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Ethnobotany, phytochemistry, cultivation and medicinal properties of Garden sage (*Salvia officinalis* L.)

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Abstract
Sage (*Salvia officinalis* L.) is an important medicinal and aromatic herb, used as a raw material for various perfumery, pharmaceutical, food, and cosmetics industries. *S. officinalis* belonging to the family Lamiaceae is commercially cultivated for the essential oil and is grown throughout Europe and the United States, and in parts of Turkey, Yugoslavia, and Canada. Leaves are highly aromatic, used for extraction of essential oil, which contains more than 49 aromatic components. The principal components in the sage oil are 1, 8-cineole, camphor, α-thujone, β-thujone, α-humulene, rosmarinic acid, and quercetin. Traditionally garden sage has been used for the treatment of a multitude of ailments such as localized pain, rheumatism, convulsion, arthritis, vertigo, diarrhea, sclerosis, respiratory, metabolic and mental disorders. As the herbal medicines gaining importance in recent years, usage and systematic documentation of such herb are found essential. Thus an effort has been made to collect review about the study on chemistry, its cultivation, medicinal utilization besides its ethnobotanical documentation. Various pharmacological studies revealed that extracts from sage have shown to possess anti-oxidant, anti-diabetic, anti-inflammatory, anti-microbial, anti-cancer and hypolipidemic properties. There were several reports on in-vitro and animal studies confirming its potential cognitive property and its use on memory and nerve related disorders. Environmental conditions suitable for the plant growth, propagation methods, cultural practices, and harvesting methodology are also discussed in detail.

Keywords: Garden sage, *Salvia officinalis*, lamiaceae, ethnobotany, cognitive, rosmarinic acid

Introduction
Sage (*Salvia officinalis* L.) is a multipurpose culinary herb that belongs to the family Lamiaceae/ Labiatae and is known as garden sage or common sage or culinary sage. It is an aromatic perennial woody sub-shrub native to the northern Mediterranean region and widely distributed over the hillsides and shores of southern Europe. It is cultivated throughout Europe and the USA, including Spain, Italy, Yugoslavia, Greece, Albania, Argentina, Germany, France, Malta, Turkey, England and Canada [32, 83]. Its use as a culinary herb has facilitated its spread into many countries, and now it is cultivated throughout the world for dried leaves, used as raw material for medicine, perfumery and food industries [34]. Sage is predominantly recognized as a culinary herb in western cooking and was used in poultry stuffing, flavoring of meat, sausages, and fish. Essential oil of sage was used in perfumes, deodorants, insecticidal treatments, for thrush, gingivitis and as a calmative [83, 29]. The herb is mainly used to improve the cognition and also used in the treatment of cardiovascular diseases, excessive sweating, nervous disorders, depression, and cerebral ischemia and to reduce nursing mother's milk when weaning, also recommended for gargling infectious throat and acts as antiseptic for wounds [38, 59, 60].

Sage is a potential aromatic plant of both tropics and temperate region, grown for food, home remedies, and commercial pharmaceuticals. It is a multipurpose plant, on which several research studies were reported supporting its traditional utilization, biological effects, and mode of action. Thus, an effort has been made to explore the research on its traditional use, cultivation practices, chemistry and medicinal uses that have been reported for sage. Also, pharmacological research supporting its traditional uses and biochemical components of sage are presented and discussed. Environmental conditions suitable for the plant growth, propagation methods, cultural practices, and harvesting methodology are also discussed in brief.

