Dalmatian Sage (*Salvia officinalis* L.): A Review of Biochemical Contents, Medical Properties and Genetic Diversity

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Summary

Dalmatian sage (*Salvia officinalis* L.) represents one of the most significant medicinal autochthonous species in flora of eastern Adriatic coast and islands. It is evergreen outcrossing perennial subshrub with short woody stems that branch extensively and violet flowers. Apart from being native to Mediterranean karst of west Balkan and Apenine peninsula it is cultivated in numerous countries worldwide with Mediterranean and temperate continental climate. From the earliest times it has been used in traditional medicine in healing gingiva, mouth cavity and the sore throat, against bacterial and fungal infections, for wound treatment, memory enhancement, for treating common cold, against sweating, stomach inflammation, ulcer formation, etc. Its essential oil has also been used in preservation of food and as spice as it gives both specific aroma and promotes digestion of food. The essential oil is extremely complex mixture of different active ingredients; however, the thujones and camphor are the dominant compounds and are the parameter by which *S. officinalis* is distinguished from other *Salvia* species. The great variability of essential oil composition and yield has been detected depending on various factors such as genotype, environmental conditions, phonological stage, plant parts used for the extraction of essential oil and drying procedure. Molecular genetic analysis of *S. officinalis* is still limited and comprises the use of RAPD markers, AFLP and SSR markers in assessing mostly the genetic variability and structure of wild *S. officinalis* populations.

Key words

Dalmatian sage; essential oil; Meditteranean; *Salvia officinalis* L.; thujone

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Introduction

Dalmatian sage *(Salvia officinalis* L.) is one of the most commercially important species within the Lamiaceae family (Avato, 2005). It is a perennial, evergreen subshrub, native to the Mediterranean region. It is cultivated in numerous countries (Raal et al., 2007). In Croatia, Bosnia and Herzegovina, Montenegro and Albania, Dalmatian sage is extensively gathered from the wild what could be a serious threat for its biodiversity.

S. officinalis has long enjoyed a reputation in traditional medicine for its healthy giving properties and for treating all kinds of ailments. This fact is evident from the Latin name of the genus *Salvia*, which is derived from the lat. *salvere*, meaning to save, in reference to the curative properties of the plant, recognized and appreciated from the ancient times (Dweck, 2000). Probably the best known use of sage tea is in healing gingiva, mouth cavity and the sore throat. The Romans called it "the holy plant" and it is assumed that they planted it all over Europe. It was recommended as a haemostatic, diuretic, tonic and emmenagogue by Pedanius Dioscorides (c. 40-90 AD), Pliny the Elder (23-79 AD) and Galen (c.130-c. 210 AD) (Dweck, 2000). Hippocrates (c. 460-c. 370 BC), Paracelsus (1493-1541), Saint Hildegard of Bingen (1098-1179), Bock (1498-1554) and Matthiolus (1501-1577) also relied on its healing properties (Madaus, 1938). These authors prescribed it as a remedy against cough, as a diuretic, wound-healing agent, for ulcers and for preservation of teeth (Panda, 2009). Both, English herbalist John Gerard (1545–1612) and physician and herbalist Nicholas Culpeper (1616-1654) claimed that sage was good for the head, brain, and improving memory (Woodword, 1994; Culpeper, 1992). In the time of the Carolingian empire the plant was cultivated in Monastery gardens of the early Middle Ages (Dweck, 2000). Even nowadays it is a mandatory plant in all Catholic monasteries (Tucakov, 1990). During the 17th century it was introduced to North America. Apart from its medicinal use sage has also been popular since ancient times as a culinary herb, especially in meat and poultry dishes due to its powerful and intense flavor.

Today, it is still used all over the world and it enjoys the same reputation. It has become a target for the search of the biologically active compounds and new drugs as it shows a broad range of medical activities. It was scientifically proven that *S. officinalis* has anti-diabetic (Eidi and Eidi, 2009), antioxidative, gastoprotective (Mayer et al., 2009), anti-inflammatory (Ninomiya et al., 2004), antiviral (Tada et al., 1994), anti-obesity (Ninomiya at al., 2004), anti-spasmatic (Todorov, 1984), fungicidal, bactericidal (Delamare et al., 2007; Pinto et al., 2007; Bouaziz et al., 2009) and anticancerogenic (Jedinak et al., 2006) effect. Therefore, it has potential in curing numerous illnesses and diseases including diabetes, depression, obesity, dementia, lupus, hearth diseases and cancer (Hamidpour et al., 2014). In addition, it is used in preparation and preservation of food (Hay and Waterman, 1993; Piccaglia 1998), and as flavoring agent in perfume and cosmetic industries (Delamare et al., 2007). Moreover, as natural disinfectant *S. officinalis* essential oils could play a vital role in preventing the spread of pathogenic microorganisms and environmental problems connected with the use of synthetic chemicals (Bouaziz, 2009).

