions were obtained from the extract for further study.

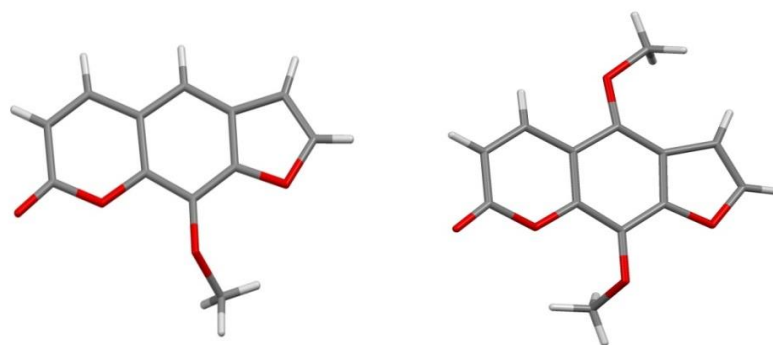
From the ethyl acetate fraction of *Ruta graveolens* seeds during acetone treatment, the precipitate was recrystallized from ethanol, and obtained compound **1**. By repeated separation of the ethyl acetate fraction of *Ruta graveolens* seeds on the column, compounds **1** and **2** were obtained. The obtained compounds were identified to be xanthotoxin (**1**) and isopimpinellin (**2**), on the basis of spectral characteristics (NMR, IR spectra) and PCA. Xanthotoxin (**1**) and isopimpinellin (**2**) were isolated from the seeds of *Ruta graveolens* for the first time.



Xanthotoxin



Isopimpinellin



## FATTY ACID COMPOSITION AND BIOLOGICAL ACTIVITY OF OILS FROM *Nitraria sibirica* FRUIT

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In order to further exploit and utilize *Nitraria sibirica* pall (NSP), various methods including conventional extraction (CE), Soxhlet extraction (SE) and ultrasound-assisted extraction (UAE) were used to extract oils from its fruit, and the resulting oils were compared in terms of fatty acid composition and biological activity. Fatty acid composition of NSB fruit oils was determined through gas-chromatography–mass-spectrometry (GC-MS) analysis. Meanwhile, biological activity was evaluated based on the determination of antioxidant capacity.

The results showed that extraction yield was 5.24, 5.73 and 7.00% for the CE, SE and UAE extraction, respectively with the principal fatty acids being linoleic acid (71.57-73.50%) and oleic acid (20.34-21.46%). The ratios of saturated fatty acids (SFA)/unsaturated fatty acids (UFA) were 1/22.86, 1/21.32 and 1/21.27 in the oils extracted by CE, SE and UAE method. The oil obtained by CE and UAE showed the highest DPPH and ABTS free radical scavenging activity, respectively.

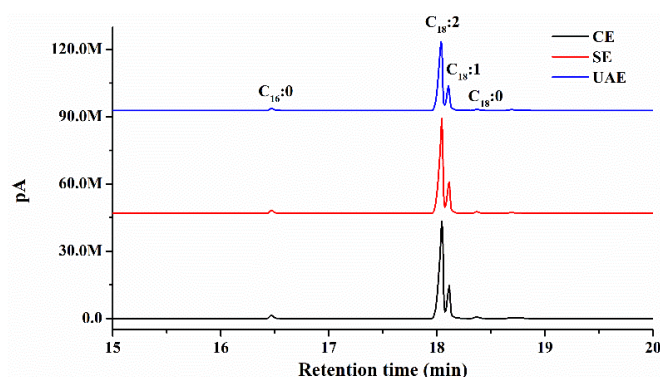


Fig. 1 Total ion-chromatograms of NSP oils

### ACKNOWLEDGEMENTS

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## POLYSACCHARIDES FROM FRUITS OF *Nitraria sibirica*

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Nowadays, polysaccharides have aroused extensive attention of researchers because of low toxicity and numerous health beneficial properties, and have a wide application in health care, food industry and material science. Several studies have indicated that polysaccharides have preferable immune regulating, antitumor and anti-inflammatory activities. In this paper, polysaccharide from *Nitraria sibirica* pall (NSP) was extracted by water extraction (WE), ultrasound-assisted extraction (UAE), cellulase-assisted extraction (CAE) and ultrasound-cellulase assisted extraction (UCAE), and the yield and bioactivity were compared.

The results showed that different extraction methods had certain effects on extraction yields and bioactivities of polysaccharides, among them UAE method obtained polysaccharides demonstrated the highest yield (16.71%) and scavenging activity against 2,2-diphenyl-1-picrylhydrazyl; di(phenyl)-(2,4,6-trinitrophenyl) iminoazanium (DPPH), hydroxyl (OH), and 2,2'-azino-bis(3-ethylbenzothiazoline-6-sulfonate) (ABTS) free radicals. Therefore, the UAE method might be the best for polysaccharide extraction from NSP. Further researches about the extraction process of UAE technique are in progress through using response surface method.

**Table 1** Extraction yield and antioxidant activity of polysaccharides

	WE	UAE	CAE	UCAE
Yield	16.57	16.71	15.57	12.55
	Half inhibition rate IC <sub>50</sub> (mg/mL)			
DPPH	0.797	0.712	0.802	0.743
OH	0.682	0.658	0.532	0.604
ABTS	0.171	0.166	0.175	0.183

### ACKNOWLEDGEMENTS

This work was supported by National Science and Technology Major Project of China (No. 2017ZX09301045).

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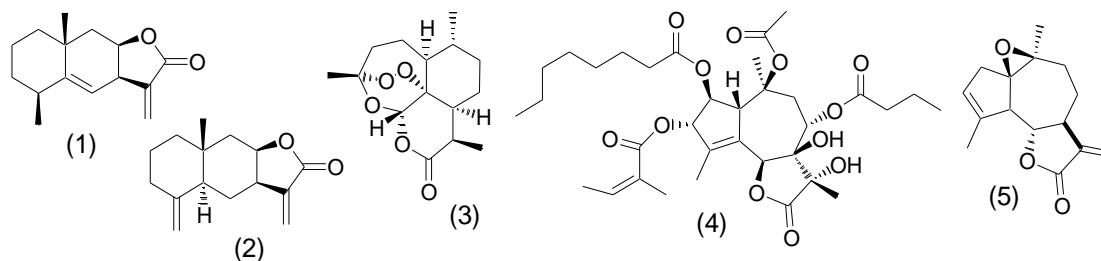
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**ORIGINAL DRUGS BASED ON NATURAL SESQUITERPENE  
LACTONES.  
PROSPECTS FOR DEVELOPMENT, TECHNOLOGY AND  
APPLICATION**

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A promising direction in the development of original drugs is the creation of new drugs based on natural sesquiterpene lactones, the number of which currently exceeds 8,000 compounds. Most of them have a wide pharmacological activity due to the presence of alkylating functional fragments in the structure of molecules ( $\alpha$ -methylene- $\gamma$ -lactone cycle, epoxide ring, peroxide group). On the basis of a number of natural sesquiterpene lactones, original drugs have been developed, among of which are tauremisin (tonify CNS and cardiotoxic), mixture of alantolactone (1) and isoalantolactone (2) (antiulcer), artemisinin (3) (antimalarial), thapsigargin (4) (cytotoxin and anti-inflammatory), arglabin (5) (antitumor and immunomodulating), parthenolide (for migraine prophylaxis), leucomisine (hypolipidemic and anti-atherosclerotic), cynaropicrin (antiparasitic), vernolepin (antitumor and antimicrobial).



The report discusses the performance potentials for chemical modification and transformation of sesquiterpene lactone molecules: obtaining a water-soluble form or forms with improved physicochemical properties; the introduction of additional functional groups that increase the number of pharmacophore centers and increase the biological activity of the compound; the use of nanotechnology to provide targeted drug transport of drugs molecules in the body.

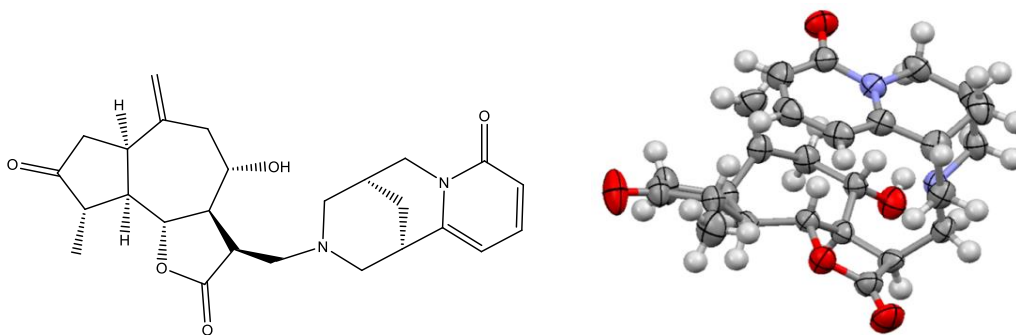
The state of the technology for the production of drugs based on alantolactones, thapsigargin, artemisinin, arglabin, parthenolide was examined, the basis of which was the extraction of plant materials with various solvents, followed by purification of the amount of extractive substances by chromatography and crystallization methods. Particular attention was paid to environmentally friendly extraction technologies using “green” solvents (supercritical carbon dioxide and water), which are becoming increasingly popular among industrial methods for the extraction of biologically active substances, as well as the technology for the separation and purification of plant extracts by centrifugal partition chromatography.

NEW  $\beta$ -CYTISINYL DERIVATIVE OF GROSSHEIMIN

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The introduction of a nitrogen atom into the molecule of sesquiterpene lactones is most often carried out by amination according to the Michael reaction. In terms of obtaining a nitrogen-containing derivative based on sesquiterpene lactone of grossheimin (**1**) isolated from *Chartolepis intermedia* Boiss., an amination reaction was carried out using the natural alkaloid cytosine as a reagent. Moreover, on the basis of two natural metabolites with quantitative yield, a new hybrid compound (**2**) was obtained with an empirical formula  $C_{26}H_{32}O_5N_2$ , melting point 224-226 °C (ethanol),  $[\alpha]_D^{20} - 25^\circ$  (c 0.16,  $CHCl_3$ ), interesting for developing the substance of a new drug.



**Figure 1** The spatial structure of the molecule (**2**)

Thus, during the amination reaction of grossheimin (**1**), 3-oxo-8 $\alpha$ -hydroxy-1,5,7,11 $\alpha$ ,4,6,8 $\beta$ (H)- guai-10(14)-en-13-cytisinyl-6,12-olide (**2**) was synthesized. The molecular structure of the synthesized compound (**2**) was determined on the basis of spectral data (IR, UV,  $^1H$ ,  $^{13}C$  NMR, 2D NMR:  $^1H$ - $^1H$  COSY, NOESY,  $^{13}C$ - $^1H$  COSY, and COLOC) and X-ray.



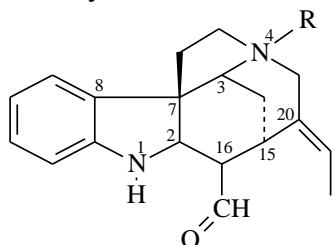
## QUARTERIZATION OF NORFLUOROCURURINE

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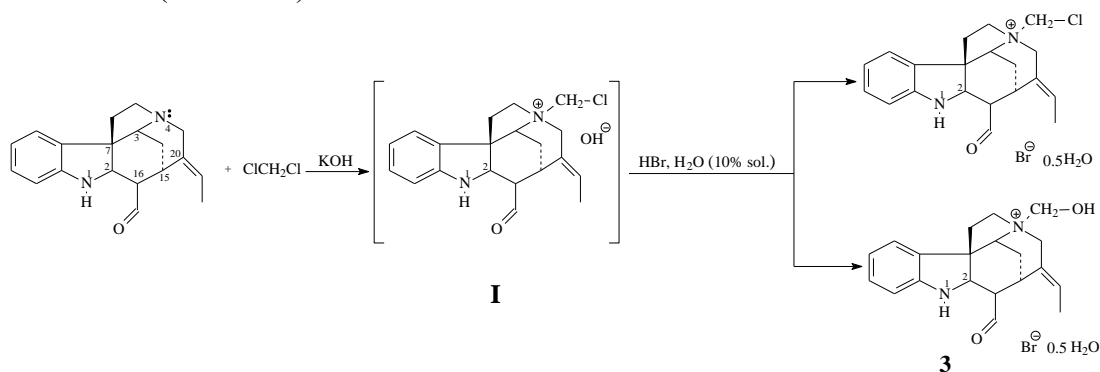
New quaternary halogen alkyl derivatives of the main indole alkaloid *V. erecta* norfluorocurarine (vincanine) were synthesized based on the quaternization reaction at the tertiary nitrogen atom N4. In this regard, the behavior of the aldehyde group in other fluorocurarine salts and their derivatives at the N4 atom was also of interest.

We have obtained by quaternization quaternary derivatives with haloalkyls of the indole alkaloid norfluorocurarine and studied their structures in the form of salts by single crystal x-ray diffraction analysis: methyl iodide (1), methyl iodide monohydrate (2), chlor methylene bromide hemihydrate (3) and brom ethyl bromide monohydrate (4).



1. R=CH<sub>3</sub>•I
2. R=CH<sub>3</sub>•H<sub>2</sub>O•I
3. CH<sub>2</sub>Cl•0.5H<sub>2</sub>O•Br
4. C<sub>2</sub>H<sub>4</sub>Br•H<sub>2</sub>O•Br

When interacting with a 10% hydrogen bromide solution, N4-methylene chloride vincanine hydroxide (I) was partially hydrolyzed and two unexpected compounds 3 were formed (scheme 1.).



Scheme 1. obtaining of compound 3.

The progress of the reaction was monitored by thin layer chromatography. The physicochemical constants of the obtained substances were determined. Their spatial structures, the nature of intra- and intermolecular interactions, the features of the crystal structure were studied, and a conformational analysis of the synthesized derivatives was carried out.

A NOVEL FLAVONOL GLYCOSIDE FROM *Thalictrum minus*

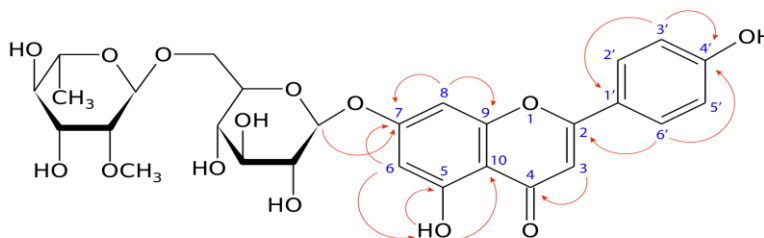
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A novel flavonol glycoside thamiflaside (**1**) has been isolated from the *Thalictrum minus* plant. The genus *Thalictrum* (Ranunculaceae) is represented by 5 species in the flora of Uzbekistan. The medicinal plant *Thalictrum minus* is widely used in traditional medicine for its anti-inflammatory, antitumor, antioxidant properties [1].

Phytochemical investigation led to the isolation of a new flavonol glycoside, thamiflaside (**1**). Plant material (6 kg) was extracted with ethanol and the obtained extract was then purified with chloroform, hexane and n-butanol. Column chromatography of the butanol fraction with chloroform-methanol-water (70:12:1) eluent system led to the isolation of compound **1** with the structure of flavonol glycoside. Compound **1** acid hydrolysis products analysis showed that aglycone part was represented by apigenin, carbohydrate part consisted of two sugar moieties - glucopyranose and rhamnopyranose - in ratio 1:1, confirmed by paper chromatography [2]. Compound **1** was a yellowish amorphous powder with mp 263-264 °C (ethanol).

On the basis of spectral data (IR, NMR <sup>1</sup>H and <sup>13</sup>C NMR, DEPT, HMBC, HSQC), the structure of thamiflaside was assigned as apigenin 7-*O*- $\alpha$ -L-2''-methoxy-rhamnopyranosyl (1-6)- $\beta$ -D-glucopyranosyl. HMBC correlations of compound **1** are shown on the Figure.



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## SEPARATION AND ANALYSIS OF ESSENTIAL OILS FROM *Delphinium oreophilum* Huth GROWING IN UZBEKISTAN

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Namangan state university

The *Delphinium oreophilum* Huth species of the *Delphinium* plant was harvested from the slopes of Zaamin in July 2018 and dried in a cool place. The composition of the essential oils did not differ significantly from the surface of the plant, which was crushed and extracted with fresh plants by hydrodistillation method.

Essential oils were obtained by hydrodistillation within 3-4 hours. The extracted essential oil was stored in 40 °C tightly sealed vials before dehydration with Na<sub>2</sub>SO<sub>4</sub>. Essential oils were a yellowish orange liquid with a specific odor.

Essential Oils and contents (%) of *D. oreophilum* Huth by Agilent Chromato-mass Spectrometer

№	Compound	RT	RI	amount, %
1.	Hexanal	2.974	1075	0.25
2.	Acetylcyclopropane	3.571	1117	0.26
3.	1-Butanol	3.841	1131	0.12
4.	2-Isopropyl-1,3-dimethyl-1-cyclopentene	4.192	1150	0.17
5.	2-Heptanone	4.567	1170	0.15
6.	3-methyl 1-Butanol	5.046	1196	3.48
7.	(E)-2-Hexenal	5.268	1205	0.35
8.	1-Pentanol	5.999	1233	0.32
9.	3-hydroxy-2-butanone (Acetoin)	6.700	1260	9.79
10.	Cyclopropaneethanol	7.727	1299	0.44
11.	2-Heptanol	7.819	1303	9.64
12.	1-Hexanol	8.637	1334	1.29
13.	(Z)-3-Hexen-1-ol	9.424	1364	5.35
14.	trans-4-Hexen-1-ol	10.064	1389	0.43
15.	3-Furfural	11.502	1440	0.53
16.	2-Nonanol	13.470	1508	1.97
17.	(-)-cis-Carane	14.232	1534	3.55
18.	1-Octanol	14.466	1542	0.29
19.	Benzeneacetaldehyde	16.440	1610	1.31
20.	α-Terpineol	18.204	1673	3.41
21.	p-Cyclohexylphenol	18.776	1693	0.32
22.	Guajol	22.330	1822	12.09
23.	Benzyl alcohol	22.791	1839	9.88
24.	Phenethyl alcohol	23.677	1871	11.21
25.	Not identified	24.402	1897	0.74
26.	Phenol	26.173	1961	16.17
27.	3-Phenylpropanol	27.169	1997	0.47
28.	2-Methoxy-4-vinylphenol	30.963	2097	1.59
29.	Not identified	36.490	2243	1.74
				97.31

The volatile compounds of the essential oils obtained from the surface of the plant by hydrodistillation method were investigated by chromatographic-mass-spectrometry.

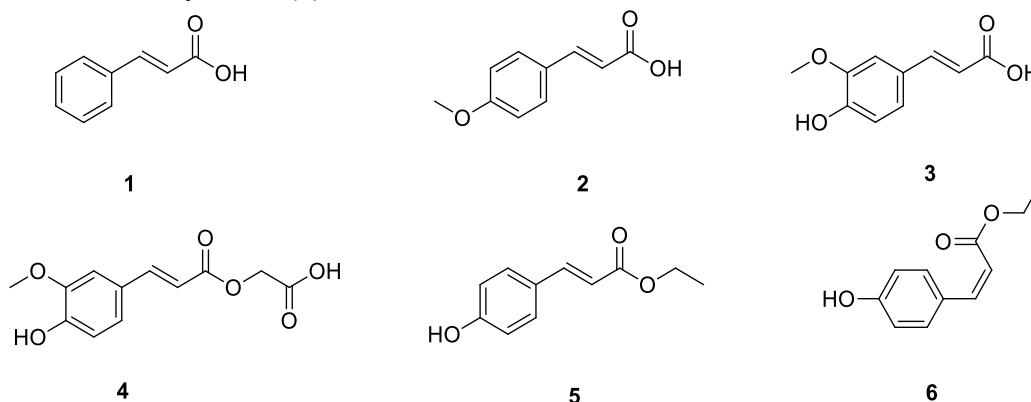
As a result of investigation, 29 essential substances were found in essential oils. The most common ones were Phenol (16.17%), guajol (12.09%), phenethyl alcohol (11.21%), benzyl alcohol (9.8%), acetoin (9.79%), 2-heptanol (9.64%), (Z) -3-Hexen-1-ol (5.35%), 3-methyl 1-Butanol (3.48%), cis-carane (3.55%), and α-terpineol (3.41%).

PHENOLIC COMPOUNDS FROM *Hyssopus cuspidatus*K. Aihaiti<sup>1,2</sup>, O. Shomirzoeva<sup>1</sup>, J. Li<sup>1</sup>, H. A. Aisa<sup>1\*</sup>

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*Hyssopus cuspidatus*, belonging to the Lamiaceae family, is widely distributed in Mediterranean regions and Central Asia. It grows naturally in southern Europe, the Middle East, North Africa and North America. The leaves, stem and flowers of *H. cuspidatus* have a pleasant aromatic fragrance and are widely used in flowering. In present work, six phenolic compounds were isolated from the combined fractions of ethyl acetate and n-butanol of the *H. cuspidatus* dried aerial parts using silica gel chromatography, Sephadex LH-20, pre-HPLC methods. Their structures were elucidated as cinnamic acid (**1**)<sup>[1]</sup>, 4-methoxycinnamic acid (**2**)<sup>[2]</sup>, ferulic acid (**3**)<sup>[3]</sup>, carboxymethyl isoferulate (**4**)<sup>[4]</sup>, *trans-p*-hydroxyl ethyl cinnamate (**5**)<sup>[5]</sup>, and *cis-p*-coumaric acid ethyl ester (**6**)<sup>[6]</sup>.



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## NATURAL METABOLITES OF MICROBE ORIGIN AND PROSPECTS FOR THEIR USE IN AGRICULTURE AND INDUSTRY OF THE REPUBLIC OF UZBEKISTAN

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As a result of excessive use of chemicals (disinfectants, pesticides, fungicides, defoliant, oxidizing agents, dyes, etc.) and mineral fertilizers in agriculture and industry for many years, many countries of the World have undergone negative changes in agrobiocenosis in general, depletion of the natural potential of the soil, water, air pollution, deterioration of the condition of animals, vegetation of the Earth, as well as the environmental situation, which is the reason for the occurrence of many diseases of humans and animals. Therefore, at present the demand for biological products of natural origin, ecologically pure, environmentally safe and easy involved in the cycle of important and vital elements in the biosphere cycle of nature has sharply increased.

This report presents the results of studies relating to the production and use of natural metabolites of microbial synthesis in industry and agriculture of the Republic. Biologically active and valuable substances from various classes of microorganisms were obtained along the path of biologization of industry and agriculture. In particular, carbon hydrolytic, hydrolytic, oxidative enzymes were obtained, potentially valuable metabolites for food, pharmaceutical, leather, textile (amylases, glucoamylases, cellulases and their forms, xylanases, inulinases,  $\beta$ -fructofuranosidases, proteases and their forms, etc.).

For agriculture, biological preparations containing a complex of hydrolytic (cellulase, xylanase, protease) and redox, phenol oxidative enzymes (peroxidase, polyphenol oxidase), phytohormones and antibiotic substances were recommended. At the same microorganisms were used, which were widespread in various ecological niches of nature and provided a profound change in any substrates of organic and anorganic nature in vitro, in vivo and in situ. By selective methods, non-pathogenic, dominant genera and species were selected from among them, which were part of the soil, taking root in the plant rhizospheres, having a positive effect on their growth and development.

The resulting biological products for humans and animals were completely safe; when introduced into the soil, the decomposition and assimilation of organic soil residues and minerals significantly improved, leading to an increase in its fertility. The created biological products "Mikrozim-1", "Mikrozim-2" were ecologically pure, environmentally safe, highly effective in cultivating valuable crops, increasing their productivity and reducing their incidence of root rot, wilt, fusariose, etc.

These drugs can sharply increase the quality, preservation and productivity of crops, the overall efficiency of agriculture. Moreover, they are very important for peoples' health, because main food products: meat, milk, butter, egg, grain of cereals, legumes, seeds and fiber of cotton, crop of melons and gourds, horticultural crops, above all, must be safe.

## EVALUATION OF ENZYME INHIBITORY ACTIVITIES OF *Lagochilus* species

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The genus *Lagochilus* (Lamiaceae) is native to Central, South-Central, and Eastern Asia. This genus is represented by 13 to 18 species and basically occurs throughout the territory of Uzbekistan, starting from the deserts to Tian-Shan and Pamir-Alay mountain systems [1]. Despite their wide application in folk and traditional medicine, the biological activities of the genus *Lagochilus* were poorly studied.

The aim of the present study is enzyme inhibitory activities of isolated compounds: 7-cinnamoyllamalbide (**1**), 7,4'-dimethoxyflavone (**2**),  $\beta$ -sitosterol (**3**), daucosterol (**4**), lagochilin (**5**), 8-acetylharpagide (**6**) from *L. gypsaceus* and methanol extracts of 7 different *Lagochilus* species (*L. acutilobus*, *L. gypsaceus*, *L. inebrians*, *L. olgae*, *L. proskorjakovii*, *L. setulosus*, *L. vvedenskyi*).

Enzyme inhibitory effects were investigated against acetylcholinesterase (AChE), butyrylcholinesterase (BChE), tyrosinase,  $\alpha$ -amylase, and  $\alpha$ -glucosidase. The enzyme inhibitory effects were evaluated as standard compound equivalents. Briefly, galanthamine was used for AChE and BChE, kojic acid for tyrosinase and acarbose for  $\alpha$ -amylase and  $\alpha$ -glucosidase [2].

The results showed that compound **2** exhibited the strongest inhibitory effects on both AChE and BChE, while compound **6** had the weakest effect on these enzymes. From the extracts, *L. olgae* and *L. gypsaceus* were the most active on these enzymes, respectively. Regarding tyrosinase inhibitory effects, the highest inhibitory effect was detected by *L. inebrians* (from Djizzakh) with 70.29 mgKAE/g, followed by *L. acutilobus* and *L. olgae*. Similar to cholinesterases, compound **2** was also the most active on tyrosinase. In amylase inhibitory assay, *L. acutilobus* and compound **2** showed the best inhibitory effects, however, the weakest ability was observed for compound **6**. In addition, *L. inebrians* extracts exhibited stronger glucosidase inhibitory effects than other species and again compound **2** was the most active of the isolated compounds. To sum up, we could suggest that compound **2** was a main active compound on the tested enzymes.

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## BIOLOGICAL ACTIVITY OF EXTRACTS OF SOME PLANTS FROM GEORGIAN FLORA

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The flora of Georgia is represented by about 4 275 species. Since ancient times, most of them have been used in traditional medicine. Chemical and biological studies conducted at the Institute of Pharmacochimistry, in many cases proved the content in them the different classes of biologically active compounds, causing their use as therapeutic agents.

On the basis of previous studies, some species are recognized as official raw materials for pharmaceuticals. So, *Astragalus falcatus* Lam. is a raw material for the production of hypoazotemic, hypoglycemic and diuretic drug "Flaronin"; *Rhododendron ungerii* Trautv. - raw materials for antiherpetic ointment; *Salvia officinalis* L. - raw material of cholesterol-lowering drug. Some species (*Rhododendron ponticum* L., *Astragalus bungeanus* Boiss., *Ononis arvensis* L., *Salvia garedji* Troitzk. - an endemic of Georgia) contain a significant amount of phenolic compounds. 32 individual substances from the group of catechins, anthocyanidins, flavonols, flavones, isoflavones and phenolic acids were isolated and characterized from these plants.

Extractive compounds of aerial parts of *Astragalus bungeanus*, on the model of cyclophosphamide-induced drug leukopenia in mice, showed moderate leukopoietic activity, increasing by 130% the number of leukocytes compared with control animals. Purified extracts from roots of *Ononis arvensis* and leaves of *Rhododendron ponticum* had a diuretic effect, increasing diuresis by 300% and 160%, respectively, compared with the control group. Crude phenolic acids of leaves of *Salvia garedji* exhibited high antioxidant activity.

The study of the chemical composition of these plants is going on in order to identify compounds responsible for mentioned biological effects.

## **EFFECT OF GLYCYRRHIZIC ACID SALTS ON THE DEVELOPMENT OF POTATO CALLUS CELLS**

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Although studies are being conducted to protect plants from external factors, the biochemical and physiological properties associated with their stability, as well as the role of physiologically active substances, are not enough to make certain decisions.

Based on this, in our studies we have studied glycyrrhizic acid in vitro with salt concentrations at various levels that affect the fertility and growth and development of potatoes. This acid solution and some of its salts, gave their properties that stimulate plant development. To do this, in order to obtain callus formation from potatoes, a plant in a test tube is usually used in a sterile manner grown without the addition of a hormone to the meristematic tissue. We sterilized meristematic tissue and kidney varieties Sarnau and Santa, belonging to the generation of Solanum potato for 5 minutes and then washed them 3 times in sterilized distilled water. Then pour into sterile wringer paper and place in a nutrient tube. In vitro we cut fabric size of 5-10 mm from the embryonic plants and set them in farming in the hormonal and glycyrrhizic acid the nutrient medium MS+2,4 D. We observed the development of Callus cells in hormone and glycyrrhizic nutrient medium in kilotech.

Tissue obtained from the spark parts of plants grown in a sterilized medium potato tissue, was identical in the case of adding sodium and potassium salts of glycyrrhizic acid with the state of cal tissue in a nutrient medium with addition of 2,4 D plant hormone, lithium, and ammonium salts with the addition of Callus cells plant hormone 2,4 D cases were observed of rapid development in comparison with Callus cells in a nutrient medium with the addition of plant hormone.

In the lithium salt of glycyrrhizic acid, higher results were observed in 1.0 and 1.5 times compared to the variants with sodium and potassium salt, and in the ammonia salt-in 1.1 times 1.8.

Thus, it can be concluded that glycyrrhizic acid has the property as a physiologically active substance that accelerates the growth and development of plants.



## TISSUE GENERATING ACTIVITY ON MODELS OF MECHANICAL WOUNDS AND THERMAL BURNS

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The skin is the largest, anatomically complex and multifunctional organ. It plays a crucial role in maintaining human life through thermoregulation and maintaining water-electrolyte balance, acts as a barrier to external influences, including microorganisms, and represents a field of receptors of various types of sensitivity. Therefore, if the integrity of the skin is damaged, the healing process immediately starts, which ends with a complete restoration of the tissue. Identification and elimination of factors that impede wound healing are the main steps for effective and successful wound healing.

The most active in the process of tissue healing and regeneration are biologically active substances of a peptide nature, belonging to the class of lipid-transporting proteins, due to interaction with bilayer lipid membranes in the presence of phospholipids such as diacylglycerol, phosphatidylcholine, phosphatidylethanolamine, and phosphatidylserine.

The aim of this work is to study the tissue-regenerating activity of a plant-derived lipid-transporting peptide isolated from the seeds of black cumin *Nigella sativa* containing phosphatidylcholine.

Studies were conducted on animals, on models of mechanical wounds and thermal burns. On the 3rd and 7th day after treatment, skin samples were taken and a histological examination was performed in the healing dynamics in comparison with control samples and samples taken after causing wounds and burns.

In skin samples examined under a microscope after mechanical wounds after 3 days of treatment, there was no lesion site, that was, complete wound healing occurred. After 7 days of treatment under a microscope, the drug presented a rather long section of rat skin, on which hair, the epithelial layer and the connective tissue part of the skin stood out well. The morphological picture of this case corresponded to the picture of control-intact animals.

On the models of thermal burns, the mechanism of secondary cell damage (apoptosis), membrane destruction and cell disintegration were observed on the 1st day. From the 3rd day, normalization of the normal state of neurons was observed, and on the 5th and 7th day there was no presence of destroyed cells, a multilayer layer of cells was created that promoted skin regeneration.

It has been established that in the presence of a lipid-transporting protein, skin regeneration without scarring occurs and fragments of the basement membrane, hair follicle cells and sebaceous gland epithelium are preserved due to increased oxygen diffusion by epithelial cells and improved anaerobic energy exchange in vascular endothelium.

This lipid-transporting protein has tissue-regenerating activity and, in the future, it is planned to create a pharmaceutical composition for the treatment of ulcerative colitis of various etiologies on its basis.

## DITERPENE ALKALOIDS FROM SPECIES OF THE *Aconitum* L. GENUS AND THEIR BIOLOGICAL ACTIVITY

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The plant species of *Aconitum* L. genus are promising source of pharmacologically active alkaloids.

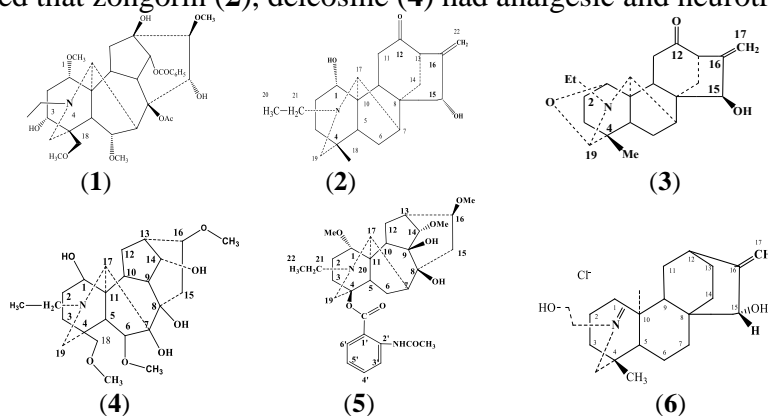
The report discusses the results of a chemical study of the roots of *Aconitum soongaricum* Stapf., *Aconitum monticola* Steinb. and aerial part of *Aconitum anthoroideum* DC.

The quantitative content of alkaloids in the extracts of the studied plants was determined by method of high performance liquid chromatography (HPLC) on the unit «Hewlett Packard» Agilent 1100 Series in isocratic mode on a column filled with Zorbax SV-C<sub>18</sub> sorbent, with the mobile phase acetonitrile - 0.1 Mol ammonia solution in a ratio of 1:1 with a speed of the mobile phase of 0.5 mL/min, at a wavelength of 230 nm, and at room temperature.

Table 1. The content of diterpene alkaloids in extracts of species of the *Aconitum* L. genus

№	Sample	The quantitative content of alkaloids according to HPLC data, %			
		Aconitine	Zongorin	Lappaconitine	Delcosine
1	Extract of <i>Aconitum monticola</i> Steinb.	0.02	18.8	Not found	11.9
2	Extract of <i>Aconitum soongaricum</i> Stapf.	50.57	12.9	2.81	15.1
3	Extract of <i>Aconitum anthoroideum</i> DC.	Not found	Not found	Not found	17.7

When chromatographic separation of the isolated amounts of extractive substances was carried out on a column with Al<sub>2</sub>O<sub>3</sub> (II degree of activity) with a summ-carrier ratio = 1:20, eluted by mixture of hexane-ethyl acetate (9:1), hexane-ethyl acetate (8:2), ethyl acetate, chloroform-methanol (1:1), we isolated and identified diterpenic alkaloids - aconitine (1), zongorin (2), zongoramine (3), delcosine (4), lappaconitine (5), atisine chloride (6). As a result of the study of biological activity of the isolated alkaloids, it was determined that zongorin (2), delcosine (4) had analgesic and neurotropic effects.



## NEW HYDRAZONE DERIVATIVES OF HARMINE

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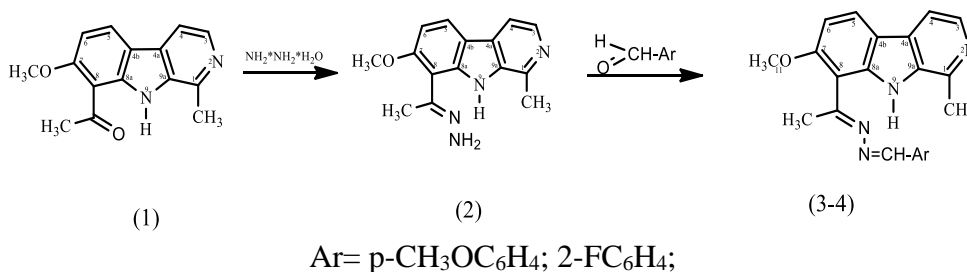
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The plant alkaloid harmine and its derivatives, as monoamine oxidase inhibitors, are hallucinogens, central nervous system stimulants.

The report discusses the synthesis of acetylharmine hydrazone (2) from 8-acetylharmine (1) and the study of reactions (2) with aromatic aldehydes with obtaining of derivatives (3-4), as well as the study of their biological activity.

For the first time, we carried out a reaction to obtain harmine N-arylidenehydrazones (3,4) from acetylharmine hydrazone (2) by reacting the latter with aromatic aldehydes (anisic aldehyde, 2-fluorobenzaldehyde). In this case, the corresponding derivatives (3) and (4) were obtained with yields of 65-83%, and their biological activity was determined.



Thus, we have synthesized new derivatives of the accessible plant alkaloid harmine, N-arylidenehydrazones and studied its neurotropic activity. The synthesized compounds are of interest for the development of substances of new drugs for the treatment of Parkinson's disease, the consequences of cerebrovascular disorders, with trauma of the peripheral nervous system, myopia and myasthenia of various origins.

## PREPARATION OF GALACTOMANNAN OLIGOMERS WITH PRESERVED MONOSACCHARIDE COMPOSITION

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Galactomannans are naturally occurring heteropolysaccharides composed by a  $\beta$ -(1 $\rightarrow$ 4)-D-mannan backbone with a single D-galactose branch linked  $\alpha$ -(1 $\rightarrow$ 6). These biopolymers structurally differ from each other regarding the mannose/galactose (M/G) ratio. Galactomannans are major polysaccharides of commercial importance in various industries due to their low cost and excellent viscosifying properties. Galactomannans are extensively used in food industries as stiffeners and stabilizers of emulsions for preparation of dietary products e.g. coffee whiteners, milk formulations, seasonings, sauces and soups, tinned meats and frozen and cured meat foods. In addition, these biopolymers are largely used in oil recovery, pharmaceutical formulations and personal care products. Recent studies showed the galactomannans potential object to prepare films and hybrid material for biomedical applications. Galactomannans usually occur in high molecular weights (Mw) and thus their aqueous solutions are highly viscous. The average Mw of the galactomannans are in the range of  $1-2 \times 10^6$  Da. The molecular mass is most significant in biological activities, functions, and biomedical applicabilities of biomacromolecules. For industrial and biomedical applications, the depolymerization of natural polysaccharides is essential. In addition, to understand the solution properties and Mw property dependences it is often necessary to degrade the native polymer to prepare samples with various Mw. Recent studies suggested various methods of depolymerization including mainly acidic or enzymatic which respectively are unselective and high cost, thus it still needs to improve a more suitable method for preparation of galactomannan oligomers with preserved monosaccharide composition.

In this study, we investigated free radical depolymerization of guar galactomannan. The galactomannan sample (Mw=570 kDa, M/G=1.89 : 1.0) was depolymerized in the presence of hydrogen peroxide and copper (II) ions. The samples obtained were characterized by molecular mass with size exclusion chromatography (SEC). Structures of the products were studied by IR- and NMR spectroscopic methods. In the results, complete water-soluble galactomannan oligomers, with galactose-mannose ratios (M/G=1.74-1.91:1.0), molecular weight (Mw=4.2-10.5 kDa) and yield (45-68%) were prepared from the guar gum through the depolymerization at 60 °C, during 45-60 min. The SEC results showed that the samples obtained possessed low polydispersity index (1.08-1.15) than that of the starting material (2.8). The degree of polymerization (DP) and product yield were dramatically decreased and with the longer times or higher concentration of hydrogen peroxide solution. The IR- and  $^{13}\text{C}$  NMR spectroscopic studies indicated that the initial structure of the guar gum remained and side-reaction such as ring-opening, the dehydration neither occurred in the reaction. The studies showed the polysaccharide underwent the degradation at the main chain selectively. In conclusion, the depolymerization method studied in this report is very suitable for the preparation of galactomannan oligomers with the preserved monosaccharide composition.

**STUDY OF GLYCOSIDES OF *Saponaria officinalis*****L. N. Ashurova, N. Sh. Ramazonov, D. A. Usmanov, U. Yu. Yusupova**Institute of the Chemistry of Plant Substances, Academy of Sciences of Uzbekistan,  
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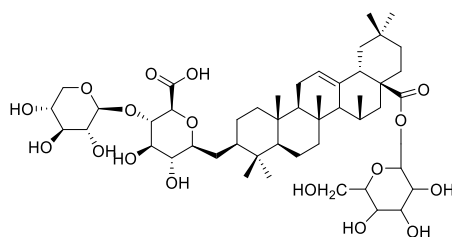
Recently, much attention has been paid to the search for new types of plant resources that contain saponins, which are surfactants. It is known to use an aqueous extract of the roots of the soapwort of *Saponaria officinalis* as medicines and food additives.

*Saponaria* is a genus of annual, biennial and perennial herbaceous plants of the family Carnation (Caryophyllaceae). The name of the genus comes from Lat. sapon - "soap", by the ability of the roots to form foam. About 15 species of these plants are common in Eurasia, about 10 species grow in the territory of Russia, one species grows the *Mylnica officinalis* (*Saponaria officinalis*) and in Uzbekistan there are 6 species. This perennial plant with large roots, a high stem and lanceolate leaves is found along river banks. In folk medicine, an infusion prepared on the basis of the roots and leaves of this plant is used for pneumonia, persistent cough, tonsillitis, bronchitis, whooping cough, laryngitis, runny nose, cholecystitis, dropsy, gout, constipation, rheumatism and various gastrointestinal diseases.

Previously, carbohydrates, triterpene glycosides (2.5–20%) saponazide, saponazides A, B, D, saporubin, hypsogenin, etc. were found from the roots of *Saponaria officinalis*. Alkaloids, ascorbic acid, flavonoids: vitexin, saponarin, saponaretin were found in the leaves. The chemical compound of butanol extract was continued to study.

Raw vegetable *Saponaria officinalis* was collected in 2019 in the city of Tashkent, in the Yunusabad region in the mass flowering phase. The whole plant was dried to an air-dry state, packed in paper bags and stored in a cool, dark place. 1 kg of air-dried plant was extracted with methanol.

The resulting amount was divided into chloroform, ethyl acetate and butanol fractions. Substances of a saponin nature were isolated from the butanol fraction during column chromatography. In the study of TLC and IR data compared with the literature, this substance was identified as Salsoloside C, isolated for the first time from the plant *Saponaria officinalis*.



## ESSENTIAL OILS AND LIPIDS OF TWO *Achillea* SPECIES GROWING IN UZBEKISTAN

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The aim of the present study was to investigate the lipids and essential oils of *Achillea filipendulina* Lam. and *Achillea millefolium* L. (Asteraceae). Although, many publications have described on the compositions and biological activities of essential oils from these widely used medicinal plants, there are not enough results regarding the lipids and essential oils of these species growing in Uzbekistan.

The plants were collected from Tashkent region (Uzbekistan) in 2013 at the full flowering phase. The essential oils from the flowers of *A. filipendulina* and aerial parts with flowers of *A. millefolium* were obtained by hydrodistillation method in a Clevenger type apparatus. Composition of essential oils was determined by GC-FID and GC-MS techniques (Agilent, USA) using polar (Innowax) and non-polar (HP-5) columns. *n*-hexane was used as an extracting solvent for neutral lipids of the same plant materials. The polar lipids were further extracted using chloroform-methanol and analyzed by TLC, CC and GC-FID methods.

The higher yield of essential oil was isolated from the flowers of *A. filipendulina* (1.2 % dry weight). Eighty-four volatile constituents were identified (total 96.6 %) on the basis of their mass spectra characteristics, retention indices and co-elution with available standards. Santolina alcohol (50.1%), (*Z*)-chrysanthenyl acetate (13.8%), 1,8-cineole (5.8%), borneol (4.7%), (*Z*)-chrysanthenol (2.9%), isopinocampone (1.8%), bornyl acetate (1.8%) and terpinen-4-ol (1.3%) were the major compounds of *A. filipendulina* oil. The sum of the yields of hexane and chloroform-methanol extracts (as the yield of total lipids) was 4.4 % on dry weight of flowers. Dominant fatty acids of the flower lipids were the unsaturated components (71.2 %) with a high content of linoleic acid (44.6 %).

The yield of the essential oil for *A. millefolium* aerial parts was 1.0 %. The essential oils consisted of 82 components (total 97.1 %). The main constituents were 1,8-cineole (14.3%), bornyl acetate (4.4%), camphor (4.1%), terpinen-4-ol (3.4%), chrysanthenol (3.9%),  $\alpha$ -terpineol (2.5%),  $\beta$ -pinene (2.0%) and borneol (1.8%). The total lipid content of this plant material was 3.6 % of dry weight. In the hexane extract, 22 % of lipophilic substances of lipids (127 mg % of carotenoids, triterpenols, sterols) and the main components of essential oils listed above were determined. Comparison of the essential oils isolated from this plant originating from different countries revealed that the yield and content of the main constituents in the oils showed significant differences. This suggests that environmental conditions have a profound effect on the composition of the essential oil.

## PROSPECTS FOR THE USE OF GLYCYRRHIZIC ACID DERIVATIVES

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The use of natural, synthetic physiologically active substances to control the influence of external factors on the germination, growth and development of plants allows us to solve a number of problems, such as fertility and the preservation of its quality. When using synthetic drugs, plants can have some adverse effects on the human body. Therefore, it is desirable to use a small dose of physiologically active substances, taking into account the effect of metabolism on cells and tissues of plants. Biologically active compounds obtained from natural compounds can be used to solve this problem. One of the works in this direction is a complex of monoammonium salts of glycyrrhizic acid with biuret.

To date, a number of biologically active compounds and hundreds of natural compounds have been obtained from 13 species of the *Glycyrrhiza* generation. The licorice root contains 40-50% water-soluble biologically active substances, of which 24% are salts of glycyrrhizic acid, 20% carbohydrates, 10% protein, 4% lipids and 4% flavonoids. There are also many pharmacological preparations prepared from this root of the plant. This is a mixture of various components (root syrup, root powder, etc.) and glycyrrhizic acid preparations (glyceram, gliderinin, carbenoxolone, nigliazine, intimate epigen, phosphogliv, etc.).

Based on the Decree of the Cabinet of Ministers of the Republic of Uzbekistan No. 63, dated on January 27, 2018 “*On measures for the further development of the cultivation and industrial processing of licorice and other medicinal plants in the Republic of Uzbekistan*”, scientific research on the production of biologically active substances from them and the development of environmentally friendly products for agricultural and the pharmaceutical industry is conducting.

A review of the literature shows that the bio-stimulating and hormonal properties of glycyrrhizic acid complexes have a positive effect on the salinization of saline soils planted with licorice and saline, on the growth, productivity and development of plants.

As you know, biuret is a biologically active substance, and its complex compounds in various proportions with monoammonium salt of glycyrrhizic acid were obtained. The structures of the obtained complex compounds were characterized by UV and IR spectra.

In order to study the biological activity of the compounds obtained according to the above data, we studied the effect of the complex obtained in a 2:1 ratio under the conditions of germination of cotton seeds.

Based on these considerations, we can conclude that the new complex compounds synthesized based on glycyrrhizic acid can be used in the development of new, environmentally friendly, inexpensive, and effective biostimulants used in agriculture.

## CARBOHYDRATE COMPOSITION FROM ROOTS AND GROUND OF *Glycyrrhiza glabra*

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One of the most used medicinal plants in medicine is licorice, with the main pharmacologically active component of glycyrrhizic acid [1-2]. However, in licorice roots, in addition to glycyrrhizic acid, there are a large number of biologically active compounds such as mono- and polysaccharides, pectin, hemicelluloses and fiber. There is enough information on the chemical composition of licorice roots, but data on the content and composition of carbohydrates in the aerial part have not been reported.

The aim of our study is to comparatively study the carbohydrate complex of underground and aboveground organs of *G. glabra*, growing in Uzbekistan.

To isolate polysaccharide fractions, 100 g of crushed raw materials (roots and aerial parts separately) of *G. glabra*, collected in 2019 in the Namangan region during the flowering period, was treated with a twice boiling mixture of methanol - chloroform (1:1) to remove coloring substances and non-carbohydrate components, the residue of the feed was extracted twice with boiling 82 °C ethanol. Then, water-soluble polysaccharides (WSPS) were extracted in two ways: WSPS-C was isolated with cold water, and WSPS-H was isolated with hot water. Pectin substances (PS) were extracted with an equal volume of a mixture of 0.5% solutions of oxalic acid and ammonium oxalate at a temperature of 70 °C, hemicelluloses (HMC) were isolated with a 5% alkali solution. The monosaccharide composition of the isolated polysaccharides was determined by complete acid hydrolysis followed by GC analysis. The results of the study showed that arabinose and galactose are the dominant monosaccharides in the aboveground WSPS, and arabinose, glucose, galactose in the roots. It should be noted that glucose is the predominant monosaccharide in all polysaccharide fractions isolated from the roots of *G. glabra*. Therefore, polysaccharides such as glucan are present in the roots.

Thus, the carbohydrate composition was studied and characterized, the predominant polysaccharides in the aerial part were WSPS (3.92%) and HMC (4.5%), in the roots - HMC- (2.1%). The degree of esterification of PS in the aerial part was 55.8%, in the roots - 71.4%, respectively.

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## TECHNOLOGY FOR OBTAINING DRY EXTRACT SEEDS OF BLACK CARAWAY

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Urinary tract inflammation is one of the most common diseases in all regions of the world. Inflammatory diseases of the genitourinary organs make up about 2/3 of all urological diseases. In order to find a drug for the treatment of inflammatory processes of the urinary tract, the fruits of black cumin were investigated. It has bactericidal, anti-inflammatory and diuretic properties, effective in the prevention and in the complex treatment of urolithiasis, nephritis, pyelonephritis, cystitis, urethritis and other diseases of the organs of the excretory system. Fruits contain 3-7% of essential oil, 12-22% of fatty oil, as well as flavonoids, coumarins, tannins, etc.

To obtain a dry extract, black cumin seeds were degreased on a Soxhlet apparatus. 50 g of crushed black cumin seeds were loaded into the extractor, extraction was carried out to the boiling of petroleum ether, and the temperature was kept at 40-50 °C for 24 hours. After being filtered off, dried at room temperature, 47 g of skimmed black cumin seeds were obtained.

To obtain a dry extract, 10 mL of skimmed seeds of black caraway seeds were added with 300 mL of 40% or 70% ethyl alcohol and extraction was carried out with periodic stirring at a temperature of 55-60 °C for 4 hours. The resulting liquid extracts were concentrated by distillation at a temperature of 60-70 °C under vacuum. The resulting thick extract was dried in a vacuum oven at a temperature of 60 °C to constant weight. The yield of dry extract from the skimmed seeds of black caraway seeds in 40% ethyl alcohol was 1.1 g (11%), in 70% ethyl alcohol 0.9 g (9%). The obtained dry extracts were dark brown in color with a specific smell of powders.

The quantitative determination of the sum of flavonoids, the sum of organic acids and tannins was carried out according to SPh XI. The results are shown table 1.

**Table 1.** The results of a quantitative determination of the amount of the main active ingredients of the dry extract from the skimmed seeds of black cumin.

Extragent	Sum of flavonoids, %	Amount of Organic acids, %	Amount of tannins, %
40%	0.9	9.0	2.4
70%	1.1	10.0	4.0

Thus, a technology was developed to obtain a dry extract from black cumin seeds. The obtained dry extracts were transferred to pharmacologists for the study of antibacterial and anti-inflammatory activity.

## SYNTHESIS, STRUCTURE AND TOXICITY OF 2,5-BIS-(IZOPROPYL-OXYCARBONYLMETHYLENTHIO)-1,3,4-THIADIAZOLE

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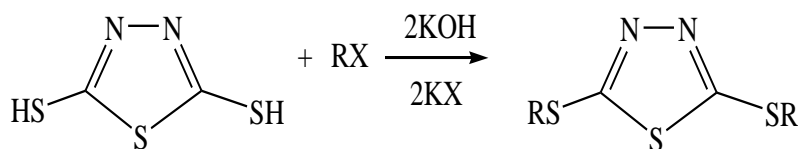
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For the obtaining of 2,5-bis-(izopropyl-oxycarbonylmethylenthio)-1,3,4-thiadiazole, 0.2 M potassium hydroxide was added to an ethanol solution of 0.1 M heterocycle and stirred for 30 minutes. At room temperature, 0.2 M of the appropriate reagent was added dropwise to the reaction mixture and boiled for 4-5 hours. Then ice water was added to the reaction mixture, filtered and recrystallized from absolute ethanol.



In the spectrum of 2,5-bis-(izopropyl-oxycarbonylmethylenthio)-1,3,4-thiadiazole, detection of the valence oscillation signals for ester bonds of terminal aliphatic groups band were at  $1732.08 \text{ cm}^{-1}$ , for  $\text{-C=S}$  bond at  $1261.15 \text{ cm}^{-1}$ , for  $\text{-CH}_2$  groups at  $2937.59 \text{ cm}^{-1}$ , for  $\text{-C(CH}_3)_2$  groups at  $1350.46 \text{ cm}^{-1}$ , for  $\text{-C-N}$  at  $1462.04 \text{ cm}^{-1}$ , which confirmed the structure of the synthesized sample.

Molecular ion of 2,5-bis-(izopropyl-oxycarbonylmethylenthio)-1,3,4-thiadiazole is characterized by peaks of hydrated ion with  $m/z$  351.5 with intensity 33.5% and with retention time on the column 9.02 minutes, as well as secondary fragmentation ions with  $m/z$  309.30, 266.9, 248.9, 226.9, 172.92, 117.02, 77.04, 85.02 и 72.02 with different intensity. Based on the obtained mass spectrums, possible ways of formation of daughter ions were determined.

The overall effect and "acute" toxicity of the compound were determined with a single oral administration in mice. Each dose of the substance was tested in six animals. Monitoring was conducted for 14 days. The research of acute toxicity of the compound showed that the substance belonged to the V class of highly toxic compounds.  $\text{LD}_{50}$  for oral administration in mice amounted accordingly 5130 (-560 +640) mg/kg.

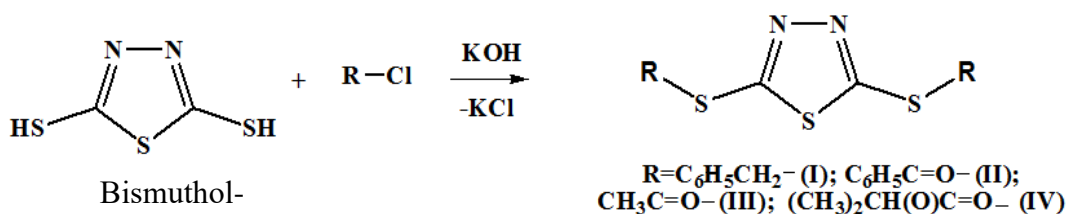
## SYNTHESIS OF 2,5-MERCAPTO-1,3,4-THIADIAZOLE DERIVATIVES AND STUDY OF THEIR TERMITICIDAL ACTIVITY

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Particular attention has been paid to investigating the toxicity of the synthetic compounds against termites that damage the historical wood-made architecture of Khiva, Samarkand and Bukhara. Some thiadiazoles extracted from actinomycetes *Streptomyces ambofaciens*, are known to be used in medicinal and agricultural practice. In our previous communications it has been reported that 5-mercapto-(3-phenyl)-1,3,4-thiadiazolyl-2-thione derivatives exert antimicrobial, antifungal activities and low toxicity against warm-blooded animals. In this paper we report on the synthesis of 2,5-mercapto-1,3,4-thiadiazole derivatives and the investigation of their termiticidal activity (toxicity) against the species of *Anacanthotermes turkestanicus*.

The synthesis of 2,5-dimercapto-1,3,4-thiadiazole derivatives was conducted according to the following reaction scheme:



The structures of synthesized derivatives of 2,5-mercapto-1,3,4-thiadiazole were verified with IR-spectroscopy and mass-spectrometry. Their physicochemical parameters have been established.

The termiticidal activity was determined based on their ability to eat the filter paper (size of 3.0 cm x 3.0 cm) processed with 0.1 mL of 0.2% ethanol solution of the substance distributed as 5.0  $\mu\text{g}/\text{cm}^2$ . The highest termiticidal activity was exhibited by 2,5-diacetylthio-1,3,4-thiadiazole (I). Its action caused more than 91% and 100% of termites to die after three and seven days, respectively. Analogical parameters for 2,5-dibenzylthio-1,3,4-thiadiazole (II) were found as 58% on the third day, and 100% on the seventh day. 2,5-dibenzoylthio-1,3,4-thiadiazole (III), bismuthol-1,2,5-S,S-diisopropyl-acetyl-1,3,4-thiadiazole (IV) were also found quite toxic. Their lethal effect on termites were 99%, 94%, and 87% after three days. Among the synthetic compounds the most rapid toxic effect belonged to 5-diacetylthio-(I) and 2,5-dibenzylthio-1,3,4-thiazole (II). Prolonged termiticidal activity was exhibited by 2,5-S,S-diisopropylacetyl-1,3,4-thiazole (IV) and bismuthol-1. This is important for trophollaxis process during which the toxic compound permeates deeper inside the colony.

## THE EFFECT OF THE DRUG DAG-1 ON ACCUMULATION OF PROLINE IN THE COTTON PLANT UNDER SALINITY CONDITIONS

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Salinity is an important abiotic stress that reduces crop productivity. Soil salinization inhibits water uptake by the plants, causes ionic imbalance leading to ionic toxicity and osmotic stress <sup>[1]</sup>. To withstand salt stress, plants accumulate compatible solutes such as proline, which decreases the cytoplasmic osmotic potential, facilitates water absorption, and scavenges reactive oxygen species (ROS) molecules <sup>[2]</sup>.

Proline is a protein amino acid and therefore expected to be present under non stress conditions also like all other amino acids. Proline accumulation occurs in plants in response to environmental stress conditions such as salinity, moisture, heat, water logging, pollution, pesticide etc. Being soluble in water it functions as an osmotic regulator and helps in the osmotic adjustment under stress. Its content increases rapidly during stress and also vanishes after release from it.

The present study was to determine the effect of the drug DAG-1, developed by the Institute of Bioorganic Chemistry of the Academy of Sciences of the Republic of Uzbekistan, on accumulation of proline in alleviating salt stress. The basis of the drug DAG-1 contains biologically active natural compounds - glycyrrhizic acid from licorice (*Glycyrrhiza glabra*) root in a supramolecular complex with salicylic acid. Pretreatment seeds of the biotechnologically developed cotton variety Ravnak-1 revealed significantly increase of free content of proline by 65 % in 7-day old seedlings grown under conditions of sodium chloride salinity (50 mM, 100 mM, 200 mM) compared to untreated control. Under the influence of DAG-1, the level of ROS decreased.

This effect of DAG-1 indicates a decrease of the salt stress despite a high level of salinity. We suggest that the salicylic acid in the composition increases the activity of antioxidant enzymes - superoxide dismutase, catalase, peroxidase, which are involved in the utilization of ROS. Also, proline can participate in the free radical scavenging. Our studies are consistent with assumptions of Hong et al. <sup>[3]</sup> that the role of proline as a free radical scavenger is more important in alleviating stress than that as a simple osmolyte.

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## SIMULTANEOUS DETERMINATION OF DOPAMINE AND URIC ACID USING GLASSY CARBON ELECTRODE MODIFIED WITH ALMOND-SHELL-BASED NANOPOROUS CARBON

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Almond-shell-based charcoal was prepared by carbonizing almond shells under nitrogen atmosphere. Nanoporous carbon (NPC) was formed using the obtained activated charcoal by using potassium hydroxide. NPC exhibited a large surface area (1075 m<sup>2</sup>/g), narrow pore-size distribution (1-2 nm). NPC with Nafion was used to modify glassy carbon electrodes to prepare a highly-sensitive electrochemical sensor for simultaneous determination of dopamine (DA) and uric acid (UA) through differential pulse anodic stripping voltammetry (DPV) and cyclic voltammetry (CV). The detection limits (S/N=3) for DA and UA were estimated to be 0.22 and 0.34 μM, respectively. The prepared electrodes were also used to detect UA and DA in human urine. The experimental data indicated that this easy, low-cost method can facilitate accurate, fast and simultaneous detection of DA and UA.

**Keywords:** Almond shell; Nanoporous carbon; Electrochemical sensor; Simultaneous determination; Dopamine; Uric acid



Fig. Schematic diagram of NPC synthesis and detection process.

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## ENVIRONMENTALLY FRIENDLY METHOD OF CULTIVATION OF SPORT PUMPKIN SPANISH -73

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In crop production, growth regulators are considered as an environmentally friendly and cost effective way to increase crop yields. In this regard, in this paper we present the results of a study on the effect of biostimulants on reducing the ripening period and yield of pumpkin varieties, as well as on the quality of marketable products. Recently, there is an increased interest in pumpkin as a dietary and therapeutic food product. Much attention is paid to expanding the range of pumpkins grown, improving the quality of marketable products. The need for it is constantly growing, especially for eatable kinds with high taste<sup>[1, 2]</sup>. It is known that pumpkin, able to delay the aging process, has a beneficial effect on the condition of the skin and hair. Pumpkin seeds are very useful as a prophylactic for helminths, and pumpkin juice is involved in hematopoiesis.

Field experiments to study the effects of the biostimulator Uchkun, Uchkun plus and Verva (Russia) were conducted in the conditions of Andijan region. The results show that all preparations accelerate the growth and development of Spanish -73 pumpkin, increase productivity at a concentration of 0.001%. On average, the yield increase is 10.58% - 41.27%, in the case of Uchkun and Uchkun plus - 7.8 t / ha and 10.1 t / ha, respectively, compared to control and 5.1 and 7.4 t / ha more than the comparison drug Verva.

The effect of biostimulants on the protein content and oil content of seeds was studied; as a result, their positive effect on the protein content and oil content of pumpkin seeds was determined.

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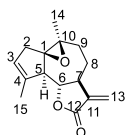
## MECHANOCHEMICAL PROCESSING OF ARGLABIN WITH ARABINOGALACTAN

A. R. Beisenbaev, A. N. Zhabayeva, S. M. Adekenov

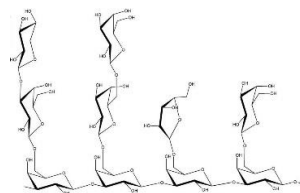
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Biologically active terpenoids, in particular, natural sesquiterpene lactone arglabin (1), with antitumor, radiosensitizing, and immunomodulating properties, are of great interest in the development and implementation of new original phytopreparations. The main source of this compound is *Artemisia glabella* Kar et Kir., growing in the territory of Central Kazakhstan. The main disadvantage of arglabin, as well as many substances based on plant compounds, is its practical insolubility in water, which negatively affects the bioavailability and complicates preclinical and clinical studies. In this regard, the urgent task is to obtain water-soluble drug substances based on arglabin.

The report discusses a method of increasing the water solubility of arglabin by mechanochemical processing of the substance of sesquiterpene lactone with arbinogalactan, which in turn will affect the improvement to increase the bioavailability of the drug. One of the most promising for the modification of drugs is arabinogalactan (2) - a water-soluble polysaccharide from *Larix* wood. Modification of drugs was carried out by the method of mechanochemical processing, which allows to obtain the target products without the participation of solvents, in one technological stage.



1



2

The mechanoprocessing was carried out in an ML-1m roller mill with a 150 mL drum. Stainless steel balls with a diameter of 9 mm were used as grinding bodies, a load of 236 g. Acceleration of grinding bodies- 1 g (free fall). The total load of the components of the processed mixture was 5.5-6 g with a ratio of arglabin: arabinogalactan 1: 5; 1:10 and 1:15, the duration of the mechanical processing was 4-20 hours. The solubility of the obtained composites in water was determined according to the State Pharmacopoeia of the Russian Federation (XII edition, issue 1).

According to the results of experiments, it was found that with a ratio of arglabin: arabinogalactan = 1:15 and a processing time of 4 hours, a five-fold increase in the solubility index can be achieved. Also, using spectral analysis methods (IR, NMR), it was shown that with prolonged mechanoprocessing, the structure of the arglabin molecule did not change.

## SYNTHESIS OF NEW 2-METHOXIBENZOYL-DERIVATIVES 20-HYDROXYECDISONE

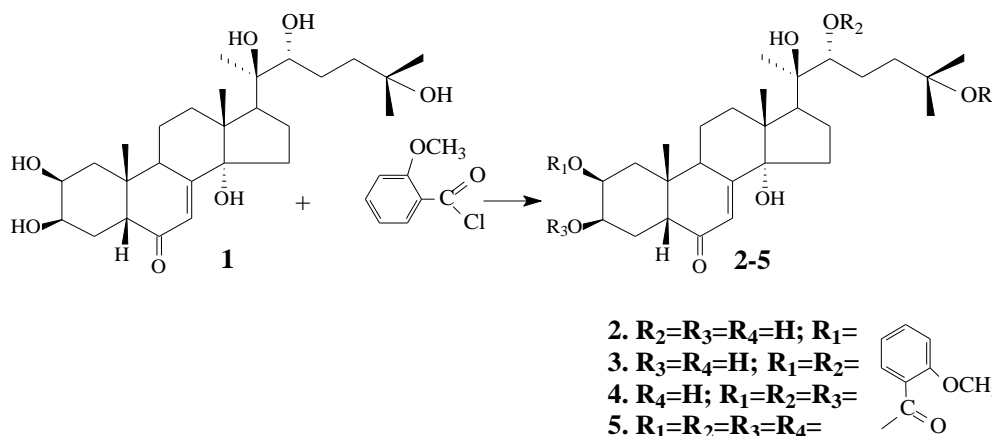
I. D. Bobaev, H. M. Bobakulov, M. M. Makhmudova, Sh. Sh. Sagdullaev

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A study of the reactions of chemical modification of 20-hydroxyecdysone and others made it possible to find out the reactivity of the hydroxy- groups to conjugate and place them according to the decrease in reactivity in the following series:  $C_2 > C_{22} > C_3 > C_{25} > C_{20} > C_{14}$ . Therefore, with direct esterification of 20-hydroxyecdysone with a large excess of an acid chloride or anhydride of an organic acid, three- and tetra-ethers were readily obtained.

The structure of 20-hydroxyecdysone contains four hydroxyl groups, and the reactivity of secondary OH groups in acetylation reactions decreases in the following order:  $C_2 > C_{22} > C_3 > C_{25}$ .

The acylation reaction of 20-hydroxyecdysone (**1**) was carried out under the action of *o*-methoxybenzoyl chloride in pyridine. Therefore, with direct esterification in a ten-fold excess of *o*-methoxybenzoyl chloride, the three-(*o*-methoxybenzoyl) -substituted 20-hydroxyecdysone ester and a small amount of 20-hydroxyecdysone mono-, di- and tetra-ester were easily obtained in high yield.