Ethnobotany

The word 'sage' meaning 'wise' popularly used as folklore medicine represents the herb of eternity, home remedy, health, and sagacity. Traditional medicinal use of garden sage documented by different communities and regions are presented in Table 1. In Europe cultivation of sage has been reported since ancient times for cooking and healing purpose, with evidence of its medicinal properties dating back to the Middle Ages [60, 40]. Traditionally garden sage is used for the treatment of localized pain, rheumatism, convulsion, arthritis, vertigo, diarrhea, sclerosis, respiratory, metabolic and mental disorders [83, 56]. Sage infusion in boiling water has been used traditionally for the treatment of mild dyspeptic complaints, inflammations in the mouth and throat and relief of excessive sweating, skin diseases, and desolation [97]. Since ancient times, sage essential oil has been employed as a local styptic, antiseptic, anti-inflammatory, antifungal and antispasmodic, used in the treatment endocrine diseases, topical pain relief with a potential anti-diarrheal activity [53, 54]. Besides this, essential oil of sage has known for its stomachic, muscle relaxation, antimicrobial and styptic properties [27, 58, 84]. Sage leaf decoction was reported to germicidal properties helpful for treating pharyngitis, nutrient absorption and revitalize metabolic enzymes. Traditionally, ground leaf paste of sage is applied locally to relieve allergic swelling, insect bites and skin inflammation. Infusion of leaves is used as an anti-depressant and in hair oils and topical application to darken hair color. Sage tea is used for the treatment of cold, cough, removal of warts and poisonous snake bites [39, 67].

S. officinalis has been cultivated since ancient times in Greece and Greeks used to consider it as a panacea. Egyptians used this plant to improve fertility and Romans were familiar with sage tea as a stimulant drink. Hippocrates used to prescribe sage poultices to heal infected wounds, sores and torpid ulcers [102]. It is also used to be very popular among Chinese, who preferred it over ordinary tea in winter. Sage leaves and infused leaf decoctions used for controlling toothache, mouth ulcers, gum bleeding, foul breath, and fresh leaves chewed as mouth freshener in Brazilian folk medicine. They were also familiar with the usage of sage leaves to prevent leucorrhea and menstrual cramps and urinary tract infections. Tribal folks were reported to use sage leaves for cleaning teeth, gum and topical wounds and other skin disorders [16, 28]. Fresh sage leaf tea was a found to be a promising remedy for a plethora of ailments such as lung, gastrointestinal, mucosal and skin disorders in traditional Austrian medicine [96].

S. officinalis, a popular ethnomedicine of Europe was used for treating cognitive impairment, Alzheimer's disorder, indigestion, acidity, various dermatological conditions, excessive sweating and respiratory tract infections [2, 78]. In traditional Indian Siddha medicine, sage known as *Karpooravalli*, that has been used for the treatment of asthma, bronchitis, migraine, and rhinitis. It was reported in folklore medicines that the hot infusion of sage leaves was inhaled to relieve respiratory infections such as cough and cold [19, 94]. As a traditional folk medicine in Iran, sage leaves were used to increase digestion, as carminative, a mild sleep-inducing agent, painkiller, tonic and relieves spasm. The leaf decoction is used to treat oropharyngeal and gastrointestinal disorders [67]. It has been used in the traditional medicine of Jordan as antiseptic, anti-scabies, anti-syphilitic, anti-inflammatory, and is frequently used against a variety of skin diseases [1].

Table 1: Ethnobotany of garden sage (*S. officinalis*) documented at different regions of the world