The aim of this paper was to summarize the available scientific data on *S. officinalis*, including taxonomy, morphology, biochemical content and genetic diversity, as well as its use in the prevention and curing various diseases.

Taxonomy and distribution

Salvia officinalis L. (Sp. Pl., 23. 1753) belongs to the mint family Lamiaceae, subfamily Nepetoideae, tribe Mentheae and genus *Salvia*. Approximately 240 genera and 7000 species belong to the Lamiaceae family and it is the largest family of the order Lamiales (Dinç et al., 2009). The genus *Salvia* is the largest genus of the Lamiaceae family comprising around 1000 species (Walker and Sytsma, 2007), which are either herbaceous or shrubby perennials, rarely biennials or annuals, often strongly aromatic species. *Salvia* species are commonly grow all around the world; however, they are abundantly distributed in Europe around the Mediterranean, in South-East Asia, and Central and South America (Ulubelen, 2000). In Flora Europea 36 taxa of the genus are described (Hedge, 1972). Synonyms for *Salvia officinalis* L. are (Hanelt i IPK, 2001): *Salvia officinalis* var. *crispa* Alef., Landw. Fl.,118. 1866, *Salvia officinalis* subsp. major Gams in Hegi, Ill. Fl. Mitt.-Eur. V, vol. 4, 2483. 1927, *Salvia officinalis* var. *latifolia* Alef. , Landw. Fl., 118. 1866 and *Salvia tomentosa* Mill., Gard. Dict. ed. vol. 8. 1768.

It belongs to a group of Balkan-Apennine endemic species. Unlike the majority of endemic species it is widespread and often abundant (Liber et al., 2014). Its indigenous distribution in Western Balkans is in the Mediterranean region of Croatia (Kvarner area and Dalmatia), Bosnia and Herzegovina, Montenegro, and Albania with outmost southern populations in northern Greece where it occurs further from the sea side (Karousou et al., 2000). The northern limit of its native distribution is around Trieste (Italy) (Pignatti, 1982; Conti, 2005). There are also disjunctive populations in southern Serbia and Kosovo (Janković, 1982). It is cultivated in many countries around the world with continental climate: in Ukraine, Moldavia, Germany, Slovakia, Bulgaria, Romania, Italy, Great Britain, Canada, USA, Turkey, India, Japan, Indonesia (Java), Tanzania, South Africa, Antilles, Brazil, Australia and New Zealand. In many countries it is naturalized (Randall, 2007).

Apart from *Salvia officinalis* L. the following species of the genus *Salvia* can be found in Croatian flora (Nikolić, 2015):

Salvia aethiopis L.
Salvia amplexicaulis Lam.
Salvia argentea L.
Salvia austriaca Jacq.
Salvia bertolonii Vis.
Salvia brachyodon Vandas
Salvia fruticosa Mill.
Salvia glutinosa L.
Salvia nemorosa L
Salvia peloponnesiaca Boiss. et Heldr
Salvia pratensis L.
Salvia sclarea L.

Salvia tomentosa L.
Salvia verbenaca L.
Salvia verticillata L.
Salvia viridis L.
Salvia x *auriculata* Mill.

Among the mentioned species along with *Salvia officinalis* L., *Salvia brachyodon* Vandas (Short-tooth sage) is an endemic species. It is one of the rarest plant species of Dinaric karst (Liber et al., 2014) as its distribution is limited only on two localities, Mt. Vipera (St. Ilija) on Pelješac Peninsula in Croatia, and on Mt. Orjen, at the border of Bosina and Herzegovina and Montenegro, where the species was first recorded and it is regarded as the *locus classicus* (Vandas, 1899). In Croatia, it is classified as nearly threatened (NT) (Nikolić, 2015). Another *Salvia* species with limited distribution in Croatia is *S. fruticosa,* commercially known as Greek sage, which could be found only in the vicinity of Komiža on the island of Vis. *S. fruticosa* is native to eastern Mediterranean including southern Italy, southern parts of the Balkan peninsula to west Syria (Pignatti 1982; Hedge 1982; Greuter et al., 1986). Due to the value of its essential oil it has been naturalized in Western Mediterranean region in Malta, Spain and Portugal (Greuter et al., 1986). The presence of this species in Croatia may be related to ancient Greek colonization of the island in the fourth century BC. In Croatian flora an interesting spontaneous hybrid of *S. officinalis* and *S. fruticosa* named *S. x auriculata* has also been observed on the island of Vis (Radosavljević et al., 2012). Natural hybrids were recently detected to exist; prior it was only known as a result of artificial crossings from breeding programs (Putievsky et al. 1990; Dudai et al., 1999).

