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Pharmacochemistry

Biologically Active Compounds and Original Remedies from Plants Growing in Georgia

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ABSTRACT. A purposeful study of plants of Georgian flora for the content of cardiac glycosides, steroid and triterpene saponins, lipids, stilbens, flavonoids, tannides, anthraglycosides etc. is carried out.

Cardiotonic, antiatherosclerotic, bronchospasmolytic, antirheumatic, hepatoprotective and bile-expelling, antiherpetic, antiuremic remedies, regulators of blood circulation and function of gastro-intestinal tract were developed on the basis of different classes of natural compounds. The raw material for the synthesis of steroid hormonal remedies and plant growth stimulator are proposed.

***Key words**: steroids, triterpene saponins, lipids, stilbenes, flavonoids.*

Plants regularly biosynthesize chemical compounds of lots of classes. Particular representatives of these compounds are characteristic of particular families, genera and species of plants. Secondary metabolites of plants exhibit valuable medicinal properties.

The diverse flora of Georgia is an inexhaustible source of biologically active compounds, which can be used in medicine. Thus on the bases of studying and utilization of plant substances the Pharmacochemical Science and the Chemical-Pharmaceutical Industry of Georgia have developed. The activities of Iovel Kutateladze Institute of Pharmacochemistry follow these trends.

Since 1960 we have carried out purposeful research of plants for the content of cardiac glycosides of cardenolide and bufadienolide groups, steroid and triterpene saponins, lipids, flavonoids, coumarins, lignan lactones, tannides, anthraquinones etc. A number of plant species having unique chemical composition and efficient pharmacological activity were revealed. Several hundred individual compounds including new ones were isolated and characterized, the structure of which was determined by modern methods.

Among cardiac glycosides – indispensable cardiotonic substances, the preparations from *Digitalis* species occupy a prominent place. In the mountain part of the Main Caucasian Ridge and its spurs, large amounts of Caucasian endemic plant *Digitalis ciliata* Trautv. are found. The plant is distributed over a large area and, in places, it makes even a continuous brushwood on a few hectares. Only the regions explored by our expeditions can give annually up to 1000 tons of a high-quality air-dried raw material.

Digitalis ciliata is an efficient medicinal plant [1]. It synthesizes almost all cardenolides of *Digitalis* with the total amount up to 3%. Twenty three cardenolides were isolated and characterized. Digitoxygenin glycosides dominate in this plant. Original autofermentative technology was developed, and *Digitalis ciliata* was used for the production of leading cardiac glycosides: digitoxin and acetyldigitoxin-α [1, 2]. Novogalenic preparations Digcilen (ampoules) and Digicil (tablets) produced from this plant, were widely used in medicine [3].

High content of cardenolides in *Digitalis ciliata* opened a new avenue for their chemical and biochemical transformation in order to confer new therapeutic perspectives to cardenolides [4].

Seeds of *Digitalis ciliata* are characterized by high content of steroid glycoside Digitonin. An original technology was developed and the production of this irreplaceable biochemical reagent was organized. The method was patented in Great Britain, Switzerland and Germany [5]. The *Digitalis ciliata* seeds contain 30-35% of neutral lipids, which differ from typical vegetable fats by their positional distribution. Among triacylglycerides of *Digitalis ciliata* 90% fall on trilinoleate, which is a rare exception. Among the lipids of *Digitalis purpurea* the scarce α-linoleic acid was found. Neutral lipids of *Digitalis* exhibit strong virus-inhibiting capability. The preparation Digipurol (aerosol) for the prophylaxis and treatment of viral flu was produced [6, 7].

Bufadienolide glycosides Hellebrin, Hellebrigeninglycoside and Desglucohellebrin were isolated from the roots and rhizomes of Georgian and Caucasian endemics *Helleborus abchasicus* A. Br. and *Helleborus caucasicus* A. Br. and characterized. 4 glycosides, including 3 new furostanols, were isolated from the steroidal substances of the roots and rhizomes of *H. caucasicus* and their structure was determined. Besides, a significant amount of 20-hydroxyekdison was isolated having a wide range of therapeutic activity. The steroids of *H. caucasicus* in total display strong cytotoxic activity against lung and colon carcinomas. It should be noted that their cytotoxic dose ($2 \cdot 10^{-9}$g/ml) is rather low [8].

14-18% of neutral lipids were isolated from the underground parts of *Helleborus*. Accumulation of such a big amount of lipids in the roots and rhizomes is a rare phenomenon. The neutral lipids of *Helleborus* differ from typical fats in a low content of triacylglycerides of main class and in a high content of free fatty acids making up about 70% in total. The neutral lipids of the underground parts of *Helleborus* are characterized by specific anticancer activity without general toxic action. On their basis the preparation Hellipol was developed for the treatment of malignant surface tumors [7, 9].

