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Article

Pharmaceutical and biological properties of *Stachys* species: A review

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The genus *Stachys* includes about 300 cosmopolitan species, making it one of the largest genera of the Lamiaceae family. The purpose of this paper is to present a review of *Stachys* species in the flora of Serbia among which some species are endemic to the Balkan Peninsula. This review comprises morphological, phytochemical, medicinal and food application of 17 taxa: *S. alopecuros*, *S. alpina*, *S. anisochila*, *S. annua*, *S. atherocalyx*, *S. cretica* subsp. *cassia*, *S. germanica*, *S. leucoglossa*, *S. milanii*, *S. officinalis*, *S. palustris*, *S. plumose*, *S. recta*, *S. tymphaea*, *S. scardica*, *S. serbica,* and *S. sylvatica*. The species of the genus *Stachys* are rich sources of biologically active substances and well known for their worldwide application. For most of the *Stachys* species, it has been shown that their extracts possess biological activities such as antibacterial, anti-inflammatory, antioxidant, and anticancer. The main goals of this review include the morphological description of species, representation of the major secondary metabolites, and presentation of traditional knowledge in food preparation.

Keywords: Essential oils. Medicinal application. Morphology. Secondary metabolites.

INTRODUCTION

Medicinal plants synthesize biologically active substances that have a positive effect on the human body. The usage of plants in traditional medicine has existed for thousands of years in many cultures around the world. Medicinal plants have been used primarily to prepare teas, powders, extracts, and other herbal remedies (Jafarirad, Rasoulpour, 2019).

The medicinal application of herbs in Europe has a long tradition, while in some parts of the world (such as India or China) herbal remedies are still a central element in the chain of health care (Evans, 2001). High quantities of plant raw materials are sold on the international market (Lange, Schippmann, 1997). Nowadays, aromatic plants from the Lamiaceae family represent very important potential sources of biological and pharmacological substances, whose action has been proven in numerous scientific studies. Since ancient times, these plants have been used for their antioxidant, antibacterial, antispasmodic, antifungal, and many other biological effects (Burt, 2004; Passos *et al*., 2019).

The Lamiaceae Martinov (Labiatae Adans.) family is one of the largest and most widespread flowering families. They are represented in tropical and temperate areas, especially in the Mediterranean, Central and Minor Asia (Raja, 2012). These are heliophytic and thermophilous plants growing on neutral to alkaline soils (Glimn-Lacy, Kaufman, 2006). They are aromatic due to the presence of essential oils that protect them from overheating (Raja, 2012). Within this family, there are more than 7,200 species and 240 genera of which the most numerous are the following: *Salvia* (900 species), *Scutellaria* (360 species), *Stachys* (300 species), *Plectranthus* (300 species), *Hyptis* (280 species), *Teucrium* (250 species), *Vitex* (250 species), *Thymus* (220 species) and *Nepeta* (200 species) (Kukić-Marković, 2013).

Genus *Stachys* L.

The genus *Stachys* L. includes about 300 cosmopolitan species, making it the largest genus of the

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Lamioideae subfamily and one of the largest genera of the Lamiaceae family (Salmaki *et al*., 2011). The genus includes perennial or annual herbaceous plants, with unbranched or branched stems. The shoots are without hairs or densely covered with woolly or silky hairs. The leaves are mainly sessile and generally serrated. The flowers are also sessile or with a very short stalk, mostly assembled into dense apparent axils in the leaves gap of tree leaves. The calyx is tubular or bell-shaped, with 5 or 10 nerves, mostly properly serrated, with five teeth. The corolla is ambiguous, red, pale yellow or white. The corolla is straight or slightly bent, at the apex slightly extended, long as the calyx longer than the corolla. The upper lip is two-lobed, slightly convex or straight, covered with hairs. The lower lip is extended and triangular. Flowers have four anthers. The front anthers are separated or parallel, mostly longer than the inner ones. Fruits could be ovate in shape or oblong, triangular, rounded in front. Plants belonging to the genus *Stachys* are widespread in the arid climates of the Mediterranean and southwest Asia, in South and North America and North Africa (Diklić, 1974).

Many species of the genus *Stachys* are used in the treatment of rheumatic, stomach, asthma, and skin disorders as infusions or decoctions. For some species, it has been shown that their extracts possess biological activities such as anti-inflammatory, antibacterial, antioxidant, and antinephritic (Gören, 2014).

According to the Flora of Serbia, 17 species of the examined genus grow in the territory of Serbia: *S. alopecuros* (L.) Benth., *S. alpine* L., *S. anisochila* Vis. & Pancic, *S. annua* (L.) L., *S. atherocalyx* K. Koch, *S. cretica* subsp. *cassia* (Boiss.) Rech. f., *S. germanica* L., *S. leucoglossa* Griseb., *S. milanii* Petrov ex Magnier, *S. officinalis* (L.) Trevis., *S. palustris* L., *S. plumose* Griseb., *S. recta* L., *S. tymphaea* Hausskn., *S. scardica* (Griseb.) Hayek, *S. serbica* Pancic, and *S. sylvatica* L. (Diklić, 1974).

In this review, the morphological characteristics, the qualitative composition of the essential oils and secondary metabolites (Table I), as well as the usage for medical purposes of 17 species of genus *Stachys* in Serbian flora will be presented.