Morphology

S. officinalis L. is an outcrossing, perennial subshrub up to 60 cm high. Stems are erect or procumbent with numerous fine hairy dark green branches. Leaves are petiolate, elongated, opposite, simple, sometimes with basal lobes (especially in juvenile stadium), with serrate margin, rugose surface and more or less contracted at the base. On lower leaf surface hairs are white and on upper surface greenish or greenish-grey. Flowers are on 2-4 mm long pedicel, in pseudoverticillasters with 5-10 flowers that form spurious composed spike. Calyx is 10-14 mm long, hairy, with five teeth. Corolla is ca. 35 mm long, rosy, violet-blue, rarely white. Flowering period of *S. officinalis* is from March to July depending on habitat climatic conditions (Hedge, 1972; Šilić, 1973). *S. officinalis* has simple and glandular hairs. Five distinct types of glandular hair (one peltate and four types of capitate) have been identified, with different sites, secretory modes, secretions and a functional role. The four types of capiatate hairs are morphologically distinguishable whereas type I capitate hair has short uni- or bicellular stalk and a large uni- or bicellular secretory head; type II is very small and has a unicellular stalk and an oblong cutinized secretory head; type III is large with a long stalk consisting of one to three cells, a neck cell and a cutinized unicellular head, while type IV is large with a long slender stalk, with a neck cell and a very large, wide, cutinized, unicellular head which could be in the shape of trapezoid. Type I capitate hairs produce hydrophilous secretions, while peltate hairs and other types of capitate hairs produce mixed secrete of hydrophilous and lipophilous components (Corsi and Botega, 1999). *Salvia officinalis* is a diploid (2n = 14) with a genome size of 0.97 pg/2C, and base composition of 38.55% GC (Maksimović et al., 2007). Mericarp is spherically ovoid, 2-3 mm long and 2 mm wide, dark brown in color (Hedge, 1972; Šilić, 1973; Tomašević, 1982). The seed usually disperse via barochory and the wind and rain carry the seeds away from the mother plant (Corsi and Botega, 1999).

Biochemical contents

S. officinalis L. is one of the most appreciated herbs for richness of the essential oil content and its numerous biologically active compounds. It is considered to have the highest essential oil yield among *Salvia* species (Newall et al., 1996). The essential oil is extremely complex mixture of different active compounds. The two major chemical classes of secondary metabolites have been identified as typical products of the plant: terpenoids and phenolics (Bakkali et al., 2008). The essential oil of *S. officinalis* manly comprises the monoterpenes α- and β-thujone, camphor, 1,8-cineole and borneol, and sometimes in larger amounts sesquiterpenes α-humulene and β-caryophyllene. The di- and triterpenes have been found in the leaves (Máthé et al., 2007), i.e. manool. There is a high chemical variability among *S. officinalis* essential oils, however, it can generally be stated that α- and ß-thujones are the predominant constituents (Newall et al., 1996). Among the phenolics *S. officinalis* contains carnosinic, rosmarinic, caffeic, salvianolic compounds, etc. (Zupko et al., 2001).

The essential oil yield of *S. officinalis* and its chemical composition has been a focus of many investigations worldwide. It depends on various factors, such as genetic background (Perry et al., 1999), locality (Perry et al., 1999, Bernotienė et al., 2007), environmental conditions (Máthé et al., 1992, Kuštrak et al., 1984; Perry et al., 1999; Hadry et al., 2010) season (Perry et al., 1999), physiological stage (i.e. time of harvest) (Kuštrak et al., 1984), plant parts used for the extraction of essential oil (Perry et al., 1999; Santos-Gomez and Fernandes-Ferreira, 2001), soil mineral fertilization (Piccaglia et al., 1989), etc. Due to strong influence of these factors essential oil composition and yield frequently does not match the profile defined by ISO 9909 standard, which according to Bruneton (1999) is: α-thujon (18-43%), β-thujon (3-8.5%), camphor (4.5-24.5%), 1,8-cineol (5.5-13%), α-humulene (0-12%), α-pinene (1-6.5%), camphene (1.5-7%), limonene (0.5-3%), linalool and bornyl acetate (2.5% maximum).

