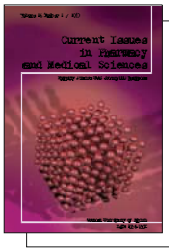

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Biological activities of *Salvia* L. species

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ABSTRACT

Salvia officinalis L. is one of the most widespread species, and because of this, is the most popular among other *Salvia* L. However, there are many other *Salvia* species with the long history of use in the treatment of a variety of disorders. The dried root of *S. miltiorrhiza* Bunge is one of the most popular herbal traditional medicines in Asian countries, while a mixture of leaves of *S. fulgens* Cav. and *S. microphylla* Kunth. is a traditional Mexican medicine, called 'mirto', and used for stomach ailments. Despite the extensive traditional use of many *Salvia* species around the world, the phytochemical and biological studies concerning sage are still very popular. The review aims to show recent research results concerning biological activities of *Salvia* species, and some of them, e.g. anticholinesterase, neuroprotective, anticancer, antiviral, anti-inflammatory, and antioxidant activity were summarized.

Keywords: *Salvia*, pharmacological studies, chemical constituents, essential oils, extracts

INTRODUCTION

Medicinal plants have provided a wide range of pharmacologically active substances. Herbs have been used since ages, in hundreds of purposes including medicine, nutrition, beverages, dyeing, fragrances, cosmetics, decorating elements, and industrial uses. Even today, in our "chemical and synthetic" world, plants or substances isolated from them, are present in 40% of pescription drugs [17].

One of the most famous medicinal plants is *Salvia officinalis* L. (common sage), the member of the Lamiaceae family. The positive benefits of *S. officinalis* to health is known from time immemorial. A quote: '*Cur moriatur homo cui Salvia crescit in horto*?'-'Why should a man die whilst sage grows in his garden?' shows how this plant was important [15]. Common sage has been used in the treatment of various disorders, such us tuberculosis, psoriasis, and seborrhoeic eczemas. It has shown strong antibacterial and antifungal activities [5, 37]. Several experimental studies have also demonstrated the antioxidant [9, 21], antiviral [31], and anti-inflammatory [3] properties of *S. officinalis* L. Sage leaves have been used in antiseptic and astringent herbal mixtures, whereas essential oil distillated from common sage can be helpful in aromatherapy (massage, bath, inhalation), and in bacterial infections, cough and bronchitis [2, 36]. It has also been used as medication against aches, wounds, insomnia, measles, rheumatism, congealed blood, seasickness, venereal disease and worms [6]. The therapeutic effects of *S. officinalis* L. are due to the presence of flavonoids, phenolic compounds such as carnosic, rosmarinic, caffeic acids, and other phenolic structure-based compounds especially found in alcohol-soluble fractions [33]. Sage leaves contain up to 2.5% of volatile oil in which the principal component is thujone, accompanied by 1,8-cineole and other mono- and sesquiterpenoids [28].

S. officinalis L. is one of the most widespread *Salvia* L. species. Although, besides common sage, this genus is represented by about 900 other *Slavia* L. species [15]. Among them, 134 species have been scientifically studied, and many these plants are characterized by interesting biological activities [37]. The dried root of *S. miltiorrhiza* Bunge is one of the most popular herbal traditional medicines in Asian countries, especially in China; *S. canariensis* L. is widely used in the popular medicine of the Canary Archipelago, while a mixture of leaves of *S. fulgens* Cav. and *S. microphylla* Kunth. is a traditional Mexican medicine – called 'mirto' – for stomach ailments [37]. Here we want to review some of the biological activities of *Salvia* L. species, e.g. anticholinesterase, neuroprotective, anticancer, antiviral, anti-inflammatory, and antioxidant, among others.

