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MEDICINAL IMPORTANCE OF *SCUTELLARIA* L. GENUS (LAMIACEAE) – A REVIEW

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Scutellaria L. is a therapeutically important genus widely used in folk and modern medicine. It is a rich source of bioactive compounds, mainly flavonoids and diterpenes with anti-inflammatory, antioxidant, anticonvulsant, antiviral, antibacterial, anticancer, hepatoprotective and neuroprotective activities. The paper presents a review on medicinal importance of eight *Scutellaria* taxa introduced and studied in the National Botanical Garden (Institute) “Al. Ciubotaru”. The review on ethnobotanical, phytochemical and pharmacological literature indicates the great therapeutic potential of the species, which points the way to conduct further multidisciplinary studies in order to establish and explore their medicinal and economic value.

Keywords: *Lamiaceae, Scutellaria, Republic of Moldova, medicinal importance.*

IMPORTANȚA TERAPEITICĂ A GENULUI *SCUTELLARIA* L. (LAMIACEAE) – REVIEW

Scutellaria L. este un gen de plante important din punct de vedere terapeutic utilizat pe scară largă în medicina populară și modernă. Speciile acestui gen sunt o sursă bogată de compuși bioactivi, în principal flavonoide și diterpene cu efect antiinflamator, antioxidant, anticonvulsivant, antiviral, antibacterian, anticancerigen, hepatoprotector și neuroprotector. Lucrarea prezintă un reviu cu privire la importanța terapeutică a 8 specii de *Scutellaria* introduse și cercetate în Grădina Botanică Națională (Institut) „Al. Ciubotaru”. Revizuirea lucrărilor etnobotanice, fitochimice și farmacologice indică potențialul terapeutic înalt al speciilor și confirmă necesitatea studiilor multidisciplinare ulterioare în vederea stabilirii și explorării valorii lor curative și economice.

Cuvinte-cheie: *Lamiaceae, Scutellaria, Republica Moldova, valoare curativă.*

Introduction

The genus *Scutellaria* L. (family Lamiaceae) includes approximately 360-470 accepted species, occurring in Europe, North America and East Asia [1, 2]. Its generic name is derived from the Latin *scutella* (“little dish”, “from the top of the calyx”).

Scutellaria (Scullcap) species have been used in folk medicine in different parts of the world for the treatment of hyperlipidemia, allergy, arteriosclerosis, hepatitis, and hypertension for hundreds of years [3]. Many *Scutellaria* species have been also used as culinary herbs, and for ornamental purposes. Phytochemical investigations of the species of this genus have resulted in the identification of a good number of important bioactive compounds, mainly flavonoids and diterpenes [4]. Therapeutically, *Scutellaria* plants possess antiviral, antimicrobial, antioxidant, antibacterial, hepatoprotective, spasmolytic, antidiarrheal, antifungal, antipyretic, anti-HIV, antiinflammatory, anticonvulsant activities [5-7]. Recently, the genus *Scutellaria* has gained considerable interest concerning anticancer activities [8]. Many of the skullcaps have impressive, beautiful blooms and there is a great potential for these species as ornamentals.

This review aims to bring information found in the literature about eight *Scutellaria* L. taxa growing in the National Botanical Garden (Institute) “Al. Ciubotaru” (NBGI) in order to argue their importance regarding traditional use, medicinal and economic value.

Material and methods

Eight *Scutellaria* L. taxa (*S. baicalensis* Georgi, *S. altissima* L., *S. albida* L., *S. albida* ssp. *colchica* (Rech. f.) Edmond., *S. supina* L., *S. incana* Spreng., *S. orientalis* L. and *S. alpina* L.) introduced in the collections of NBGI served as research objects. The current review is based on books and published studies from the library and electronic sources, as well as the online ethnobotanical databases. The search was carried out using scientific databases Scopus, Science Direct, PubMed, Google Scholar and the following keywords were typed: *Scutellaria* synonyms and common names; *Scutellaria* and botanical description; *Scutellaria* and World distribution; *Scutellaria* and ethnomedicinal uses; *Scutellaria* and phytochemistry; *Scutellaria* and therapeutic effects; *Scutellaria* and cultivation.