The interesting chemical composition and diverse pharmacological activity of *Helleborus* prompt to preserve its natural resources in Georgia from unrestricted despoilment.

At the Institute of Pharmacochemistry, the presence of steroid glycosides of diosgenin in a widely spread plain plant *Tribulus terrestris* L. was revealed for the first time. From this plant, spiro- and furostanol glycosides were isolated. Tribusponin – a noothropic, nonspecific anabolic remedy for prophylaxis and treatment of atherosclerosis developed on the basis of steroid saponins is widely used in NIS countries [10].

Yucca gloriosa L., introduced in Georgia, contains mainly steroidal saponins of tigogenin. Tigogenin was transformed into key products for the synthesis of steroidal hormonal preparations: 5α-androstanol acetate and 5α-pregnenolone acetate. Medandrosterenole, dihydrotestosterone and its ethers, altesine, dexamethasone and others were synthesized from these compounds. Isonicotinoyl derivatives exhibit antituberculosis activity. 5α-androstane-3β-17-diol, the so-called 3β-adiol, designed for the treatment of prostate tumors, was also synthesized from tigogenin by a simplified scheme [11-14].

Tigogenin was acknowledged as one of the most profitable raw materials for the synthesis of 5α- row steroids. Industrial plantations of *Yucca gloriosa* L. were founded on about 190 hectares in Eastern Georgia in order to provide tigogenin production with raw materials [11, 12].

Because of abundant blossoming this wonderful evergreen decorative plant is widely used for plant verdure of Tbilisi and its suburbs.

New aglycon – yuccagenol-25R,5α-spirostan-3-one and new glycosides – monodesmosides of smilagenin and tigogenin were isolated from the leaves of *Yucca gloriosa* [15, 16].

Yucca gloriosa L. develops a strong root system. In contrast to the leaves and blossoms, the rhizomes accumulate 5β-steroids but not 5α- ones. Eight spiro- and three furostanol glycosides, the derivatives of smilagenin, sarsapogenin, gloriogenin and shidigeragenin, four of which appeared new compounds, were isolated from the rhizomes and characterized. In the rhizomes of *Yucca gloriosa* L. regular changes in the ratio between furo- and spirostanols were observed. The furostanols prevail in winter, when the endoenzymes converting the furo-form into the spiro-form are less active [17].

The steroid saponins of *Yucca gloriosa* have found use in allelochemistry. From the saponins of blossoms, the preparation Alexin, an efficient stimulator of growth and development of plants, was produced. This preparation is characterized by membranotropic activity, it participates in metabolic processes and, most likely, plays the part of metabolism bioregulator. Presowing treatment of seeds or spraying of seedlings with water solutions of Alexin increases wheat, barley, frigole, soya, potatoes and tomatoes yields by 20-55%. At the same time, it improves the quality of products and promotes the production of ecologically pure agricultural products. Total saponins from rhizomes of *Yucca gloriosa* also exhibit growth-stimulating activity [18].

In recent decades phenolic compounds arouse active interest due to their antioxidant properties. It was found that the roots of *Yucca gloriosa* contain no steroid saponins, but are rich (up to 10%) in phenolic compounds which appeared to be stilbenes. From the enriched crude phenolic compounds of the roots, 11 stilbenes were isolated. Six of them are identical to yuccaoles, the substances isolated from *Yucca schidigera* at the beginning of the 21st century. The rest stilbenes named gloriosaols are new compounds of scarce spiro-structure; they consist of three parts: two identical C_{15} fragments of fluorglucinol bonded to the stilbene center by γ-lactone rings. The chemical structure of gloriosaol-A was established. The remaining four stilbenes are its diastomers and are distinguished by the orientation of carbon atoms at C_3 [19].

As expected, both total and individual stilbenes from the roots of *Yucca gloriosa* display high antioxidant activity, which is 2-3 times higher than that of well-known compounds, such as ethylenediaminetetraacetic acid, α-tocopherol and quercetin, and of other plant substances described in the literature. The stilbene compounds of the roots of *Yucca gloriosa* could be used for production of the corresponding remedies.

From hard-fiber leaves of *Yucca*, denim-type cloth is produced in many countries. Therefore, the use of *Yucca gloriosa*, cultivated in Georgia, can produce an opportunity for development of a number of fields of pharmacochemical, agricultural and even textile industry of a country.

