Review Paper

Ethnobotanical Study and Phytochemical Profiling of Traditionally Used Medicinal Plants of Georgia and Armenia: *Symphytum caucasicum* M. Bieb. (Boraginaceae) and *Cyclamen coum* Mill. (Primulaceae)

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Abstract:

A variety of climate zones and unique relief make the Caucasus a hotspot, characterized by the highest biological diversity of any area with temperate forests worldwide. The Caucasus hotspot shelters 6350 species of vascular plants, at least 25% of which are unique to the region. For centuries, many Caucasian plants have been used in traditional medicine. Interestingly, in different countries, the same plant could have different applications in traditional medicine. In this study, we considered botanical characteristics, distribution, biochemical composition and use in traditional medicine of *Symphytum caucasicum* M. Bieb. and *Cyclamen coum* Mill., medicinal plants used in the traditional medicine of Armenia and Georgia. The review demonstrates that Caucasian medicinal plants *Symphytum caucasicum* M. Bieb. and *Cyclamen coum* Mill. are an important source of alkaloids, saponins and phenolic compounds. The review demonstrates the benefits of using *Symphytum caucasicum* M. Bieb. and *Cyclamen coum* Mill. for the treatment of different disorders, indicates different applications of these plants in traditional Armenian and Georgian medicine and offers information to produce safe plant-based medications.

Keywords: *Symphytum caucasicum* M. Bieb., *Cyclamen coum* Mill., Armenia, Georgia, medicinal plants, alkaloids, saponins and phenolic compounds.

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Introduction

Although synthetic pharmaceuticals are increasingly produced, there is a rising global interest in and demand for herbal medicines. The Great Caucasus is renowned for its spectacular flora. This biodiversity hotspot has evolved due to a variety of factors, such as a rich topography and geology, sharp climate gradients, and the location between the flora regions of Asia, Europe, and the Mediterranean. The Caucasus is home to 6350 vascular plant species, including more than 2900 endemic species. [1]. Two neighbouring countries of the South Caucasus, Armenia and Georgia, are characterised by a rich and diverse flora [2], [3]. There are about 3800 plant species described in the Armenian flora, out of which about 800 species could be used as medicinal plants [4], [5]. The flora of Georgia includes more than 4,100 vascular species; the latest register published in 2018 lists 4275 species [6], and one-fifth of them are endemic. Around 700 species are used in Georgian traditional medicine, and 200 taxa have been listed in the country's official pharmacopoeia [7]. Throughout human history, various parts of medicinal plants, including leaves, stems, bark, roots, seeds, and fruits, have been utilized for the treatment and prevention of the primary types of diseases. Biologically active compounds isolated from plant material exhibit antioxidant, anti-inflammatory, antibacterial and anti-cancer activities and serve as the major sources of new drug molecules today [8], [9]. Even though many plant species occur in the territories of both Armenia and Georgia, and the folk medicine of both countries has a long history, the comparison of the traditional medicinal use of the same plant species in these countries has not been performed. In this review, the systematization of knowledge on biology, phytochemical profile and use in folk medicine of two medicinal plant species, grown on the territory of both Armenia and Georgia, *Symphytum caucasicum* M. Bieb. and *Cyclamen coum* Mill. was performed. The literature search was carried out in PubMed, Scopus, Google Scholar and eLibrary databases between 10th of July - 10th and August 2025. The name of each medicinal plant was used as a search criterion. The search was performed in Armenian, Georgian, English and Russian languages.

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Botanical characteristics of *Symphytum caucasicum* and *Cyclamen coum* Mill. *Symphytum caucasicum* M. Bieb.