The citation of the authors of the species was made according to the global networks: The Plant List [9] and International Plant Names Index (IPNI) [10].

Results and Discussions

Synonyms and Common Names

According to the Plants of the World Online [2], the genus *Scutellaria* L. has 8 following synonyms: *Anaspis* Rech.f., *Cassida* Ség., *Cruzia* Phil., *Harlanlewisia* Epling, *Hastifolia* Ehrh., *Perilomia* Kunth, *Salazaria* Torr., *Theresa* Clos. Another source [11] indicates the synonym *Perilomia* Kunth.

The most often used common name for *Scutellaria* species is Skullcap. The English name "skullcap" describes the shape of the calyx, which look like miniature medieval helmets. Other popular names include: American skullcap, European skullcap, blue skullcap, hoodwort, Quaker bonnet, helmet flower, greater skullcap, mad dog weed, mad weed and side-flowering skullcap.

Botanical description and distribution

Scutellaria L. is a cosmopolitan genus within Lamiaceae family, with its main centre of diversity in Irano-Turanian region. Eastern Mediterranean and the Andes are a secondary centre of diversity [12].

The genus *Scutellaria* L. includes herbaceous, perennial plants or subshrubs. The stems erect or prostrate at base, hairy, rectangular, branched, 20 to 90 cm tall. Leaves are opposite; entire to pinnatifid with scalloped or toothed margins, 1 to 6 cm long, flowers – axillary, opposite or sometimes alternate apically, tube-shaped, blue-purple or white, calyx – short, tubular, 2-lipped; lips entire; upper lip – deciduous, with a transverse, rounded, concave scutellum (protection) or without and abaxially evidently saccate; lower lip persistent. Corolla – 2-lipped; tube exerted, arcuate or suberect; upper lip erect; lower lip 3-lobed. Stamens 4. Style is unequally bifid. Fruit – nutlets globose to ovoid.

The systematic position and distribution of the genus *Scutellaria* is given in table 1.

Table 1

Systematic position and distribution of *Scutellaria* L. genus

Kingdom:	Plantae	
Filum:	Angiospermae	
Class:	Magnoliopsida (Dicotyledones)	
Order:	Lamiales	
Family:	Lamiaceae	
Subfamily:	Scutellarioideae	
Genus:	<i>Scutellaria</i> L.	
		Geographical distribution adapted from https://powo.science.kew.org/

Synonyms, common names, native range and morphological characteristics of *Scutellaria* taxa growing in the collection of NBGI are given in Table 2.

Table 2

Synonyms, native range and morphological characteristics of *Scutellaria* L.

Species name/ Common name	Synonyms*	Native range	Morphological characteristics
<i>Scutellaria altissima</i> L. Tall skullcap	<i>Cassida altissima</i> (L.) Moench <i>S. altissima</i> subsp. <i>commutata</i> (Guss.) Nyman <i>S. commutata</i> Guss.	Eastern and Central Europe to Caucasus	Stem simple or slightly branched, pubescent, erect, 25-100 cm tall. Leaves opposite, long-petiolate with cordate base and obtuse or acuminate tip. Flowers bilabiate, blue-purple, grouped in racemose, unilateral inflorescences. Fruit – compressed, ovate nutlet.