Pentacyclic triterpenes were found in many plant species of Georgian flora. From liana-like *Hedera* evergreens: *Hedera caucasigena* Pojark., *H.colchica* C. Koch. and *H. pastuchowii* Wor. *(*Fam. *Araliaceae)* about 60 triterpene glycosides were isolated, among them 21 new chemical compounds including 17 derivatives of oleanolic acid and hederagenin. Four compounds represented the glycosides of arjunolic acid – new and rare aglycon for both *Hedera* and *Araliaceae* saponins.

A regular relationship between the structure of *Hedera* glycosides and their fungistatic, antiprotozoal, antileishmanial, cytotoxic and antiproliferative activity was established [20-25]. Causuron – efficient bronchospasmolytic remedy – was developed from the leaves of *Hedera caucasigena* Pojark.

The endemic Caucasus plant *Cephalaria gigantea* (Ledeb.) Bobr. has a well-developed root system (the length of roots exceeds 1.5 m), rich in triterpene glycosides, consisting of, at least, 18 components. Twelve new compounds named giganteosides were isolated from *C. gigantea* roots. The presence of glucuronic acid in the carbohydrate part of glycosides is noteworthy. Saponins from *C. gigantea* exhibit diverse biological activity. An extract from the roots of this plant containing alkaloids along with triterpenoids displayed antimalarial effect [26-29].

According to the developed optimal technology triterpene saponin (yield 20%) was isolated from the tubers of *Cyclamen vernum* Sweet. and *Cyclamen adzaricum* Pobed. Basic triterpene glycosides, among them 3 new ones, and, what is of primary importance, a new aglycone, being 16α-hydroxy-13,28-epoxy-30,30 dibutoxyolean were identified and described. Kochivardinum – remedy for treating acute and recurrent paranasal sinusitis – was worked out on the basis of purified triterpene saponins from *Cyclamen adzaricum* [30-32].

Fatsia japonica (Thumb.) Decne et panach., plant, which was primarily introduced and cultivated in Georgia for decorative purposes was studied. The seven triterpene glycosides named fatsiosides were isolated from the leaves and on their basis a new non-steroid antirheumatic, anti-inflammatory remedy Fatsiflogin was developed for the treatment of rheumatoid arthritis, spondyloarthritis, osteoarthritis and other rheumatic diseases. The remedy appeared as effective as Voltaren, but, at the same time about 20 times less toxic [33, 34].

A great demand for triterpene saponins on the one hand, and huge raw material resources up to 100 tons annually from tea plantations of Georgia, such as tea seeds, on the other, governed our investigation along these lines.

Well-reproducible technology of triterpenoids isolation from tea seeds, which allowed to obtain up to 20% of high-quality final product - theasaponin - was developed and a special department for its production with the capacity of 10 tons per year was built at Tbilisi Bioplant. Theasaponin apperared to be an efficient adjuvant of veterinary vaccines. Besides, it found wide application in the production of high-speed X-ray films and was used in great amounts at Holding Company "Tasma" – a leading enterprise in the chemical-photographic industry of Russia [35].

Theasaponin was also included as a constituent in the medicinal-prophylaxis toothpaste Tbilisuri, enhancing its cleaning activity and promoting tooth enamel strengthening.

The fatty oil of tea seeds, obtained as a by-product (up to 20%) during theasaponin production was used as a constituent of cosmetic face cream. Besides, this oil may also be used in other fields of industry [7]. Complex processing of tea seeds, the wastes of tea plantations, for the above-mentioned purposes should become one of the priorities of industry in Georgia.

The plants of Georgian flora are especially rich in phenolic compounds. The dominating flavonoid robinin – caempherol-3-O-β-robinobiosyl-7-O-α-L-rhamnopyranoside was isolated from the leaves and blossoms of *Astragalus falcatus* L. and exhibited high antiuremic and diuretic properties. On its basis Flaroninum – a remedy widely used in NIS countries for treatment of chronic renal insufficiency with uremia – complication which accompanies chronic glomerulonephritis and other renal diseases – was developed [36].

Paliurus spina-christii Mill., plant, widely spread in Georgia, abundantly blossoms. Neutral lipids from its seeds are characterized by high content of unsaturated fatty acids, 80% of which falls on oleinic and linolic acids. Tsarubol, a hepatoprotective and bile-expelling remedy was developed from the fruits of this plant. Tsarubol contains a complete spectrum of initial raw material, generally lipid-soluble phenolic compounds. Its effective choleretic and hepatoprotective properties are determined by its chemical composition. Tsarubol combines the properties of flavonoid preparation Flamin, Cilibor, Legalon and well-known lipid drug Essentiale [37].