Some studies were focused on determining the essential oil content of indigenous populations (Ivanic et al., 1978; Kuštrak et al., 1984; Pitarevic et al., 1985; Jug-Dujaković et al., 2012; Stešević et al., 2014) while others on the analysis of cultivated *S. officinalis* (Perry et al., 1999; Putievsky et al., 1986). Recent investigation of 25 indigenous *S. officinalis* populations from Croatia revealed essential oil content ranging from 1.93-3.7% (average 2.83%). The 62 compounds were detected, and among them α-thujone, camphor, β-thujone, 1,8-cineol, β-pinene, camphene, borneol and bornyl acetate represented 78.13 to 87.33% of the essential oil content. The most abundant compounds were α-thujone (%), camphor and β-thujone. The authors identified three chemotypes

with predominant: (1) α-thujone, (2) β-thujone and (3) camphor/β-pinene/borneol/bornyl acetate (Jug-Dujaković et al., 2012). Analysis of the chemical composition of the essential oils of 12 indigeous *S. officinalis* populations from Montenegro resulted in the identification of 40 oil constituents. The ten main components were α-thujone (16.98-40.35%), camphor (12.75-35.37%), 1,8-cineole (6.40-12.06%), β-thujone (1.5-10.35%), camphene (2.26-9.97%), borneol (0.97-8.81%), viridiflorol (3.46-7.8%), limonene (1.8-6.47%), α-pinene (1.59-5.46%), and α-humulene (1.77-5.02%) (Stešević et al., 2014). The essential oils yield ranged from 1.84 to 2.84%. Cvetkovic et al. (2015) analysed 17 indigeous *S. officinalis* populations and eight cultivated/naturalized ones from nine Balkan countries. The essential oil yield ranged from 0.25 to 3.48%, whereas southeastern populations tended to have higher essential oil yields than the northwestern ones. The correlation between essential oil composition and geographical distance between indigenous populations was not significant.

Perry et al. (1999) analyzed essential oil variations among individuals, plant parts, sites and season. They grouped the essential oils in three chemotypes, according to the total amount of thujone (high, 39-44%; middle, 22-28%; low, 9%) and the ratio of α- and β-thujone (α/β 10:1; 1.5:1; 1:10). Tucker and Maciarello (1990) suggested that *S. officinalis* essential oil should be divided into five chemotypes, depending on the amount of main compounds: (1) camphor > α-thujone > 1,8-cineole > β-thujone; (2) camphor > α-thujone > β-thujone > 1,8-cineole; (3) β-thujone > camphor > 1,8-cineole > α-thujone; (4) 1,8-cineole > camphor > α-thujone > β-thujone and 5) α-thujone > camphor > β-thujone > 1,8-cineole.

Wide variation in essential oil composition was determined in the investigation of Bernotiené et al. (2007). The analysis was performed on the essential oils of samples collected from eight gardens in Eastern Lithuania. The quantity of particular components in the analyzed essential oils varied 2 to 25 times. Essential oils were prepared by the hydro - distillation of air-dried plant and analyzed by gas chromatography. In this case, the diterpen manool was dominant constituent (14.4-20.9%) in two samples, 1,8-cineole (12.4-17.6 %) and β-thujone (12.6%) in two samples. The second major compound was viridiflorol (11.2-16.5%) in four samples, manool (10.3-11.5%) in two samples, and α-thujone (11.5%) and β-caryophyllene (9%) in one sample. Similar investigation was performed on *S. officinalis* samples collected on different localities in Vilnius district, Lithuania (Mockuté et al., 2003). A total of 89 compounds was identified, accounting to 97.5-98.2% of total constituents. The authors reported that main constituents of the essential oils were 1,8-cineole (6.8-8.2%), α-thujone (14.8-19.0%), borneol (6.6-8.0%), α-humulene (7.6-8.7%), viridoflorol (7.2-8.2%) and manool (6.4-10.4%). Other limited compounds, such as α-pinene, camphene, limonene, 1,8-cineole, camphor, linalool and its derivates, bornyl acetate and α-humulene as well as the α- and β-thujone, fulfilled the requirements of ISO 9909 standard (Bruneton, 1999).