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BIOLOGICAL ACTIVITY

Salvia L. species have produced an array of secondary metabolites. To date, over 730 compounds have been reported from this genus. More than 80% of all the secondary metabolites occurring in *Salvia* L. are terpenoids, especially abietane and clerodane diterpenoids. Flavonoids are second important group of compounds biosynthesized by *Salvia* L. plants [37]. These components have been observed to possess various pharmacological activities including anticholinesterase, neuroprotective, anticancer, antiviral, anti-inflammatory, and antioxidant.

CHOLINESTERASE INHIBITORY ACTIVITY

Alzheimer's disease (AD) is a neurodegenerative illness affecting the brain. It is characterized by irreversibility and progressivity in brain damage. In most people, AD symptoms appear usually after age 60 and are connected with lack of brain neurotransmitter, acetylcholine. For that reason, most of the drugs used in pharmacotherapy of AD, block the breakdown of acetylcholine. Since some *Salvia* L. species, especially *S. officinalis* L. and *S. lavandulifolia* Vahl. were used in folk medicine against memory loss, this genus became popular and interesting target for scientists as potential drug of natural origin for treatment AD through cholinesterase inhibitory activity [22, 26].

Orhan and coworkers [22] investigated cholinesterase inhibitory potential of different extracts received from fourteen *Salvia* L. species (*S. argentea* L., *S. bracteata* Banks et Sol., *S. caespitosa* Montbret & Aucher ex Benth., *S. cryp- tantha* Montbret & Aucher ex Benth., *S. glutinosa* L., *S. indica* L., *S. microstegia* Boiss. & Balansa, *S. multicaulis* Vahl, *S. pinnata* L., *S. quezelii* Hedge & Afzal-Rafii, *S. syriaca* L., *S. tobeyi* Hedge, *S. verticillata* subsp. *Amasiaca* (Freyn & Bornm.) Bornm., and *S. viscose* Jacq.) growing in Turkey. The dichloromethane and ethanol extracts of the aerial parts of *S. cryptantha* Montbret & Aucher ex Benth. were the most active against acetylcholinesterase (AChE) (~56%) and butyrylcholinesterase (BChE) (~34%), respectively [22].

Anticholinesterase studies were also performed of the essential oils hydrodistilled from various *Salvia* L. species. Essential oil of the Iranian *S. leriifolia* Banth. was reported to show cholinesterase inhibitory properties with IC_{50} values of 0.32 and 0.29 μl/ml for AChE and BChE, respectively [19]. Savelev et al. [29] concluded, that time-dependent anti-BChE activity of essential oils obtained from *S. fruticosa* Mill. and *S. officinalis* L. subsp. *purpurea* was due to synergistic interaction between the essential oils component.

NEUROPROTECTIVE ACTIVITY

The neuroprotective effects of five diterpenoids, including cryptotanshinone, dihydrotanshinone I, tanshinone I, tanshinone II A and tanshinone II B isolated from *Salvia miltiorrhiza* Bunge (Danshen in Chinese traditional medicine) roots, against ischemic damage were examined. All tested compounds showed a potential to preserve neurons in the ischemic hippocampal CA1 region. Among them, especially CA1 pyramidal neurons were well protected from transient ischemic damage, by tanshinone I and cryptotanshinone [23].

Zhang et al. [39] proved, that salvianolic acid B isolated from *S. miltiorrhiza* Bunge was capable of promoting bone marrow derived neural stem cells (BM-NSCs) proliferation and differentiation towards neuronal lineage, protecting BM-NSCs from H_2O_2-induced oxidative cell damage and induced BDNF production by BM-NSCs. Thus, this compound offer a possible approach to facilitate the cells survival and differentiation in unfavorable environment, promoted neuronal repopulation and upgraded the therapeutic efficiency of BM-NSCs in Central Nervous System diseases [39].

The Chinese scientists tested *Salvia miltiorrhiza* Bunge extract to induce the differentiation of multi-functional stem cells into neuron-like cells. Muscle-derived stem cells (MDSCs) was induced by cilairy neurotrophic factor (CNTF) together with extract of *S. miltiorrhiza* Bunge to repair sciatic nerve injury in rats. Experiments confirmed, that *S. miltiorrhiza* Bunge can promote peripheral nerve regeneration [38].