**Scheme 1.** Synthesis of *o*-Methoxybenzoyl derivatives of 20-hydroxyecdysone

The reaction mixture was separated by column chromatography into individual components. In this case, new derivatives were obtained as 2-*O*-(*o*-methoxybenzoyl)-20-hydroxyecdysone (**2**), 2,22-*O*-di-(*o*-methoxybenzoyl)-20-hydroxyecdysone (**3**), 2,3,22-*O*-tri-(*o*-methoxybenzoyl)-20-hydroxyecdysone (**4**), 2,3,22,25-*O*-tetra-(*o*-methoxybenzoyl)-20-hydroxyecdysone (**5**) (scheme 1).

The structures of *o*-methoxybenzoyl derivatives of 20-hydroxyecdysone were studied using  $^1H$ ,  $^{13}C$  NMR spectra, DEPT and HETCOR experiments.



## **PROSPECTS FOR THE TINCTURE OF *Galleria mellonella* LARVAE FOR THE TREATMENT OF A NUMBER OF DISEASES**

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The use of raw materials of natural origin for the creation of medicines has been known since ancient times. For this purpose, plant raw materials, minerals and other natural products are used. In Chinese medicine, more than 5 centuries ago, animal products were used. They have not lost their significance in our days. The National University of Pharmacy conducts research on the development of medicines from beekeeping products of different directions of pharmacological action. One of such objects of research is the larvae of *Galleria mellonella*. Bee fire is used in folk medicine for a very long time. From literary sources it is known that preparations based on it improve the general condition of a person and increase its protective properties. There is evidence of a positive effect of the drug on the cardiovascular system. They reduce pain in the heart, increase the resistance of the heart muscle to ischemia, and have a positive effect on the veins, reducing their permeability. Such medicines can be used in the treatment of angina pectoris, myocardial infarction, thrombophlebitis. The larvae of *Galleria mellonella* is resistant to pathogens of a number of infectious diseases. Of particular interest is the fact that the larvae are resistant to the causative agents of tuberculosis, plague, diphtheria and other pathogenic microorganisms. The extract from the larvae for the treatment of tuberculosis was recommended by the outstanding microbiologist I.I. Metchnikov.

The work presents the results of 15 years of experience in the development of medicines based on the larvae of *Galleria mellonella* and the study of their pharmacological action. From this natural raw material, the composition and technology of the medicinal product in the form of tincture was developed, biologically active substances, pharmacological effect and toxicity of the medicine were studied. The tincture includes a variety of biologically active compounds, which determine the spectrum of its pharmacological action. The experiment established the presence of the antimicrobial action of the drug. Tincture exhibits a bacteriostatic effect in relation to mycobacteria. The mechanism of the anti-tuberculosis activity of the tincture is apparently based on the presence of the cerase enzyme in it, which breaks down wax, and as it is known, mycobacterium has a lipid membrane, which is difficult to destroy using synthetic anti-tuberculosis drugs. The experiment revealed anti-inflammatory and antioxidant effects associated with the presence of tocopherols and chitosan in the medicine. It is also positive that the tincture belongs to a practically non-toxic medicine. Side effects from its use have not been identified. Contraindication is individual intolerance to beekeeping products. Thus, the prolonged use of the medicine in the complex pharmacotherapy of tuberculosis, diseases of the upper respiratory tract, etc. is possible.

Thus, the larvae of *Galleria mellonella* are a promising raw material for the creation of medicines with a wide spectrum of pharmacological action. The developed tincture can be used both for prophylaxis and in complex pharmacotherapy of tuberculosis, compatible with synthetic drugs, as well as for the treatment of inflammatory diseases of the upper respiratory tract.

## VOLATILE COMPOUNDS OF *Salix triandra* SHOOTS OF THE UKRAINIAN FLORA

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Willows are one of the largest genera of wood species in temperate climate. It is believed that in the world there are about 350-370 species. Of these, 23-25 species are naturally growing in Ukraine. They are the sources of highly active natural compounds used in folk medicine for a long time for the treatment of many diseases.

As a result of the research conducted at the Department of Pharmacognosy of the National University of Pharmacy of Ukraine the presence of phenolic glycosides, salicylates, flavonoids, tannins (mainly condensed group), coumarins, hydroxycinnamic acids, volatile compounds, polysaccharides, amino acids, higher fatty acids, macro- and microelements in the raw material of the *Salix* genus has been found.

Therefore, special attention is given to the study of biologically active substances of shoots of plants of the Salicaceae family. It gives the possibility for the rational and complex use of the herbal raw material of the components of the phytomass of tree species. The aim of the present research was to study the composition of the volatile compounds of *Salix triandra* L. shoots.

The plant raw material was collected in the National Botanical Gardens, named after M. M. Grishko National Academy of Sciences of Ukraine in June 2017, with the herbarium voucher stored at the Herbarium of Pharmacognosy Department of the National University of Pharmacy.

The study of volatile compounds was also performed by GC/MS on an Agilent Technologies 6890 chromatograph with a mass spectrometric detector 5973 using the DB-5 capillary column with the internal diameter of 0.25 mm and the length of 30 m; the rate of the sample injection was 1.2 mL/min for 0.2 min; the flow rate of the carrier gas (helium) was 1.2 mL/min; the temperature of the sample injection heater was 250 °C; the thermostat temperature was from 50 °C to 320 °C at the rate of 4 °C/min.

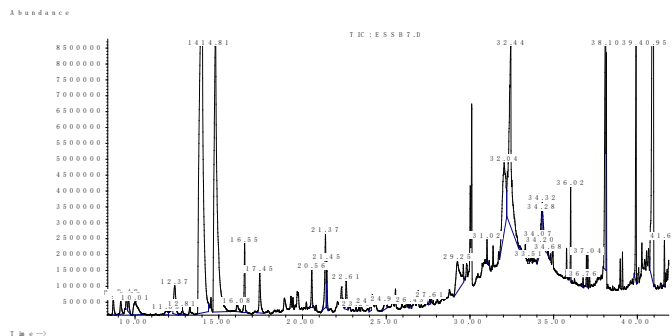


Fig. 1 The chromatogram of the volatile substances of *Salix triandra* L. shoots.

40 components in the investigated raw material were identified, among which nerol (1440.80 mg/kg), geraniol (915.00 mg/kg) and squalene (966.98 mg/kg) prevailed, there were also terpene hydrocarbons and their oxygenated derivatives, aromatic and heterocyclic compounds, 10 fatty acids (6 saturated and 4 unsaturated fatty acids).

The results indicate the prospects of using *Salix triandra* L. shoots, and they will be used in further study of this raw material.

## A SERIES OF ANNELATED PYRIMIDINES: BIOACTIVE THIENO[2,3-*d*]PYRIMIDINES

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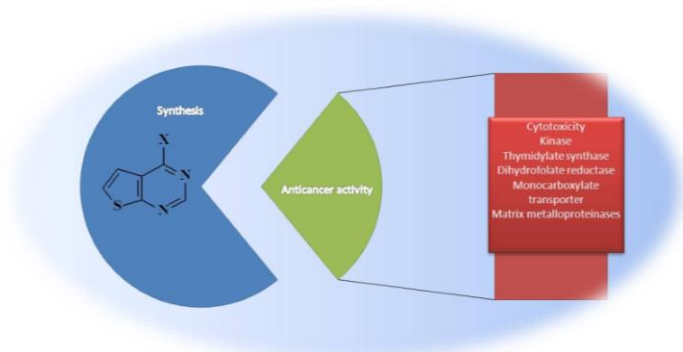
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Most of the currently available drugs for transplantation are known to be accompanied with serious side effects such as nephrotoxicity, neurotoxicity, hyperlipidaemia, new-onset post-transplant diabetes mellitus and hypertension. Thus, development of potent and safe immunosuppressants and such as potentials has been desired. However, in the first decade of the new millennium, no new medication specifically indicated for organ transplantation has been approved. There are currently three small compounds in various stages of clinical development in renal transplantation. One of the novel class scaffolds are an annelated thienopyrimidinones.

Recently we have synthesized a set of thienopyrimidinone derivatives in order to evaluate their diverse biological properties.



An obtained thienopyrimidinones has been found as perspective drug-candidate towards cancer and melanoma screening.

**A SERIES OF ANNELATED PYRIMIDINES: BIOACTIVE TRIAZOLO[4,5-*d*]PYRIMIDINES****Kh. Bozorov<sup>1,2</sup>, B. Song<sup>1,3</sup>, L. F. Nie<sup>1</sup>, J. Y. Zhao<sup>1</sup>, I. R. Askarov<sup>4</sup>, H. A. Aisa<sup>1</sup>**

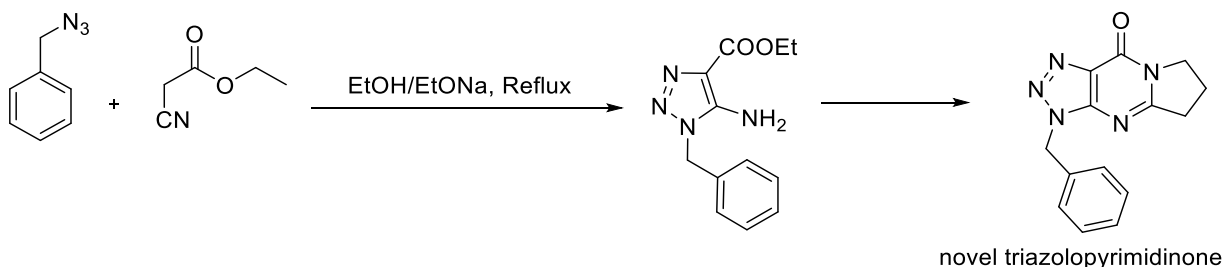
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Lead compounds bearing the 1,2,3-triazole fragment will serve as promising drug candidates in medicinal chemistry. Most of synthesized annelated triazoles hybrid molecules are unique as well as important factors in drug design and delivery. Although the selectivity and solubility of the most common triazole-hybrids have been well improved, the *in vivo* assay results still indicate that further developments are needed. If a 1,2,3-triazole ring was inserted instead of the imidazole portion in the purine skeleton, this type of fused pyrimidines may exhibit interesting properties for medicinal chemistry. In this regard we have synthesized other one novel heterocyclic system based on the annelated triazole-pyrimidines. In the future, we believe that it will assist in the development of 1,2,3-triazole-based pyrimidine compounds with selective bioactive scaffolds.



## MOLECULAR DOCKING OF FLAVONOIDS WITH RNA POLYMERASE OF HEPATITIS C VIRUS

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NS5B polymerase is a key enzyme involved in the replication of the hepatitis C virus genome and, therefore, is a potential drug target for antiviral drugs aimed at treating hepatitis C. Given the numerous side effects of existing drugs against hepatitis C virus, we attempted a computer search for NS5B polymerase inhibitors based on the molecular docking of natural flavonoids.

Docking was done by autodock4 (<http://www.autodock.scripps.edu/>). The addition of polar hydrogen atoms, Hasteiger charges, and solvation parameters were performed using MGLTools-1.5.6-rc3 tools. Fully optimized DFT ligand structures were taken as starting configurations and prepared by calculating the Hasteiger atomic charges and nonpolar hydrogen atoms using AutoDockTools 1.5.6. The ligands were attached using the default software parameters, with the exception of the number of runs (1000), and the Lamarckian genetic algorithm (LGA) with local search and 25000000 energy estimates per run. Initially, blind docking was carried out with a mesh size of  $120\text{\AA} \times 120\text{\AA} \times 120\text{\AA}$  in x, y, and z measurements, with the catalytic binding site of the enzyme inhibitors as the center of the mesh. The resulting binding conformations were analyzed by AutoDockTools using cluster analysis.

Analysis of the simulation results showed that the most promising inhibitors of the hepatitis C virus RNA polymerase were natural flavonoids cynaroside and thermopsoside containing sugar substituents at the 7th position of ring A. Inhibitors interacted with residues Arg422, Met423, Leu474, His475, Tyr477, Lys501 and Ttp528.

## PROSPECTS FOR CREATION OF A NEW DRUG BASED ON A MODIFIED EXTRACT OF BEARBERRY LEAVES

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Bearberry (*Arctostaphylos uva-ursi*) leaves are one of the most widely used medicinal plants with the diuretic and urinary antiseptic action. Herbal medicines or a dry raw material are part of many drugs and functional additives. One of the most widespread medicines based on this medicinal plant is a decoction of bearberry leaves; however, there are no standardized domestic galenic or neogalenical medicines on the basis of this raw material at the market of Ukraine.

The method of obtaining a decoction of bearberry leaves is well known. However, the disadvantage of this dosage form is volatility of the chemical composition, and as a consequence, inconstancy of pharmacodynamics, short term of storage, the absence of standardization and the long preparation. Therefore, creation of a standardized therapeutic and prophylactic agent with the diuretic action from bearberry leaves is relevant. The aim of the study was to develop a method for obtaining a modified extract from bearberry leaves, to conduct its phytochemical and pharmacological study in order to determine the possibility of creating a new drug.

The extraction from bearberry leaves was carried out twice with 50 % solution of ethyl alcohol in the ratio of 1:10 of the raw material to the extractant; purification was performed by settling and separating the supernatant sterilized, after that the amino acid phenylalanine was added to the extract in a 3-fold equimolar amount in relation to the total amount of phenolic compounds and dried to a dry extract. The dry extract obtained from bearberry leaves contains  $17.46 \pm 0.04$  % of the amount of phenolic compounds calculated with reference to gallic acid and at least  $5.64 \pm 0.02$  % of hydroquinone derivatives calculated with reference to arbutin. The diuretic activity was determined by the method of E. B. Berkhin on outbred rats weighing 150-220 g, kept in standard conditions on a normal diet with free access to water and food.

The complex of BAS of bearberry with phenylalanine led to an increase in the amount of urine excreted in 2 hours from the beginning of the experiment compared to the indicator in the group of control animals. Diuresis of the experimental animals receiving aqueous solutions of the bearberry extract complex with phenylalanine in the dose of 50 mg/kg in 2 hours was more than 60 % compared to the group of control rats and more than 16 %, respectively, compared to animals receiving the decoction of bearberry leaves. The antibacterial activity of bearberry complexes with amino acids was studied by the method of diffusion into agar. The complex of the extract from bearberry leaves and phenylalanine was active against *Staphylococcus aureus*, *Escherichia coli*, *Proteus vulgaris*, *Pseudomonas aeruginosa*, *Basillus subtilis*, and *Candida albicans* at the level of the decoction of bearberry leaves.

Therefore, a new modified extract from bearberry leaves with the diuretic and antimicrobial activity has been created; by the potency of its pharmacological action it exceeds the decoction from this raw material.

# QUALITY EVALUATION OF THE TRADITIONAL MEDICINE KURSI XIWAK VIA CHROMATOGRAGHC FINGERPRINTING AND THE ANTIOXIDANT

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The fingerprint of traditional Chinese medicine (TCM) can reflect the variety and quantity of chemical components. We analyzed the chemical composition of Kursi Xiwak (KXWK), a traditional medicine commonly used in Uygur medicine, through the fingerprint of ten batches, and found 32 common peaks and 5 characteristic peaks, with the similarity of fingerprint more than 0.955. We determined the contents of 5 characteristic compounds: gallic acid, isoquercetin, 3,5-*O*-dicaffeoyl quinic acid, 4,5-*O*-dicaffeoyl quinic acid, rupestonic acid, and established a methodological study, with the linear coefficient more than 0.9992, the RSD values of precision, repeatability, stability and recovery all less than 3%, indicating that this method can accurately determine the contents of 5 characteristic compounds simultaneously, which can be used for the quality control and estimate of KXWK. In addition, we carried out the antioxidant activity of the KXWK samples by ABTS and DPPH methods, showing that the active components provided the theoretical and material basis for the liver protection of KXWK. To sum up, this study established an effective quality control method for KXWK and an evaluation method of in vitro antioxidant capacity.

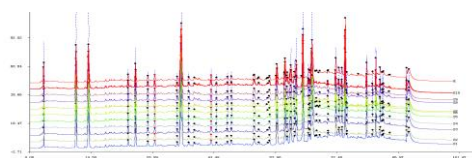


Figure 1. HPLC fingerprint of 10 batches of KXWK

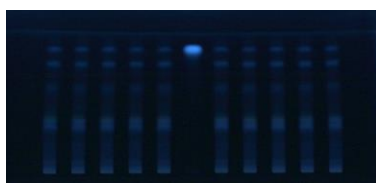


Figure 2. TLC of KXWK under UV360nm

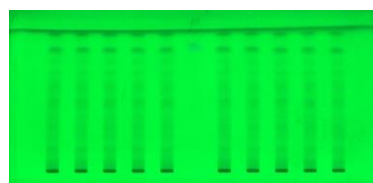


Figure 3. TLC of KXWK under UV254nm



Figure 4. TLC of KXWK after dipping in ABTS<sup>+</sup>



Figure 5. TLC of KXWK after dipping in DPPH

## ACKNOWLEDGEMENTS

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## ACYLATION AND BENZOYLATION REACTIONS OF $\alpha$ -AMINONITRILES

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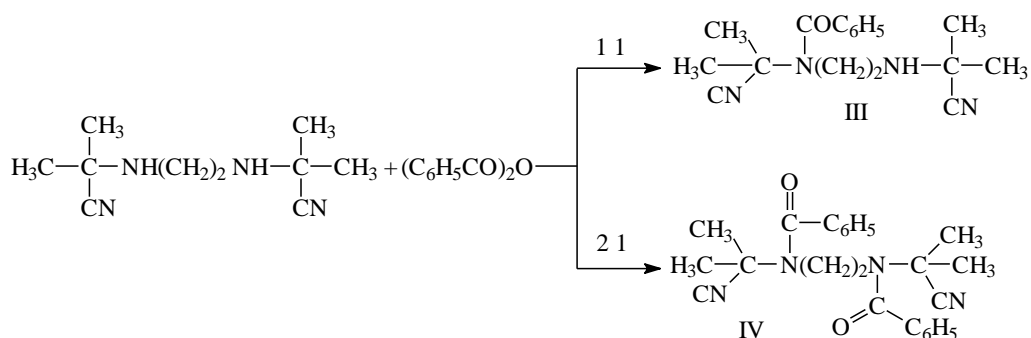
<sup>2</sup> Karshi State University;

<sup>3</sup> Institute of the Chemistry of Plant Substances, named after Academician S. Yu. Yunusov of the Academy of Sciences of the Republic of Uzbekistan

The use of chemical plant protection products, including plant growth regulators, helps to increase the resistance of plants to diseases and adverse conditions, early ripening of crops, increase yield and produce a higher-grade product. One of the promising classes of compounds as plant growth stimulants is  $\alpha$ -aminonitriles-nitriles of vital  $\alpha$ -amino acids.

A method for the synthesis of N, N-bis ( $\alpha$ -cyanisopropyl) ethylenediamine from acetone cyanohydrin and ethylenediamine is known in the literature. This compound was obtained both by the interaction of acetone with potassium cyanide and an aqueous solution of ethylenediamine, and from acetone cyanohydrin and ethylenediamine [1]. It should be noted that during the reaction of N, N'-bis- ( $\alpha$ -cyanisopropyl) ethylenediamine with acid chlorides, the structure of the resulting product depended on the molar ratio of the reagents used. At a ratio of  $\alpha$ -aminonitrile-acid chloride-1: 1, N-monoacyl products were formed, and when reactants reacted in molar ratios of 1: 2, bisacyl products were formed.

In the reaction of N, N'-bis- ( $\alpha$ -cyanisopropyl) ethylenediamine with acid chlorides of aliphatic acids, acetyl chloride was used as the latter. The reaction of N, N'-bis- ( $\alpha$ -cyanisopropyl) ethylenediamine with aromatic acid chlorides was examined using benzoyl chloride as an example. The reaction proceeded in the presence of triethylamine and gave N-monobenzoyl-N, N'-bis ( $\alpha$ -cyanisopropyl) ethylenediamine in 85% yield.



It should be noted that the reactions in all cases were carried out in the presence of triethylamine. An analysis of the results showed that the reaction products in all cases were formed with good yields.

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## BIOLOGICAL ACTIVE SUBSTANCES OF LEAVES OF *Catalpa bignonioides* FROM UKRAINE

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The *Catalpa* genus includes 11 species and belongs to Bignoniaceae family. The most widespread species are *Catalpa bignonioides*, *Catalpa speciosa* and *Catalpa ovate*.

The aim of this study was to determine the qualitative and quantitative amino acids, phenolic compounds, macro- and microelements composition in the leaves of *Catalpa bignonioides* from Ukraine.

*Catalpa bignonioides* is a medium-sized deciduous tree, but under favorable conditions can be forever green. This plant grows up to 15–18 meters. It is widely grown as an ornamental tree and cultivated in the parks and gardens of all temperate countries.

*Catalpa bignonioides* has several varieties: Aurea, Nana, Kene and Purpurea. The variety “Aurea” is medium size tree with rounded and spreading crown, whose leaves during flowering are golden and then turn light green. “Nana” is undersized variety of catalpa with distinct spherical crown up to 4 meters in diameter that does not bloom and is used in landscape design. The variety “Kene” has yellow leafy plates with green veins and a speck of dark green color in the center. The variety “Purpurea” is up to 8 meters high plant with conical crown. This variety leaves have terracotta color at the beginning of the growing season, that gradually turns green.

The chemical composition and pharmacological properties of *Catalpa bignonioides* have not been sufficiently studied despite its long history of usage. This plant has long been applied as an antiseptic, laxative and sedative and now in consequences of introduction of modern technologies new properties of *Catalpa bignonioides* have been discovered. There is a possibility of using catalpa in the complex treatment of cancer, which is extremely relevant in modern times.

The leaves of *Catalpa bignonioides* variety “Aurea” were collected in Botanical Garden of the National University of Pharmacy (Kharkiv, Ukraine) in July, 2017.

The amino acids composition of leaves of *Catalpa bignonioides* was studied by HPLC method on Agilent Technologies (model 1100). In result of analysis 16 substances were identified. Nine essential amino acids were determined in test sample. The largest content had histidine (2.146  $\mu\text{g}$  / mg), threonine (1.508  $\mu\text{g}$  / mg) and isoleucine (1.172  $\mu\text{g}$  / mg) among essential amino acids. Proline (5.473  $\mu\text{g}$  / mg) and aspartic acid (1.341 mg / mg) were predominant and constituted 67.38% of the total amount of nonessential amino acids.

Phenolic compounds content was evaluated by spectrophotometry in leaves of *Catalpa bignonioides*. The total phenolic substances content was  $4.76 \pm 0.04\%$ . The test sample contained  $3.42 \pm 0.02\%$  hydroxycinnamic acids and  $1.88 \pm 0.02\%$  flavonoids.

16 macro- and microelements were identified from the leaves of *Catalpa bignonioides* by atomic emission spectroscopy. The highest contents were determined for K (2125 mg / 100g), Ca (1190 mg / 100g), Mg (380 mg / 100g).

The leaves of *Catalpa bignonioides* are a promising raw material for further phytochemical research and development of new medicines.

## **ANATOMIC STRUCTURE OF THE LEAF AND SPINES *Astragalus pterocephalus* GROWING IN UZBEKISTAN**

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A number of representatives of plants of the genus *Astragalus* are used in traditional medicine for many peoples of the world. This genus is represented in the flora of Central Asia by 592 species, in Uzbekistan - 239, in the world flora - more than 2200<sup>[1]</sup>. In the early 80s, it was first shown in plants of the genus *Astragalus* (Leguminosae) in the glycoside chemistry laboratory of the Institute of Plant Chemistry of the Academy of Sciences of the Republic of Uzbekistan that triterpene glycosides of the cycloartan series were produced. Glycosides isolated from plants of the genus *Astragalus* had a broad spectrum of biological activities including cardiotoxic, anti-inflammatory, hypotensive, antioxidant, and antibacterial<sup>[2]</sup>.

The studies were conducted according to generally accepted anatomical methods<sup>[3-4]</sup>. The results of a study conducted by light microscopy of the anatomical structure of the leaf and spines of *Astragalus pterocephalus* growing under conditions in Uzbekistan. The following diagnostic features were identified: leaf - isolaral-palisade type of mesophyll leaf; thick-walled outer walls of the epidermis; the outline of epidermal cells was rectilinear, the projection was polygonal; amphistomatic leaves; numerous, submerged stomata of the hemiparacytic and anomocytic type; chlorophyll-bearing palisade and spongy parenchyma; closed collateral type of vascular bundles and more sclerified, due to sclerenchymal cells. Thorn - parenchymal-beam type of structure; thin-walled outer walls of the epidermis; under the epidermis was a lamellar collenchyma; closed collateral type of vascular bundles and more sclerified, due to sclerenchymal cells.

The complexes of the above features reflect the species specificity of the structure of the leaves and spines. Identified and described features can be used in the taxonomy of the studied tribes and can serve to identify plant materials.

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## THE ROLE OF STUDYING THE SECONDARY METABOLITES IN PLANT CHEMOSYSTEMATICS

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In this research, as a part of the project “*Systematics of dicotyledonous plants*”, a database on the chemical composition and biological activity of different families Apiaceae, Rutaceae, Linaceae, Nitrariaceae, Geraniaceae, Zygophyllaceae in the flora of Uzbekistan was obtained.

The purpose of this study was to provide a broad overview of the chemical components and biological activity of these families. For a creation of a complete database, a high quantity of articles and dissertations from PubMed, Research Gate, Sci-Hub, Springer and Wikipedia and other sites on the period from 1965 to 2019 were collected.

Analyzing the data, it was revealed, that the families representatives contain a group of plant secondary metabolites in various quantity and quality.

Thus, Umbelliferae family (Apiaceae) includes essential oil and coumarin containing species. In Uzbekistan, this family is represented by 72 genera and 231 species, of which 14 genera and 23 species are endemics. Of these, more than 150 species are examined by chemical composition, 102 species are coumarin containing plants, 95 species are essential oil bearing plants, 54 species are flavonoid containing species.

Rutaceae family is known for the high diversity of alkaloid and coumarin containing species. 18 species, distributed in the flora of Uzbekistan, belonging to two genera: *Haplophyllum* Juss. and *Dictamnus* L. There is information about the chemical composition of 17 species (except for *Haplophyllum vvedenskyi* Nevski). According to the literature data, these species contain alkaloids, lignans, coumarins, flavonoids, essential oil and other compounds of the secondary metabolites and manifested many pharmacological activities, including antioxidant, antimicrobial, insecticidal, cytotoxic, cardiovascular, anti-inflammatory and acetylcholinesterase inhibitory effects. All studied species contain alkaloids, 10 species contain coumarins, 8 species contain lignans, 6 species contain steroids and 2 species contain essential oil.

There are 18 species of the Geraniaceae family in Uzbekistan flora, belonging to two genera *Geranium* L. and *Erodium* L’Her. 13 species are examined by chemical composition. Species are promising sources of polyphenols (8 species), tannins (10 species), flavonoids (10 species).

The results of this kind of studies are a necessary prerequisite for understanding the functions of the studied compounds in plants. This has a great practical importance for the searching for promising products of biologically active compounds.

## EFFECTIVENESS OF THE NEW ANTITUMOR DRUG DECOCINE

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**Background.** In the NSCO of MH of RUz, it has developed a new anti-tumor drug Decocine, made on the basis of alkaloid of colchicines, possessing both moderate toxicity in comparison with known drugs of analogous tubulin-interacting mechanism of action and expressed anti-tumor activity both in vitro (according to data of NCI USA) and in vivo and also breadth of action. Moreover, the drug possesses a feature to considerably increase action of irradiation on tumors.

**Materials and methods.** At present, action of the Decocine drug is studied on volunteer patients. For skin cancer treatment, Decocine is applied in the form of 3-4% ointment form (3% - for basal cell treatment and 4% - for planocellular cancer) for patients with I-III stages. Decocine was also applied for treatment of tumors of large intestine (3-5% ointment with suppositories), vulva and neck of uterus (1-3% ointment and suppositories) and breast cancer.

**Results.** 8-10-fold application to basaliomas led to 50-70% reduce of tumor sizes, further application of Decocine promoted its disappearance.

Patients with morphologically verified diagnosis of different stages of disease underwent to cure, and Decocine with appropriate concentrations was set for them. Among these patients, cured by the ointment, suppositories, Decocine solutions (carcinoma of uterine cervix, vagina, vulva, rectum), were noticed - direct dependence of medical pathomorphism upon histological structure of tumor, noted flattening of exophytic tumors, decrease of volume and ulcerous surface of entophytic tumors, relief of pain syndrome, and reduce of bloody issues.

There are some histories with amelioration of patients and reduces of sizes of tumors with bowel adenocarcinomas (4<sup>th</sup> stage), adenocarcinomas breast cancer (4<sup>th</sup> stage), and also a case of 9-years remission (for today) of 3<sup>rd</sup> stage patient after Decocine and 33 Gy irradiation.

**Contusion.** The obtained data point to high sensitivity of skin cancer to 2-5% Decocine ointment, and also other localizations, although at its application side effects are not appeared, furthermore it doesn't cause leucopenia and depression of immune system of patients even at long-term application.

## ACTIVITY OF NEW ANTINEOPLASTIC PREPARATION K-26-V ON STRAINS THE SARCOMA 180 AND WALKER CARCINOSARCOMA

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In National cancer Center of Uzbekistan workings out of the new antineoplastic preparations received by updating tropolone alkaloids are conducted. By results of the screening spent on the panel of tumors of the person at National institute of a cancer of the USA (NCI) in vitro high activity was preparation of K-26 on the basis of selection in vivo on animals with tumors, which has been offered further for preclinical tests as an antineoplastic preparation. However K-26 will badly dissolve in water, water-soluble salt of this preparation (K-26-B) thereupon has been received, toxicity and activity demands studying.

**The work purpose.** An estimation of antineoplastic activity of new preparation K-26-v on animals with tumoral strains the Sarcoma 180 and Walker carcinosarcoma (WCS).

**Materials and methods.** The activity of antineoplastic preparation K-26-v has been investigated on 38 not purebred mice with an intertwined tumor the Sarcoma 180 and on 20 not purebred rats with intertwined tumor WSC. For 3rd day after sub inoculation tumors to mice and rats, intraperitoneal introduction of K-26-v 5 and 8-multiply in different doses, in comparison with taxol, etoposide and K-26. An estimation of results spent by standard criteria: tumor growth inhibition (TGI), weight of body and spleen of animals. Authentic considered distinctions at  $p < 0.05$ .

**Results.** K-26-v was low-toxic for mice,  $LD_{50} = 350$  mg/kg and highly active on 2 tumors to the Sarcoma 180 and WSC, level  $TGI = 91-97\%$ . Its action was above effect of taxol and was equal to effect of etoposide at decrease in by-effects on tumor the Sarcoma 180. The effect of K-26-v in comparison with K-26 on tumor WSC was close, more than effect of taxol. On tumor WSC efficiency at etoposide was low.

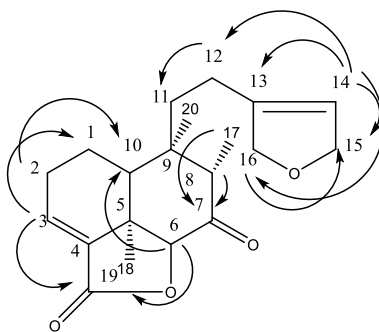
**Conclusion.** Studying of new preparation of K-26-v on animals with tumors the Sarcoma 180 and WSC has revealed its more expressed activity in comparison with original K-26 and with taxol and etoposide. Smaller level of by-effects speaks ability to emission of a colony of forming cages new preparations that protects an organism from consequences of their cytotoxic action.

NEW CLERODANE DITERPENOID FROM *Pulicaria gnaphalodes*K. A. Eshbakova<sup>1\*</sup>, B. D. Komilov<sup>1</sup>, H. A. Aisa<sup>2</sup>

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In continuation of research on the chemical constituents of the aerial part of *Pulicaria gnaphalodes* (Asteraceae) collected during flowering in Jizzakh region [1–5], a new clerodane-type diterpenoid C<sub>20</sub>H<sub>26</sub>O<sub>4</sub> called gnapholone was isolated. Its structure was established using IR, PMR, and <sup>13</sup>C NMR spectra and HSQC, COSY, and HMBC experiments.

The structure of gnapholone based on all results was determined as 7-oxo-15,16-epoxy-*trans*-cleroda-3,13(14)-dien-19,6-olide.



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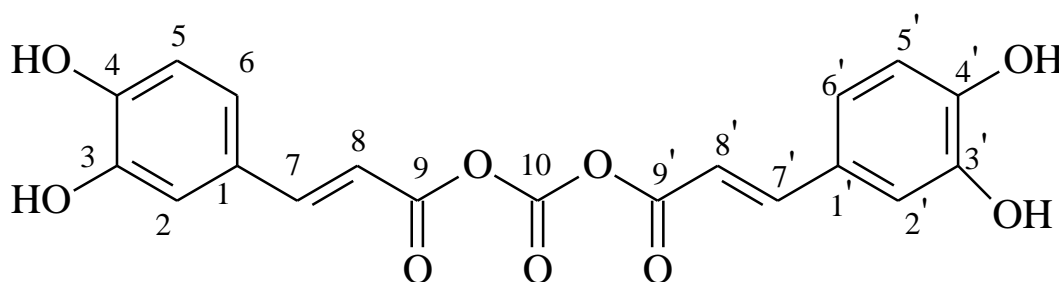
**PUNAFOLID - NEW PHENOL COMPOUND FROM *Pulicaria gnaphalodes*****K. A. Eshbakova<sup>1\*</sup>, B. D. Komilov<sup>1</sup>, H. A. Aisa<sup>2</sup>**

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As a result of studying the chemical composition of *Pulicaria gnaphalodes*, several phenol substances were isolated. It turned out to be a new compound, which was given the name Punafoloid. The structure Punafoloid was established on the basis of the analysis of the data of the IR, Mass, <sup>1</sup>H, and <sup>13</sup>C NMR spectra, and of the HSQC, COSY, and HMBC experiments.

Based on the spectral characteristics, it was found that the substance has the structure of 3,4-dihydroxy-*O*-caffeoyl-carboxy.



**TERPENOIDS, ESTERS, COUMARINS, IRIDOIDS, STEROLS,  
FLAVONOIDS AND THEIR GLYCOSIDES FROM THE FLORA  
OF UZBEKISTAN AND THEIR BIOLOGICAL ACTIVITIES**

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The Uzbek flora is a rich source of medicinal plants. Plants of the genus *Ferula*, *Pulicaria*, *Scutellaria*, *Dracocephalum* and *Helichrysum* are widely distributed in Uzbekistan and are a rich source of biological activity of compounds. Representatives of these genera are successfully used in traditional and alternative medicine as antitumor, hepatoprotective, antioxidant, anti-inflammatory, anti-RSV, antimutagenic, neuroprotective, anxiolytic, and other activities. We studied the secondary metabolites of some species from these genera. Therefore, the search for plants containing secondary metabolites, methods for their isolation, the establishment of their chemical structure and the study of biological activity based on the chemical structure in order to create effective new drugs is an important and urgent problem of modern bioorganic chemistry. From the studied plants *Ferula samarcandika*, *F.ovina*, *F.tunuisakta*, *F.kuhistanika*, *F.feruloides*, *F.foetida*, *Pulicaria salviifolia*, *P. gnaphalodes*, *P.uliginosa*, *Scutellaria schachristanica*, *S.holiceracea*, *S. gutata*, *Dracocephal Komaroviy*, *D.moldovii*, *Helichrysum arenarium*, more than 200 new and known terpenoids, esters, coumarins, iridoids, sterols, flavonoids and their glycosides have been isolated. The structures of isolated compounds were established on the basis of their physical and chemical properties, IR, UV, PMR, <sup>13</sup>C, <sup>1</sup>H NMR, HSQC, HMBC, COSY and DEPT spectral data, RSA and also TLC analysis. Among isolated compounds, compounds were found with diabetic, cardioprotector, antioxidant, relaxant, hypotensive, antitumor, hepatoprotective, anti-inflammatory, neuroprotective, and other activities.



## SEASONAL DYNAMICS OF POLYSACCHARIDES ACCUMULATION IN THE WASES OF *Phaseolus vulgaris*

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Due to the healing properties, bean leaves have been actively used in folk medicine. The use of natural raw materials is for therapeutic and prophylactic purposes <sup>[1]</sup>. The aim of the report is to study the seasonal dynamics of the accumulation of water-soluble polysaccharides (WSPS) and pectin substances (PS) during the growth and development of *Phaseolus vulgaris* fruits.

The raw materials were collected from the beginning of the period of milk ripeness to the full ripening period of beans, and the bean folds were studied. WSPS and PS were isolated according to the well-known scheme <sup>[2]</sup>. The results of the study showed that the content of WSPS in the period of milk ripeness was 2.5% and the dominant monosaccharides were glucose and galactose. With the growth and development of the plant, a decrease in the content of these monosaccharides was observed. The yield of pectin (PS-1) at the beginning of plant development was 5%; as the fruit ripened, the yield of PS-2 increased to 10% and the degree of esterification (DE) to 84.4%. Aqueous solutions of PS had a high relative viscosity index (12.5-13.8 mg/mL), characteristic of pectins. Differences in mm were insignificant (200-250 kDa). The monosaccharide composition of PS was represented by neutral and acidic monosaccharides. It should be noted that at the end of the growing season, there was a decrease in the content of uronic acids (Table.1).

Table 1. Characterization of pectin substances from *P. vulgaris*

Type of Substation	Yield, %	The ratio of monosaccharides						UA, %	DE, %
		Rha	Ara	Xyl	Man	Glc	Gal		
ПВ-1	5	9.9	3.9	2.2	1.0	7.7	1.1	45.9	75
ПВ-2	10	9.1	5.9	2.0	1.0	1.0	16.5	37.5	84.4

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## ISOLATION AND DETERMINATION OF COMPOSITION OF AMINO ACIDS OF SOYBEAN PROTEIN FOR USING IN ELISA

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The protein of soybean has been used extensively in pharmaceuticals for producing enzyme-linked immunosorbent assays (ELISA) [1]. The aim of this study is to select carrier protein for synthesis of hapten-protein conjugates to develop ELISA diagnostic kits for determination of drug addicts. Bovine serum albumin (BSA), ovalbumin, lysozyme and fibrinogen were used as a carrier protein by different researchers [2]. In our work, soybean protein was chosen for obtaining morphine-protein conjugates, because, soybean protein contained large amounts of  $\epsilon$ -amino acids [3]. In fact, the carboxyl group of hapten binds with amino groups of amino acids during the reaction.

In this study, the total protein of soybean was isolated by the method of extraction with buffer (M Tris-OH; SDS; M EDTA). After that, the extract of the protein was separated by the column chromatography sephadex G 75. As a result, the protein extract was divided to two fractions with high (35-135 kD) and low (17-35 kD) molecular weights. Finally, the amino acids analysis of proteins separated into two fractions was performed.

Table 1. Amino acid composition of fractions of soy protein, in%.

Amino acids	High molecular weight fraction	Low molecular weight fraction	Amino acids	High molecular weight fraction	Low molecular weight fraction
Asp	4.9436	7.9863	Pro	2.69	1.8186
Glu	0	10.735	Tyr	2.159	1,3291
Ser	3.2848	2.7102	Val	3.9094	2.0003
Gly	3.923	2.4028	Met	0	0.2945
Asn	0	0	Ile	5,502	3,1467
Gln	0	0	Leu	6,7436	3,1123
Sys	0.5014	0.7322	His	0	0
Thr	2.2597	1.632	Trp	0	0
Arg	6.8781	3.6215	Phe	2.4034	1.3404
Ala	2.9997	1.9397	Lys	1.2983	0.7047

In conclusion, the high molecular weight fraction of soy protein could be used as a carrier protein for obtaining conjugate for ELISA diagnostic test system, for the determination of haptens such as opiates and their derivatives, etc., since it included larger percentage of  $\epsilon$ -amino acids than low molecular weight fraction.

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NEW ALKALOIDS OF THE PLANT *Haplophyllum acutifolium*

M. A. Eshonov, Kh. A. Rasulova, K. K. Turgunov

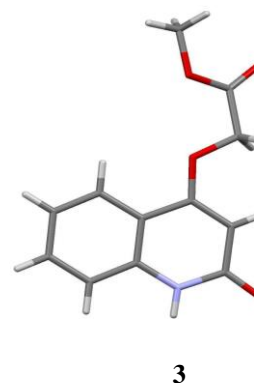
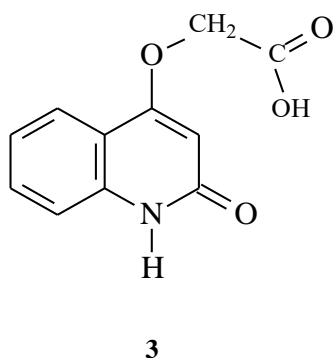
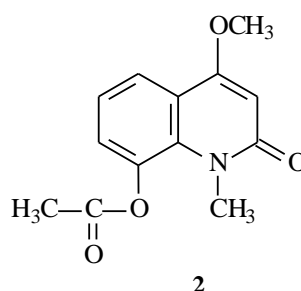
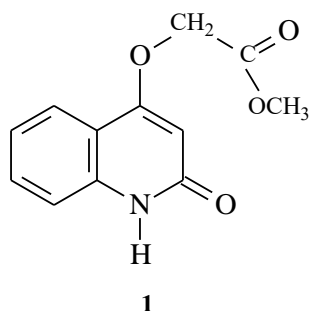
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Plants of the genus *Haplophyllum* have long been known for their medicinal properties. Tinctures of a number of plants are widely used in folk medicine as an anesthetic for toothache, chest and stomach diseases, externally for skin diseases, as a sedative for increased nervous irritability and nervous heartbeat.

The aerial part of the *H. acutifolium* plant, harvested in the vicinity of Jizzakh, was studied and afforded haplamine, N-methyl-2-phenylquinolin-4-one, skimminiane, haplatine, flindersine and  $\beta$ -sitosterole from the chloroform sum of alkaloids.

Separation and rechromatography on silica gel of the ethyl acetate partition, resulted in new alkaloids: base **1**, called akutinine, with mp 290-295 °C, base **2**, akuzine with mp of 151 °C, and base **3**, pedicine with mp of 222-224 °C.

The structures of new alkaloids were established on the basis of analysis of the data of UV, IR,  $^1\text{H}$  and  $^{13}\text{C}$  NMR spectra, as well as DEPT experiments. The structure of pedicine was confirmed by X-Ray.



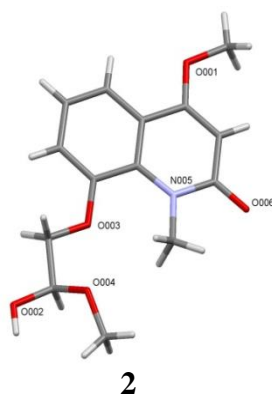
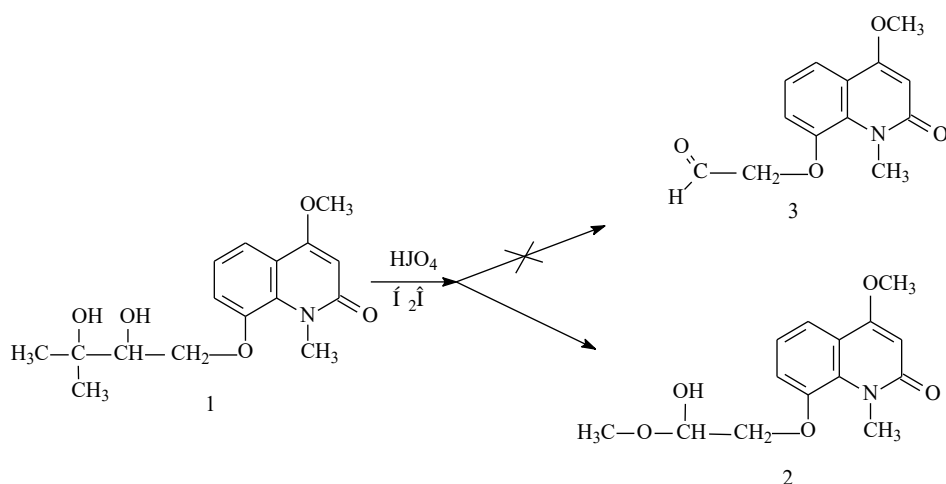
## OXIDATION OF FOLIOZIDINE BY IODIC ACID

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Alkaloid Foliosidine have been isolated from the aerial part of the plant *Haplophyllum foliosum* Vved. Plant *Haplophyllum foliosum* Vved (leafy leaves) were extracted with chloroform. The chloroform extract was dissolved in acid, the acidic solution was made alkaline, and the alkaloids were extracted with chloroform. When grinding the resulting oil with acetone, formed crystals of foliosidine, with mp of 141-143°C. The yield was 0.023% of the dried weight of the plants.

**The oxidation of foliozidine with iodic acid.** Recrystallization of the reaction product from methanol, obtained compound **2**, and the expected compound **3** with mp 155-160 °C.



The structure of derivative **2** was established on the basis of <sup>1</sup>H and <sup>13</sup>C NMR spectra and X-Ray.

## IDENTIFICATION OF *Peganum harmala* TOXIC ALKALOIDS FROM AZERBAIJAN FLORA

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From ancient times, *Peganum harmala* has been claimed to be an important medicinal plant with antibacterial, antifungal, and monoamine oxidase inhibition properties. Its seeds possess hypothermic and hallucinogenic effects, and oral administration also causes calming and abortion. Especially in eastern regions of the world, many people use *P. harmala* in traditional medicine for its wide effects. So toxicity history of this plant begins here. Intoxications usually happen from an overdose of plant parts, especially seeds. Toxicity of this plant traditionally used in the Middle East has been reported in humans with poisoning symptoms similar to what has been reported for domestic animals. The signs of *Peganum harmala* overdose include hallucinations, bradycardia, nausea, and vomiting. The physical aspect of poisoning included neurological, gastrointestinal, and cardiovascular signs with seven deaths being deplored.

The main cause of intoxication are alkaloids in *P. harmala*. The plant is rich with  $\beta$ -carboline alkaloids such as harmine, harmaline, tetrahydroharmine, harmol, harmalol, harman and quinazoline derivatives such as vasicine and vasicinone.

Dried and ground seeds of *P. harmala* were extracted 3 times by 95% ethanol. Ethanol extracts were combined, evaporated on the water bath until 10 mL, added 5% HCl and the obtained solution was filtered. The solution was alkalinized by 25% ammonia solution and extracted by liquid/liquid extraction with chloroform 4 times. Chloroform fractions were combined, concentrated and analyzed by TLC. On TLC plates, 4 orange spots with  $R_f$  0.69, 0.31, 0.2 and 0.1 (stationary phase "Sorbfil" (Russia), mobile phase chloroform/methanol, 9/1, v/v (both of Merck, Germany); revelator Dragendorff reagent) were observed. Preparative TLC plates were used ("Machery-Nagel", Germany) mobile phase chloroform/methanol, 8.5/1.5, v/v) for the purification. Lines appropriate to each compound were scraped, extracted by ethanol and filtered. These compounds were identified as harmine, harmaline, and vasicine based on UV, IR, and NMR spectroscopy data.

## THIN LAYER CHROMATOGRAPHY OF ALKALOIDS FROM *Hyoscyamus niger* LEAVES

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Black henbane (*Hyoscyamus niger* L.), is a biennial herb indigenous to Europe, Western and Northern Asia, and Northern Africa. It has been introduced to Eastern Asia, North America and Australia, and cultivated in several other countries. Henbane is found in many regions of Azerbaijan naturally. It is an important medicinal plant belonging to Solanaceae family. *H. niger* is well documented in traditional medicine for its effects of spasmolysis, analgesia, relieving cough, and anti- asthma, prescribed for the treatment of stomach cramps, heavy coughs, neuralgia, and manic psychosis. This plant is a rich source of medicinal substances including tropane alkaloids.

*H. niger* leaves were gathered from Gadabay district, Azerbaijan in 4 September 2018. Plant material was dried in well ventilated place, in the shade, in the room temperature. 40 g leaves were powdered and extracted with chloroform-methanol-25% ammonium hydroxide - 15:5:1. Extraction was repeated 3 times. After filtration, solvent mixture was evaporated. The residue was washed twice with  $\text{CHCl}_3$ . The pooled filtrate was evaporated to dryness. To the residue, 20 mL of  $\text{CHCl}_3$  and 30 mL of 1 N  $\text{H}_2\text{SO}_4$  were added, then the solution was mixed well. The  $\text{CHCl}_3$  phase was removed and the  $\text{H}_2\text{SO}_4$  phase was adjusted to pH 10 with 25%  $\text{NH}_4\text{OH}$  in an ice-bath. From the solution, alkaloids were extracted once with 40 mL and twice with 30 mL of  $\text{CHCl}_3$ . The combined extracts were filtered after adding anhydrous  $\text{Na}_2\text{SO}_4$  and then the residue was washed with 10 mL of  $\text{CHCl}_3$ . The combined filtrates were evaporated to dryness at 40 °C.

Thin layer chromatography (TLC) has been used for determination of alkaloid compounds. The alkaloid fraction thus obtained was dissolved in an appropriate volume of ethanol, applied on silica gel plate (60 F254, Merk, Glass, thickness 0.2 mm), and then analyzed with chloroform-methanol solvent mixture (7.5:2.5). The alkaloidal spots were detected with Dragendorff's reagent. As a result, 5 different alkaloids were observed and distinguished with different  $R_f$  parameters (0.05, 0.1, 0.2, 0.35, 0.85, respectively). Studies are continued in this direction!

## COMPARATIVE STUDY OF THE CHEMICAL COMPOSITION OF FATTY OIL FROM SEEDS INCLUDING SOME SPECIES OF THE FAMILY OF ASTERACEAE BERCHT. ET J. PRESL

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Fatty oil (FO), providing fatty acids (linoleic, linolenic and arachidic) that are not synthesized in the human body is an indispensable nutritional factor. They are also used in the production of medicines. Considering these, we aim to study FO from some species of the family Asteraceae Bercht. Et J. Presl (*Silybum marianum* (L.) Gaertn., *Actium lappa* L., *Xeranthemum cylindraceum* Sibth. et Sm., *Carthamus lanatus* (L.) Boiss.) that are widespread in Azerbaijan and have a lot of natural resources.

As a result of our research, it was found that the amount of FO obtained from the seeds of *X. cylindraceum* was 41.8% higher than that of the other species, while in *A. lappa*, it was relatively low at 24.3%, and that of the other two species was approximately equal in size (33.3% and 36.8%). FO of these plants contained linoleic, oleic acids and other acids. *X. cylindraceum* contained more oleic acid in the plant and the other three species (*S. marianum*, *A. lappa* and *C. lanatus*) bore more linoleic acid. The composition of fatty acids of *S. marianum*, *A. lappa*, *C. lanatus* and *X. cylindraceum* consisted mainly of 8-9 fatty acids of trans-isomers, including prevailing linoleic acid (17.3% - 75.2%) and oleic acid (13.3% - 55.4%). In addition, fatty acids contained palmitic (5.4-9.5%), stearic (2.2 - 5.5%), as well as linolenic, erucic, eicosenoic, myristic acids and other compounds. Most of these substances belong to the unsaturated fatty acids of  $\omega$ -3 and  $\omega$ -6, whose benefits for human have been scientifically proven. The amount of saponification in *S. marianum* and *A. lappa* plants was 199.4 and 190.6, respectively, and that of *C. lanatus* and *X. cylindraceum* plants was 192 (KOH) each. The amount of free fatty acids in *S. marianum* and *A. lappa* plants was approximately 2.5% and 3.5%, respectively, while that in *C. lanatus* and *X. cylindraceum* plants was less than 0.8% and 0.3%, respectively, compared to the other two plants. The amount of peroxide was the least for *C. lanatus* (2.1 mmol O<sub>2</sub> / kg), most of which was in the FO of *A. lappa* (27.8 mmol O<sub>2</sub> / kg), compared with *S. marianum* (3.9 mmol O<sub>2</sub> / kg) and *X. cylindraceum* FO (3.1 mmol O<sub>2</sub> / kg). The higher the number of iodine, the greater the fat able to dry. The amount of iodine in the FO of *A. lappa* and *C. lanatus* plants was 130.8 and 142.5 (IV), respectively. Iodine oils, from 85 to 130, were semi-lubricant oils mainly used for food purposes. The amount of iodine in the FO of *X. cylindraceum* and *S. marianum* was 112.9 and 116.7 (IV), respectively.

Studies have shown that in two regions (Shamakhi and Ismayilli) of the mentioned plants, the annual delivery capacity of surface unit is 40.7 tons at 23 ha for *A. lappa*, 6.5 tons at 29 ha for *X. cylindraceum*, 69.4 tons at 43 ha for *S. marianum*, and 150.4 tons at 40 ha for *C. lanatus*. Given the large natural reserves in the flora of Azerbaijan, it can be argued that the studied species have quite good prospects for use as medicinal, food and industrial plants

## FLAVONOID COMPOSITION OF *Vicia faba* L. FROM THE FLORA OF AZERBAIJAN

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Genus *Vicia* L. (pea or vetch), belongs to Fabaceae family (150 species), widely spread in North hemisphere, with 40-42 species growing in Azerbaijan, mainly found in gardens, on road sides and in fertile lands. It is known that, therapeutic effects of plants are associated with biologically active compounds, such as alkaloids, flavonoids, saponins, essential oils, microelements and etc. These components are responsible for their pharmacological effects. Species of the genus are widely used in folk and scientific medicines. Thus, extract of flowers is utilized for dermal diseases, allergies and spots on skin. Acetone extract of *Vicia Faba* is used as an antifungal agent. Therefore the aim of this work is to study flavonoid content of the specie of *Vicia Faba* L. from Azerbaijan flora for exposure new possible medicinal resources.

Raw materials of *Vicia Faba* L. were harvested in the beginning of June, 2019 in the neighbourhood of Kusary city of the Azerbaijan Republic. UV spectra of the compounds were obtained in Agilent Cary 60 UV-VIS Aligent Technologies and IR spectras were obtained in Agilent Cary 6000 (USA). Melting point was determined in the Stuart SMP 20. Specific rotation was measured by Rudolf Research Analytical Autopal. For paper chromatography a Filtrak FN5 paper was used and evaporation was carried out on the rotary evaporator IKA RV 8.

For isolation of flavanoids 0.8 kg grinded and air dried flowers were twice extracted with the 80% ethanol in the ratio of material to ethanol 1:8 and 1:6, respectively. At the end of extraction, all the extracts were mixed, concentrated in the rotary evaporator until the aqueous solution (150 mL) and step-by-step treated, at first by chlorophorm, and after that by the mix of hexane with ethylacetate. From the isolates, carried out by the mix of hexane with ethylacetate, using multi-step crystallisation method two compounds: compound-1 (0.202 gr) and compound-2 (0.203 gr) were isolated.

**Compound 1** –  $C_{15}H_{10}O_5$ , yellow crystal, mp 350-352 °C (methanol-chloroform), UV spectra: maximal absorbance at 272 and 333 nm. UV and IR spectra corresponded to Apigenin.

**Compound 2** –  $C_{30}H_{26}O_{13}$ , light yellow crystal, mp 253-260 °C,  $[\alpha]_D^{20}$  -70° (*c* 0.8, methanol), UV spectra: maximal absorbance at 268 and 320 nm. At the acidic hydrolysis Kampferol, D-glucose and *p*-coumaric acid could be observed. IR and UV spectra for compound 2 were similar to *trans*-tyriloside (6''-*O*-*p*-coumaroyl-astragalin).

Thus, from the raw materials of *Vicia Faba* L. from the flora of Azerbaijan Republic, flavanoids Apigenin and *trans*-tyriloside were isolated and identified for the first time.

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## DEVELOPMENT OF A NEW DENTAL DRUG TECHNOLOGY FOR THE TREATMENT OF STOMATITIS IN CHILDREN AND ADULTS

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Inflammatory diseases of stomatitis are one of the most pressing problems in dentistry. According to experts of the world health organization, oral diseases in persons aged 35 to 44 years are 69-98%, among children the prevalence of dental pathology reaches 75-95%.

In connection with the resistance of the body to many antibiotics, drugs from other groups of antimicrobial agents are of increasing interest, while plant substances are of particular importance. Currently, there is an extensive Arsenal of local effects on erosive-ulcerative lesions of the oral mucosa. Drugs with analgesic, anti-inflammatory, antimicrobial, keratoplastic, immunostimulating and other therapeutic effects are used.

For our research, we used dry Aloe extract obtained from fresh Aloe leaves, as well as dry extract produced by the pharmaceutical company "GFL Ltd" which met all requirements. As a result of complex physico-chemical, technological, biopharmaceutical and biological studies, we developed the following composition in the form of a powder, called "Denta Aloe", for the treatment of stomatitis: powder Composition per 1 package (3.0 g):

Aloe leaf (*Aloe arborescens*, mill) dry extract – 1.0 g;

Menthol (Mentol) – 0.05 g;

Sodium chloride (*Natrii chloridum*) – 0.54 g;

Sodium bicarbonate (*Natrii hydrocarbonas*) 1.4 g;

Sodium benzoate (*Natrii benzoatum*) 0.01 g;

In the course of pharmaco-Toxicological studies, the specific wound healing activity and harmlessness of the drug "Denta Aloe" were examined and showed that the drug for wound healing activity superior to the control variant at 54%, when referred to toxic substances, did not show allergic, cumulative and irritant properties.

On the basis of the requirements of the State Pharmacopoeia XI edition and other normative documents, regulations on the quality of the drug "Denta Aloe" has been set. Stability, along with efficiency and safety, is an important factor in the quality of the drug powder, as it determines the possibility of influence of external and internal factors (physical, chemical, microbiological changes) on the safety and therapeutic effect of the powder. Therefore, forecasting and timing of storage is an important stage of development. The results of our tests to determine the shelf life of the drug "Denta Aloe" *in vivo* are not less than 2 years. The drug "Denta Aloe" is recommended for use by dissolving one sachet bag weighing 3 g in 100 mL of hot water and rinsing the mouth 2 times a day with stomatitis.

Methods of analysis and standardization of the drug "Denta Aloe" were developed on the requirements of the State Pharmacopoeia and drafted (SAF) Pharmacopoeia monograph of the enterprise.

## INFLUENCE OF NEW PREPARATIONS K-26 AND K-26W ON SYNTHESIS DNA AND RNA OF TUMOR CELLS OF SARCOMA 180 AND KIDNEY TUMORS OF THE HUMAN

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The screening spent on the panel of tumors of the person at National institute of a cancer of the USA (NCI) *in vitro*, has shown high cytotoxic activity of substance K-26 on all lines of a cancer of a kidney of the person. On the basis of K-26 water-soluble salt K-26-B which has been received it has appeared in 1.5 times less toxic and more active on a number of experimental tumors. However, it is known that the kidney cancer - one of the steadiest against chemotherapy caused by a hyper expression of gene MDR, therefore the efficiency of applied medicinal substances makes no more than 5 %. As there are no experimental tumors for a cancer of a kidney. Studying of influence K-26 and its water-soluble analogue on synthesis DNK/RNK of a tumors of the Sarcoma of 180 and tumor cages of a kidney of 4 patients *in vitro*, the with substance DNA synthesis, the theoretically above at a preparation ability of influence on object more chokes was the purpose of the present work.

**Methods.** To suspension of cages of tumors, in 96-lunochnyh tablets added preparations in ТД mkg/mL and инкубировали 2ч, at 37 °C and 5 % CO<sub>2</sub> in CO<sub>2</sub> incubator. Then spent allocation of DNA and PHK on a method of Maniatis T, 1984 the Quantitative estimation of concentration of DNA and PHK control and skilled tests defined Spectrophotometric at a wave length of 260 nm.

**Results.** If on a tumors the Sarcoma 180 preparation K-26 after the spent treatment by 10-fold introduction of a preparation (with activity in 92-90 %) inhibition synthesis of DNA of a tumors to 85.0 % and synthesis PHK - to 65.0 % on tumors of a cancer of a kidney *in vitro* at unitary influence K-26 ингибирует DNA synthesis on 51 % and RNK - on 39 %, i.e., its influence compared with a tumor the Sarcoma 180 decreased on 3426 %. Influence K-26-B, in comparison with K-26, on synthesis of DNA and PHK in tumor cages of a kidney above on 11 % and 2 % accordingly, i.e. reception of the water-soluble form has not lowered its influence on a kidney cancer. It is visible that the more DNA synthesis chokes, the more preparations show activity in experiment, i.e. their activity at influence on carriers of tumors can be considerable above since at a preparation the action mechanism does not consist from alkaloid, and are present also influence on a mitosis, and on topoizomerase. Probably, decrease in influence on synthesis of DNA of fabrics of a cancer of a kidney of new preparations is connected not so much with resistance of these tumors as K-26 possesses ability of overcoming of resistance, as with unitary influence of preparations.

## MECHANISM OF ANTINEOPLASTIC AND RADIOSENSITIVITY ACTION OF THE PREPARATION K-26

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In National Cancer center of Uzbekistan workings out the new antineoplastic preparations received by updating tropolone alkaloids are conducted. By results of the screening spent on the panel of tumors of the person at National institute of a cancer of the USA (NCI) in vitro high activity was preparation of K-26 on the basis of selection in vivo on animals with tumors, which has been offered further for preclinical tests as an antineoplastic preparation and a radio sensitizer.

**The purpose of the work.** The study of fragments of the mechanism of action: alkylating ability, effects on topoisomerase II, on mitotic activity, effect on drug resistance, on CFU of a new preparation K-26.

**Materials and methods.** The study of mitotic activity was carried out with the histological analysis of the duodenum 12 after exposure to the drug, as well as on Sarah's tumors. The alkylation effect of a / effect on the synthesis of DNA and RNA preparations was studied using a spectrophotometric method on Sarcoma 180 tumor cells b / internucleosomal DNA degradation sarcoma 180 cells after exposure to drugs and K-26 were studied by the method of etoposide Samusenko AV. Effect of drugs on MDR and p53 on sarcoma cells 180 studied by Cdna level using RT-PCR according to the manufacturer's protocol. Study of CFUs was performed on outbred mice on «THERATRON» apparatus at a dose of 6 Gy to 9th day after irradiation.

**Results.** K-26 inhibits DNA synthesis by 85%, and RNA synthesis by 65% relative to the control, etoposide, respectively, by 55% and 35%. Rated and matched topo S Ngibiruyuschaya K-26 activity with an activity of topoisomerase marker Etoposide II, K-26 inhibits this enzyme by 80%, and Etoposide- 60%. The expression of the gene of drug resistance of MDR 2 was quantified by RT-PCR: K-26 suppressed the expression of the MDR 2 gene by 85%, etoposide- by 65%. K-26 significantly increases the expression of the p53 gene up to 80%, and etoposide up to 55%, which determines the greater ability of K-26 to induce tumor apoptosis. Shown the ability of K-26 to induce the induction of CFUs to 12 units.

**Conclusion.** Revealed ability of K-26 to suppress NK synthesis, topoisomerase activity and p53, as well as to suppress the expression of the drug gene sustainability MDR 2, explains its high antitumor, and Wyes mitotic activity resulting in synchronization of cell division, and radiosensitizing activity. Stimulation of CFU, which ensures the formation of hematopoietic and immune cells, can protect the body from its intense cytotoxic action.

## DECREASE IN RESISTANCY OF YEAST *Saccharomyces cerevisiae* WITH PREPARATIONS FROM TROPOLON ALKALOIDS, AND THEIR COMBINATIONS WITH COMMERCIAL CYTOSTATICS

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**Introduction.** The Phenomenon of development of plural medical stability of a tumoral cells in reply to influence of antineoplastic preparations is widely known. Our team decreased in level of resistance with a number of the preparations received from tropolon alkaloids (K-42, K-18, decovin and K-19), in comparison with a number of commercial antineoplastic preparations at first on model of yeast *Saccharomyces cerevisiae* (intact and with resistance to investigated preparations), further - on animals with tumors in comparison with etoposidyum (a method from-PTSR) has been shown. It has allowed to estimate quantitatively an expression of a gene of medicinal stability MDR2 on tumors. However, it was interesting to study influence of new preparations in a combination with other antineoplastic preparations, and to reduce caused cross resistance.

The research objective consisted in research of influence of the new preparations received from tropolon alkaloids, on decrease in resistance of their combinations with commercial cytostatics on modelling cages *S. cerevisiae*.

**Methods.** Models of resistant cages *S. cerevisiae* to K-42, K-18, decovin and K-19 in doses are received: 12 mkg/mL K-42, 18 mkg/mL K-18, 50 mkg/mL decovin and 40 mkg/mL K-19, compared with etoposidyum (15 mkg/mL) and Doxorubicin(1.8 mkg/mL). Growth of cages of each investigated variant analyzed in cups of Petri on the firm environment for yeast *S. cerevisiae*, on intact and on the environments containing specified concentration of a preparation. Level Pdr5p analyzed by quantity of growth of colonies of cages under the influence of the given investigated preparation against a control variant.

**Results.** It was shown that application K-42, verapamil (VER), Doxorubicin (DOX) and etoposidyum (ETOP) inhibited growth of resistant cells of *S. cerevisiae* within 64 %, 0.2 %, 5 % and 9 %, accordingly. At application of combinations K-42 with VER, K-42 with DOX and K-42 with ETOP growth of resistant cages *S. cerevisiae* was inhibited within already 40-55 %. Application K-18, decovin and K-19 as it is independent, and in a combination with VER, DOX or ETOP also promoted decrease in growth of resistant cages.

**Conclusion.** As K-42, K-18, decovin and K-19, it is possible to apply application in a combination with other antineoplastic preparations, and to reduce resistance which cause at repeated applications. Further these experiments will be made on animals with tumors.

## INFLUENCE OF CYTOSTATICS K-1, K-2, K-30 TO THE RESISTANCY OF THE CELLS *S. cerevisiae* AND SARCOMA 180

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It is known that cells of yeast *Saccharomyces cerevisiae* (models for studying of biology of cells of mammals) were analyzed for mechanisms of action of cytotoxins: Camptothecin - inhibitors of Topoisomerases I and II, verapamil, reserpine, cephalosporines, being modulators transmembrane squirrel Pgp and etc.

**The purpose of study.** Consisted in research of influence of new derivatives thropolonoid alkaloids K-1, K-2 and K-30 on resistance of modelling cells *S. cerevisiae* and tumours sarcoma 180.