DISCUSSION

Morphological characteristics of the species from the genus *Stachys* represented in the flora of Serbia.

***Stachys alopecurus* (L.) Benth.**

A perennial plant with erected stems, unbranched, covered with long hairs. The leaves are periphery serrated, densely covered with long hairs. The bracts are small and egg-shaped. The flowers are arranged in the apparent axil. At the top of the stem, flowers build a densely compacted, elongated ovoid. The calyx is densely covered with hairs. The corolla is a pale yellow, thinly covered with hairs at the outside. The corolla tube is long as a calyx, and in the inner part it possesses a ring of hairs. It grows on rocky pastures and meadows in the subalpine and alpine zones (Diklić, 1974).

Stachys alpina L.

A perennial herb with a strong developed rhizome. The stem is upright, unbranched or branched. The leaves are with a leaf stalk, covered with hairs. The bracts are egg-shaped. The flowers are long, arranged in 6-18 apparent axils. The calyx is tubular, covered with long hairs and densely glandular hairs. The crown is reddish, externally covered with long woolly hairs. The crown tube is funnel-shaped, long as the calyx, and in the inner part it possesses a ring of hairs. The fruits are ovoid, gray brown (Diklić, 1974).

Stachys anisochila Vis. et Pančić

A perennial herbaceous plant, with branched, stems from the base. The leaves are ovoid, large, serrated at the edge. The bracts are elongate, narrow, and long as the flowers. Six flowers are arranged in apparent clusters, which are grouped at the top of the stem. The calyx is with two lobes, covered with thin hairs. The corolla is pale yellow, with reddish spots, and the ring of hairs inside the crown tube. It grows on limestone habitats. This species is endemic to the Balkan Peninsula (Diklić, 1974).

Stachys annua (L.) L.

An annual plant, with branched or unbranched erected stems. At the lower and upper part covered with thin hairs, often glands. The leaves are spherical or lanceolate. The upper bracts are sessile, lanceolate, long as flowers or even smaller. The flowers are with short flower petals, often densely covered with hairs. The calyx is tubular and bell-shaped, mostly covered by short hairs and glands. The corolla is a whitish yellow, covered with hairs at the outside. The corolla tube is straight, longer than the calyx. The fruits are ovoid, black, with blunt angles. It grows in monoculture fields, on railways, especially on limestone parent material, up to 1 500 m above sea level (Diklić, 1974).

Stachys atherocalyx K. Koch

A perennial plant, the rhizome is woody, branched, thick, and with developed stolons. The stem is erect, slightly branched or unbranched, covered with hairs. The leaves are linear or elongated, lanceolate, both on the abaxial and adaxial side densely covered with gray hairs. The flowers are with a short petal, all grouped in an apparent cluster. The calyx is bell-shaped, covered with long gray hairs. The corolla is white-yellowish or whitish, covered with hairs. The corolla tube is the same length as the calyx. The fruits are brown, triangular, punctate. It grows in meadows and shrubs (Diklić, 1974).

Stachys cretica subsp. *cassia* (Boiss.) Rech. f. (syn. *Stachys cassia* (Boiss.) Boiss.))

A perennial plant, mostly unbranched, densely covered with woolly hairs, primarily in the upper part and without glandular hairs. The leaves are elongated, rarely narrowed into a handle, covered with thin woolly hairs. The bracts are sessile. The flowers are clustered in dense apparent axils. The calyx is covered with long woolly hairs. The corolla is pink. The upper lip is covered with woolly hairs. It grows on rocky fields and dry meadows. It is widespread in the Balkan Peninsula (Diklić, 1974). The synonym for the name of this species is *Stachys cretica* subsp. *cassia* (Boiss.).

Stachys germanica L.

A perennial plant, with branched or unbranched erect stems. The leaves are mostly elongate ovate or lanceolate. The leaves are serrated along the edge. Flowers are sessile, arranged in 5-10 dense apparent axils, grouped at the tips of the stem and branches into dense apparent clusters. The calyx is tubular, densely covered with silky hairs. The corolla is light red and densely covered with long silky hairs at the outside. The corolla tube is long as a calyx and in the inner part possesses a single ring of hairs. The fruits are triangular, smooth, and black. It grows on rocky habitats, along roads, in forests and shrubs (Diklić, 1974).

Stachys leucoglossa Griseb.

A perennial plant, with a heavily branched stem covered with short hairs. The leaves are narrow, lanceolate, covered with short hairs, and serrated along the edge. The bracts are egg-shaped or lancet-shaped. Each of 6 flowers is arranged in an apparent cluster, grouped one above the other at the top of the stem. The calyx is partially covered with hairs. The corolla is pale pink or white, with one ring of hairs inside the same. It grows on rocky habitats (Diklić, 1974).

Stachys milanii Petrov ex Magnier

An annual plant, with branched or partially branched stems, densely covered with glandular and long hairs. The leaves are densely covered with glandular hairs, with barely serrated edges. The bracts are almost as long as flowers, ending with a spike at the top. At the top of the stems, 4-6 flowers are arranged in apparent axils and build up an apparent cluster. The calyx is bell-shaped, externally densely covered with glandular hairs. The corolla is a matte yellow, covered with glandular hairs along the back and upper lip. It grows in crop fields and meadows. It is endemic to the eastern part of the Balkan Peninsula (Diklić, 1974).