Sl. No.	Region	Traditional use of Garden sage	Reference
1	Valencia region of Spain	As folk medicine: leaf decoction used as an appetizer, hypotensive and emmenagogue. Hot tea used for detoxification, cold, throat infections and skin diseases. Dry leaves – as a spice and essential oil extraction.	Frances *et al*., 2012 [26]
2	Greeks and Romans	As meat preservative, fresh and dry leaves as spice and appetite stimulant for easy digestion of fatty foods. Leaf tea for ulcers, sore throats, and laryngitis. Consumption of leaf decoction- enhance memory and brain power.	Petrovska, 2012 [80]; Zargari, 1990 [102]; Hamidpour *et al*., 2013 [40]
3	Brazil	Hydroalcoholic tincture and leaf tea are used to relieve stress, inflammation, prevent excessive bleeding and as a mouth freshener. Commonly used as condiment and beverage to increase memory power.	Garcia *et al*., 2016 [28]; Czygan *et al*., 2001[16]
4	Turkey, Serbia, and Iran	Flower, leaf and stem extracts – used as folk medicine as antiseptic in wounds, pharyngitis, mouth ulcers and consumed internally for dysmenorrhea. Leaf tea is used as stimulant, digestive, sedative and analgesic	Melo *et al*., 2012 [65] Miraj and Kiani, 2016 [67]
5	Jordan	Leaf extract – anti-bacterial, anti-inflammatory and anti-septic and sage hydrosol - used as veterinary medicine for mastitis	Alekish *et al*., 2017 [4]; Abu-Darwish *et al*., 2013 [1]
6	Europe and the Mediterranean region	Sage leaf tea – relieve stress, indigestion, bloating, heartburn, acidity, sore throat, and sunburn. Leaf extract- used for treating excessive sweating, bronchitis and Alzheimer's disease.	Ghorbani and Esmaeilizadeh, 2017 [29]; Perry *et al*., 1995[78]; Adams *et al*., 2007 [2]; Low *et al.*, 1994 [60]
7	South east Asia and India	Fresh leaves and decoction: anti-spasmodic, refreshing tea, hypotensive and used to treat respiratory disorders	Yadav and Mukundan, 2011 [99]; Devansh, 2012 [19]; Suneetha & Chandrakanth, 2006 [94]; Prakash, 1990 [83]
8	Latin America	Sage tea and essential oil – used to treat convulsion, nerve related disorders, and high blood pressure	Ghorbani and Esmaeilizadeh, 2017[29]; Walch *et al*., 2011 [97]; Lewis and Elvin-Lewis, 2003 [56]

Botany and cultivation

Among 900 different specis in the genus *Salvia*, the garden sage (*Salvia officinalis* L.) yields the highest essential oil and is commercially cultivated for centuries in the Old World for its food and healing properties [8]. It is a medium-sized perennial evergreen bushy herb or undershrub having a quadrangular and pubescent stem at the base, with many branches. The species can grow up to 60- 70 cm height with an erect growing branch more or less white woolly appearance. The opposite leaves petiolate, oblong, 2.5-6.0 cm long, crenulate, pubescent, wrinkled and light green to a silver gray color [85]. It blooms in early summer, and the flowers are blue, variegated with white and purple color, up to 3 cm long arranged in terminal spikes at distant whorls. Each spike composed of a few flowers in groups of 7-10, provided with ovate, deciduous bracts. The calyx is tubular and striated, with two lips, of which the upper has three acute teeth, the lower has two. Petals of the flowers fused with two cleft lips, a curved upper lip and three-lobed lower lip. Two filaments joined at base bent along the corolla with free anthers and a long curved bifid stigma. The highly aromatic camphor-scented showy flowers with abundant nectar are found to be attractive to butterflies, honey bees and sometimes to hummingbirds [5, 8].

S. officinalis could be grown in dry, hilly regions, on heavy clay soils, up to 750 m altitudes and found in a range of habitats including dry shrubby vegetation, dry meadows and rocky steppes. It prefers cool temperate to subtropical conditions prevailing warm, dry weather for its growth and development. Area getting ample of sunshine with fertile loamy soil in slightly acidic pH and proper drainage facility is ideal for sage cultivation. It could tolerate drought and poor soil fertility, but higher leaf biomass was produced with consistent water [62]. It is commonly propagated by seeds and also by layering, division, and stem cuttings. Though seed propagation is a more convenient and effective method of multiplication, seed dormancy is a major hindrance for rising of seedlings [73]. Very little information has been reported on seed priming and seedling production of sage, especially on organic cultivation practices. Higher seed germination in sage (78.5%) was reported, when they were treated with plant growth promoting rhizobacteria strain (*Pseudomonas putida*) compared to control (41.25%). Hydropriming of *S. officinalis* seeds found to increase germination, root length, shoot length and seedling vigor as compared to that of non-primed seeds [30]. For higher germination, bio-primed or hydro-primed seeds can be directly sown in the seedbeds on after the fall, when temperature start raising or could be started 45 to 60 days indoors before planting [17, 46]. Softwood stem cuttings in summer treated with auxin containing rooting hormones in sand-peat mixture found ideal for obtaining a rooting system strong enough to assure cutting development. Rooting of cutting in sage was good from spring to the end of autumn, later on, it reduced when the plants entered dormancy in winter [76].