**Methods.** Models of resistant cages *S. cerevisiae* to K-1, K-2 and K-30 in doses are received: 40 mkg/mL K-1, 100 mkg/mL K-2 and 9 mkg/mL K-30, as comparison were Acetamide (15 mkg/mL) and Doxorubicin (1.8 mkg/mL). Growth of cells of each investigated variant were analyzed in cups of Petri on the firm environment for yeast *S. cerevisiae*, on intact and on the environments containing specified concentration of a preparation. Level Pdr5p analyzed by quantity of growth of colonies of cages under the influence of the given investigated preparation against a control variant. For an estimation internucleous DNA degradations, the allocated preparations of DNA analyzed by means of electrophoresis. For research of influence of investigated preparations on an expression of gene MDR2, from a tumoral fabric of a sarcoma 180 under the influence of each preparation total preparations PHK have been received. Then by a method of return Transcriptas (FROM) have been received mRNA and are synthesised κДНК (expression MDR2/).

**Results.** It was shown that K-1, K-2 and K-30 inhibited growth intact cells of yeast within 65-80 % (etopozin within 40 %). On resistant cages *S. cerevisiae* K-1 both on 1, and in 3 days inhibited growth of these cages on 35 % and 36.7 %. K-30 on 55 % and 37.5 %, K-2 on 30 % and 18.2 % (on 1 and in 3 days). Etopozin both on 1, and in 3 days promoted growth of resistant cages above control, within 20 %-25 %. On a tumour of a sarcoma-180 by a method FROM-PTSR it was shown that K-1 and K-30 suppressed expression MDR2 within 80 %, and K-2 and Etopozin suppressed an expression of this gene on 70 % and 65 %, accordingly.

**Conclusions.** New preparations K-1, K-2 and K-30 did not promote development MJIY, as caused Pdr5p *S. Cerevisiae*, and gene MDR2 of a sarcoma 180, apparently because of internucleos degradations and DNA fragmentations. Results of these experiments testified that *S. Cerevisiae* was a convenient model for studying.

## THIOCARBAMIDE COMPLEX COMPOUNDS OF CALCIUM AND MAGNESIUM NICOTINATES

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The chemistry of complex compounds has developed rapidly due to the opening of the new applications in various objects with identification of their effective properties. The divalent metal complexes were found to have high biological activity in plant growing, which led to wide use of these complex compounds in agriculture. Thiocarbamide, nitrocarbamide, nicotinamide molecules and anions of nicotinic acid are representing such bioorganic compounds.

Their synthesis was performed by mechanochemical (enzyme) method, because this method did not require scarce organic solvents and required a short time to synthesize complexes of different composition with a high output. Necessary components for the experiment included magnesium and calcium nicotinate: amid 1: and amid 2. They were mixed in a ratio of 1:1:1 for 20 minutes at a room temperature in 1 liter ball mill. Complex compound composition of  $\text{Mg}(\text{NC}_5\text{H}_4\text{COO})_2 \cdot \text{CS}(\text{NH}_2)_2 \cdot \text{NC}_4\text{H}_5\text{CONH}_2 \cdot 2\text{H}_2\text{O}$  was achieved by intensive mixing of 1.5226 g dihydrate magnesium nicotinate with 0.3806 g thiocarbamide and 0.6103 g nicotinamide. Output of the product was 98.48%. 1.5115 g  $\text{Ca}(\text{NC}_5\text{H}_4\text{COO})_2 \cdot \text{H}_2\text{O}$  with 0.3806 g thiocarbamide and 0.6103 g nicotinamide were triturated to obtain the complex compound of  $\text{Ca}(\text{NC}_5\text{H}_4\text{COO})_2 \cdot \text{CS}(\text{NH}_2)_2 \cdot \text{NC}_4\text{H}_5\text{CONH}_2$ . The output of the product was 94.90%. The complex compound of  $\text{Ca}(\text{NC}_5\text{H}_4\text{COO})_2 \cdot \text{CS}(\text{NH}_2)_2 \cdot \text{H}_2\text{NCONHNO}_2$  was synthesized by intensive mixing of 1.5115 g monohydrate calcium nicotinate with 0.3806 g thiocarbamide and 0.5253 g nitrocarbamide. The output of the product was 94.72%. Part of the loss might be due to dehydration, which took place during the mixing. The synthesis was conducted according to the procedure described in the literature. The amount of metals in the synthesized compounds was determined on a novAA 300 atomic absorption spectrophotometer from Analytik Jena AG (Germany). Nitrogen, hydrogen, carbon, and sulfur were determined on an EA-1108 elemental analyzer (Carlo Erba). To establish the identity of the synthesized complex compounds, X-ray diffraction patterns were recorded on a PanalyticalEmpyrean X-ray diffractometer equipped with a Cu tube ( $K\alpha_1 = 1.5406 \text{ \AA}$ ). To calculate the interplanar distances, the tables were used and the relative intensity of the I / II line was determined as a percentage of the most pronounced reflection at the maximum.

IR absorption spectra were recorded in the region of 400–4000  $\text{cm}^{-1}$  on a Perkin Elmer IR Fourier spectrometer System-2000 using the technique of pressing samples with KBr. The thermal analysis was performed at derivatograph with F. Paulik-J. Paulik-L. Erdey system with heating rate of 10  $^\circ\text{C}/\text{min}$ , and sample mass 0.1 g at sensitivity galvanometer T-900, TG-100, DTA, DTG-1/10. The recording was performed in an atmospheric condition. Platinum crucible with diameter of 10 mm without lid was used as a holder. Powder of  $\text{Al}_2\text{O}_3$  was used as an etalon.

**CARBOXYLIC ACIDS OF *Galium boreale* HERB****T. V. Ilina, O. V. Goryacha, A. M. Kovalyova, O. M. Koshovyi, N. V. Borodina**

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*Galium boreale* L. or northern bedstraw is widespread over the temperate and subarctic regions of Europe, Asia and North America, including most of Canada and the northern United States. It is found all over the territory, except the arid southern areas in Ukraine. Currently, *Galium boreale* is used in folk medicine for treatment of cardiac conditions, liver and kidney problems, and externally as a healing remedy.

The aim of the present research was to study the composition of the carboxylic acids of *Galium boreale* herb. The plant material was harvested in the Botanical gardens of V. N. Karazin Kharkiv National University in June 2017, with the herbarium voucher stored at the Herbarium of Pharmacognosy Department of the National University of Pharmacy. In *Galium boreale* herb, 21 carboxylic acids were identified, including 13 monobasic acids, 7 dibasic acids (oxalic, succinic, malonic, 2-hydroxy-3-methylglutaric, fumaric and aselainic) and 1 tribasic (citric) acid. By the radical linked to the carboxyl group the acids were classified as 3 aromatic acids (benzoic, salicylic and vanillic) and 18 aliphatic acids, including 10 fatty acids (6 saturated and 4 unsaturated fatty acids).

For the analysis of the content of carboxylic acids in the air-dried plant material (50 mg) in a 2 mL vial, an internal standard (50 mg of tridecane in hexane) was added as well as 1.0 ml of a methylating agent (BCl<sub>3</sub> in methanol, 14% solution, Supelco 3-3033). For the extraction and hydrolysis of fats and other esters as well as for a simultaneous methylation of fatty acids and other organic acids, the mixture was heated in a sealed vial for 8 hours at 65 °C. Then, the reaction mixture was decanted from the plant material and the precipitate was diluted in 1 mL distilled water, from which methyl esters of the carboxylic acids were extracted with 0.2 mL methylene chloride. The mixture was gently shaken several times within an hour and then the obtained extract of the methyl esters was chromatographed. The sample injection (2 µL) was performed in a splitless mode at an injection rate of 1.2 mL/min per 0.2 min.

The content of hydroxyl acids totaled 11311.2 mg/kg, which comprised 42.69 % of the total fatty acid content; the dibasic acids content totaled 3411.4 mg/kg, which comprised 12.88 % of the total fatty acid content; the aromatic acids content totaled 283.4 mg/kg which comprised 1.07 % of the total fatty acid content; whereas the content of fatty acids was 11485.9 mg/kg, which comprised 43.36 % of the total fatty acid content. The content of the saturated fatty acids equaled 55.29 % of the total fatty acid content, and the unsaturated fatty acid content was 44.71 %. The dominating acids (mg/kg) among the hydroxyl acids was tribasic citric acid (7427.0), among the dicarboxylic acids dominating was oxalic acid (2387.4). Among aromatic acids, prevailing was vanillic acid (157.7), and among fatty acids, palmitic acid (5052.3) and linolenic acid (2571.6) dominated. The total carboxylic acid content in *Galium boreale* herb was 2.65 %. The presence of benzoic, salicylic, fumaric and succinic acids may account for antimicrobial and fungicidal effect in the substances of *Galium boreale* herb.

## **OBTAINING A COMPLEX OF NANOPARTICLES BIOACTIVE EXTRACT OF *Cynara scolymus* WITH MAGNESIUM SULFATE SALTS**

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The herb *Cynara scolymus* belongs to the family Asleraceae and widely distributed in Europe, South America and other countries of the world. Since ancient times, concoction or tea from various parts of this herb has been used in folk medicine as hepatoprotector, choleric, stercoral ulcer, as apetizer, analeptic medicine for lever, heart, as antihaemorrhagic, to treat hepatitis, fever and other diseases.

In the development of modern nanotechnology, a significant role is played by studies of nanoparticles obtained from extracts of medicinal plants using solutions of metal salts.

To research on pharmacological activity, we have obtained a complex of nanoparticles 70% bioactive components of *Cynara scolymus* with magnesium sulfate salts.

The obtained complex of nanoparticles 70% bioactive components of *Cynara scolymus* with magnesium sulfate salts has been confirmed with HPLC and TLC analyses.



## TECHNOLOGY OF OBTAINING DRY EXTRACT OF *Scutellaria iscanderi*

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Plants of the genus *Scutellaria* from the family of Scutellaria Lamiaceae in particular, the *Scutellaria baicalensis* is one of the promising raw materials for the production of medicinal herbal preparations with different biological activities. The healing properties of *Scutellaria baicalensis* as a hypotensive and sedative are known since ancient times.

Plants of the genus *Scutellaria* also grow in the territory of Uzbekistan, like *Scutellaria Iscanderi*. A study of the chemical composition of plants showed that, they contained such active ingredients as flavonoids, glycosides, essential oils, organic acids, macro and micro elements, tannins, etc.

The purpose of this study is to develop technologies for the production of a dry extract (substance) of *Scutellaria Iscanderi*, which has pronounced hypotensive and sedative activity due to an increase in the yield of active substances.

The raw material used to obtain the dry extract was the aerial part of the grass of *Scutellaria Iscanderi* growing on the territory of Uzbekistan, collected in the flowering phase and dried by the air-shadow method.

The dry extract was obtained by fractional maceration in 3 stages (the time interval for infusion at each stage was 2 hours, 1 hour, 0.5 hour at a temperature of 60 °C. The establishment of optimal technological parameters of the process of obtaining a dry extract, provided the maximum yield of active substances, the influence of the main factors: the nature and concentration of the extragent, the ratio of raw materials to the extragent, the degree of grinding of raw materials, temperature, duration and frequency of extraction on the extraction processes of plant material.

The choice of optimal extraction parameters of raw materials was controlled by the yield of extractives and phenolic compounds. The yield of extracts was determined by known methods.

Quantitative determination of flavonoids was carried out by UV -spectrophotometry in terms of apigenin (standard) on a Shimadzu-1800 spectrophotometer with a wavelength of 200-450 nm.

Based on the results of the experiment, it was found that the optimal technological parameters of the process for obtaining dry extract of *Scutellaria* were: particle size of the raw material-0.5-3 mm, extragent-40% ethyl alcohol, the ratio of raw material and extragent-1: 15, temperature extraction - 60 °C, extraction ratio-3. Under these conditions, the yield of dry extract was 3.2 -4.5%. Based on the results of the studies, normative documentation was developed (Temporary Pharmacopoeia article on “Dry extract of *Scutellaria Iscanderi*”).

## PYRROLIZIDINE ALKALOIDS FROM *Senecio jacobea*

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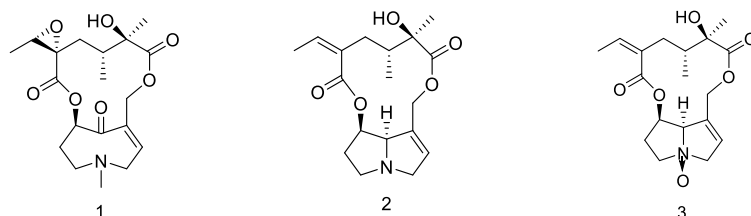
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Pyrrolizidine alkaloids (PAs) are secondary plant metabolites with considerable hepatotoxic, tumorigenic and genotoxic potentiality. To date, more than 660 PAs and their N-oxide forms (PANOs) have been identified in over 6000 plants. Most of them occur mainly in genus of Asteraceae, Boraginaceae, Orchidaceae and Fabaceae [1]. *Senecio* genus were used in Traditional Chinese Medicine (TCM) as a treatment for various ailments, such as bacterial diarrhea, enteritis, conjunctivitis, and respiratory infections [2]. So, it attracted our curiosity to study the chemical constituents and biological activities of *Senecio jacobea*.

PAs occur as free necines or as mixtures of bases and their N-oxides. The unsaturated necine base with a double bond at the C-1/C-2 position exhibits high level of toxicity, while the saturated type are reported to be nontoxic [3, 4]. In this study, the total alkaloid extracts were fractionated and purified by using chromatography technic (Silica gel, Flash chromatography, HPLC, p-HPLC), and isolated 3 known compounds otosenine (1), senecionine (2) and senecionine N-oxides (3). Their structures were determined by spectroscopic analyses (NMR and MS) [5-7].



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## CHEMICAL COMPOSITION AND BIOLOGICAL ACTIVITY OF ESSENTIAL OIL FROM *Valeriana jatamansi* Jones. RHIZOME

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The genus *Valeriana* (Valerianaceae) consists of about 200 species used for many diseases as folk medicine among many cultures, as well as in Chinese medicine. Chinese Valerian (*Valeriana jatamansi* Jones) is widely distributed in southwest China, including Hubei, Yunnan, Guangxi, Sichuan and other provinces. Its earliest record was in the "Compendium of materia medica", the rhizome was used for the treatment of abdominal distention, gas pains, dyspepsia, diarrhea, rheumatic arthralgia, lassitude loin and legs.

Studies on variation in essential oil (Eos) composition of *V. jatamansi* from different part of India and different cultivation/growing conditions have been reported, and showed great location-specific variation in Eos constituents like patchouli alcohol,  $\alpha$ -bulnesene,  $\alpha$ -guaiene, guaiol, seychellene, viridiflorol, etc. In recent years, more and more attention has been paid to the development of medicinal value of Chinese valerian. However, there are few reports of the phytochemical and biological studies on its underground parts.

To rapidly screen and detect the antioxidant and antibacterial activities of the Eos from *V. jatamansi* rhizome, steam- and hydrodistillation methods were used for the preparation of Eos, thin layer chromatography-bioautography (TLC-bioautography) and chemical screening method for the bioactive test. In order to investigate the active constituents, gas chromatography-quadrupole time of flight-mass spectrometry (GC-QTOF/MS) method was established with polar and nonpolar capillary columns, the retention indices (RI) of every peak in both columns were calculated, then identified by comparing its RI and mass spectrum with the MS library (NIST 14).

The results revealed that Eos exhibited potential antioxidant activity ( $IC_{50}$ (ABTS)=31.907 $\pm$ 2.08 g/mL,  $IC_{50}$ (DPPH)=97.043 $\pm$ 13.23 g/mL) and antibacterial activities against *Escherichia coli*, *Staphylococcus aureus*, *Bacillus subtilis*, *Candida albicans* with inhibition zone at 20 mg/mL loading 8 $\pm$ 7~12 $\pm$ 7 mm. Minimum inhibitory concentration (MIC) values of Eos were ranged 14.65~937.50  $\mu$ g/mL respectively. 47 compounds were identified from the Eos representing 98.158% of the oil. The major components were sesquiterpene (90.738%), predominated by alloaromadendrene (12.048), Patchouli alcohol (11.842), cis-g-Bisabolene (11.728%), cedrenol (8.913%), cyperene (7.102%), valerenol (6.710%),  $\beta$ -Eudesmene (5.837%), while other components presented in acids (6.176%), monoterpene (0.648%), esters (0.438%), and ethers (0.158%). These results suggested that the Eos from Chinese valerian rhizome would be a potential resource for the natural product based antimicrobial as well as antioxidant agents.

### ACKNOWLEDGMENTS

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## **EFFECT OF GLYCYRRHIZIC ACID AND PHYTOHORMONES ON COTTON PLANT (*Gossypium hirsutum* L.) PRODUCTIVITY**

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Cotton plant (*Gossypium hirsutum* L.) is one of the valuable types of crops receiving raw materials that can be used for a variety of purposes and a wide range around the world. It is known that ~60% of the natural fiber used in industry is cotton fiber, so the world pays special attention to the cultivation of high-quality cotton fiber.

Along with the use of advanced agricultural technologies in increasing resistance and preventing the development and death of cotton to external stress factors, special attention is paid to the use of natural compounds.

Accordingly, this study showed that the sweetness (*Glycyrrhiza glabra* L.) supramolecular complexes with phytohormones (FH) glycyrrhizic acid (GA) (FH: IAA, NAA, IBA and kinetin) isolated from the root synthesized/chemically identified and synthesized as cotton (*Gossypium hirsutum* L.). The effect of varieties "Sulton" on reproduction was investigated. The study selected cotton plant (*Gossypium hirsutum* L.) variety "Sulton" as an object in the analysis of the biological activity of supramolecular complexes.

Increase in morphometric parameters of cotton under the influence of GA: FH (FH: IAA, NAA, IBA and kinetin) supramolecular complexes (100  $\mu$ m), and the rate of multiplication of seed for 10 days is to 82.4 $\pm$ 3.4% in control group; a decrease of 36.5 $\pm$ 4.2% in the experimental conditions of salinity (NaCl=200 mm) and under these conditions GH: FG in incubation supramolecular complexes (100  $\mu$ m), respectively– 74.1 $\pm$ 5.6%; 56.8 $\pm$ 2.4%; 63.2 $\pm$ 3.5% and it was discovered that it will recover to 70.9 $\pm$ 2.6 percent. In the control group, the energy of cotton cultivation has increased by 54.6 $\pm$ 2.7% for 7-days, a decrease of 21.8 $\pm$ 2.6% in experimental salt deficiency and, accordingly, under the influence of GA: FH supramolecular complexes (100  $\mu$ m) – 42.5 $\pm$ 3.6%; 30 $\pm$ 2.5%; 39.6 $\pm$ 2.8% and it was found that 28.3 $\pm$ 3.7% will be restored.

The obtained experimental results confirm the high prospects for further growth and development of crops by stimulating in practice biochemical/physiological processes, the use of super-molecular complexes of GA and FH (FH: IAA, NAA, IBA and kinetin) on the basis of economic resource saving in order to optimize productivity.

## ULTRASTRUCTURAL TRANSFORMATIONS OF STAPHYLOCOCCUS AUREUS CELL WALL ELEMENTS UNDER *Achillea nobilis* L. ESSENTIAL OIL

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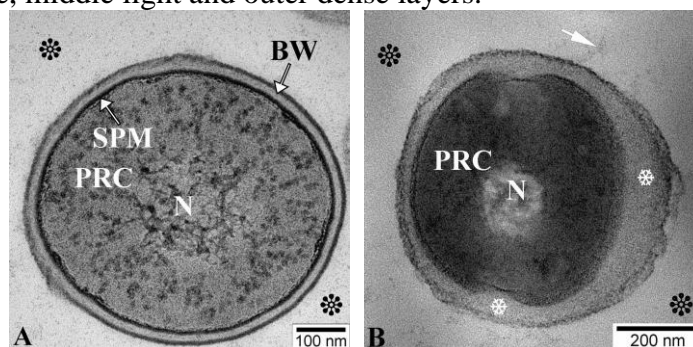
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This report was an electron microscopic study of the effect of *Achillea nobilis* L. essential oil on the structures of *Staphylococcus aureus* (SA). The essential oil was obtained from the aerial part of the noble yarrow, collected in the mass flowering phase, by hydro-distillation method. An electron microscopic study was performed on the effect of noble yarrow essential oil and its 1.7% alcohol-water solution on SA cells. The samples were incubated for 15 min, then centrifuged to separate chemical substances. The produced centrifugates were twice washed by sterile distilled water. Then they were fixed by immersion in situ during 15 min using the mixture of 2.5% wt. solution of glutaric aldehyde, 2.5% solution of paraformaldehyde and 0.1% solution of picric acid on phosphate buffer (pH = 7.4) at least 4 hours and then processed using standard EM. Ultrathin sections (50-70 nm) were prepared by using TEM (Jeol 1400).

In electronograms obtained from control series (Fig. 1A), in the center of SA cytoplasm, there was DNA consisting of a roughly fibrillar filament nucleoid (N), at the periphery of which there were numerous protein-ribosomal complexes (PRC). The matrix of the cytoplasm was separated from the structural elements of the wall using the cytoplasmic membrane (SPM). The ultrastructural wall bacterial walls (BW) consisted of an inner dense, middle light and outer dense layers.



When exposed to yarrow essential oil for 15 minutes, the following were noted (Fig.B): enlightenment at the location of the nucleoid; homogenization of protein-ribosomal complexes; the impossibility of follow elements of plasma membranes; disturbance of the three-layer structure of the structural elements of the wall (shown by snowflakes); numerous small-granular osmiophilic residues around bacterial cells (shown by arrow) and osmiophilic condensation of the matrix (shown by flowers). An analysis of the data showed that when exposed to the essential oil of *Achillea nobilis* L., the destruction of the integrity of plasma membranes led to a disturbance of their selective permeability.

## NEW ECDYSTEROIDS AND FLAVONOIDS FROM *Silene* plants (CARYOPHYLLACEAE)

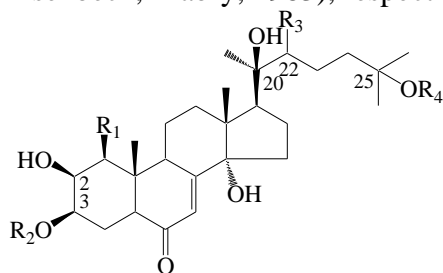
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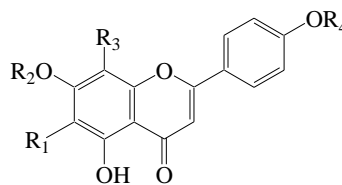
*Silene* plants (Caryophyllaceae) are the source of the various phytochemicals and ecdysteroids and glycosylflavones in particular (Mamadaliyeva et al., 2014). As a part of our ongoing study, we found six new compounds in two *Silene* species.

*Silene italica* is a species native to Europe and the Middle East which introduced samples contain ecdysteroids (Meng et al., 2001) and flavonoids (Darmograi, 1977). We studied the chemical composition of wild-growing *S. italica* collected in Georgia earlier (Olennikov, Kashchenko, 2019). Thirty-four compounds were detected including ecdysteroids and their glycosides and some *C*-, *O*- and *C,O*-glycosylflavones. The additional study allowed us to isolate four new compounds (**1–4**) from methanolic extract of *S. italica* herb after column chromatography and preparative HPLC. Based on UV, IR, NMR, and mass spectrometry data, the structures of new compounds were identified as 22-desoxyintegristerone A 3-*O*- $\beta$ -D-glucoside (**1**), 22-desoxyintegristerone A 25-*O*- $\beta$ -D-glucoside (**2**), genkwanin-6-*C*-(2''-*O*- $\beta$ -D-glucosyl)- $\beta$ -D-glucoside-8-*C*- $\alpha$ -L-arabinoside (**3**), and schaftoside-2''-*O*- $\beta$ -D-glucoside (**4**). To our knowledge, this is the first report of 22-desoxyintegristerone A glycoside isolation as well as detection of *O*-glycoside of genkwanin-6-*C*-glucoside-8-*C*-arabinoside.

By continuing our investigation of the secondary metabolites of *Silene repens*, a species with a widespread distribution in Siberia and Far East of Russia (Olennikov, 2019), we found one new ecdysteroid **5** and new flavone **6**. Ecdysteroid **5** isolated from the flowers of *S. repens* was identified as 22-oxo-20-hydroxyecdysone 3-*O*- $\beta$ -D-glucoside. It should also be noted that 22-oxo-20-hydroxyecdysone was a predominant component in the glandular trichome exudate of the surface of *S. repens* calyxes. The structure of compound **6** was determined as apigenin 7,4'-dimethyl ether 6,8-di-*C*- $\beta$ -D-glycoside, whose monoglycosylated analogs embigenin and isoembigenin were found in *Iris tectorum* (Iridaceae) (Hirose et al., 1962) and *Dianthera sessilis* (Acanthaceae) (Hilsenbeck, Mabry, 1983), respectively.



- 1:** R<sub>1</sub>=OH; R<sub>2</sub> = Glcp; R<sub>3</sub>, R<sub>4</sub> = H  
**2:** R<sub>1</sub> = OH; R<sub>2</sub>, R<sub>3</sub> = H; R<sub>4</sub> = Glcp  
**5:** R<sub>1</sub>, R<sub>4</sub>= H; R<sub>2</sub> = Glcp; R<sub>3</sub> = =O



- 3:** R<sub>1</sub> = Glcp<sup>1-2''</sup>Glcp; R<sub>2</sub> = CH<sub>3</sub>; R<sub>3</sub> = Arap; R<sub>4</sub> = H  
**4:** R<sub>1</sub> = Glcp<sup>1-2''</sup>Glcp; R<sub>2</sub>, R<sub>4</sub>= H; R<sub>3</sub> = Arap  
**6:** R<sub>1</sub>, R<sub>3</sub>= Glcp; R<sub>2</sub>, R<sub>4</sub>= H

### ACKNOWLEDGEMENTS

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## OBTAINING AND STUDYING OF PHYSICAL AND CHEMICAL PROPERTIES OF CYCLOSIVERSIGENIN DERIVATIVES

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It is known that the most promising direction of creating new drugs is the structural modification of molecules of known natural compounds.

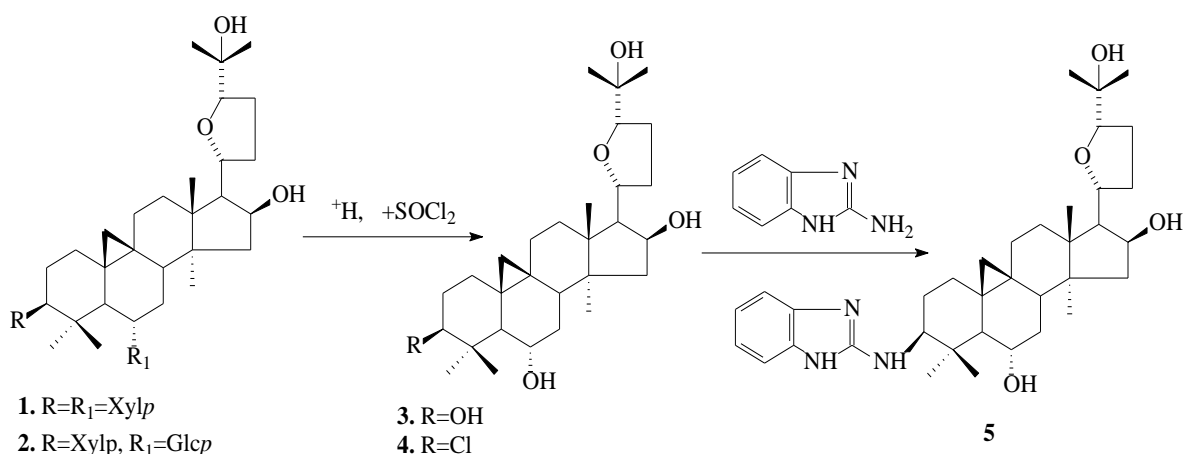
The purpose of this work is to study the possibility of modifying new derivatives of cycloartanes, studying their physicochemical and biological properties.

Cyclosiversiosides E (1) and F (2) were isolated by the known method from the aerial part of the plant *Astragalus filicaulis*.

Acid hydrolysis of compound 1 and 2 gave compound 3 identified with cyclosiversigenin (3).

The interaction of cyclosiversigenin (3) with thionyl chloride gave a new derivative - 3-chloro-6 $\alpha$ , 16 $\beta$ , 25-trihydroxo-20*R*, 24*S*-epoxycycloartan (4).

The interaction of compound 4 with benzimidazole-2-amine was carried out in acetone and a new derivative of cyclosiversigenin (5) was obtained.



All isolated compounds were identified on the basis of physicochemical constants using  $^1\text{H}$  and  $^{13}\text{C}$  NMR data and by chromatographic behavior on TLC in comparison with genuine samples.

## RELATIONSHIP BETWEEN MOLECULAR STRUCTURE AND ANTIOXIDANT ACTIVITY IN A NUMBER OF FLAVONOIDS

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The purpose of this work was to study the antioxidant activity of synthetic derivatives of certain flavonoids *in vitro*. Determination of antioxidant activity (AOA) was performed *in vitro* using the method of determining iron-reducing antioxidant capacity (FRAP-method) in accordance with the method based on the determination of iron-reducing ability of the object under study, which was evaluated by a spectrophotometric method. Comparison of the AOA compounds was performed with ascorbic (AA) and gallic (GA) acids. The received results were shown in the table.

Sample	0.25mg/mL	0.5 mg/mL	0.75 mg/mL	1 mg/mL
Pb-1-AC	0.0291±0.0023	0.0313±0.0028	0.0622±0.0319	0.1262±0.0097
PgC-AN	0.0774±0.0132	0.1041±0.0102	0.1099±0.0235	0.2327±0.0482
PgC-N	0.0815±0.0102	0.1814±0.0539	0.2178±0.1752	0.1780±0.0499
Pgb-3-Cu	0.0903±0.0060	0.1005±0.0047	0.1237±0.0048	0.1314±0.0175
AA	1.9256±0.2967	2.2844±0.0114	2.2571±0.1435	2.2316±0.1623
GA	1.2133±0.0502	1.2043±0.0245	1.1618±0.0137	1.1782±0.0063

On the basis of the obtained data, it was established that 8-piperidinylcyr sineol (PgC-AN) exhibited relatively increased antioxidant activity compared to other compounds, therefore, this substance could be recommended for further *in vitro* and *in vivo* studies. To expand the spectrum of the potential biological activity of the synthesized polyphenolic compounds, we perform a complex of theoretical methods, particular molecular docking. Analyses of the results of computer predictive modeling and biological screening of natural flavonoids and their derivatives allowed us to establish that the biological activity of the compounds was due to their chemical structure and spatial arrangement of pharmacophore groups. Thus, polyphenolic compounds and flavonoids are of high chance with the ability to bind free radicals, realizing antioxidant and antiradical effects.

Based on the performed *in vitro* experiments, the antioxidant activity of PgC-AN was established, inferior to the effect of AA and GA, which acquired a pronounced antioxidant property. Thus, the study of AOA *in vitro* pinostrobin acetate (Pb-1-AC), PgC-AN, 8-methylpiperazinylcyr sineol (PgC-N) and chrysin derivative (Pgb-3-Cu) showed the activity of PgC-AN.



## PREPARATIONS USING VEGETABLE RAW MATERIALS FOR THE PROTECTION OF GRAIN CROPS AND POTATOES

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The widespread use of pesticides is a necessary reality, as only in Russia chemical plant protection products retain crops worth up to 134 billion rubles. At the same time, etching is considered one of the environmentally friendly methods of protecting plants from diseases and pests of crops. One of the ways to increase the efficiency and safety of the etching method is to improve the assortment of pesticides, aimed at improving their sanitary, hygienic and environmental characteristics, high efficiency in combination with the leveling of toxic effects on the environment.

Improving the etching efficiency and preventing the formation of pathogen resistance to pathogens in pathogens was achieved through the use of combined preparations with multifaceted fungicidal activity. In this aspect, we offered protectants obtained in two alternative ways:

- on the basis of mechanochemical modification of active substances (AI) of known fungicides (tebuconazole, imazalil, metalaxyl, prochlorase, carbendazim, thiram, etc.) using plant metabolites (arabinogalactan, glycyrrhizic acid derivatives). In this case, preparations were obtained in the form of solid dispersions, which formed supramolecular complexes with increased solubility and biological efficiency with a decrease in the dosage of AI of the initial fungicides;

- by suspending of AI preparations in grinders with controlled energy intensity in the aqueous medium of polysaccharides (in particular, kelp) without the use of traditional formative components. The resulting suspension forms can be recommended for practical use.

The approaches proposed by us made it possible to develop multicomponent protectants with a wide spectrum of biological action. So, the dressing of crops with the preparations proposed in the work allowed 60-100% to limit the manifestation of seed infection, 30-80% - primary aerogenic, soil and contained in plant residues. At the same time, an increase in the yield of spring wheat by 0.2-0.3 t / ha was observed.

Biological tests of the preparations we developed with respect to causative agents of dry rot during storage and black scab of potato during the growing season showed a decrease in the number of ill dry rot tubers by 1.6-2.0 times in comparison with the control variant, and also significantly reduced the development of the disease in sprouting period 5.8-7.3 times, and in the bud-formation - the beginning of blooming 2.7-5.5 times. The complex effect of protectants on the development of the disease, development and growth of potato plants led to an increase in crop productivity by 1.7-2.3 t / ha.

## INNOVATIVE ANTIHELMINTICS MODIFIED BY VEGETABLE METABOLITES

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According to the World Health Organization in 2010, more than 16 million people are caused by infectious and parasitic diseases, which are mainly transmitted from sick animals that transmit these diseases. The total number of diseases and deaths from intestinal helminthiasis is higher than from bacterial, viral and other parasitic diseases combined.

In this regard, the problem of combating animal helminthiasis is a national task. Currently, methods of treating animal helminthiasis are based on the use of a wide range of anthelmintic drugs, some of which often do not provide the necessary effectiveness and often their use can cause unwanted side effects that are harmful to animal health.

One of the reasons for the low effectiveness of benzimidazole anthelmintic drugs is the low solubility of their substances in water and physiologically active media. In this regard, it is necessary to overestimate the dosage of these drugs, thereby causing many undesirable consequences: overdose of the active substance and overpricing of the drug, increase in toxicity and environmental damage, etc.

We have proposed an innovative approach to increase the solubility of poorly soluble anthelmintic substances by mechanochemically modifying them using water-soluble polymers, including plant metabolites (polysaccharides, saponins, etc.). The essence of the method is that they conduct joint solid-phase mechanical treatment of the substance of a medicinal substance with a plant metabolite in grinders-activators with controlled energy intensity.

Obtained according to the proposed technology, the preparations had increased anthelmintic activity with a decrease in the consumption rate of active substances by 2-10 times. The report will present examples and solutions to the above problems.

## ISOLATION AND CHARACTERIZATION OF MUSHROOM POLYSACCHARIDES

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Polysaccharides are a complex group of structural and functional macromolecules widespread in nature, in a great variety of organisms such as plants and animals. These polymers are found in pericellular locations, on the external surface of cell membranes, and play a crucial role in recognition mechanisms, cell-cell communication, acting as a barrier between tissues and protection against pathogens. Some polysaccharides isolated from fungal species contain a large variety of polysaccharides such as pectin, chitosan, and glucose-rich polysaccharides that have a number of biological activities. In addition, these polysaccharides are natural resources to prepare bio- and nanomaterials by chemical modification. Recent studies have been revealed that polysaccharides isolated from fungal materials possess a wide range of biological activities which mainly include antiviral, immuno-enhancing, antimicrobial and antitumor activities.

In this study, polysaccharides of the *Polyporus Hispidus* (a locally growing fungus) were isolated, purified, and characterized with respect to their molecular mass parameters, monosaccharide compositions and structural constitutions. In the results, water-soluble polysaccharides were isolated by the sequential extraction methods in neutral, acidic and alkaline fractions. The polysaccharides from the neutral, acidic and alkaline fractions were isolated in the yields of 14.7, 1.6 and 13.5%, respectively. A preliminary analysis for monosaccharide composition indicated the fraction in the acidic extract was pectic polysaccharides and thus further studies were conducted with neutral and alkaline fractions. The fractions were further purified by deproteinization, ion-exchange and gel-chromatography methods. Molecular mass and structural characteristics of the purified polysaccharides were studied with size exclusion chromatography, elemental analysis, gas chromatography, IR and NMR spectroscopy methods. Molecular weights of the polysaccharides purified were determined to be 12500 and 17400 Da for the polysaccharides from the neutral and alkaline fractions, respectively. This result describes the basidiomycete generally contain low molecular weight polysaccharides. Monosaccharide composition analyses showed that the polysaccharides from the neutral and alkaline fractions mainly consisted of glucose residues, and contained minor amounts of fructose, xylose, mannose, and galactose residues. NMR spectroscopic studies of the samples indicated the polysaccharides obtained consisted of glucan structures linked by  $\alpha$ - and  $\beta$ -glycosidic bonds. In the structure of  $\beta$ -glucans, the primary chains are constituted mainly through  $\beta$ -1,3-, partially by  $\beta$ -1,4-glycosidic bonds. The branches were found to be occurred by  $\beta$ -1,6-glycosidic bond and to be constituted by one or more  $\beta$ -D-glucose residues that are linked via  $\beta$ -1,3-glycosidic bonds.

The results obtained by this study show that the polysaccharides isolated from *Polyporus Hispidus* are  $\beta$ -glucan type polysaccharides structured by  $\beta$ -1,6-branched  $\beta$ -1,3/1,4-glycosidic bonds and the basidiomycete can be used as a resource for the  $\beta$ -glucans.

FEROVINOLAL A NEW HUMULAN FROM *Ferula ovina*

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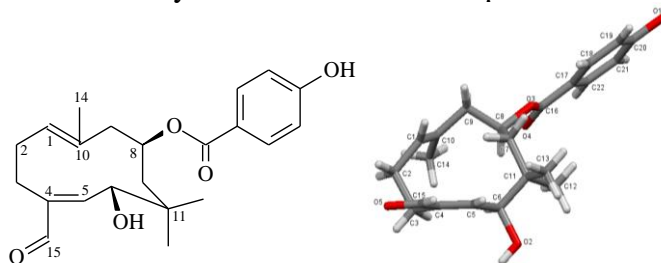
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Plants of the genus *Ferula* (family Apiaceae), widespread in the world, include more than 150 species, and are rich sources of terpenoids and coumarins. About 100 species of the genus *Ferula* grow in Central Asia. In folk medicine, plants of this genus are used as antitumor, wound healing, antimicrobial and estrogen agents.

*Ferula ovina* (Boiss), a perennial herbaceous plant of 50-120 cm tall, grows on gravelly slopes, screes, rocks, in bushes, mountain steppes up to 3000 m above sea level.

From the roots of the plant *Ferula ovina* Boiss, a new ester of the humulan ( $\alpha$ -apien) type, ferovinolal, was isolated. The structure of ferovinolal was established on the basis of the analysis of the data of IR, <sup>1</sup>H and <sup>13</sup>C NMR spectra, experiments of DEPT, HSQC, COSY, NOESY and HMBC, as well as with PCA. The spatial structure and absolute configuration of the  $\alpha$ -apien, the chiral centers of 6S and 8R configuration, were established by X-ray diffraction. It was established that the <sup>14</sup>U<sup>7</sup><sub>8</sub> conformation of the 11-membered humulan macrocycle was realized in  $\alpha$ -apien.



Thus, the new compound ferovinolal isolated from *Ferula ovina* has the structure of 8 $\beta$ - (4'-hydroxy-hydroxybenzoyl) -4-formyl-6-hydroxy-humulan-1 (10) Z, 4 (5) E-diene with a macrocycle conformation <sup>14</sup>U<sup>7</sup><sub>8</sub>.

## STEREOCHEMISTRY OF MACROCYCLIC $\alpha$ -, $\gamma$ -APIENES OF *Ferula ovina*

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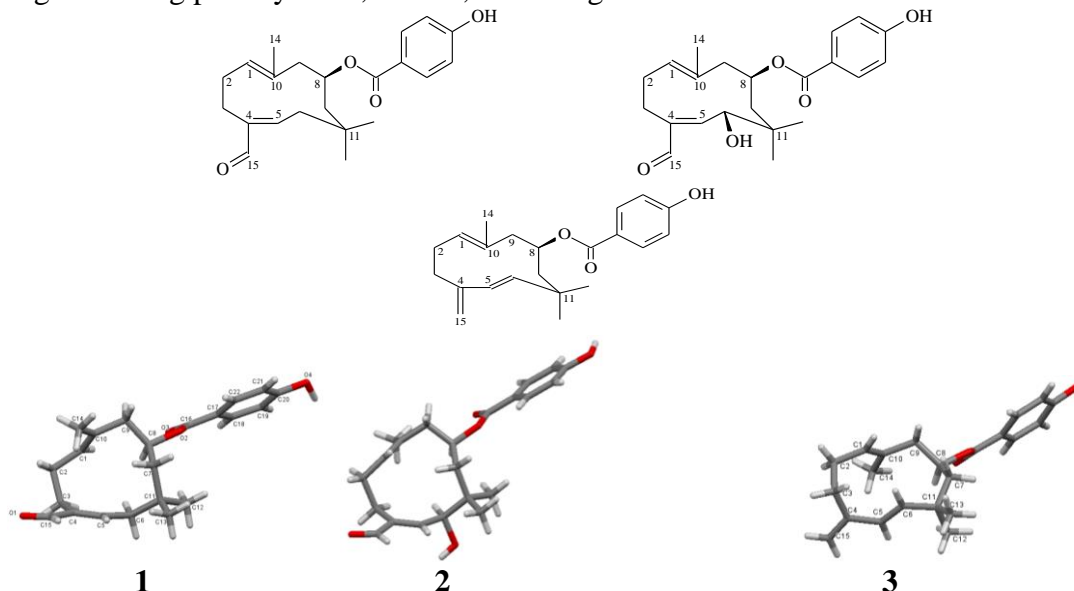
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This report is devoted to stereochemical analysis of macrocyclic esters isolated from *Ferula ovina* (fam. Apiaceae). These esters (apienes) are  $\alpha$ - and  $\gamma$ -humulanes: the newly isolated ferovinal (**1**) and ferovinolal (**2**), and the known ferocin (**3**).

Humulane - cycloundecadiene with 1(10)*E*-, 4(5)*Z*-double bonds and its natural derivatives are isolated exclusively from plants of the family Apiaceae, therefore they are called  $\alpha$ -apienes (apienes).  $\gamma$ -apienes are also isolated only from plants of Apiaceae, characterized by the presence of 1(10)*E*-double bond and mutual anti-arrangement of exocyclic 4(15)- and endocyclic 5(6)*E*-double bonds in the humulane macrocycle.

The absolute configuration of these natural  $\alpha$ -,  $\gamma$ -apiens has not been established, and the relative configurations of asymmetric centers correspond to the known apiens. The absolute configuration of the chiral centers and the prevailing conformation of the 11-membered macrocycle in the crystal were determined by X-ray diffraction. According to the Flack parameters the chiral centers of isolated molecules, according to Cahn-Ingold-Prelog priority rules, had 6*S*, 8*R* configuration.



In apienes, the actual conformation of the 11-membered macrocycle was determined by the mutual arrangement of two planar sites containing double bonds (C14 and C15 atoms), as well as by the conformation of the polymethylene section (arrangement of C7 and C8 atoms in the -C11-C7-C8-C9- single bond fragment with p-benzoate group, linking planar sites). Calculations showed that the conformation of the macrocycle in  $\alpha$ - and  $\gamma$ -apienes had four pronounced energy minima. What can be noticed by visual comparison of the molecular structures of ferovinal and ferovinolal with the conformation of <sup>14,15</sup>U<sub>8</sub> and <sup>14,15</sup>U<sub>7</sub> of the 11-membered macrocycle, respectively. Similarly, the macrocycle in ferocin accepted the <sup>14,15</sup>U<sub>7</sub> conformation. The calculated torsion angles of the model (unsubstituted)  $\alpha$ -,  $\gamma$ -apienes were in good agreement with the experimental angles obtained by XRD (average deviation  $\pm 5^\circ$ ).

**$\alpha$ -,  $\gamma$ -APIENES, FEROVINAL AND FEROCIN FROM *Ferula ovina***

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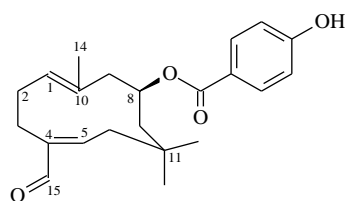
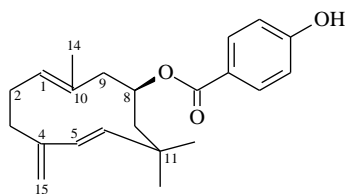
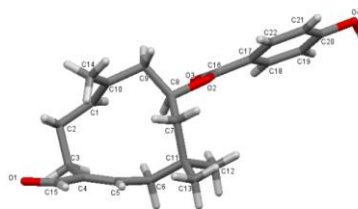
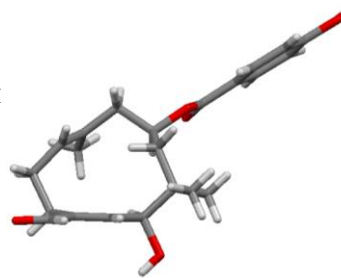
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Continuous studies on the chemical composition of *Ferula ovina* led to the isolation of a new ester, ferovalinal (**1**), with mp 140 °C, molecular weight 155 [M-H]<sup>-</sup>, as well as the well-known  $\gamma$ -apien ferocin (**2**) previously isolated from *F. cerotophylla* [1, 2], from the plant root extract using column chromatography on KSK silica gel, eluted with a mixture of extraction benzene – ethyl acetate (25: 1-8: 1). The structure of ferovalinal was established on the basis of the analysis of the data of IR, Mass, <sup>1</sup>H, and <sup>13</sup>C NMR spectra, and of the DEPT, HSQC, COSY, and HMBC experiments.

The new compound ferovalinal (**1**) isolated from *Ferula ovina* has the structure of 8 $\beta$ -(4'-hydroxy-hydroxybenzoyl) -4-formyl-humulan-1 (10) Z, 4 (5) E-diene.

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## **POLYISOPRENOIDS OF THE PLANTS FAMILY MALVACEAE, MORACEAE, VITACEAE AND THEIR BIOLOGICAL ACTIVITY**

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It is known that the flora of Uzbekistan has about 4230 kinds, 1028 genera from 138 families. About 577 kinds of the wild are medicinal plants. Interest in medicinal plants is growing very much nowadays. Among them, polyprenol-containing plants occupy a special place.

Recently, along with other classes of natural compounds, studies have been intensively conducted to study the chemistry and pharmacology of polyisoprenoids (PI) in order to obtain potential biologically active substances. Among these compounds, along with related ubiquinones, and vitamins of groups A, E and K, many substances were found combining valuable healing properties with almost complete absence of harmful side effects, such as Ropren, Sitopren, Oleoprene, Gamapren and others <sup>[1,2]</sup>.

This report will summarize studies on the isolation, distribution, identification, methods of qualitative and quantitative determination, as well as the biological activity of polyisoprenoids of some plants of the family Malvaceae, Moraceae, Vitaceae, Anacardiaceae, etc, in particular, 20 varieties and lines of cotton – *Gossypium hirsutum*, *Althea officinalis*, *A. armeniaca*, *Alcea nudiflora*, *A. rosea*, *Abutilon theophrasti*, *Hibiscus trhonum*, *Morus nigra*, *Morus alba*, *Vitis vinefera L.*, *Rhus coraria*, etc.

Materials will be presented about preparations created on the basis of the polyisoprenoids of the above plants (Uchkun, Gossipren) and their pharmacological activity.

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## TWO-PHASE ULTRASONIC EXTRACTION OF *Calendula officinalis* AND *Ajuga turkestanica*

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To obtain oil extracts from medicinal plants enriched with biologically active substances, we used two-phase alcohol-oil extraction with ultrasonic treatment (UST).

Crushed air-dry flowers of *Calendula officinalis* with a moisture content of 10.3% was placed in a container and filled with 70% ethyl alcohol, heated to 50 °C, and refined safflower oil in the container plant materials : ethanol : oil 1 : 5 : 2 (by volume). The mixture was treated with ultrasound at a frequency of 35 kHz at a temperature of 50 °C for 30 minutes. Then the container was placed in a heated to 80 °C water bath and kept under these conditions for 2.5 hours. At the end of extraction, the container was cooled, the mixture was divided into liquid and solid phases. The liquid phase containing oil and aqueous-alcohol was centrifuged, separated and analyzed.

According to chemical analysis, *C. officinalis* flower oil extract contained 9.35 mg% of chlorophyll, 12.5 mg% of carotenoids, 225 mg% of tocopherols and 1.32% of phytosterols. Water-alcohol extract contained 35.3 mg% flavonoids. Compared with two-phase extraction without UST in this case, 1.2 times more chlorophylls and carotenoids and 1.1 times more flavonoids were obtained.

96% ethyl alcohol and refined safflower oil heated to 50°C in the container of plant materials : ethyl alcohol : oil 1 : 5 : 2 (by volume) were added to the crushed air-dry above-ground part of *Ajuga turkestanica* with a moisture content of 7.3%. The mixture was treated with ultrasound, as described above, and then boiled with a reverse refrigerator in a water bath for 3 hours. Then the mixture was cooled, divided into solid and liquid phases, the liquid phase was fractionated into oil and alcohol extracts, which were analyzed. In the oil extract of the aerial parts of *A. turkestanica* contained 34.22 mg% chlorophyll, of 185.6 mg% carotenoids, 94.2 mg% tocopherols, 0.94% phytosterols and 320 mg% of flavonoids. The alcohol extract contained 14 mg% flavonoids. Compared to two-phase extraction without the UST in this case, 1.22 times more chlorophyll, 1.24 times more carotenoids and 1.2 times more flavonoids were obtained.



## CHEMICAL INVESTIGATIONAL OF *Haplophyllum ferganicum*

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Genus *Haplophyllum* Juss. belongs to one of the large families Rutaceae, containing unites about 150 genera and 1600 species. Plants of the genus *Haplophyllum* (family Rutaceae) have long been used in folk medicine as an anesthetic for toothache, chest and stomach diseases, restorative, reducing fatigue, soothing with increased nervous excitation and frequent palpitation, anti-inflammatory, as well as external to skin diseases. In the flora of the states of the former Union, the genus *Haplophyllum* is represented by 32 species, 23 of which grow in Central Asia. Of the 32 species, 16 are endemic: they do not grow anywhere outside of Central Asia. The greatest number of species was recorded in Uzbekistan - 16, which was the center of the species diversity of these plants. Of the 23 species growing in Central Asia, 11 species have been studied for their chemical constituents. Conducted pharmacological studies at the Institute of the Chemistry of Plant Substances have shown that alkaloids of the whole leaves have a calming effect on the central nervous system with low toxicity. Along with painkillers, anticonvulsants, hypnotics, sedatives, some of them showed estrogenic and antitumor activities.

Plants of this family are diverse in life forms such as trees, Chemical investigation on *Haplophyllum ferganicum* collected from Chimgan, revealed 9 compounds, haplopine, 7-izopenteniloksi- $\gamma$ -fagarin, Evodine, Evoxine (haploperine), Evoxine acetate, Glycoferine, Eudismine, skimmianine and flindersine from the exact of the aerial part, and 5 compounds, Haplamine, Methilevovine, skimmianine, flindersine, Evoxine were obtained from the exact of the aerial part of the plant collected from Sadkok.

Antioxidant, antidiabetic, antibacterial activities for *H. ferganicum* petroleum ether extract and other compounds were measured. Only the fraction exhibited good inhibition on PTP1B, weak DPPH free radical scavenging ability, and moderate antibacterial activity. H. f-4 showed mild average activity against Colon cancer cells HT-29 with IC<sub>50</sub> 19.77±1.4  $\mu$ M.

GC-MS analysis research on these two plants was firstly adopted to make a comparison among different samples, which was not reported previously. By GC-MS analysis, the major components for *H. ferganicum* were Hexadecanoic acid, methyl ester (31.61%), 9, 12, 15-Octadecatrienoic acid, methyl ester (12.93%) and Methyl stearate (9.81%).

## TECHNOLOGY OF OBTAINING A NEW WATER-SOLUBLE FORM OF ECDYSTERONE-SUBSTANCE FROM *Silene wolgensis*

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The development of a technology for the production of the substance of steroid preparations that meet international quality standards as much as possible is a key solution for ensuring the entry of domestic medicines into the international pharmaceutical market.

Considering the biological importance and economic feasibility of isolation the pharmaceutical substance ecdysterone (20E), the active principle of many adaptogenic and anabolic drugs, a method that allows obtaining a 20E substance suitable for the preparation of solid dosage forms (tablets and capsules) from *Silene wolgensis* (Hornem.) Bess. has been proposed.

In the framework of this study, the ecdysterone production technology has been optimized which includes the stage of materials preparation (preparation of the extractant and processing raw materials), 5 main stages of the technological process (TP): TP1 is production of a thick extract of *Silene wolgensis*, TP2 is processing of a thick extract of *Silene wolgensis*, TP3 is chromatographic separation on alumina, TP4 is purification of technical 20E and TP5 is obtaining a water-soluble form of 20E.

The regulated parameters and the main stages of the isolation of the ecdysterone substance and obtaining of a water-soluble form based on it are included in the laboratory technological regulation for their production from industrially significant plant materials - *Silene wolgensis* (Hornem.) Bess. ex. Spreng.

## SYNTHESIS, STRUCTURE AND BIOACTIVITY OF A NEW WATER-SOLUBLE 20-HYDROXYECDYSONE DERIVATIVE

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It is known that acyl derivatives of 20-hydroxyecdysone or ecdysterone are of interest for the development of wound healing drugs, the effectiveness of which increases significantly when incorporated into liposomes.

In this regard, a new water-soluble derivative has been synthesized by the interaction of equimolecular amounts of ecdysterone triacetate with  $\beta$ -cyclodextrin in order to obtain new bioactive compounds and determine the effect of new functional groups on the formation of supramolecular complexes.

A new supramolecular complex of 1:1 stoichiometric composition was formed with the entry of ring A of the steroid nucleus of the substrate molecule into the internal cavity of the receptor  $\beta$ -cyclodextrin.

The spatial structure of the 3,22-acetoxy-14,20,25-hydroxy-5,9(H)-cholest-7-en-6-one original synthon and the fine structure of the new water-soluble inclusion complex synthesized based on it were fully confirmed by the X-ray diffraction analysis data and NMR spectroscopy 2D correlation.

As a result of bioscreening, it has been revealed that the new derivative has anti-inflammatory activity on the model of acute exudative reaction at a dose of 25 mg/kg.

## DETERMINATION OF THE XANTHON GLYCOSIDE MANGIFERIN CONTENT IN THE RHIZOMES OF *Iris hungarica* BY HPLC METHOD

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*Iris hungarica*, belonging to genus *Iris*, is the source of different biologically active compounds, including xanthenes. Mangiferin – a xanthone C-glycoside, which was firstly isolated from the different parts of *Mangifera indica* [1]. Mangiferin has a pronounced anti-inflammatory, antibacterial, antiviral effect. As *Iris hungarica* is represented of the Ukraine natural flora, the development of preparations based on the biologically active compounds of this plant is a promising aim of the modern pharmaceutical industry.

The objects of the study were leaves and rhizomes of *Iris hungarica*, harvested in September 2017 in the National Botanical Gardens named. N. N. Grishko (Kyiv, Ukraine). The quantitative determination of mangiferin was carried out by the method of HPLC specified in the article of State Pharmacopoeia of Ukraine «Anemarrhenae asphodeloides rhizoma» [2]. Liquid chromatography separation was performed using the Shimadzu Nexera X2 LC-30AD HPLC system (Shimadzu, Japan), the CTO-20AC thermostat (Shimadzu, Japan), SPD-M20A diode array detector (DAD).

0.1 g of powdered rhizomes were dispersed in 25.0 mL of a 50 % (v/v) methanol solution and sonicated for 30 minutes, filtered through a membrane filter (nominal pore size - 0.45  $\mu\text{m}$ ). Mangiferin (Fluka) was used as a reference solution- 5.0 mg in 50 % (v/v) methanol. Chromatographed on the silica gel column (0.15 m  $\times$  4.6 mm), mobile phase acetonitrile - 0.2% (v/v) glacial acetic acid solution (15:85). The speed of the mobile phase was 1.0 ml/min, the injection was 10  $\mu\text{L}$ . Detection was performed spectrophotometrically at a wavelength of 258 nm. According to the results, the content of mangiferin in the *Iris hungarica* rhizome was 0.22 $\pm$ 0.1%.

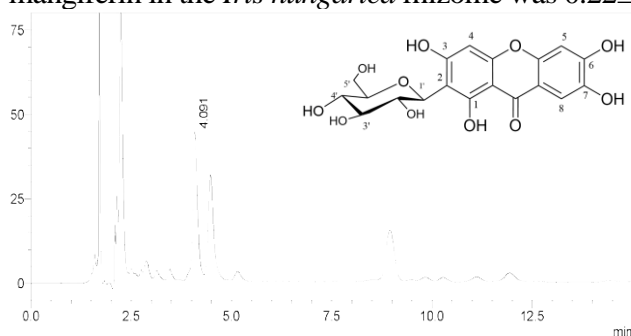


Fig. 1. HPLC chromatograms of *I. hungarica* recorded at 258 nm

**Conclusion:** the chosen method showed high resolution, recommend for qualitative and quantitative analysis of mangiferin in *Iris hungarica* rhizome, corresponding to the literature data [3]. The above method is recommended for the standardization of *Iris* raw material for pharmacopoeial analysis.

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## EFFECT OF SALINITY STRESS ON SUGAR CONTENT OF COTTON PLANT

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Soil salinity is a major factor limiting agricultural productivity of nearly 20% of the cultivated area and half of the irrigated area worldwide <sup>[1]</sup>. Cotton (*Gossypium hirsutum* L.) is a salt-tolerant crop that can improve productivity on saline soil and lead to economic development in regions of high salinity. Plants normally cope with salinity stress in various ways. Among these responses, accumulation of compatible solutes including proline, soluble sugars, sugar alcohols and glycine betaine has received most attention in terms of their functions in osmotic adjustment <sup>[2]</sup>. Osmotic adjustment refers to the net accumulation of solutes in cells in response to a fall in the water potential of their environment. As a consequence, the cell osmotic potential lowers, and turgor pressure tends to be maintained. Their role in terms of osmotic adjustment is, however, still under debate. In many species, the absolute osmolyte concentrations are unlikely to mediate osmotic adjustment <sup>[3]</sup>. Sugars, owing to their regulatory function, affect all phases of the life cycle of plants and, interacting within phytohormones, control the processes of growth and development of plants.

The material of the study is 7-day old seedlings of tolerant cotton varieties “Ravnak”. The samples were subjected to salt stress by exposing them in a solution of 1% and 5% sodium chloride, followed by determination in the seedlings of the content of reducing sugars.

“Ravnak” varieties are an example of modern selection based on the precise selection of genome sites that do not contain gene engineering and are suitable for useful agronomic traits.

According to the results, as the salinity increased, the sugar levels also increased relative to control. Sugar content in shoots had a significant increase under salinity stress. Increased accumulation of sugars has been reported in many plant species exposed to salinity <sup>[4]</sup>. According to Stoop and Pharr <sup>[5]</sup>, the increase in glucose pool induced by salinity in celery petioles appeared to be due to decreased demand of carbon. It is believed that under salinity stress accumulation of sugars along with other compatible solutes contribute to an osmotic adjustment, which allows the plants to maximize sufficient storage reserves to support basal metabolism under stressed environment

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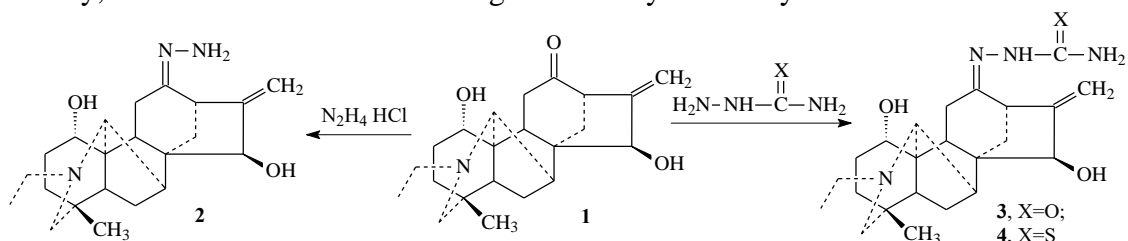
## SYNTHESIS OF NEW DERIVATIVES OF DITERPENE ALKALOID ZONGORIN

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Aconitine-type diterpene alkaloids are very valuable natural compounds with high biological activity and availability of raw materials, for example, in the territories of Altai and Siberia. The investigations of the “structure-activity” relationship in the series of C<sub>20</sub>-diterpenoid alkaloids and their analogues showed that many alkaloids with napelline type carbon skeletons were characterized by pronounced antiarrhythmic activity and were actively used in medical practice.

Zongorin (**1**), a diterpene alkaloid of the napelline series and the main alkaloid of the genus *Aconitum* plant, differed significantly in pharmacological action from aconitine alkaloids and exhibited properties characteristic of both psychostimulants and antidepressants. Therefore, it seemed to us a promising synthesis and study of the biological activity of derivatives based on zongorin. In order to synthesize new derivatives of zongorin (**1**), and to obtain new compounds with potential biological activity, we conducted reaction of zongorin with hydrazine hydrochloride:



Similar reactions were performed with semicarbazide and thiosemicarbazide. The structures of the synthesized hydrazone (**2**) and (thio)carbazones (**3**, **4**) were confirmed by spectroscopic analysis of IR, <sup>1</sup>H and <sup>13</sup>C NMR.

## STUDY OF THE GROWTH REGULATING PROPERTIES OF *Datura stramonium* EXTRACT

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An environmentally friendly method of improving the quality of crop production is the use of growth regulators. At the same time, priority should be given to environmentally friendly preparations based on herbal substances. In the manufacture of medicines based on herbal compounds, one of the problems is the disposal of unused residual raw materials. It is urgent to develop plant growth regulators from waste products from the production of pharmaceuticals using energy-saving and environmentally friendly technologies.

The plant *Datura stramonium* L (fam. Solanaceae) is widely used in folk medicine for the treatment of mental and nervous diseases, with rheumatism, shortness of breath, etc.<sup>[1, 2]</sup>. The plant is a good source of vitasteroids, compounds with anti-inflammatory activity. The aim of this work is to study the growth-promoting activity of the plant extract *Datura stramonium* obtained after extraction of vitasteroids on the growth and development of cotton.

Sulton cotton seeds were treated with an aqueous extract of *D. stramonium* by seed lock method at 0.0001% concentration for 18 hours. Uchkun at a concentration of 0.0001% was used as a reference. Sowing was carried out on the vegetation site of the Institute of Plant Chemistry.

It was revealed that during seed treatment with *D. stramonium* aqueous extract, the germination energy was 71.3%, while in the control it was 67.2%. Germination rate was 92.7%, against 84.3% of the control and 93.1% of the reference. On the 21st day, according to the height of the stem, the experimental variant was at the level of the reference one and amounted to 11.6 cm. By the number of true leaves, it was also at the level of the experimental variant - 3.7 pcs / plant. In the control version, this indicator was 3.3 pcs / plant.

Thus, it was found that the aqueous extract of *Datura Stramonium*, obtained after the extraction of vitasteroids, had a growth-stimulating effect in 0.0001% concentration, increased the germination of cotton seeds and activated the growth and development of plants.

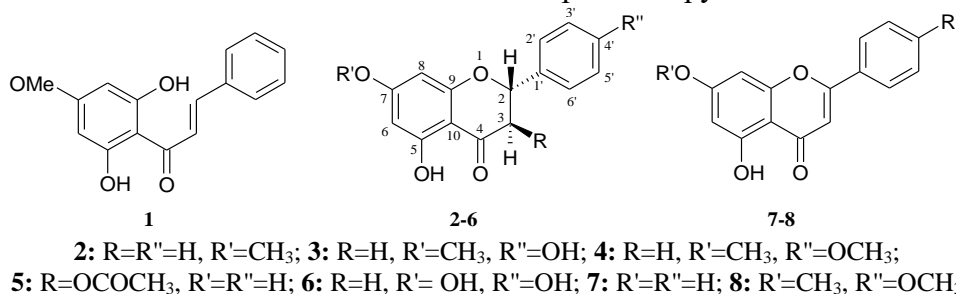
## ISOLATION AND BIOLOGICAL ACTIVITY OF PROPOLIS FLAVONOIDS FROM WILD HIVE BEES *Apis mellifera mellifera* OF BASHKORTOSTAN

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The search and identification of chemicals that determine the biological properties of propolis is highly relevant. It is known that the chemical composition of propolis largely determines the range of its pharmacological properties, and flavonoids are the main components of propolis. In this regard, we have studied the flavonoid composition and biological activity of individual compounds from propolis of *Apis mellifera mellifera* in Bashkortostan. Using column chromatography and HPLC, we isolated eight individual flavonoids, and their structures were identified by the mass spectra MALDI-TOF, 1D- and 2D-homo and heteronuclear H<sup>1</sup> and C<sup>13</sup> NMR spectroscopy.



The study of cytotoxic properties of isolated compounds **1** (pinostrobin chalcone), **2** (pinostrobins), **5** (pinobanksin-3-acetate) and **7** (chrysin) in relation to a panel of conditionally normal and cancer human cell lines (HEK293, SH-SY5Y, A-549, MCF-7 and Jurkat) were performed *in vitro* using PrestoBlue® vital dye. According to the results, the incubation for 48 hrs with compounds **1**, **2**, **5** in concentration range 1-100 μM did not suppress the viability of all cell lines (IC<sub>50</sub> > 100 μM). Compound **7** had the ability to reduce the survival of cells HEK293 (IC<sub>50</sub> = 52.20 ± 8.44 μM), SH-SY5Y (IC<sub>50</sub> = 21.30 ± 2.27 μM), A-549 (IC<sub>50</sub> = 64.14 ± 1.79 μM), MCF-7 (IC<sub>50</sub> = 73.89 ± 9.25 μM), Jurkat (IC<sub>50</sub> > 100 μM). Next, we analyzed the effect of compounds **1**, **2** and **5** on the adhesion of Jurkat cells to fibronectin *in vitro*. According to the obtained data, compounds **5** positively and **1** negatively affected on the adhesion properties of Jurkat cells in dose-dependent manner. Thus, for the first time, we isolated individual flavonoids from propolis of Bashkir wild hive bees *Apis mellifera mellifera*, characterized their cytotoxic properties in relation to tested cancer cell lines, and demonstrated their ability to influence the adhesion of immune cells. This work was done with the financial support of the Russian Foundation for basic research (project No. 17-43-020483 p\_a) and the Presidential Grant of the Republic of Bashkortostan and the Academy of Sciences of the Republic of Bashkortostan (D 17 GR, 12.03.2019).