Quantitative and qualitative compositions of essential oils are greatly influenced by environmental conditions such as temperature, day length, light intensity (Figueiredo et al., 2008), water availability, salinity, etc. According to Bernáth et al., (1991) both biomass and essential oil yields are reduced in cold and shady environments and in general, essential oil concentration tends to be higher in warmer and drier regions (Kargiolaki et al., 1994). Effect of light intensity on essential oil yield and composition was investigated by Li Yan Li et al. (1996). The plants were grown in various light conditions (shade or without shade, 15%, 27%, 45% and 100% of sunlight). The plants grown at 45% of full sunlight had the highest level of essential oil (0.38% FW) with higher content of β-thujone and a decreased accumulation of camphor in comparison to the essential oils grown at other light levels. According to Putievsky (1986) cit. Burmeister and Guttenbetg (1960), a long dry period in vegetative phase may result in higher production of essential oil. Bettaieb (2009) studied the effect of different water deficit levels (moderate water deficit; MWD and severe water deficit; SWD) on essential oil composition and yield. MWD increased the essential oil yield and the main essential oil constituents were camphor, α-thujone and 1.8-cineole. Under these conditions biosynthesis of these main compounds increased as well. The influence of soil salinity on yield and composition of essential oil was investigated by numerous scientists (Solinas and Deiana, 1996; Tabatabie and Nazari, 2007; Taarit et al., 2009). The results of Taarit et al. (2009) showed that the increase of NaCl level up to 100 mM significantly decreases the plant growth (65%) and content of essential oil. On the other hand the content of essential oil significantly increased at 75 mM NaCl. At 25 mM NaCl viridiflorol was predominant compound and at 50 and 75 mM NaCl 1, 8-cineole, while at 100 mM NaCl manool was the predominant compound. Environmental conditions change greatly during the vegetation period, leading to a pattern of seasonal variation in active compounds content. In Dalmatian sage, the monoterpenes 1,8-cineole, camphor, and the α and β-thujone show pronounced dynamics during a vegetative cycle (Pitarevic, 1984). According to Grausgruber-Gröger et al. (2012) 1,8-cineole steadily decreases approximately from May to October while α and β-thujone content increases gradually during the vegetative period and the highest concentration of camphor is in the middle of the vegetative period. Perry et al. (1999) found the lowest total thujone levels (25%) around flowering in spring and summer. Similar results were obtained by Bouverat-Bernier and Marquis (1993) where lower thujone and camphor levels were determined in flowering stage of the plants but higher levels of β-pinene and 1,8-cineole. Numerous authors report the highest essential oil yield after flowering is complete (Pitarevic et al., 1984; Putievsky et al., 1986; Hay, 1993). The same results were obtained in the study Maric at al. (2006). The authors investigated the influence of development stages and locality altitudes on essential oil composition and yield. The oil yield between vegetative period, prior to flowering and after the flowering greatly differed whereas the highest yield was noticed after the flowering of the plants. Lakušić et al. (2013) analysed variations in the yield and composition of essential oil in leaves, in two genotypes of different geographic origin and in various phenological stages. They determined significant impact of both factors. There were large variations in the essential oil yields in three distinguished phenological phases (young leaves, early old leaves and late old leaves) ranging from 0.2-2.9%. Furthermore, leaves of the same plant in different stages of development synthesized different essential oil types. In the young leaves collected in April sesquiterpenes were dominant (50.7-57.0%), while in

later development stages increased the amount of monoterpenes (55.4-88.4%). Essential oils analyzed in the same stages differed among genotypes.

Avato et al. (2005) investigated the essential oil composition in micropropagated *S. officinalis* plants. The major compounds of the essential in all analyzed samples, but in different extent, were 1,8-cineol, camphor, borneol, bornyl acetate, camphene, α- and β-thujone, linalool, α- and β-caryophyllene, α- humulene, α- and β-pinene, viridiflorol and pimaradiene. They determined variations in α and β-thujones and camphor contents in different physiological stages of development. The amount of camphor was high and inversely correlated with the total thujones content.

Various studies have demonstrated that the essential oils isolated from flowers, leaves and stems differ in composition. The results of the research by Santos-Gomes and Fernandes-Ferreira (2001) showed that flower oil contains less α-thujone, camphor and viridiflorol than the oil extracted from leaves. An opposite correlation was found for borneol. Viridiflorol was among the five major constituent of the oil isolated from the leaves. Moreover, the leaves growing on different position on the plants produced essential oils containing different amounts of particular compounds. The α-tujon was the major compound of the leaves essential oil from Albania (Asllani, 2000). In investigations of Couladis et al. (2002) the major compound of the flower essential oil from Serbia and Montenegro was diterpene manool. The essential oils isolated from flowers, leaves and stems, originating from southeast Serbia, had similar composition (Veličković et al., 2003), with manool as the predominant component (9.0-11.1%). Perry et al. (1999) reported higher essential oil yield, higher β-pinen contents and lower thujone levels in the flowering parts of *S. officinalis* than in the leaves (1.6 vs. 1.1%; 27 vs. 10% and 16 vs. 31%, respectively).