The beginning of the spring season is the best time for planting of sage, and the rooted cuttings or seedlings are transplanted at 30-45 cm apart at a row distance of 90 cm. Plants should be pruned in summer for 2 to 3 times for developing robust, sturdy new shoots which help to accumulate intense aromatic compounds [24]. It takes around 10-12 weeks from transplanting to harvesting, and subsequent harvesting can be done at 60-70 days interval in a tropical and subtropical region. The shoots could be harvested two times during the growing season from the top 20-25 cm of the plants in temperate regions. Harvesting should be done before the plant flowers to obtain high-quality essential oils and a healthy crop could yield 1750-2250 kg/ha herbage in a year [23]. No pests were reporting in Sage if they were grown in well-aerated soils with good drainage facilities [62].

Chemistry

Among the different species of *Salvia*, Common sage, *S. officinalis* is known to contain the maximum amount of essential oil in leaves on a dry weight basis [6, 53]. The yield of essential oil from sage leaves reported to vary from 1.1 to 2.8% on dry weight basis, and it depends on environmental factors, such as average temperature, humidity, and rainfall [14, 57]. *S. officinalis* dry leaves from Rio de Janeiro reported yielding high quality of 2.3 percent essential oil through the hydro-distillation process [82].

The gas chromatography-mass spectrometry (GC/MS) analysis of sage essential oil was reported to contain α-thujone, camphor, α -pinene and β -pinene in principal amount compared to other components, and it was found to vary according to soil and climatic condition. Similar results were found in oils from Italy, Romania, Serbia and Montenegro, Brazil and Turkey [14, 50, 69, 81, 84, 95]. Hussein *et al*. analyzed the essential oil composition of *S. officinalis* grown in Egypt by GC/MS representing major volatile components of the oil extracted from fresh herb and found the presence of camphor (23.38%), α-thujone (22.82%), sclareol (10.46%), β-thujone (9.96%), 1,8-cineole (7.83%), γ-selinene (7.73%), α-humulene (5.59%), caryophyllene, (3.16%), borneol (3.06%), limonene (1.74%) and humulene epoxide (1.02%) [45]. Ben Khedher *et al*., evaluated the chemical composition of Tunisian *S. officinalis* essential oil and identified 97.97% of components as displayed in Table 2 [10]. It was characterized by the presence of 49 components with camphor (25.14%), α-thujone (18.83%), 1, 8-cineole (14.14%), viridiflorol (7.98%), β-thujone (4.46%) and β-caryophyllene (3.30%) as the major components, determined by GC/MS. Among them, the different terpenoid fractions of essential oil of *S. officinalis* are represented in Fig.1. The monoterpene fraction of oil amounted to 75.93% with oxygen containing monoterpenes as the largest group of this fraction (48.43%) followed by 17.4 percent sesquiterpene fraction [10].

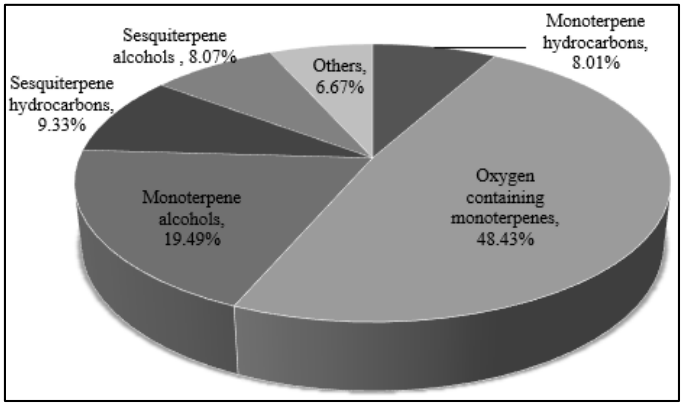

Fig 1: Terpenoid composition of the essential oil from leaves of *Saliva officinalis*

Table 2: The chemical composition of the essential oil from leaves of *S. officinalis* (Ben Khedher *et al*., 2017) [10]