## GAS CHROMATOGRAPHY-MASS-SPECTRAL STUDIES OF *Scutellaria adenostegia* Briq

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The genus *Scutellaria* L. includes about 350 species commonly known as “skullcaps”. It is represented by 32 species in the flora of Uzbekistan. Many of them are used in folk medicine for the treatment of epilepsy, allergies, neurosis, hypertension and other diseases. It has a rich and diverse phytochemical profile mainly represented by flavonoids, phenylethanoid glycosides, diterpenes, and iridoids.

We have initiated a study of some promising skullcap species. Data on the study of natural components of hexane and benzene extracts of the aerial parts and roots of *Scutellaria adenostegia* Briq were given. Air-dry chopped raw material was extracted sequentially with hexane and benzene in a Soxhlet apparatus. The extracts were purified on a silica gel column. The main components of the mixture were determined by the method of gas chromatography-mass spectrometry apparatus «Clarus 500MS» (Perkin Elmer). The components of the extracts were identified by comparing the mass fragmentograms of chromatographic peaks with the data of the electronic library of mass spectra "NIST" and experimental indices of chromatographic peak retention (relative to the homological series of n-alkanes) with reference data.

The method of chromatography-mass spectrometry in the composition of hexane and benzene extracts of the aerial part revealed aliphatic normal hydrocarbons C<sub>21</sub>-C<sub>33</sub>, aliphatic carboxylic (n-pentadecanoic, n-hexadecanoic, n-octadecanoic, n-docosanoic) acids, ethyl esters of n-octadecanoic, n-nonadecanoic, n-eicosanoic, n-docosanoic, n-tetracosanoic, *cis*-9-octadecenoic, *cis*-9-eicosenoic acids, 3-methoxyphenol, phytol,  $\beta$ -amyryn, 1-(6-methoxy-2-naphthalenyl) ethanone, as well as saturated and unsaturated aliphatic alcohols. The hydrocarbon content in the hexane extract was 75.96%, and the aliphatic carboxylic acids in the benzene extract were 33.79%.

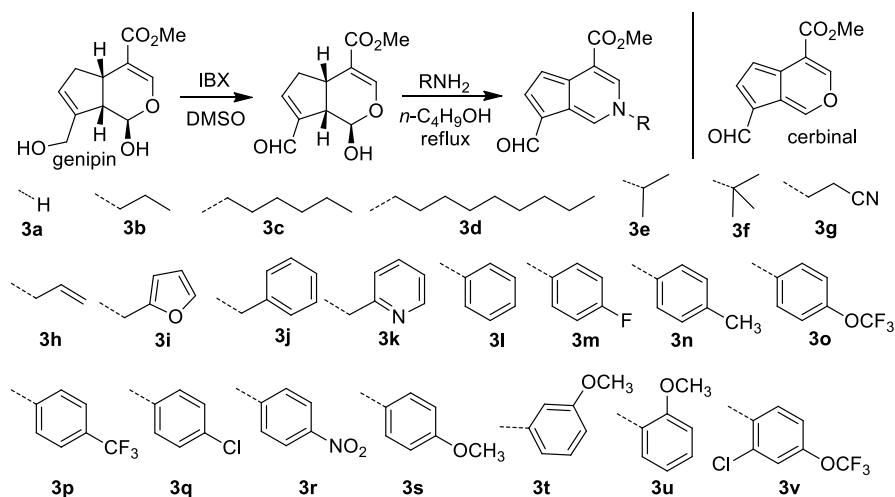
Aliphatic hydrocarbons (44.38%) and carboxylic acids (42.31%) predominated in the hexane root extract, while ethyl esters of aliphatic carboxylic acids (45.45%) prevailed in the benzene root extract. In addition to hydrocarbons, root extracts included dibutyl phthalate, 4-hydroxy-3-methoxyphenylmethyl ketone, n-hexadecanoic, n-eicosanoic, n-docosanoic, n-tetracosanoic and 9,12-octadecadienoic acids, ethyl esters of n-hexadecanoic, n-octadecanoic, *cis*-9-octadecenoic, n-tetracosanoic, *cis*-9-eicosenoic, 5,8-eicosadienoic, 5,8,11-eicosatrienoic acids. A high content of n-hexadecanoic (18.99%), n-docosanoic (32.74%) and 9,12-octadecenoic acids (21.31%) was noted. Many of the identified compounds were found in the composition of non-polar components of medicinal plants.

## SYNTHESIS AND DISCOVERY OF NATURAL PRODUCT CERBINAL AND ITS ANALOGUES CYCLOPENTA[C]PYRIDINES AS NOVEL PEST CONTROL AGENTS

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Owing to the changing needs of agriculture, the exploration of new pest control agents remains as critical as ever. The analogues **3a–3v** of natural product cerbinal were synthesized from genipin by an efficient and practical method under additive-free condition. The antiviral and insecticidal effects of cerbinal and these cyclopenta[c]pyridines (**3a–3v**) were evaluated systematically. Most of the synthesized compounds exhibited higher anti-TMV activities than the lead compound cerbinal. Compound **3s** (2-(4-methoxyphenyl)) had the most promising inhibitory activities against TMV (inactivation effect  $49.0 \pm 0.8$  %, curative effect  $41.2 \pm 4.3$  %, protection effect  $51.5 \pm 2.7$  % at  $500 \mu\text{g/mL}$ ). Among the synthesized compounds, only **3v** (2-(2-chloro-4-(trifluoromethoxy)phenyl)) reached the activity level of cerbinal against *Plutella xylostella*. Those suggested that the cyclopenta[c]pyridines obtained by modifications of cerbinal at position 2 were very significant for anti-TMV activity, and yet were exceptionally less active for the insecticidal activities.



## ANTIMICROBIAL AND ANTIOXIDATIVE EFFECT OF ESSENTIAL OIL FROM *Schizonepeta annua*

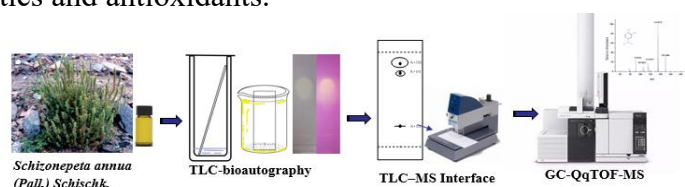
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Traditional medicine is a means of health care for more than 65% of world population [1], among which, special place belongs to essential oils, known as strong antimicrobial and antioxidative effects. *Schizonepeta annua* (Pall.) Schischk, an endemic annual plant from the Lamiaceae family, has been employed to cure tracheitis in traditional herbal medicine [2]. The aim of this study was to evaluate the antibacterial and antioxidant profile of *S. annua* essential oil obtained by hydrodistillation. First, disk diffusion method and microdilution broth method were adopted to determine against three human pathogens bacterial strains: Fungi *Candida albicans* (ATCC 10231), Gram positive *Staphylococcus aureus* (ATCC 6538), Gram negative *Escherichia coli* (ATCC 25922). The DPPH and ABTS tests were used to assess the antioxidant effect of *S. annua* essential oil, resulting in a strong antimicrobial and antioxidative effect. Next the high-performance thin-layer chromatography combined with direct bioautography were applied for investigation of bioactive pure compounds of *S. annua* essential oil, and GC-Q-TOF-MS system was used to the subsequent identification of pure compounds. It resulted in the characterization of three active compounds and two of them were tentatively identified as thymol and carvacrol. The *S. annua* essential oils with high antibacterial and antioxidative properties are considered as good alternatives to synthetic antiseptics and antioxidants.



**Keywords:** High performance thin-layer chromatography, direct bioautography, *Schizonepeta annua* (Pall.) Schischk, essential oil, GC-Q-TOF-MS

### ACKNOWLEDGEMENTS

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## CHEMICAL COMPOSITION AND SPECTRUM-EFFECT RELATIONSHIP OF *Rosa rugosa* Thunb FORMULA

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*Rosa rugosa* Thunb formula (RPC) consists of three traditional ethnic medicines: *Rosa rugosa* Thunb, *Punica granatum* flower and *Cichorium glandulosum* Boiss. Et Huet. These three medicines are recorded in the prescription of "Standards for Preparations of Uygur Medical Institutions in Xinjiang Uygur Autonomous Region", and can be used to treat diabetes, diarrhea, fatty liver diseases. Prepared according to the prescription, the chemical composition and spectrum-effect relationship of the RPC extract were studied, which provided a theoretical basis for the quality control of the hypoglycemic active fraction of RPC.

Rapid analysis and identification of the main components in the RPC were based on HPLC-QTOF-MS method. As summarized in Table 1, 45 phenolic compounds including 19 gallic acid derivatives and 26 flavonoids were identified through retention time, molecular ions, characteristic fragment ions and molecular formula. The results of spectrum-effect relationship (Fig.1, Tab.2 and Tab.3) showed that the  $\alpha$ -glucosidase inhibitory activity of ten different ratios of RPC was related to the 22 common peaks obtained in the fingerprint, and the correlation of 7 peaks was more than 0.8. These results indicated that the 22 peaks had a good synergistic hypoglycemic effect.

Table 1. Identification of RPC by HPLC-QTOF-MS

No	t <sub>R</sub> (min)	Identification
1	6.11	Galloyl-HHDP-glucoside
2	6.11	Digalloyl-gallic acid
3	7.64	Taxifolin diglucoside
4	7.71	Digalloyl-gallic acid
5	9.72	Eriodictyol diglucoside
6	10.34	Methyltaxifolin-diglucoside
7	13.62	Galloyl-hexahydroxydiphenol-glucoside-digalloyl-glucoside
8	14.03	Digalloyl-hexahydroxydiphenol-glucoside
9	15.01	Tri-O-galloyl-gallic acid
10	15.31	Granatin A
11	16.60	Galloyl-hexahydroxydiphenol-glucoside-dehydrodigalloyl
12	16.61	Dihydrogossypetin-O-glucoside-C-glucoside
13	18.44	Galloyl-hexahydroxydiphenol-glucoside-dehydrodigalloyl
14	18.44	Digalloyl-hexahydroxydiphenol-glucoside
15	20.93	Ellagic acid-galloyl-gallic acid
16	21.77	Taxifolin-diglucoside
17	23.29	Digalloyl-hexahydroxydiphenol-glucoside
18	23.58	Tri-O-galloyl-gallic acid
19	26.00	Galloyl-hexahydroxydiphenol-glucoside-methyl-dehydro
20	26.15	Bis-HHDP-glucoside
21	26.47	Granatin B
22	29.03	Digalloyl-hexahydroxydiphenol-glucoside-digalloyl
23	30.12	Quercetin-galloyl-gallic acid
24	31.36	Dihexahydroxydiphenol-glucoside-galloyl
25	31.36	Quercetin-galloyl-gallic acid
26	32.39	Quercetin-glucoside-rhamnoside
27	33.29	Ellagic acid
28	34.40	Quercetin-glucoside
29	35.51	Quercetin-glucoside
30	38.50	Quercetin-galloyl-gallic acid
31	38.84	Quercetin-xyloside
32	39.91	Kaempferol-glucoside-rhamnoside
33	41.65	Quercetin-glucoside-rhamnoside
34	42.33	Quercetin-xyloside
35	43.40	Kaempferol-glucoside
36	44.04	Quercetin-rhamnoside
37	47.42	Kaempferol-glucoside
38	48.39	Kaempferol-xyloside
39	49.73	Kaempferol-glucoside-rhamnoside
40	50.40	Quercetin-glucoside
41	50.40	Kaempferol-xyloside
42	51.45	Kaempferol-rhamnoside
43	52.18	Quercetin-acetyl-gallic acid-rhamnoside
44	53.87	Quercetin-glucoside-hydroxycinnamic acid
45	54.58	Kaempferol-glucoside-acetyl-rhamnoside

Table 2.  $\alpha$ -glucosidase inhibition rate of 10 different ratio of RPC.

No.	S1	S2	S3	S4	S5	S6	S7	S8	S9	S10
IC <sub>50</sub>	4.82±	2.99±	2.44±	2.21±	1.79±	1.56±	1.60±	1.68±	1.46±	1.28±
( $\mu$ g/mL)	0.32	0.15	0.21	0.10	0.18	0.16	0.16	0.17	0.15	0.16

Table 3. Spectrum-effect relationship of RPC.

No.	Gray relation	No.	Gray relation
Peak 1	0.7847	Peak 12	0.7871
Peak 2	0.8283	Peak 13	0.8448
Peak 3	0.7725	Peak 14	0.7925
Peak 4	0.7933	Peak 15	0.7857
Peak 5	0.7839	Peak 16	0.8585
Peak 6	0.6311	Peak 17	0.784
Peak 7	0.8962	Peak 18	0.788
Peak 8	0.7661	Peak 19	0.8688
Peak 9	0.8254	Peak 20	0.785
Peak 10	0.7861	Peak 21	0.8026
Peak 11	0.7926	Peak 22	0.7936

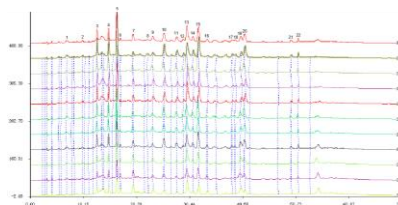


Figure 1. The HPLC fingerprint of ten different ratio of RPC (254 nm)

### ACKNOWLEDGEMENTS

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## SPECTRUM-EFFECT RELATIONSHIP AND CHEMICAL COMPOSITION OF *Nigella glandulifera* FREYN

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The Ranunculaceae annual herbaceous plant *Nigella glandulifera* Freyn was found widely in the southwest and western part of China. The seeds of *N. glandulifera* have been used as food for asthma, bronchitis, rheumatism and related inflammatory diseases as well as medicine for the treatment of digestive tract, respiratory system, kidney and liver function, cardio vascular system and immune system support. Until now, except for several literatures concerning the chemical component and biological research, *N. glandulifera* has rarely been investigated concerning the diabetic complications. In order to explore the industrial and medicinal values of *N. glandulifera*, phytochemical and biological research on *N. glandulifera* were carried out.

In the study, twelve samples under different methods were selected for HPLC fingerprint analysis. 64 common peaks were matched from 12 spectra. The results of peak area and spectra similarity of common peaks (Figure 1) showed that the similarity R were all greater than 0.7, which met the requirement and laid theoretical foundation for further study. The connection between HPLC fingerprint and its pharmacodynamics results needs to be converted into data and then implemented through data processing. The gray correlation degree between the aldose reductase activities of the 12 extracts and the 28 common peaks (Table 1) showed that 19 peaks met the standard, with 7 peaks greater than 0.75, indicating that the chemical components might have synergistic effects and could improve the diabetic complications.

The chemical components of *N. glandulifera* extract were analyzed by high resolution hybrid quadruple-orbitrap mass spectrometry (UHPLC-Q-Orbitrap-HRMS). Thirty compounds, including one alkaloid, four flavonoid glucosides, seventeen triterpenoid saponins, and eight phenolic compounds were identified by the retention time, accurate mass measurements, formula, errors, fragment ions and proposed identification of those identities were summarized in Table 2 and Figure 2. These methods provide theoretical basis for the search for effective active parts, and have far-reaching significance in the quality control of herbal extracts.

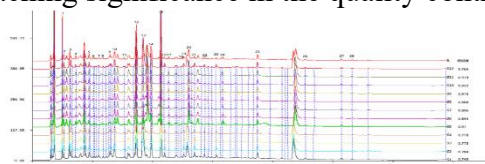


Figure 1 The HPLC fingerprint and similarity R of twelve samples (254nm)

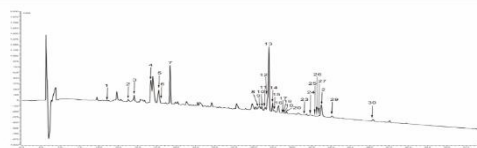


Figure 2 Identifications from *N. glandulifera* with HPLC (210nm)

### ACKNOWLEDGEMENTS

This work was supported by the Grants No. 2018 - XBQNXZ - B - 007 and 2018 - YDYLT - 001 from the West Light Foundation of the Chinese Academy of Sciences, and Tianshan Talent Program 2018.

**DEVELOPMENT OF AN OINTMENT CONTAINING  
VITASTEROIDS FROM *Datura stramonium* AND ITS INFLUENCE  
ON THE COURSE OF EXPERIMENTAL INFLAMMATION IN  
RATS CAUSED BY KAOLIN**

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Withanolides are polyoxysteroids (C-28), based on cyclopentane perhydrophenanthrene, which have a six-membered lactone ring at position of 20. Accordingly, C-22 and C-26 are oxidized to the form of  $\delta$ -lactone. The keto-group in ring A (C-1) is characteristic of all the isolated vitanolides. In some compounds, 4 $\beta$ -hydroxy-5 $\beta$ , 6 $\beta$ -epoxy groups were found.

Withasteroids have a wide range of pharmacological activities - antimicrobial, antitumor, immunomodulating, antifibrotic, insecticidal and others.

In continuation of these studies, an ointment based on the extract of *Datura stramonium* with a content of 5% of the sum of vitasteroids was developed, the study of the effectiveness of which in this aspect was devoted to this study.

Separation by column chromatography (SiO<sub>2</sub>) from ethyl acetate fractions gave the individual substances crystallized as daturalactone, vitastramonolide, (22*R*) -27-hydroxy-7 $\alpha$ -methoxy-1-oxovita-3,5, 24-trienolide, (22*R*) -7 $\alpha$ , 27-dihydroxy-1-oxovit-2,5,24-trienolide.

Pharmacological experiments showed that a 5% ointment based on the sum of vitasteroids from *Datura stramonium* showed a rather pronounced anti-inflammatory effect in rats on the model of kaolin arthritis used. Thus after 4 hours, inflammatory edema of the paws of experimental animals was 33.7%, and control 56.5%. After 1, 2, 3 days, the inflammatory edema of the paws of rats in the experiment with respect to the initial one were 36.8, 15.8, 4.2%, and after 5 days did not differ from the original. In the control, during these periods, the increase in the volume of the paws of rats were 72.8, 52.2, 30.4 and 18.5%. In addition to reducing the severity of inflammatory edema, the ointment used also shortened the duration of the course of inflammation.

Thus, the cutaneous use of an ointment created on the basis of *Datura stramonium* withasteroids in the area of the experimental focus of inflammation had a pronounced antiflogistic effect, accompanied by a decrease in edema and a shortened duration of the course of the inflammatory reaction.

**MORPHOLOGICAL FEATURES OF DISSOCIANTS OF  
*Rhodococcus ruber*-8/4/1 - PRODUCER OF NITRILE HYDRATASE**

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A characteristic feature of actinobacteria of the genus *Rhodococcus* is their ability to utilize a wide range of hydrophobic organic compounds (aliphatic and aromatic hydrocarbons, sterols, etc.). This property, along with the unique biological characteristics of rhodococci, the ability to synthesize glycolipid surfactants, the presence of a lipophilic cell wall and resistance to adverse environmental factors leads to an increasing interest in this group of microorganisms as a promising object of biotechnology. At the same time, cultures of *Rhodococcus* may be subject to dissociation, consisting in the existence in populations of genetically identical microorganisms of subpopulations that differ phenotypically. This dissociation of bacterial cultures is based on intragenomic rearrangements involving extrachromosomal or mobile genetic elements.

During conduction of this study the *Rhodococcus ruber* - 8/4/1 strain, which was isolated from soils contaminated with acrylonitrile, was dissociated into 3 forms that differed from each other: *S-forms* form round, smooth, shiny colonies, *R-forms* form folded matte colonies, while *M-forms* had mucous colonies. It was shown that the composition of the medium, cultivation conditions and the pH of the nutrient medium can effect the dissociation of the strain. The morphological and cultural properties of the *S-*, *R-*, and *M-* forms of the obtained dissociants have been studied. In result of the development of this strain on various nutrient media, it was shown that the most pronounced differences in bacterial dissociants were found on nutrient agar + wort. It should be noted that all morphological forms possessed for biotransformation of acrylonitrile to one degree or another. However, the *S-forms* of *Rhodococcus ruber* - 8/4/1 had the greatest nitrile hydratase activity in the biotransformation of acrylonitrile into acrylamide.

## VOLATILE COMPONENTS OF *Nepeta badachschanica* Kudrjasch GROWING IN UZBEKISTAN

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Kotovnik - *Nepeta badachschanica* Kudrjasch is distributed in the flora of Central Asia and Afghanistan. It grows in adyrs, in areas near mountains with gravels, as well as shallow, gypsum-like foothills. Kotovnik is a perennial herb with beautiful flowers, wonderful aroma and many useful properties.

Catnip grass is traditionally used in traditional medicine in the treatment of chronic bronchitis, catarrh of the stomach, liver diseases, female diseases, atony, anemia, shortness of breath and spasms. It is used as an antipyretic, tonic, diaphoretic and stimulant.

To obtain the volatile composition of *Nepeta badachschanica* Kudrjasch, a hydrodistillation method was used. 50 g of the aboveground part was placed in a flask with a capacity of 500 mL and distilled water was poured to the mark of the flask. The distillate was distilled off for 4 hours using a Clevenger apparatus. The oil was separated from water using dichloromethane, dried over anhydrous Na<sub>2</sub>SO<sub>4</sub>. Prior to use, the resulting oil was stored in a refrigerator at -4 °C. The resulting volatile oil of *N. badachschanica* Kudrjasch was a pale yellow mobile liquid with a specific odor.

The analysis showed that the main components were the following compounds: 2-Methyl Cyclopentanone (3.75), 1,8-Cineole (2.81), (*R*) - (+) - 3-Methylcyclopentanone (1.03), Acetylcyclohexanone (8.27), 1- (1-Cyclohexen-1-yl) -Ethanone (12.68), 4-Terpineol acetate (1.22), Phellandral (1.14), Eugenol (3.66).

For the first time, 59 volatile components were isolated from the aerial part of the plant *N. badachschanica* Kudrjasch, of which 50 substances were identified.



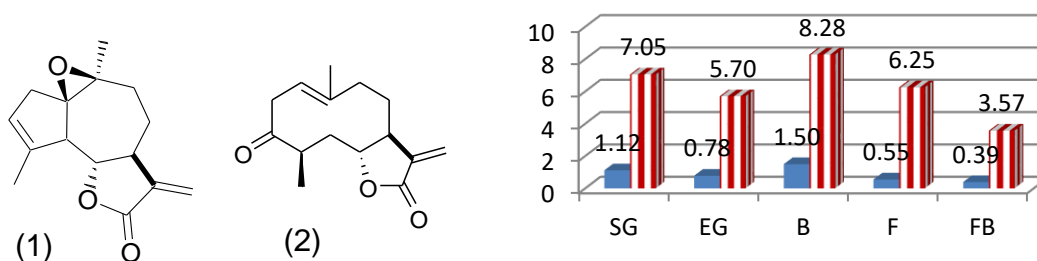
## DYNAMICS OF THE ACCUMULATION OF SESQUITERPENE LACTONS ARGLABIN AND ARGOLIDE IN *Artemisia glabella*

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The determination of the periods of quantitative accumulation of biologically active compounds in a plant is an important step in the study of the biosynthesis of secondary metabolites of methods molecular genetics, for example, in the search, isolation, and sequencing of genes encoding the enzymes of the biosynthetic pathway of one or another compound.

The report discusses the results of studying the dynamics of accumulation of sesquiterpene lactones arglabin (**1**) and argolide (**2**) in individual bodies of the aerial part of *Artemisia glabella* Kar. et Kir. (Asteraceae) according to the main phases of the plant vegetative season: start of growing (SG), end of growing (EG), budding (B), flowering (F), fruit-bearing (FB). The diagram shows the obtained data on the content of arglabin in % on air-dry materials and the yield of CO<sub>2</sub>-extract in % on air-dry materials respectively.



Raw materials for analysis were collected in accordance with plants phenospectrum, separated into separate organs - stems, leaves, and buds/inflorescences/fruit (depending on the vegetation phase), dried by the air-shadow method. Secondary metabolites were extracted from raw materials on the supercritical fluid extraction unit SFEU-5/2. The process was carried out with the following parameters: pressure 16 MPa, temperature 60 °C, duration 180 min, loading 100 g of raw materials. Quantitative analysis of CO<sub>2</sub> extracts components was carried out by the reverse phase HPLC method with a UV-detector (Hewlett Packard Agilent 1100 Series, isocratic mode, sorbing agent - Zorbax SB-C18, mobile phase - mixture of acetonitrile: water (1:1) 0.5 mL/min, detection at 204 nm, analysis time - 40 minutes).

In the course of studies, it was found that the organ with a quantitative content of arglabin was *Artemisia glabella* Kar. et Kir. buds, the optimal period for collecting raw materials and/or searching for promising genes encoding arglabin biosynthesis enzymes was the budding phase.

## BLOOD-REPAIRING PRODUCTS BASED ON CELLULOSE AND LAGOCHILIN DERIVATIVES

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Bleeding is one of the life-threatening complications in various diseases and conditions of the body, especially in surgery, obstetric pathology, infectious diseases, otorhinolaryngology and others.

Medicines isolated from plants are in many ways superior to those obtained by organic synthesis, firstly, they are non-toxic, with a high physiological and selective effect, and the cost is several times cheaper than synthetic ones.

Plants of the genus *Lagohilus*, which contains a diterpenoid lagohilin grow in Central Asia, and various diterpenoids with hemostatic properties have been isolated from it. On the basis of many years of work, the authors obtained and introduced into medical practice the hemostatic preparation "Lagoden" based on the diterpenoid lagohirzidine and the anti-allergic drug "Inebrin" based on aqueous extracts of the plant *lagochilus*.

Studies found that the use of medicinal substances with polymers led to many positive properties of the active substance, for example, good solubility in water, reduced toxicity, prolongation of the drug, etc.

In studies, we used water-soluble cellulose acetate, obtained by acid hydrolysis of cellulose diacetate, as the polymer base. The introduction of reactive groups into the cellulose molecule (for example, aldehyde groups are formed by the oxidation of cellulose with iodic acid) led to the modification of cellulose derivatives with the drug. As already mentioned above, prolonging the action of a medicinal substance makes it possible to use it better, lengthens or eliminates completely concentration fluctuations of the active substance in the blood and tissues that occur with periodic doses of medicinal substances. To this end, we have solved the following tasks:

- Isolation from the plant of the genus *Lagohilus lagohilina* afforded lagohirzidine and synthesis of Lagoden based on it;
- Synthesis of water-soluble cellulose acetate and its oxidation with iodic acid;
- Modification (addition) to the oxidized water-soluble cellulose acetate lagohilina, lagohirzidine and Lagoden by chemical and physical methods;
- Establishment of the chemical structures of the resulting products;
- Study of the hemostatic properties of the obtained substances, depending on the modification methods.

In particular, we obtained absorbable fibers and cast films based on water-soluble cellulose acetate and Lagoden. The use of water-soluble films with 5% Lagoden on the model showed the ability of the proposed drugs to stop parenchymal bleeding, which confirmed their hemostatic properties.

**ESSENTIAL OIL AND VOLATILE COMPONENTS OF  
*Dracocephalum diversifolium***

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The genus *Dracocephalum* L. belongs to the family Lamiaceae. In the flora of Central Asia, 26 species are found, in the world flora - more than 70 species, in the flora of Uzbekistan - 16 species. In folk medicine it is used as a sedative, hypotensive, wound healing, antiseptic, antibacterial, antifungal, with diarrhea, vomiting, hemostatic, antipyretic, with gastric colic, spasmolytic, with rheumatism, nephritis, stomatitis. All species of this genus are considered essential oil plants.

A number of biologically active compounds, such as triterpenoids, steroids, diterpenoids, sesquiterpenes, monoterpenes, flavonoids, alkaloids, lignans, phenols, coumarins and cyanogenic glycosides, have been isolated and identified from plants of the genus *Dracocephalum* L.

We studied the essential oil and gasoline extract of the aerial part of *Dracocephalum diversifolium* collected in July 2018 in the Zamin People's Park (Uzbekistan), located on the northern slope of the Turkestan mountain range, on the southeastern slopes of the middle and high mountain zones in the washed-out red-sand slopes, around junipers and highland shrubs. The sample is a finely chopped aerial part of the plant collected in the flowering phase. Herbarium specimens were stored in the collections of the National Herbarium of the Botanical Institute of the Academy of Sciences of the Republic of Uzbekistan TASH, under number 7250.

The yield of volatile substances from the air-dry aerial part of *D. diversifolium* obtained by hydrodistillation was 0.18%, by weight of dry matter.

The resulting *D. diversifolium* essential oil was a yellow, oily liquid with a pronounced tart characteristic odor and a burning, spicy taste. In the composition of volatile substances of *D. diversifolium* essential oil, 50 components were identified, constituting 95.4% of volatile compounds. Among them, sabinene, pinene, isolongifolene, D-limonene, isocaryophyllene, *o*-simen, 1,8-cineole, D-cadinene, cis-calaminene,  $\alpha$ -amorphous, (+) - aromadendrene, trans-karyophyllene dominated.

## STUDIES ON THE CHEMICAL CONSTITUENTS OF *Artemisia argyi*

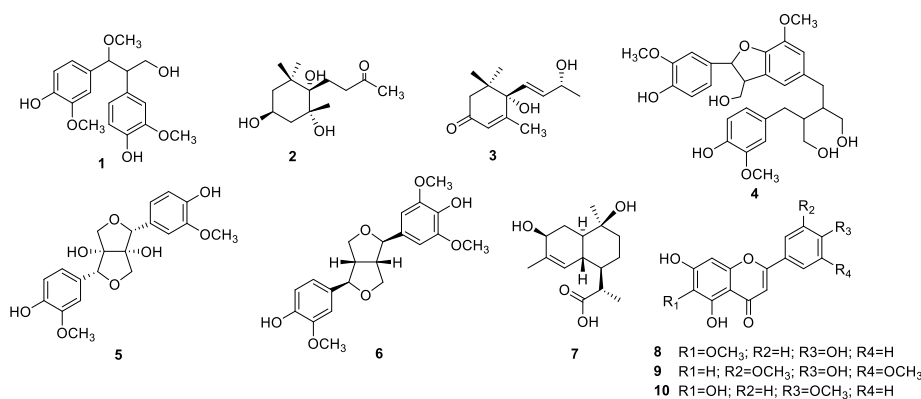
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The genus *Artemisia* belongs to the Asteraceae family and is the largest of the flowering plants. *Artemisia* species are aromatic or fragrant plants which contain essential oil. *Artemisia argyi*, one of the most widely distributed *Artemisia* species, is native to China, Japan, and Russian Far East regions. It has been used as a drug in traditional medical practices for treating eczema, diarrhea, hemostasis, menstruation-related symptoms, and tuberculosis. Phytochemical researches on this species have led to the isolation of sesquiterpenoids, triterpenoids, steroids, coumarins and flavonoids, showing anti-inflammatory, immunomodulatory, antitumor, antimutagen and antimicrobial activities.

As a continuation of our work on the bioactive constituents from *Artemisia* species, ten compounds (**1–10**) were isolated from the air dried aerial part of *A. argyi*, collected from Xinjiang province of China. Based on their spectroscopic data (IR, MS, 1D and 2D NMR), and by comparison with those reported in the literature, the structures of the isolated compounds were elucidated as threo-2,3-bis-(4-hydroxy-3-methoxyphenyl)-3-methoxy-propanol (**1**), (3*S*,5*R*,6*S*,7*E*)-3,5,6-trihydroxy-7-megastigmen 9-one (**2**), vomifoliol (**3**), sesquipinsapol B (**4**), pinoresinol (**5**), medioresinol (**6**), indicumolide C (**7**), tricin (**8**), hispidulin (**9**), and ladanein (**10**), including one phenyl praponiod (**1**), two magastigmane sesquiterpenes (**2–3**), three lignans (**4–6**), one cadanine sesquiterpene (**7**) and three flavonoids (**8–10**). Compounds **1–8** have not been recorded before in this plant.



### ACKNOWLEDGEMENTS

This work was financially supported by the National Natural Science Foundation of China (U1703235); the International Science & Technology Cooperation of the Xinjiang Uygur Autonomous Region (2019E01017); and the Central Asian Drug Discovery & Development Centre of Chinese Academy of Sciences.

## PURIFICATION OF *Lactobacillus plantarum* Mal BACTERIOCIN

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The bacteriocins produced by lactic acid bacteria (LAB) have been the center of attention as they are generally regarded as safe (GRAS) and have potential application in the food industry and pharmacy. Further, bacteriocins have several attributes which make them suitable as food-biopreservative such as ability to inhibit pathogenic and spoilage bacteria, e.g. *L. monocytogenes*, *S. aureus*, *B. cereus*, *C. botulinum*, etc., susceptibility to digestive proteases, constancy in a wide range of temperature and pH, no alteration of the organoleptic properties of food, no toxicity to eukaryotic cells and simplicity to scale-up production. *L. plantarum* is used for cultured dairy, cheeses, and a number of other commercially fermented foods. The probiotic effects of *L. plantarum* is important in both food and pharmaceutical industries.

*L. plantarum* Mal strain was isolated from *Malva neglecta* flowers and its bacteriocinogenic activity has been established by protease treatment. The culture media of *L. plantarum* Mal strain was found to be active against *L. monocytogenes* and *S. aureus* strains. Culture media free of cells was heated to 96 °C and further bacteriocin was purified by three-step chromatography. At each phase of purification, every obtained fraction was investigated for antimicrobial activity. The culture media containing 4265 mg of total protein was filtered through a 0.22 µm filter membrane and loaded onto SP-Sephadex C-25 cation exchange column. Active fractions were eluted with 1 M NaCl in 10 mM citrate buffer (pH 5.0). The yield of partially purified protein was 130 mg at this stage.

The active fractions from cation exchange chromatography were loaded onto a Sep Pak C18 cartridge (volume 1.6 mL). At this stage, bacteriocin fraction was purified from sodium chloride, other soluble proteins and peptides without antimicrobial activity, as well as from some of the colored substances.

At the next step the active fractions were loaded onto Zorbax 300 sb-C18 reverse phase column (5 mm, 4.6 x 250 mm, Agilent, USA) and chromatographed using HPLC system by a linear gradient elution with water-acetonitrile (5–80%) containing 0.1% trifluoroacetic acid (TFA) in 40 min. The flow rate was 0.5 mL/min and the absorbance was monitored at 280 nm. After HPLC re-chromatography, the purity of bacteriocin reached 95%. Highly purified bacteriocin showed antimicrobial activity against indicator strains of *Listeria monocytogenes*, *Staphylococcus aureus* and *Pseudomonas aeruginosa*. This peptide will be further processed for chemical structure analysis.

Thus, the three-step chromatography method for purification of *Lactobacillus plantarum* Mal bacteriocin allowing the isolation of bacteriocin with 95% purity was elaborated for the first time.

## ANTIMICROBE PEPTIDES FROM THE *Bufo viridis* venom

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Over the past years, researchers have developed various antibiotics that provide defense to human body. Although they have successfully guarded our body, later many bacteria have evolved diverse mechanisms that override these killer antibiotics. The resistance acquired by bacteria against antibiotics leaves health issues still under danger. However, antibiotics having peptide nature cannot be easily resisted as like organic antibiotics. Thus, peptide based antibiotic drugs are promising to protect human body from invading bacteria. Toad skin secretions are potent source of drugs. It's probably the only such source in nature from where we can get nearly six types of drugs possessing analgesic, painkiller, antibiotic, anti-viral and anti-cancerous properties as well as possessing potential of treating cardiovascular diseases.

In this work we studied new antimicrobial peptides from Central Asian green toad *Bufo viridis* venom. To prepare soluble fraction of toad venom, 0.6 g of fresh toad venom (FTV) was extracted with 10 mL PBS (0.2 M, pH 7.2) in a 15 mL tube. The tube was incubated at 16°C for 4 h on an agitator at 210 rpm and followed by centrifugation of 12,000 x g at 4°C for 15 min. Supernatant was collected as soluble fraction of FTV.

For the isolation of peptides, soluble fraction of FTV was step by step subjected to gel filtration and ion-exchange chromatography. At first, soluble fraction of FTV was filtrated on a TSK-HW-55 (2.6 × 50 cm) column at a flow rate of 30 mL /h and obtained three fractions, which were freeze-dried. At the second step freeze-dried powders were purified on a TSK-CM-650 ion-exchange column (1.6 × 10 cm) at a flow rate of 30 mL /h with the result: fraction-1 was separated to three fractions; fraction-2 was separated to two fractions and fraction-3 was separated to three fractions. HPLC analysis of samples was performed on an Agilent 1260 Liquid Chromatography. All the fractions were filtrated by a 0.2 μm filter and 30 μL of each filtrated sample was loaded onto an Agilent reverse phase (RP) C8 column and eluted at a flow rate of 1 mL /min in a gradient of 5% buffer B (100% acetonitrile), 90% buffer A (0.1% H<sub>3</sub>PO<sub>4</sub> in water) for 10 min. So according to HPLC data all fractions after ion-exchange chromatography were individual and among them two peptide compounds at the same time had antibacterial and antimicrobial activities. Nowadays primary structures of those peptides are being established. These works will give an opportunity to create technology for large-scale production of antimicrobial peptides.

### ACKNOWLEDGEMENTS

We thank to the PIFI foundation of CAS for visiting scientists (№ 2019VBA0013).

## GENERAL PHARMACOLOGIC ACTIVITY OF *Ferula foetida* GUM

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In step and desert regions of Central Asia, there are growing several types of *Ferula* plants (Umbellifera fam.) and *Ferula foetida* in most degree. Compositions of this plant have wide spectrum of biological activities and are widely used in different branches of medicinal practice. Besides it is used in quality of spices. *Ferula* is also known as Aurvedic plant. Pharmacologic and chemical studies of *Ferula* plants are studied in weak degree in Uzbekistan. The presented study may be accepted as primary attempt to cover given state. Used in study drug presented as gum was collected from rhizomes and roots of *Ferula foetida*. During investigation influence of drug on locomotor activity was studied. Drug administration in doses 10 and 30 mg/kg per os led to constant decrease of movements intensity during initial 7 days, but during further times drug administration gave various results on movements. Gum in test by Hall in mentioned doses at per os administration during initial 20 days had called decrease of locomotor activity approximately to 50%. At 33<sup>th</sup> day of administration it was conducted experiment by Kilfoil method for determination drug influence on anxiety sense. It was observed that treated mice prefer dark cameras in 2-3 times more degree, compared with control animals. It evidenced about activation of anxiety emotion called by drug. In experiments by Raevsky method the gum in dose 10 mg/kg at single administration did not influenced on haloperidol catalepsy, but in dose 30 mg/kg decreased immobilization period down to half. The dose 10 mg/kg was ineffective, at 30 g/kg twice decreased the latency of salivation and tremor effect of arecoline and increased the intensity of mentioned effects up to 60-80%. At 13<sup>th</sup> day of gum administration the influence of gum (10 and 30 mg/kg) on amphetamine (7 mg/kg s.c.) locomotor action was studied. It was shown that this CNS stimulant in mentioned doses as well control mice accelerated the locomotor activity and verticalisation, but in different degree. Intensity of locomotor and verticalisation actions increased at control group for 385±12%, at dose 10 mg/kg – 410±14% and at dose 30 mg/kg – 530±17%. Influence of gum on inflammatory process had been studied on rats. On the model of ovalbumin oedema on rats hind legs, it was observed that dose 10 mg/kg decreased inflammation degree for 40%, while dose 30 mg/kg only for 17%.

Thus, pharmacologic studies of *Ferula foetida* gum collected from underground parts of plant growing in Uzbekistan showed decrease of locomotor activity, induced anxiety emotion, and tendency to eliminate of haloperidol catalepsy, increased locomotor action of amphetamine and revealed anti-inflammatory action. Further investigation would be conducted by comparative manner with known standard compounds with relative activity.

## METAL-BINDING AND ANTIOXIDANT PEPTIDE FRACTIONS FROM PROTEIN HYDROLYSATE OF *Cicer arietinum* L. SEEDS

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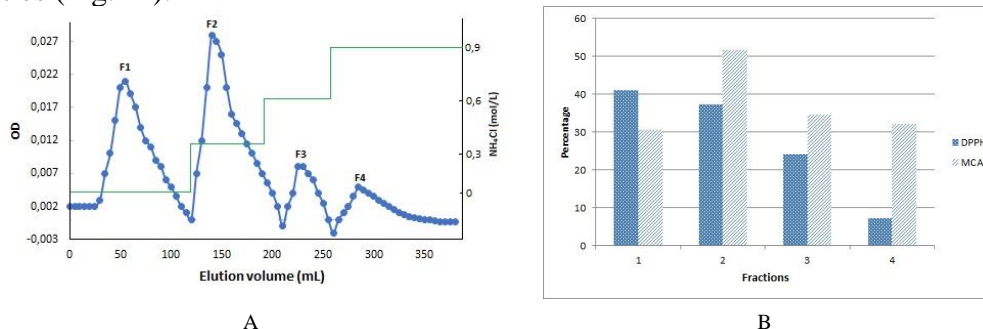
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Nowadays metal chelating and antioxidant peptides are under high interest because of their crucial role on delivery of minerals into living organisms and protect human bodies from free radicals accordingly. Such condition encouraged us to carry out this investigation.

Albumin fraction extracted from chickpea (*Cicer arietinum* L.) seeds was hydrolyzed using trypsin with enzyme to substrate ratio of 50/1 (w/w) for 24 h, under optimum pH (8.0) and temperature condition (37 °C). Solution of the hydrolysate was loaded onto the Zn<sup>2+</sup> immobilized metal affinity column (IMAC) which equilibrated with 0.1 M phosphate buffer at pH 6.0. Following the unbound fraction of the hydrolysate was washed off by the same buffer and collected as fraction 1. Then the bound peptides were eluted with 0.05 M phosphate buffer at pH 8.0 and its NH<sub>4</sub>Cl containing solutions. Thus, obtained fractions 2, 3 and 4 (Fig.1A). Flow rate was 1 mL/min and the absorbance of the eluate was monitored at 254 nm during the elution.

According to the results of DPPH and metal-chelating assays, Fraction 1 had the strongest antioxidant activity, while Fraction 2 and 3 had higher metal chelating activities (Fig.1B).



**Figure 1.** (A) Immobilized metal affinity chromatography (IMAC) of the hydrolysate. (B) The fractions were tested for antioxidant and metal chelating activity.

On the base of the results, it can be concluded that it is facile to produce natural antioxidant and metal chelating peptides from chickpea protein by enzymatic hydrolysis.



## SECONDARY METABOLITES OF THE ENDOPHYTIC FUNGUS *Penicillium brevicaula alba* - CC 200 - PANCREATIC $\alpha$ - AMYLASE INHIBITORS

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A dramatic increase in the number of patients with diabetes mellitus around the world necessitates the search for new microbial producers of biologically active compounds with hypoglycemic properties. A modern therapeutic strategy for controlling hyperglycemia is the inhibition of  $\alpha$ -amylase and  $\alpha$ -glycosidase, which leads to a significant delay in the digestion of carbohydrates into adsorbed monosaccharides. However, it is known that endophytic plant microorganisms as alternative sources of various bioactive compounds of various chemical classes exhibit antimicrobial, anticancer, immunomodular and hypoglycemic activities.

In this regard, the aim of this work was to elucidate the nature of bioactive secondary metabolites in the endophytic fungus *Penicillium brevicale alba* Thom - CC 200, exhibiting a high level of suppression of  $\alpha$ -amylase - 60-80%, comparable to the action of a commercial glycosidase inhibitor - Acarbose.

The cultivation of *P. brevicaula alba* - CC 200 was carried out on a liquid Chapek-Doks medium at a temperature of 28 °C for 7 days deeply on a shaker at 180 rpm. Secondary metabolites from the biomass of the fungus were extracted according to the method of Hazalin et al with polar and non-polar solvents: methanol, ethanol, water, n-butanol, ethyl acetate, acetonitrile and hexane, in a ratio of 1: 5 for 24 hours on a circular shaker at room temperature. The mixture was filtered through paper (Whatman No.1) and Na<sub>2</sub>SO<sub>4</sub> (40  $\mu$ g / mL) was added to the filtrate. The extracts were obtained by evaporation in a vacuum unit. The inhibition of the  $\alpha$ -amylase activity of the extracts was determined according to the modified method of Picot et al. Qualitative analysis of secondary metabolites was carried out on TLC plates (Sigma-Aldrich, Germany) in benzene: methanol (5: 1) and chloroform: methanol (8: 2) systems.

As a result of the studies, it was found that the highest yield of secondary metabolites with inhibitory activity - 93% and 86% occurred when the biomass was extracted with ethyl acetate and methanol. Qualitative analysis of ethyl acetate extracts by TLC showed the presence of eight determined chemical classes of compounds corresponding in quality to terpenoids, saponins, phenols and glycosides. When extracts were separated by TLC in two solvent systems and the plates were treated with a detecting reagent, corresponding staining of individual fractions occurred, indicating the predominant content of saponins (foaming triterpenes).

Given that saponins have a fairly wide range of bioactive properties, it can be assumed that the inhibitory activity of the extract of *P. brevicaula alba* - CC 200 may be due to saponin compounds.

## OPTIMIZATION OF ACTIVE COMPONENTS FROM SOME PLANTS AND THEIR ANTI-INFLAMMATORY ACTIVITY

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The Uzbek research chemical and pharmaceutical Institute is developing a dental medicine based on local herbals. The purpose of these studies is to determine the optimal conditions for the extraction of certain medicinal plants to obtain an effective dental drug. Based on the literature sources, the following list of raw materials was selected, to be investigated in the framework of the project: flowers of *Calendula officinalis*, Oak bark, leaves of *Nettle dioecious*, rhizome with roots of Rhubarb Tangut, grass Oregano, herb St. John's Wort rough, leaves of *Sage officinalis*, leaves of Plantain large. Such groups of compounds as flavonoids, tannins and extractive components were selected as the main objects of active components control. After detection of extracts with the greatest number of biologically active substances, these extracts were subjected to pharmacological examination for anti-inflammatory activity. The analysis of extracts on the index of extraction efficiency for Calendula flowers, Nettle leaves, Oak bark and Rhubarb rhizomes was carried out. Key factors affecting extraction were identified for all objects. Extracts with the highest content of active substance were transferred to pharmacological screening to determine specific activity and study toxicity

The experiments revealed the factors significantly affecting the extraction process (hydromodule and particle size of raw materials), the regression equations of the extraction processes were obtained. According to the results of pharmacological studies, the extracts obtained were not toxic. LD<sub>50</sub> for extracts were: "calendula Extract" >1600 mg/kg "nettle Extract" >1600 mg/kg, "oak Extract" >2880 mg/kg and "rhubarb Extract" >3520 mg/kg. The study of specific activity - inflammation of the oral mucosa (stomatitis model) was carried out in rats. Complete healing of the mucous membrane of the rats by the treatment with calendula extract was observed after 16.5 ± 1.6 days, which was 22.0% faster, nettle extract was observed to 15.8 ± 1.5 days, 25.0% faster, extract of oak was observed to 13.8 ± 1.1 days, 34.0% faster, and extract of rhubarb – was observed for 13.6 ± 1.0 day, 35.8% faster compared to untreated control. Specific (anti-inflammatory) activity was in the following order: Rhubarb > Oak > Nettle > Calendula.

## FATTY ACID COMPOSITION OF OILY FRACTIONS FROM *Glycyrrhiza glabra*

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*Glycyrrhiza glabra* is an immensely important plant belonging to the family Leguminosae. In commerce and market, it is well known as licorice. The plant is known for its high economic value and numerous therapeutic applications. The plant is of great interest because of its rhizome or stoloniferous roots which contain numerous important bioactive compounds. According to the WHO, licorice is being used as a demulcent in the treatment of sore throats and an expectorant for coughs and bronchial catarrh. Licorice also has an important role in the prophylaxis and treatment of gastric and duodenal ulcers. In China, licorice is also documented to be effective for fatigue and debilitation [1-3]. Current studies have showed that the main bioactive constituents of licorice are triterpene saponins, flavonoids and polysaccharides. However, there is no systematic research about the fatty acid components of licorice.

In this study fatty acid components of licorice were analyzed by GC-MS. The chemical compositions of oily fractions from the roots of *Glycyrrhiza glabra* was studied using GC-MS and FT-IR spectroscopy. The GC-MS study identified the presence of linoleic acid (55.76%), palmitic acid (16.12%), oleic acid (10.5%) and behenic acid (5.68%) as the major fatty acids. A majority of the studies on linoleic acid and its derivatives showed a direct/indirect link with inflammation and metabolic diseases [4]. Also, all these results support the folkloric uses of the licorice for the treatment of sore throats and an expectorant for coughs and bronchial catarrh.

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## STRUCTURAL INVESTIGATION OF A NEUTRAL POLYSACCHARIDE OBTAINED FROM *Glycyrrhiza glabra*

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*Glycyrrhiza glabra* is a well-known herbal medicine used for the treatment of various diseases as well as a tonic medicine for thousands of years. This herb has long been valued as a demulcent to relieve respiratory ailments, stomach burn including heart burn, gastritis, inflammatory disorders, skin diseases and liver problems <sup>[1]</sup>. Current studies have demonstrated that the main bioactive constituents of *G. glabra* are triterpene, saponins, various types of flavonoids and polysaccharides. However, most of the studies focused on the effect and structure of triterpene, saponins and flavonoids <sup>[2]</sup>. Polysaccharide, known as exhibiting anticancer, antimicrobial, anti-inflammatory activities and improving human immune system, has a wide application in the medicine, cosmetics and food industry. In this study, a water-soluble polysaccharide, named GPN, with molecular mass 38.7 kDa was isolated from *Glycyrrhiza glabra* with hot water extraction, ethanol precipitation, and purified by column chromatography. Monosaccharide composition analysis confirmed the presence of predominant glucose (98.03%) and trace amount of mannose, arabinose, galactose. Methylation and GC-MS analysis revealed that the main glycosidic bonds in GPN comprised 1,4-linked Glcp, T-linked Glcp, 1,4,6-linked Glcp, and 1,6 linked Glcp. Based on these results and 1D/2D NMR spectroscopy, GPN had a linear backbone of 1,4-linked  $\alpha$ -D-Glcp and 1,6-linked  $\alpha$ -D-Glcp substituted at C-4 of glucose. The side chain was probably composed from 1,4-linked to main side  $\alpha$ -D-Glcp and terminal 1-linked  $\beta$ -D-Glcp to the residue of D6. Congo red assay confirmed the existence of triple helix structure. Moreover, SEM and XRD analysis revealed that the GPN had the irregular fibrous, filaments like surface, and both crystalline and amorphous structure. GPN also displayed favorable thermal stability.

### ACKNOWLEDGEMENTS

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## STUDYING ROLE OF COLLAGEN-FILM IN THE WOUND HEALING PROCESS

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In recent years, much attention has been paid to absorbable materials, which act as a temporary addressing carcass for the wound regeneration, that is gradually replaced by the organism own tissues. It has been believed that the most promising in this regard is the natural biopolymer collagen, which combines the positive qualities of synthetic polymers and tissue transplants, however lacks a number of their negative aspects.

A medical material in the form of collagen-based film was developed in the Institute of Bioorganic Chemistry. To study the role of collagen-film in wound healing, 30 male white rats were selected which were divided into 2 groups, modeled a surface wound on the parietal surface of the rat skull  $2 \times 2$  cm in size with excision of the hair, skin and subcutaneous fat to the periosteum under the general injectable pain relief was performed equally in all 30 rats. The first group of individuals included an experimental group of rats, with the planned treatment of a modeled wound by applying a collagen-film on it and further observing the wound healing process. The second group included the control group of rats, for the treatment of the modeled wounds of which collagen film was not applied. In the postoperative period, the general condition of rats was monitored regarding their degree of activity and wound healing rate. For histological analysis of the degree of regeneration of the wound surface, rats were slaughtered with tissue sampling at 1, 3, 5, 7, and 10 days after surgery.

According to histological analysis, it was noted that from the moment of surgery, the collagen-film causes the formation of tender, relatively looser connective tissue, with blood vessels. Characteristically, wound epithelization and a decrease in the area of the defect are observed around the circumference. Apparently, a wound in the presence of a collagen-film, since the surgery, is characterized by a moderate or reduced inflammatory reaction compared to a wound and an inflammation process without a film. In addition to protecting against additional infection of the wound, the collagen-film contains a number of biologically active factors that induce the regeneration and restoration of the defect with inducing the proliferation and differentiation of epithelial cells.

In conclusion, the collagen-film covering the wound surface promotes to reduce the severity of inflammation, the formation of a tender structure of connective tissue and epithelization.

## POLYMERIC PROANTHOCYANIDINES AS EFFECTIVE ANTIHYPOXIC PRODUCTS

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Hypoxia underlies the development of many diseases. Therefore, the use of antihypoxic agents in these cases, along with specific therapy, gives, as a rule, a faster and more pronounced therapeutic effect. In recent years, it was found that a number of drugs: calcium ion antagonists, nootropics, and some others contribute to a more "economical" consumption of oxygen by tissues, its better utilization and thereby reduce hypoxia, increase the body's resistance to oxygen deficiency. However, the greatest interest in this regard began to attract many plant polyphenolic compounds. This is especially true for polymer proanthocyanidins isolated from *Alhagi pseudalhagi*, *Rhodiola pamiroalaica*, *Polygonum coriarium*, *Geranium saxatile*. These compounds are more pronounced than many other drugs exhibiting antihypoxic effect. So when placing mice (males 20-24 g), which were previously injected with proanthocyanidins, in a pressure chamber (normobaric hypoxic hypoxia), their greater survival was revealed compared with the control (the effect was 84.0 -87.0%). Under conditions of tissue hypoxia (caused by intraperitoneal administration of sodium nitroprusside at a dose of 20 mg/kg, resulting in the death of 100% of the animals), administration of proanthocyanidins 30 minutes before the experiment increased the life expectancy by 46-68%. In all these cases, the studied proanthocyanidins acted at or even exceeded the effect of known drugs with the antihypoxic effect of mildronate and mexidol.

The revealed ability of polymer proanthocyanidins to level out the phenomena of hypoxia was quite clearly revealed by us on the models of hypoxia of the brain, heart, and lungs. The most active in these pathologies were the polymeric proanthocyanidins from *Geranium saxatile* (geranyl), *Polygonum coriarium* (catacin) and *Alhagi pseudalhagi* (alkahine). The course administration of geranyl, cavergal, and alkahine not only eliminated the characteristic signs of a hypoxic state under experimental pathologies, but also positively influenced the carbohydrate metabolism in the studied organs, maintained homeostasis of energy production, and contributed to maintaining increased activity of catalase and superoxidedismutase enzymes, improving the antioxidant defense of the body. The effectiveness of the antihypoxic effect of the studied proanthocyanidins under the conditions of the above described pathological conditions was comparable in its severity with the drug mildronate widely used in medical practice.

## THE EFFECT OF NATURAL COMPOUNDS ON COTTON FIBER DEVELOPMENT UNDER CONDITIONS OF SOIL SALINIZATION

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Cotton crops are very sensitive to soil salinization, heat and drought and can lead to serious crop losses and become a serious problem for sustainable crop production. Cotton fibers are single-cell trichomes arising from the epidermis of developing cotton ovules and fibers development occurs in four overlapping stages: initiation, elongation, secondary cell wall (SCW) deposition, and maturation <sup>[1]</sup>. Reactive oxygen species (ROS) are involved in secondary cell wall biosynthesis. Superoxide and H<sub>2</sub>O<sub>2</sub> play important roles in the covalent crosslinking between protein and carbohydrate cell wall components, thereby increasing the tensile strength of the wall <sup>[2]</sup>.

The aim of our study was to study the effect of the supramolecular complex of glycyrrhizic acid with salicylic acid (commercial name DAG-1) on cotton fiber development under conditions of soil salinization. Cotton plants (Sultan variety) were grown under standard field conditions on saline soils of the Syrdarya region of Uzbekistan during the summer and were treated with DAG-1 during anthesis. Cotton flowers were tagged at day of anthesis. Three biological replicates of cotton bolls from Sultan variety were harvested at 20, 30, and 40 DPA.

Superoxide radicals were detected by semi-quantitatively staining freshly harvested developing fibers (20, 30, and 40 DPA) with nitroblue tetrazolium (NBT) staining <sup>[3]</sup>. The intensity of the purple color was used as a measure of superoxide amounts present in the fibers. In cotton plants treated with DAG-1, the intensity of purple dyeing decreased as the fibers matured and increased superoxide dismutase activity. Lower intensity of purple color under the influence of DAG-1 in the developing cotton fibers at 30 and 40 DPA cotton fibers suggested a decreased amount of superoxide radicals. Fiber cell wall thickness between cotton treated with DAG-1 and control were compared using a microscopic image analysis. At 20 DPA under the influence of DAG-1 fibers were detectable secondary cell walls, while control fibers appeared linear due to a lack or very low level of SCW cellulose. At 30 DPA under DAG-1 fibers were thicker than the control fibers. At 40 DPA, the fiber cell wall in the control fibers was clearly thinner than that in experience with DAG-1.

These results clearly show that the DAG-1 greatly affects thickening of the secondary cell wall in both developing and mature fibers under salinity conditions.

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## PREPARATION OF SEMISOLID MEDICINAL FORMS, CONTAINING MEGA FERONE

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According to published sources, the numerous derivatives of gossypol - megaferone is inducer of interferon - a drug that stimulates the formation of endogenous  $\alpha$ -,  $\beta$ -,  $\gamma$ -interferon plant origin. Currently, this is a tendency of growth of viral diseases among the population, in particular disease herpes. In this connection, this study is to provide highly topical antiviral drugs for the treatment and prophylaxis of the respective disease etiology. The aim of this study is selection of scientifically sound composition and development of the technology of soft medicinal form megaferone providing quality, high bioavailability and stability of the storage. From soft dosage forms were prepared and suppositories and ointments. Suppositories are prepared the pouring out method. This is more convenient, hygienic, provides obtaining suppositories of the same shape. It consists of pouring out the molten suppository mass which is on the verge of freezing in special shapes. Before pouring out of suppositories in the form of socket the moulds are lubricated in order to the finished products will not stick. By pouring out method can be prepared suppositories, balls and sticks on almost any basis (the fatty base is melted; gelatin-glycerol is prepared similarly to hydrophilic ointment bases).

With good solubility in the basis of the composing the suppository substances the preparation process reduces to pouring out the molten mixture into moulds followed by cooling. Quality evaluation of suppositories is carried out in accordance with the requirements placed upon them by SPh XI. Suppositories should have the right identical shape, smooth consistency and homogeneous hardness, providing the ease of use, matching of color, odour to properties of the ingredients. Technique of preparing emulsion ointments is a thoroughly mixed in a mortar of emulsifier with an aqueous solution of medicinal substances until complete absorption then the base is blended. Compared with fatty suspension ointments ointment-emulsions faster will penetrate the skin and medicinal substances, which are in an aqueous, phase having more rapid and strong action. In the form of aqueous components in these ointments are added solutions of megaferone. Composition of 3% megaferone emulsion ointment :Megaferone 5.0, Aquae purificatae 4.5, Lanolini anhydrici 13.5, Basis emulgens 27.0. This emulsion-type ointment containing 10% of the medicinal substance.

Technology: 3gr megaferone dissolved in water and the resulting solution is emulsified with written amount of anhydrous lanolin. To the obtained emulsion is added with stirring 27 gr of emulsion base of Kutumova (PhA 42-125-72). The latter is a 30% emulsion of water in alloy of 60gr of Vaseline and 10 gr of emulsifier T-2, emulsion consistent water / petrolatum are also used for preparing ointments sulfuric and turpentine. The ointment is transferred to a jar of dark color and designed for dispense.

**Table 1.** The results of quality indicators ointment megaferone relatively standard sample

Compositions	Appearance	pH	structural-strength properties	
			thermostat	centrifuge
Composition of research	Plastic mass of yellow color with a smell	5.7	satisfactorily	satisfactorily



## NOVEL TRICYCLIC PURINES

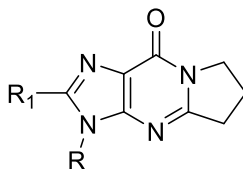
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Purine nucleoside analogues are an important class of nitrogen-containing heterocycle that exhibit great therapeutic potential, possessing anticancer, anti-HIV, antimicrobial, and other various bio-activities. Although investigations into the modification of purine nucleosides have attracted increasing attention, formation of the tri- and polycyclic purines remain challenging due to their expensive starting materials.



Novel tricyclic purines

Herein we have been working in order to synthesis novel heterocyclic ring system – tricyclic purines. Target compounds were synthesized via 2 or 3 steps, in good yields and were used as available materials. Anticancer and neuroprotective properties are under evaluation process.

## ONTOGENESIS OF SILYBUM MARIANUM UNDER INTRODUCTION IN THE CONDITIONS OF TASHKENT

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*Silybum marianum* - Milk thistle, ostropestro, has green glossy, strongly spiky leaves ("spicy") with white spots and stains ("motley"). Milk thistle was used medicinally by Galen. They are also used in modern medicine and are part of the preparations Karsil, Silibor, Legalon. Milk thistle is a folk remedy for cirrhosis of the liver, acute and chronic hepatitis, jaundice, diseases of the bile ducts, and colic. The main active ingredients are flavonoids and flavonolignans (silibin, silicristin, silidianin).

In recent years, flavonoids and flavolignans, which exhibit hepatoprotective activity and may well be pharmaceutical raw materials for the production of biologically active compounds (BAC), have been isolated from the aerial part of milk thistle at the Institute of Plant Chemistry of the Academy of Sciences of Uzbekistan. Therefore, the cultural introduction of the Milk thistle in the conditions of Tashkent is considered very important.

Germination of seeds was about 80-82% in September. At this time of the year, the air temperature was 28-32 °C, the temperature of the soil surface was 18.6-20 °C. Seeds began to germinate after 10-15 days. The roots deep until 5-6 cm.

The juvenile stage began 18-20 days after the appearance of the first pair of true leaves. In spring, intensive plant growth was observed at the end of March and at the beginning of April. By the immature stage, the plant formed a stem and lateral shoots. Their length reached 7-15 cm and 20-30 cm in April and in May respectively. In the virginal period, the height of the plant reached 100-140 cm and had a powerful outlet in late April and early May. The total virginal period was 210-225 days.

The generative period lasted 60-70 days. In the second and third decades of April, *S. marianum* entered the budding phase. The beginning of flowering was observed in mid-May and the height of the plant reached 140-150 cm at the time. The beginning of fruiting was noted at the end of May. Seed ripening continued until the end of the June and they passed through all phases of development. The phases of budding, flowering and ripening of seeds, depending on weather conditions, lasted 60-70 days. The total vegetative period of the plant was 300-310 days.

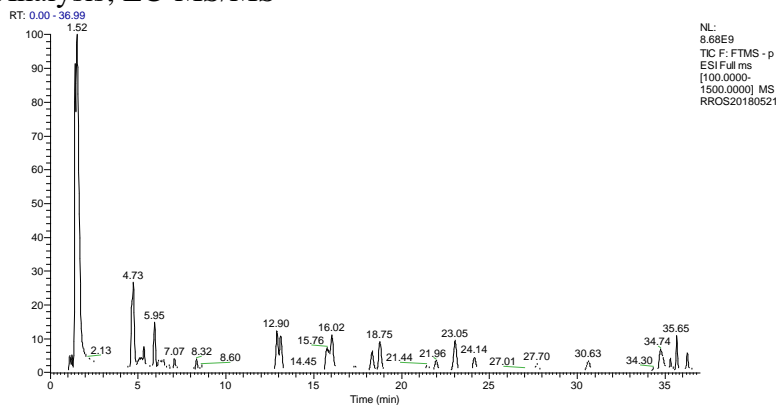
## QUALITATIVE AND QUANTITATIVE ANALYSES OF PHENOLIC COMPOUNDS IN MEIGUIHUA ORAL SOLUTION BY LC-MS/MS

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Meiguihua Oral Solution (MOS), approved by the China Food and Drug Administration and obtained the drug production (NO. Z65020019), was prepared by water extraction of a traditional Chinese medicine *Rosa rugosa* Thunb. petals [1], used for the treatment of cardio-cerebro-vascular diseases, stomach pain, vomiting, limb paralysis pain and tonic agents. In this study, a total of 46 compounds were qualitatively analyzed by UPLC-Q-orbitrap-HRMS, including 21 flavonoids and 25 tannins. Simultaneously, a quantitative method was established by HPLC-Tri-Q-LIT-MS for the ten main compounds: gallic acid, quercetin-3-*O*-sophoroside, ellagic acid, sophoraflavonolside, hyperoside, isoquercitrin, avicularin, astragalol, quercitrin and juglanin, respectively. The developed methods were stable, reliable and could support the potential evidence for the quality control of MOS.

**Keywords:** Meiguihua Oral Solution; phenolic compounds; Qualitative Analysis; Quantitative Analysis; LC-MS/MS



**Figure 1.** TIC chromatogram of MOS analyzed by UPLC-Q-orbitrap-HRMS in negative ESI mode.

### ACKNOWLEDGEMENTS

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## COMPARATIVE ANALYSIS OF THE DNA EXTRACTION TECHNIQUE ON SOME WILD SPECIES OF THE *Salvia*, *Dracocephalum*, *Tulipa*, *Allium*, *Iris*, *Ranunculus* GENERA

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Isolation of high-quality DNA from plants is very important for molecular research. There are many different DNA isolation protocols that differ in modifications of cell wall destruction methods, stages of lysis of cellular components and DNA purification, and the required time. This work presents the comparison of protocols for isolating DNA techniques from leaves of representatives *Salvia*, *Dracocephalum*, *Tulipa*, *Allium*, *Iris*, *Ranunculus* genera.

Particular attention has been paid to the species characterized by various biochemical features such as, the presence of polysaccharides, tannins, polyphenols and their quinone oxidation products, which complicates their complete separation from DNA and further inhibits the polymerase chain reaction. *Salvia* species are rich with polyphenolic compounds. So, our protocol modification includes polyvinylpyrrolidone (1%) for removing polysaccharides and other carbohydrate contaminants.

According to the first protocol, DNA was isolated using the *Genomic DNA Purification Kit* (Thermo Scientific). In the second case, total DNA was isolated using the *DNeasy Plant Mini Kit* (Qiagen, Germany) with RNase. Primers were used for amplification rbcLaF- rbcLaR, ITS2, matK-xF -MALPR1 5'. PCR for rbcL, matK, and ITS2 had been attempted using *ReadyMix PCR master mix* with Taq polymerase.

The spectrophotometry data characterizing the concentration and purity of the obtained DNA extracts were evaluated using an *Implen P360 spectrophotometer* (Implen, Germany).