Stachys officinalis (L.) Trevis

A perennial plant, the stem is erect, branched or unbranched, covered with hairs. Most leaves are grouped in the rosette, except for 2-3 pairs located on the stems. The bracts are ovoid, barely longer than the calyx. About 10 flowers are clustered in apparent axils. The calyx is tubular and bell-shaped, covered with hairs at the top. The corolla is red in the upper part, rarely white. The corolla tube is longer than the calyx, white, covered with thin hairs on the upper side. The fruits are ovoid, smooth, and brown. It especially grows on mountain ranges and in moderately dry to moist meadows (Diklić, 1974).

Stachys palustris L.

A perennial plant, with branched or unbranched stems. The leaves are sessile, elongated, lanceolate, covered with short hairs. Each of 6-12 flowers is arranged in 5-20 apparent axils, grouped one above the other at the top of the stem and branches, forming a dense apparent cluster. The calyx is tubularly bell-shaped, almost naked or covered with hairs and glands. The corolla is reddish or purple. The corolla tube is straight, long as a calyx. The fruits are with cracks, dark-brown, glossy. It grows near the river meadows and inhabits wet fields (Diklić, 1974).

Stachys plumosa Griseb.

A perennial herbaceous plant, the stem is erect, branched or unbranched, covered with short glandular and woolly hairs. The leaves are lanceolate, covered with short glandular hairs and long hairs. Each of the 6-12 flowers is arranged in dense apparent axils. The flowers are grouped one above the other at the top of the stem and branches into clusters. The calyx is covered with short glandular hairs. The flowers are yellow or reddish. It grows on arid habitats, on limestone and siliceous substrates (Diklić, 1974).

Stachys recta L.

A perennial plant, with numerous branched or unbranched erected stems. The leaves are ovoid, elliptical to lanceolate, thinly covered with short hairs. The bracts are seated. Flowers (6-15) are arranged in 6-12 apparent axils. The calyx is tubular, bell-shaped, covered with short hairs and glands. Corolla is yellowish white to pale yellow, naked or covered with short hairs. The corolla tube is longer than the calyx or equal. The fruits are ovoid and smooth. It grows in shrubs, in pine and oak forests, on arid rocky slopes, meadows, and pastures (Diklić, 1974).

Stachys tymphaea Hausskn. (syn. *Stachys reinertii* Heldr.)

A perennial plant, with unbranched stems, covered with long hairs but without glands. The leaves are elongated or ovoid, covered with short gray hairs. The flowers are arranged at the apex of the stem into thick apparent axils. The calyx is covered with long hairs. The corolla is red, with a hairy ring inside the tube. It grows in pastures, meadows, and rocky habitats in the subalpine and alpine regions (Diklić, 1974).

Stachys scardica (Griseb.) Hayek

A perennial plant, with unbranched erect stems, densely covered with long hairs. All leaves are elongate, lanceolate, serrated at the edge, covered with hairs on the abaxial and adaxial side. The flowers are clustered in a dense apparent axil, grouped at the top of the stem into an elongated apparent cluster. The calyx is tubular, covered with hairs. The corolla is white, with reddish parts, covered with short hairs at the outside. The corolla tube is barely longer than the calyx. It grows in shrubs and coniferous forests in the subalpine and alpine regions, pastures, and dry meadows. It is endemic to the Balkan Peninsula (Diklić, 1974).

Stachys serbica Pancic

An annual plant, branched or unbranched, covered with hairs. The leaves are elongated or ovoid, serrated along the edge and covered with hairs. The bracts are sessile, large, lanceolate, longer than the flowers. Each of the 3-6 flowers is arranged in the apparent axil, compacted at each other, at the apex of the stems. The calyx is covered with hairs. The corolla is red, covered with hairs, barely

longer than the calyx. It is endemic species to the Balkan Peninsula and inhabits meadows (Diklić, 1974).

Stachys sylvatica L.

A perennial plant with erected branched or unbranched stems. The leaves are with a leaf stalk. They are egg-shaped, with serrated edges, thinly covered with hairs on the abaxial and adaxial side. The bracts are elongated, lanceolate, covered with glandular hairs. The flowers are with short flower petals, 2-6 in 8-15 apparent axil. The calyx is bell-shaped, covered with glandular hairs. Corolla is dark red, almost naked. The corolla tube is straight, on the basis extended with a ring of hairs inside. Fruits are spherical, smooth, and purple brown. It grows in coniferous, deciduous and mixed deciduous forests, in meadows in the subalpine zone (Diklić, 1974).

Secondary metabolites of the *genus Stachys*

A large number of compounds have been isolated from medicinal plants. The pharmacologically active compounds of plants are included in the group of secondary metabolites (Kovačević, 2002; Almeida *et al*., 2019). The yield, composition, and intensity of secondary metabolites accumulation in plants depend on a number of factors, such as habitat conditions (geographical location, water regime, light intensity, nutrients), genotype, phenological phase, and the selection of isolation procedures (Agostini *et al*., 2009; Mulinacci *et al*., 2011; Stagos *et al*., 2012; Kontogianni *et al*., 2013; Verma, Padalia, Chauhan, 2015).