Piccaglia and Marotti (1989) studied the effect of soil fertilization on *S. officinalis* essential oil composition. The authors determined that various concentrations of fertilizers affect concentrations of β-thujone, camphor, p-cymene, β-caryophyllene, α-humulene and caryophyllene oxide. The extraction procedure and extraction agents (Veličković et al., 2006), distillation (Mastelić, 2001) and drying (Venskutonis, 1997) are among other factors that affect the yield and composition of *S. officinalis* essential oils.

Medical properties

The species is a well-known medicinal and culinary herb, widely used in the food, pharmaceutical and cosmetic industries. The areal parts (*Salvia folium*) are included in several European Pharmacopeias and the council of Europe lists the drug as a natural source for food flavoring (Council of Europe, European Pharmacopeia, seventh ed., 2010). It has been used as an antidiabetic (Swanston-Flatt et al., 1991; Eidi and Eidi, 2009; Hamidpour et al., 2013), antioxidans (Nickavar et al., 2007; Yadav and Mukundan, 2011), anti-inflammatory (Baricevic et al., 2001), antimicrobial (Khalil and Li, 2011), antiviral (Schnitzler et al., 2008; Smidling et al., 2008), gastroprotective and antimutagen (Patenković et al., 2009) agent. Also, it has been proven to be effective in cardiovascular and cancer diseases (Itani et al., 2008; Pedro et al., 2010; Keshavarz et al., 2011) and in the treatment of mental and nervous conditions (Baricevic and Bartol, 2000; Perry et al., 2003; Iuvone et al., 2006; Eidi et al., 2006; Khan et al., 2011).

Preparations of *S. officinalis* leaves have traditionally been used as a remedy against diabetes. The potential anti-diabetic properties of *S. officinalis* extract against type I and type II diabetes were investigated by Swanston-Flatt et al. (1991). The results have shown that ethanol extracts of *S. officinalis* significantly reduce the blood glucose in healthy rats and decrease hyperglycemia in type I diabetic rats (Alarcon-Aguilar et al., 2002). Moreover, Eidi et al. (2005) found that methanolic extract of *S. officinalis* diminish serum glucose in type I diabetes, without affecting pancreatic insulin production. In addition, Lima et al. (2006) have noticed that tea-infusion of *S. officinalis* reduces liver glucose production and increases the action of insulin in type II diabetes, similar as metformin, which is often used in clinical treatment of diabetes. Furthermore, Eidi and Eidi (2009) have found that oral administration of *S. officinalis* extract exerts remarkable lowering of serum glucose, trigycerides, total cholesterol, urea, uric acid creatinine, AST, ALT and increase plasma insulin in dose-dependent manner in diabetic rats. The activity of *S. officinalis* extract was similar to the glibenclamide, the standard antidiabetic drug. Broadhurst et al. (2000) have demonstrated insulin-like activity of aqueous extract of *S. officinalis*.

Antioxidants play a major role in the protection of the body from oxidative stress and free-radical damages, which cause various illnesses such as diabetes, heart disorders, cancer, dysfunction of brain, weakened immune system, etc. (Eidi et al., 2005; Yadav and Mukundan, 2011). Numerous studies showed that variety of plants, among them *S. officinalis* exhibits antioxidant and free radical scavenging activity. The flavonoid and phenolic plant compounds are the strongest antioxidant agents (Nickavar et al., 2007; Yadav and Mukundan, 2011; Hussain et al. 2011). Phenolic compounds found in the ethanol extract of *S. officinalis* are carnosol, carnosic and rosmaric acids, rosmadial, rosmanol, epirosmanol, methyl carnosate, luteolin-7-O-beta-glucopyranoside (Aleksovski and Sovova, 2007) and coffeic acid (Cuvelier et al., 1996). However, intensive studies of *S. officinalis* antioxidant activity resulted in knowledge that the rosmaric and carnosic acids mainly contribute to this activity (Lu and Yeap Foo, 2000; 2001). Moreover, Lu and Yeap Foo (2000) have proven that salvianolic acid, the dimmer of rosmaric acid also exerts very significant antioxidant and free radical scavenger activities. Stanojević et al. (2010) found that aqueous extract of *S. officinalis* may improve the liver antioxidant status in two weeks. Due to antioxidant and free radical scavenging activities *S. officinalis* might be an important source of food additives (Babović et al., 2010). Apart from antioxidative activity, phenolic compounds and flavonoids are also known for their anti-inflammatory and antimicrobial activities. Thus, the variety actions of *S. officinalis* can be attributed to the content of these compounds. Veličković et al. (2003) examined potential antimicrobial activities of *S. officinalis* flower, leaves and stems extracts that showed remarkable activity against *Bacillus mycodis*, *Bacillus subtilis*, *Enterobacter cloacae* and *Proteus sp.* (Itani et al., 2008). In addition Khalil et al. (2011) determined a significant antibacterial activity of *S. officinalis* extract against the bacteria resistant to the antibiotics. This