S. caucasicum is an herbaceous perennial species, covered in fine greyish hairs, with a reduced rhizome, short, fusiform, with long, thick roots (Fig. 1A). The stem is 40–60 cm high, thick, soft-villous, and has a few short lateral branches. The cauline leaves are quite numerous and oval or oblong, while the lower leaves have a reasonably long petiole and are obtuse, truncate, or rounded at the base. The leaves are 5–10 cm long and 2–4 cm wide. The radical leaves wither at flowering. Inflorescence in cymes apical on the stem and upper lateral branches. Inflorescences are few-flowered, leafless and twisted to one side: pedicels drooping, 3–5 mm long, greyish downy and sometimes with prickly short bristles [10]. Calyx incised at 1/3, 3 times shorter than the corolla, with unequal lobes.

Fig. 1. *Symphytum caucasicum* M. Bieb. (A) and *Cyclamen coum Mill.* (B) in the flowering phase.

Flowers are small. Corolla red in bud, light blue when open. The fruit is oblong, brownish, sharply netted-wrinkled, finely tuberculate within this net, 3–3.5 mm long. The flowering phase is from April to June, and fruiting occurs in June-July [10].

Cyclamen coum Mill.

The name of the plant refers to the Greek Kos Island in the Aegean Sea. Perennial tuberous plant. The tuber is shaped like a compressed sphere and frequently flattens on top as it ages. It is medium in size when fully grown, reaching a diameter of 5 cm, brown, smooth, and has fine, velvety hairs. It can occasionally have small floral trunks, thin branching roots with a diameter of 1 mm, originating from the center of the underside. The leaves are rounded, kidney-shaped leaves in the fall or winter, which are either plain green or marked with silver on top and purple underneath. It lacks an above-ground stem. The corolla is dark pink, with a dark purple spot at the base. The fruit is a spherical box, with hemispherical, small seeds [11]. The corolla consists of 5 petals that are up to 15 mm long. The flowering phase begins in February-March and ends in April.

Geographical distribution of plants

S. caucasicum is distributed in Central European Russia, the North Caucasus, North European Russia, South European Russia, and the Transcaucasus [12], growing in shrubberies, glades, damp forest fringes, near ravines and at watersides. It is a winter-hardy plant, but not very tolerant of moisture.

In Armenia, plants grow in humid habitats, near water streams, and in ruderal places. It was revealed up to the upper mountain belt, on an elevation of 400–2000 m. It was described in Upper Akhuryan, Lori, Idjevan, Sevan, Darelegis, Zangezur, Meghri floristic regions [13].

In Georgia, plant grows in meadows and wetlands in the middle and lower montane regions. Distributed in Abkhazia, Racha-Lechkhumi, Adjara, Kartli, Tsakhia-Pshav-Khevsureti, Kakheti, Trialeti, Meskheti [10] .

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The native range of *C. coum* is from Bulgaria to Caucasus and Israel. It is a tuberous geophyte and grows primarily in the temperate biome [14]. *C. coum* occupies contrasting habitats from the forest belt to the alpine belt, in deciduous forests, mainly in oak forests and in shrubbery. *C. coum* has a wider distribution from the Black Sea region to the southern part of Turkey. *C. coum* accessions are distributed in Ukraine, Armenia, Georgia, Bulgaria, Lebanon, Syria, Israel and the south Caspian coast of Iran, but nowhere else in the world [15]. In Georgia, it is widespread in Abkhazia [10]. It was observed on the Gagra ridge, in the Gegi and Bzipi Gorges [16].

The use of *Symphytum caucasicum* M. Bieb. and *Cyclamen coum* Mill. in traditional Armenian and Georgian medicine

The medicinal importance of the genus *Symphytum* have already been acclaimed by Dioscorides in the ancient Greek pharmacopoeia, De Materia Medica. The genus's name is derived from the Greek word *symphuo* ("to grow together"), and it is indicative of the wound-healing properties [17]. Throughout the Middle Ages, burns, bruises and fractures were treated with different preparations of plants of the genus *Symphytum*; in some countries, medical uses include pulmonary and gastroduodenal conditions, tonsillitis, metrorrhagia, and phlebitis [18]. The plants of the genus are still widely used in European and Western Asian countries for wound-healing, skin-regeneration, treatment of ulcers, wounds, bone fractures, and rheumatic complaints [19]. Fresh or dried parts of plants can be administered after homogenisation, or plant extracts are included in topical preparations (such as collars, compresses, pastes, ointments, and poultices) and formulations that indicated an internal use were also retrieved [17].