Stachys species have been extensively studied over the last 20 years. The great structural diversity of secondary metabolites of this genus was caused by the great morphological diversity, various ecological factors, hybridization, and polyploidy. Flavonoids, iridoids, phenolecarboxylic acids, phenylethane heteroids, and terpenoids have been most commonly studied (Buchwald, Czapska, 1995; Bankova *et al*., 1999; Meremeti *et al*., 2004; Piozzi, Bruno, 2011, Kukić-Marković, 2013).

Flavonoid aglycones (Table I) are found on the surface of leaves and other aboveground organs, either in the form of exudates, or dissolved in a lipophilic matrix. The aglycones isolated from species of the genus *Stachys* are mainly flavonic (Kukić-Marković, 2013).

Flavonoid heterozoids (Table I) are the most abundant type of flavonoids in species of the genus *Stachys*. They are heteroids of apigenin, luteolin, and chrysoeryl. The most abundant monosaccharides are glucose, aldose, mannose and glucuronic acid. An essential characteristic of species of this genus is the presence of allozylglucoside 8-hydroxyflavones, occurring in the form of monoacetylated, diacetylated and nonacetylated heteroids (Kukić-Marković, 2013).

The production of phenylethane heteroids is characteristic for species of the genus *Stachys*, from which a large number of compounds of this class have been isolated. Some of these species are widespread in the plant kingdom (martinoside, forsitoside B, acteoside), whereas some have been identified only in species of this genus (Kukić-Marković, 2013).

A number of iridoids and their heteroids have been identified in species of the genus *Stachys* (Table I). These compounds are thought to have phytoalexin function in plants. In some species of this genus, iridoid heterozoids with specific structures have been identified, such as acetylmyoporosis and alobetonicoside, which are present in the species *S. officinalis* and *S. glutinosa* (Kukić-Marković, 2013).

Diterpenes are isolated from underground organs, rarely from aboveground parts of the *Stachys* genus. The most common diterpenes are of the neo-clerodane type, labdane type, as well as derivatives of ent-kaurene. So far, about 30 diterpenes have been isolated from species of this genus (Kukić-Marković, 2013).

Phenolecarboxylic acids represent derivatives of hydroxybenzoic acid and hydroxycitric acid. They could be free or in the form of esters, amides or heteroids. Phenolecarboxylic acids exhibit different pharmacological effects. Caffeic acid and its conjugates are considered to be chemotaxonomically significant markers of the Lamiaceae family. Caffeic acid is present in many species of the genus *Stachys* (Table I). Rosemarinic acid has been identified in several species of the genus *Stachys*, but at a very low concentration (Kukić-Marković, 2013).

The alkaloids are represented in minimal quantities in the species from genus *Stachys*, e.g., in species: *S. sylvatica*, *S. atherocalyx* (0.03-0.74%). These are mainly compounds of the pyrrolidine structure, and the stachydrine is the most common (Kukić-Marković, 2013).

TABLE I - Secondary metabolites of *Stachys* species

Species	Secondary metabolites	Compound	References
S. alopecuros	Flavonoid heterozoids	Isoscutellarein 7-*O*-*β*-D-glucopyranoside	Marin *et al*., 2004.
	Flavonoids	Apigenin 7-*O*-(6 ‘’-*p*-coumaroyl)-*β*-D-glucopyranoside	
S. alpine	Phenol carboxylic acids	Caffeic acid; Chlorogenic acid; Rosmarinic acid; Protocatechuic acid; Sinapic acid	Buchwald, Czapska, 1995; Bilušić Vundać *et al*., 2005; Buchwald, Czapska, 1995.
S. anisochila	Flavonoid heterozoids	Isoscutellarein 7-*O*-[6 ‘’ ‘- acetyl-*β*-D-allopyranosyl (1-2)]-*β*-D-glucopyranoside; 4’-*O*-Methylisoskutelarein 7-*O*-[6 ‘’ ‘- acetyl-*β*-D-allopyranosyl (1-2)]-*β*-D-glucopyranoside; 4’-*O*-Methyl hypo ethanol 7-*O*-[6 ‘’ ‘- acetyl-*β*-D-allopyranosyl; (1-2)]-*β*-D-glucopyranoside; Hypolaetin 7-*O*-[6 ‘’ ‘- acetyl-*β*-D-allopyranosyl (1-2)]-*β*-D-glucopyranoside	Marin *et al*., 2004; Lenherr, Meier, Sticher, 1984a; Lenherr, Mabry, 1987.
	Flavonoids	Apigenin 7-*O*-(6 ‘’-*p*-coumaroyl)-*β*-D-glucopyranoside	Marin *et al*., 2004.
S. annua	Flavonoid aglycones	Baicalin; 4′-*O*-methyl skutelarine	Sheremet, Komissarenko, 1971.
	Flavonoid heterozoids	Scutellarein 7-*O*-*[β*-D-man pyranosyl-(1-2)]-*β*-D-glucopyranoside (stachyflazide); 4’-*O*-Methylisoskutelarein 7-*O*-[6 ‘’ ‘- acetyl-*β*-D-allopyranosyl (1-2)]-*β*-D-glucopyranoside; 4’-O-Methyl hypo ethanol 7-*O*-[6 ‘’ ‘- acetyl-*β*-D-allopyranosyl (1-2)]-*β*-D-glucopyranoside	Lenherr, Meier, Sticher, 1984a; Sheremet, Komissarenko, 1971.
	Phenol carboxylic acids	Caffeic acid; Chlorogenic acid; Rosmarinic acid; Protocatechuic acid; Sinapic acid	Buchwald, Czapska, 1995; Czigle *et al*., 2007; Buchwald, Czapska, 1995.
	Diterpenes	Clerodane	Orgiyan, Popa, 1969.
S. atherocalyh	Flavonoid heterozoids	Isoscutellarein 7-*O*-[6 ‘’ ‘- acetyl-*β*-D-allopyranosyl (1-2)]-*β*-D-glucopyranoside; Scutellarein 7-*O*-*[β*-D-mannopyranosyl-(1-2)]-*β*-D-glucopyranoside (stachyflazide)); 4’-*O*-Methylisoskutelarein 7-*O*-[6 ‘’ ‘- acetyl-*β*-D-allopyranosyl (1-2)]-*β*-D-glucopyranoside; 4’-*O*-Methyl hypo ethanol 7-*O*-[6 ‘’ ‘- acetyl-*β*-D-allopyranosyl (1-2)]-*β*-D-glucopyranoside	Lenherr, Meier, Sticher, 1984a; Komissarenko *et al*., 1976; Kostyuchenko *et al*., 1982; Lenherr, Meier, Sticher, 1984a;
	Phenol carboxylic acids	Caffeic acid; Chlorogenic acid; *p*-Coumaric acid	Kostyuchenko, 1982.
	Diterpenes	Clerodane	Piozzi, Bruno, 2011.