Caucasian endemic plant *Rhododendron ungernii* Trautv. is spread locally, though its resources as a raw material are significant in Western Georgia. The following compounds: quercetin, quercitrin, isoquercitrin, hyperin, rutin, (+)-gallocatechol, (+)-catechol and (-)-epicatechol were isolated from the leaves of *Rhododendron ungernii.* The presence of leucoanthocyan and cyanidine is also proved. The purified crude phenolic compounds from *Rhododendron ungernii* completely inhibits the reproduction of *Herpes* virus. Based on this phenolics 5% ointment Rodopes was developed. The therapeutical activity of Rodopes is similar to the well-known antiviral remedy Zovirax and much more effective than traditional Interferon; besides, normalization of immune indices is observed. Rodopes is indicated for all types of herpetic diseases and for wide application in dermatology, dentistry and gynecology [38].

The remedies developed from the leaves of an ancient relict plant *Ginkgo biloba* are nowadays of great demand due to the unique chemical composition of its leaves. *Ginkgo biloba* was brought to Georgia from Japan as a decorative tree in 1860 and adapted easily to local conditions. The aim of studying the chemical composition of the leaves of *Ginkgo biloba* growing in Adjara was to reveal the possibility of their application in medicine. As a result, compounds were found, which corresponded to literary data: ginkgolides, bilobalides and biflavonoids – ginkgoheterozides. The ratio of flavonolglycosides quercetin, caempherol and isorhamnetin 9.2:10.2:3.5 also corresponds to international standards. Based on the above-mentioned, we can infer that the leaves of *Ginkgo biloba* growing in Georgia represent an excellent raw material. Liquid spirit extract Ginkgo-Bathi, obtained from the leaves of *Ginkgo biloba* is recommended for the improvement of cerebral and peripheral blood circulation, prophylaxis and treatment of atherosclerosis, treatment of after-effects of strokes and brain injuries, memory and attention disorders, decreased intellectual capabilities, dizziness etc. [33]. The remedy Ginkgo-Bathi is distributed in Georgia via the network of chemist's shops [39].

A rational technology of reduction of 1,8-dioxyanthraquinone to 9-anthrone was developed. The preparation Psorantron was produced in the form of 1%, 15% and 3% ointment. The remedy was tested in the Russian Center of Psoriasis and other special clinics. It is efficiently used for the treatment of psoriasis [40].

The preparation Rhamnil, which is produced by autofermentation of anthraglycosides of the bark of *Rhamnus frangula* L., holds a firm position in medicine and is used for treatment of malfunction of the gastrointestinal tract [41].

All the above-mentioned remedies are provided with stable bases of raw material from agrarian or medicinal plants cultivated on experimental plots at the Institute of Pharmacochemistry. The scientific and technical issues related to the production of these remedies were resolved, and production is organized.

A number of promising plants have been revealed containing representatives of particular chemical classes with different pharmacological activity, which pave the way for the development of new effective remedies.

ფარმაკოქიმია

საქართველოში მოზარდი მცენარეებიდან მიღებული ბიოლოგიურად აქტიური ნივთიერებები და ორიგინალური სამკურნალო საშუალებები

ე. ქემერტელიძე

აკადემიის წევრი, ი.ქუთათელაძის ფარმაკოქიმიის ინსტიტუტი, თბილისი

საქართველოში მოზარდი მცენარეები გამოკვლეულია ისეთი ქიმიური კლასის ნივთიერებათა შემცველობაზე, როგორიცაა: კარდენოლიდური და ბუფადიენოლიდური საგულე გლიკოზიდები, სტეროიდული და ტრიტერპენული საპონინები, ლიპიდები, ფლავონოიდები, სტილბენები, ტანიდები, ანტრაგლიკოზიდები.

სხვადასხვა ქიმიური კლასის ნივთიერებების საფუძველზე შემუშავებულია: კარდიოტონური, ათეროსკლეროზის საწინააღმდეგო, ბრონქოსპაზმოლიზური, ანტირევმატული, ანტიურემიული, ჰეპატოპროტექტორული და ნაღვლის დამდენი, ანტიჰერპესული, ფსორიაზის საწინააღმდეგო, სისხლის მიმოქცევისა და კუჭ-ნაწლავის ფუნქციის მომწესრიგებელი საშუალებები. მოწოდებულია მცენარეთა ზრდა-განვითარების სტიმულატორი და ნედლეული სტეროიდული ჰორმონალური პრეპარატების სინთეზისათვის.

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