<i>Scutellaria albida</i> L. Skullcap	<i>S. pallida</i> M. Bieb. <i>S. subalbida</i> Klokov <i>S. albida</i> subsp. <i>albida</i> , <i>S. cretica</i> Mill. <i>S. decumbens</i> Sieber ex Rchb., <i>S. hirta</i> Sieber ex Rchb., <i>S. nigrescens</i> Spreng.	South-Eastern Europe to Iran	Stem erect, usually branched, 15-30 cm tall. Leaves 2-3 cm long, triangular to deltoid, crenate, obtuse. Flowers white, 10-15 mm long, grouped in racemose, slightly pubescent inflorescences with internodes about 10 mm long.
<i>Scutellaria albida</i> ssp. <i>colchica</i> (Rech. f.) Edmond.	<i>Scutellaria vacillans</i> subsp. <i>colchica</i> Rech.f. <i>Scutellaria woronowii</i> Juz	Krym, North-Eastern Turkey to Transcaucasus	The plant has a close affinity to <i>S. albida</i> , having practically a corolla of the same colour (white or cream) but differs in that it has acuminate and short-petiolate bracts.
<i>Scutellaria alpina</i> L. Alpine skullcap	<i>Cassida alpina</i> (L.) Moench, <i>S. albida</i> Benth. <i>S. alpina</i> subsp. <i>jabalambrensis</i> <i>S. alpina</i> subsp. <i>olympica</i> Stoj. & Jordanov <i>S. lupulina</i> L. <i>S. compressa</i> A.Ham. <i>S. jabalambrensis</i> Pau <i>S. variegata</i> A.Spreng. <i>S. viscida</i> A.Spreng.	Central and Southern Europe and Russia	Stem square, prostrate-ascending, simple or branched, woody at the base, more or less pubescent, 10-30 cm tall. Leaves arranged in opposite pairs, ovate, rarely lanceolate, serrated-toothed, rarely entire, short-petiolate and crenulate margins. Inflorescence terminal tetragonal spike, elongated. Corolla blue-violet or purple-white, with the tube on the outside pubescent.
<i>Scutellaria baicalensis</i> Georgi Chinese skullcap	<i>S. adamsii</i> A.Ham. <i>S. baicalensis</i> f. <i>albiflora</i> <i>S. davurica</i> Pall. ex Ledeb. <i>S. lanceolaria</i> Miq. <i>S. macrantha</i> Fisch. ex Rchb. <i>S. speciosa</i> Fisch. ex Turcz.	South Siberia to North Korea and Vietnam	Stem erect, square, branched near base, slightly pubescent, up to 30–120 m tall. Leaves simple, opposite, short-petiolate or sessile, lanceolate, ciliated edge, entirely obtuse tip. Flowers dark blue, bilabiate, located in the axils of the upper leaves, raceme orientation. Fruit – black ovoid, nearly globular, nutlet, leathery in appearance.
<i>Scutellaria incana</i> Spreng. Hoary skullcap	<i>S. canescens</i> Nutt. <i>S. incana</i> f. <i>rhodantha</i> Mohlenbr. <i>S. incana</i> var. <i>incana</i> <i>S. pubescens</i> Muhl. <i>S. serrata</i> Spreng., <i>S. villosa</i> Elliott	North America, United States	Stem erect, branched, pubescent, 30-40 cm tall. Leaves dark green, ovate, with serrated edge. Purple-blue flowers united in branched racemes located at or near the top of the plant.
<i>Scutellaria orientalis</i> L. Yellow-flowered skullcap	<i>S. hercegovinica</i> Formánek <i>S. heterochroa</i> Juz. <i>S. hirtella</i> Juz. <i>S. hypopolia</i> Juz. <i>S. stevenii</i> Juz. <i>S. subalbida</i> Klokov <i>S. taurica</i> Juz.	Mediterranean region to Caucasus	Stem decumbent, up to 30 cm tall, woody, rarely tomentose. Leaves petiolate, broad-ovate or ovate-oblong, deeply crenate-toothed to penat-sectate. Inflorescence dense, elongated, usually 4-angular. Corolla yellow, rarely pink; lower lip often reddish.

*Synonyms are given according to Plants of the World Online database

Ethnomedicinal uses

Scutellaria species, popularly known as skullcaps have been widely used in traditional medicine of China, India, Korea, Japan, European countries and North America. The genus is used in traditional medicine as an anti-inflammatory, antispasmodic, abortifacient, astringent, emmenagogue, nervine, febrifuge, tonic, and sedative. *Scutellaria* species are also used to treat a wide range of nervous disorders, including insomnia, epilepsy, hysteria, anxiety and delirium tremens. They are helpful for skin and urinary tract infections, hypertension and chronic fatigue syndrome. An infusion is used for treating neuralgia, headaches and to promote menstruation. In European countries skullcap is a traditional treatment for epilepsy [13]. In Turkey *Scutellaria* has been used in Anatolian folk medicine as haemostatic, wound healing and strengthening [14]. Recently, Shen et al. [15] mentioned a total of 50 species, 5 subspecies and 17 varieties of the genus *Scutellaria* used in traditional medicine. Many of them have a long history, being used as traditional remedies to treat respiratory, peptic, neurological, hepatic and gall diseases.