Sl. No.	Name of the compound	%	Sl. No.	Name of the compound	%
1.	α-thujene	0.36	26.	α-bourbonene	0.12
2.	α–Pinene	0.84	27.	β-bourbonene	0.29
3.	Camphene	0.78	28.	α-Gurjenene	0.17
4.	Sabinene	0.30	29.	Sinularene	0.17
5.	β-Pinene	0.85	30.	Calarene	0.14
6.	β-Myrcene	1.93	31.	β-Caryophyllene	3.30
7.	α-Terpinene	0.30	32.	Aromadendrene	0.08
8.	1.8-Cineole	14.14	33.	α-Humulene	2.48
9.	Eugenol	0.28	34.	Allo-Aromadendrene	0.06
10.	Limonene	1.43	35.	Germacrene D	0.17
11.	γ-Terpinene	0.61	36.	α-amorphene	0.30
12.	α-Terpinolene	0.52	37.	Valencenne	0.05
13.	Linalool	0.39	38.	β-Himachalene	0.95
14.	α-Thujone	18.83	39.	cis-Calamenene	0.08
15.	β-Thujone	4.46	40.	γ–Cadinene	0.12
16.	Camphor	25.14	41.	Δ-Cadinene	0.45
17.	Borneol	2.81	42.	α-Calacorene	0.23
18.	Terpinen-4-ol	0.74	43.	β-Caryophyllene oxide	0.06
19.	α-Terpineol	1.33	44.	Longibornene	0.04
20.	Naphtalene	0.20	45.	Viridiflorol	7.98
21.	Myrtenol	0.30	46.	T-Muurolol	0.09
22.	Bornyl acetate α	1.05	47.	Thujyl alcohol	0.17
23.	Carvacrol	0.18	48.	ent-pimara-8,15- diene	0.13
24.	β-Patchoulene	0.42	49.	Epimanool	1.18
25.	α-copaene	0.07		Identified components (%)	97.97

The pharmacological properties of sage essential oil were found to be dependent on vital volatile components like thujone, camphor, and 1, 8-cineole. Studies have shown that these contents might vary according to the cropping area and soil conditions. As the plants grow concentration of camphor and thujone seems to increase over some time, till the plants show a wilting symptom [15, 84]. Quantitative and qualitative constituents of sage essential oil found to vary as per prevalence of surrounding environment, critical day length, temperature fluctuation, and light intensity. One of the major compounds 1, 8-cineole content reported to reduce as the vegetative stage advanced and camphor appeared to be at its apex in August month and α- and β-thujone were maximum at the end of the growing season showing seasonal variation in production of secondary metabolites in sage [36, 64].

There were around 160 polyphenolic compounds were identified from sage leaves with a wide range of different phenolic acids and flavonoids. Various phenolic compounds such as rosmarinic acid, caffeic acid and its derivatives, salvianolic acids, sagernic acid, lithospermic acids, sage coumarin, and yunnaneic acids have been reported from polyphenol analysis of *S. officinalis* leaf extract. The six most important flavonoids comprise hispidulin, luteolin 7-O-glucoside, apigenin, cirsimaritin, kaempferol and quercetin [61]. The study also reported that environmental factors, such as average temperatures and rainfall found to influence the phenolic compound biosynthesis in sage leaves [31].

Polyphenols and phenolic composition in hydro-alcoholic extracts of *S. officinalis* are presented in Table 3. The results of the study showed that there was a wide variation in on total polyphenol content where the values ranged from 321.23-404.21µg/ml. The main polyphenols identified in the analyzed extracts were rosmarinic acid, coumaric acid, caffeic acid, myricetin, and quercetin. The extract also contained 1.04-1.72 mg/ mL of proteins, 26.01- 99.48 mg/mL of flavones and 35.05- 138.16 µg/ mL of sugars [75]. Caffeic acid derivatives are considered to be the major phenolic acids in Salvia species, which acts as a building block of various plant metabolites. In the biochemistry of the Lamiaceae family, caffeic acid plays a central role and remains in subdued form as rosmarinic acid [49].