TABLE I - Secondary metabolites of *Stachys* species

Species	Secondary metabolites	Compound	References
S. germanica	Flavonoid heterozoids	4'-*O*-Methylisoskutelarein 7-*O*-[6 '' '- acetyl-*β*-D-allopyranosyl (1-2)]-*β*-D-glucopyranoside	Bankova *et al*., 1999.
	Flavonoids	Apigenin 7-*O*-(6 ''-*p*-coumaroyl)-*β*-D-glucopyranoside	Marin *et al*., 2004.
	Phenylethane heteroids	Acteoside; Martinoside	Bankova *et al*., 1999.
	Phenol carboxylic acids	Caffeic acid; Chlorogenic acid; Rosmarinic acid; Protocatechuic acid; Sinapic acid	Buchwald, Czapska, 1995.
S. leucoglossa	Flavonoid heterozoids	Isoscutellarein 7-*O*-[6 '' '- acetyl-*β*-D-allopyranosyl (1-2)]-*β*-D-glucopyranoside; 4'-O-Methylisoskutelarein 7-*O*-[6 '' '- acetyl-*β*-D-allopyranosyl (1-2)] - β-D-glucopyranoside; 4'-*O*-Methyl hypo ethanol 7-*O*-[6 '' '- acetyl-*β*-D-allopyranosyl (1-2)]-*β*-D-glucopyranoside	Lenherr, Meier, Sticher,1984a;
S. officinalis	Flavonoid aglycones	Apigenin; 7-*O*-Methyltricin	El-Ansari *et al*., 1991. Kobzar, Nikonov, 1986.
	Flavonoids	Apigenin 7-*O*-(6 ''-*p*-coumaroyl)-*β*-D-glucopyranoside	Marin *et al*., 2004.
	Phenylethane heteroids	Acteoside; Martinoside; Betonioside F; Forsythoside B; Leucosceptoside B	Miyase, Yamamoto, Ueno, 1996a; Bankova *et al*., 1999.
	Phenol carboxylic acids	Caffeic acid; Chlorogenic acid; Isochlorogenic acid; Rosmarinic acid; *p*-Coumaric acid; Protocatechuic acid; Sinapic acid	Kobzar, 1986; Buchwald, Czapska, 1995; Bilušić Vundać *et al*., 2005; Czigle *et al*., 2007.
	Iridoidi	6-*O*-acetylmioporoside; Alobetonicoside	Jeker *et al*., 1989.
	Diterpenes	Clerodan	Bankova *et al*., 1999.
S. palustris	Flavonoids	Apigenin 7-*O*-(6 ''-*p*-coumaroyl)-*β*-D-glucopyranoside	Marin *et al*., 2004.
	Phenol carboxylic acids	Caffeic acid; Chlorogenic acid; Rosmarinic acid; Protocatechuic acid; Sinapic acid	Buchwald, Czapska, 1995; Czigle *et al*., 2007.
	Diterpenes	Clerodan	Piozzi, Bruno, 2011.
S. pulmosa	Flavonoid heterozoids	Isoscutellarein 7-*O*-[6 '' '- acetyl-*β*-D-allopyranosyl (1-2)]-*β*-D-glucopyranoside; 4'-*O*-Methylisoskutelarein 7-*O*-[6 '' '- acetyl-*β*-D-allopyranosyl (1-2)]-*β*-D-glucopyranoside	Marin *et al*., 2004; Bankova *et al*., 1999.
	Flavonoids	Apigenin 7-*O*-(6 ''-*p*-coumaroyl)-*β*-D-glucopyranoside	Marin *et al*., 2004.
	Phenylethane heteroids	Acteoside; Martinoside; Forsythoside B	Bankova *et al*., 1999.
	Diterpenes	Labdane	Paternostro *et al*., 2000.