With reference to the species involved in this study, *Scutellaria baicalensis* is the most studied and widely used species of this genus. It is a valuable medicinal plant with a long history of use in alternative medicine, one of the 50 fundamental herbs of the traditional Chinese medicine used since ancient times. It is listed in Chinese Pharmacopoeia, Japanese Pharmacopoeia, and European Pharmacopoeia [13, 16]. Chinese physicians use the root of *S. baicalensis* or *Huang-Qin* as an antibacterial, diuretic, antispasmodic, and promoter of bile flow. It also improves the general condition of the body, the functional state of the cardiovascular system and central nervous system. *Wogon Scutellariae Radix* is also a famous ancient drug in the traditional Chinese medicine [17]. It is prepared from *S. baicalensis* roots and is one of the most widely used crude drug for the treatment of hepatitis, bronchitis, diarrhea, and tumors [13]. Chinese skullcap is also used for tea production and as a flavoring agent in the food industry [3].

Scutellaria altissima is a common traditional Chinese medicinal plant, commonly used for upper respiratory infections, pneumonia and high blood pressure [18]. In folk medicine, *S. altissima* has been also used as a cough suppressant, expectorant, vasodilator and haemostatic. The herbal infusion is an effective remedy for hypertension, inflammation and oedema.

Scutellaria incana is used by Native Americans as a sedative in the treatment of anxiety and neurosis [19]. The infusion of the roots is used as an abortifacient and antidiarrheal remedy. The decoction of *S. incana* roots is beneficial in the treatment of nerve diseases, breast pain, gynaecological and kidney diseases [20, 21].

The infusion of *Scutellaria orientalis* is a popular remedy to treat hypertension, neurosis, insomnia [22]. It is useful in case of stomach pain, abdominal and kidney diseases, haemorrhoids, tumours [23]. In some European countries *S. orientalis* is used against diarrhoea, as tonic and wound healing [24]. Aerial parts of *S. orientalis* are used in Turkish traditional and folk medicine as an astringent and against pain [25], for constipation, as a haemostatic, tonic and cicatrizing [26].

Bioactive compounds

The chemical compounds of the genus *Scutellaria* have been studied since 1889. More than 295 compounds have been obtained from 35 species [3]. Phenolic compounds (flavonoids, phenylethanoid glycosides) and terpene compounds (iridoid glycosides, diterpenes and triterpenoids) are the two main groups of constituents identified in *Scutellaria* species. Other *Scutellaria* phytochemicals include alkaloids, phytosterols, polysaccharides, iridoids, saponins, essential oil, resins, micro and macro elements [13, 27]. The phytochemistry and pharmacology of the genus *Scutellaria* have been developed intensely in the last decades. In the past ten years, 208 chemical constituents have been identified from 16 species and 1 variety of the genus *Scutellaria*, such as neo-clerodane diterpenoids, sesterterpenoids, terpenoids, and flavonoids [15]. Many studies are performed on the essential oils of different species of *Scutellaria* [14, 28-32].

Regarding to the species involved in this study, the presence of polyphenols, flavonoids, organic acids and carbohydrates in the aerial parts of *Scutellaria albida* plants were revealed. The flavonoids scutellarin, baicalin, baicalein, wogonin, wogonoside, luteolin, chrysin and a phenylethanoid glycoside-verbascoside have been identified in different extracts from *S. albida* [33]. Other bibliographic sources showed the presence of iridoids, phenolic derivatives and essential oil with the basic components linalool and (E)-nerolidol in the aerial part of *S. albida* [29, 34]. Iridoid glycosides and diterpenoids were also identified in the aerial part of *Scutellaria albida* ssp. *colchica* [35, 36].

Scutellaria alpina species is characterized by the presence of polyphenolic metabolites (baicalin, wogonoside, luteolin, luteolin 7-O-glucoside, verbascoside), compounds with numerous therapeutic properties [37, 38].