Table 3: The concentration of polyphenols and phenols in hydro-alcoholic extracts of *Salvia officinalis* expressed in µg/g (Neagu *et al*., 2014) [75]

Sl. No.	Polyphenols	Concentration (µg/g)
1.	Gallic acid	0.85
2.	Chlorogenic acid	0.50
3.	Caffeic acid	1.91
4.	Rutin	1.30
5.	Coumaric acid	4.50
6.	Ferrulic acid	1.21
7.	Rosmarinic acid	17.25
8.	Myricetin	1.45
9.	Quercetin	2.80

Medicinal uses and pharmacological studies

There are a significant number of uses of sage comprising herbal remedies, aromatic, and pharmaceutical. The clinical studies, in-vitro and animal studies on different medicinal properties of sage are discussed and presented in brief under following subsections.

Anti-oxidant property

The antioxidant properties of sage have been studied in detail and were predominantly due to the existence of terpenoids compounds, phenolic acids, and flavonoids. It was found that salvianolic acid which is an indistinct form of rosmarinic acid, isolated from the sage leaves have great antioxidant potential with a very significant free radical scavenging property [61]. Hussain *et al*. revealed that higher concentration of 1, 8-cineole in the sage essential oil is responsible for high radical scavenging property intern with higher antioxidant capacity [44]. Though the extent of antioxidant activity varied across different *Salvia* species and extraction methods used, the highest antioxidant activity was recorded in ethanolic extract

of *S. officinalis* [44, 93]. There was evidence of *S. officinalis* containing the most potent antioxidant constituents such as caffeic acid, rosmarinic acid, carnosol, carnosic acid, followed by rosmanol, rosmadial, genkwanin, and cirsimaritin. The radical scavenging activity of these compounds was comparable to that of α-tocopherol [20, 70]. The inhibition activity of superoxide dismutase was recorded 20 times more than trolox in rosmarinic acid derivatives. Other flavonoids of *S. officinalis* particularly quercetin and rutin were also reported to have potent antioxidant activities in addition to rosmarinic acid, [7]. The study on *in vitro* antioxidant activity of methanolic extracts of *S. officinalis* L. leaves recorded the IC_{50} (Inhibition concentration 50) value from 5.52 mg/mL to 8.79 mg/mL, suggesting its use in the development of free radical scavengers and antioxidant agents [99]. Walch *et al*. chemically analyzed the sage tea for polyphenolic content and antioxidant potential, which varied between 0.4 to 1.8 mmol trolox equivalents/100mL and was highly dependent on rosmarinic acid and its derivatives [97].

A study on the effect of the sage extract on growth performance, blood parameters, oxidative stress and DNA damage in partridges resulted in a significant decrease in linear DNA damage on dose-dependent manner. It was concluded that supplementing sage extract in the partridge diet at 5-7.5 ml/kg does not lead to a negative effect on the growth performance of these birds [101]. The concentrated hydro-alcoholic extracts of *S. officinalis* showed promising levels of DPPH radical scavenging activity (42.12%–70.82%), and it was mainly due to the presence high quantity of polyphenols in sage leaves [75]. Ben Khedher *et al*. studied the anti-oxidant activity of Tunisian *S. officinalis* essential oil [10]. The level of antioxidant activity, namely 2, 2-diphenyl-1-picrylhydrazyl (DPPH) radical-scavenging (IC_{50}= 6.7 mg/mL), linoleic acid peroxidation (IC_{50}= 9.6 mg/mL) and ferric reducing assays (IC_{50}= 28.4 mg/mL) were relatively moderate.

Anti-microbial property

Monoterpenes and terpenoid compounds were found to be responsible for the antimicrobial property of *S. officinalis* herb. Among the terpenoids, camphor, thujone, and 1,8-cineole were shown to have antibacterial effects against *Aeromonas hydrophila*, *Aeromonas sobria, Bacillus megatherium*, *B. subtilis*, *B. cereus* and *Klebsiella oxytoca* [18, 95]. A strong anti-bacterial activity has been recorded against Gram-positive and Gram-negative bacteria when they were treated with alcoholic extract and essential oil of sage. Among Gram-positive pathogens, *Bacillus cereus*, B. *megaterium, B. subtilis, Enterococcus faecalis, Listeria monocytogenes* and *Staphylococcus epidermidis* exhibited significant sensitivity to sage oil. Screening of sage essential oil resulted in good to moderate inhibitions for most of the tested microorganisms [12, 42, 69].