ANTICANCER AND CYTOTOXIC ACTIVITY

Polysaccharides (SMP-W1) isolated from *Salvia miltiorrhiza* Bunge presented anti-tumor activity *in vitro* as well as *in vivo* [18]. Studies showed that SMP-W1 could effectively prevent the H22 (hepatoma) tumor growth. During the treatment the experimental animals with SPM-W1, the researchers observed the absence of side effects, like inhibitory action on immune organs or loss of body weight. Meanwhile, the appetite, activity and coat luster of each animal in SMP-W1 treated group were better than in control group. Furthermore, polysaccharides significantly increased the concentration of TNF-α in a serum of H22-bearing mice. These results provide a scientific basis for developing the polysaccharide as a safe antitumor agent for patients [18].

Study conducted by Kontogianni and coworkers [17] illustrated, that *S. officinalis* L. extract possessed anticancer properties, which is attributed to the presence of ursolic and olenaloic acids, as well as flavonoids. Furthermore, it was found, that common sage extract exerted direct cytocydal effect *via* up-regulation of nitric oxide (NO) in cancer cells, which in turn acts in a pro-apoptotic manner and induces cell apoptosis. On the other hand, through activation of macrophages and their secretion of inflammatory mediators, the extract could indirectly induce cancer cell death [17].

The anticancer activity of the South African *Salvia* L. species was investigated by Kamatou and coworkers [16]. The experiment was conducted on human cancer cell lines, including the breast adenocarcinoma (MCF-7), the colon adenocarcinoma (HT-29), and the glioblastoma (SF-268) cell lines, using the sulforhodamine B assay. IC_{50} values were ranged between 9.69 and 43.65 μg/ml against the MCF-7 and between 8.72 and 59.12 μg/ml against the SF-268, with *S. radula* Benth. and *S. africana-caerulea* L. being the most active. *S. lanceolata* Lam. extract was the most active against the HT-29 cell line, with IC_{50} value of 17.05 μg/ml [16].

ANTIVIRAL ACTIVITY

The water-soluble extract of the roots of *S. yunnanensis* C.H. Wright were found to have a potent effect against human immunodeficiency virus type 1 (HIV-1), as well as against hepatitis B virus (HBV) [40]. The same studies concerning anti-HIV activity of the compounds isolated from the mentioned extract showed that the most active component is salvianolic acid N. This compound was inhibited on HIV-1 RT and IN, and the IC_{50} values were 67.10-193.39 μg/ml and 1.78-18.5 μg/ml, respectively [40].

The anti-HIV-1 activities of salvianolic acid A, methyl salvianolate A, ethyl salvianolate A, lithospermic acid and *cis*-lithospermic acid were tested for the inhibition of P24 antigen in HIV-1 infected MT-4 cell cultures. Experiment showed that all tested components were active with EC_{50} values ranging from 1.44 to 6.11 μg/ml [41].

ANTI-INFLAMMATORY ACTIVITY

Cyclooxygenase-1 (COX-1) and cyclooxygenase-2 (COX-2) are two key enzymes in the inflammation process. The essential oils from *S. repens* Burch. ex Benth., *S. runcinata* L.f., and *S. stenophylla* Burch. ex Benth. showed inhibition of the COX-2 enzyme, when tested at a concentration of 1%. Among these three species, *S. stenophylla* Burch. ex Benth. exhibited the highest inhibition (73%) [8].

S. stenophylla Burch. ex Benth. had also the potential to inhibit the 5-lipoxygenase (5-LOX) enzyme [4, 13]. The 5-LOX assay was also used to test the *in vitro* anti-inflammatory activity of other *Salvia* L. species. Essential oils exhibited better anti-inflammatory activity when compared to the solvent extracts with the IC_{50} values ranging between 22.81 and 77.32 μg/ml [13, 15].