knowledge made a *S. officinalis* a good alternative for traditional antibiotics and food preservatives. Study of Kermanshah et al. (2009) have shown that the hydroalcoholic extract of *S. officinalis* inhibit the growth of *Streptococcus mutans*, *Lactobacillus rhamnosus* and *Actinomyces viscosus*, bacteria causing dental caries. The results support the use of *S. officinalis* as a natural remedy for treatment of mouth and teeth diseases, instead of chemical solutions. George et al. (2009) demonstrated the effectiveness of herbal toothpaste with *S. officinalis* extract in the control of plaques and gingivitis. Aqueous and ethanolic extracts of *S. officinalis* were also effective against herpes simplex virus type 1 and 2 (Schnitzlera et al., 2008; Smidling et al., 2008).

Mayer et al. (2009) examined the gastro-protective action of hydroalcoholic extracts of *S. officinalis*. It was shown that the extracts prevent gastric mucosal lesions, reduce gastric secretion and inhibit the H^+,K^--ATP-aze activity. Medical use of *S. officinalis* was also examined in diarrhea and abdominal spasm by *in vivo* and *in vitro* tests (Khan et al., 2011). The study demonstrated that a crude extract of *S. officinalis* protects from diarrhea with gut relaxation. These results provide the pharmacological base for medicinal use of *S. officinalis* in treatment of gut disorders, such as diarrhea and abdominal colic.

Patenković et al. (2009) demonstrated potential antimutagenic effect of *S. officinalis* tea whose mode of action might be through suppression of metabolism by antioxidative action. On the basis of these findings, the anticancerogen activity of *S. officinalis* was also investigated. As it is known, cancer is characterized by uncontrolled proliferation, and needs a potential for producing a new blood vessels (angiogenesis) for nutrients supply (Keshavarz et al., 2011). Study of Keshavarz has shown that extract of *S. officinalis* at pharmacological concentrations *in vivo* inhibited angiogenesis, which should be a novel start for development of a new anti-angiogenic drugs. Earlier it was reported that urosolic acid in *S. officinalis* inhibits angiogenesis, tumor invasion and metastasis, and suppresses the lung colonization of B16 melanoma (Jedinak et al., 2006). Prevention of colon cancer was examined on rats treated with *S. officinalis* tea (Pedro et al., 2010). It was noticed that water extract of *S. officinalis* remarkably decreases DNA damage *in vitro*. Some diterpenoids isolated from the roots of *S. officinalis* showed strong cytotoxic and DNA damage activities in human colon carcinoma (Caco2) and hepatoma (HepG2) (Hadri et al., 2010). Same authors have demonstrated that sesquiterpene fraction of the essential oil with α-humulene exerts a strong cytotoxic activity in human prostate cancer cells (LNCaP). In addition, trans-cariophyllene, a main component of sesquiterpene fraction, exhibited a strong cytotoxic effect on melanotic melanoma and renal adenocarcinoma cells.

S. officinalis has been used in folk medicine (Bommer et al., 2011) as well as in clinical trials (Walch et al., 2011) for suppressing the menopause symptoms. These include hot flashes, insomnia, night-time sweating, dizziness, headaches and palpitations. Application of a fresh *S. officinalis* extract once a day demonstrated a good clinical value regarding safety, efficacy and tolerability in the treatment of menopausal symptoms. *S. officinalis* is also known for beneficial effects on memory disorders, depression and cerebral ischemia (Perry et al., 2003). *S. officinalis* has also been used in treating Alzheimer's disease, whereas essential oil acts as inhibitor of acetylcholinesterase, which may play a role in the loss of memory associated with the disease, and enhances the acetylcholine, neurotransmitter substance in the transferring signal between the synapses in the brain (Ferreira et al., 2006). Furthemore, a variety of studies has shown that *S. officinalis* improves memory and cognition (Tildesley et al., 2005; Eidi et al., 2006). In addition, the aroma of essential oil influences mood and cognition and produces remarkable enhancement of quality memory factor (Moss et al., 2010). *S. officinalis* can be used in skin care to relieve sores, wound, bumps, cuts and other skin injuries. Its embrocation is helpful in relieving muscular pain. It can also be used as a lotion or compress for wounds (Fluck, 1988) and ulcers (Grieve 1984). It is a good hair tonic and the infusion can be rubbed on to the scalp every other day for healthy hair. The essential oil is used in perfumes as a deodorant. Apart from its medical uses *S. officinalis* is used for flavoring meat, fish and poultry dishes and the amount of sage leaf consumed as a culinary herb in food presents no hazard.