The obtained DNA samples according to Protocol № 1 showed the absorbance ratios  $\lambda = 260/280$  nm average, 1.82, revealing lack of contamination. The highest DNA concentration was 73 ng/ $\mu$ L, and the lowest - 6.00 ng/ $\mu$ L.

In turn, the measure of DNA purity, obtained by Protocol № 2 showed the absorbance ratios  $\lambda = 260/280$  nm average, 1.84, also revealing lack of contamination. The maximum DNA concentration was 335.00 ng/ $\mu$ L, and the minimum 11.50 ng/ $\mu$ L. It is important that DNA contained in the diluted sample was more than 10 ng/ $\mu$ L.

The research with *Salvia* species showed the biochemical “problem” due to a large quantity of substances, inhibiting amplification processes in insufficiently purified DNA extracts.

Electropherograms of amplification results of marker sequences with DNA of *Salvia*, *Dracocephalum*, *Tulipa*, *Allium*, *Iris*, *Ranunculus* species were obtained.

As a result of PCR with ITS2, rbcL and matK primers, using the standard method, a sufficient quantity of amplification product and the absence of “comet tail”, on the electropherogram, indicated the removal of PCR inhibitors in the most cases.

Thus, summarizing the obtained data, we can conclude that these DNA extraction methods are effective for plants of the *Tulipa*, *Allium*, *Iris*, *Ranunculus* genera, with 90% reproducibility of amplification results.

## TECHNICS TO PRODUCE TRANSGENIC PLANTS

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Transgenic plants are genetically modified plants where transgene is introduced into the nuclear genome. So, to achieve the genetic transformation in plants, the vector (*genetic vehicle*) with necessary controlling sequences (*promoter* and *terminator*) need to construct and to deliver the interest genes into the host plant.

There are numerous different methods of DNA delivery into the cell.

Generally, all methods of DNA transferred into plants can be divided into three top groups. The first group includes **natural systems** of gene transfer: the plant viral vectors delivered by *Agrobacterium*.

The second group is an **artificial transfer system**, which can be divided into two subgroups: indirect and direct ones. **The direct DNA transfer methods**, where the foreign interest gene is delivered into the host plant cell without vector. The direct transfer occurs due to the protoplasts permeability and cells by chemical (*polyethylene glycol*), physical (*electroporation, ultrasound*) or mechanical methods (*silicon carbide crystals, laser*) and the **use of artificial vector systems** - *microparticles, microinjections* or *liposomes*.

In the third group with various methods, which, unlike the first two, do not require an *in vitro* culture and are commonly called ***in planta* transformation methods**.

The greatest practical application of all these methods are received the agrobacterial method, the biolistic and direct transfer to protoplasts. The other methods have not been widely used for a number of reasons

*Agrobacterium*- mediated plant transformation is the introduction of a plasmid-carrying gene construct into the target cell by means of bacteria known as “natural genetic engineer” - *Agrobacterium tumefaciens* or *Agrobacterium rhizogenes*.

So, this indirect method is a naturally evolved genetic engineering process, based on the *Agrobacterium* pathogenic organism ability to transfer the certain DNA fragments from its Ti-plasmid (*tumor- inducing plasmid*) into the plant cells. At this, a fragment (segment) of Ti-plasmid, referred to as T-DNA, is actually transferred from the bacterium into the host where it gets integrated into the plant cell chromosome (i.e. host genome).

Compared with artificial method of gene transfer (such as widely used *biolistic method*), *Agrobacterium* method has two important advantages.

The first, *Agrobacterium* transfers only the fragment localized between the two specific DNA sequences into the genome plants. Whereas, at artificial methods using, the transformed cells contain genes fragments or plasmid DNA also.

The second, *Agrobacterium* method usually leads to insertion only one or, at least, a limited number of gene copies, at the certain chromosomes loci. Nevertheless, other methods result in an unsystematic insertion of multiple copies, which are linked to each other in most cases.

## EFFECT OF SOWING METHODS ON THE YIELD OF *Lepidium sativum* L.

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Commonly used in ethnic medicine for the treatment of gastrointestinal diseases in Xinjiang Autonomous, the seeds of *Lepidium sativum* L. possess various therapeutic properties such as anti-cancer, antioxidant, antimicrobial, anti-inflammatory, hypoglycemic, antihypertensive, antifungal and efficacy in gastrointestinal diseases. The *Lepidium sativum* L. has good adaptability to cultivation in Hetian, Xinjiang. In order to explore its high-yield cultivation mode and study the effect of different sowing methods on the yield of *Lepidium sativum* L., so as to provide important reference for the large-scale cultivation of *Lepidium sativum* L., two sowing methods were set up to study the seeds of *Lepidium sativum* L. purchased from Hetian medicinal material market: the first one was 35 cm row spacing and 10 cm plant spacing; the second one was 40 cm row spacing and no seedling. The agronomic traits were measured, such as plant height, crown width (length  $\times$  width, cm<sup>2</sup>), effective stem number of main stem and yield of the two sowing methods. The results showed that the first sowing method, the plant spacing was 10 cm  $\times$  35 cm, the plant height was 45.8~60.4 cm, average plant height 51.1 cm; crown width was 200.2~368.7 cm<sup>2</sup>, the average 286.1 cm<sup>2</sup>; effective stem number of main stem was 5-9, with an average 7 and the yield of *Lepidium sativum* L. was 1219.35 kg/hm<sup>2</sup>. The second sowing method, row spacing 40 cm and no seedlings, plant height was 57.3~83.4 cm, average plant height 68.6 cm; crown width 300.2~568.7 cm<sup>2</sup>, average 419.4 cm<sup>2</sup>; the effective stem number of main stem was 8-12, with an average 10 and yield of *Lepidium sativum* L. is 2175.9 kg/ hm<sup>2</sup>. Compared with the first sowing method, the second sowing method showed very significant differences in plant height, crown width and yield. For the yield of *Lepidium sativum* L., the best sowing method was 40 cm row spacing and no seedling, and the yield increased by 78.4%.

**Keywords:** *Lepidium sativum* L.; sowing methods; yield; seed; plant height

### ACKNOWLEDGMENTS

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## COMPONENT COMPOSITION OF THE ROOT OF *Haplophyllum bucharicum*

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We investigated the plant *Haplophyllum bucharicum* Litv. collected in the Surkhandarya region in the flora of Uzbekistan. Extraction of the roots of air-dry raw material (2.5 kg) by 80% ethanol in an ultrasonic bath, was combined after removal of solvent, resulting in extractives in an amount of 240 g. Treatment of the extract with various solvents obtained benzene, chloroform, acetone, methanol and water fractions. The components of benzene and chloroform fractions were investigated. The data are presented in table 1.

**Table 1.** The Components of the benzene eluate of benzene fraction

№	Names of Substans	(RT)	Content, %	Quality, %
1	N-Tetradecane	10.303	0.73	93
2	3,6-dimethyl- Hexadecane	11.576	0.49	74
3	Pentadecane	13.212	3.31	97
4	Spiro[5.5]undec-2-ene	15.788	0.93	81
5	n-Cetane	16.126	5.29	99
6	Beta.-Chamigrene	17.983	1.37	97
7	2,6,10,15,19,23-hexam ethyl Tetracosane	18.364	2.58	78
8	N-Heptadecane	18.985	7.15	97
9	N-Octadecane	21.801	6.17	94
10	N-Nonadecane	24.611	6.93	95
11	Eicosane	27.477	6.67	93
12	Heneicosane	30.582	15.35	97
13	2-Methyl-7,9-dinitro-1,2,3,4-tetrahydro-dibenzofuran	32.180	8.21	90
14	Naphthalene	33.078	4.16	72
15	1-Chloro-Octadecane	33.908	6.38	87
16	Tricosane	37.837	5.76	76
17	Diphenylethyne	43.992	5.03	90

The components of the benzene eluate of chloroform fraction were as follows:

Dodecane, 3-methyl-nonane, n-eridecane, 2,6,10-trimethyl-dodecane, 3-methyl-tridecane, n-tetradecane, 1-nonadecene, 7-methyl-pentadecane, germacrene B, 1,2,4-metheno-1H-indene, 3-methyl-tetradecane,  $\alpha$ -copaene, n-pentadecane, 4-methyl-pentadecane, 2-methyl-pentadecane, 1,5,5-trimethyl-6-methylene-cyclohexene, hexadecane, 2,6,10,14-tetramethyl-pentadecane,  $\alpha$ -gurjunene, hexatriacontane, 1H-3a,7-methanoazulene, 3,7,7-trimethyl-11-methylene-spiro[5.5]undec-2-ene, 2,6,10,14-tetramethyl-pentadecane, cyclohexane, hepta-decane, 1-(1,5-dimethyl-4-hexenyl)-benzene, 1-methyl-4-(1,2,2-trimethylcyclo-pentyl)benzene, octadecane, nonadecane, naphthalene, eicosane, heneicosane, 2-methyl-7,9-dinitro-1,2,3,4-tetrahydro-dibenzofuran, kaur-16-ene (8-B,13-B), docosane, tricosane, octadecane.

## DUBAMINE-BASED SYNTHESIS

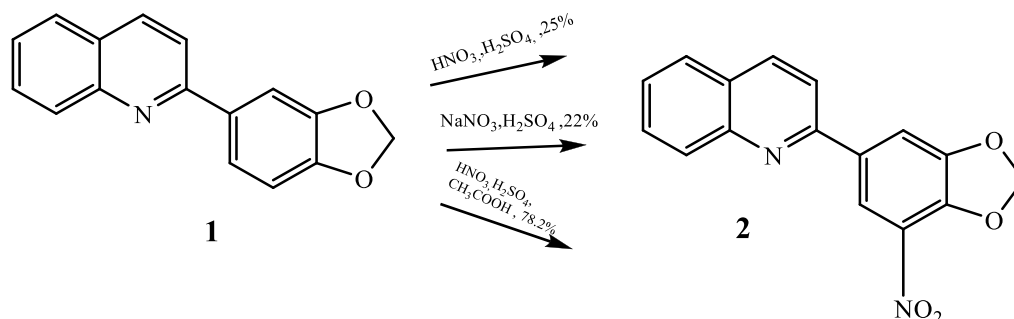
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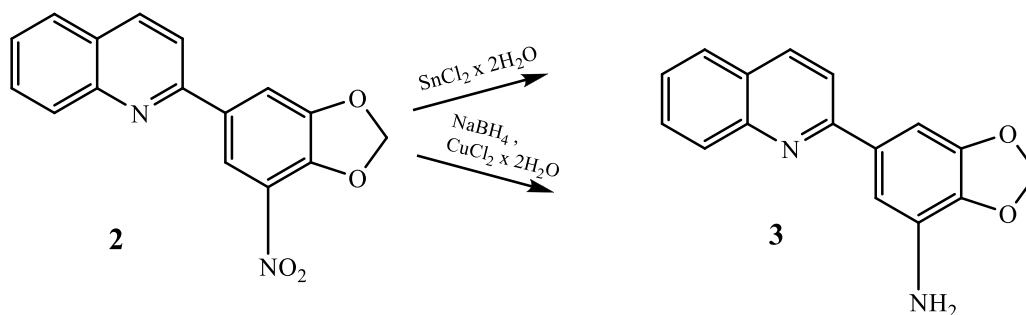
Quinoline alkaloids and their synthetic analogues are of undoubted theoretical and practical interest.

In order to obtain new biologically active derivatives, the nitration reactions of dubamine (**1**) were carried out under different condition.

When a nitrating agent is added to the dubamine (**1**) solution in conc. sulfuric acid at 0 °C, as well as NaNO<sub>3</sub> was added to original dubamine solution at room temperature, obtaining nitrodubamine (**2**) with a 25 % yield. The use of acetic acid to dissolve dubamine increased the yield of reaction product **2** to 78.2 %.



The reduction of nitrodubamine was carried out in two ways. The reaction resulted in an amine product with 76% and 40% yield using SnCl<sub>2</sub> and NaBH<sub>4</sub>, respectively.



The structures of the synthesized compounds were confirmed by IR, <sup>1</sup>H and <sup>13</sup>C NMR spectroscopy.



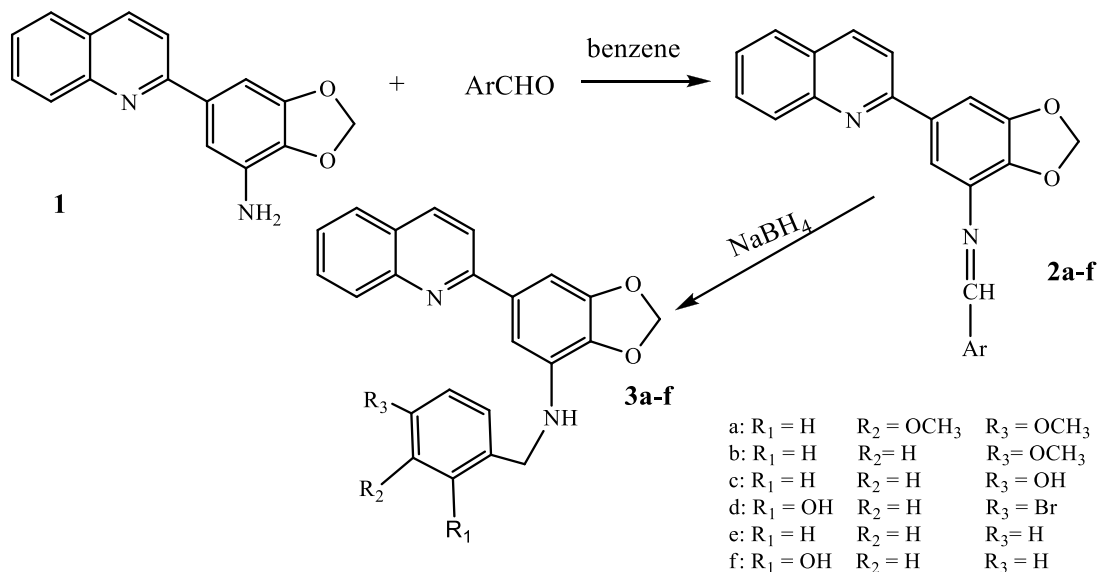
## REACTIONS OF AMINODUBAMINE WITH AROMATIC ALDEHYDES

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Currently, more than half of the drugs introduced are related to natural compounds. Of particular interest are the transformations of quinoline alkaloids in order to enhance their natural activity. To this end, the available alkaloid dubamine isolated from plants of the genera *Dictamnus* and *Haplophyllum* was used as a starting material.

The aminodubamine (**1**) obtained in two stages upon condensation with substituted aldehydes and subsequent reduction of the imines **2a-f** NaBH<sub>4</sub> gave a series of benzylamines **3a-f** with yields of 40-90%.



The structures of the synthesized compounds were confirmed by IR, <sup>1</sup>H and <sup>13</sup>C NMR spectroscopy.

## **EXTRACTION TECHNOLOGY OF JUICE FROM GREEN HUD FRUITS OF WALNUTS NUT AND EVALUATION OF PRODUCED PRODUCTS QUALITY**

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One of the main tasks of the National Health System is to provide the population with effective, low toxic, safe drugs with high pharmacological activity. In Uzbekistan, the natural resources of medicinal herbs are sufficient for the production of natural compounds. A wide range of pharmacological properties of medicinal herbs is based on the properties of biologically active compounds (BAC) contained in them <sup>[1]</sup>.

Vitiligo is a skin disease characterized by a violation of skin pigmentation. Although vitiligo has long been known to mankind, its treatment is still one of the pressing problems. The aim of this study is to create a ready-to-use drug from a walnut burn for the treatment of the aforementioned disease <sup>[2]</sup>. Green peel of walnut, according to literature data, contains many tannins. Pericarp can be used to tan skin.

Unripe nuts were harvested in the Bustanlik region of Tashkent. For extraction of biologically active substances, green shell was first pulverized, then the resulting mass was added with water in a ratio of 7:3. Mass was defended 3 days at 8-10 °C. Then this mass was divided into 3 parts and juice was squeezed out. Usually mixtures from plant are safe during 3 days. The prepared peel juice from unripe fruits of walnut was placed in 100 mL of a dark glass vials and held 60 days, but not observed any spoilage. For prolonged storage fermenting juice did not occur, indicating that the juice contained bactericide substances. The purpose of our work was to identify the biologically active tannic compounds of the green peel walnuts. It was established that the content of the main active substances corresponded to the indicators of the State Pharmacopoeia XI.

Technology for producing juice from green peel walnuts is developed. It is shown that in thick juice it contains 8% tannins.

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## JAM FROM NUTS IS AN IMPORTANT SOURCE OF MICROELEMENTS

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In the human diet, nutrients and processed foods play a role. The local population consumes nuts, especially Greek nuts, directly as a fruit and by making a variety of ingredients. In particular, many people plant peanuts in their backyard farms and use it as a prophylactic agent to prevent the disease caused by the lack of iodine in the body by making jams before the fruit peel. However, there is little scientific evidence in the literature.

That's why we conducted experiments with jam from unripe walnuts to find out what is the content of iodine and other trace elements. The content of trace elements was measured by the mass spectral method. The equipment was used together with the ICP-MS 7500A Agilent technologist. The results are presented in the table.

№	Microelement	Dosage, in mg of 100g product
1	Boron	1.13
2	Magnesium	0.60
3	Phosphorus	0.37
4	Manganese	0.033
5	Cobalt	0.0023
6	Copper	0.30
7	Zinc	0.012
8	Iodine	0.12
9	Cadmium	0.01
10	Silicon	2.77

Comparison of the amount of iodine in the nut jam can be obtained by comparing the amount of apple fruit with that of walnut jam. The amount of iodine in apple fruit does not exceed 5 mcg in the literature. This means that the amount of iodine in the walnut jam is several hundred times higher than that no. In other words, consuming 100 g of unsweetened peanut fruit means that 80 to 90 percent of the iodine required by the body is consumed.

Thus, jam made from ripe nuts can be used as an important preventive measure in iodine deficiency.

## INVESTIGATION ON SOME PHYSICOCHEMICAL PROPERTIES OF *Elaeagnus* L. GUM

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Natural gums are obtained as natural exudates of different tree species and exhibit unique properties in a wide variety of application including pharmaceutical, food, adhesive, paper, textile and other industries<sup>[1,2]</sup>. The polysaccharide obtained from the *Elaeagnus* L. Gums by the method of water extraction and alcohol precipitation, and the yield of the purified polysaccharide from the gum was 85%. Present article was devoted to the investigation on the preparation method of polysaccharide, determination of monomeric composition, molecular weight and measuring its solubility in various solvents. Monosaccharide composition analysis were carried out by precolumn derivation HPLC, and comparative content and composition of monosaccharide were Arabinose of 41.8%, Galactose of 22.7%, Rhamnose of 8.7%, Glucuronic acid of 3.5%, Mannose of 1.2%, and uncertain content of 4.5%. The molecular weight of the polysaccharide was determined by HPLC-GPC and Mn of  $3.91 \times 10^5$ , Mw of  $7.59 \times 10^5$ . This gum dissolved in cold and hot water, but insoluble in alcohols, acetone, chloroform, ethyl acetate and hydrocarbons.

**Keywords:** *Elaeagnus* L. Gum; Polysaccharides; Physicochemical Parameters

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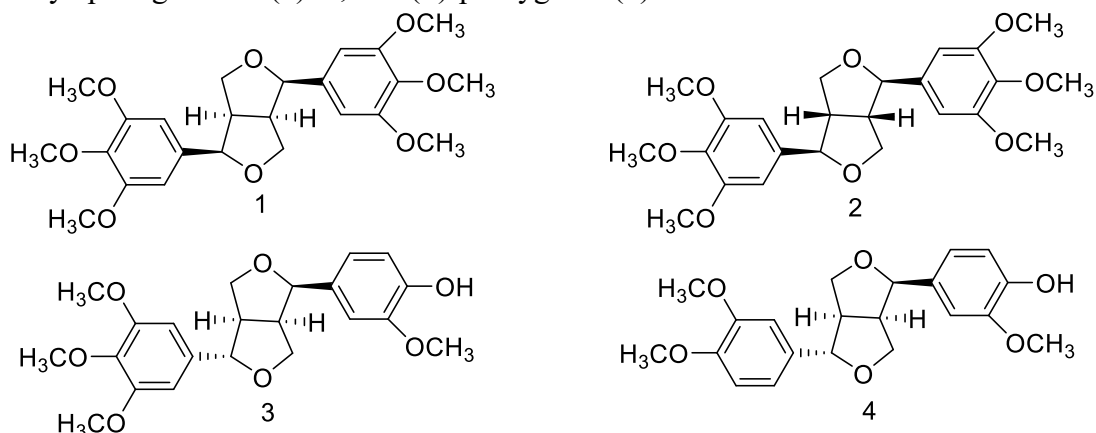
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CHEMICAL CONSTITUENTS OF *Artemisia sieversiana*M. Nuermaiti<sup>1,2</sup>, A. Turak<sup>1</sup>, H. A. Aisa<sup>1,\*</sup>

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*Artemisia sieversiana* Ehrhart ex willd., one of the widespread *Artemisia* species in China, is an annual or biennial herb, widely distributed in Qinghai, Gansu, Ningxia and Sichuan provinces. It is a traditional Chinese medicine which have been used as antimicrobial agents for nearly a thousand years [1]. In this study, four lignans were isolated from the chloroform part of 95% extract of the *A. sieversiana*, using silica gel chromatography, Sephadex LH-20, pre-HPLC methods. Their structures were elucidated as Diyangambin (**1**) [2], Syringaresinol Dimethyl Ether (**2**) [3], (+)-De-*O*-methylepimagnolin A (**3**) [4], and (+)-phillygenin (**4**) [5].



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## COMPARISON OF DIFFERENT EXTRACTION METHODS OF PECTIN FROM *Orchis chusua* D. Don (salep)

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*Orchis chusua* D. Don (salep) is the dried tubers belonging to the orchid family. For thousands of years, it has been used as a source of medicine to the treatment of various diseases <sup>[1,2]</sup>. Pectin, an important class of plant polysaccharide, is widely used in the food industry as a gelling agent in the production of jams, jellies and dairy products. Pectin is also used in the pharmaceutical industry, suggested reducing heart disease and gallstones. At present, a variety of advanced technologies have been applied to pectin extraction. Each extraction method has its advantages and disadvantages. In this research, hydrochloric acid extraction and citric acid extraction were carried out to extract the pectin from the salep residue after water extraction. The results revealed that citric acid extraction manifested a yield of 32.2%, higher than hydrochloric acid extraction 2.1%. Then citric acid was used as solvent to compare ultrasonic assisted extraction with traditional extraction, showing that the yield of ultrasonic assisted extraction increased from 32.2 to 42.5%, and saved nearly half the time. This research demonstrated that the ultrasonic-assisted extraction by citric acid was suitable for pectin extraction from salep residue.

### ACKNOWLEDGMENTS

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## FATTY ACID COMPOSITIONS AND BIOLOGICAL ACTIVITIES FROM THE SEEDS OF *Amaranthus caudatus* L.

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*Amaranthus caudatus* L. (ACL), a member of the Amaranthaceae family and native to the tropics, cultivated throughout the world. According to Chinese herbal medicine collection, it's used for nourish and strengthens, dizziness, weakness of limbs and infantile malnutrition. Till now, the fatty acid composition of this plant has not been studied yet. Therefore, the aim of this work was the investigation of the fatty acid composition of this medicinal plant, to discover new bioactive compounds. The fatty acid was extracted by petroleum ether from the seeds of ACL, and identified by gas chromatography and mass spectrometry (GC-MS). The antibacterial activities of obtained fatty acids were determined by using *Escherichia coli*, *Candida albicans*, *Bacillus subtilis* and *Staphylococcus aureus* as test bacteria.

The results showed that linoleic acid (61.40%) was the dominant component, followed by oleic acid (21.40%). The IR spectrum displayed typical absorption peaks of fatty acids in the range of 4000-500 cm<sup>-1</sup>. Meanwhile, bioactivity tests revealed that obtained fatty acids demonstrated antibacterial activities against pathogenic *Escherichia coli*, *Candida albicans*, *Bacillus subtilis*, and *Staphylococcus aureus*, with the strongest inhibition effect against *Staphylococcus aureus*. Also, all these results support the herbal uses of the treatment of nourish, dizziness, weakness of limbs and infantile malnutrition for *Amaranthus caudatus* L.

TABLE 1. The Fatty Acid Compositions of *Amaranthus caudatus* L.

Fatty acids	Molecular Formula	Quantity(%)
15: 1 7-Hexadecenoic acid,	C <sub>16</sub> H <sub>30</sub> O <sub>2</sub>	0.04
15: 0 palmitic acid	C <sub>16</sub> H <sub>32</sub> O <sub>2</sub>	14.10
16: 0 Heptadecanoic acid	C <sub>17</sub> H <sub>34</sub> O <sub>2</sub>	0.01
17: 2 linoleic acid	C <sub>18</sub> H <sub>32</sub> O <sub>2</sub>	61.40
17: 1 Oleic acid	C <sub>18</sub> H <sub>34</sub> O <sub>2</sub>	21.40
17: 0 Octadecanoic acid	C <sub>18</sub> H <sub>36</sub> O <sub>2</sub>	2.14
17: 1 Oleic acid	C <sub>18</sub> H <sub>34</sub> O <sub>2</sub>	0.56
19: 0 arachidic acid	C <sub>20</sub> H <sub>40</sub> O <sub>2</sub>	0.09
19: 1 cis-11-Eicosenoic acid	C <sub>20</sub> H <sub>38</sub> O <sub>2</sub>	0.10
Saturated		16.34
Unsaturated		83.50

### ACKNOWLEDGMENTS

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## BIOLOGICALLY ACTIVE SECONDARY METABOLITES OF *Artemisia juncea*

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*Artemisia juncea* Kar. et Kir. is a widespread species of sagebrush in Uzbekistan belonging to *Artemisia* genus *Seriphidium* subgenus section *Junceum*. In folk medicine, herbal infusion is used for epilepsy, typhus, fevers, kidney diseases, as well as anti-inflammatory and anthelmintic, and oil infusion of grass is taken for asthma, dropsy, seizures.

As a result of our phytochemical research of the aerial parts of *Artemisia juncea*, growing in Uzbekistan, the following metabolites were first isolated: **monoterpenoids** (major) -  $\alpha$ - and  $\beta$ -thujone, 1,8-cineole, camphor; **sesquiterpene lactones** - leucomisin (**1**), ausricin (**2**); **triterpenoids** -  $\beta$ -sitosterol (**3**), stigmasterol (**4**); the **flavonoids** – cynaroside (**5**), jaceosidin (**6**), eupatilin (**7**), 4',5-dihydroxy-3',5',6-trimethoxyflavone-7-*O*- $\beta$ -D-glucoside (**8**), 5,6,4'-trihydroxy-3',5'-dimethoxyflavone-7-*O*- $\beta$ -D-glucopyranoside (**9**), of which flavonoids **8** and **9** were new.

**Biological activity of isolated metabolites.** 1,8-Cineol has anti-inflammatory, analgesic and antifungal properties. Camphor – analeptic and cardiogenic agent.  $\alpha$ -Thujone has strong stimulating effect on the Central nervous system,  $\beta$ -thujone has spasmolytic effect. 1,8-Cineole,  $\alpha$ - and  $\beta$ -thujone shows antibacterial properties.

$\beta$ -Sitosterol (**3**) shows gypoholesterinemic and hepatoprotective actions, and plays a structural role in the composition of cell membranes of plants. Sterols **3** and **4** serve as starting materials for the industrial synthesis of steroid hormones and hormonal preparations.

Sesquiterpene lactones **1** and **2** have angioprotective and hypolipidemic actions. Based on **1**, an anti-atherosclerotic drug "Oligvon" is created, antiatherosclerotic activity of which exceeds anginin (Japan), prodektin (Hungary), pravastatin (USA).

Flavonoid cynaroside (**5**) - hypoazotemic drug, which action exceeds the drug lespenefril (France). Compounds **6** and **7** have antitumor and antioxidant effects. Compound **7** also has antifungal, anti-inflammatory, antimutagenic activity and antidiabetic effect. New flavonoids **8** and **9** exhibit antioxidant and enzyme inhibitory activity.

Thus, phytochemical studies have shown that the widespread practice in folk medicine of the ariel part of *Artemisia juncea* is due to the presence of the above mentioned biologically active secondary metabolites.



## NEW ECDYSTEROIDS AND LIGNAN GLYCOSIDES FROM *Rhaponticum uniflorum* (COMPOSITAE)

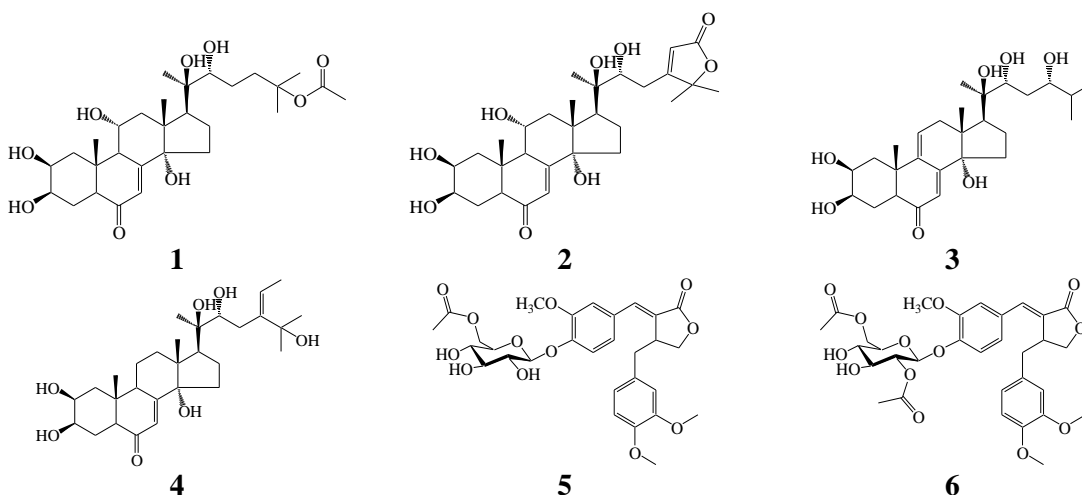
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*Rhaponticum uniflorum* (L.) DC. is a famous medicinal plant of Chinese, Mongolian and Tibetan Traditional Medicines. Previous data of chemical components of *R. uniflorum* collected in the Baikal region showed the presence of ecdysteroids, sesquiterpenes, polysaccharides, and flavonoids in leaves (Olennikov, 2018; Olennikov, Kashchenko, 2019). Continuing the thematic research intended to a better understanding of *R. uniflorum* chemodiversity, we studied secondary metabolites of roots and seeds.

As a result of chromatographic separation of methanolic extract of *R. uniflorum* roots, fifteen known compounds were isolated as well as four new ecdysteroids (**1–4**) and their structures were identified based on UV, IR, NMR, and mass spectrometry as turkesterone-25-*O*-acetate (**1**), rhapunisterone (**2**), 11-desoxyrhapontisterone (**3**) and 24(28)-dehydromakisterone C (**4**). The interesting thing was a detection of compound **2** with dehydrofurane lactone cycle at C-25 atom close to known carthamosterone (Girault et al., 1988) and rhapontisterone R1 (Li et al., 1998) found in *Rhaponticum* genus.

The seeds of *R. uniflorum* were also found as a source of ecdysteroids like 20-hydroxyecdysone (up to 2.7% of seed endosperm dry weight) and 2-desoxy-20-hydroxyecdysone. Phenolic components were the various hydroxycinnamates, flavonoids, serotonin derivatives and lignans including two new lignan glycosides **5** and **6**. The latter compounds were carthamoside (carthamogenin 4-*O*- $\beta$ -D-glucoside) derivatives with followed structures as carthamoside-6''-*O*-acetate (**5**) and carthamoside-2'',6''-di-*O*-acetate (**6**). Isoferuloyl serotonin and cartamogenin showed high inhibitory activity against pancreatic  $\alpha$ -amylase.



### ACKNOWLEDGEMENTS

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## FUNCTIONAL PROPERTIES OF SERICIN AND SERICIN HYDROLYSATES ACHIEVED BY TRYPSIN HYDROLYSIS

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Sericin was abundant in serine, aspartic acid, threonine, and glycine, containing some essential amino acids, therefore sericin and sericin hydrolysates might be used as multifunctional and nutritive ingredients in food industry. To investigate the relations between hydrolysis characteristics and functionalities, sericin obtained by autoclave method from cocoon was hydrolyzed by trypsin. Furthermore, functional properties of hydrolysates (DH: 3.59, 4.58, 5.23, 6.05, 7.03, and 7.35%) were evaluated. The results showed that sericin hydrolysates with different degree of hydrolysis had different functional properties compared with sericin. Though, solubility of sericin hydrolysates improved significantly, gelation property, water-holding capacity (WHC), oil-holding capacity(OHC) decreased with the increase of degree of hydrolysis. The minimum gelation concentration of sericin was 25 mg/mL, however, the minimum gelation concentration of sericin hydrolysates varied from 80-90 mg/mL. The values of WHC (12.47 g/g) and OHC (19.00 mL/g) of sericin were significantly higher than sericin hydrolysates. According to the protein solubility profile of sericin and sericin hydrolysates, all hydrolysates showed relatively flat curve without obvious isoelectric points, however sericin showed U-shaped profile across the pH range from 2.0 to 10.0. More detailed studies on the sericin and sericin hydrolysates will be reported later.

## **PROPERTIES OF ANTIHELMINTH PREPARATIONS OBTAINED BY MODIFICATION OF THEIR SUBSTANCES BY POLYSACCHARIDES**

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Considering the main and most effective link in the fight against animal helminthiasis is deworming using anthelmintic drugs of various chemical nature, the development and research of new anthelmintic agents remain one of the urgent problems of veterinary medicine. This position is also important because helminths, like other biological objects - parasites, microorganisms, etc., are characterized by adaptation to the action of certain drugs, including anthelmintics, which suggests the need for a systematic update and expansion of the anthelmintic arsenal.

At present, a number of highly effective, low-toxic benzimidazole drugs (including albendazole, fenbendazole, mebendazole, etc.) with a wide spectrum of anthelmintic action have been developed and are widely used in veterinary practice. One of the disadvantages of these drugs is their low solubility in water and physiological environments of their substances, which does not allow their effective use, namely, part of the drug is excreted from the body before it dissolves and exhibits the necessary biological effect. Along with economic aspects, environmental problems arise with environmental damage.

To improve the solubility and bioavailability of such drugs, we are conducting research on the development of drugs in a series of benzimidazole drugs by mechanochemical modification of their substances with plant metabolites (polysaccharides).

The aim of the work was to conduct research, including the development, improvement and study of the anthelmintic activity of innovative benzimidazole drugs (albendazole, fenbendazole) obtained by mechanochemical modification using polysaccharides such as arabinogalactan and chitosan.

According to the results of the studies, it was found that the solubility of drugs based on albendazole increased by 20 times, fenbendazole by 14 times, which suggested an increase in anthelmintic action. Test data of anthelmintic activity showed that preparations at a dose of 5 mg / kg had a rather high anthelmintic effect on the main, most widespread, helminths of sheep (marshallagia, nematodiruses, other gastrointestinal strongilates, moniesia and fascioli) and they could be recommended for use in veterinary practice.

**EVALUATION OF *Stachys anamurensis* AND *S. euadenia*  
POTENTIAL EFFECTS ON OXIDATIVE DAMAGE,  $\alpha$ -AMYLASE,  
LIPOXYGENASE, XANTHINE OXIDASE AND TYROSINASE  
ENZYMES**

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The chemical profiles of the volatile and non-volatile metabolites of *Stachys anamurensis* Sümbül and *S. euadenia* P.H. Davis (Lamiaceae) were investigated with GC-FID/MS and LC-MS/MS techniques. The essential oil yields were calculated as 0.05% and 0.02%, respectively (on dry plant basis). The methanol extracts from both plants were obtained by maceration method and the yields were determined as 9.1% and 11.3%. Fatty Acid Extraction Kit was used for extraction of fixed fatty acids. Boron trifluoride methanol solution was used for the methylation of free fatty acids.

The oil of *S. anamurensis* was characterized with  $\beta$ -eudesmol (43.0%) as major constituent, while the oil of *S. euadenia* contained  $\beta$ -eudesmol (26.5%), linalool (10.8%), linalyl acetate (9.5%), 8,12-epoxy-13-hydroxy-labd-14-ene (8.0%) and  $\alpha$ -eudesmol (7.5%) as main constituents. Phenolic constituents, verbascoside, 4'-O-methylisoscutearein 7-O-allosyl(1 $\rightarrow$ 2)glucoside, 4'-O-methylisoscutearein-7-O-[6''-acetylallosyl(1 $\rightarrow$ 2)]glucopyranoside, dihydroxy-trimethoxy flavone were detected in the methanol extracts. The methanol extracts of *S. anamurensis* and *S. euadenia* showed free radical scavenging effects with IC<sub>50</sub> 0.30 and 0.34 mg/mL and TEAC 0.35 and 0.57 mM, respectively. Inhibitory effects on  $\alpha$ -amylase expressed as acarbose equivalent mg/mL were found as 0.46 and 0.38. Antityrosinase activity (Inh. 46% and 32%) and anti-XOD activity (30% and 31%) were detected. The extracts weakly inhibited peroxidation of lipids in LOX test (Inh. 19% and 18%), while the essential oils of *S. anamurensis* and *S. euadenia* noteworthily inhibited LOX enzyme (46% and 29%).

**Keywords:** *Stachys*, Lamiaceae, essential oil, extract, LOX, XOD,  $\alpha$ -amylase, tyrosinase.

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## ANALYSIS OF BIOLOGICAL ACTIVITIES IN THE CYANOBACTERIUM *Spirulina platensis*

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*Spirulina* is a multicellular cyanoacterium well-known for its nutritive values. It has been certified by the Food and Drug Administration (FDA) and generally recognized as safe (GRAS), thus assuring its safety for human consumption. There are many reports on the health benefits of *Spirulina*. This study was carried out to evaluate several therapeutic potential of the extracts of this organism. Initially the antidiabetic property was checked using the extent of inhibition of alpha-amylase enzyme. The extract of *Spirulina platensis* was also incubated with the *in vitro* glycation system consisting of sugar and protein. The amount of glycation products in the presence/absence of *Spirulina* extracts were measured by established methods like NBT assay, carbonyl content, Thioflavin T assays and total AGEs. The DNA damage induced by glycation was also checked by agarose gel electrophoresis. The antioxidant potential was checked using DPPH and FRAP methods. The antityrosinase activity was also checked using standard substrate and compared with other traditional creams. The results obtained with alpha-amylase inhibition indicate that the *Spirulina* extracts had significant antidiabetic potential. The significant decrease in the amount of glycation in the presence of *Spirulina* extract also suggested the antiglycating potential of phytochemicals present in this organism. It also possessed significant antityrosinase activity. These results indicated the significance for antidiabetic and antiglycating potential of the extract of *Spirulina platensis*. Further characterization will help in the identification of active constituent from *Spirulina* which can be used for the prevention of Diabetes.

## CHEMICAL CONSTITUENTS AND BIOLOGICAL ACTIVITIES OF THE LEAVES OF *Apocynum venetum* L.

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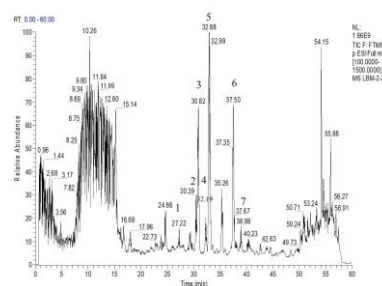
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*Apocynum venetum* L. (Apocynaceae family), a natural medicinal plant, is widely distributed in Xinjiang of China, where its leaves have been used as an anti-oxidation and hepatoprotection, for the treatment of cardiocerebrovascular diseases, hypertension, depressant, nephritis and other diseases.

The effective extract of *A. venetum* leaves (AVL) obtained by 50% ethanol extraction and purification, showed strong scavenging activity and protein tyrosine phosphatase 1B (PTP1B), aldose reductase (AR) and  $\alpha$ -glucosidase (GAA) inhibitions in vitro. IC<sub>50</sub> of DPPH, ABTS, PTP1B, AR and GAA were  $7.54 \pm 0.67 \mu\text{g/mL}$ ,  $15.23 \pm 1.31 \mu\text{g/mL}$ ,  $0.12 \pm 0.01 \mu\text{g/mL}$ ,  $17.38 \pm 0.15 \mu\text{g/mL}$  and  $9.96 \pm 0.87 \mu\text{g/mL}$ , respectively. Those results suggested that it might have anti-diabetes activity.

HPLC analysis was performed with an Ultimate 3000 Binary RSLC system on a Shim-pack GIS C18 ( $4.6 \times 250 \text{ mm}$ ,  $5 \mu\text{m}$ ). The solvent system consisted of solvent A (0.1% HCOOH) and solvent B (MeCN) with a linear gradient (0 min 10% B, 15 min 15% B, 30 min 22% B, 45 min 30% B, 55 min 100% B) at a flow rate of 1.0 mL/min. Mass spectrometry was carried out using a Q Exactive mass spectrometer with a highly sensitive heat electrospray ionization probe. Data acquisition was performed in data-dependent acquisition (DDA) mode with MS1 scan range  $m/z$  100 to 1500. The instrument was controlled by Xcalibur 4.0. AVL was identified by liquid chromatography tandem mass spectrometry (LC-MS/MS), the main chemical components were Quercetagenin glycoside (**1**), Quercetin glucosyl-rhmanoside (**2**, **3**), Quercetin glucoside (**4**), Quercetin glucuronic acid (**5**) and Quercetin glucuronic acid ethyl esters (**6**, **7**). Such studies will offer credible data for the pharmacological research on AVL.

No	Rt (min)	Exact mass ( $m/z$ ) [M - H] <sup>-</sup>	Molecular formula	MS <sup>2</sup> data ( $m/z$ )
1	27.22	479.08365	C <sub>21</sub> H <sub>20</sub> O <sub>13</sub>	316, 287, 271, 259, 227, 151
2	30.39	609.14691	C <sub>27</sub> H <sub>30</sub> O <sub>16</sub>	300, 271, 255, 243, 227, 151
3	30.82	609.14667	C <sub>27</sub> H <sub>30</sub> O <sub>16</sub>	300, 271, 255, 243, 227, 151
4	32.19	463.08887	C <sub>21</sub> H <sub>20</sub> O <sub>12</sub>	301, 300, 271, 255, 243, 227, 151
5	32.88	477.06812	C <sub>21</sub> H <sub>18</sub> O <sub>13</sub>	301, 255, 227, 151, 107
6	37.50	505.09937	C <sub>23</sub> H <sub>22</sub> O <sub>13</sub>	301, 300, 271, 255, 243, 227, 178, 151
7	38.88	505.09961	C <sub>23</sub> H <sub>22</sub> O <sub>13</sub>	301, 300, 271, 255, 243, 178, 227



### ACKNOWLEDGEMENTS

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## FEATURES OF FATTY-ACID COMPOSITION OF OIL OF FLAX SEEDS “BAHORIKOR” AND “BAKHMAL-2”

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It is known that determination of the chemical composition of plants is of great help to specialists in their identification. This is especially valuable for seed breeders. Varietal seeds must have clearly defined features of their chemical composition.

Sorts “Bahorikor” and “Bakhmal-2” are listed in the State Register, recommended as the most suitable varieties for growing flax cures in our republic, and these seeds are widely distributed in the distribution network.

When developing agrotechnical measures for farms, when drawing up research programs to improve the agrotechnics of drawing flax curls in order to increase the seed yield and improve its quality, it is necessary to know exactly the type of seeds purchased. Flax seeds – small curls, whose grade cannot be visually determined.

The content of the oil in the seeds was determined in a Sokslet apparatus. Lipid extraction was carried out by extraction with petrol (bp. 72-80 °C) for 15-18 hours. Hydrolysis of oil, release of fatty acids, their methylation was carried out according to conventional techniques. Identification of their methyl esters was carried out on the Agilent 6890N Gas chromatography (GC).

Determination of the fatty acid composition of the oil of flaxseed seeds of the sorts “Bahorikor” and “Bakhmal-2” showed clear differences in the content of certain fatty acids, which persist even with the application of mineral nitrogen, phosphoric and potassium fertilizers.

The seeds of the “Bahorikor” variety contain myristic, pentadecanoic, palmitoleic, margaric, arachinic, behenic and lignoceric acids in “trace” amounts.

In the seeds of the “Bakhmal-2” variety, the content of myristic acid was 0.06%, pentadecanoic - 0.02%, palmitoleic - 0.16%, margarine - 0,16%, arachinic - 0.21%, behenic- 0.13%, and lignoceric acids- 0.09%.

The increase in the content of these acids in the sort ”Bakhmal-2”relative to the sort “Bahorikor” is associated with a decrease in the content of palmitic acid from 7.24 % (sort “Bahorikor”) to 6.83 % (sort “Bakhmal-2”), and with a decrease linoleic acid content from 14. 81 % (sort “Bahorikor”) to 13.83% (sort “Bakhmal-2”).

It is irreplaceable to note that the content of the sum of unsaturated fatty acids in both varieties of curly flax turned out to be almost the same: 87.47% in the sort “Bahorikor” and 86.74% in the sort “Bakhmal-2”.

Oil content of seeds on absolutely dry matter of both varieties was 40.6% and 41.9%, respectively.

## SCREENING OF NATURAL STRAINS OF MYCELIAL FUNGI FOR THE BIOSYNTHESIS OF CITRIC ACID

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Citric acid (CA) is used in the food, pharmaceutical, electronic, radio engineering, oil and gas industries. In addition, it is currently part of detergents, for example, instead of polyphosphates hazardous to the environment, sodium citrate is used as part of washing detergent mixtures. Representatives of the genus *Aspergillus*, in particular *A. niger*, *A. oryzae* and others are the most important producers for commercial use, since they are capable of producing large quantities and a wide range of low molecular weight organic acids, including CA. Currently, food citric acid in Uzbekistan is widely represented by foreign companies. In this regard, obtaining a highly effective local strain of the producer of LA acquires not only scientific, but also commercial importance.

The aim of this work is to screen natural strains of mycelial fungi for the biosynthesis of CA. From various substrates 63 strains of mycelial fungi were isolated. The initial assessment of the acid-forming ability of these strains was carried out on an agar plate containing calcium carbonate (quality screening). It was established that among the studied strains of fungi, 5 strains did not show any zone of dissolution of chalk on the agar plate test. The highest zone of dissolution of chalk was only observed in 10 strains, where the zone of dissolution of chalk varied from 5.0 to 7.1 mm. As a result of screening on a medium with chalk, 16 strains of microscopic fungi were selected. In order to quantitatively determine the CA, as well as to verify the results obtained by selection on a solid medium, the selected strains were cultured in a liquid nutrient medium with sucrose. It was found that the selected strains were able to synthesize LA when cultured on the liquid nutrient medium. Among them, 4 strains possessed a high acid-forming ability, where the content of CA varied from 4.2 to 14.2 g/L.

Thus, on the basis of screening for the biosynthesis of CA by natural strains of mycelial fungi, 4 strains were selected for further studies.

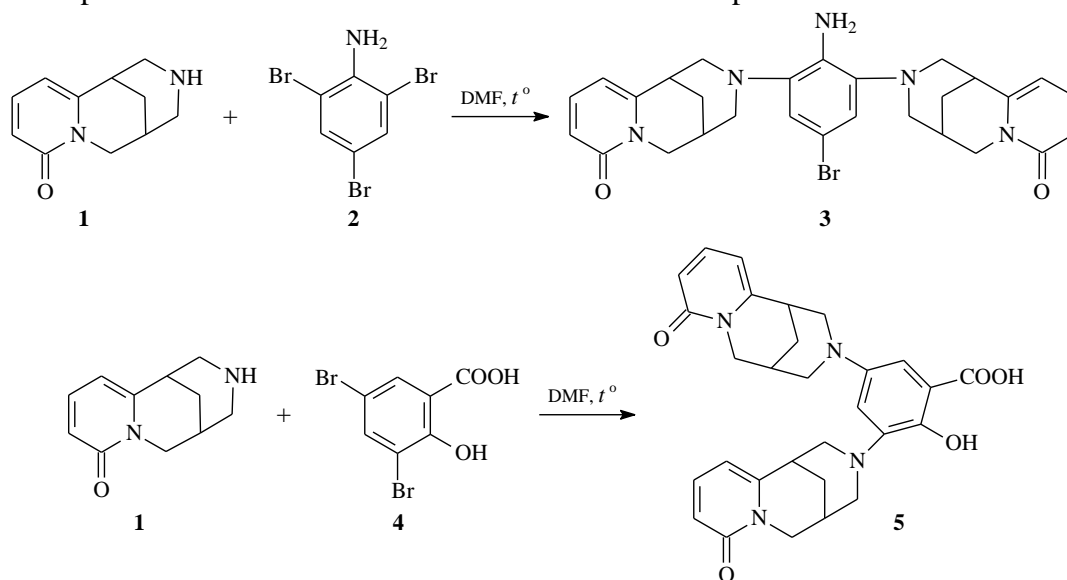


## SYNTHESIS OF DICYTIZIL SUBSTITUTED OF ARYLS

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In order to search for new biologically active substances, we studied the amination reaction of bromine derivatives of aryls with cytisine (**1**). It was established that the amination of compounds **2** and **4** in the condensation reaction with cytisine, taken in molar amounts in DMF by heating and stirring, gave two amine derivatives of aryls **3** and **5**. Spectral data showed that **3** and **5** were dimeric compounds.



## **PREPARATION AND PURIFICATION OF PAPAYA ENZYMES AND ALBUMIN FRACTION OF CORN GRAIN**

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One of the most promising ways to intensify the extraction of plant raw materials is the use of ultrasound, with the plants which can afford physiologically active compounds. When processing fine materials, the accelerating effect of ultrasound extends to almost the entire volume of particles of the material from which the extraction is made. The use of ultrasound is carried out in order to intensify the extraction process of biologically active compounds and increase their content in the solution. Technology for producing papaya enzyme and albumin fractions from corn using ultrasound has been developed. The possibility of application at the first technological stage of ultrasonic processing (RCD), in order to intensify the extraction process. Use of an RCD for carrying out extraction allows to reduce extraction time and thereby improve the performance of a process without changes of proteolytic activity in protein-component composition and structure of protein molecules of the substance of the drug Kukumazim. To increase the yield and purification of papaya enzymes, the extract was precipitated at different concentrations with ammonium sulfate. According to the results of 80% deposition of ammonium sulfate, a relatively high yield of the enzyme complex and albumin fraction from the extract were obtained. To clarify the effect of ultrasonic treatment on the structure and biological properties of the complex of enzymes of papaya and albumin fraction of corn grain, we conducted a comparative study of amino acid composition, proteolytic activity, electrophoretic analysis in PAAG, IR spectral analysis, HPLC, and obtained scanning electron microscopy (SEM) data.

Thus, the use of RCD in the extraction of papaya latex and albumin fraction of corn can significantly reduce the extraction time and thereby increase the productivity of the process without changes in proteolytic activity in the protein-component composition and structure of protein molecules.

## PROPERTIES, STRUCTURE, AND BIOLOGICAL ACTIVITY OF GALACTOMANNANES AND ARABINO GALACTANES OF PLANTS GROWING IN UZBEKISTAN

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Currently, the search for new highly effective, low-toxic biologically active preparations from available natural sources is relevant. The most recognized substances were polysaccharides -galactomannans and arabinogalactans, since they do not have toxicity, allergenicity, or pyrogenicity. The search for new competitive biologically active compounds among plant polysaccharides, determining their structural features and studying the structure-activity relationship and finding ways to use them is an urgent task. The aim of this study was to isolate and study the structure of galactomannans and arabinogalactans of promising plants in the local region, and to study the relationship in the system "properties-structure-biological activity". We studied galactomannans from plants of the family Fabaceae (*Gleditsia*, *Crotalaria alata*, *Astragalus*, etc.) introduced in Uzbekistan, examined the influence of soil and climatic conditions on the content and composition of polysaccharides. It was established that the content of WSPS and the Gal: Man ratio in galactomannans depended on the place of growth and GM as markers.

The structure of galactomannans of *G. triacanthos*, *C. alata* was established, showing that the main polymer chain consisted of  $\rightarrow 4) -\beta\text{-Manp-}(1 \rightarrow$  residues, some of which were replaced by C-6 residues of  $\alpha\text{-Galp}$ . Average chain length  $\rightarrow 4) -\beta\text{-Manp-}(1 \rightarrow$  was approximately 100 units. The distinctive side was the different sequence of galactose residues of the side chain of galactomannans, which affected biological activity. In galactomannan *C. alata*, one side chain had three residues of mannose, and in galactomannan *Gleditsia* - on two residues. These data affected the bioactivity of polysaccharides. In a comparative study of the hypocholesterolemic and hypoglycemic activity of GM, it was found that GM *Gleditsia* had a rather noticeable hypoglycemic effect in animals with alloxan hyperglycemia and diabetes, eliminating the toxic effect of alloxan on the body. It was established that GM *Gleditsia* had the property of precipitating peripheral blood lymphocytes, unobserved in the case of GM *C. alata*, making it possible to create, on its basis, the import-substituting reagent "gledol" in immunodiagnostics.

Due to the significant content in higher plants and the unique properties of arabinogalactans (AG), they occupy a special place after galactomannans among plant polysaccharides. Arabinogalactans was isolated from the aerial parts of this Apiaceae plants and it was found that the main chain of AG was a polygalactan core with 1.6 and 1.3 types of bonds and their prebiotic activity was revealed.

## COMPONENTS OF EXTRACTIVE MATERIALS OF CULTURED *Alcea rosea*

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The family of Malvaceae is very extensive, with more than 80 genera and more than 1500-1600 species, their representatives *Alcea nudiflora* L. (Stem rose) and *Alcea rosea* L - terry stem (leafy) are biennial or perennial honey plants producing honey, common in Eastern Europe, Western Ukraine, the Caucasus, Central Russia and Central Asia. *Alcea* is a medicinal plant and is used in medicine as a moisturizer and as a sedative in diseases of the upper respiratory tract, gastritis, hemorrhoids, pancreatitis and skin diseases<sup>[1, 2]</sup>.

*Alcea rosea*'s country is Caucasus and it is cultivated in our republic as well. Although cultivated *Alcea rosea* - "rosea" means pink, but in appearance it refers to roses. It is cultivated in Uzbekistan as an ornamental plant. It is known that all parts of the plant - the root, stem, leaf store mucus and carbohydrates<sup>[3]</sup>. Plants of the Malvaceae family differ from deciduous plants by the abundance of polyphenols above the ground. Accordingly, continuing to study the polyisoprenoids of plants of this family, we selected two varieties of cultivated *Alcea rosea* L.: pink terry (I) and dark red terry (II).

When determining neutral substances from the leaves of this plant, we used the method of ultrasonic extraction. As a result, we found that the amount of neutral substances relative to the dry weight of the plant was: (I) from 4.7 to 5.8% and (II) from 4.4 to 5.3%. Using column chromatography, PP fractions (polyprenols) were isolated from their composition. In case (I), the yield of polyprenols was 2.60%, and in case (II) it was 2.36%.

The homological composition of polyrenols of the plant *Alcea rosea* was studied by high performance liquid chromatography (HPLC) and contained 9-13 isoprene units, among which undecaprenol and dodecaprenol dominated. In addition to *Alcea nudiflora* polyprenols, no isoprene units were found in the leaves of *Alcea rosea* n = 8, 14, and this plant serves as a raw material for medicines or biologically active additives.

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## NEOANGIOGENESIS AND ENDOTHELIAL DYSFUNCTION IN PATIENTS WITH ISCHEMIC STROKE ASSOCIATED WITH KIDNEY PATHOLOGY

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Ischemic stroke and chronic kidney disease (CKD) are the important global medical and social problems worldwide. Patients with CKD have a high risk of developing stroke, and its presence in stroke often worsens the course and prognosis of this acute cerebrovascular disease.

**The purpose of study:** The study of neoangiogenesis and endothelial dysfunction (ED) in patients with ischemic stroke (IS) associated with kidney pathology.

**Materials and Methods.** A prospective study included 78 patients admitted in the acutest and acute period of IS. Neurostatus was evaluated according to a generally accepted scheme. The diagnosis of kidney pathology and the stage of the disease were established in accordance with the classification NKF-KDOQI (2003, modification 2013). The pathogenetic role of ED and the process of neoangiogenesis were studied using nitroxide and endothelin-producing functions of the vascular endothelium (serum nitric oxide – NO, and endothelin-1 – ET-1), markers of the cholinergic system (serum acetylcholinesterase - ACE), and neoangiogenesis (vascular endothelial growth factor - VEGF) in patients with IS, depending on the presence of kidney pathology by immunofluorimetric and spectrophotometric methods.

**Results.** Studies have shown significant differences in the values of ED and angiogenesis markers in blood serum of patients with IS in acute period. The level of NO significantly decreased in 1.56 times, indicating pronounced violation of the dilated properties of the vascular wall. At the same time, the level of vasoconstrictor ET-1 increased statistically significantly in 4 times. The level of neuroangiogenesis factor VEGF A in serum increased statistically significantly in 1.4 times. The level of ACE in blood serum decreased in 1.25 times, indicating a deficiency of the cholinergic system in IS. Depending on the severity of IS, the levels of ED markers were unidirectional, depending on associated pathology, and did not reach the control values. The level of VEGF was somewhat controversial: increase in 37.6, 47.3 and 33.3 times, respectively, at mild, moderate and severe IS. Apparently, if the elevated level of ET-1 indicated its negative effect, then VEGF overexpression was a protective mechanism that was initially reduced in severe cases of stroke patients. Analysis of markers of ED and neoangiogenesis in patients with IS depending on the presence of kidney pathology showed the absence of statistically significant differences in the groups with and without renal diseases. Only there remained a statistically insignificantly increased ET-1 value and a decreased VEGF value in stroke patients associated with kidney pathology.

**Conclusion.** Thus, in example of nitroxide and endothelin-producing functions of vascular endothelium, cholinergic system marker and VEGF, it was proved the pathogenetic role of ED and neoangiogenesis process in IS patients, depending on pathogenetic subtypes, severity, age, gender, and presence of kidney pathology.

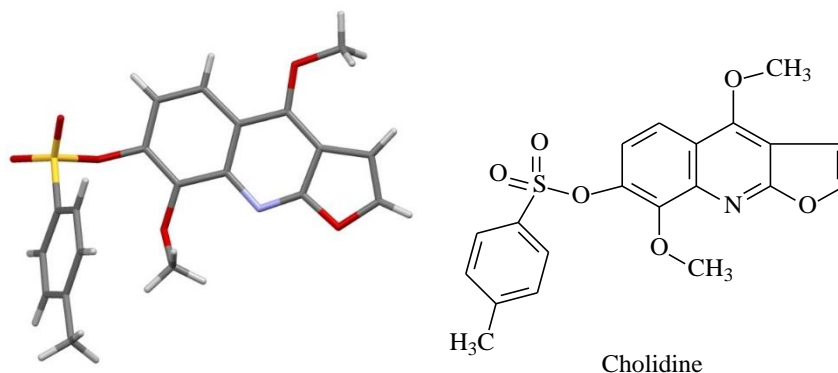
**STRUCTURE OF THE NEW ALKALOID OF CHOLIDINE****Kh. A. Rasulova, Z. Ch. Abrayeva, K. K. Turgunov**

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On the separating chloroform part of the roots of the plant *D. angustifolius* collected in Pskom during the drying period, the compound L, composition  $C_{20}H_{17}NO_6$  with m.p. 183 °C was isolated, which we called choline. The structure of cholidine was established on the basis of the analysis of the data of IR,  $^1H$  NMR spectra, as well as DEPT experiments.

The data obtained allow us to propose the compound L structure for the base, which was also confirmed by analysis of the  $^{13}C$  NMR and X-Ray spectra. In the  $^{13}C$  NMR spectrum of the base, the assignment of cholesterol signals of carbon atoms were carried out on the basis of the multiplicity of signals from the spectrum of compound L and haplopine, dictamine, evoxine, obtained under conditions of incomplete suppression of interactions with protons and by comparison with the literature data of cholesterol of furanoquinoline alkaloids.

Compound L belongs to the type of furanoquinoline and was firstly isolated from a plant. The structure of the compound L was confirmed by X-ray diffraction analysis. Compound L is the first quinoline type alkaloid containing sulfur.



Thus, the sulfur-containing quinoline alkaloid cholidine was isolated from the plant, which is the first representative of the Rutaceae family.

## ISOLATION AND IDENTIFICATION OF CULTIVABLE ENDOPHYTIC FUNGUS AND THEIR BIOLOGICAL ACTIVITIES

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Endophytic fungus symbiosis live inside plants and have been extensively researched in recent decades for their functions associated with plant responses to environmental stress. Endophytic fungus are one of the rich sources to produce bioactive natural metabolites from medicinal plants. In this study, fungal endophyte was isolated from freshly *Baccharoides (Vernonia) anthelmintica*. Pure fungus strains were identified by the 16S rRNA sequences, similar to species *Schizophyllum commune*, *Talaromyces sp*, *Aspergillus strain*, *Aspergillus terreus strain*. The ethyl acetate extract of fermentation of the fungal endophyte showed several biological activities, such as antimicrobial, vitiligo, antidiabetic, antioxidant, anticancer.

The antimicrobial tested fungus, *Aspergillus strain XJA6* exhibited strong (23 mm) antifungal activity against pathogens *Candida albicans*. *Aspergillus terreus strain XJA8* showed higher exhibited antifungal activity against *Candida albicans* (20 mm) and antibacterial against *Staphylococcus aureus*(16mm). *Aspergillus strain*, *Schizophyllum commune* and *Talaromyces sp* showed moderate growth inhibition against *Staphylococcus aureus* (11, 12, 11mm). But that endophytic fungus showed lowly exhibited *Escherichia coli* (8, 9.5, 9 mm). The effect of the crude ethyl acetate extract of endophytic fungus were evaluated for in vitro inhibition of the enzyme PTP-1B. The crude extract of fungal isolates *Aspergillus strain* and *Talaromyces sp* showed good effect on PTP-1B inhibition with IC<sub>50</sub> value of 5.662±1.099, 4.789±1.222, respectively. The *Aspergillus terreus strain Schizophyllum commune* extract inhibited antidiabetic activity with moderate IC<sub>50</sub> 23.439±0.734, 11.964±0.484, respectively.

The crud extract of endophytic fungus were determined against the following human cancer lines: HT-29 (colon cancer), MDA-MB-231 (breast cancer), Hela (cervical cancer) by MTT assay method. The positive control used potent anticancer drug as doxorubicin (DOX). When tested on Hela (cervical cancer), HT-29 (colon cancer) endophytic fungus as *Aspergillus strain XJA6* and *Aspergillus terreus strain XJA8* showed strong activity, with IC<sub>50</sub> 9.99±0.8 and 5.73±0.6 μM. IC<sub>50</sub> values of *Aspergillus strain XJA6*, *Talaromyces sp XJA4* against colon cancer cell HT-29 were 19.31±0.8, 90.43±0.01 μM. Only *Schizophyllum commune XJA1* displayed no activity. When screening on breast cancer cell, *Aspergillus strain XJA6* and *Aspergillus terreus strain XJA8* showed moderate IC<sub>50</sub> 33.55±0.1 and 56.3±0.6 μM. IC<sub>50</sub> of *Aspergillus terreus strain XJA8*, *Talaromyces sp XJA4*, *Schizophyllum commune XJA1* on Hela (cervical cancer) cell were 24.69±0.2, 85.46±0.3, 89.8±0.4 μM respectively. The antioxidant capacities of crude extracts of endophytic fungus in 0.005 mg/mL concentrations were evaluated by the most commonly used antioxidant assays: DPPH method. *Schizophyllum commune XJA1* extract showed moderate activity with IC<sub>50</sub> 55.21±0.3 μg/mL. *Talaromyces sp XJA4* and *Aspergillus terreus strain XJA8* extracts showed lowly inhibitions with IC<sub>50</sub> 171.78±8.06, 215.838±7.25 μg/mL, respectively. Extract of *Aspergillus strain XJA6* displayed no activity.

## NOVEL PYRAZOLO[3,4-*d*]PYRIMIDIN-4-ONES AS ANALOGUES OF THE QUINAZOLINONE ALKALOIDS

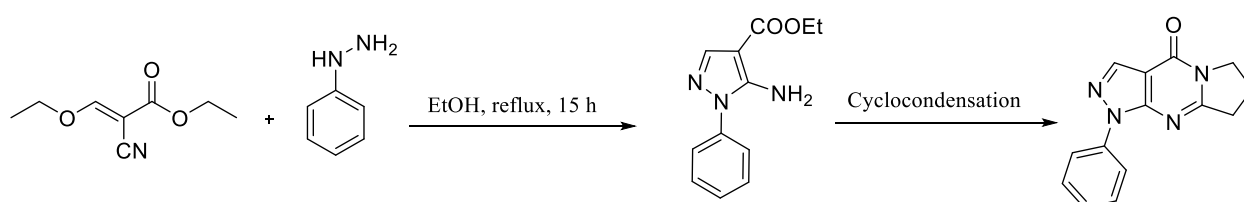
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Heterocyclic compounds are significant part of both organic and medicinal chemistry research. A lot of the commercially available drugs are built on heterocyclic scaffolds and these scaffolds are core part of the drugs responsible for desired pharmacological activity. An annelated heterocyclic products have important roles in bio-processes, as well as present in a wide variety of drugs, antibiotics, vitamins, natural products and other biomolecules. Besides, N-bearing annelated heterocycles have gained a substantial attention and occur in a variety of bioactive natural products, pharmaceuticals, organic materials, dyes and agrochemicals. Among these N-annelated heterocycles, pyrazolopyrimidine is one of the attractive fused heterocyclic moiety owing to its synthesis and immense pharmacological importance. Pyrazolo[3,4-*d*]pyrimidin-4-one is a tricyclic quinazolinone type heterocyclic alkaloids, considered as privileged ring system in biologically active compounds. A broad spectrum of biological potentials impart in diversely substituted pyrazolo[3,4-*d*]pyrimidin-4-ones, which are exemplified as diverse biological relevant agents. In this regard, we have provided novel 1-phenyl-1,6,7,8-tetrahydro-4*H*-pyrazolo[3,4-*d*]pyrrolo[1,2-*a*]pyrimidin-4-one skeleton.



Present reaction have opened the door for the discovery of novel drug candidates and other target activities based tricyclic pyrazolo[3,4-*d*]pyrimidin-4-one scaffolds.