The essential oil of *S. runcinata* L.f. exhibited the highest activity in 5-LOX assay, while it was less active against COX-2 enzyme. On the other hand essential oil of *S. repens* Burch. ex Benth. with the moderate inhibition of 5-LOX was the most active against COX-2 assay [14].

The *S. plebeia* R.Br. extract had potent anti-inflammatory activity through heme oxygenase-1 (HO-1) induction in RAW264.7 macrophages. Jeong et al. [11] showed that *S. plebeia* R.Br. extract induced the expression of heme oxygenase-1 (HO-1) in a dose dependent manner, and blocked HO-1 activity abolished the inhibitory effects of extract on NO production.

ANTIOXIDANT ACTIVITY

There is increasing evidence suggesting that many degenerative diseases such as brain dysfunction, cancer, heart disease, and immune system decline could be the result of cellular damage caused by free radicals and that antioxidants may play an important role in disease prevention [1, 15].

The examination of the antioxidant activity using the DPPH free radical-scavenging test system of *Salvia* L. species from Turkey, showed that the most active plant was *S. euphratica* Montbret & Aucher ex Benth. with IC_{50} value of 20.7 μg/ml. In the β-carotene/linoleic acid test system, the extract of *S. hypargeia* Fisch. & C.A. Mey. was the most active, with 69.2% inhibition rate [32].

Other studies concerning antioxidant activity of Turkish sage were done by use of DPPH radical scavenging activity, metal-chelation capacity, and ferric-reducing antioxidant power (FRAP) assays [22]. In these studies, the ethanol extracts of tested *Salvia* L. species appeared to be stronger in FRAP assay, while ethyl acetate extracts seemed to have better chelation capacity. The finest metal-chelation capacity displayed ethyl acetate extracts of *S. pinnata* L. and *S. bracteata* Banks & Sol. roots (66.4%). The most remarkable DPPH scavenging effect showed ethanol extract of aerial parts of *S. glutinosa* L. (89.57%). The ethanol extract of the aerial parts of *S. verticillata* subsp. *amasiaca* (Freyn & Bornm.) Bornm. (1.652) had the most prominent FRAP as compared to the reference, chlorogenic acid (3.618) [22].

The solvent extracts of the South African *Salvia* species were found to display antioxidant activity tested by use of DPPH and ABTS methods, and IC_{50} values were 1.61-74.50 μg/ml and 11.88-69.26 μg/ml, respectively. The extract received from *S. schlechteri* Briq. was the most active in both tests [13, 15].

OTHER ACTIVITIES

Park and coworkers [24] investigated whether *Salvia plebeia* R.Br. extract influences cholesterol handling of J774A1 murine macrophages. Results showed that sage weed extract antagonized oxidized LDL uptake and promoted cholesterol efflux in lipid-laden macrophages. Therefore, this plant may serve as a protective therapeutic agent against the development of artheriosclerosis [24].

Other studies highlighted that *Salvia splendens* Sellow ex Roem. & Schult. leaves are characterized by broad diversity of phenolic components, among which caffeic and rosmarinic acids are the major compounds [20]. Eighty-

percent-methanol extract of this *Salvia* species was non toxic to mice up to 5g/kg b.wt., and it exhibited significant hypoglycemic activity at 250 and 500 mg/kg in streptozotocin induced-diabetic mice. This extracts showed also significant anti-inflammatory and antioxidant effects [20].

Hepatic fibrosis is the important pathological features of chronic liver diseases. Wang et al. [35] showed, that salvianolic acid B isolated from *S. miltiorrhiza* Bunge, possessed therapeutic effect on CCl_4-induced hepatic fibrosis rats. The anti-fibrotic effect of salvianolic acid B is associated with ability of this compound to up regulation the expression on NF-κB in the nucleolus, and to down-regulation the expression of NF-κB and IκBα in the cytoplasm. These results suggest that salvianolic acid B is a promising drug candidate in the treatment of hepatic fibrosis [35].