In Georgia, concentrated *S. caucasicum* root extracts are used to cure fractures [20]. The tea prepared from the roots is used to treat diseases of the gastrointestinal system [21], and the leaves and roots of this plant are used in ointments and to treat fractures [3]. In Armenia, *S. caucasicum* is used as a good remedy to treat inflammation of the sciatic nerve and fractures [3].

The name of the genus Cyclamen originates from Medieval Latin *cyclamen*, and Greek *kyklaminos*, meaning circle, referring to the round shape of the tubers and this part of the plant is used in traditional medicine [22]. Various *Cyclamen* species were used in the traditional medicine of many countries. Thus, the tubers of *C. repandum* were used in Sardinian folk medicine as a laxative and abortive; other species of this genus are used in Turkey against infertility [23]. In Georgian traditional medicine, alcohol tincture is prepared from tubers of *Cyclamen*, and it is used as a remedy that completely and permanently cures chronic sinusitis, nasal polyps and adenoids, and also treats arthritis and headaches [11]. The raw tubers of the *C. coum* are used against frontitis, sinusitis and pansinusitis and other such diseases [20]. Also, dried tubers of *C. coum* are used in traditional Georgian medicine for the

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stimulation of intestinal peristalsis, as remedies for haemorrhoids, rheumatism, some uterine diseases and snakebites [24]

Phytochemical composition of *Symphytum caucasicum* M. Bieb. and *Cyclamen coum* Mill. and the biological activity of compounds

Phenolic acids, saponins, flavonoids and pyrrolizidine alkaloids are the most representative compounds in all *Symphytum* species and *Cyclamen* [25], [26].

Alkaloids

Alkaloids are a type of secondary metabolites which contain at least one nitrogen in their chemical structure, generally forming a ring. Alkaloids are present as salts of organic acids in different parts of plants and are involved in seed dispersal and pollinator attraction, also protecting plants from pathogens and herbivore grazing [27].

The production of alkaloids in plants is closely linked to environmental conditions. Because these compounds are mainly synthesized in young, actively developing tissues, any factor that affects tissue growth - such as light intensity, nutrient availability, soil moisture, temperature, and elevation - can significantly impact alkaloid levels [28] .

Pyrrolizidine alkaloids were revealed in *S. caucasicum* [29] and were generally more abundant in the roots than in the aerial parts [25]. Among these, the following alkaloids were detected using paper chromatography and thin-layer chromatography: the N-oxide of echimidine, asperumine, echinatine, intermedine, intermedine-N-oxide, 3'-acetylsymphytine-N-oxide, 7-acetylintermedine, heliosupine-N-oxide, and lasiocarpine [29], [25], [30], [31]. The aerial part of *S. caucasicum* contained intermedine, intermedine-N-oxide, 7-acetylintermedine, heliosupine-N-oxide, symphytine-N-oxide, 3'-acetylsymphytine-N-oxide [25]. Some of the alkaloids, isolated from *S. caucasicum,* had significant biological activity (Table 1). Thus, echmidine and N-oxide of echimidine exhibited significant acetylcholinesterase inhibitory activity with IC50 0.276-0.769 [32]. Intermedine was shown to induce cell apoptosis via excessive ROS generation, changing the mitochondrial membrane potential and releasing cytochrome *c* [33]. Heliosupine-N-oxide caused significant inhibition of muscarinergic (mACh) and serotonin$_2$ (5-HT$_2$) receptors [34]. Lasiocarpine caused inhibition of RNA synthesis and induction of tryptophan pyrrolase activity in rats [35].