**NEW ANTI-ARITHMIC DRUG FROM WASTE OF PRODUCTION  
OF SUBSTANCE OF PREPARATION ALLAPININ OBTAINED  
FROM RHIZOME WITH ROOTS OF *Aconitum septentrionale***

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It is known that for many years a medicinal drug having antiarrhythmic action, allapinin, obtained from rhizomes with roots of *Aconitum septentrionale*, has been produced and widely used in medical practice. For the production of the drug using plant raw material growing on the territory of the Russian Federation, Kazakhstan, Kyrgyzstan, the People's Republic of China and others.

Our study of the pharmacology of the remaining amounts of alkaloids after separation of allapinin showed that uterine alkaloids with a high content (30-40% of the air-dry mass of the uterine alkaloids) of ranocanitin alkaloid had high antiarrhythmic activity. Our studies have shown that it is possible to significantly increase the antiarrhythmic activity of the drug when enriched with alkaloid N-deacetyl lappaconitine, which is obtained from the waste from the production of the drug substance allapinin formed after recrystallization of technical allapinin from methyl alcohol.

Currently, work is underway to develop an industrial production technology and standardization of the resulting drug, and a full package of regulatory and technical documentation is being prepared for submission to the Pharmacological Committee at the Ministry of Health of the Republic of Uzbekistan to obtain permission for its clinical trials.

**ON THE TECHNOLOGY OF THE SUBSTANCE OF THE  
PREPARATION N-DEACETYLLAPPACANITIN HYDROBROMIDE  
WITH ANTIARRHYTHMIC ACTION**

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As we reported earlier, a new drug N-deacetylappacanitine hydrobromide (antiarrhythmic) with antiarrhythmic action was created at the institute. The drug is obtained from the secondary products of the production of the substance of the antiarrhythmic drug allapinin which is obtained from rhizomes with the roots of *Aconitum septentrionale*. The drug is approved for extensive clinical trials in the Republic of Uzbekistan. The drug consists mainly of hydrobromic salts of alkaloids of N-deacetylappacanitine, lappaconitine, acetylsepacanitine, ranocanitine, sepacanitine, etc. According to the regulatory document, the proportion of N-deacetylappacanitine hydrobromide in the preparation should be at least 97.5%.

We have developed a new technology for obtaining the substance of the drug N-deacetylappacanitine hydrobromide allowing obtaining a high-purity product - N-deacetylappacanitine hydrobromide without accompanying alkaloids (99.0-100.0% purity). The technology for the production of a substance of high purity N-deacetylappacanitine hydrobromide was developed using the solubility degree of hydrobromide salts of alkaloids, which was contained in the composition of the technical product substance in a heterophase system consisting of purified water and chloroform. Experimentally optimal ratios of the heterophase system were found, allowing separating completely alkaloid impurities from a technical product and getting high purity of N-deacetylappacanitine hydrobromide, without impurities of the accompanying alkaloids. The high purity of the obtained product was proved by our developed method of thin-layer chromatography and a modern analysis method of HPLC.

## ANTIMICROBIC MACROMOLECULAR DERIVATIVES BASED ON DIALDEHYDE PECTIN

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Advances in the chemistry of macromolecular derivatives, including the synthesis of biologically active macromolecular compounds, are increasingly used to solve a number of problems in the field of medicine and pharmaceuticals related to the introduction of highly effective and low-toxic drugs into practice. One of the methods for producing polymers with biological activity is the addition of low molecular weight drugs to water-soluble or water-insoluble polymers. Currently, the purposeful design and study of new physiologically active polymers has rightfully become considered one of the leading areas in the chemistry of biomedical polymers. In this way, biologically active macromolecular systems with highly effective antimicrobial, hemostatic, antiviral and antitumor properties are obtained based on polymers.

Based on the foregoing, for the synthesis of biologically active polymers, we used dialdehyde pectin obtained by periodically oxidizing the polysaccharide, and the drug sulfamethoxazole widely used in practice as the nucleophilic reagent.

The synthesis of the polymer derivative of sulfamethoxazole consisted of the following stages: oxidation of pectin and addition of the drug to dialdehyde pectin by nucleophilic substitution reaction. By controlling the amount of aldehyde groups in the structure of pectin, the ratio of reacting components and the reaction time, water-soluble sulfamethoxazole derivatives with various physicochemical parameters (molecular weight, degree of substitution, amount of the drug in the polymer, etc.) were obtained.

The structure, composition and molecular parameters of sulfamethoxazole pectin have been proved by IR, UV spectroscopy, gel chromatography, viscometry, thermal and elemental analysis.

Using infrared spectroscopy, it was proved that the binding of the drug to dialdehyde pectin occurred through the azomethine bond ( $-C=N-$ ). In the IR spectra of the obtained samples, absorption was found in the region of  $1660-1675\text{ cm}^{-1}$ , characteristic of  $-C=N-$  bonds.

Absorption bands in the region of 255 nm were found in the UV spectra of the samples. The content of the drug in the polysaccharide was 5.3-26.5%.

It was found that after the introduction of sulfamethoxazole into the structure of pectin dialdehyde, toxicity decreased, the solubility and bioavailability of the drug increased.

*In vitro*, it was found that sulfamethoxazole pectin at a concentration of 10-50  $\mu\text{g}/\text{mL}$  had antimicrobial activity against *Enterococcus faecalis*, *Klebsiella pneumonia*, *Escherichia coli*, *Pseudomonas aeruginosa* and *Staphylococcus aureus*.

In this way, on the basis of the studies, water-soluble sulfamethoxazole derivatives having a wide spectrum of antimicrobial activity were obtained. Physicochemical methods of analysis established the structures and composition of the reaction products of nucleophilic substitution.

## ***Kochia scoparia* IS A NEW SOURCE OF 2-DEOXYECDYSONE**

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Plants of Kazakhstan have not been sufficiently studied in terms of the content of ecdysteroids. In this aspect plants of the Chenopodiaceae family are of certain interest, since wild plants halophytes containing ecdysterone are found in this family. Some available species of the genus *Kochia* L. are among them.

We have carried out a chemical study of the composition of the aerial part of *Kochia scoparia* (L.) Schrad, an annual weed halophyte, collected in the territory of botanical garden of the IRPH «Phytochemistry» in 2018 in the flowering phase.

As a result of phytochemical research on this species, we for the first time isolated the most important synthone for chemical modifications, 2-deoxyecdysone ( $3\beta$ ,  $14\alpha$ ,  $22R$ ,  $25$ -tetrahydroxy- $5\beta$  (H)-cholest-7-en-6-on) previously isolated by us from plants *Silene cretaceae* Fisch, *Silene wolgensis* (Hornem.) Bess., *Silene altaica* Pers. of Caryophyllaceae family. The fine and spatial structure of the isolated synthone was established by the data of X-ray diffraction analysis and NMR spectroscopy <sup>[1,2]</sup>.

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## DETERMINATION OF INDUCING CONDITIONS FOR HIGH LEVEL EXPRESSION OF RECOMBINANT PROTEINS IN *Pichia pastoris*

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The methylotrophic yeast of *Pichia pastoris* is widely used for obtaining of biologically active recombinant proteins. *Pichia pastoris* can express recombinant proteins in high cell density fermenter without loss of product yield and efficiently secrete the target proteins into the protein free mineral salt media <sup>[1]</sup>. The yield of expressed proteins can be increased by adapting of cultivation conditions of the recombinant yeast strain such as concentration of inducer, temperature, pH, etc. Expression is controlled by a methanol-inducible promoter, which allows a biomass generation phase before protein synthesis is initiated.  $\beta$ -galactosidase is a glycoprotein that catalyzes the hydrolysis of  $\beta$ -D-galactosides, in particular in milk sugar - lactose disaccharide. The amount of biomass of cells obtained under certain cultivation conditions is one of the main factors in the preparation of recombinant proteins. In this study, the influence of induction time and methanol concentration on biomass production in recombinant *P. pastoris* strain expressing of  $\beta$ -galactosidase (Mw=117 kDa) was investigated. Usually the cultivation of yeast *Pichia pastoris* consists of three stages. Glycerol in different concentrations is used as a carbon source in the first and second stages of cultivation, and the synthesis of the target (recombinant) protein is induced by methanol, which serves as carbon sources in the third stage <sup>[1,2]</sup>. The entire cultivation stage takes about 96- 120 hours and the wet biomass of cells is up to 450 g/L. We conducted the cultivation in two stages. At the first stage, 5% glycerol and 0.4% sorbitol were added to the culture and cultured for ~ 20 hours, by adding methanol 0.1-1.0% after 10 hours of cultivation. At this phase of cultivation, the mass of wet cells was 220-230 g/L. At the second stage of cultivation, 1.0% methanol and an additional 0.4% sorbitol were added to the nutrient medium every hour for 50 hours. At the end of this phase, the mass of wet yeast cells was 430-450 g/L. Further cultivation did not increase biomass. Expressed protein was monitored at all stages of cultivation by using X-Gal assay and SDS PAGE. As a result, the cultivation time was reduced from ~ 96 to ~ 70 hours, while the biomass of the culture was up to 450 g/L. Thus, the optimal concentration of inducer and induction time for the cultivation of the recombinant strain *Pichia pastoris*, allowing to obtain the highest amount of cell biomass during a short cultivation period were determined.

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**BIOLOGICAL ACTIVITY OF OLEO-GUM-RESIN OF *Ferula tadshikorum* GROWN IN UZBEKISTAN**

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It is known that plants of the genus *Ferula* (family Apiaceae), containing biologically active components, are a perspective source for the creation of pharmacological preparations for medicine and for agriculture. On the basis of *Ferula tenuisecta* Korovin, *Ferula kuhistanica* Korovin, *Ferula varia* (Schrenk) Trautv. already created drugs Tefestrol, Panoferol, Cynaroside etc.

Two of the promising objects, according to our research and scientific literature, are *Ferula foetida* (Bunge) Regel and *Ferula tadshikorum* Pimenov. Earlier, we established antiparasitic and fungicidal activity of *Ferula foetida* resin<sup>[1, 2]</sup>.

The biological activity of the oleo-gum-resin of *Ferula tadshikorum* Pimenov was investigated, and results *in vitro* screening showed that the benzene extract of the oleo-gum-resin of *Ferula tadshikorum* exhibited pronounced antibacterial activity against gram-positive bacteria *Bacillus subtilis* and *Staphylococcus aureus* (diameter of zones of inhibition 15.04±0.10 and 10.12±0.13 mm, respectively) and antifungal activity against *Candida albicans* (14.08±0.12 mm). Benzine extract of *Ferula tadshikorum* showed a noticeable antifungal activity against *Candida albicans* (12.16±0.20 mm).

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## STUDIES ON ANTIOXIDANT AND ANTIRADICAL ACTIVITY OF EXTRACTS OF PLANTS FROM KAZAKHSTAN

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Medicinal plants are the raw material for the production of herbal remedies with a wide range of pharmacological actions. In this direction, it is important to study the antioxidant and anti-radical activity *in vitro* of endemic plants. The aim of the work was to study *in vitro* the antioxidant and anti-radical activity of extracts of some endemic plants of Kazakhstan.

An *in vitro* study of the antioxidant and anti-radical activity of extracts of *Hypericum perforatum* (Hp-1), Sea Buckthorn (Hr-1), Tansy (Tv-1), and tripartite sequence (Bt-1) was performed. An indicator of the degree of antioxidant activity was the dynamics of the optical density of working solutions when the concentration of the analyte was changed. Ascorbic acid (AA) was used as a standard to compare the obtained data. Antiradical activity was studied *in vitro* by determining the ability of inhibition of 2,2-diphenyl-1-picrylhydrazyl (DPPH) radical.

Sample	0.25mg/mL	0.5 mg/mL	0.75 mg/mL	1mg/mL
Hp-1	0.7215±0.1352	1.0847±0.0468	1.1066±0.0854	1.2542±0.0922
Hr-1	0.9520±0.2141	1.1338±0.0547	1.2224±0.0071	1.2472±0.0392
Tv-1	1.0166±0.1033	1.4011±0.1242	1.8939±0.0597	2.3011±0.1523
Bt-1	0.6006±0.0179	1.0935±0.0245	1.6452±0.0467	1.9531±0.0550
AA	1.9256±0.2967	2.2844±0.0114	2.2571±0.1435	2.2316±0.1623

The study of the FRAP - *in vitro* antioxidant activity of these extracts showed the activity of Tv-1 and Bt-1 solutions, comparable to the effect of AA. Analysis of antiradical activity by determining the ability of DPPH inhibition *in vitro* of these extracts revealed a pronounced activity of the studied solutions, which is comparable with the property of butylhydroxyanisole exhibiting antiradical property.

## CONSUMER PROPERTIES AND CHEMICAL COMPOSITION OF APPLES BROWN UNDER CLIMATE CONDITIONS OF BELARUS

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As the most common fruit in Belarus, apples are widely used in food in fresh and processed form, due to the high taste and nutritional properties. Apples are a source of alkaline compounds, which neutralize acids, promote better absorption of proteins by the body and support the alkaline reaction of the blood. Apples contain soluble solids (7 - 18.2%), sugars (6 - 15.7%), organic acids (0.26 - 1.4%), vitamin C (4.5 - 45 mg / 100g), and tannins (0.06 - 0.11%). The objects of research were 20 samples of apples growing on the territory of the Republic of Belarus.

The most significant indicator used in the technological evaluation of fruits is the content of soluble solids, which of the studied samples averaged 11.1%. As for the production of canned food, normative documentation provides for the use of apples with a content of at least 11% solids, then the studied varieties can be used for canned food. For a quantitative assessment of taste, the sugar-acid index (SQI) was used, which of the studied samples varied from 1.0 to 44.3. It is believed that the fruits usually have the greatest harmony in taste with an SRI of 15-25, among which, Syabryna (16.4), Imrus (14.8), Memory of Syubarova (14.5), Belarusian Sweet (21.2). High sugar content was found in apples of the Belarusian Sweet variety (13.3%), Zaslavskoe (11.8%), Syabryna (11.5%), and Radiant (11.4%). Sugars accounted for 48% of RSV (Antonovka) to 97% (Syabryna).

Different varieties of sugars are characterized by different grades of apples. Apple varieties Radiant and Pospheh 40%, and Belarusian sweet 67% consist of fructose. 9% of sugars (Antonovka, Imrus) and 42% (Nadzeyny) are represented by glucose. In apples of the varieties Pospekh, Verbnoe, Radiant 45% of sugars are sucrose, and in apples of the varieties Nadzeyny, Belorussian sweet only 3% sucrose of the total sugar content.

The content of organic acids in apples ranged from 2.8 g/kg (Belarusian sweet) to 12.8 g/kg (Palm from the Institute of Fruit Growing RUE). Analysis of macro- and microelement composition showed that the average phosphorus content in 1 kg of apples was 100.1 mg, potassium 1104 mg, the iron content from 0.8 to 1.36 mg, the average zinc 0.33 mg. The maximum content was typical for the varieties Zaslavskoye, Nadzeyny and did not exceed 0.6% of the daily intake of this element per 100 g of product, and the average copper was 0.51 mg/1 kg of product. The average ascorbic acid in apple samples was 9.8 mg/100 g. Therefore, 100 g of apples contains 14% of the daily intake of vitamin C.

Using gas chromatography with a mass spectrometric detector, and preliminary solid-phase (SPME-GC-MS) microextraction, 48 volatile compounds were identified, including 36 esters, 5 alcohols, 4 terpenes, 1 aldehyde and 2 acids, corresponding for the aroma of yalok. The most significant aroma-forming components in terms of quantity were: ethyl butanoate, ethyl 2-methyl butyrate, ethyl hexanoate, hexyl acetate, 2-methyl hexyl butanoate,  $\alpha$ -farnesene.

Thus, according to the sum of all indicators for cultivation, processing and use in the climatic conditions of the Republic of Belarus for the purpose of further processing, the varieties Belorusskoe Sweet, Zaslavskoye, Imrus, Luchezarnoye and Syabryna turned out to be the best.



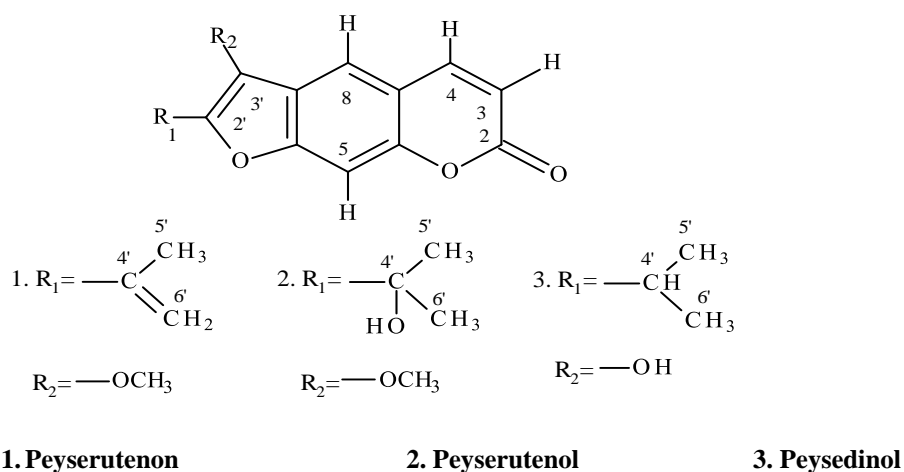
## MINOR FUROCOUMARINS PEYCEDANINE GROUP ROOT RESIN *Peucedanum ruthenicum*

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Using a rechromatography method over a mixture of the substances of the mother liquor of isoimperatorin, peysedanin, osthrutin, peyseruten and peyserutenin led to the separation of three new furocoumarins peyserutenon (C<sub>15</sub>H<sub>12</sub>O<sub>4</sub>, mp 176-178 °C), peyserutenol (C<sub>15</sub>H<sub>14</sub>O<sub>5</sub>, mp 159-161.5 °C) and peysedinol (C<sub>15</sub>H<sub>12</sub>O<sub>4</sub>, mp 141-142 °C), the structures of which were established on the basis of <sup>1</sup>H NMR spectra: **1.** H-3 6.42, d, *J* = 9.60; H-4 7.98, d, *J* = 9.60; H-5 7.84, s; H-8 7.63; 3'-OMe 4.20, s; CH<sub>3</sub>-4' 2.20, s; 6' = CH<sub>2</sub> 5.32; **2.** H-3 6.38, d, *J* = 9.60, H-4 8.10, d, *J* = 9.60, H-5 7.75, s; H-8 7.43, s; 2'-C (2CH<sub>3</sub>) - OH 1.78, s; 3'-OMe 3.90, s; **3.** H-3 6.29, d, *J* = 10.00; H-4 7.80, d, *J* = 10.00; H-5 7.76, s; H-8 7.35, s; 2'-CH (2CH<sub>3</sub>) 3.15, s; 1.30, *J* = 7.00 Hz.



## SOLID-PHASE MICROEXTRACTION OF PLANTS OF THE ASTERACEAE FAMILY

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Essential oils of plants are composed of thermosensitive chemical compounds, the use of steam distillation and hydrodistillation in their isolation will inevitably affect the structure of molecules and component compositions. Along with traditional extraction methods, modern extraction methods are currently used, one of which is micro-steam distillation with solid-phase microextraction, which allows isolating components in a short period of time without leading to their destruction and maximally preserving the biological value of all components.

For the chemical study of the volatile components of four species of the Asteraceae family growing in Kazakhstan (*Doronicum altaicum* Pall., *Artemisia rupestris* L., *Artemisia glabella* Kar. et Kir., *Pulicaria prostrata* (Gilib.)), the modern method of micro-steam distillation with solid-phase microextraction (SPME) was used for the first time. To obtain volatile components, the powdered raw materials were extracted using SPME, and subsequent methods analysis of chromatography-mass spectrometry and gas chromatography with flame ionization detector (GC/FID and GC/MS) for a relatively complete definition of chemical compositions.

According to the results of GC/FID and GC/MS, main components for *Doronicum altaicum* Pall. were eupatoriochromene (38.02%), 8-acetyl-7-hydroxy-2,2-dimethyl-2H-chromene (8.2%), eudesm-4(15),7-dien-1-ol (6.0%), hexahydrofarnesylacetone (3.4%). In *Artemisia rupestris* L., quantitative content revealed the presence of myrcene - 5.5%,  $\beta$ -elemene - 3.6%, (*Z*)- $\beta$ -farnesene - 4.9%, valencene - 9.2%,  $\beta$ -selinene - 5.4%,  $\alpha$ -selinene - 5.7%. *Artemisia glabella* Kar. et Kir. was discovered to produce 1,8-cineole - 12.8%, camphor - 5.2%, cumin aldehyde - 16.0%,  $\alpha$ -terpineol - 4.8%, borneol - 5.4%, cumin alcohol - 6.9%. *Pulicaria prostrata* (Gilib.) contained artemisiaketone - 10.0%, camphor - 10.1%, cumin aldehyde - 9.1%, buddledin C - 4.1%.

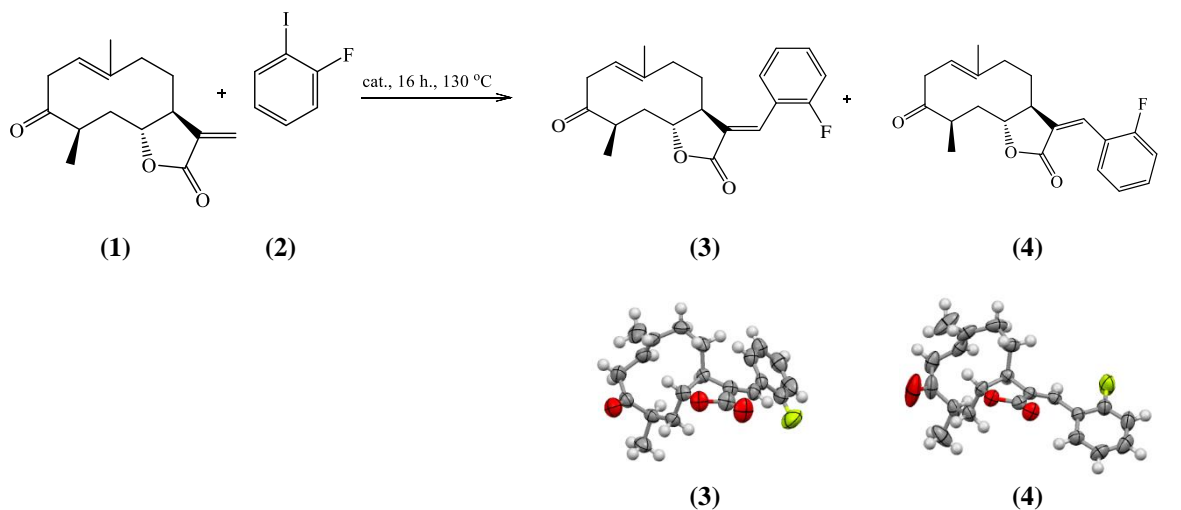
Thus, the chemical compositions of volatile substances from *Doronicum altaicum* Pall., *Artemisia rupestris* L., *Artemisia glabella* Kar. et Kir., *Pulicaria prostrata* (Gilib.), growing in the Republic of Kazakhstan, were determined using method of micro-steam distillation with solid-phase microextraction (SPME) for the first time.

## NEW FLUORO DERIVATIVES OF 3-KETO-4,7(A),6B(H)- GERMACR-1(10),11(13)-DIEN-6,12-OLIDE

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The germacrane-type sesquiterpene lactone argolide (3-keto-4,7( $\alpha$ ),6 $\beta$ (H)-germacr-1(10),11(13)-dien-6,12-olide) (**1**) was firstly isolated from the aerial parts of *Artemisia glabella* Kar. et Kir. Molecule (**1**) has reaction centers bonded with the presence of an  $\alpha,\beta$ -unsaturated  $\gamma$ -lactone cycle, a keto-group at C-3 and a triple-substituted double bond at C1 - C10. The exocyclic double bond of the lactone ring in the molecule (**1**) allows to carry out the synthesis according to the Heck reaction, due to the addition of an aryl substituent to the C-13 carbon atom, which has a relatively high electron density. Thus, reaction of compound (**1**) with 2-fluoriodobenzene (**2**) in the presence of a catalyzing system Pd(OAc)<sub>2</sub>-(*o*-Tol)<sub>3</sub>P-Et<sub>3</sub>N-DMF resulted in the formation major derivative 13-(*E*)-(2-fluorophenyl)-3-oxogermacr-1(10),11(13)-dien-6,12-olide (**3**) and minor 13-(*Z*)-(2-fluorophenyl)-3-oxogermacr-1(10),11(13)-dien-6,12-olide (**4**), with the yield of 40.0% and 2.34%, respectively.



**Figure 1** The spatial structure of molecules (**3**) and (**4**) according to X-ray diffraction analysis

Thus, two new fluoro derivatives (**3**) and (**4**) based on argolide were obtained, the structures of which were established on the basis of spectral data (IR, UV, <sup>1</sup>H, <sup>13</sup>C NMR, and <sup>13</sup>C-<sup>1</sup>H COSY) and by the method of X-ray diffraction analysis (**Figure 1**). The obtained derivatives (**3**) and (**4**) were studied for antimicrobial activity and cytotoxicity.

## HYGIENIC AND TOXICOLOGICAL INDICATORS FOR SYNTHETIC ANALOGUE OF THE SITOPHILUS WEEVILS AGGREGATION PHEROMONE

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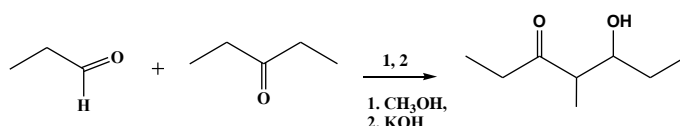
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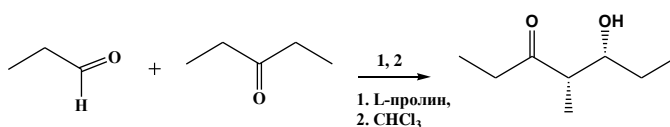
The weevils *Sitophilus*, is an important economic pest of stored grains in tropical and sub-tropical regions of the world. It attacks various stored foodstuffs including maize, wheat, oats, barley, rye, and dried cassava roots, as well as processed food such as macaroni, noodles, biscuits, and hardened cake. Post-harvest crop losses due to storage pests such as weevils *Sitophilus* pose major [1].

Controlling of the level grain products destruction in granaries, by using of natural bioregulators - pheromones of pests insect lets to preserve the quality of grain and to avoid environmental pollution, into storage protective measures.

We synthesized diastereomers of 5-hydroxy-4-methyl-3-heptanone – aggregation pheromone of *Sitophilus*, into different methods: at the first way - in the conditions of aldol condensation between diethylketone and propylaldehyde [2]. (scheme 1)



And second way, the asymmetric catalytic aldol reaction was carried out in the condition of interaction 3-pentanone and propylaldehyde with L-proline initiation [3]. (scheme 2)



Especially for recommendation into system of protection storage products, it is necessary to whole study the hygienic and toxicological indicators. With this goal, the toxicity of synthetic analogue *Sitophilus* weevils's aggregation pheromone was carried out and the indicators of acute toxicity racemic mixtures of 5-hydroxy-4-methyl-3-heptanone, was determined. The results of toxicological studies of 5-hydroxy-4-methyl-3-heptanone showed that in a comparison with conventional pesticides, pheromone's toxicity to warm-blooded animals was extremely low.

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## THERMAL STUDY OF THE COORDINATION COMPOUND OF ZINC NITRATE WITH NICOTINIC ACID AND BENZAMIDE

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A complex compound of zinc nitrate with nicotinic acid and benzamide was synthesized. The thermal behavior of the synthesized compound was studied and thermolysis products were identified.

The scientific basis of the synthesis and the establishment of the features of new complex metal compounds to create effective, environmentally friendly plant growth regulators are very relevant. Thermal analysis was carried out on a Paulik-Paulik-Erdey derivatograph with a speed of 9 deg / min and a 0.1 g sample at a sensitivity of T-900, TG-100, DTA-1/10, DTG-1/10 galvanometers.

The coordination compound was synthesized by a mechanochemical (solid-phase) method. A compound of the composition  $Zn(NO_3)_2 \cdot NC_5H_4COOH \cdot C_6H_5CONH_2 \cdot 2H_2O$  was obtained by vigorous stirring of 0.001 mol zinc nitrate hexahydrate with 0.001 mol nicotinic acid, 0.001 mol benzamide in a ball mill at room temperature for 30 minutes.

The appearance of the first two endothermic effects was due to the stepwise removal of two water molecules. The nature of the remaining thermal effects was due to the splitting of the coordinated molecules of nicotinic and benzoic acids.

The temperature range of the effect, °C	Peak effect, °C	Mass loss, %	Total weight loss	Total weight loss	Compounds formed
<b><math>Zn(NO_3)_2 \cdot NC_5H_4COOH \cdot C_6H_5CONH_2 \cdot 2H_2O</math></b>					
110 – 140	126	7.57	7.57	Exothermic	$Zn(NO_3)_2 \cdot NC_5H_4COOH \cdot NC_5H_4CONH_2$
140 – 180	152	5.40	12.97	Endothermic	Thermolysis Product
180 – 220	206	5.40	18.37	Exothermic	Thermolysis Product
220 – 310	301	29.73	48.10	Exothermic	Thermolysis Product
310 – 340	328	6.76	54.86	Exothermic	Thermolysis Product
340 – 410	395	12.16	67.02	Endothermic	Thermolysis Product
410 – 467	459	8.11	75.13	Exothermic	Thermolysis Product
467 – 500	480	4.46	79.59	Exothermic	Thermolysis Product
500 – 590	579	1.10	80.69	Endothermic	Thermolysis Product
590 – 650	640	0.95	81.64	Endothermic	Thermolysis Product
650 – 690	660	0.68	82.32	Endothermic	Thermolysis Product
690 – 750	703	0.41	82.73	Endothermic	Thermolysis Product

The endothermic effects observed upon heating can be caused by physical phenomena such as melting, evaporation, a change in the crystal structure, or chemical reactions of dehydration and dissociation. Transformations, accompanied by exothermic effects upon heating, are much less common: due to oxidation processes and some structural transformations.

## ANTIDIABETIC ACTIVITY AND DETERMINATION OF MAJOR METABOLITES BY LC-ESI/MS/MS OF "NOVOBET"

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*Geranium collinum* Stephan ex Willd., *Glycyrrhiza glabra* L., and *Rhus coriaria* L., are species growing in Tajikistan, and are characterized as natural sources of phenolic compounds that have several known biological activities and serve as a traditional medicine against various disorders including type 2 diabetic disease. *G. collinum* is a perennial plant of the family Geraniaceae. In Tajikistan, it grows in the wild areas of Zarafshan, Varzob and Hissar valley, Darwaz and Western Pamir. *G. collinum* has been used for the treatment of rheumatism, gout, dysentery, external and internal bleeding, as well as in skin wounds, eczema, scabies, tenosynovitis and pruritus. *G. glabra* (licorice) has been used since ancient times as a sweetener and a remedy for a great diversity of ailments. Roots of *G. glabra* contain a high concentration of the saponin glycyrrhizin, the main sweet-tasting component. The hot decoction prepared from the roots of *G. glabra* is known in Tajik and Uzbek traditional medicines for its therapeutic effects against nervous disorders, flatulence and other digestive disorders. *R. coriaria* (family Anacardiaceae) is a shrub known as "sumac", traditionally used as a table spice particularly with rich dishes and is highly recommended for adjustment of the blood lipids in diabetic patients. It is used in traditional medicine owing to its anti-fibrogenic, antifungal, anti-inflammatory, antimalarial, antimicrobial, antimutagenic, antioxidant, antithrombin, antitumorogenic, antiviral, cytotoxic, hypoglycaemic, leukopaenic and atheroprotective effects. This investigation is related to the preparation of the new antidiabetic phytomedicine, "Novobet", made up from the roots of *G. collinum* and *G. glabra*, and the fruit of *R. coriaria* growing wild in Tajikistan.

"Novobet" was screened for *in vitro* antidiabetic (PTP-1B enzyme inhibition) and antioxidant effects (DPPH radical scavenging). The *in vivo* antidiabetic and acute toxicity of "Novobet" was evaluated in animal models. Glucose and lipids levels and the concentration of malondialdehyde (MDA) in serum of laboratory animals treated with "Novobet" were investigated. The blood sugar level in experimental rabbits, after treatment with 5 mL/kg of "Novobet", was decreased after 7, 15 and 30 days, respectively, which indicated active hypoglycemic action. In addition, the total lipids in the blood decreased to 44.5%, and blood cholesterol decreased to 32.2%. The MDA level of rabbit's blood decreased significantly. A total of 25 major compounds were identified in "Novobet" by LC-ESI-MS/MS spectroscopy. The new phytomedicine "Novobet", exhibited potent antidiabetic and antioxidant activity and can serve as a natural antidiabetic and antioxidant nutraceutical.

### ACKNOWLEDGMENTS

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## INDOLE ALKALOIDS FROM KERNELS OF *Corylus avellana* L.

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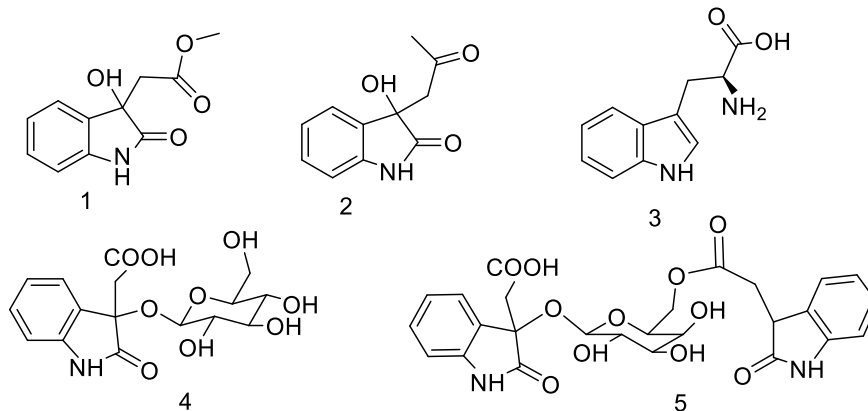
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Hazelnut (*Corylus avellana* L.), belonging to the Betulaceae family, is a well-known nut, production of which ranks second after almond on a worldwide basis.

*Corylus avellana* L. is introduced to western areas of China from the original countries such as Turkey and Italy. Hazelnut provides a unique and distinctive flavor as an ingredient in a variety of food products, and plays a major role in human nutrition and health. Thus, studies on the chemical constituents of this plant is greatly important.

In this study, five indole alkaloids were isolated from the kernel of *Corylus avellana* L. by using macroporous resin, octadecylsilica (ODS), sephadex LH-20 column chromatography and preparative HPLC. They were Methyl dioxindole-3-acetate (**1**), 3-acetyl-3-hydroxyoxindole (**2**), L-Tryptophan (**3**), 3-(*O*- $\beta$ -D-Glycosyl) dioxindole-3-acetic acid (**4**), 2-(3-Hydroxy-2-oxindolin-3-yl) acetic acid 3-(*O*-6'-galactopyranosyl-2''-(2''-oxindolin-3''-yl) acetate (**5**), respectively. Their structures were elucidated by HR-ESI-MS, IR and 1D- and 2D-NMR experiments.

**Keywords:** *Corylus avellana* L.; Indole alkaloids; Isolation



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**COMPOSITION OF OIL FROM *Rumex confertus* Willd****G. D. Shermatova, K. A. Eshbakova**

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In this paper we report about a new rich source of phytol (PYT) from the aerial parts of *Rumex confertus* Willd, which is the second object of research belonging to the family Polygonaceae. Since ancient times, concoctions and tea from leaves and roots of this herb have been used to treat various intestinal inflammations [1]. Clinical trials of the use of *R. confertus* Willd rootstock against children's salmonellosis have been successful [2]. Similar therapeutic studies have been shown to be effective in treating acute intestinal infections (dysentery), high blood pressure [3], and also used in veterinary for the treatment of diarrhea in animals [4]. Phytol is an acyclic diterpene alcohol that can be used as a precursor for the manufacture of synthetic forms of vitamin E and vitamin K1 [5]. Phytol shows significant anti-inflammatory activity (68.03%) with respect to standard (Diclofenac 5mg/kg) [6]. The results obtained in this study demonstrate that phytol produces antinociceptive activity in mice, suggesting central and peripheral effect, without changing the motor function of animals. The antinociceptive activity may be associated with the antioxidant activity of phytol as demonstrated by in vitro methods used. More studies are needed to elucidate the possible action mechanisms that mediate the central and peripheral antinociception, as well as the antioxidant activity of phytol against other free radical generating systems and with other different concentrations of this diterpene evaluated in this study, since the concentrations tested were more efficient in removing the hydroxyl radical [7].

**GC-MS Analysis.** The continuing studies of the chemical composition of *R. confertus* Willd identified forty-seven components by GC-MS analysis, accounting for 93.61% of the total oil. The major components in the oil of *R. confertus* were identified as 1,2,3-Propanetriol, diacetate (CAS) (1.67%), Benzeneethanol (CAS) (3.77%), 5-Undecene 1-Tridecanol (CAS) (4.48%), 2-Methoxy-4-vinylphenol (7.88%), and Phytol (62.68%). Phytol showed high percentation than other components and we found a new rich source of phytol. All components were firstly separated from *R. confertus* Willd.

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COMPOSITION OF OIL FROM *Rumex pamiricus*

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The herb *Rumex pamiricus* belongs to family Polygonaceae and there are over 200 types on the earth. In Uzbekistan there are 16 types, of which both two plants are widely spread types. Since ancient times, concoction or tea from various parts of this herb has been used in folk medicine to treat diarrhea, dysentery, stercoral ulcer, as appetizer, analeptic medicine for liver, heart, as antihaemorrhagic, to treat hepatitis, fever and other diseases [1-2].

**Plant Material.** The aerial parts of *Rumex pamiricus* were collected from Botanic Garden, Tashkent, Uzbekistan, on May 2018.

**Isolation of the Essential Oil.** The aerial parts of *R. pamiricus* at the flowering time (100 g) was cut into small pieces and the essential oil was obtained by hydrodistillation with a Clevenger-type apparatus until there was no significant increase in the volume of the oil collected (6 h).

**GC-MS Analysis.** Fifteen components were identified by GC-MS analysis method and accounted for 83.05% of the total oil. The major components in the oil of *R. pamiricus* were identified as 2-Methoxy-4-vinylphenol (8.24%), Nerolidol 2 (8.22%), Triacetin (46.69%), cis-Jasmone (4.68%). The percentage composition of the various oil components was listed in Table 1. All components were firstly separated from *R. pamiricus*.

TABLE 1. Percentage Composition of the Essential Oil isolated from *Rumex pamiricus*

№	Components	RT	RI	%
1	p-Xylene	6.588	1174	3.09
2	Dodecane	7.104	1196	1.26
3	Nonanal	12.404	1382	1.16
4	Tetradecane (CAS)	12.841	1396	1.18
5	Hexadecyl pentyl ester, sulfurous acid	14.120	1439	0.94
6	Pentadecane	15.878	1497	0.43
7	Hexadecane (CAS)	18.885	1500	2.39
8	1-methyl-2-Pyrrolidinone	20.262	1639	0.83
9	1,2,3,4-tetrahydro-1, 1,6-trimethyl- naphthalene	20.945	1662	0.51
10	Benzeneethanol (CAS)	27.007	1827	1.39
11	cis-Jasmone	27.788	1839	4.68
12	2-hexyl-1-decanol	27.966	1841	2.04
13	Nerolidol 2	31.053	1886	8.22
14	Triacetin	31.809	1897	46.69
15	2-Methoxy-4-vinylphenol	34.595		8.24
			Total %:	83.05%

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## HETARENOCHROMONES BASED ON NATURAL ISOFLAVONES

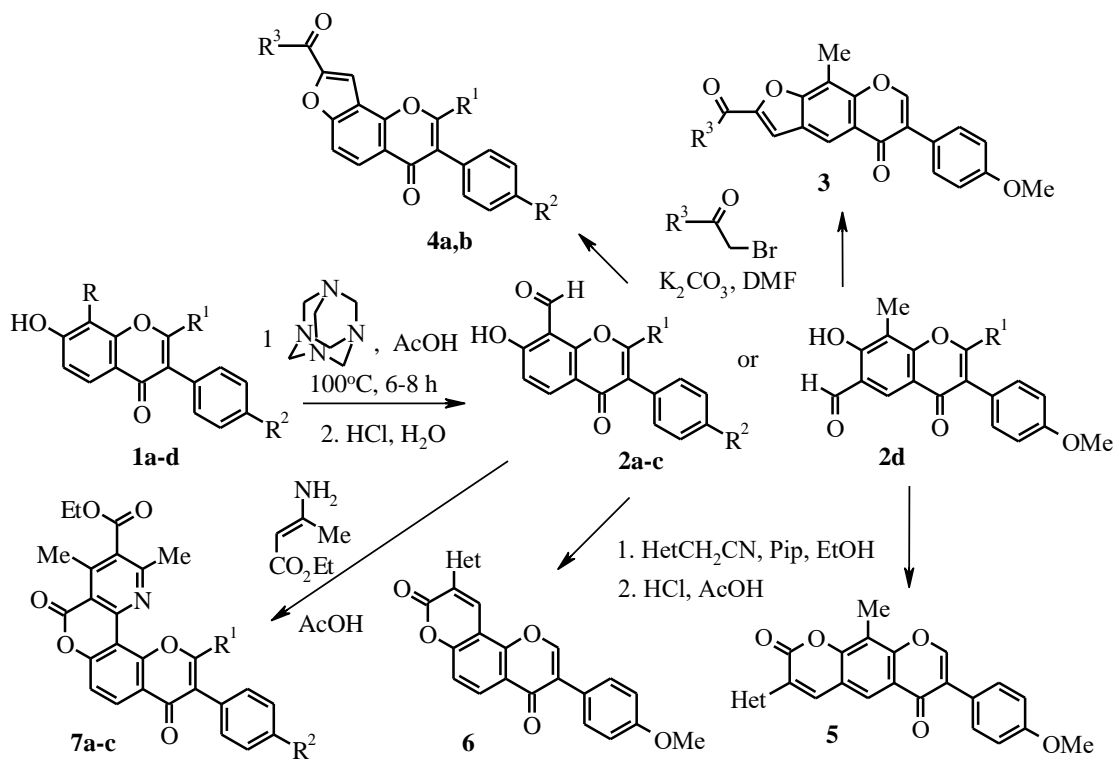
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Fused chromones have attracted a great deal of attention owing to a prevalence of such motifs in different kinds of natural flavonoids and some alkaloids and a wide range of biological activities inherent to naturally occurring compounds of this type and their synthetic analogs.

Herein we report on our investigations in the syntheses of linear and angular hetarenochromones on the base of natural isoflavones **1a-c** and 8-methylisoflavone **1d** via their Duff formylation to give 8- or 6-formyl-7-hydroxychromones (**2**) proved to be versatile synthones for the annulation of heterocycle to the chromone core.

Thus furo[3,2-g]chromones (**3**) and furo[2,3-h]chromones (**4**) were prepared by condensation of formylchromones **2a,b,d** with phenacyl bromides and their hetaryl analog.  $\alpha$ -Pyrono[3,2-g]chromones (**5**) and  $\alpha$ -pyrono[2,3-f]chromones (**6**) were obtained upon treatment of formylchromones **2a,d** with 2-hetarylacetonitriles under the Knoevenagel conditions. The Hantzsch reaction was a convenient one-step method for annulation of  $\alpha$ -pyrone and pyridine rings to chromone system leading to 9H-pyrano[2',3':5,6]chromeno[4,3-b]pyridin-5,9-diones **7**.



**a** R=R<sup>1</sup>=H, R<sup>2</sup>=OMe; **b** R=R<sup>1</sup>=R<sup>2</sup>=H; **c** R<sup>1</sup>=Me, R<sup>2</sup>=H; **d** R=Me, R<sup>1</sup>=H, R<sup>2</sup>=OMe;

R<sup>3</sup>=MeOC<sub>6</sub>H<sub>4</sub>, NO<sub>2</sub>C<sub>6</sub>H<sub>4</sub>, benzofuran-2-yl;

Het=pyridin-2-yl, 4-methylthiazol-2-yl, 4-(4-bromophenyl)thiazol-2-yl, 5-phenyl-1,3,4-thiadiazol-2-yl

## MICROBIAL TECHNOLOGY OF OBTAINING ANIMAL PRODUCTS

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Recently, the introduction of biotechnological methods in the technology of production of feed products has opened up broad prospects for the creation of waste-free, resource-saving technologies that allow the rational use of waste of various origins. We have shown that the waste of many agricultural plants, such as bran, straw, stalks, corn cobs, husks, meal, stalks and flaps of cotton, wood (sawdust, wood shavings), as well as Jerusalem artichoke stalks and squeezes turned out to be potential sources of various biologically valuable products microbial synthesis.

In particular, enzymes, valuable proteins, mycolipids, carbohydrates, free amino acids, vitamins, etc. were obtained from the stalks of Jerusalem artichoke by enzymatic conversion of the basidiomycetes *Pleurotus ostreatus*, *Agaricus bisporus*, *Fomes fomentarius*, and yeast *Saccharomyces cerevisiae*. The accumulated biomass of *Aspergillus oryzae* *Pleurotus ostreatus* fungus with vitamin composition and biological conversion products, mycoproduct was used in feeding animals and birds, which gave positive results.

The valuable chemical composition of Jerusalem artichoke stems served as the basis for silage, received good food for all form animals. The presence in the stems of plants of a large amount of sugars (up to 25-30% to dry matter) led to their easy absorption, humidity in the range of 60-75%, the fiber content decreased, there was more digestible protein of high quality up to 1, 5% of lactic acid, comprising at least 50% of the total amount of acid. In the process of silage, the pH decreased to 4.2-3.9, due to the high solids content (25-30%), the artichoke silage was not acidified, almost all of the nutrients and vitamins were preserved.

Thus, the waste of tubers, the green and dried mass of Fais Baraka and Muzhiz varieties was due to the high nutritional value and the content of carbohydrates, mainly fructosans, among which inulin was the most valuable. Enriched with enzymes, proteins, mycolipids, carbohydrates, free amino acids, vitamins and other biologically valuable substances, accumulated biomass of *Aspergillus oryzae* *Pleurotus ostreatus* fungi, can serve as a potential source of feed for form animals.

This feed is the cheapest and economically viable of the available alternatives for fattening cattle, small cattle, and birds of various breeds. and allows you to replace the traditional component of grain crops in their diet by 30-40%. Animals ate this food more readily than other grass crops. At the same time, their gain and productivity were significantly higher than conventional feeding.

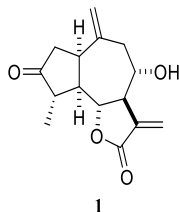
**ULTRASONIC EXTRACTION OF *Chartolepis intermedia* Boiss. RAW MATERIALS**

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The basis of the technology for the isolation of sesquiterpene lactones is the extraction of raw materials with various organic solvents followed by chromatographic purification. Classical extraction methods (percolation and maceration) are time-consuming and laborious. One of the promising methods for the effective isolation of biologically active substances is ultrasonic extraction of medicinal raw materials, the advantage of which is that it provides relatively complete penetration of the extractant through the membrane of plant tissue, reduces the duration of the process, increases the yield of the target substance, reduces the consumption of solvents, allows you to isolate thermolabile compounds.

In terms of the development and implementation of new original drugs in practical medicine, *Chartolepis intermedia* Boiss. is a promising object, a renewable source of biologically active sesquiterpene lactone - grossheimin (**1**). The plant is widespread in the territory of Central Kazakhstan, the annual harvest of which on an area of 5.3 ha is 8.5 tons.



The report discusses the method of ultrasonic extraction of pharmacologically active component of grossheimin (**1**) from the aerial part of *Chartolepis intermedia* Boiss. As the extractant was used 96% ethyl alcohol and its 50% aqueous solution. Extraction of *Chartolepis intermedia* Boiss was carried out on an ultrasonic device HO-230.00 at a frequency of ultrasonic radiation of 22 kHz and room temperature for 30, 60, 90, 120, 150 min. According to result of the experiment, it was found that the quantitative yield of grossheimin (0.17% in terms of air-dry raw materials) is achieved by extraction of *Chartolepis intermedia* Boiss. raw materials with 50% ethyl alcohol for 90 minutes.

Thus, the extraction of *Chartolepis intermedia* Boiss raw materials by ultrasonic extraction allowed to increase the yield of grossheimin by 1.8 times and reduced the process duration, which showed the prospects of this method for the quantitative extraction of sesquiterpene lactones.

CELLULASES OF FUNGI *Trichoderma harzianum* THNUU1V. V. Shurigin<sup>1</sup>, D. F. Djamalova<sup>2</sup>, S. A. Abdusamatov<sup>1</sup>, A. A. Umruzokov<sup>1</sup>,  
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Cellulases are one of the most popular enzymes and are widely used in the processing of cellulose-containing waste, pulp, paper, textile, food and other industries.