The antimalarial activity of essential oils and solvent extracts from *Salvia* L. species growing in South Africa were investigated [15, 16]. These studies showed that all essential oils and extracts inhibited the *in vitro* growth of *Plasmodium falciparum* FCR-3 strain. The IC_{50} values of the essential oils ranged from 1.20 to 13.50 μg/ml and displayed promising activity compared to the solvent extracts (IC_{50} values were 3.91-26.01 μg/ml) [15, 16].

Essential oil hydrodistilled from the Italian *S. sclarea* L. was reported to show antifungal activity against *Fusarium oxysporum*, *Botrytis cinerea*, *Rhizoctonia solani*, and *Alternaria solani* [7]. The authors concluded that linalool, as the major component of essential oil, could be responsible for this activity. Other studies showed that essential oil from the Bugarian *S. sclarea* L. demonstrates antifungal activity against five clinical isolates of *Candida* species – *C. albicans*, *C. tropicalis*, *C. krusei*, *C. glabrata*, and *C. parapsilosis*. Essential oil of *S. sclarea* L. had stronger anticandidal activity in comparison with linalool and linalyl acetate [10]. Based on the studies conducted by Jirovetz and coworkers [12], essential oil from *S. lavandulifolia* Vahl possessed the strongest anticandidal activity, followed by essential oils hydrodistilled from *S. sclarea* L. and *S. officinalis* L. *C. albicans* ATCC 10231 responsible for skin infections was the most susceptible strain to essential oils.

The essential oils of the Brazilian *S. officinalis* L., *S. sclarea* L., *S. lavandulifolia* Vahl, and *S. triloba* L.f. were used to test the antimicrobial activity against Gram-positive and Gram-negative microorganisms [27]. Gram-positive bacteria presented larger sensitivity to essential oils. Weak microbiostatic inhibitory activity was seen against *Staphylococcus aureus*, *S. epidermidis*, and *Escherichia coli* when essential oils from the Italian *S. desolea* Atzei & Picci and *S. sclarea* L. were tested. But, since the inhibition increased progressively with contact time, better results could be obtained by using these oils in bioadhesive formulations [25].

SALVIA AS FUNCTIONAL FOOD

Salvia hispanica L., commonly known as chia, is a species native to central and southern Mexico and Guatemala. Chia was principal crop for ancient Mesoamericans culture and has been cultivated in these regions for thousands of years. Recent evaluation of chia's properties and possible uses has shown that it has a high content of oil (32%) and 60% of this, is linolenic acid, a fatty acid denominate omega-3 associated with various benefits to consumer health. After extracting the oil from the seeds, defatted chia is rich in fiber (22 g/100 g) and protein (17 g/100 g), which contents is similar to those of other oil seeds currently used in the food industry [34]. Everyday consumption of chia seeds provides numerous health benefits, but this plant is also a very promising source of biologically-active peptides. Production of bioactive peptides from protein-rich fraction, obtained from chia's seeds by enzymatic hydrolysis, is the way to receive hydrolysates with enhanced biological activity. Inclusion of these hydrolysates in white bread and carrot cream increased product biological potential without notably affecting product quality. Chia protein hydrolysates with enhanced biological activity could prove an effective functional ingredient in a wide range of foods [30].

SUMMARY

Salvia L. is a large and widespread genus with a diversity of ethnobotanical uses. Many plants from *Salvia* L. genus have been used for centuries, especially by Chinese to promote longevity, e.g. *S. miltiorrhiza* Bunge. In the past few decades, *Salvia* L. species and their constituents have attracted considerable attention from many research groups as antimicrobial, antitumor, anticancer, antioxidant, neuroprotective, antiviral, anti-inflammatory, and antioxidant agents, among many others. One of the important result arose from these studies was the confirmation of many traditional uses for plants of genus *Salvia* L. in various diseases. There is, however, a need of further studies to evaluate other folk uses of these plants and to test other less known species for their potential therapeutic effects, and for searching of new bioactive components.

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