TABLE I - Secondary metabolites of *Stachys* species

Species	Secondary metabolites	Compound	References
S. recta	Flavonoid heterozoids	Isoscutellarein 7-*O*-[6 ‘’ ‘- acetyl-*β*-D-allopyranosyl (1-2)]-*β*-D-glucopyranoside; 4’-O-Methylisoskutelarein 7-O- [6 ‘’ ‘- acetyl-β-D-allopyranosyl (1-2)]-β-D-glucopyranoside; 4’-O-Methyl hypo ethanol 7-O-[6 ‘’ ‘- acetyl-β-D-allopyranosyl (1-2)]-β-D-glucopyranoside	Marin *et al*., 2004; Lenherr, Meier, Sticher, 1984a; Lenherr, Lahloub, Stcher, 1984b.
	Flavonoids	Apigenin 7-*O*-(6 ‘’-*p*-coumaroyl)-*β*-D-glucopyranoside; Apigenin 7-*O*-(3 ‘’-*p*-coumaroyl)-*β*-D-glucopyranoside	Karioti *et al*., 2010.
	Phenol carboxylic acids	Caffeic acid; Chlorogenic acid; Rosmarinic acid; *p*-Coumaric acid; Protocatechuic acid; Sinapic acid	Buchwald, Czapska, 1995; Czigle *et al*., 2007.
	Diterpenes	Clerodan	Adinolfi *et al*., 1984.
S. sylvatica	Flavonoid heterozoids	4’-*O*-Methylisoskutelarein 7-*O*-[6 ‘’ ‘- acetyl-*β*-D-allopyranosyl (1-2)] - *β*-D-glucopyranoside	Bankova *et al*., 1999.
	Flavonoids	Apigenin 7-*O*-(6 ‘’-*p*-coumaroyl)-*β*-D-glucopyranoside	Marin *et al*., 2004.
	Phenylethane heteroids	Acteoside; Martinoside; Forsythoside B	Bankova *et al*., 1999.
	Phenol carboxylic acids	Caffeic acid; Chlorogenic acid; Rosmarinic acid; *p*-Coumaric acid; Protocatechuic acid; Sinapic acid	Buchwald, Czapska, 1995; Bilušić Vundać *et al*., 2005; Czigle *et al*., 2007.
	Diterpenes	Kauran; Clerodan	Popa, Pasechnik, 1974; Piozzi, Bruno, 2011.

Essential oils

Species of this genus are poor in yield of essential oils (0.01-0.5%) (Gören *et al*., 2011) being the characteristic of other genera of the Lamioideae subfamily as well. The largest number of essential oils of the *Stachys* genus is rich in sesquiterpenes. Hydrocarbons have the main function, while oxidized sesquiterpenes are the dominant components of essential oils. The most common sesquiterpenes are (*E*)-caryophyllene, germacrene D, and caryophyllene-oxide (Gören *et al*., 2011).

Aliphatic and aromatic compounds constitute a significant percentage in the essential oils of some species of the genus *Stachys* (Çakir *et al*., 1997). In the essential oils of more than 30 species of this genus, about 45 diterpenes have been identified, mainly derivatives of labdane, kaurene, primarane, and abietane (Piozzi, Bruno, 2011). Diterpene compounds are most commonly represented in low quantities in these essential oils. A small number of essential oils of the *Stachys* genus are dominated by monoterpenes, and the most abundant are *α*- and *β*-pinene, linalool, and linalyl acetate (Gören *et al*., 2011).

The selected species of the genus *Stachys* have so far only been partially chemically and pharmacologically examined. The presence of labdane diterpenes was found in the herb of *S. pulmosa* (Paternostro *et al*., 2000), as well as 7-*O*-*β*-coumarylglucosides (Marin *et al*., 2004). The antimicrobial activity of *S. pulmosa* essential oil samples was observed (Ristić *et al*., 2008).

Chemical analyses performed on *S. atherocalyx* are were characterized by spathulenol as a major component of the species. Therefore, 18 monoterpenes (*α*-pinene, linalyl, linalyl acetate), 13 sesquiterpenes, and aromatic

hydrocarbons were perceived as components (Rezazadeh *et al*., 2009).

Sesquiterpene hydrocarbons and (*E*)-caryophyllene were noticed to be the most abundant in the analysis of the essential oil of *S. alopecuros*. Germacrene D, *α*-humulene and oxidized *cis*-sesquisabinene hydrates were also observed (Venditti *et al*., 2013). Significant cytotoxic activity was demonstrated by *S. alopecuros* essential oil, which exerts a potent inhibitory effect on human cancer cells (Conforti *et al*., 2009). The antioxidant effect of the essential oils of this species was also proven (Calleja, 2012).

In the chemical composition of *S. annua* species, monoterpenes, aldehydes, and sesquiterpene hydrocarbons were shown to be the most abundant. The *α*-pinene, *β*-pinene, (*E*)-*β*-ocimen, *γ*-murolen, *α*-cedar, and limonene were also recorded (Venditti *et al*., 2015).