From natural sources, we isolated more than 20 isolates from mycelial fungi, among which the representative of the genus *Trichoderma* was the most active cellulose-decomposing fungus. The primary characterization of morphological, physiological, biochemical, and cultural properties showed that the isolates belonged to the species *Trichoderma harzianum* that was confirmed by the determination of 18S rRNA gene sequence. The *Trichoderma harzianum* strain THNUU1 was deposited to the collection of industrially important microorganisms of the Institute of Microbiology of the Academy of Sciences of the Republic of Uzbekistan and was stored under number 857, registered in GenBank under number MH173850.1. Below is the nucleotide sequence of 18S rRNA of this strain:

```
AACCAGCCGAGGGATCATTACCGAGTTTACAACCTCCCAACCCAATGTGAAC
GTTACCAAACCTGTTGCCTCGGCGGGATCTCTGCCCCGGGTGCGTTCGAGCCCC
GGACCAAGGCGCCCGCCGGAGGACCAACCAAACTCTTATTGTATACCCCTC
GCGGGTTTTTTTATAATCTGAGCCTTCTCGGCGCCTCTCGTAGGGCGTTTCGAAA
ATGAATCAAACTTTCAACAACGGATCTCTTGGTTCTGGCATCGATGAAGAAC
GCAGCGAAATGCGATAAGTAATGTGAATTGCAGAATTCAGTGAATCATCGAATC
TTTGAACGCACATTGCGCCCCGCCAGTATTCTGGCGGGCATGCCTGTCCGAGCGT
CATTTC AACCCCTCGAACCCCTCCGGGGGGTTCGGCGTTGGGGATCGGCCCTCCC
TTAGCGGGTGGCCGTCTCCGAAATACAGTGGCGGTCTCGCCGCAGCCTCTCCT
GCGCAGTAGTTTGCACACTAGCATCGGGAGCGCGGCGGTCCACAGCCGTTAA
ACTCCCAACTTCTGGAATGTTG
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In the culture fluid of the fungus *Trichoderma harzianum* THNUU1, multiple molecular forms of endonuclease and cellobiohydrolase were determined by two-stage ion-exchange chromatography. It was found that the molecular forms of enzymes differed in optimum pH and molecular weight. For example, endonucleases were represented by three molecular forms with molecular weight 28, 47 and 60 kDa and optimum pH of 5.74, 4.8 and 3.8, respectively. The cellobiohydrolases were represented by two molecular forms with a molecular weight of 43 kDa (optimum pH 4.2) and 65 kDa (optimum pH 4.4).

Further study of the endonucleases and cellobiohydrolases isolated from the fungus *Trichoderma harzianum* THNUU1 will allow us to reveal the mechanisms of cleavage of cellulose-containing substrates under the action of different molecular forms of these 2 enzymes.

NEW PHENOLIC COMPOUNDS FROM *Geranium charlesii*

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Earlier by us from the aerial part of the *Geranium charlesii* Vved. (*Charles geranium*, family Geraniaceae), a number of phenolic compounds, namely gallic acid, methyl gallate, flavonoids: kaempferol, quercetin, isorhamnetin, isorhamnetin-3-*O*- $\beta$ -D-glucopyranoside, isoquercitrin and isorhamnetin-3-*O*-vicianoside, were isolated<sup>[1]</sup>.

In continuation of our research, two new phenolic compounds, 5-*epi*-sawaranin (**1**) (diastereoisomer of sawaranin<sup>[2]</sup>), with composition C<sub>14</sub>H<sub>16</sub>O<sub>7</sub>, m.p. 231-233 °C, R<sub>f</sub> 0.27, (chloroform-methanol-acetic acid-ethyl acetate, 9:3:0.5:0.5), as well as a new butyrolactone, which we named charlesolid (**2**), with composition C<sub>23</sub>H<sub>24</sub>O<sub>10</sub>, m.p. 204-205 °C, R<sub>f</sub> 0.34, (chloroform-methanol-acetic acid-ethyl acetate 7:3:0.5:0.5) were isolated from this plant by column chromatography. The structure of compounds **1** and **2** were determined based on analysis of <sup>1</sup>H and <sup>13</sup>C NMR spectra (DEPT, HSQC and HMBC), and the obtained single crystals, which established their absolute configuration as 5-*epi*-sawaranin (**1**) and 3-hydroxy 4-(4-hydroxyphenyl)-5-methoxycarbonyl-5-(4-hydroxy-3-formylbenzene)-2,5-dihydro-2-furanone (charlesolid) (**2**), shown in Fig. 1.

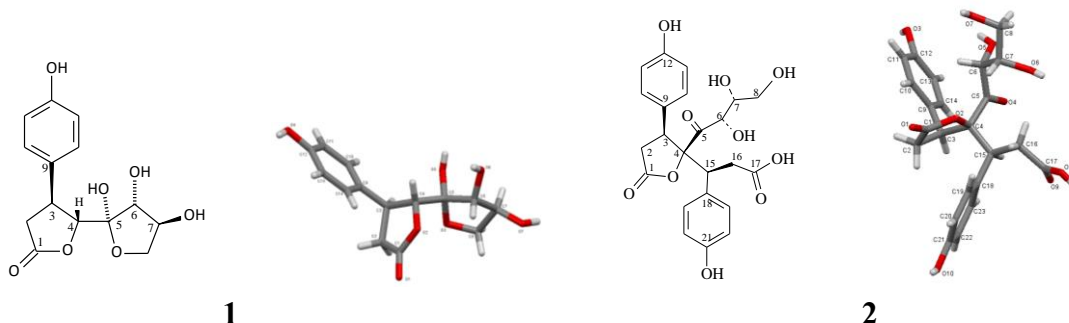


Fig. 1. The chemical and spatial structures of 5-*epi*-sawaranin (**1**) and charlesolid (**2**).

## ACKNOWLEDGEMENTS

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## NOVEL FURO[2,3-D]PYRIMIDIN-4-ONES AS ANALOGUES OF THE QUINAZOLINONE ALKALOIDS

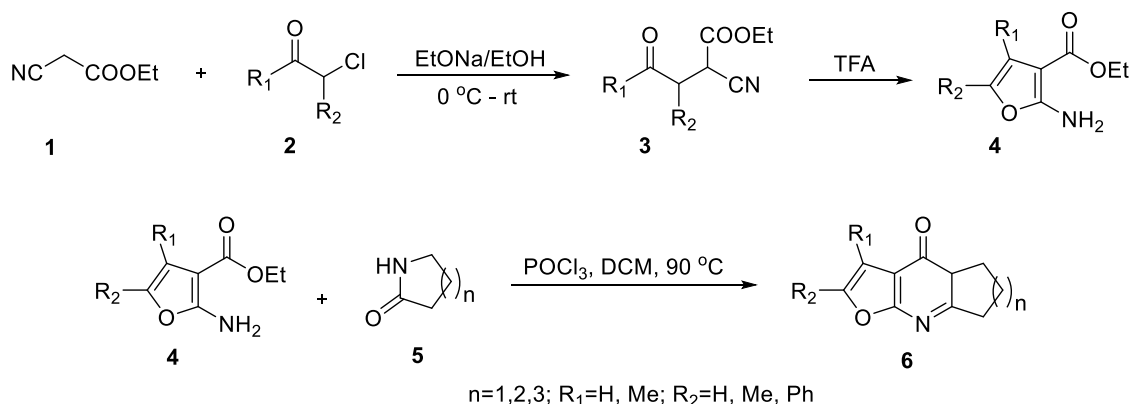
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Furo[2,3-*d*]pyrimidin-4-ones are one of the major heterocyclic ring systems, which are structural analogues of quinazolinone alkaloids. Besides, furo[2,3-*d*]pyrimidin-4-ones were subjected to biological investigations to assess their potential therapeutic usefulness. Furopyrimidines attract considerable attention because of their wide range practical importance via exerting different biological activities such as anticancer, antimicrobial, antiviral and etc. Based upon their practical importance in medicinal chemistry we paid our attention to synthesize novel heterocyclic system based natural compounds.



The total synthetic route of the novel 5,6-disubstituted tricyclic furo[2,3-*d*]pyrimidin-4-ones were displayed on scheme 1. 2-Aminofuran derivatives (4) were prepared via two steps using ethyl cyanoacetate (1) as starting material. Cyclization reaction was completed under condition phosphorus oxychloride and dichloromethane as reaction solvent. This type of new heterocyclic system (6) will be investigated as purine and quinazolinone alkaloids, as well as their biological potentials, along with chemical modifications under process.

## ACUTE TOXICITY OF ANALGESICALLY ACTIVE COMPONENTS OF THE CENTRAL ASIAN COBRA (*Naja oxiana* Eichwald)

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**Aim.** The work was initiated to study acute toxicity of the cobra venom demonstrating analgesic effect to determine range of their therapeutic effect.

**Materials and methods.** Venom of *N. oxiana* Eichwald (NO), the Central Asian cobra, equipment and consumables for chromatography, electrophoresis and isoelectric focusing (Pharmacia, Sweden; Bio Rad and Sigma, USA), p.a. or chemically pure reagents were used in the experiments. A combination of chromatographic techniques was used to isolate components with antinociceptic effect; SDS-PAAG was used to assess their purity and molecular mass. Acute toxicity was measured by Litchfield and Wilcoxon; analgesic activity was measured by standard “hot plate” and “mouse acetic writhing” tests in white mice of both sexes with the weight of 18-20 g with all ethic requirements taken into account<sup>[1]</sup>.

**Results.** Acute toxicity ( $LD_{50}$ ) of the NO venom was 0.86  $\mu\text{g}/\text{kg}$ , while the one of NT-1 and NT-2 neurotoxins facilitating its analgesic effect<sup>[2]</sup> was 0.48 and 0.56  $\mu\text{g}/\text{kg}$ , respectively. 8 NO venom fractions (S-0 – S-7) were obtained; polypeptides with molecular mass of about 6 kDa were found to form S-4 – S-7 fractions. The fractions in question were administered to the mice. The highest analgesic effect with no side effects (apathy, grouping, tremor) was demonstrated by S-6 and S-7 fractions ( $LD_{50} = 2.05$  and 10.3  $\mu\text{g}/\text{kg}$ , respectively) manifesting by increase of the latent time and pain response suppression (2-4-times higher than that of the controls) in the both pain models.

Thus, despite the fact the materials under study belong to the II toxicity class, the concentration facilitating manifestation of the effect in question opens new horizons for their use as a base of novel analgesic in practice.

**Conclusions.** Polypeptide fractions with the low molecular mass with high analgesic activity in the standard pain models were found in the Central Asian cobra's venom. Their  $LD_{50}$  allows excluding presence of neurotoxins in them. Following pharmaco-therapeutic studies, the polypeptides above could be recommended for practical use as a base of drugs for treatment of some types of pains.

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## PREPARATION OF CHITOSAN HYDROGELS FOR THE TREATMENT OF GENITAL HERPES

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One of the most common diseases of viral etiology worldwide is considered genital herpes. None of the known antiviral drugs is able to eliminate the herpes virus from the body. The classic drugs for treating genital herpes are acyclic nucleosides (acyclovir, valacyclovir, famciclovir). Recently, however, an increasing number of acyclovir-resistant (and similar drugs) viruses have appeared. It was found that in patients with recurrent herpes, the process of formation of interferon is significantly reduced in comparison with healthy people. Therefore, in the treatment of herpes, inducers of endogenous interferon are used. Interferon inhibits the proliferation of herpes virus *in vitro*. So, topical application of  $\alpha$ -interferon gel 6 times a day is a relatively effective treatment for genital herpes. Conventional vaginal delivery systems - creams, foams, and jellies, are held relatively briefly inside the body due to the self-cleaning action of the vaginal tract. At the same time, the retention period of the drug decreases, the dose and frequency of taking the drug increases. This ultimately leads to inconvenience to the patients.

Chitosan is a cationic aminopolysaccharide of natural origin. The use of chitosan in medicine and pharmaceuticals is due to its properties such as biodegradability, biocompatibility, lack of toxicity, mucoadhesion, as well as antioxidant, antibacterial, and antiviral effects. Megosin - / imino derivative of gossypol / is able to induce  $\alpha$ ,  $\beta$ ,  $\gamma$  - interferons in the body. Therefore, megosin, affecting the interferon system, exerts its antiviral effect indirectly. The combination of the antibacterial properties of chitosan and the antiviral properties of megosin will make it possible to more effectively treat genital herpes. The use of mucoadhesive vaginal gel with prolonged release of the drug prolongs the effect of the drug, improves bioavailability. In combination with medicinal substances, chitosan is able to prolong their action.

Chitosan hydrogels with the antiviral drug megosine have been developed. The salient features of these gels are their swellability and biodegradability. In addition to the inherent properties of chitosan, such as antibacterial and antifungal activities, biocompatibility and biodegradability, mucoadhesiveness, the obtained gels have antiviral properties.

The conditions (concentration of polymer solution, crosslinking agent and drug substance) of the formation of a hydrogel without separation of the liquid phase were selected. The possibility of prolonged release of megosine from the developed chitosan hydrogel was shown.

It has been proven that the megosin contained in gels, when administered vaginally, does not penetrate the blood and organs, which allows us to suggest the creation of a local drug. Within 7 hours, 59% of megosine is evenly released from the gel. The use of chitosan gels with megosin in medical practice will reduce the dose of megosin and the frequency of application of the gel itself, which will make the gel more convenient to use.

## BIOACTIVE CONSTITUENTS OF *Tamarix* HALOPHYTE

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The genus *Tamarix* belongs to the family Tamaricaceae, including several species commonly known as tamarisks. The *Tamarix* species prefer alluvial soil but grow well on saline and alkaline soil also. They're excellent as wind breaks on sea coasts as they can thrive in salty spray, and are also useful in arresting soil erosion. These are halophyte plants that can tolerate a wide range of environmental conditions and can resist different abiotic stresses, such as high temperature, salt and drought. About 13 species found in Kazakhstan and are used in traditional medicine. The *Tamarix* species have been widely use in traditional medicine in Asia and Africa mainly for curing dysentery, old chronic diarrhoea, leucoderma, spleen troubles and eye diseases. The chemical and pharmacological studies on *Tamarix* species have been intensified in the last years.

Our work is the detailed investigation on the compositions of aerial part of *Tamarix ramosissima* and *Tamarix hispida*, *Tamarix laxa*, *Tamarix elongate*, collected from different regions of Kazakhstan. Halophyte ability to withstand salt-triggered oxidative stress is based on several factors, including the production of antioxidant molecules, such as phenolic compounds. All original species contain flavonoids, hydrolysable tannins, phenolics acids, terpenoids. The flavonoids isolated from these species are mostly isorhamnetin, tamarixetin, quercetin and their glycosides. From tannins isolated metabolites of gallic acid and ellagitannins; from phenolics acids - isoferulic, vanilic, gallic and ellag acids. Besides phenolic compounds, it included terpenoids, steroids, long chain hydrocarbons, alcohols, lignans, carbohydrates and amino acids. The structures of individual substances were determined by complex of chemical (acidic, alkaline hydrolysis, alkaline destruction) and spectral analysis techniques ( $^1\text{H}$ ,  $^{13}\text{C}$  NMR, 2D NMR, MS). In order to optimize the yield of secondary metabolites, different extraction techniques including dynamic maceration (DM), ultrasound-assisted extraction (UAE) and Soxhlet extraction (SE), were used to obtain a high recovery of the compounds of interest. Extracts and individual substances of investigated species possessed antioxidant, antibacterial, fungal, antidiabetic and growth-regulating activities. Nowadays the investigated wild species of *Tamarix* is introduced as a medicinal agent used in medicine of the Republic of Kazakhstan. Continuing research on *Tamarix* species, phytopreparations, based on which prolonged gel dosage forms, were obtained and optimized. Bentonite clays and their compositions with self-structuring polymers were used as carrier.

## PLANTS OF THE CENTRAL-ASIAN REGION A PERSPECTIVE SOURCE OF SUBSTANCES WITH A METABOLIC DIRECTION OF ACTION

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In experiments on experimental animals, it was found that many plants of Central Asia contain substances belonging to different classes of natural compounds that have an optimizing effect on metabolic processes in the body, especially in the conditions of their pathological condition. So *Ajuga turkestanica* contains phytoecdysteroids (ecdysterone, turkesterone, etc.), which activate metabolism and, above all, protein biosynthesis in organs and tissues and, therefore, increase the general nonspecific resistance of the body. Among the local plant species of the genus *Astragalus*, cycloartan glycosides (cyclosiversioside F, cycloorbicoside G, etc.) have been identified that improve the processes of oxidative phosphorylation and support homeostasis of energy production in cardiomyocytes, which is extremely important in the treatment of many diseases of the cardiovascular system. Flavonoids: apigenin, luteolin, cinaroside, etc., inhibiting lipid peroxidation, especially in the conditions of their sharp activation (various somatic diseases), were found in the *Thermopsis alterniflora* plant. Some of them have a hypoazotemic effect.

Polymeric proanthocyanidins with antihypoxic effect were isolated from *Quercus robur* and *Clematis Semenovii*, thereby improving the physiological capabilities of the body in situations related to oxygen starvation. *Zygophyllum oxianum*, due to its content of triterpene glycosides (zygophyloside E and others), exhibits a pronounced hypoglycemic effect when reproducing alloxan hyperglycemia and diabetes.

Of great interest are *Artemisia leucodes*, *A. annua*, *Tanacetum pseudoahillea* due to the lactones contained in them: leukisin, austricin, artemisinin, tachyllin, etc., exhibiting hypolipidemic and choleric action, eliminating various parasites from the intestine. *Alcea nudiflora* is interesting in its high content of polyprenols, which have a stimulating effect on regenerative processes, thereby accelerating the healing of skin wounds and ulcerative destruction of the gastric mucosa. *Ferula kuhistanica* is a good producer of esters of terpenoid alcohols (ferutin, ferutinin, etc.) with an estrogen-like effect, arabinogalactan and pectin polysaccharides, which exhibit a pronounced prebiotic effect.

The data obtained opens up the prospect of developing, on the basis of some of these substances, effective drugs and biologically active food additives for therapeutic and prophylactic use in various fields of medical practice.

## SOVONTA - SYNTHETIC ANALOGUE OF SOFOSBUVIR

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Currently, for the treatment of patients with chronic hepatitis C, mainly interferon-free therapy with direct-acting antiviral drugs or direct-acting antivirals is recommended. In this regard, the Institute of the Chemistry of Plant Substances of Academy of Sciences of the Republic of Uzbekistan based on the synthetic analogue of Sofosbuvir obtained the «Sovonta» antiviral agent according to the original method. For this, the technical product is slowly dissolved in purified water at 500 °C and then the suspension obtained by gradient cooling (50 °C → 22 °C → 22 °C → 2-5 °C) is filtered off, washed with cold water and dried. Thus, with a good yield, the substance of the notorious Sovonta product is synthesized, which according to all constants corresponds to the standard sample. <sup>1</sup>H and <sup>13</sup>C NMR spectra (Varian Unity 400 plus, CDCl<sub>3</sub>) also confirm the proposed structure.

“Sovonta” is a nucleotide prodrug that intracellularly passes into the active analog of triphosphaturidine - a specific inhibitor of RNA-dependent HCV RNA polymerase. The drug has pangenetic activity against hepatitis C virus. With the help of NS5B polymerase, GS-461203 can be integrated into the building chain of HCV RNA and thus causes chain termination. This active metabolite (GS-461203) inhibits NS5B polymerases - polymerases of the HCV1b, 2a, 3a, and 4a genotypes at concentrations that cause 50% inhibition (IC<sub>50</sub>) in the range from 0.7 to 2.6 μmol.

Studies in rats showed that according to their pharmacokinetic parameters [T<sub>max</sub>, C<sub>max</sub> and AUC (Area Under ROC Curve), calculated by the dynamics of changes in the concentration of sofosbuvir in blood serum when it is orally administered], the Sovonta preparation is bioequivalent to the reference commercial drug Sofgen (India). Toxicity studies in mice when administered orally confirmed that Sovonta also corresponded to Sofosbuvir in terms of acute toxicity. The resulting sample of Sovonta in its physicochemical parameters corresponds to the analogue of Sofosbuvir, which has been present on the world market since 2013 under the trade name Sovaldi. Compared with other drugs, it showed higher efficacy, fewer side effects and a 2-4 times shorter duration of therapy.

Thus, according to the original method, we obtained the active antiviral drug Sovonta, which, in terms of its physicochemical, pharmacological parameters and bioequivalence, corresponds to and exceeds the currently used dosage forms of Sofosbuvir in the therapeutic effect.

## PREPARATION AND INVESTIGATION OF SULFUR ALBUMIN NANOPARTICLES LOADED WITH ANTITUMOR DRUGS

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One of the important problems of modern medicine is the treatment of dangerous diseases without harm to the organism. Targeted drug delivery systems are of great interest<sup>[1]</sup>. The bases used are liposomes, polymers of synthetic and natural origin. The results of the preparation of nanoparticles based on human serum albumin, polylactic acid and its copolymer with glycolic acid, their immobilization by a number of antitumor drugs, including those of natural origin, have been presented in this study. The water-soluble cyclophosphamide, hydroxycarbamide, organophilic tamoxifen, and naturally occurring preparation Arglabin were used as synthetic drugs.

One of the anti-cancer drugs is «Arglabin» obtained by Kazakhstani scientists from the plant *Artemisia glabella* growing in Central Asia<sup>[2]</sup>. The investigation of Arglabin and a number of its derivatives showed that the epoxyarglabin and dimethylaminoarglabin hydrochloride possessed the best antitumor activity. No application of epoxyarglabin (substance or native arglabin) have been found because of its insolubility in water. Further a hydrophilic drug from preparation «Arglabin» for parenteral administration was developed on the base of dimethylaminoarglabin hydrochloride. «Arglabin» (substance) and dimethylaminoarglabin hydrochloride was provided by the International research and production holding «Phytochemistry» (Karaganda, Kazakhstan).

Methods of emulsification (simple and reverse emulsions), nanoprecipitation and desolvation were used for the nanoparticles synthesis. The polymer nanoparticles, depending on the preparation method, the nature of the carrier and the drug, have linear dimensions in the range from 80 to 250 nm. Particles had a narrow size distribution (polydispersity index from 0.02 to 0.13). The relatively high on modulus  $\zeta$ -potential values indicate the stability of the NPs formed during the time and the lack of coagulation factors (from -20 to -35 mV). The degree of inclusion of the drug in the polymer matrix is from 73 to 89%, the yield of nanoparticles by gravimetry is 74-82%, spectroscopy is 84-88%, which is a high indicator.

Binding of Arglabin and other biologically active compounds with nanoparticles of albumin was determined by UV-spectrophotometry and High Performance Liquid Chromatography. Solutions were washed with water-ethanol mixture and passed through a Sephadex column before carrying out the spectrophotometric analysis of particles with a drug substance.

The release of drugs was found to be slow, which gave the possibility of prolonging the drug action using polymer nanoparticles.

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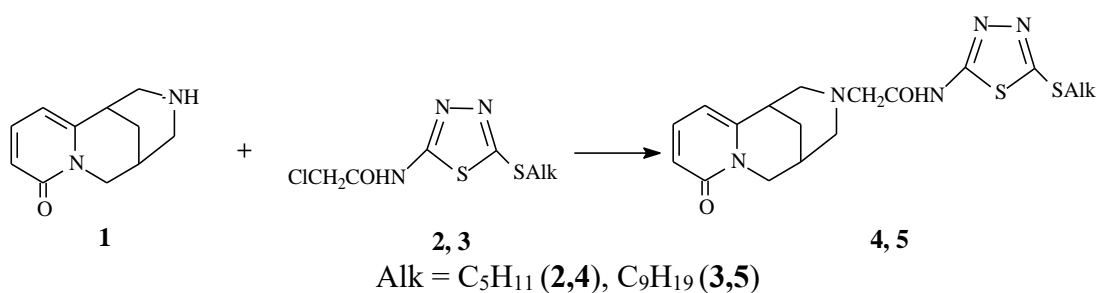
## SYNTHESIS OF N-(2-ALKYLTHIO-5-ACETYLAMIDO-1,3,4-THIADIAZOLE) CYTISINES

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Currently, there are many reports in the scientific literature on the synthesis of derivatives of the cytisine alkaloid (including fragments of heterocyclic compounds) and the study of their biological activity. The discovery of active substances among the compounds obtained further increases interest in them [1-2].

Continuing the earlier begun work [3], we studied the reactions of 2-alkylthio-5-chloroacetyl-amido-1,3,4-thiadiazole with cytisine (benzene, 20-25 °C). New N-(2-amylthio-5-acetyl-amido-1,3,4-thiadiazole) cytisine 4 and N-(2-nonylthio-5-acetyl-amido-1,3,4-thiadiazole) cytisine 5 s were obtained 80, 85% yield, respectively:



The structures (IR, UV, MS, and  $^1\text{H}$  NMR) and the physicochemical properties of the synthesized compounds were established, and antimicrobial and insecticidal activities were studied.

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## STUDY OF THE EFFECT OF ERBAHASI (GAZAKUT) LIQUID EXTRACT ON DIURESIS

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In traditional and modern medicine, because of its essential oils, flavonoids, carotene, saponins, glycosides and mucosa, plant *Gentiana olivieri* is widely used in the herbal extracts as a curative medicine to the urinary tract, kidneys, bladder and gall bladder, etc. Taking into account the above, it is intended to thoroughly study *G. olivieri*, known with a local name as *Elbakhor* growing in Uzbekistan, develop the technology of extracting its liquid extracts and thus develop the drug form of extracts and introduce them into medical practice. Researchers from Tashkent Pharmaceutical Institute have recommended that tincture of herbaceous herbs be widely used in medicine as a diuretic. However, the tincture has some disadvantages, given the short shelf life of the tincture, the uncertainty of the dose, and the fact that the plant has a shortage of storage and drug formulations. Therefore, it is important to obtain the liquid (fluid) extract of the herb, determine its biological activity and create a new drug form that meets the modern requirements.

Acute toxicity and resorptive effects of *Elbakhor* extract were studied in laboratory mice. The fluid extract studied was administered intravenously to 100–250 mg / kg and 500–1000 mg / kg in mice. Each dose was administered to 5-6 mice. The drug did not cause any adverse changes in animal status, such as tincture in the studied doses. The heartbeat and breathing movements were similar to those of the control animals. Laboratory mice receiving liquid extract were monitored for 12 days in vivarium. No deaths were recorded during that period. In turn, the effect of the herbal extract on diuresis was studied. The experiment was conducted in 30 laboratory rats of 146–200 g by Kau method (J Pharmacol Methods. 1984, 11(1):67-75). For this purpose, the amount of urine excreted daily in rats was measured. Then the amount of urine excreted per day was measured by sending 4 mL of distilled water per 100 g of rats. This experiment was performed 3 times, and an average of urine excretion was determined for each rat in 1 day. The rats were then divided into 5 groups: the 1st group was the control group, which was distilled water accordingly. Groups 2-3, 2-3 and 5, respectively, were given 3 mL of distilled water per 100 grams of rats in aq. solution of 40% and 70% of the diluted extract per 10 mL / kg respectively. and at the same time, 10% / kg of “Pol-Pala” (*Aerva lanata*) was injected with aq. solution of 40% and 70% of the fluid extract of *A. lanata*.

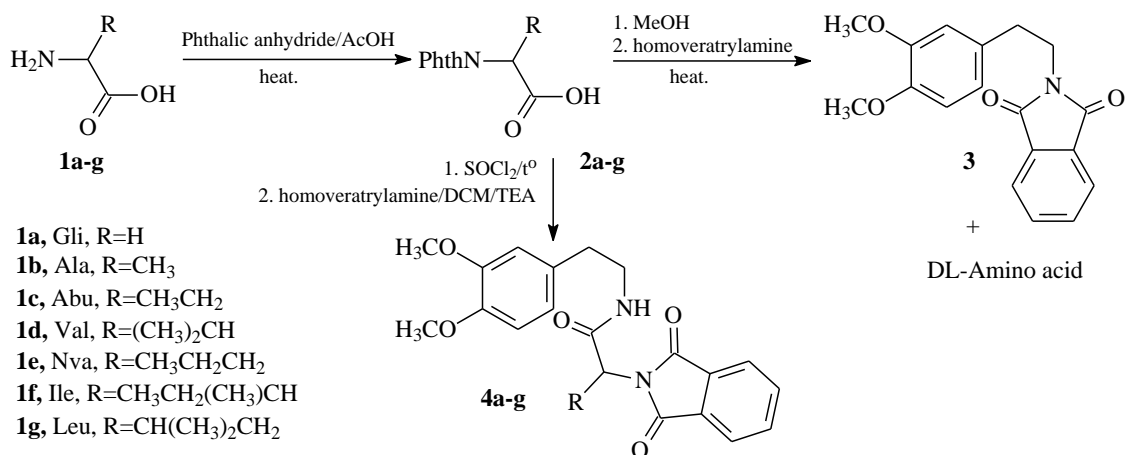
Results indicated that the control group had an average urinary excretion of  $6.05 \pm 0.85$  mL per day. Under the same conditions, rats injected with 40% aq. solution of 100 mL / kg studied fluid extract had an average daily of  $14.98 \pm 1.24$  mL, and 70% of aq. solution of the *Elbakhor* fluid extract was  $10.98 \pm 1.41$  mL. In rats given aq. solutions of 40% and 70% extracts of *Elbakhor*, the amount of urine extracted per day was 14.98 mL and 10.98 mL, respectively. Consequently, the studied extract of the extract of the herb increases the excretion of urine by 239% and 175%, respectively, and its effect on the excretion of urine has been shown to be much better than that of the “Pol-Pala” extract.

SYNTHESIS OF AMIDES OF N-PHTHALOYL- $\alpha$ -AMINO ACIDSD. B. Tukhtaev<sup>1</sup>, V. I. Vinogradova<sup>2</sup><sup>1</sup> Samarkand state University, 15 University blvd., 140104, Samarkand, Uzbekistan,  
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Amino group protection is one of the main steps in the research involved carboxylic group of amino acids. Sometimes N-protected products may be on focus of study. This is connected to the N-protecting agent of choice. Particularly, N-phthaloyl amino acids and their derivatives have been an important task in the research of medicinal chemistry.

In this paper we give results of our study of the synthesis and condensation with homoveratrylamine of N-phthaloyl- $\alpha$ -amino acids. In our study we synthesized N-phthaloyl derivatives **2a-g** based on the cyclocondensation reaction of amino acids **1a-g** with phthalic anhydride. Firstly, condensation reaction at high temperatures of prepared N-phthaloyl derivatives gave the result that imide of phthalic acid **3** and DL-amino acids were formed.

Experiments made it available to carry out preparation of chloroanhydrides of N-phthaloyl amino acids and condensation reaction at lower temperatures. As a result, amides of N-phthaloyl amino acids **4a-g**, which were the objects of research, were synthesized with high yield.



All reactions were controlled using thin layer chromatography. Structures of N-phthaloyl amino acids were confirmed using IR and <sup>1</sup>H NMR spectroscopy. Synthesized amides were extracted and purified for further experiments. Their structures were also confirmed in IR and NMR studies.

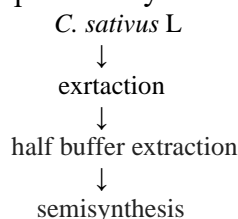


## DEVELOPMENT OF A TECHNOLOGY FOR PRODUCING THE *Crocus sativus* RADIANCE EXTRACT

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It is known that 68% of the total range of pharmaceutical products are accounted for drugs and biologically active additives from plant materials. High therapeutic effect, safety for the human body and relative accessibility determine their widespread use. Therefore, special attention has recently been paid to the cultivation of medicinal plants in Uzbekistan. The aim of our research is to ensure the implementation of the Decree of the Cabinet of Ministers of the Republic of Uzbekistan dated August 21, EDO-03 / 1-421 "On measures to create saffron plantations, meet the needs of the pharmaceutical industry and grow exported medicinal plants", by isolating and studying biologically active substances contained in plant materials and the development of analysis methods for *C. sativus*. Analysis of literary sources showed the effectiveness of the use of stigmas of the flowers of the corms *C. sativus*. For research, a standardized batch of raw materials were used according to GOST 21722-84. The stigmas of *C. sativus* L. were extracted three times in succession with hexane, then with benzene (2 g, in a ratio of 1:6 (weight-volume of solvent) at room temperature by these stations:



The obtained extracts were analyzed on an Agilent 5975C inert MSD / 7890A GC chromat-mass spectrometer. The components of the mixture were separated on an Agilent HP-INNOWax quartz capillary column (30m×250 $\mu$ m×0.25 $\mu$ m) in the temperature regime: 50 °C (1 min) – 4 °C / min to 200 °C (6 min) – 15 °C / min to 250 °C (15 min). The volume of the introduced sample was 1.0  $\mu$ L (hexane, benzene), the flow rate of the mobile phase was 1.1 mL / min, the temperature of the injector 220 °C. EI-MS spectra were obtained in the  $m/z$  range of 10-550 amu. The components were identified by comparing the characteristics of the mass spectra with electronic library data (Wiley Registry of Mass Spectral Data-9th Ed., NIST Mass Spectral Library, 2011). Comparing the retention indices (RI) of the compounds, determined with respect to the retention time of the n-alkane mixture (C<sub>9</sub>-C<sub>28</sub>), as well as comparing their mass spectral fragmentation with those described in the literature. It turned out that *C. sativus* grown locally in all respects met the quality standard. The standards given in the literature on the chemical composition of *C. sativus* methanol were 68.2%, ethanol 57.6% and  $\alpha$ -tocopherol flavonoids 95.6%. The hexane extract of the feed contained a large amount of 2,6,6-trimethyl-1,3-cyclohexadiene-1-carbaldehyde (23.40%), while the benzene extract contained 10.56% of dibutyl phthalate, which proved the compliance of chemical composition of saffron grown in the territory republic with international standards.

## SYNTHESIS AND BIOLOGICAL ACTIVITY OF 2,4-SUBSTITUTED QUINAZOLINES

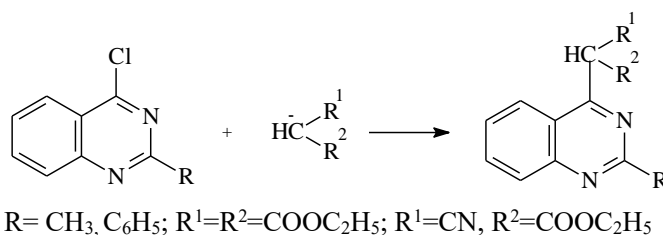
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Quinazoline derivatives represent one of the most active classes of compounds, possessing wide range of biological activities. Researchers have already determined many therapeutic activities of quinazoline derivatives, including anti-cancer <sup>[1]</sup>, anti-diabetes <sup>[2]</sup>, anticonvulsant <sup>[3]</sup>, etc. And the potential applications of the quinazoline derivatives in fields of biology, pesticides and medicine have also been explored.

Therefore, the synthesis of unknowns in the literature of derivatives 2-substituted of quinazolines having in 4 position residues of compounds with activated methylene groups, as malonic, aceto-, cyanoacetic esters, acetylacetone and others were of interest.

In this report we give the obtained results on syntheses 2-methyl-phenylquinazoline-4-ylidencyanoacetic and acetic esters. These compounds have been synthesized by interaction of corresponding 2-substituted 4-chloroquinazolines with anions cyanoacetic and malonic esters.



The reactions in the dimethyl formamide (DMF) went easily and the reaction products were obtained with good yields. It should be noted that reactions with the anion of malonic ether proceeded abnormally, i.e. in place of the expected 2-R-quinazoline-4-ylidene malonic ether, we obtained ethyl ester of 2-R-quinazoline-4-ylidene acetic acid.

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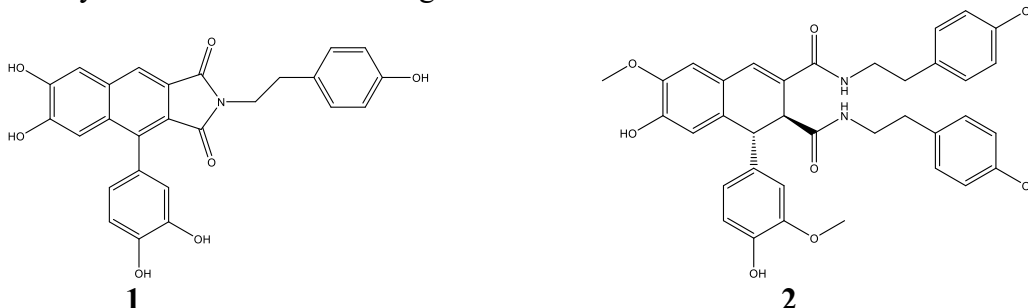
CHEMICAL CONSTITUENTS OF *Limonium gmelinii*A. Tuohongerbieke<sup>1,2</sup>, H. A. Aisa<sup>1,\*</sup>

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Plants of *Limonium* genus, exceedingly hardy halophytes, grow on saline soils and can regulate the content of sodium and calcium salts in soils. The most common species is *Limonium gmelinii*, the roots of which are used in folk medicine as an astringent and for acute gastro-intestinal diseases and the upper respiratory tract disorders [1].

In this study, an attempt was made to investigate the chemical constituents of ethyl acetate extraction from the roots of *Limonium gmelinii* growing in Xinjiang, China. The ethyl acetate extract was chromatographed over a silica gel column to divide into several fractions by gradient elution using chloroform/methanol. These fractions were further chromatographed subsequently with silica gel, sephadex LH-20 and ODS column to obtain two compounds. Their structures were confirmed to be cannabisin I (**1**) [2] and cannabisin D (**2**) [3] by NMR and mass data. As we know, compounds **1** and **2** were firstly isolated from *Limonium* genus.



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## EFFECTIVENESS OF A VEGETABLE INSECTICIDE AGAINST *Tuta absoluta*

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*Tuta absoluta* is recognized worldwide as one of the most dangerous quarantine insects. Therefore, the fight against the pest is relevant. The fight against *Tuta absoluta* is hampered by the rapidly developing resistance to chemicals in the insect. Previously, organophosphorus compounds, chlorfenapira and abamectin, which contribute to the destruction of larvae, were used to effectively combat *Tuta absoluta*. Extracts of tropical plants: *Trichiliapallens* and *Azadirachta indica* are used as plant-based insecticides against moths. Their advantage lies in the absence of harmful effects on the soil and cultivated plants with a sufficiently high toxicity to insect pests. Their use for processing field crops is less dangerous for human health and the environment. Along with this, a variety of plant extracts containing biologically active substances with insecticidal and antifeedant properties, but poor knowledge of their chemical composition and spectrum of action, provide a wide field for the scientific study of many aspects of a theoretical and practical plan.

The Institute of Plant Chemistry created an insecticidal agent of plant origin, Haplocid, which showed high insecticidal activity against sucking pests of fruit trees. The aim of this work was to study the insecticidal effect of the drug against *Tuta absoluta*.

Processing was carried out in the phase of the beginning of fruit formation in the first decade of July. Barlos tomato plants grown in closed ground conditions were sprayed using a hand sprayer with *Haplocid* at a 1.0% concentration. The counts were carried out on the 3rd, 7th day after the treatment of plants. Toxicity to *Tuta absoluta* larvae was assessed by the number of live pest larvae. As a reference, the insecticide *Praklane plus* (0.4 kg / ha) was used.

As a result of the work, a high toxicity of the drug was established in relation to the *Tuta absoluta* tracks. Its biological effectiveness on the 3rd day after treatment was 74.8%, when sprayed with *Proclain plus*, it was 66.1%. In the control group (without treatment), mortality of larvae was not observed. The effectiveness in the experimental version on day 7 was 68.3%, in *etholon* - 69.6%.

## INSECTICIDAL ACTIVITY OF BENZIMIDAZOLE AND BENZOTHIAZOLE DERIVATIVES AGAINST PESTS OF GRAIN LEGUMES CROPS

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One of the dangerous pests of leguminous plants is the four-spotted seed beetles (*Callosobruchus maculatus*) and the rice weevil (*Sitophilus oryzae* L.), which damage the plant generative organs, and recently their harmfulness is constantly increasing. *C. maculatus* develops on pea seeds, various legumes, chickpeas, cowpea, chickasano pea, and other legumes, with the exception of soybeans and beans<sup>[1,2]</sup>. *S. oryzae* L. is one of the most serious stored grain pests worldwide, originated from India and distributed worldwide for commercial purposes<sup>[3]</sup>.

The aim of the presented work was a comparative assessment of the insecticidal activity of benzimidazole and benzothiazole derivatives relative to imago *C. maculatus* and *S. oryzae* L. To determine the activity, testing substances were prepared in 3 concentrations: 10 mg/mL, 5 m/mL, 1 mg/mL. The systemic insecticide *Cypermethrin* at a dose of 0.32 l/ha was used as a reference. Accounting for the viability of the pest was carried out after 10-30 minutes, 1-3 hours according to the standard technique. As a result of laboratory testing, it was found that biological efficacy of the substance benzimidazole-amide in 1 mg/mL was 70.0-60.0% and in 5 mg/mL was 80.0% for adults of *C. maculates* and *S. oryzae* L. benzimidazole-amide in a 10 mg / mL dose and benzothiazole-nitrile in 5-10 mg / mL doses showed high insecticidal activity against *C. maculates* and *S. oryzae*. After 1 hour, mortality was noted at the level of the reference standard *Cypermethrin* (100.0%).

As a result, it was found that benzimidazole-amide and benzothiazole-nitrile in 5-10 mg / mL dose had a high insecticidal activity of contact action, turned out to be quite toxic against pests. It was also determined that the insecticidal activity of the preparation was not significantly different from the activity of the chemical reference standard.

Thus, since a comparative assessment of the activity of benzimidazole and benzothiazole derivatives under laboratory conditions did not reveal significant differences in their efficiency. We think that in the future for the protection of plants, it makes sense to use benzimidazole derivatives. It was established that on the basis of the conducted research, we can state that preparations benzimidazole-amide and benzothiazole-nitrile ensure the protection of crops from pests of cereal and leguminous plants.

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## PRECLINICAL STUDY OF THE POLYSACCHARIDE-BASED ANTITUBERCULOSIS DRUG CANDIDATE

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Tuberculosis, an infectious disease caused by the bacillus *Mycobacterium tuberculosis* is remaining a major threat to public health. Due to the specific treatment of tuberculosis such as complex therapy simultaneously with several antituberculosis drugs, duration of treatment, the necessity of prescribing multiple intakes of high doses of drugs and the occurrence of toxic-allergic complications, it is still very important to find a way to reduce the dosage of antituberculosis drugs. One of the approaches towards reducing the complexations of tuberculosis chemotherapy is developing and use of polymer-conjugated antituberculosis prodrugs with long-term acting properties. Such macromolecular drug systems can be prepared by introducing antituberculosis drugs into the macromolecules of the polymer vehicle.

In this regard, we obtained macromolecular drug system - Biomairin, by chemically conjugating to the modified polygalacturonic acid macromolecule: the antituberculosis drug isoniazid (25 mol%) via the azomethine bond, ethambutol (30 mol%) and rifampicin (15 mol%) via the ionic bond. The physicochemical properties and the structure of Biomairin were studied by UV, IR, NMR spectroscopy, and elemental analysis methods.

Pharmaco-toxicological properties and specific activity were studied. The results showed that the Biomairin belonged to non-toxic drugs with exhibiting 5-10 times less toxic effect with respect to the initial drugs isoniazid, ethambutol, and rifampicin. In addition, the results indicated that Biomairin did not possess allergenicity, mutagenicity, a toxic effect on the reproductive function of animals.

The *in vitro* and *in vivo* studies for the specific activity of Biomairin showed that the drug had a pronounced bacteriostatic effect on virulent strains of *Mycobacterium tuberculosis* H37Rv, *Humanis*, and *Bovis*.

Pharmacokinetic studies showed that with the introducing Biomairin with the therapeutic concentration of active substances (isoniazid, ethambutol, and rifampicin) in the blood the conjugated drugs remain 3-4 times longer than their low molecular weight analogs (isoniazid, ethambutol, and rifampicin), indicating a prolongation of their action against mycobacteria tuberculosis. It was also found that the introduction of isoniazid in the polysaccharide matrix delayed its metabolism into the therapeutically inactive acetyl isoniazid. Thereby, studies showed that Biomairin possessed low toxicity, a pronounced and prolonged antituberculosis effect.

## QUALITY CONTROL OF “YUYUZIN” CAPSULES

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At the Uzbek Scientific Research Chemical-Pharmaceutical Institute, based on the fruits of *Ziziphus jujuba* Mill, developed the antihypertensive drug Yuyuzin in the form of capsules of 0.35 g. The aim of the study is to control the quality of the obtained capsules according to the requirements of GF XI in terms of indicators: description, average weight, dissolution and disintegration.

Description. Hard gelatin capsules size "0", the body and lid are yellow. Contents of capsules: granules of brown color. The smell is peculiar. The taste is sweet-mucous, with a specific smell.

Determination of the average weight of the contents of the capsules according to the requirements of GF XI (issue 2., p. 144), the average weight of the contents of the capsules was normalized as follows: the mass of the contents of one capsule should be from 340 mg to 360 mg. Deviation from the average weight of the contents of individual capsules should be  $\pm 10\%$  in 18 capsules and  $\pm 25.0\%$  (but not more) in 2 capsules. During the tests, it was found that all capsules met these requirements.

Determination of capsule dissolution. The test was carried out in accordance with the requirements of FS 42 Uz-0003-00. For testing, the Rotating Basket device ERWEKADT 80 was used. Dissolution medium - water, volume - 200 ml, rotation speed - 100 rpm, temperature -  $37 \pm 2$  °C. 1 capsule was placed in the basket, after 45 min a sample was taken, filtered through a thick paper filter, and discarded the first portions of the filtrate. The optical density of the filtrate of the obtained test solution was measured on a photocolormeter at a wavelength of  $400 \pm 5$  nm in a cuvette with a layer thickness of 10 mm, using water as a comparison solution. The amount of substance transferred to the solution after 45 minutes was 92%.

Determination of capsule disintegration. Disintegration of the capsules was determined on a laboratory identifier ERWEKAZT 44 in accordance with GF XI. For the analysis, 6 capsules were taken, placed one in each slot of the identifier, the medium for the analysis was 0.1% hydrochloric acid solution at a temperature of  $37 \pm 2$  °C. As a result of the determination, all capsules completely disintegrated within 14 minutes. Carrying out the same analysis in an aqueous medium showed that the disintegration of the capsules in water was -19 min.

The research results showed that Yuyuzin capsules with an average weight of 0.450 g, obtained by the recommended technology, in appearance and other indicators satisfied the quality requirements of the capsules.

FLAVONOIDS FROM *Nitraria sibirica* LEAVESC. Turghun<sup>1,2</sup>, K. Bobakulov<sup>1,3</sup>, M. Bakri<sup>1,\*</sup>

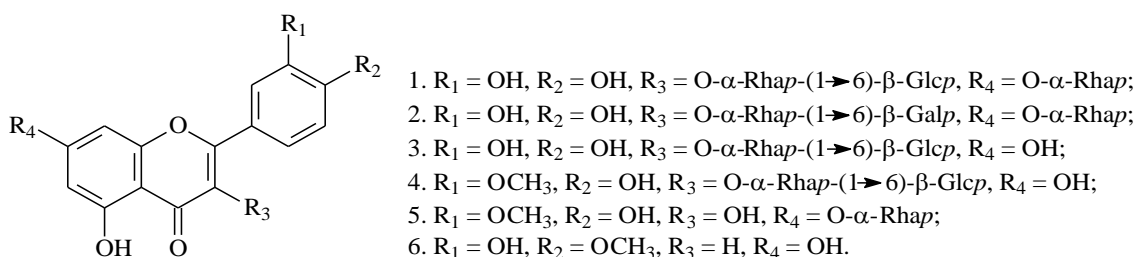
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The species of *Nitraria sibirica* Pall. (Nitrariaceae) is widely distributed in the Central Asia and North West of China. Its leaves and fruits have been used for the treatment of indigestion, irregular menses, and hyperpiesia for thousands of years in Middle East and Central Asia. As far as we know, the chemical constituents of *N. sibirica* mainly focus on alkaloids, while other types of compounds have been rarely reported.

In order to clarify the active constituents of *N. sibirica* leaves, the chemical components of the plant were studied, and six flavonoids were isolated from the ethyl acetate fraction of *N. sibirica* by Flash chromatography, Sephadex LH-20 and semi-preparative HPLC. Their structures were elucidated by MS and NMR spectra and were identified to be rutin-7-*O*- $\alpha$ -rhamnopyranoside (**1**), clovin (**2**), rutin (**3**), narcissin (**4**), quercetin-7-*O*- $\alpha$ -L-rhamnopyranoside (**5**), diosmetin (**6**) (**Fig. 1**). Earlier among which, compound **3** was isolated from *N. sibirica* fruits. All other compounds were isolated from *N. sibirica* species for the first time. Compounds **1,2,4** and **6** were isolated from *Nitraria* genus for the first time.



**Fig. 1.** The chemical structures of flavonoids isolated from *Nitraria sibirica* leaves.

## ACKNOWLEDGEMENTS

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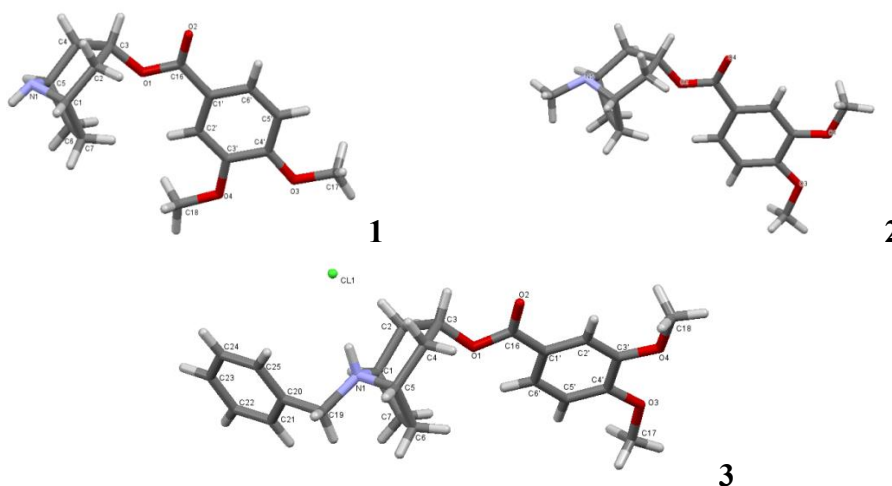


## STEREOCHEMISTRY OF THE TROPANE ALKALOIDS AND THEIR DERIVATIVES

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It is known that some tropane alkaloids (atropine, scopolamine) have a cholinolytic effect and are used as medicines. For the purpose of search of physiologically active substances, modification on the basis of available substances is carried out. So, plants of the genus *Convolvulus* are a source of alkaloids convolvine, which can be acquired on an industrial scale. Based on this alkaloid, earlier we carried out the synthesis of a number of derivatives. The methylation convolvine (**1**) obtained convolamine (**2**), reaction with benzyl chloride obtained benzylconvolvine (**3**). Biological studies on some cultures of cancer cells showed that benzylconvolvine had high superior anticancer activity, used in medicine for anti-cancer drugs.



The stereochemical behavior of the nitrogen atom and radicals in derivatives is of interest. To this end, for the consideration of structural issues, the RSA of the derivatives was carried out, which allowed to establish the relative configuration of the C3 center. Deputy of veratroyloxy group in position C3 is  $\delta$ -axial orientation relative to the tropane core. The orientation and location of the substituents of the N atom and C3 in compounds 1 - 3 are similar to those observed in convolinine and the hydrochloride of *O*-benzoyltropine. In molecules 1 - 3, veratroyloxy group is flat to an accuracy of  $\pm 0.040$ ,  $\pm 0.039$   $\pm 0.036$  E, respectively, and a benzyl group at N1 of  $3 \pm 0.008$  E.

Veratroyloxy group is distorted from the plane of symmetry of the tropane nucleus that is characterized by the torsion angle N3-C3 O1-C1', the values of which for 1 - 3 equal to 33, 29 and 33 °, respectively. The carbonyl group in these compounds and known analogues in the literature is always *sin*-directed with respect to the  $\beta$ -axially located hydrogen atom at C3. But methoxy group in ortho-position with 3' of veratroyloxy fragment in these compounds are different relative to the tropane nucleus (fig.1), indicating free rotation around the C16-C1' bond.

## REACTION OF 1-(3,4-DIMETHOXYPHENYL)-6,7-DIMETHOXYTETRAHYDROISOQUINOLINE WITH ALYLBROMIDE

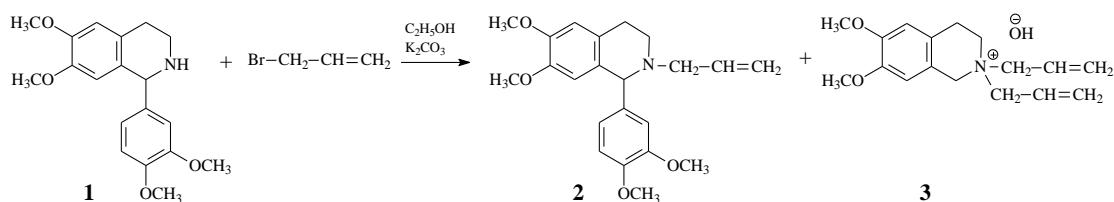
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Particular importance for medicine, are the alkaloids of the isoquinoline series and their numerous derivatives, which have a wide spectrum of biological activity and are part of many drugs.

In continuation of the search for potential biologically active compounds and the identification of their activity, we studied the reaction of 1-(3,4-dimethoxyphenyl)-6,7-dimethoxytetrahydroisoquinoline (**1**) with allylbromide. An interesting feature was found in the reaction that along with product **2**, unexpected product **3** was obtained. Carrying out the reactions in boiling alcohol with the addition of K<sub>2</sub>CO<sub>3</sub> gave, along with the expected product **2**, an unusual quaternary amine **3**.



The structures of the obtained substances were proved on the basis of IR, <sup>1</sup>H and <sup>13</sup>C NMR spectra.

## CORRECTION OF ANEMIA IN PATIENTS WITH CHRONIC KIDNEY DISEASE

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Anemia is one of the complications of renal dysfunction and is pathogenetically associated with decrease in erythropoietin production and/or chronic systemic inflammatory response.

**Purpose of research.** To assess the severity and pathogenesis of anemia in patients with chronic kidney disease (CKD) of V degree, who were treated on program hemodialysis, and the effectiveness of therapy was evaluated.

**Materials and Methods.** The study included 43 patients with CKD of V degree, who were treated on hemodialysis program 2 times a week. Therapy for anemia was not carried out for at least 3 months. In all patients, what were determined involved hemoglobin level in peripheral blood, hemoglobin concentration in red blood cells, reticulocyte concentration in peripheral blood, including immature (with high level of fluorescence, reflecting the nucleic components of the cell), the concentration of iron and serum ferritin. After the initial examination, all patients were prescribed anemia therapy, including injections of recombinant erythropoietin (2000 Units 2 times a week) and oral iron II drug. Control examination was carried out in 3 months. Statistical processing included the calculation of arithmetic mean and its standard error. Intergroup comparisons were performed using unpaired Student's t-test.

**Results.** The level of hemoglobin in peripheral blood of the source amounted to  $83.37 \pm 4.37$  g/L, the concentration of hemoglobin in erythrocytes  $72.85 \pm 9.42$  g/L, the number of reticulocytes with high fluorescence  $1.5 \pm 0.36\%$  and the iron concentration of the serum –  $14.35 \pm 2.47$  mmol/L, ferritin –  $963.46 \pm 16.43$  ng/mL 3 months after initiation of therapy, iron supplementation and recombinant erythropoietin, the hemoglobin level increased to  $97.84 \pm 13.26$ . At this stage, all patients were distributed depending on the relative dynamics of hemoglobin: groups with an increase in hemoglobin concentration by 10% or more (28 patients) and less than 10% (15 patients) were identified.

## SYNTHESIS OF N-(3,4-DIMETHOXYPHENYLETHYL) -(1,3-DIOXISOINDOLIN-2-IL) BENZAMIDE DERIVATIVES

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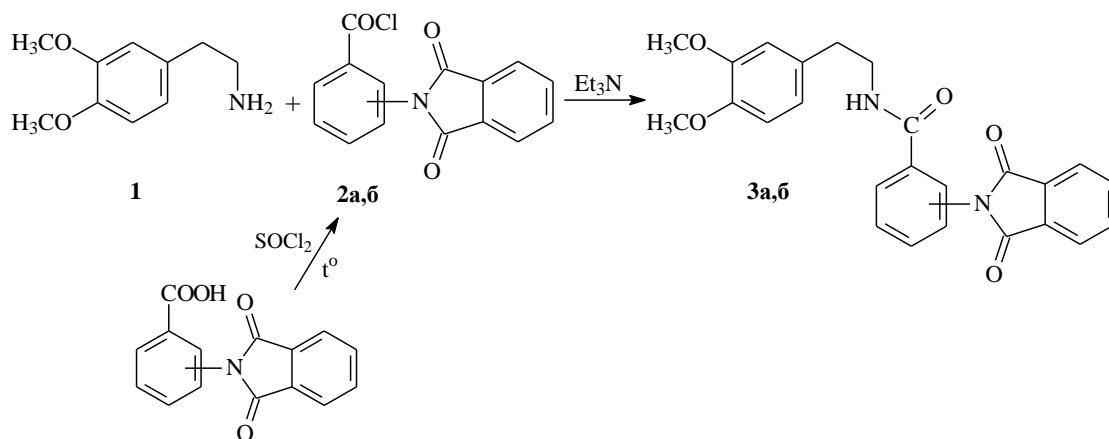
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N-phthaloyl is used as an important semi-product in the organic synthesis of amino acids. For example, in medical and pharmaceutical chemistry they are used as chiral sources and are widely used in the synthesis of polymeric materials.

Studies show that phthalimide derivatives exhibit such important pharmaceutical properties as hypolipidemic, analgesic, anti-inflammatory and antiviral activities.

N-phthaloyl is usually prepared by cyclocondensation of *m*- and *p*-aminobenzoic acids using phthalic acid.

Imid was prepared by the reaction of condensation of N-phthaloyl-benzoic acids with homoveratrylamine (**1**). To obtain N-phthaloyl-benzamide, chlorineanhydrides of N-phthaloyl-benzoy acid (**2a, b**) were formed by exposure of thionylchloride to N-phthaloyl-benzoic acid, then N-phthaloyl-benzamide (**3a, b**) derivateves were prepared by exposure of amine (**1**) to that at room temperature at the Et<sub>3</sub>N medium with the yield of 85-92%.



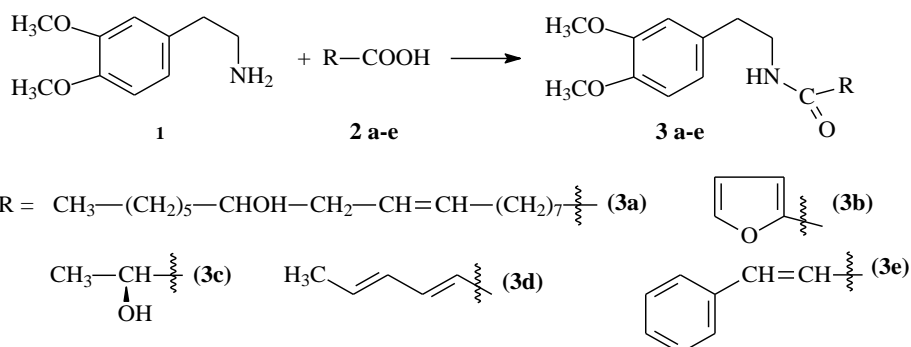
The purity and individuality of the synthesized products were monitored by TLC in various solvents systems. The structures of the obtained compounds were proved by the data of IR and PMR spectra.

## SYNTHESIS OF AMIDES BASED ON HOMOVERATRILAMINE

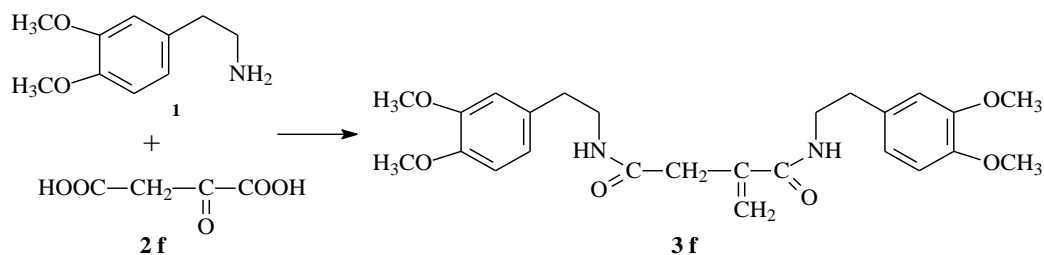
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The development of efficient approaches to the design of biologically active compounds is a high-priority problem for medicinal chemistry.

Amides, fundamental chemical structural units, are used widely in synthesis to form amines, and have important applications. It seemed interesting to us to use *N*-[2-(3,4-dimethoxyphenyl)ethyl]amides of ricinolic (**2a**), pirosilic (**2b**), lactic (**2c**), sorbic (**2d**), cinnamic (**2e**), and itaconic (**2f**) acids as synthons for various quinoline compounds.



Amides were synthesized from acids and homoveratrylamine. The high yields of amides and simplicity of method (Equimolar amounts of homoveratrylamine (**1**) and acids (**2a-f**) were dissolved in a sufficient volume (1-2 mL) of MeOH to complete salt formation. The resulting salt was heated at 175-178 °C on a glycerin bath for 2-4 h. The course of the reaction was monitored using TLC) were reproduced in reactions of amine **1** with acid **2a-f** to afford amides **3a-f** in 80-86% yields.



The structures of the synthesized amides were studied using IR and PMR spectroscopy.

## COMPONENT COMPOSITION OF ESSENTIAL OILS OF *Lophanthus schtschurowskianus* GROWING IN UZBEKISTAN

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Namangan state university

The plant is distributed as wild, and is also cultivated for the extraction of essential oil. Perhaps due to the use of lofant in the form of spices, the greatest distribution of lofant is observed in the middle climatic zone. Wild lofant is found throughout the United States, as well as in the surrounding regions of Canada. In Russia, lofant can be met in the Caucasus and Siberia, on the European continent in all countries with a temperate climate: in Ukraine, Poland, Moldova.

For the good growth of the lofant, the dry soils of the steppe zone, as well as the stony soils of the foothills, are ideally suited. Lofant loves good lighting, and grows rapidly under the sun's rays, forming shrubs.

The plant belongs to herbaceous perennials, although in appearance it can be confused with a shrub. The fact is that the aboveground part of the herb actively branches, and each individual branch of the plant ends with its own inflorescence, forming a volumetric likeness of a shrub crown.

The main component of the chemical composition of the plant, accounting for 15% of the amount of all compounds, is essential oil. In addition to essential oil, lofant is rich in other specific compounds with pharmacological activity. All chemical compounds that are part of the lofant, improve metabolic processes in the human body.

Essential oil was obtained by steam distillation. For this, 50 g of aerial parts of *Lophanthus schtschurowskianus* were placed in a 500 mL working flask, and filled with distilled water (about 200 mL). The distillate was distilled off for 3-4 hours using a Clevenger apparatus. The obtained distillate was extracted with dichloromethane, the extract of essential oils was dried with anhydrous sodium sulfate. The resulting oil was stored in a refrigerator at -4 °C until use. The resulting essential oils of *Lophanthus schtschurowskianus* is a pale yellow mobile liquid with a specific odor.

The analysis showed that the essential oils of *Lophanthus schtschurowskianus* obtained by hydrodistillation contained 33 substances, and the main components were as following:  $\alpha$ -Thujone (32.00),  $\beta$ -Thujone (10.00), Camphor (18.91), 1,8-Cineole (12.37), trans-Caryophyllene (2.45),  $\alpha$ -Humulene (3.60), Borneol (1.66), Sclareol (1.11),  $\beta$ -Pinene (1.58), Camphene (1.60), D-Limonene (1.09).

For the first time from the aerial part of the plant *Lophanthus schtschurowskianus*, 33 substances of volatile components were detected, of which 28 substances were identified.

## PREPARATION OF LECITHIN ORGANOGELS WITH A CARCINOGENIC DRUG K-2, ANTIVIRAL DRUGS OF MEGOSIN, RAGOSIN AND GOSSYPOL FOR TRANSDERMAL DELIVERY

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Currently, various lipid-based systems are being developed and successfully used for the dermatological purposes, including such a very effective and promising system as lecithin organogels (LOs)<sup>[1]</sup>. LOs - thermodynamically stable, transparent, viscoelastic, biocompatible isotropic gels, consist of phospholipids (lecithin), an appropriate organic solvent and a polar solvent, most often water. These jelly-like phases, which are a three-dimensional network of intertwined cylindrical whisker lecithin micelles, immobilize the continuous external organic phase, thus turning the liquid into a gel.

Ease of preparation, easy quality control, thermodynamic stability, improved penetration, along with biocompatibility and safety when used for a long period, make organogels the preferred choice for effective drug delivery. Their improved ability to penetrate the deeper layers of the skin has been confirmed by numerous studies<sup>[2,3]</sup>.

The studied drugs, anticancer “K-2” (a derivative of colchamine), antiviral megosin and ragosin (derivatives of gossypol), as well as gossypol itself, which were hydrophobic compounds, were introduced into the gel as a solution in the organic liquid phase in an amount of 0.5-1% of the total gel mass. First, they were previously dissolved in suitable solvents (ethanol, isopropanol, chloroform, toluene), mixed with a base, then the solvent was evaporated on a rotary evaporator. The resulting mixture was hydrated. The success of the experiment was determined visually by the fact of gel formation which was stable for some rather long time (about several days). The most stable lecithin organogels were formed on the basis of hexadecane (cetane) and paraffin oil with a lecithin content of 10% by weight of the gel. As a result, we settled on paraffin oil as the most affordable.

Thus, we selected the ratios of the starting components and optimized the hydration conditions. As a result, samples of stable LOs with a number of antitumor and antiviral drugs were obtained. The use of the obtained LOs for transdermal delivery of the studied drugs was supposed.

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## **INFLUENCE OF POLYPRENOLS FROM *Vitis vinefera* LEAVES ON THE PROCESS OF HEALING OF PLANEAN SKIN WOUNDS IN RATS**

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Polyprenols are a fairly extensive class of natural compounds, which has undergone intensive biological studies in recent years. It has been repeatedly shown that they enhance the regenerative processes in the body. In this regard, we have analyzed the wound healing effect of polyprenols isolated from leaves of a local species of wild grape (*Vitis vinefera* L.). The experiments were carried out on male rats weighing 180-200 g., to which round full-layer wounds  $230 \pm 1.2 \text{ mm}^2$ , the bottom of which was the fascia, were applied with a special stamp on the depleted back skin. All traumatic procedures were carried out under aseptic conditions under mild ether anesthesia. The studied preparation of polyprenols (PP) was applied to wound skin defects with an even layer once a day throughout the experiment. In parallel, there was a group of rats whose wound defects were treated with sea buckthorn oil. During the experiment it was found that visually by bioclinic indicators and by measuring the area of the wound surface, the wound healing effect of PP significantly exceeded the corresponding effect of sea buckthorn oil. Most of all, this was revealed histomorphological analysis of the wound healing process. So, daily application of PP and sea buckthorn oil to the planar skin wound (in the latter case is noticeably weaker), earlier stimulation of the activity of cellular elements in the wound with an increase in the number of epithelial cells and fibroblasts was noted, the newly formed structures were characterized by an increased content of glycogen and ribonucleotides. There was an intensification of the growth of vascular elements, acceleration of the formation of the demarcation shaft and scab rejection, a decrease in the severity of tissue edema. When studying granulation tissue formed in planar skin wounds, it was revealed that in it, taken from experimental animals compared to the control, the RNA/DNA ratio increased, the accumulation of collagen, as well as other connective tissue biopolymers, increased. These changes under the influence of sea buckthorn oil were also less pronounced.

Thus, according to histomorphological and biochemical studies, the studied polyprenols have a pronounced effect on proliferative and biochemical processes in the cells of the epidermis and dermis. It is the effect on the cells of these two regenerative systems that promotes the rapid healing of wounds. So, while in the control, planar full-layer skin wounds healed on average in  $25.2 \pm 1.6$  days, then in rats treated with polyprenols from *Vitis vinefera* L., complete healing was observed for  $16.2 \pm 1.2$  days, in rats treated with sea buckthorn oil, complete wound healing was observed for  $20.8 \pm 1.8$  days. Therefore, polyprenols from *Vitis vinefera* L. are of practical interest as an effective wound healing agent.



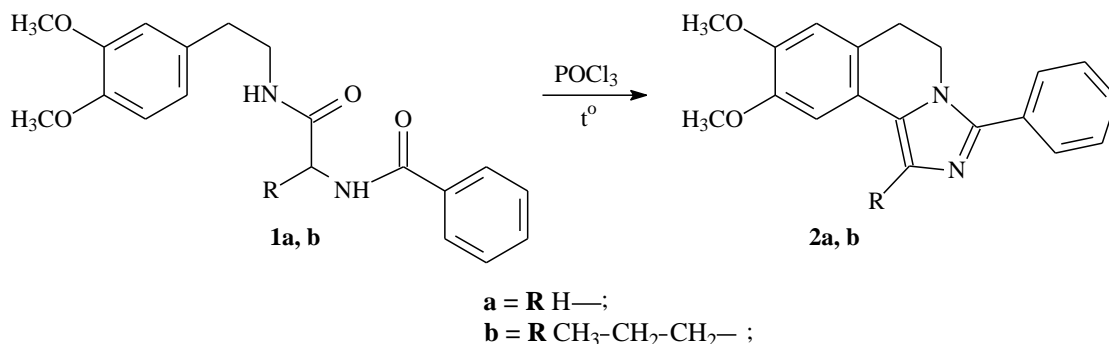
## SYNTHESIS OF DIHYDROIMIDAZO [5,1-a] ISOQUINOLINES

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One of the methods of medicinal chemistry is the synthesis of hybrid multifunctional drugs that can interact with various biological targets.

The importance of imidazole derivatives for medicine is difficult to overestimate. Due to the wide range of their biological and pharmacological activities, they are used to produce drugs to treat fungal, viral, oncological and other diseases<sup>[1,2]</sup>. The core of imidazole is part of vitamins, enzymes and proteins. Of particular interest to researchers are tricyclic derivatives of imidazole containing sites of a nitrogen atom, for example, imidazo [1,2-a] pyrimidines, imidazo [1,2b] - quinolines and isoquinolines.

In the present work, cyclization reactions of amides **1a-c** and the preparation of derivatives of 5,6-dihydroimidazo[1,5-a] isoquinoline (**2a, b**) are reported.



The presence of two urea groups in the molecules of the obtained amides creates the condition for the formation in one stage of a mutually condensed tricyclic compound containing a nodal nitrogen atom and imidazole and isoquinoline fragments.

Amides **1a, b** were cyclized by the Bischler-Napiralsky reaction with POCl<sub>3</sub>, used both as a reagent and as a solvent. By heating for 4 hours (in a boiling water bath), imidazo [1,5-a] isoquinolines **2a, b** were obtained with a yield of 74% and 76%, respectively.

The purity and identity of the substances were monitored by TLC in various solvent systems. The structures of the obtained compounds were confirmed by the data of IR and PMR spectra.

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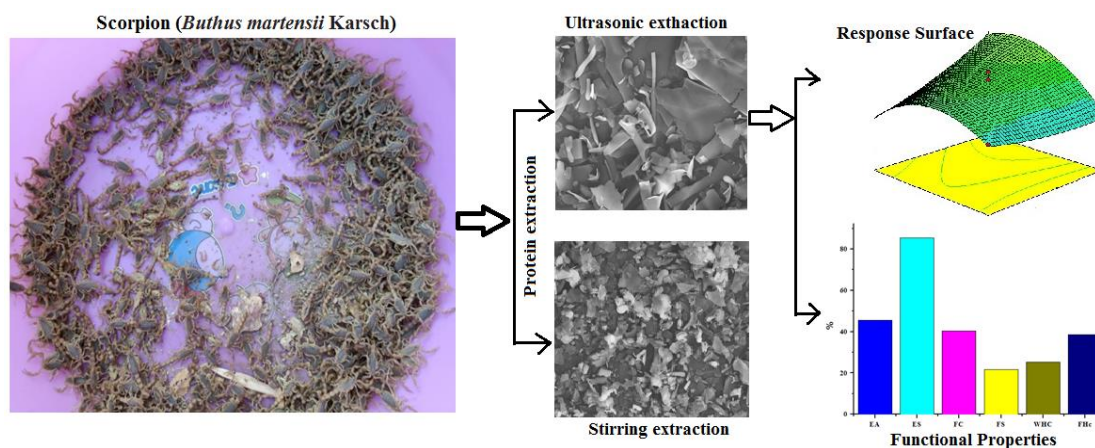
## OPTIMIZATION OF ULTRASONIC EXTRACTION OF SCORPION (*Buthus martensii* Karsch) PROTEINS BY RESPONSE SURFACE METHODOLOGY

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Scorpion (*Buthus martensii* Karsch) has a long history of being used in folk medicine in China. To make full use of this medicinal material, it is necessary to find an efficient extraction method. The purpose of this study was the optimization of ultrasonic extraction (UE) of scorpion proteins using response surface methodology (RSM) and the characterization of the protein functional properties. Response surface methodology was applied for the determination of the optimal parameters of UE. Based on single factor experiments, three factors: ultrasonic power (w), liquid/solid (mL/g) ratio and extraction time (min) were used for the determination of scorpion proteins (SP). The order of effect of the three factors on protein content and yield were ultrasonic power > extraction time > liquid/solid ratio and the optimum conditions of extraction proteins were as follows: extraction time 60.00 min, ultrasonic power 400.00 w and liquid/solid ratio 18.00 mL/g.



## PHENOLIC ACIDS ISOLATED FROM *Microsorium fortunei*

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*Microsorium fortunei* (T. Moore) Ching, belonging to the family Polypodiaceae, is widely distributed in most regions of southern and southwestern China. In Chinese medical practice, it is regarded as Chinese herbal medicine to treat viper bite, dysentery, rheumatoid arthritis, lymph node tuberculosis etc <sup>[1,2]</sup>. In this study, fifteen known compounds, including seven phenolic acids, *trans*-caffeic acid (**1**), (-)-*trans* blechnic acid (**2**), rosmarinic acid (**3**), 5-*O*-caffeoylshikimic acid (**4**), (*R*)-3-(3,4-dihydroxyphenyl)-lactic acid (**5**), polybotrin (**6**), (-)-*trans* -brainic acid (**7**), fern-9(11)-ene (**8**), fern-9(11)-en-28-oic acid (**9**),  $\beta$ -sitosterol (**10**), daucosterol (**11**), uracil (**12**), stigmast-4-ene-3, 6-dione (**13**), (22*E*, 24*R*)-ergosta-4, 6, 8(14), 22-tetraen-3-one (**14**), vitexin (**15**) were isolated from the petroleum ether and ethyl acetate fractions of *Microsorium fortunei* (T. Moore) Ching <sup>[3]</sup>. Compounds **2**, **4**, **5**, **7**, **9**, **13**, **14** and **15** were isolated from *M. fortunei* (T. Moore) Ching for the first time. The anticancer and antibacterial activities of these phenolic acids will be investigated in due course.