Scutellaria altissima species contain valuable compounds similar to those occurring in *S. baicalensis* [39]. Four neo-clerodan diterpenes, β -sitosterol and one glycoside-linked iridoid identified as globularin were isolated from the aerial parts of *S. altissima* [40, 41]. Bozov et al. [42] isolated and characterized nine neo-clerodane diterpenoids in the aerial parts of *S. altissima*, some of them being reported in this species for the first time. Recent studies [33, 41, 43] have demonstrated the presence of flavonoids (scutellarin, baicalin, baicalein, wogonin, wogonoside, luteolin, chrysin) and verbascoside in *S. altissima* extracts. A high concentration of flavone glycosides baicalin and wogonoside, as well as the phenylethanoid verbascoside were identified in callus cultures of *S. altissima* [40]. Further studies have also reported luteolin in *S. altissima* callus cultures in addition to the baicalin and wogonoside, which are characteristic for the species [44]. The study on comparative analysis of biologically active metabolites in extracts from *in vitro* and *in vivo* propagated *S. altissima* plants reported similar levels of flavones, baicalin and wogonoside in both extracts. Thus, the roots of *in vitro* propagated *S. altissima* plants can be considered as alternative sources of these compounds [45]. The plant also contains essential oil, iridoids, fatty acids, alkaloids [22].

Multiple scientific studies have shown that over 40 compounds have been isolated and identified from *Scutellaria baicalensis*, including flavonoids, terpenoids, volatile oils and polysaccharides [46-48]. Hattori S. [49] was first to isolate wogonin from *S. baicalensis* roots. There are over 50 flavones isolated from *S. baicalensis* [17, 50]. Baikal skullcap roots also contain coumarins, steroids, tannins, saponins, essential oil, resins, micro- and macro elements [27].

Scutellaria incana is also a potential source of bioactive compounds, especially flavonoids. The flavonic profile is reliable with other species of *Scutellaria*. Nurul et al. [51] reported the presence of 40 flavonoid compounds, including 2 phenolic glycosides in the extract of leaves, stems and roots. The first study on the composition of the essential oil in the aerial parts of *S. incana* reports a rich content of 1-octen-3-ol (a component of the volatile oil known for its antibacterial and antifungal effect), linalool, (E)-nerolidol and phytol [52].

Scutellaria orientalis contains a wide range of bioactive metabolites, including volatile oil, phenolic compounds, flavonoids [22, 53-55]. Baicalein, wogonin, baicalin, wogonoside, and chrysin are the main flavonoids of *S. orientalis* [56]. Gharari et al. [57] underlined the phenolic profiles and the presence of flavonic compounds characteristic for *Scutellaria* species, as well as phenylethanoid glycosides, such as actoside and verbascoside. A study by Zengin et al. [23] on total phenolic and flavonoid contents in aqueous extract of *S. orientalis* grown in Turkey revealed the presence of high amounts of flavones and several phenolic acid derivatives. The roots also contain tannins, ascorbic acid; flavonoids are present in the aerial part of *S. orientalis* species [22].

Health benefits and therapeutic effects

Numerous pharmacological studies demonstrated a wide range of biological activities of the extracts and compounds identified in *Scutellaria* genus [3, 14, 15, 58, 59]. Some *Scutellaria* species have also shown strong insect antifeedant bioactivity [3, 60, 61]. Recent literature reported the biological activities of *Scutellaria* essential oils, such as antioxidant, antimicrobial, antifeedant, phytotoxic, and acaricidal toxicities [32].

Scutellaria albida plant has antioxidant [33, 34] and antimicrobial effects [28]. The species is a sedative, nervine, tonic and antispasmodic. It is reported to support and sustain the nervous system, relieving stress and anxiety. Its antispasmodic properties are also considered useful in muscular tension. It has a specific use in the treatment of hysteria and epilepsy [62].

Scientific studies [44, 63, 64] indicate the antioxidant effect of *S. alpina* and *S. altissima* plants, suggesting their benefits in preventing diseases associated with oxidative stress, such as cancer, cardiovascular and inflammatory diseases. Baicalin, a flavonic glycoside detected in *S. alpina* has antiallergic properties [65]. Scutellarin, an active major flavone glycoside isolated from the *S. altissima* has been shown to offer beneficial effects on cerebrovascular diseases and inflammation. It exerts an antitumor effect and the result of scientific studies [18] suggest its potential use as a new and effective antitumor treatment for prostate cancer patients. Verbascoside, found in callus culture of *S. altissima* has shown anti-inflammatory, antibacterial, antioxidant and antitumor activity [66]. The methanolic extracts of roots of micropropagated plants showed also interesting antioxidant capacities comparable to the root extract of conventionally propagated plants [45]. Other recent studies [33] reported the antioxidant, antimicrobial and antifeedant activity of *S. altissima* extracts. Infusion and decoction are prescribed for hypertension, oedema, as an expectorant, antitussive and haemostatic [6, 22].