For the first time, diterpene lactone betolide was isolated from the root of *S. officinalis* (Tkachev *et al*., 1987); the diterpene lactone was not identified in other species of the genus *Stachys*. In *S. officinalis*, *γ*-murolene, *β*-caryophyllene, benzaldehyde, phytols, allo-aromadendrenes, *δ*-cadinol and *β*-bourbonen were identified in the leaf, and *γ*-murolene, benzaldehyde, phytol and germacrene in the flower (Dimitrova-Dyulger *et al*., 2015).

In the leaf samples of species *S. sylvatica*, different compounds were identified: *γ*-murolene, phytols, *β*-caryophyllene, benzaldehyde, heptadecane, *t*-cadinol, germacrene, *α*-farnesene. The presence of *γ*-murolene, benzaldehyde, phytol, and germacrene was identified in the flowers (Dimitrova-Dyulgerova *et al*., 2015).

The essential oil of the species *S. palustris* is mainly composed of carbonyl compounds, fatty acids, and their esters, sesquiterpenoid compounds, and phenols. Unlike other species of this genus, *S. palustris* essential oil showed significant presence of carbonyl compounds and fatty acids, whereas ketones predominate over aldehydes. The major components of the oil are caryophyllene oxide, hexahydrofarnasyl acetone, hexadecanoic acid, (*Z, Z, Z*)-9,12,15-octadecatrienoic acid, (*Z*)-phytol, thymol, *p*-methoxyacetophenone, 4-vinylguaiacol, tetradecanoic acid, (*E*)-caryophyllene, *β*-ionone and *β*-damascenone (Senatore *et al*., 2007).

Testing of the essential oil content was the prior aim of the chemical analyses performed on *S. germanica*. The analyzes of the essential oil revealed unique terpenoid structures. The most common are borneol, bicyclogermacrene (Grujić-Jovanović *et al*., 2008), (*E*)-*β*-farnesene, germakren D (Grujić-Jovanović *et al*., 2004) caryophyllene oxide, (*E*)-nerolidol, *β*-caryophyllene (Radulović *et al*., 2007). Several scientific studies have shown that essential oil of this species exhibits antioxidant and antimicrobial activity (Skaltsa *et al*., 2003; Conforti *et al*., 2009; Lazarević *et al*., 2010).

Chalchat *et al*., (2000) found that monoterpenes and sesquiterpene hydrocarbons were poorly represented in *S. recta* essential oil. The 40% of the identified components were alcohols, ketones, oxides, and esters. 1-octen-3-ol was the main constituent of the tested oil, while other important components were caryophyllene oxide, humulene oxide, and nerolidol.

Biological activities of secondary metabolites

Plant extracts of *S. alpina* (subsp. *alpina*) have been investigated for antioxidant activity and have been found to inhibit lipid peroxidation in homogenates of the bovine brain. For the aqueous extract of the plant *S. alpina* (subsp. *alpina*), anti-inflammatory activity was investigated on a model of carrageenan-induced rat paw edema. After intraperitoneal administration (5 mg/kg), the extract suppressed edema by about 80% (Háznagy-Radnai *et al*., 2006).

Anti-inflammatory, antitoxic, and hypoazotemic activity in rats is manifested by the flavonoid fraction isolated from *S. recta* (Háznagy-Radnai *et al*. 2012). Háznagy-Radnai *et al*. (2012) found that aqueous extracts of aboveground parts of *S. recta, S. germanica*, *S. officinalis* and *S. alpina* exhibit better anti-inflammatory effect on carrageenan-induced edema rat paws compared to the same dose of diclofenac sodium. Methanolic extracts of aboveground parts of *S. recta*, *S. annua*, *S. officinalis*, *S. sylvatica* were found to inhibit lipid peroxidation in bovine brain homogenizers (Háznagy-Radnai *et al*., 2006). The methanolic extracts of *S. recta* subsp. *recta* and *S. palustris* showed a significant

antioxidant activity substantially neutralizing the DPPH radicals (Bilušić Vundać, Brantner, Plazibat, 2007).

The usage and application of *Stachys* species in food and folk medicine

The species of the genus *Stachys* are used in folk medicine. In different cultures, cosmopolitan species such as *S. officinalis, S. recta,* and *S. palustris* are used in a similar way; however, some species are applied in a different way in regions where they are specific (eg. *S. lavanduli folia* in Iran and Turkey). Therefore, species with pleasant smell are used in the preparation of jelly and yogurt as flavorings (Venditti *et al*., 2013).