**Keywords:** *Microsorium fortunei*; phenolic acids; anticancer activity; antibacterial activity

### ACKNOWLEDGMENTS

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## DISCOVER, SYNTHESIS AND TARGET IDENTIFICATION OF NOVEL TOXINS FROM *Myrmeleon sagax* LARVAE

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The larvae of the medicinal insects *Myrmeleon sagax* are known as ant-lion. Since ancient time, ant-lion has been used as a traditional medicine to deal with a variety of incurable disease. At present, the research of *Myrmeleon sagax* mainly focused on molecular and morphological identification. Ant-lion body may contain a variety of proteins and some unknown proteins may have medicinal functions and special use.

This research took the *Myrmeleon sagax* larvae from Xinjiang as the research object and constructed its head tissue cDNA library. By means of sequence alignment, a known peptide with 44 amino acid residues including six cysteine, three disulfide bridges with the name CL44 was found. The primary structure of CL44 was found to show similarity to  $\omega$ -superfamily conotoxins, which mainly target voltage gated calcium channels. Linear CL44 were synthesized by solid-phase synthesis methods and were folded in the folding solution at 28°C for 24 h, pH 7.4. After folding, the target peptide was enriched and purified. CL44 may have the same activity as  $\omega$ -conotoxins and it needs to be screened for potential activity.

### ACKNOWLEDGMENTS

This work was supported by Major Special Project of National Science and Technology, Research and Development of New ethnic Drug varieties and its key Innovation Technology (2017ZX09301045), “Tianshan Excellence Project” in 2017, and the Central Asian Drug Research and Development Center of Biologically Active Compounds of the Chinese Academy of Sciences.

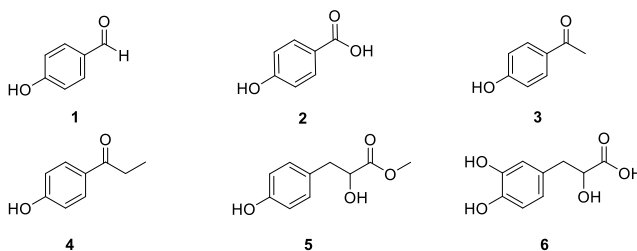
## PHENOLIC COMPOUNDS FROM THE SEEDS OF *Cordia dichotoma*

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*Cordia dichotoma* Forst, belongs to the family Boraginaceae, widely distributed in tropical and subtropical regions. The seed of *C. dichotoma* is a traditional drug and edible fruit. There are some activity investigations on the methanol extracts of the seeds, but few reports about the phytoconstituents responsible for those activities. In present work, six phenolic compounds were isolated from the ethanol extract of *C. dichotoma* seeds using silica gel chromatography, Sephadex LH-20, pre-HPLC methods. Their structures were elucidated as *p*-hydroxybenzaldehyde (1) [1], 4-hydroxybenzoic acid (2) [2], *p*-hydroxyacetophenone (3) [3], *p*-hydroxypropiophenone (4) [4], Latifolicinin C (5) [5], and danshensu (6) [6].



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## NEW MOLECULAR COMPLEXES OF QUERCETIN WITH IVY TRITERPENE SAPONINS

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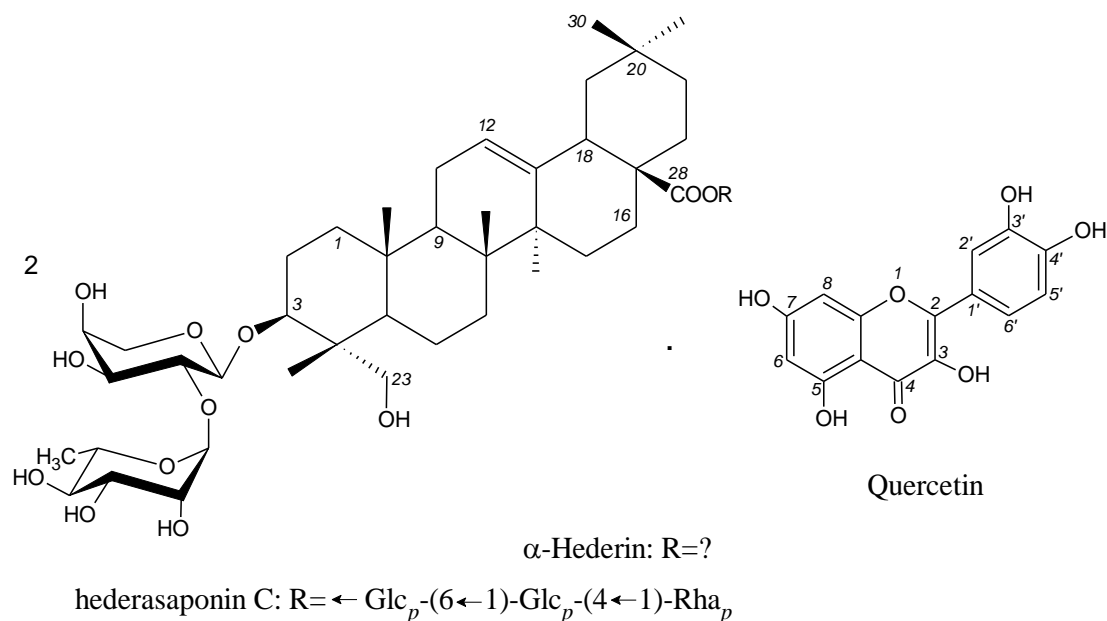
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The molecular complexation of ivy triterpene saponins  $\alpha$ -hederin (hederagenin 3-*O*- $\alpha$ -L-rhamnopyranosyl-(1 $\rightarrow$ 2)-*O*- $\alpha$ -L-arabinopyranoside) and hederasaponin C (hederagenin 3-*O*- $\alpha$ -L-rhamnopyranosyl-(1 $\rightarrow$ 2)-*O*- $\alpha$ -L-arabinopyranosyl-28-*O*- $\alpha$ -L-rhamnopyranosyl-(1 $\rightarrow$ 4)-*O*- $\beta$ -D-glucopyranosyl-(1 $\rightarrow$ 6)-*O*- $\beta$ -D-glucopyranoside) with different drugs and biologically active molecules has been widely studied.

We prepared new molecular complexes of  $\alpha$ -hederin and hederasaponin C with quercetin. Quercetin is one of the most famous flavonols. Quercetin has P-vitamin activity and exhibits antioxidant, anti-inflammatory, antispasmodic, antisclerotic, diuretic, and antitumor effects. Previously, we studied the molecular complex of quercetin with triterpene glycoside glycyram (monoammonium salt of glycyrrhizic acid).

The molecular complexes of quercetin with ivy triterpene saponins were preparatively obtained by liquid-phase method. The composition of the complexes was determined by the isomolar series method in spectrophotometric version. This method gave a molar ratio  $\approx 2.0$ , which corresponded to a 1: 2 complexes of quercetin with ivy saponins, respectively.

The complexation was studied by ATR FT-IR spectroscopy. Intermolecular interactions in the complexes were carried out by hydrogen bonds formation and hydrophobic contacts.



## SYNTHESIS OF 2-METHYL-3-ALKYLQUINAZOLIN-4-ONE SULPHONAMIDES

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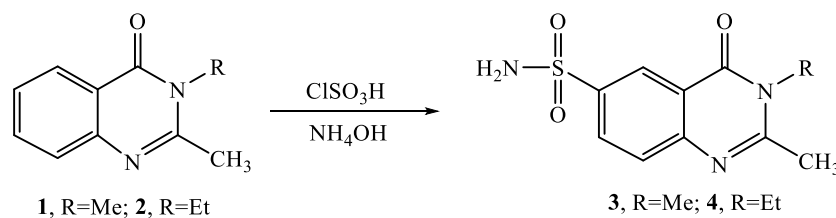
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It is known that the derivatives of quinazolinone are interesting objects for synthetic organic and bioorganic chemistry. Many drugs in the field have been synthesized and are widely used in agriculture and medicine.

In addition, these compounds are chemically interesting due to presence of different reaction centers in their molecules. We aimed to carry out the reaction 2-methylquinazolin-4-one with chlorosulfonic acid on the aromatic ring of starting compounds.

The presence of H (**1**, R=H) or alkyl groups (**1**, R=Me; **2**, R=Et) in N-3 influence to the chlorosulfonylation reaction. No reaction was observed in the case of compound **1** (R=H). Before chlorosulfonylation we conducted alkylation of **1** (R=H) with methyl iodide and ethyl bromide, and corresponding N-alkyl products (**1,2**) were synthesized. After that reactions of 2-methyl(ethyl)quinazolin-4-ones (**1, 2**) were carried out with chlorosulfonic acid and desired sulfonamides (**3, 4**) synthesized in good yields:



It should be noted that the obtained sulfonamides were key intermediates for the synthesis of potentially active sulfonylurea.

Structures of the synthesized compounds were confirmed by IR and <sup>1</sup>H NMR spectra.

## CHEMICAL COMPOSITION OF THE ESSENTIAL OIL EXTRACTED FROM THE *Mentha piperita* OF UZBEKISTAN

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Herbal medicinal compounds are used all over the world as the most natural way to intake of phytochemicals. The use of natural products that are rich in bioactive substances is growing along with the demand for plants containing wide range of antioxidant properties and bioactive molecules capable of neutralizing free radicals slowing the progress of many chronic diseases associated with oxidative stress [1].

Among the diversity of plants, *Mentha piperita* (Lamiaceae family) is one of the herbs most widely used worldwide, with a long history of safe use in medicinal preparations. Its leaves are used as a remedy for common cold, inflammation of the mouth, pharynx, liver, as well as disorders in the gastrointestinal tract such as nausea, vomiting, diarrhea, cramps, flatulence and dyspepsia. It is also used as antioxidant, antimicrobial, antiviral, antiinflammatory, and anti-carcinogenic [2]. Plant is known for having several phytochemicals, including polyphenols that are highly effective antioxidants and are less toxic than the synthetic ones. This property makes it of great interest to the Food Industry, since the phenolic compounds retard the oxidative degradation of lipids improving the quality and nutritional value of food [2].

It is also of great interest for Medicine due to its medicinal activities as antinociceptive, antiinflammatory, antimicrobial and antioxidant properties.

Medicines made on the basis of substances with high biological activity are characterized by their low toxicity, compatibility with the body and distinctive properties, several advantages from synthetic drugs. Such properties have been studied in the development of drugs based on compounds menthol and its derivatives [1-2].

Menthol is an organic compound made synthetically or obtained from peppermint or mint oils with flavoring and local anesthetic properties. When added to pharmaceuticals and foods, menthol functions as a fortifier for peppermint flavors. It also has a counterirritant effect on skin and mucous membranes, thereby producing a local analgesic or anesthetic effect.

The aim of this study is to investigate for the first time the chemical composition of the essential oil extracted from *Mentha piperita* cultivated in Gulistan, Uzbekistan. The other objective is to determine the antioxidant and antibacterial activities against certain bacterial strains in order to find new metabolite products, which are characterized by a biological activity. Thirty-three compounds were identified representing 90.99% of the total oil. The principal components are: menthol (97.54%), L-menthol (98.37%) and neomenthol (93.36%), which compose 97.54% of the oil.

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## METABOLIC PROFILING ANALYSIS OF CORILAGIN *IN VIVO* AND *IN VITRO* USING HPLC-Q-TOF-MS/MS SPECTROMETRY

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Corilagin is an Ellagitannin with favorable pharmacological activities [1, 2]. But there was no report regarding the metabolism of corilagin in vitro or in vivo. In this study, the metabolic profile of corilagin in rats as well as in rat intestinal bacteria and liver microsomes incubation system in vitro were investigated comprehensively for the first time. Consequently, with the aid of sensitive high-performance liquid chromatography quadrupole time-of-flight mass (HPLC-Q-TOF-MS/MS), corilagin and its twenty-four metabolites (fourteen phase II conjugate metabolites of corilagin, three hydrolyzed metabolites EA, GA, M3 and their seven derived metabolites) were absolutely or tentatively identified in rat biological samples (urine, feces, plasma and tissues) after oral administration of corilagin. In vitro, the three hydrolyzed metabolites were identified in rat intestinal microflora and liver microsomes. These results demonstrated that corilagin itself not only could undergo extensive phase II metabolism in rats, but also could undergo hydrolysis reaction in rats as well as in rat intestinal bacteria and liver microsomes in vitro. This study was the first report to identify phase II conjugate metabolites (except mono-methylate conjugated metabolites) of pure Ellagitannin and distribution of these metabolites in vivo. In addition, clear, detailed metabolic pathways of corilagin were shown to involve hydrolysis, methylation, glycosylation, reduction, glucuronidation and sulfation.

**Keywords:** Corilagin; Ellagitannin; Metabolism; HPLC-Q-TOF-MS/MS

### ACKNOWLEDGMENTS

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## DEVELOPMENT OF PERSPECTIVE DRUGS OF DIRECTED ACTION ON THE BASIS OF MEDICINAL PLANTS

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It is known that modern health care is based on the treatment and prevention with the use of herbal preparations. In local conditions, the medicinal plant *Catharanthus roseus* (L.) G. Don. was introduced, which took root well in the hot climate of Uzbekistan. Vinblastine, terpeno-indole alkaloids isolated from the leaves of *Catharanthus roseus* (L.), standardized by VFS 42-1106-81, was a cytostatic blocking cell mitosis at the mitophase stage. The use of an alkaloid in an immobilized form of directed action increased antitumor activity in the treatment of lymphogranulomatosis, hematosarcoma, myeloma, choriocarcinoma.

We used UV spectrophotometry with a maximum absorption for aqueous solutions of terpene-indole alkaloids at  $214 \pm 1$ ,  $268 \pm 1$  nm, respectively. Purified water was chosen as the optimal solvent for the development of quantitative determination methods (analytical maximum 268 nm for vinblastine). To study the analytical field of methods, a number of working solutions (solution B) were prepared from a standard solution (solution A) in the concentration range of 1-250  $\mu\text{g} / \text{mL}$ . In the obtained results, it was found that the optimal analytical region for quantitative determination was the concentration range from 5 to 50  $\mu\text{g} / \text{mL}$ , since the optical density index was in the range of 0.1-1.0. The accuracy of the methods was determined by adding a standard amount of vinblastine to the sample solutions of 50, 125 and 250  $\mu\text{g}$ . The detection limit for the drug was calculated according to the equations of the calibration graphs. The sensitivity of the method was determined by the influence of the pH of the medium (buffer solutions with pH = 3-10) on the measurement results, presented in table 1.

**Table 1.** Evaluation results of the developed spectrophotometric methods for the determination of vinblastine in immobilizate.

Qualitative parameters	Received data
Experimentally established detection limit, ( $\mu\text{g} / \text{mL}$ )	1,2718
Reproducibility	$\bar{X} = 100,03\%$ ; $SD = 0.36003$ ; $RSD = 0.0036$ $\bar{X} \pm \Delta\bar{X} = 100.03 \pm 0.42\%$ ; $P = 95\%$ ; $\xi = 0.9456\%$
Sensitivity	The position of the absorption maximum remains stable in the range from 3.0 to 7.0 units pH

Thus, the possibility of obtaining an immobilized form of vinblastine from local raw materials using previously developed methods was studied. Spectrophotometric methods for quantitative determination of vinblastine in an immobilizate model mixture were evaluated, which could be further used to determine the active substance in various dosage forms of antitumor activity. The results obtained will undoubtedly contribute to an increase in the range of effective anticancer drugs obtained on the basis of local plant materials.

## CHEMICAL ANALYSIS OF SUBSTRATES FROM THE WASTE OF MEDICINAL HERBS *Aconitum L* and *Thermopsis alterniflora* FOR MICROBIOLOGICAL FERMENTATION

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The processing of renewable plant materials into industrially important chemicals is of great practical interest. Due to the abundance, low cost and high content of carbohydrates (60-70% of the absolute dry matter of raw materials), close to cereals, lignocellulos biomass is an attractive raw material for bioconversion to produce fuel and other valuable products of microbiological origin. Processing and production of valuable products of national economic value from lignocellulos biomass has become one of the main areas of intensive research and development.

The Institute of Plant Chemistry of the Academy of Sciences of the Republic of Uzbekistan established the production of medicinal herbs substances, where tens of tons of various medicinal herbs processed annually, including *Aconitum L* and *Thermopsis alterniflora*. In the process of medicinal plant materials, the main quantitative waste product was depleted raw materials (meal), after extraction with 80% alcohol solution.

In medicinal plants, the content of chemical compounds with biological activity is only from 0.1% to 5%. Therefore, in the process of processing plant materials at pharmaceutical enterprises, huge amounts of plant waste is accumulated in the form of crushed mass of stems, leaves or roots, the mass of which reaches an average of 85-90% of the consumed raw materials. Having in its composition most of the same components as in the feedstock, technological waste is a valuable secondary raw material for their further microbiological processing. **The aim** of this study was to study the component composition of waste herbs of *Aconitum L* and *Thermopsis alterniflora*, as raw materials for biofuels and other products of microbiological origin.

The TS, VS, TC, TN (volatile solid) and pH were measured according to the Standard Methods for the Examination of Water and Wastewater (APHA, 2005). The contents of hemicellulose, cellulose, and lignin were determined by standard methods. The results of the study showed that the total solids (TS%) of *Aconitum L* and *Thermopsis alterniflora* was 94–91% and volatile solids (VS%) 89–86%, respectively. The total carbon content (TC%) was 40 - 36%, respectively. Total nitrogen (TN% TS) - 1.2 - 1.0%, respectively. The ratio of nitrogen and carbon (C / N) was 33 - 36%, respectively. The content of lignin was 24.8 and 22.4%, cellulose 46.3 - 47.4% and hemicellulose 24.7 - 26.2%, respectively. The results of the analysis showed that the waste of medicinal herbs was a full-fledged substrate for further biological processing to produce biofuels and other products of microbiological origin.

## INFLUENCE OF AEROBIC TREATMENT OF LIGNOCELLULOSE SUBSTRATES FROM *Aconitum* L and *Thermopsis alterniflora* ON ANAEROBIC FERMENTATION

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The article discusses the effects of substrate preliminary aeration on the process of anaerobic methane fermentation of plant waste *Aconitum* L and *Thermopsis alterniflora*. To intensify the process, it is necessary to pre-treat the substrate with physical, chemical, biological or combined methods in order to destroy the strong structures of lignin and polymeric carbohydrates. In this regard, the preliminary processing of lignocellulos substrate is the most important and expensive stage, limiting the process of anaerobic fermentation as a whole. However, traditional physicochemical pretreatment methods are expensive because they require appropriate equipment, chemical reagents, as well as additional energy and money costs. Recently, in world practice, increasing attention has been paid to biological methods for the preliminary processing of lignocellulos raw materials. Most authors cite the effectiveness of pre-controlled aeration of raw materials with air or oxygen, as a simple and convenient pre-treatment.

**The aim** of our study was to study the effect of preliminary aeration of the substrate on the process of anaerobic methane fermentation of plant waste of medicinal herbs *Aconitum* L and *Thermopsis alterniflora*.

As the reactor used plastic containers with a volume of 1,500 mL, sealed plastic containers that operated on a batch principle of loading with the ability to conduct both aerobic and anaerobic fermentation of the substrate. Loading and unloading of raw materials was carried out periodically through the lid of the tank. 50 g of plant waste and a certain amount (500 mL) of inoculant were added to each reactor to initiate aerobic fermentation. Aerobic fermentation was carried out according to the recommendations. After aerobic fermentation, 200 mL of the substrate was added to the inoculum to initiate anaerobic fermentation. After that, the reactor was sealed with a rubber stopper and anaerobic fermentation was carried out in a water bath at 37 °C. The reactors were manually stirred for 15 seconds twice a day at a fixed time, and the volume of gas and components was measured once a day at a fixed time. Anaerobic tests were carried out for approximately 30 days, until the release of biogas was stopped.

The results of anaerobic fermentation showed that the highest biogas yield (485 mg / g VS - 470 mg / g VS) was shown by the substrates from *Aconitum* L and *Thermopsis lanceolata*, aerated for 24 hours. Thus, in our opinion, the method of pre-aeration of plant waste is a reliable, simple and cost-effective method that significantly affects the rate of decomposition of lignocellulose and the yield of biogas.

**LIPIDS FROM SEED OF *Marrubium alternidens* GROWING IN UZBEKISTAN**

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*Marrubium alternidens* Rech. (Lamiaceae family) grows in Ferghana, Bukhara, Namangan and other regions of Uzbekistan. It has been reported that species of the genus *Marrubium* contain diterpenic, triterpenic substances, phytosterols, flavonoids, tannins and other compounds. Preparations based on *Marrubium* species are used to treat respiratory diseases, pathologies of the cardiovascular and endocrine systems, and liver diseases [1]. *M. alternidens* seed lipids were not studied. 22.64% of the total lipids were isolated from crushed mature seeds of *M. alternidens* collected in the Namangan region by extraction with a mixture of chloroform and methanol (2:1, v/v). Lipids were separated by silica gel column chromatography to obtain 89.24% neutral lipids (hexane, NL), 7.10% glycolipids (acetone, GL) and 3.66% phospholipids (methanol, PhL). Using TLC on silica gel in a solvent system of hexane-diethyl ether (4:1; 7:3, v/v), triacylglycerides (basic), hydrocarbons, free fatty acids (FA), cyclic alcohol esters with FA and phytosterols were identified in the composition of NL.

GL was separated by this method in a solvent system of chloroform-acetone-methanol-acetic acid-water (65: 20:10:10: 3, v/v) and resulted in sterilyglycosides (basic), esters of sterilyglycosides with FAs, digalactosyldiglycerides and monogalactosyldiglycerides. According to TLC in the solvent system chloroform-methanol-ammonia (65:35:5, v/v), the PhLs consisted of phosphatidylcholines (basic), phosphatidylethanolamines, phosphatidylinositol, and phosphatidic acid. FA was isolated from NL, GL, and PhL by alkaline hydrolysis, converted to methyl esters by treatment with diazomethane, the obtained ME FAs were analyzed by gas chromatography on an Agilent 6890N chromatograph with a flame ionization detector using the FAMES.M method using a 30 m × 0.32 mm capillary column with a stationary phase HP-5, carrier gas-helium, programming temperature 150-270 °C.

Fatty acids of NL (% by weight): 14:0 (0.07); 16:0 (7.73); 16:1 (0.18); 17:0 (0.08); 18:0 (8.22); 18:1+18:3 (33.04); 18:2 (49.23); 20:0 (0.36); 20:1 (0.77); 22:0 (0.17); 22:1 (0.07); 24:0 (0.08).

Fatty acids of GL (% by weight): 12:0 (0.89); 14:0 (1.55); 16:0 (35.85); 17:0 (0.57); 18:0 (25.21); 18:1+18:3 (19.25); 18:2 (10.99); 20:0 (2.20); 22:0 (1.92); 24:0 (1.57).

Fatty acids of PhL (% by weight): 12:0 (0.59); 14:0 (1.16); 15:0 (0.38); 16:0 (43.09); 16:1 (0.30); 17:0 (0.51); 18:0 (11.69); 18:1+18:3 (21.78); 18:2 (17.49); 20:0 (1.29); 22:0 (1.18); 24:0 (0.54).

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**LIPIDS FROM SEEDS OF *Chenopodium album* L.****N. Yuldasheva, Sh. Ibotov, S. Gusakova**

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*Chenopodium album* L. (family Chenopodiaceae) is a widespread halophytic weed plant. In arid regions, the aerial part of *C. album* is used as fuel, raw material for dyes and feed, as well as for food. In folk medicine, in a number of countries, the herb of the plant is used as an anthelmintic, laxative, analgesic, diuretic and expectorant. Seeds are prescribed for diseases of the liver, spleen, abdominal pain. It is known that the plant contains saponins, essential oil, flavonoids, phytoecdysteroids, phenolcarboxylic acids. Plant lipids are poorly researched. We investigated the lipids of the seeds of the plant *C. album* growing in Tashkent region. The moisture content of mature seeds was 4.2%.

From crushed seeds of *C. album* with hexane in a Soxhlet apparatus, neutral lipids (NL) were extracted with a yield of 8.4%. Polar lipids (PL, 0.75%) were isolated from the meal by repeated extraction with a mixture of chloroform and methanol (2: 1, v/v). Using TLC on silica gel in a 4: 1 hexane: ether solvent system, it was found that NL consisted mainly of triacylglycerides accompanied by hydrocarbons, free fatty acids, fatty acids esters with phytosterols and triterpenols, free triterpenols and phytosterols. Polar lipids were fractionated on silica gel CC, eluted with glycolipids (GL) and methanol phospholipids (PhL). Their output was 0.28% and 0.47%, respectively (of the mass). Monogalactosyl- and digalactosyldiacylglycerides, steryl glycosides and their esters with fatty acids were identified in GL. The main components of PhL were phosphatidylcholines, phosphatidylethanolamines, phosphatidylinosites, and in minor amounts phosphatidic acid. The composition of NL, GL, and PhL fatty acids was determined by GC in the form of methyl esters on an Agilent 6890N chromatograph with a flame ionization detector according to the FAMES.M method, using a 30 m × 0.32 mm capillary column with a stationary phase HP-5, carrier gas-helium, programming temperature 150-270 °C.

Fatty acids of NL (% by weight): 14:0 (0.18); 16:0 (9.40); 16:1 (0.46); 18:0 (1.40); 18:1+18:3 (30.26); 18:2 (55.64); 20:0 (0.48); 20:1 (1.25); 22:0 (0.56); 24:0 (0.18); 26:0 (0.19).

Fatty acids of GL (% by weight): 10:0 (0.22); 12:0 (0.30); 14:0 (0.96); 15:0 (0.46); 16:0 (20.61); 16:1 (0.55); 17:0 (0.43); 18:0 (5.54); 18:1+18:3 (24.80); 18:2 (40.78); 20:0 (0.83); 20:1 (0.77); 22:0 (1.58); 24:0 (1.26); 26:0 (0.91).

Fatty acids of PhL (% by weight): 14:0 (0.36); 15:0 (0.24); 16:0 (34.72); 16:1 (1.87); 17:0 (0.27); 18:0 (2.79); 18:1+18:3 (28.87); 18:2 (28.58); 20:0 (0.28); 20:1 (0.46); 22:0 (0.93); 24:0 (0.63).

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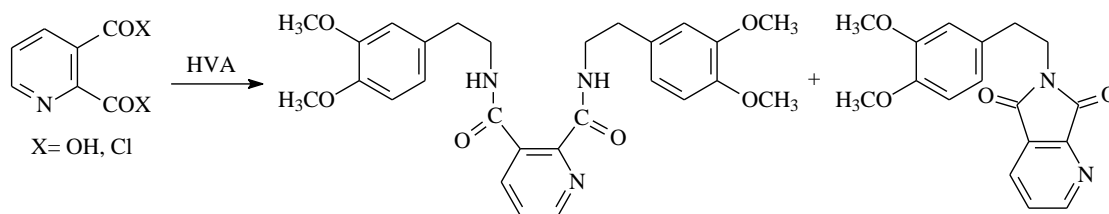
## SYNTHESIS OF HETEROCYCLIC ACIDS DIAMIDES

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Nitrogen-containing heterocyclic compounds play an important role in the research and development of pharmacologically active compounds. The synthesis of heterocyclic acid amides is one of the methods of activating chemical compounds. The acid amides are the most active compounds, and recently the number of researches in this area has been increasing. In addition, incorporation of the heterocycle into amide composition through acid or amine molecule causes a unique biological activity to be induced.

Amides of pyridine mono- and dicarboxylic acids have been used in medicine. The main purpose of our study is also to prepare new amides containing heterocyclic ring.

Heating quinolinic acid with homoveratrylamine (HVA) at high temperature directly formed a small amount of acid diamide with the main product - acid imide. In the reaction carried out with an acid chloroanhydrides, the main product an acid diamide and a small amount of an acid imide were formed.



In the synthesis of dicarboxylic acid diamides, the reactions involving acid chloroanhydrides were observed to be carried out easily, and with a relatively high yield in an optimal condition. The progress of the reactions was monitored by TLC. The structures of the obtained compounds were proved by the data of IR and <sup>1</sup>H NMR spectra.

## NEW WATER-SOLUBLE SESQUITERPENE LACTONE FROM *Artemisia absinthium* L.

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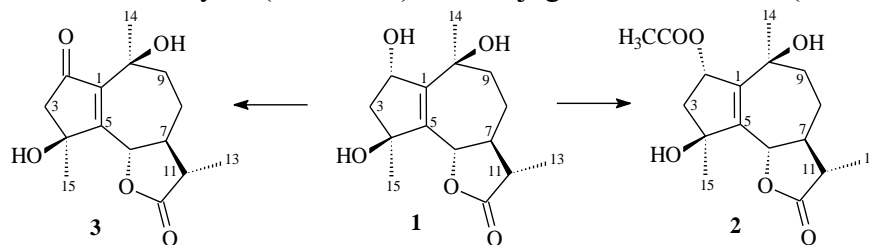
By study of components of an aqueous extract of the aerial parts of *Artemisia absinthium* L., the water-soluble sesquiterpene lactone (**1**), with composition C<sub>15</sub>H<sub>22</sub>O<sub>5</sub>, MP 164-165 °C (ethanol), M<sup>+</sup> 282, was isolated.

<sup>1</sup>H NMR (CDCl<sub>3</sub>, 0-TMS): 1.47 and 1.46 ppm (each 3H, s, H-14, H-15), 1.23 (3H, d, <sup>3</sup>J = 6.4 Hz, H-13), 1.93 (1H, dd, J = 14.0, 2.2 Hz, H-3a), 2.32 (1H, dd, <sup>2</sup>J = 6.8 Hz, H-3b), 5.01 (1H, dd, <sup>3</sup>J = 6.8, 2.2 Hz, H-2), 5.18 (1H, d, <sup>3</sup>J = 9.4 Hz, H-6), protons of hydroxyl groups resonate at 2.8-3.6 ppm; <sup>13</sup>C NMR (C<sub>5</sub>D<sub>5</sub>N): 145.4 (C-1), 75.2 (C-2), 51.2 (C-3), 83.7 (C-4), 142.9 (C-5), 80.0 (C-6), 49.5 (C-7), 24.9 (C-8), 39.6 (C-9), 72.9 (C-10), 42.4 (C-11), 177.9 (C-12), 12.7 (C-13), 29.4 (C-14), 27.8 (C-15).

Acetylation of the **1** with acetic anhydride in pyridine formed monoacetyl derivative **2** with mp 197-199 °C. In the IR spectrum this derivative shows an absorption bands of the tertiary hydroxyl group at 3440 cm<sup>-1</sup>. The formation of this product is a chemical confirmation of the presence of a secondary hydroxyl group.

The location of the signal lactone proton in PMR of the compound **1** in a weaker field at 5.18 ppm, and doublet nature of its cleavage indicate the close location of lactone proton to the double bond and its interaction with only one neighboring hydrogen atom. Experimental data allow to establishing the identity of the compound **1** to a number of guaianolides in the molecule, in which tetrasubstituted double bond was forming on C1 and C5, and lactone ring at C6 and C7 and is characterized by *trans*-connection with the basic hydrocarbon skeleton.

Two groups of CH<sub>3</sub>-C-OH formed on C4 and C10, and the secondary OH group in the molecule were located at C2, which was confirmed by an absorption maximum (λ<sub>max</sub>) 232 nm in the UV spectrum obtained by the oxidation of **1** by oxide chrome (VI) of ketoderivative **3** with mp 183-184°C. In the IR spectrum, it was marked by absorption bands of C=O γ-lactone cycle (1775 cm<sup>-1</sup>), OH groups (3420-3480 cm<sup>-1</sup>), C=O in a five-membered cycle (1710 cm<sup>-1</sup>) and conjugated double bond (1635 cm<sup>-1</sup>).



Physico-chemical constants and spectral data of the obtained ketoderivative **3** are identical with those of the known lactone artabsinolide B. Consequently, a new lactone **1** is an epimer of artabsinolide C and has the structure 2 $\alpha$ ,4 $\beta$ ,10 $\beta$ -trihydroxy-1,5-diene-6 $\beta$ ,7 $\alpha$ ,11 $\beta$ (H)-6,12-olide.



## **INFLUENCE OF GROWTH REGULATOR FLOROXAN ON THE FORMATION OF FRUIT ELEMENTS OF THE COTTON IN THE CONDITIONS OF HIGH TEMPERATURES**

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Growth regulators are low-consumption preparations, aimed not only at increasing the yield, but also at improving product quality and increasing plant resistance to adverse factors. The use of plant growth regulators in arid regions significantly increase the adaptive properties of agricultural plants.

The aim of the work was to study the effect of presowing seed treatment with floroaxane on the growth and formation of cotton fruit elements under high temperature conditions.

Due to the fact that in April-May of 2019, there were heavy rains, re-sowing of seeds was carried out at a later date - June 4. Presowing treatment of cotton seeds of the Sulton cultivar was carried out by soaking them for 18 hours in a 0.00001% solution of floroaxane, with the control in water.

The period of formation of fruit elements occurred in the June-July, when extremely high temperature conditions were recorded - up to 45 degrees.

According to the results of field tests, it was found that the drug contributed to the active formation of fruit elements. Accounting showed that the number of buds of experimental plants (7.2 pcs. / plant) exceeded the control (5.1 pcs / plant) by 41.2%. By the number of flowers, the experimental variant (1.85 pcs / plant) exceeded the control (0.89 pcs / plant) by 107%, in the number of boxes (4.2 pcs /plant), and in the control- 2,4 pcs / plant by 75%.

Thus, it was revealed that for the given accounting period, in the total number of fruit elements, the experimental plants exceeded the control ones by 57.9%.

## POSSIBILITY OF CREATING BIOPESTICIDES BASED ON BIOLOGICALLY ACTIVE COMPOUNDS OF THE PLANTS OF FLORA OF UZBEKISTAN

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It is known that many plant compounds participate in the ecological interactions of microorganisms, plants, and animals and play an important role in the protective mechanisms of plants developed during evolution. Biochemical studies show that plants synthesize protective substances in response to adverse environmental conditions. Such substances can be used to increase the stability and productivity of crops. Expanding the range of biological products with growth-stimulating, insecticidal, acaricidal and other activities based on natural compounds remains an urgent task. Their advantage is the absence of harmful effects on the soil and the environment. In the production of such drugs, environmentally friendly and energy-saving technologies are used.

The Institute of the Chemistry of Plant Substances is actively working on the creation and implementation of medicines for agriculture [1]. A protective stimulating preparation based on plant monoterpenoids of the plant *Achillea millefolium* (Asteraceae) and polyphenols *Gossypium hirsutum* L. (Malvaceae) has been developed. The drug has a toxic effect on the red spider mite and helps to restore the content of chlorophyll in damaged leaves of plants [2]. The composition can replace the treatment with a chemical protective agent - the drug Vertimek. A toxic activity of the extract of the plant *Achillea millefolium* L. revealed in relation to the *Tuta absoluta* larvae upon contact exposure is working on. The development of biopesticides from waste products from the production of plant medicines. Their activity against the main sucking pests of cultivated plants was revealed.

Tests of the new formulation of the growth regulator based on polyphenols in combination with microelements showed that the treatment of cotton seeds with the proposed composition, increased the yield of raw cotton by 3.2 c / ha compared to the control variant, and when spraying plants on vegetation of budding period the chlorophyll content "a" was higher than the control by 40.9%, chlorophyll "b"- by 80.0%, and the sum of pigments "a" and "b"- by 55.5%.

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## **DEVELOPMENT OF NTD AND OF TECHNOLOGY OF OBTAINING THE MEDICINAL REMEDIES ON THE BASE OF GLYCYRRHIZIC ACID**

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Glycyrrhizic acid (GA) obtained from licorice root, and its derivatives show high antiinflammatory, antiulcer, antiviral, hepatoprotectory and other activities. In this connection, the organization production for issue domestic medicinal preparation on the base GA, showing above-said activities are actual.

The possibility of the creating such medicinal remedies, has brought us the need of the development normative-technical documentation (NTD) and organizations production medicinal remedies on the base glycyrrhizic acid. Authors were workered higheffective, suitable with industrial standpoint, technology of obtaining substance - GA (OPR), with contents of main acting material no less than 85% from thick extract of licorice root. NTD on glycyrrhizic acid was realized (FS 42 Uz-0979-2017).

For the reason of creating higheffective antiulcer remedy on the base of GA, threesodium salt GA was synthesized. Authors were workered technology of obtaining substance- threesodium salt GA ("Glycythrinat") (OPR), possessing high antiulcer activity, with contents of main acting material not less 97%, as well as the whole necessary NTD (FS 42 Uz-1104-2017).

It was revealed that Glycytrinate had antiulcer and antiinflammatory effect. It was sufficiently effective and had no side-effects. Its efficiency and tolerance was similar to the agent for comparison De-nol. The mechanism of glycytrinate's antiulcer effects was linked with its antioxidant property and suppression of the secretory function of gastric glands.

"Glycythrinat" was little toxic, even in doses over 4000-5000 mg/kg, in case of per oral administration on rats, it had no toxic effect, as it did not cause lethal outcome.

Authors were workered technology of obtaining on the base of glycyrrhizic acid, antiviral preparation "Glycytogen" with contents acting material-glycyrrhizic acid 0.1%.

On the base of glycyrrhizic acid, at present, authors were workered technology of obtaining hepatoprotectory preparation "Gepatogliv". Realized selecting the optimum composition of the preparation, with contents of acting material - threesodium salt GA (35 mg) and lecithin (65 mg). Gepatoprotectory preparation "Gepatogliv" was also an enough efficient immunomodulating remedy. Preparations based on GA are found to be increasingly used in hepatitis therapy.

## NOVEL TRICYCLIC RING SYSTEM: OXAZOLE/THIAZOLE ANALOGUES OF QUINAZOLINE ALKALOIDS

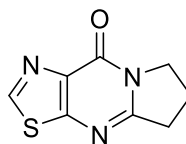
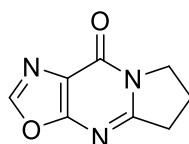
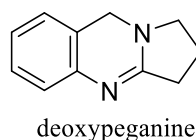
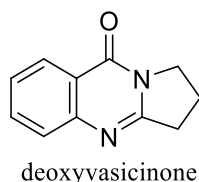
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The *Peganum harmala* L. extracts exhibit fungicidal, bactericidal, anti-inflammatory and anticancer activity, neuroprotective property and other biological importance. Besides, this herb contains quinazoline alkaloids which are responsible for the toxicological and pharmacological effects of the plant. For example, major quinazoline alkaloids are identified as peganine, deoxypeganine, vasicine and deoxyvasicinone etc. Our own group has discovered two novel synthetic heterocyclic systems based on above described alkaloids. Hereon, derivatives 6,7-dihydrooxazolo[5,4-*d*]pyrrolo[1,2-*a*]pyrimidin-9(5*H*)-one and 6,7-dihydropyrrolo[1,2-*a*]thiazolo[5,4-*d*]pyrimidin-9(5*H*)-one were reported as novel tricyclic heterocycles that can be suggested for the further modification and biological screening in the organic and bioorganic chemistry fields.



## NEW PHYTOSYRUP “ECDISOP”

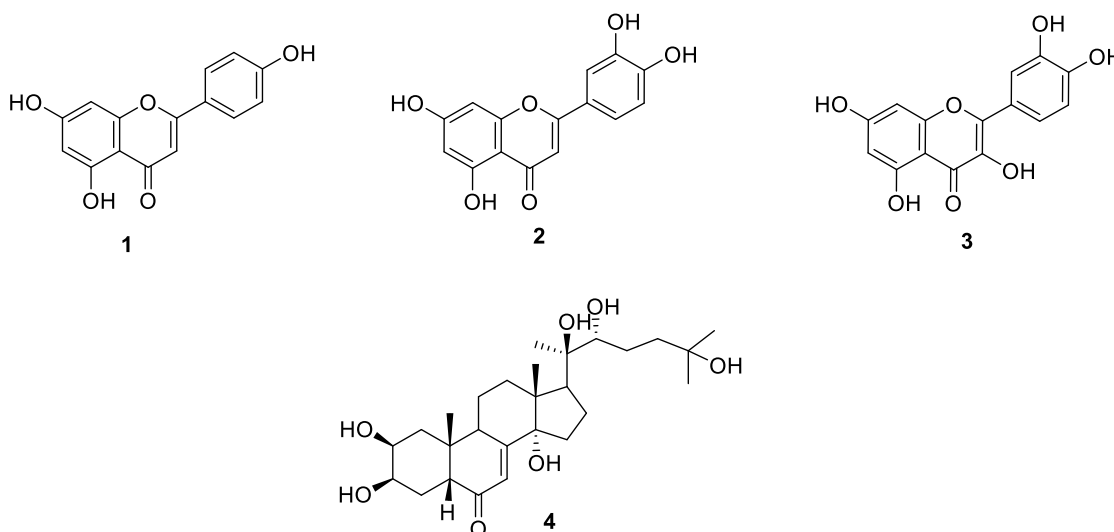
A. N. Zhabayeva, I. R. Tarybaev, S. M. Adekenov

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The report gives information on the new “Ecdisop” phytosyrup, obtained on the basis of biologically active compounds of *Serratula coronata* L.

In recent years, there has been an increase of interest in metabolic-type drugs with the ability to activate processes in various organs and tissues, improve the energy status of their cellular systems and thereby increase the body's resistance to various adverse factors. According to the results of pharmacological studies, one of the effective drugs of this series may become a drug developed at JSC IRPH "Phytochemistry", which is the sum of biologically active substances of *Serratula coronata* L.

Flavonoids are identified as the main active components of the phytosyrup "Ecdisop": apigenin (1), luteolin (2), quercetin (3) and their glycosides, as well as the sum of ecdysteroids, with the majority of ecdysterone (4).



The new “Ecdisop” syrup components were selected. The following excipients were used as fillers for “Ecdisop” syrup: sugar syrup, propylene glycol, honey, citric acid, nipagin, nipasol, ethyl alcohol, tween-80, glycerin, essential oils. The optimal composition of the original “Ecdisop” phytosyrup: active ingredient, sugar, honey and essential oils. The technology of phytosyrup production consists of 7 auxiliary works and 9 technological processes. The main critical points of syrup production were determined: pH medium, temperature setting, number of mixer rotations, microbiological purity. The production of “Ecdisop” phytosyrup was organized according to the developed technology. Experimental batches of a new phytosyrup for pharmacological and preclinical studies were obtained.



## CHEMICAL CONSTITUENTS AND ANTIOXIDANT CAPACITY OF *Drynaria roosii* Nakaike

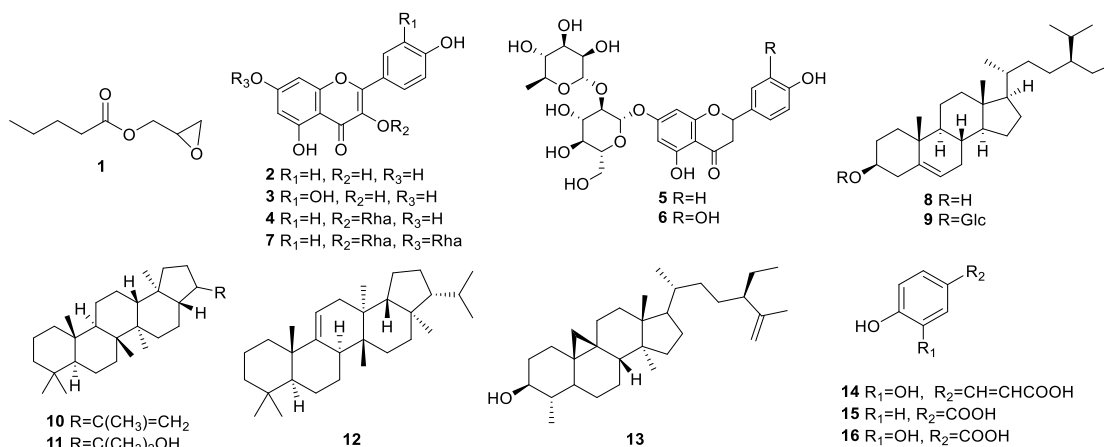
L. Zhang<sup>1</sup>, J. G. Cao<sup>1, \*</sup>, G. Z. Huang<sup>1, 2, \*</sup>

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*Drynaria roosii* Nakaike is a perennial fern plant of the Drynariaceae family [1]. The dry rhizome is a commonly used traditional Chinese medicine, known as "Gushuibu", which has the effects of anti-osteoporosis, anti-inflammatory, healing of the bone [2]. In the present study, a new lipid (1) together with fifteen known compounds, including six flavonoids, kaempferol (2), quercetin (3), afzelin (4), naringin (5), neoeriocitrin (6), kaempferol-3,7-*O*- $\alpha$ -L-dirhamnoside (7), two steroids,  $\beta$ -sitosterol (8), daucosterol (9), four triterpenes, hop-22(29)-ene (10), hydroxyhopane (11), fern-9(11)-ene (12), cycloeuoalenol (13), and three phenolic acids, caffeic acid (14), *p*-hydroxybenzoic acid (15), protocatechuic acid (16) were isolated from *D. roosii*. The isolated flavonoids and phenolic acids were evaluated for their antioxidant capacity (DPPH). Compounds 2, 3, 6, 14, and 16 exhibited significant antioxidant capacity.

**Keywords:** *Drynaria roosii* Nakaike, chemical constituents, antioxidant capacity



### ACKNOWLEDGMENTS

This work was financially supported by Recruitment Program of Global Experts (Thousand Talents Program)

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## INCORPORATION OF AMINO MOIETY TO ALEPTEROLIC ACID IMPROVES ACTIVITY AGAINST CANCER CELL LINES

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*Aleuritopteris argentea* is a medicinal fern consisting of an ent-labdane diterpene, alepterolic acid, as the major metabolite [1]. We recently isolated large amounts of alepterolic acid from *A. argentea* enabling subsequent structural modification. By incorporation of amino moiety to alepterolic acid, fifteen amide derivatives were synthesized, characterized, and further biological evaluated regarding their activity against four cancer cells and normal human liver cells [2]. The potency of synthesized amides dramatically improved as compared to alepterolic acid itself.

The best hit (compound **11**) inhibited Hela cells with an IC<sub>50</sub> of 7.39±0.80 μM, and is nearly nontoxic to normal cells. In addition, compound **11** exhibited an inhibitory effect on the colony forming ability of different cancer cells, and the inhibition of Hela is most obvious. Moreover, it induced cervical cancer cells by decreasing mitochondrial membrane potential and inducing expression of apoptosis-associated proteins. Specifically, it could release cytochrome c, activate caspases and alternate Bax/Bcl-2 balance. These results indicated that compound **11** could inhibit the proliferation of cervical cancer cell line Hela and induce apoptosis through the mitochondrial pathway. These findings encouraged further rational structural modification of 15- carboxyl group of alepterolic acid.

**Keywords:** *Alepterolic acid*, Apoptosis, Mitochondrial pathway

### ACKNOWLEDGMENTS:

This work was financially supported by Recruitment Program of Global Experts (Thousand Talents Program)

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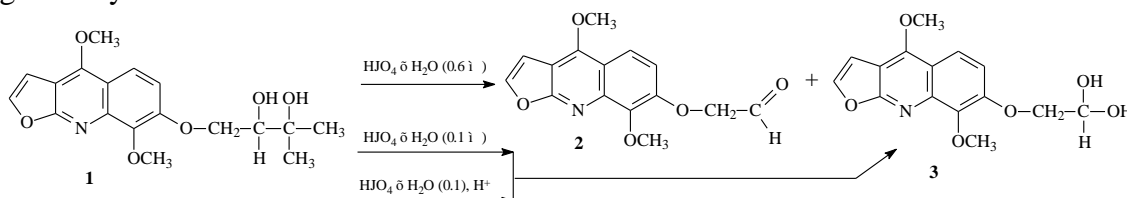
## OXIDATION REACTION OF QUINOLINE ALKALOIDS EVOXIN AND BUKHARAIN WITH METAPERIODIC ACID

Sh. N. Zhurakulov<sup>1</sup>, V. I. Vinogradova<sup>1</sup>, K. K. Turgunov<sup>1,2</sup>

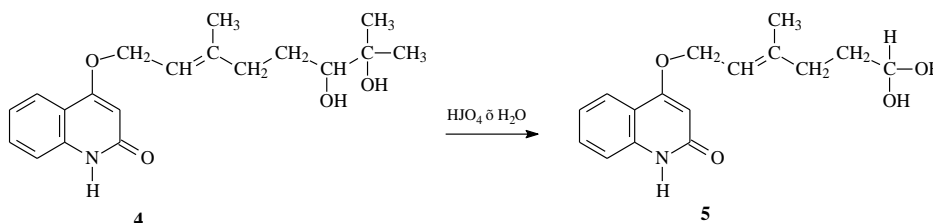
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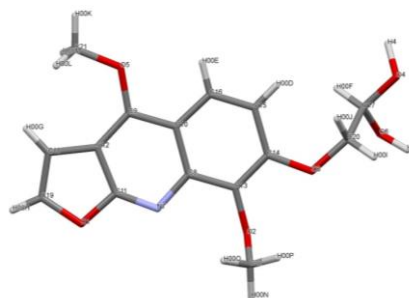
Quinoline bases, one of the interesting groups of alkaloids, are widespread in plants of the *Rutaceae* family of Central Asia. One of the leading areas of medical organic chemistry is the transformation of natural metabolites. For this purpose, we carried out the oxidation of quinoline alkaloids of evoxin and bukharain with metaperiodic acid. In the oxidation of evoxin (**1**) with a 0.6 M solution of HIO<sub>4</sub>, a mixture of two products of aldehyde **2** and dihydroxyl product **3** in a ratio of 1:2 was obtained. Using a solution gave only **3**.



Similarly, in the oxidation reaction of the alkaloid of Bukharain (**4**) with HIO<sub>4</sub>, instead of the expected aldehyde product, dihydroxyl product **5** was obtained.



The structures of the obtained substances were proved on the basis of IR, <sup>1</sup>H and <sup>13</sup>C NMR spectra and x-ray diffraction data (XRD).



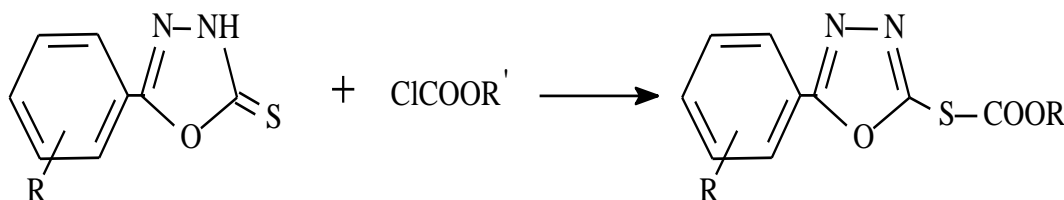
Structure of **3** determined by XRD

## SYNTHESIS AND ANTIMICROBIAL ACTIVITY OF 2-ALKYLOXYCARBONYLTHIO-5-ARYL-1,3,4-OXADIAZOLES

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Continuing our studies on the synthesis and properties of various derivatives of 1,3,4-oxadiazole-2-thione, we have determined the selective conditions of acylation of 5-aryl-1,3,4-oxadiazole-2-thiones (ratio of reagents 1: 1, boiling in dry acetone in the presence of  $K_2CO_3$ ) with alkyl chloroformates. Only 2-alkyloxycarbonylthio-5-aryl-1,3,4-oxadiazoles were synthesized in high yield (80-92%). The structures of the obtained compounds were established by the UV, IR and  $^1H$ -NMR spectra:



$R = H, 2\text{-Cl}, 2,4\text{-Cl}; R' = C_3H_7, CH_2CH(CH_3)_2, CH_2C_6H_5$

It is known that compounds containing a 1,3,4-oxadiazole core have a wide spectrum of biological activity (antibacterial, antifungal, analgesic, anti-inflammatory, antiviral, antitumor, etc.) [1, 2]. We have studied the antibacterial and antifungal activity of the obtained substances by using the modified agar-diffusion method. Following microorganism strains were used as a test cultures: gram-positive bacteria *Bacillus subtilis* (RKMUZ-5), *Staphylococcus aureus* (ATCC 25923), gram-negative bacteria *Pseudomonas aeruginosa* (ATCC 27879), *Escherichia coli* (RKMUZ-221) and one fungal strain *Candida albicans* (RKMUZ-247). The relationship between biological activity and the structure of synthesized compounds was studied. It was found that all 2-alkyloxycarbonylthio-5-aryl-1,3,4-oxadiazoles exhibited weak antibacterial activity against only gram-positive bacteria *Bacillus subtilis* and *Staphylococcus aureus* (diameters of inhibition zones 6-8 mm).

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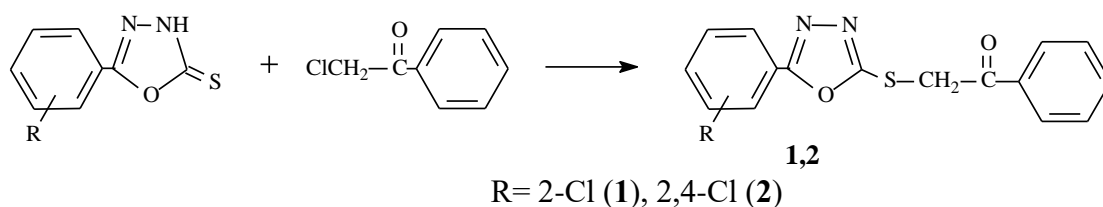
## SYNTHESIS AND CRYSTAL STRUCTURES OF 2-PHENACYLTHIO-5-ARYL-1,3,4-OXADIAZOLES

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5-Substituted-1,3,4-oxadiazole-2-thions with several heteroatoms in their molecule (oxygen, sulfur and two nitrogen atoms) are one of the intensively studied representatives of five-membered heterocyclic compounds, which have great synthetic possibilities associated with the chemical nature of these compounds. But in the literature, there are few reports of studies of the structure (including X-ray diffraction analysis) of various derivatives of 5-substituted-1,3,4-oxadiazole-2-thiones.

Based on the foregoing, we synthesized 2-phenacylthio-5-aryl-1,3,4-oxadiazoles (acetone, 56 °C, K<sub>2</sub>CO<sub>3</sub>, 88-92%) and studied their crystal structures:



The crystal structures of 2-phenacylthio-5-(2-chlorophenyl)-1,3,4-oxadiazole **1** and 2-phenacylthio-5-(2,4-dichlorophenyl)-1,3,4-oxadiazole **2** contain a planar (with accuracy  $\pm 0.0024$ ,  $\pm 0.0031$  Å, respectively) aromatic oxadiazole core. The position of the phenacylthio group relative to the plane of the oxadiazole core is approximately close (the values of the torsion angle are O1-C2-S12-C13  $-176.5$  and  $-173.5^\circ$  for **1** and **2**, respectively). But the position of the phenyl group relative to the plane of the oxadiazole core is slightly different (the value of the torsion angle O1-C5-C6-C7 is  $164.0$  and  $176.1^\circ$  for **1** and **2**, respectively).

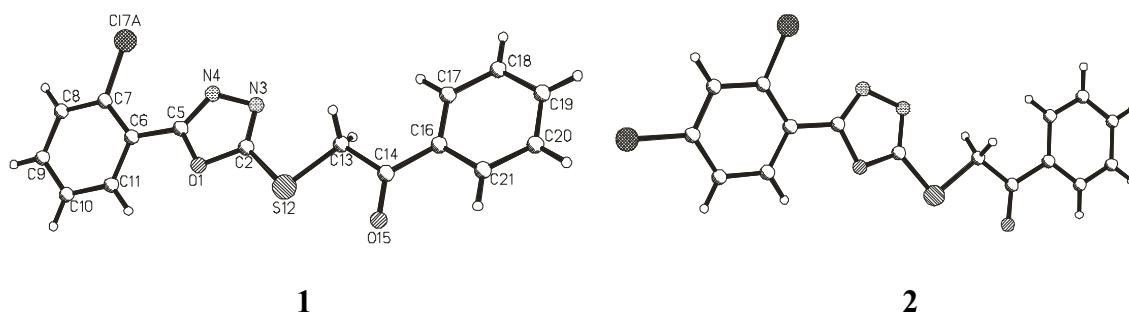


Fig. 1. Atom numbering and spatial structure of molecules **1** and **2**.

## SYNTHESIS OF NEW DERIVATIVES OF 4,5-DIPHENYL-1,2,4- TRIAZOLE-3-THIONE

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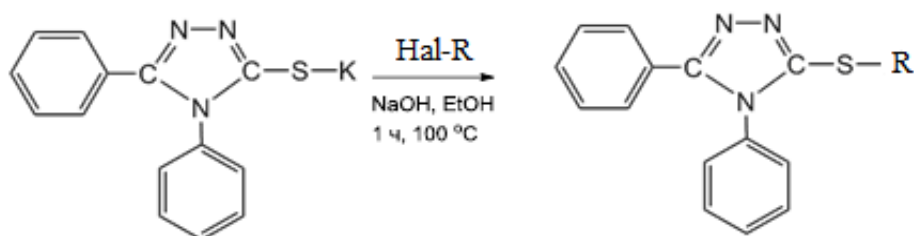
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Heterocyclic compounds on the basis of 1,3,4-thiadiazole arouse great scientific interest, since they have wide potential possibilities for practical use. So, various representatives of this class of heterocycles exhibit high antimicrobial, anti-inflammatory, antifungal, anticancer, anti-tuberculosis activities, have an anticonvulsant effect and have many other valuable properties. Based on this, the aim of this work was the synthesis of new derivatives of 4,5-diphenyl-1,2,4-triazole-3-thione and the confirmation of their structures.

Synthesis of new derivatives of 4,5-diphenyl-1,2,4-triazole-3-thione was carried out in alkaline media by interaction between ethanol solutions of heterocycle and halogen derivatives of modifying agents:



R = C<sub>6</sub>H<sub>5</sub>CH<sub>2</sub>-, C<sub>4</sub>H<sub>9</sub>-, C<sub>5</sub>H<sub>11</sub>-, C<sub>10</sub>H<sub>21</sub>-, CH<sub>3</sub>COOCH<sub>2</sub>-, C<sub>6</sub>H<sub>5</sub>CH<sub>2</sub>COO-,  
C<sub>6</sub>H<sub>5</sub>CH<sub>2</sub>COOCH<sub>2</sub>-, C<sub>4</sub>H<sub>9</sub>COOCH<sub>2</sub>-

The structures of the synthesized compounds were confirmed by the data of UV, IR and chromato-mass spectra. The weak signals (3066.93 cm<sup>-1</sup>) of valence deformation vibrations (1595.72 cm<sup>-1</sup>) of C<sub>6</sub>H<sub>5</sub>-N- group were detected in IR spectra of synthesized compounds. In spectra deformation vibrations of the following groups were also detected: -CH<sub>2</sub>- (2977.71 cm<sup>-1</sup>), CH<sub>3</sub>- (2897.71 cm<sup>-1</sup>), C-N - (1331.65 cm<sup>-1</sup>), C-C - (1293.72 cm<sup>-1</sup>), C-S - (695.69 cm<sup>-1</sup>), C<sub>ar</sub>-H - (773.26 cm<sup>-1</sup>), C<sub>6</sub>H<sub>5</sub> - (four signals in the interval of 1498 - 1446 cm<sup>-1</sup>), C-C valence vibrations (1224.42 cm<sup>-1</sup>), CH<sub>2</sub>-CO- (1427.18 cm<sup>-1</sup>), -COO (1742.85 cm<sup>-1</sup>).

The structures of the compounds were also confirmed on the basis of mass spectrometric decomposition of substances. According to the results of the research, the possible pathways of decomposition of the molecular ion of each synthesized substance were presented.

## COMPLEX FORMATION AND BIOLOGICAL ACTIVITY OF MEGOSIN WITH $\gamma$ -CYCLODEXTRIN

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Modern technologies and a variety of excipients with wide parameters of properties make it possible to significantly vary the characteristics of drugs when creating their dosage forms, providing directional development of compositions and technologies for creating drugs with the desired pharmacokinetic and therapeutic properties. One of the main biopharmaceutical characteristics is the solubility of the drug substance. Solubility largely determines the possibility of creating a dosage form with an effective dose of the drug, the kinetics of its optimal release from the dosage form, and the speed and completeness of absorption.

The solubility of many medicinal and biologically active compounds, their bioavailability, as well as resistance to hydrolysis, thermal and oxidative degradation, increase in the presence of cyclodextrins as a result of the formation of host-guest inclusion complexes. Cyclodextrins are oligosaccharides formed by enzymatic decomposition of starch. The gosypol imino derivative Megosin has pronounced virucidal and virus-inhibiting actions against a number of mycoviruses. The disadvantage of Megosin is its low solubility in water and poor permeability through the stratum corneum.

By the method of coprecipitation, the inclusion complex of  $\gamma$ -cyclodextrin and megosine was obtained. The method of IR spectroscopy and powder diffractometry proved the hydrophobic interaction of the ligand and the matrix. The results showed that between the matrix and the ligand there was an interaction with the formation of hydrogen bonds.

In vitro experiments studied the effect of megosine,  $\gamma$ -cyclodextrin and complex compounds on the functional processes of mitochondria - lipid peroxidation (POL), the conductivity of the ion channel of the mitochondria mPTP and mitoKATP. In the studies, the water-soluble complex of megosine had a high antioxidant and membrane-trophic activity and cardioprotective properties. The high antioxidant activity of megosin and its complex is of interest for further study on their antihypoxic properties.

The results of the study can be used to create new-generation drugs with antioxidant, membrane-active and cardioprotective effects aimed at the rehabilitation of the pathophysiology of the cell, which is a water-soluble complex of megosine with  $\gamma$ -cyclodextrin.

## ISOLATION, IDENTIFICATION AND BIOLOGICAL ACTIVITY OF POLYPHENOLS FROM *Euphorbia* PLANT

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The Euphorbiaceae family includes about 8,000 species, most of which are characterized by the production of toxic, skin-irritating, milk latex. It is known that the genus *Euphorbia* contains diterpenes, which are responsible for skin irritation, tumor stimulation and cytotoxic activity, phenolic compounds, including lactones with the skeleton of ellagic acid, triterpenes, flavonoids and coumarins. Studies conducted at the Institute of Ethics and Chemistry of the Academy of Sciences of Uzbekistan have shown the promise of using natural phenolic compounds as antiviral, antioxidant, antitumor and anti-AIDS agents. In order to study the composition of polyphenols contained in plants of *Euphorbia triodontus* Prokh, growing throughout the territory of our Republic, in particular the Ferghana Valley, the roots were collected after flowering. The isolation of polyphenols from dried raw materials was carried out according to standard methods.

An HPLC analysis of the obtained polyphenol fraction revealed more than 65 components in various ratios. To obtain individual components, fractionation was carried out by hydrophobic chromatography. Individual components from the E-20 fraction were isolated by HPLC. As a result, 6 individual major polyphenols were obtained, designated as: E-20-1, E-20-2, E-20-3, E-20-4, E-20-5 and E-20-6. The substances were identified by mass spectrometry. In the mass spectra of individual polyphenols, molecular ion (M-H) signals and daughter ions characteristic of the galloyl glucose derivatives were noted. When decoding the mass spectra, it was found that the test substances consisted of glucose residues and several gallic acids linked via an ester bond.

The experiments on the suppression of lipid peroxidation in rat mitochondria showed that under the action of the E-20-1 fraction at 5  $\mu\text{g}$  / mL, the inhibition process was 77.8%, while under the action of the E-20-2, E-20-3 fractions, E-20-4, E-20-5 and E-20-6, the inhibition process was 81.9%, 94.9%, 73.9, 78.2 and 71.1%, respectively.

Thus, 4 fractions of polyphenols were isolated from a plant of the Euphorbiaceae family by hydrophobic chromatography in a four-step gradient of methanol. By the method of HPLC, 6 individual polyphenols were isolated from the E-20 fraction and their structures were determined using chromatography-mass spectrometric analysis.

## PHYSICOCHEMICAL CHARACTERISTICS OF STRUCTURE FORMATION OF THE COMPLEX MONOAMMONIC SALT OF GLYCIRRIZINIC ACID - ALLAPININ

**Zh. F. Ziyavitdinov, U. Z. Ishimov, N. Sh. Berdiev, Yu. I. Oshchepkova, Sh. I. Salikhov**

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Currently, the issue of creating prolonged dosage forms that can ensure the long-term effect of the drug while reducing its daily dose is becoming increasingly relevant. Among modern dosage forms, a special place is occupied by polymer matrix systems, since they are able to provide a given release profile of drugs in a fairly strict range of blood concentrations. Due to the wide spread among the population of all countries of diseases of the cardiovascular system, this requirement of pharmacotherapy is especially important when taking antiarrhythmic drugs, which include allapinin. This drug, developed in the USSR at the end of the 70s of the 20th century, is a hydrobromic salt of the alkaloid of lappaconitin obtained from plant materials. The main reason for the creation of drugs based on glycyrrhizic acid (HA) and its derivatives is its solubilizing property. The reason for the solubilizing properties is the intermolecular interaction that occurs upon contact of HA with various organic substances in solution.

A method has been developed for the preparation of a complex of allapinin with MASHA in a ratio of 1: 4 (mol / mol). The resulting complex is an amorphous white powder with a grayish tint. In order to identify the complex, chromatographic and physicochemical studies were carried out.

Chromatographic studies of the obtained complex by HPLC analysis revealed peaks with a retention time of 3.9 and 12.3 min, which corresponded to the individual components - allapinin and MASHA. This is most likely due to the rupture of the formed hydrogen bonds and Van der Waals interactions between the components of the complex in the process of reverse phase chromatography. The developed technique is quite suitable for the qualitative and quantitative determination of the components of the created drug. In the IR spectrum of the complex under study, there is an expanded and intense signal for OH groups participating in the formation of hydrogen bonds, biased signals for C = O, N-CH<sub>3</sub> and O-CH<sub>3</sub> groups participating in the formation of hydrogen bonds between H - O and H - N. The carried out thermogravimetric analysis showed the strong thermal stability of the complex in comparison with individual substances. Over the entire measurement range, a 5% mass loss was observed, without any thermal effects. Peaks characterizing the components of the complex (allapinin and MASHA) were absent, which indicated the presence of complexation.

The identification of samples based on diffraction patterns proved the crystallinity of allapinin based on the symmetric peaks of the diffraction grating. On the X-ray diffraction pattern of MASHA, both symmetric peaks and hilly peaks of the diffraction grating were observed, indicating a semicrystalline state of the substance. On the diffraction pattern of the complex, crystallinity was completely absent, and the substance was in a state of amorphous powder. The results obtained by the complex of physicochemical studies indicated the existence of the Allapinin - MASHA complex.

## STRUCTURE AND ACTIVITY OF POLYPHENOLS FROM PLANT *Rhus coriaria* L.

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Sumac (*Rhus coriaria* L., Anacardiaceae family) in traditional medicine and traditional Arab-Palestinian herbal medicine, has been used to treat cancer, stroke, hypertension, dysentery, hematoma, ophthalmia, abdominal pain, diuresis, diabetes, atherosclerosis, measles, liver diseases, diseases of the teeth and gums, headaches, dermatitis and liver diseases. Based on this, the purpose of this study was to study the polyphenolic composition of the ethyl acetate fraction of the chloroform extract of leaves of *R. coriaria* grown in Uzbekistan. The isolation of polyphenols from dried raw materials was carried out according to previously generally accepted methods.

An HPLC analysis of the obtained polyphenol fraction revealed more than 45 components in various ratios. To obtain individual components, hydrophobic chromatography was carried out on a column with a Silochrome 80 C<sub>18</sub> sorbent and, as a result, fractions P-10, P-30, P-40 and P-96 were obtained. The optimal conditions for the semi-preparative separation of the major components of the R-30 fractions were selected by HPLC and as a result, the main polyphenolic components were obtained, in the amount of: R-1 - 0.5 mg, R-2 - 0.8 mg, R-3 - 2.3 mg, R-4 - 12.6 mg, R-5 - 34.5 mg, R-6 - 15 mg, R-7 - 8 mg, R-8 - 7.1 mg, R-9 - 45.5 mg. To determine the structural features of the isolated polyphenols, mass spectrometric studies were performed. The table shows the data from the mass spectra and the retention time of analytical HPLC.

№	Rt, min	M-H,		Fragment ions										
		m/z, (%)		m/z, (%)										
R-1	8.5	331.06 (32)	169.01 (100)	162.9 (43)										
R-2	10.1	485.09 (37)	423.06 (12)	331.07 (17)	169.01 (100)									
R-3	12.3	635.7 (45)	465.2 (70)	313.0 (65)	169.01 (100)	125.0 (10)								
R-4	13.5	787.41 (33)	635.73 (67)	465.1 (43)	313.0 (30)	169.01 (100)	125.0 (5)							
R-5	14.3	939.05 (15)	769.09 (100)	617.08 (35)	447.04 (5)	313.02 (12)	169.01 (5)							
R-6	18	1091.2 (10)	939.17 (45)	769.12 (100)	617.09 (33)	447.03 (27)	276.9 (16)	169.01 (35)	124.9 (12)					
R-7	19	1243.4 (10)	1091.8 (5)	939.4 (100)	769.13 (45)	617.08 (20)	447.05 (15)	276.9 (8)	169.8 (38)	124.9 (10)				
R-8	21.5	1395.6 (5)	1243.4 (8)	1091.8 (27)	939.3 (33)	769.12 (100)	601.03 (16)	447.03 (28)	276.9 (7)	169.8 (40)	124.9 (10)			
R-9	24.5	1547.4 (8)	1395.6 (12)	1243.4 (10)	1091.8 (33)	939.4 (100)	770.9 (45)	601.4 (32)	447.5 (16)	276.9 (37)	169.8 (40)	124.9 (8)		

It was established that the polyphenols isolated by us in an individual state consisted of gallic acid and glucose linked by an ester bond: mono-, di-, tri-, tetra-, penta-, hexa-, hepta-, octa- and non-*O*  $\beta$ -galloyl- $\beta$ -D-glucose. A study of the "acute" toxicity of the isolated compounds showed that they belonged to class VI of relatively harmless compounds. A study of the activity of polyphenols against HCV NS3 protease inhibitor showed that polyphenols R-5, R-7 and R-9 at a concentration of 5  $\mu$ g/mL inhibited the growth of the virus by 95%, 79% and 90%, respectively.



## POWDERED DRUG FORMULATION OF ALPEC

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Previously we developed polymer compositions of albendazole with pectins in the form of gels and liquids.

The aim of this work was to prepare compositions of Albendazole with pectins in the form of powders using spray drying. It is well known that the powdered forms of drug formulations are more stable than liquid and gel forms, which improves the quality, stability and effectiveness of the products.

Various natural pectins, *Beta vulgaris*, *Malussieversii*, *Citrus reticulate*, *A. leiosporum*, *S. marianium* were used to formulate pectin compositions albendazole.

To obtain polymer composition, pectin + albendazole = Alpec, albendazole was dissolved in 7% aqueous ethanol solution that was acidified with hydrochloric acid, pectin was dissolved in distilled water, and albendazole solution was added to the pectin solution at 35-40°C while stirring, and the final solution was filtered using a 0.5 mm sieve.

Powder forms of Alpec was obtained by spray drying. X-ray powder-diffraction analysis of the starting materials and the product was carried out on a Shimadzu XRD-6100 powder diffractometer, the samples were measured in the Bragg-Brentano geometry with scanning at  $2\theta$  from 4 ° to 50 °. Comparison of powder x-ray patterns of albendazole, pectin and Alpec indicated the formation of an Alpec complex with pectin, Fig. 1.

Preliminary studies indicated a high biological activity and increased solubility of Alpec formulation in water, as well as lower toxicity compared to albendazole.

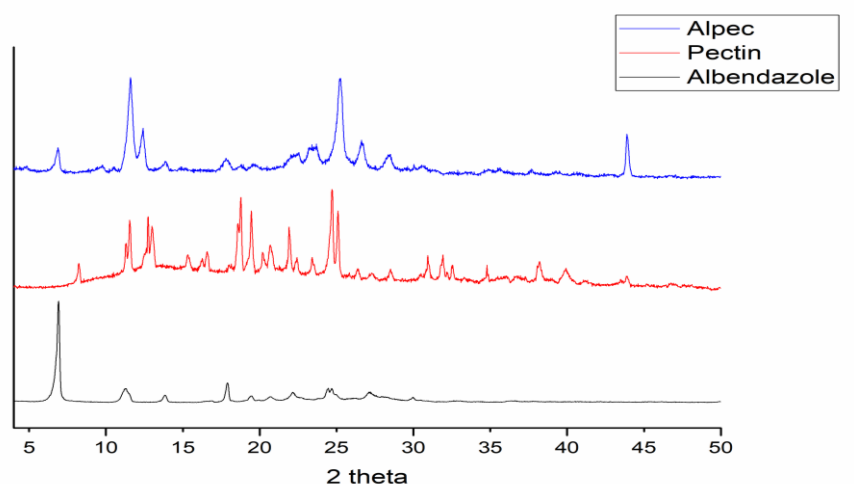


Fig. 1 X-ray diffraction patterns of Alpec (powder), pectin and albendazole.

## DEVELOPMENT OF PARAMETERS FOR STANDARDIZATION OF DRY EXTRACT OF *Poligoni aviculare*

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Urolithiasis is one of the most common diseases in the world. For the prevention and in the complex therapy of diseases of the genitourinary system, phytopreparations are often used, the advantage of which is relative non-toxicity, the possibility of prolonged use and the complexity of the action. In the treatment of diseases (urolithiasis), it is often recommended to use the infusion of herbs common knotgrass *Poligoni aviculare*.

Knotgrass drugs are commonly used in complex therapy for kidney stone disease, chronic renal failure, chronic glomerulonephritis, pyelonephritis, bladder inflammation in remission. Knotgrass contains flavonoids and glycosides (quercetin, avikulyarin, hyperoside), vitamins C, E, carotene, tannins, wax, resins, mucus etc. The combination of these biologically active substances (makes it possible to counteract the formation of urates - urinary stones. The anti-inflammatory, astringent and antibacterial actions of the knotweed help to improve the condition of patients with movement of stones. It also increases blood clotting, lowers blood pressure, increases urine output. Herb of common knotgrass is most often used as a monopreparation and in combination with other plants (phytolite). It was advisable to devise a method of obtaining a dry extract from the herb of common knotgrass and determine the standardization of the obtained extract to create new dosage forms based on it.

We have experimentally determined that it was most appropriate to use water as an extractant to obtain a dry extract. The actual task was to develop a quality control method for this substance. The purpose of the study was to develop the parameters of standardization of dry extract from the herb of common knotgrass. The object of our study were 5 series of dry extract derived from the herb of common knotgrass (*Poligoni aviculare* L.) (extractant - water). Dry extract of herb common knotgrass was amorphous powder from light brown to dark brown with a gray or orange hue, with a slight specific odor, hygroscopic.

It is suggested to identify the extract by TLC, using caffeic acid P, hyperoside P as quantitative indicators of the quality of the dry extract, suggesting weight loss when dried (not more than 5.0%), the content of heavy metals (not more than 0.01%), the quantitative content of flavonoids in terms of hyperoside (not less than 0.25%) and in conversion to routine and dry matter (not less than 1.0%). Five series of extracts were obtained, which were analyzed according to the draft quality control methodologies developed. The content of flavonoids in terms of hyperoside and dry raw material in the obtained extracts was 0.42, 0.3, 0.36, 0.31, and 0.38, respectively.

As a result, our research suggested parameters for standardization of dry extract of the herb knotgrass. All five series of extract met the requirements of the developed documentation. Thus, the parameters of standardization of dry extract from the herb of common knotgrass were determined.