Referring to *Scutellaria baicalensis*, flavonoids are the basic chemical constituents that induce the antiviral, anti-inflammatory, hepatoprotective, hypotensive, vasodilator, antioxidant, antimicrobial, antihistaminic and sedative properties [6, 7, 67, 68]. The anticancer effect of *S. baicalensis* extracts has been also reported [59]. Due to the active principles (baicalin, baicalein and wogonin), the roots of the plant are a promising remedy in the treatment of blood cancer [69]. Flavones isolated from *S.baicalensis* roots were found inhibitory to HIV-1 by Li et al. [5].

Scutellaria orientalis possesses antimicrobial [70], astringent, wound healing, analgesic and carminative effects. Experimentally was demonstrated the antioxidant potential of *S. orientalis* extracts [23]. The root extract shows promising anticancer activity, indicating the presence of major anticancer agents on human colon cell lines [57]. Under experimental conditions, the liquid extract of the plant also has a stimulating effect on the cardiovascular system and hypotensive properties. Clinical and pharmacological studies recommend decoction, tincture and root extract for the treatment of hypertension. The fresh aerial part of the plant is used externally in the form of poultices for tumours [22]. The tincture from the aerial part shows sedative effect. Liquid alcohol extract has diuretic and choleric properties [6].

Scutellaria supina species is less studied in terms of content of biologically active substances and therapeutic uses and it is important to initiate biological and phytochemical studies in order to be able to use it as a medicinal plant or for ornamental purposes.

Cultivation

Actually, only some *Scutellaria* species are cultivated in China, United States and Central Europe [71]. No studies regarding cultivation and propagation aspects on *Scutellaria* species, except *S. baicalensis*, have been carried out in Republic Moldova. The current research started in 2015 and is ongoing. The experiments were done at the experimental field of the Collection of Medicinal Plants of the NBGI. The plants were propagated by seeds and in the vegetative way. The local pedo-climatic conditions fully satisfy the biological requirements of allochthonous *Scutellaria* species, being suitable for introduction into conditions of Republic of Moldova as medicinal plants. The optimal method of multiplication of *Scutellaria* species is vegetative (plant division), which allows to obtain mature plants faster, compared to those obtained from seeds. The research on *S. baicalensis* cultivated plants has shown, that in mature specimens, the adventive root system does not develop enough to make it possible for plants to propagate by vegetative means. Therefore, for *S. baicalensis* it is recommended the propagation by seeds as optimal method for multiplication. For easy cultivation, the plants require humid soils with good drainage. The plants do not succeed in very dry soils. The species will perform best in full sun to partial shade.

Scutellaria supina is a critically endangered species because of environmental pollution and destruction of their natural habitat. The species is included in the Red Book of The Republic of Moldova, 3rd ed. [72, p.76]. Thus, conservation by cultivation is an effective method for the protection of its genetic resources. Future studies on propagation, cultivation, and germplasm conservation of this species are required.

Conclusions

This review underlined the medicinal importance of eight *Scutellaria* L. taxa (*S. baicalensis* Georgi, *S. altissima* L., *S. albida* L., *S. albida* ssp. *colchica* (Rech. f.) Edm., *S. supina* L., *S. incana* Spreng., *S. orientalis* L. and *S. alpina* L.), summarizing the ethnobotanical information, data on bioactive compounds and biological activities. Because of having a wide range of pharmacological properties, investigated *Scutellaria* species are very important as medicinal plants. The available literature indicated the great therapeutic potential of these species, which point the way to conduct further multidisciplinary studies in order to establish and explore their scientific, medicinal and economic value. The complex studies and cultivation of *Scutellaria* species, which have not been so commonly used in our republic, will contribute to the enrichment of the range of medicinal plants with applications in the national economy.

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