Stachys officinalis (L) Trevis (synonym: *Betonica officinalis*) is the most frequently used species of this genus. The healing ability of this plant has been known since ancient times and it has been used to treat as many as 47 diseases. In the Middle Ages, many magical and healing powers were assigned to this species (Gören, 2014). It was used as a protection against evil spirits and spells. It was also known as a medicinal plant, mainly in monasteries (Grieve, 1971). *Stachys officinalis* was considered as an inviolable cure for all mental disorders. According to ''*Britannica Medicine*'' (1666), the decoct is considered useful in hysteria, headache (caused by high blood pressure), in neuralgia and in all neurotic conditions associated with tension and anxiety. It is also used as an aromatic and an astringent, as a tonic for dyspepsia in combination with other herbs, for cleaning the blood and as an alternative therapy for rheumatism. The dried aerial part of the plant is used for the treatment of headache together in combination with the herb of the *Tussilago farfara* L., Asteraceae and the *Euphrasia officinalis* L., Scrophulariaceae (Grieve, 1971). Čajkanović (1994) described the species as a popular balm for wounds and snake bite, a cure for pulmonary disease, fever, and headaches. Due to the high content of tannins, the aerial parts of the plant are used as an astringent and antidiarrheal (Hoppe, 1958). In large doses, it acts as purgative. Dried and milled leaves are used in the cold treatment. In homeopathy, it is used for weakness and asthma. The tincture of fresh leaves is used for the treatment of diarrhea. The decoction is applied to varicose veins and externally for the treatment of infected wounds (Hoppe, 1958; Schauenberg, Paris, 1969). It is part of the Swiss Tea (*Species vulnerariae*) which is used to treat wounds, bruises, cuts, burns (Tucakov, 1971). In Bosnia and Herzegovina, the tea of the species *S. officinalis* is used for 'blood purification' (Šarić-Kundalić *et al*., 2010). In Kosovo, in the Golak area, fresh leaves are applied externally for skin infection, fresh herb juice is used for ear pain, and the infusion is applied externally for the treatment of wounds. It is used internally for menstrual pain and reduction of bleeding (Mustafa *et al*., 2011). *S. officinalis* could be used in the treatment of ulcers and lichen in domestic animals (Willfort, 1978). In Italy (Tuscany), fresh chewed leaves of this plant (known as concretion) are applied to wounds in horses, cattle, dogs, and cats, even if they are fertilized and infected (Manganelli, Camangi, Tomei, 2001). The flowers and leaves of *S. officinalis* are suitable for the preparation of meat dishes, due to their pleasant aroma and taste (Grieve, 1971).

Stachys recta are used in folk medicine for the treatment of nasopharyngeal catarrh, fever, burns, wounds and are also used as the astringents. The dried aboveground part of the plant (known as *Herba sideritis*) is used in folk medicine against hysteria and epilepsy (Thoms, 1931; Garnier, Bezanger-Beaquesne, Debraux, 1961). In Italy (Liguria), the aerial parts are used as a coat for painful places on the skin. Decoct has an application in magic rituals, and it is also used for toothache and nervousness (Cornara *et al*., 2009). *S. recta* are also reported to be poisonous (Gören, 2014).

Stachys palustris is used as spasmolytic and antiseptic remedy. It is also used to treat fever, wounds, abdominal pain and menstrual problems (Grieve, 1971; Gruenwald, Brendler, Jaenicke, 2004). The crushed leaves of a fresh plant are used to quickly prevent bleeding. The plant is effective against the treatment of cramps, gout, and pains in the joints (Senatore *et al*., 2007). It is used internally for dysentery (Grieve, 1971). In North America, it has been used by members of the Delaware tribe to treat venereal diseases (Luczaj, Svanberg, Köhler, 2011). The species *S. palustris* is known in Italy as the *erba strega o scabbiosa* (witch or scabbard grass). Although the whole herb possesses

unpleasant smell, root, leaf and seeds can be used in the diet (Senatore *et al.*, 2007). The root of this plant is tubular, it can be eaten boiled, baked or raw. In Poland, Sweden, Ukraine and Great Britain, the tubers of *Stachys palustris* are used as food – for the preparation of salads, soups and vodka additives (Gören, 2014). After milling aerial parts, the powder could be used as flour for bread preparation (Luczaj, Svanberg, Köhler, 2011). Young shoots can be used and prepared as asparagus (Grieve, 1971; Senatore *et al.*, 2007; Luczaj, Svanberg, Köhler, 2011). The cooked part of the plant possesses a sweet taste because of the presence of digestible carbohydrates which could be consumed against diabetes (Gören, 2014). Aboveground parts of *S. palustris* have been used in Scotland to produce blue and yellow textile colors (Luczaj, Svanberg, Köhler, 2011).

In Iran, the leaves of the species *Stachys germanica* are prepared in the form of infusions for gastric pain and painful menstruation (Gören, 2014). In Italy, it is used to treat warts in domestic animals (Viegi *et al*., 2003). The aboveground part of *S. sylvatica* is used to treat inflammation of the salivary glands, varicose veins and swelling (Grieve, 1971). Also, it has been reported that tea of species *S. sylavtica* has an unpleasant smell (Gören, 2014). The infusion of the aboveground parts of *S. athorecalyx* is used in the treatment of arthritis, respiratory disorders and other types of infections. The decoct of *S. atherocalyx* is used to prevent nausea (Rezazadeh *et al*., 2009). In northern parts of Albania, aboveground parts of *S. alpine* L. are used as food for cattle (Pieroni *et al*., 2005). The flowers of *S. annua* are used in insomnia treatments (Hoppe, 1958) and it is reported that species *S. annua* could be poisonous (Gören, 2014). The infusion of *S. leucoglossa* is used for the treatment of breast and uterine cancer (Kültür, Sami, 2009).

CONCLUSIONS

Stachys species are widely used in traditional and modern medicine due to their active substances that improve physiological functions through pharmacological or metabolic actions. Aboveground parts of plants are most commonly used to prepare teas or decoctions. The species of the genus *Stachys* are mainly used in alternative medicine as supplements due to their expressed biological activities such as antibacterial, anti-inflammatory, and antioxidant activity. The species extracts could also find applications in the pharmaceutical industry for making drugs and supplements.

CONFLICT OF INTEREST

The authors declare that they have no competing interests.

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