Use of *S. officinalis* in prescribed doses is safe and there are no reports of negative side effects (Tildesley et al., 2005). Therefore, recommended doses should never be exceeded and preparations of *S. officinalis* should not be used for prolonged periods. The adverse effect is caused by high content of thujones (Baricevic et al., 2001), hence its overdose can lead to a permanent damage of the nervous system and cause dementia and seizures. Their permitted proportion is 0.0005 g/kg (Tisserand and Balacs, 1995). Pure essential oil should never be consumed and sage preparations should be avoided during pregnancy and lactation.

It has been employed as an ornamental garden plant (Armitage, 1997) and several cultivars were developed for that purpose. Furthermore, cultivation of *S. officinalis* can bring a double benefit. In addition to preventing erosion (Kušan, 1941; Tucakov, 1984) *S. officinalis* plants are grazed by bees that produce honey with characteristic aroma and high medical value (Devetak, 1950; Tucakov, 1984).

Genetic diversity

Molecular genetic studies of *S. officinalis* are limited and mostly focused on the analysing of localized wild populations. Židovec (2004) and Liber et al. (2014) analysed genetic diversity and structure of ten populations from the East-Adriatic coastal region using Random Amplified Polymorphic DNA markers (RAPD). The Amplified fragment length polymorphism markers (AFLP) were employed in the analysis of 25 natural *S. officinalis* populations (Jug-Dujaković, 2010), covering the distributional range of *S. officinalis* in Croatia with two populations being from Bosnia and Herzegovina. All the abovementioned investigations revealed high genetic diversity levels of natural *S. officinalis*. The isolation and characterization of specific *S. officinalis* microsatellite loci was recently provided by Molecular Ecology Resources Primer Development Consortium et al. (2010) and Radosavljević et al. (2011). The developed SSRs were used in assessing genetic diversity, population structure, geographic differentiation, the occurrence of demographic bottlenecks, and ecotypic divergence of wild *S. officinalis* from the east Adriatic coastal region. The authors also examined the transferability of *S. officinalis*

microsatellite markers to the analysis of *S. fruticosa*, *S. pratensis* L., *S. sclarea* L., *S. verticillata* L., and *Rosmarinus officinalis* L. The results have shown that the developed SSRs are potentially useful for the analysis of closely related species, especially *S. fruticosa*. Moreover, Radosavljević et al. (2012) tested the developed SSRs on the natural *S. brachyodon* populations; whereas 15 out of 30 developed SSRs were successfully amplified. More recently Stojanović et al. (2015) performed a plastid DNA-based phylogeographic survey on eight *S. officinalis* populations from Serbia, Montenegro and Macedonia with the aim of elucidating the origin (anthropogenic vs natural) of four disjunct inland populations. The authors found seven haplotypes and high total gene diversity (H_T = 0.695) and genetic differentiation (G_{ST} = 0.682). Moreover, two lineages, a sub-structured inland-Adriatic lineage and a purely Adriatic lineage have been determined, with the latter being less diverse (H_d = 0.426 vs.0.403). On the basis of their findings as well as previous scientific data assumptions on their anthropogenic origin were rejected. Genetic analysis of cultivated forms of *S. officinalis* is also very scarce. Mader et al. (2010) analysed genetic structure of nineteen *S. officinalis* genebank accessions of different origin with RAPD, SNP and SSR markers, Böszörmenyi et al. (2009) investigated chemical and genetic relationships among *S. officinalis* cultivars using GC-FID, GC-MS and RAPD markers and Bazina et al. (2002) compared the genetic patterns, assessed by RAPD markers and volatile oil composition in *S. officinalis* clones. The RAPD markers were also employed in assessing genetic relationships between commercial cultivars and Brazilian landrace accessions of *S. officinalis* (Echeverrigaray and Agostini, 2006).

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