A piperidine-type alkaloid was isolated from the whole *C. coum* plants, and the structure was established as 2-β-D-4glycopyranosyl-2-undecil-3,5-dihydroxy-6-carboxypiperidine [36].

Phenolic compounds

Monomeric and polymeric phenolics are secondary aromatic metabolites synthesised via the shikimate/phenylpropanoid pathway or polyketide acetate/malonate pathway [37]. Phenolic compounds are typically classified into two categories: flavonoids and non-flavonoids, and are involved in preventing stress and regulating physiological activities [37].

Various phenolic compounds were identified in *S. caucasicum*. Hydroxybenzoic

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acid-O-hexoside, hydroxybenzoic acid, caffeic acid, rabdosiin, rosmarinic acid, and dihydrogloboidnan A were found in the aerial part and roots of *S. caucasicum* [25]. Caffeic acid exhibits antioxidant and anti-inflammatory properties, cardioprotective effects against dyslipidemia, and hypercoagulability [38]. Hydroxybenzoic acid and its derivatives exhibit antioxidant and anti-inflammatory properties, modulate the immune response in inflammatory bowel diseases, regulate glucose levels, exhibit antimicrobial and neuroprotective effects, and inhibit the aggregation and propagation of α-synuclein [39]. Dehydrorabdosiin, globoidnan A, and danshensu were detected only in the aerial part of *Symphytum caucasicum* [25]. The aerial part of *S. caucasicum* also contained quercetin-O-hexoside and quercetin-O-malonylhexoside, while these flavonoids were not revealed in the roots [25]. Quercetin-O-hexoside exhibits cytotoxic, phytotoxic, antimicrobial and antioxidant effects [40].

New, biologically active phenolic polymers poly[3-(3,4-dihydroxyphenyl)glyceric acid] and poly[oxy-1-carboxy-2-(3,4-dihydroxyphenyl)ethylene] were revealed in *S. caucasicum* [41], [42]. It was demonstrated that poly[oxy-1-carboxy-2-(3,4-dihydroxyphenyl) ethylene] is the main component in four water-soluble high-molecular preparations obtained from roots and stems of *Symphytum asperum* and *S. caucasicum* [43]. This polymer is a representative of a new class of natural polyethers with a residue of 3-(3,4-dihydroxyphenyl)-glyceric acid as the repeating unit [44]. Poly[3-(3,4-dihydroxyphenyl)glyceric acid] was also isolated from roots of *S. asperum* and *S. caucasicum,* and the antibacterial activity of this compound was demonstrated [43], [45].

The total phenolic content in leaves and roots of *C. coum* was compared, and the highest phenolic content was revealed in the leaves [46]. Gallic acid, 3,4-dihydroxybenzoic acid, 4-dihydroxybenzoic acid, chlorogenic acid, vanillic acid, caffeic acid, *p*-coumaric acid, ferulic and cinnamic acids were revealed in the leaves and roots of *C. coum* [46]. Antioxidant, anti-inflammatory, anti-cancer, anti-diabetic, and anti-melanogenic properties of *p*-coumaric acid were demonstrated [47]. Such phenolic compounds as phloretin, *C*-dihexoside, quercetin 3-galactoside, and catechin were identified from *C. coum* tuber extracts [48]. Phloretin exhibits antidiabetic, antioxidant, anti-inflammatory, and antitumor activities, inducing apoptosis in tumour cells and possessing an inhibitory effect on S180 sarcoma [49]. Quercetin-3-β-galactoside is effective for treating allergies and preventing heart disease and cancer, and it was identified as a new class of inhibitors of the 3-chymotrypsin-like protease of SARS-CoV [50].

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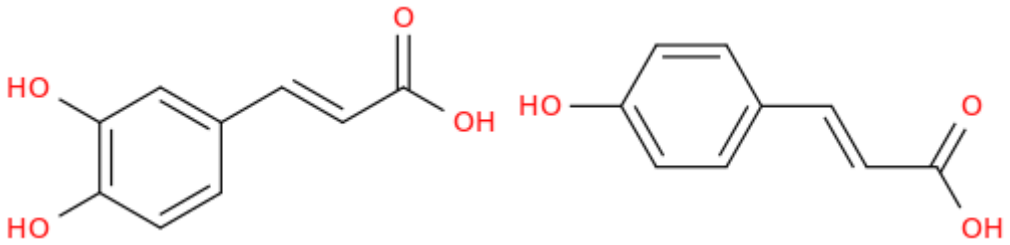

caffeic acid (A) p-coumaric acid

Fig. 2. Two structurally-related phenolic compounds isolated from *Symphytum caucasicum* M. Bieb. (A) and *Cyclamen coum* Mill. (B).

Saponins

Saponins are a category of plant specialised metabolites, which are produced in plants in response to various biotic stresses. These compounds have a hydrophobic aglycone backbone attached to a hydrophilic saccharide, like glycosides [51]. Different studies have shown the activity of saponins against major herbivorous insects and strong antibacterial activity [52].

The presence of saponins was demonstrated for plants of the genus *Symphytum* [31]. Thus, the presence of symphytoxide-A and leontoside-A and B was shown for the most studied species of the genus, *Symphytum officinale* L. [53]. However, data on the saponin composition of *S. caucasicum* are not available in the literature.

The composition of saponins from *C. coum* was investigated in several studies. Thus, cydaminorin, cyclacoumin, mirabilin lactone, and deglucocyclamin, were isolated from the *C. coum* tubers and their molecular structures were elucidated [48], [54]. A new triterpenoid saponins, coumoside A and coumoside B, have been isolated from the whole *C. coum* plant and structures of these compounds were deduced by NMR methods [55], [56]. The coumoside A has the structure 3 beta-O-[beta-D-glucopyranosyl-(1-6)-[alpha-L-arabinopyranosyl- (1-2)]-beta-D-glucopyranosyl-(1-4)-[beta-D-gluco-pyranosyl-(1-2)]-alpha-L-arabinopy-ranosyl]-16 alpha-hydroxy-30,28 beta-lactone-olean-12-ene and the structure of coumoside B was 16α-hydroxy-3β-[β-xylopyranosyl-(1→2)]-[β-glucopyranosyl-(1→4)]-[β-glucopyranosyl-(1→2)]-α-arabino-pyranosyl]-oxy]olean-12-eno-30,28-lactone [56]. From the tubers of *C. coum*, deglucocyclamin and three new saponins, cyclaminorin, cyclacoumin, and mirabilin lactone, were isolated [54]. According to NMR methods, the new compounds had the following structures: cyclaminorin: 13 beta,28-epoxy-3-beta-(([beta-D-gluco-pyranosyl-(1-->2)]- [beta-D-glucopyranosyl-(1-->4)]-alpha-L-arabinopyranosyl) oxy) 16 alpha-hydroxy-olean-30-al, cyclacoumin had the structure 13 beta, 28-epoxy-3 beta-((([beta-D-xylopyranosyl-(1-->2) -beta-D-glucopyranosyl-(1-->4)]-[beta-D-gluco-pyranosyl-(1-->2)]-alpha-L-arabinopyra-nosyl)oxy)-16 alpha,23-dihydroxy-olean-30-al and the structure of mirabilin lactone was 16 alpha-hydroxy-3 beta-((([beta-D-

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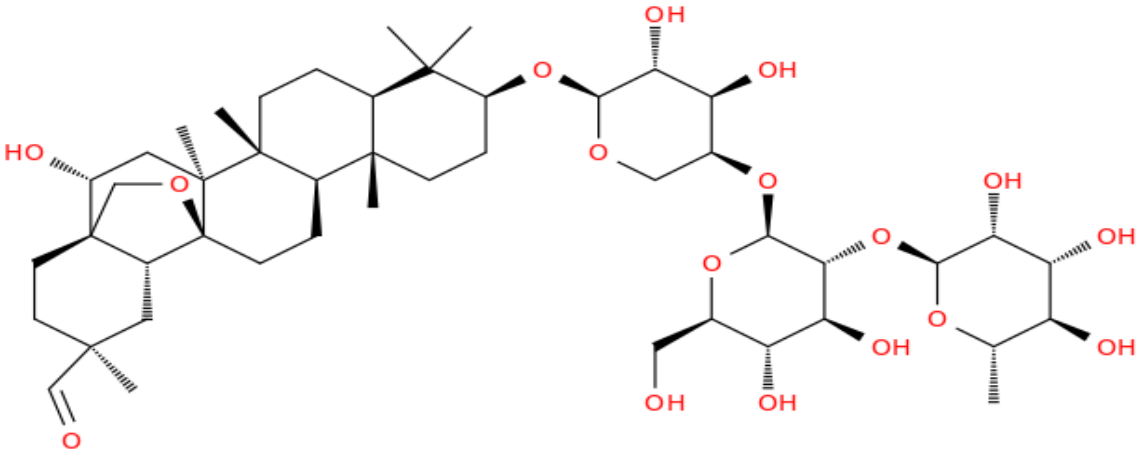
xylopyranosyl-(1-->2)]- [beta-D-gluco-pyranosyl-1-->6)]-beta D-glucopyranosyl-(1-->4))-[beta-D-glucopyranosyl-(1-->2)]-alpha-L-arabinopyranosyl)-oxy) olean-12-eno-30,28-lactone [54]. Sapogenins cyclamiretin A, C, D, cyclamigenin A and primulagenin were isolated from tubers of *C. coum* [57]. Hemolytic activity of cyclamiretin A was demonstrated [58]. The potential of primulagenin for modulating immune responses in inflammatory and autoimmune diseases was shown [59].



Cyclamiretin

Fig. 3. An example of a saponin endowed with a complex strucuture isolated from *Cyclamen coum* Mill. (Table 1).

Table 1. Biological activity of compounds isolated from *Symphytum caucasicum* M. Bieb. and *Cyclamen coum* Mill.

Class of compounds	Compound	Plant	Organ	Biological activity
Alkaloids	N-oxide of echimidine [29]	*Symphytum caucasicum* Bieb.	The whole plant	Acetylcholinesterase inhibitory activity [32].
	Intermedine, intermedine-N-oxide [25]	*Symphytum caucasicum* Bieb.	The whole plant	Hepatotoxicity through mitochondria-mediated apoptosis [33] .
	Heliosupine-N-oxide [25]	*Symphytum caucasicum* Bieb.	The whole plant	Inhibitor of muscarinergic (mACh) and serotonin$_2$(5-HT$_2$) receptors [34].
	Lasiocarpine [31]	*Symphytum caucasicum* Bieb.	The whole plant	Inhibition of RNA synthesis and induction of tryptophan pyrrolase activity [35].

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Phenolic compounds	Hydroxybenzoic acid-O-hexoside, hydroxybenzoic acid [25].	*Symphytum caucasicum* Bieb.	The whole plant	Antioxidant, anti-inflammatory properties, modulate the immune response, regulate glucose level, antimicrobial effect, and neuroprotective effect, [39].
	3,4-dihydroxybenzoic acid, 4-dihydroxy benzoic acid [46]	*Cyclamen coum* Mill.	Leaves and roots	
	Caffeic acid [25], [46]	*Symphytum caucasicum* Bieb.	Leaves and roots	Antioxidant and anti-inflammatory properties, cardioprotective effect [38].
		Cyclamen coum Mill.	Leaves and roots	
	Quercetin-O-hexoside [25]	*Symphytum caucasicum* Bieb.	Aerial part	Cytotoxic, phytotoxic, antimicrobial and antioxidant effects [40].
	Poly[3-(3,4-dihydroxyphenyl)glyceric acid] [43].	*Symphytum caucasicum* Bieb.	Roots	Antibacterial activity [45]
	p-coumaric acid [46]	*Cyclamen coum* Mill.	Leaves and tubers	Antioxidant, anti-inflammatory, anti-cancer, anti-diabetic, and anti-melanogenic properties [47].
	Phloretin [48]	*Cyclamen coum* Mill	Tubers	Antidiabetic, antioxidant, anti-inflammatory, and antitumor activities [49].
	Quercetin-3-β-galactoside [48]	*Cyclamen coum* Mill	Tubers	Treatment of allergies, prevention of heart disease and cancer, inhibitor of 3-chymotrypsin-like protease of SARS-CoV [50].
Saponins	Cyclamiretin A [57]	*Cyclamen coum* Mill	Tubers	Haemolytic activity [58].

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	Primulagenin [57]	*Cyclamen coum* Mill	Tubers	Modulation of immune responses [59].

Conclusions

An understanding of the ethnopharmacology and phytochemical composition of Armenian and Georgian medicinal plants, *Symphytum caucasicum* M. Bieb. and *Cyclamen coum* Mill. was the aim of the review. According to the current review, these species, for centuries used in medicine in both countries, are valuable sources of a variety of biologically active compounds, such as alkaloids, phenolic compounds and saponins. Nevertheless, more research is required to clarify the composition and structures of biologically active substances, mechanisms of action, and side effects in the treatment of a particular disease. The compounds found in Caucasian medicinal plants discussed in this review have a lot of potential for creating new therapeutic agents and are useful resources for drug discovery.

საქართველოსა და სომხეთის ტრადიციული სამკურნალო მცენარეების: *Symphytum caucasicum* M. Bieb. (Boraginaceae) და *Cyclamen coum* Mill. (Primulaceae) ეთნობოტანიკური კვლევა და მათი ფიტოქიმიური პროფილი

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აბსტრაქტი

კლიმატური ზონების მრავალფეროვნება და უნიკალური რელიეფი კავკასიას მსოფლიოს ერთ-ერთ ცხელ წერტილად აქცევს, რომელიც ზომიერი ტყეების მქონე ნებისმიერ სხვა რეგიონებს შორის ყველაზე მაღალი ბიოლოგიური მრავალფეროვნებით ხასიათდება. კავკასია უმაღლესი მცენარეების

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დაახლოებით 6350 სახეობის თავშესაფარია, რომელთაგან სულ მცირე 25% მხოლოდ ამ რეგიონში გვხვდება. საუკუნეების განმავლობაში, კავკასიური მცენარეების უმეტესობა ტრადიციულ მედიცინაში გამოიყენებოდა. აღსანიშნავია, რომ სხვადასხვა ქვეყანაში ერთი და იგივე მცენარე სხვადასხვა სამკურნალო მიზნით გამოიყენებოდა. მოცემულ კვლევაში განხილულია ***Symphytum caucasicum M. Bieb.***-ისა და ***Cyclamen coum Mill.***-ის ბოტანიკური მახასიათებლები, გავრცელება, ბიოქიმიური შემადგენლობა და მათი გამოყენება ტრადიციულ მედიცინაში - კერძოდ სომხეთსა და საქართველოში. ლიტერატურულმა მიმოხილვამ აჩვენა, რომ ეს მცენარეები ალკალოიდების, საპონინებისა და ფენოლური ნაერთების მნიშვნელოვანი წყაროა. მათი გამოყენება ტრადიციულ ქართულ და სომხურ მედიცინაში მიუთითებს მათ სამკურნალო პოტენციალზე სხვადასხვა დაავადებების მიმართ და საფუძველს ქმნის მომავალში უსაფრთხო მცენარეული პრეპარატების წარმოებისთვის.

საკვანძო სიტყვები: *Symphytum caucasicum M. Bieb.*, *Cyclamen coum Mill.*, სომხეთი, საქართველო, სამკურნალო მცენარეები, ალკალოიდები, საპონინები და ფენოლური ნაერთები.

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