The study on assessment of sage essential oil from Jordan resulted in a significant antifungal activity against dermatophyte strains and significantly inhibited nitric oxide production stimulated by lipopolysaccharides in macrophages, without affecting cell viability, in concentrations up to 0.64 μL/ml. As the bioactive concentrations sage essential oil has not been affected mammalian macrophages and keratinocytes viability revealed a significant *in vitro* anti-inflammatory activity that makes the herb suitable for skin care formulations, cosmetic and pharmaceutical purposes [1]. It also exhibited important insecticidal activity against *Spodoptera littoralis* larvae and *Tribolium castaneum* adults with LC_{50} values of 55.99 and 97.43 µl/L air, respectively. The oil also exhibited promising antimicrobial and antifungal activities and seems to have a potent fumigant activity against Lepidoptera and Coleoptera pests. The effect of the oil on seeds germination and growth showed different activities against radical and hypocotyl elongation of the tested species [10].

Cognitive property

Various studies on animal and laboratory experiments supported that *S. officinalis* contain a great number of active ingredients that enhance cognitive property and protect against neurodegenerative disease. Since time immemorial, sage has been used for memory restoration, cognitive impairment and Alzheimer's disease [79, 22]. The presence and activation of Acetylcholinesterase (AChE) enzyme in the body degrades the acetylcholine which acts as a neural signal transmitter. Sage essential oil has shown to inhibit 46% of Acetylcholinesterase activity at a concentration of 0.5 mg/ml [25]. *In vitro* and animal studies have revealed that aqueous and ethanolic extract of garden sage lowered AChE activity with more significant effects on butyrylcholinesterase [52, 91, 92, 87]. Phenolic diterpenes isolated from a sage plant long with 7a-methoxyrosmanol and isorosmanol were seemed to develop AChE inhibition activity. Rosmarinic acid, carnosic acid, and quercetin, the active phenolic constituents of sage essential oil were also reported to suppress the AChE activity [63, 66, 89]. Hence sage could be considered as one of the potential therapeutic agents for treating Alzheimer's disease by inhibiting acetylcholinesterase enzyme.

A study on garden sage showed improved memory and cognition with the increase of the dosage, along with elevated mood as well as alertness, calmness, and contentedness [52]. In a randomized, double-blind clinical study, the ethanolic extract from sage was found to be a promising drug for the management of Alzheimer's disease without any adverse effect on patients due to the intake of sage [3]. Rosmarinic acid present in sage has exhibited neuroprotective, anti-oxidative, and anti-apoptotic effects against Aβ (amyloid beta plaques) toxicity and this could contribute to the neuroprotective effect of sage. A potential aromatic compound from sage, which is known as rosmarinic acid helped for significantly increasing memory factor and also it is found to be a low toxic natural compound and a reliable therapeutic agent used in the treatment of Alzheimer's disease [47, 71, 72].

Administration of ethanolic extract of sage (50mg/kg) significantly potentiated memory retention in rats and enhanced the interaction with muscarinic and nicotinic cholinergic systems that are involved in the memory retention process [22]. The primary flavonoid content of sage hydroalcoholic extract, rosmarinic acid has proved to enhance cognition in healthy rats and prevent learning and memory deficits induced by diabetes enhancing antioxidant defense systems [41]. Clinical trials on animal studies confirmed the enhancement of cognitive performance in healthy participants and as well as patients with cognitive impairment or dementia and it also helped to attenuate morphine-induced memory impairment [33, 68].

Anti-diabetic property

There was a significant reduction in the blood sugar, and cholesterol levels in patients treated with *S. officinalis* extract as compared to control group, and there were no significant changes in glycosylated hemoglobin [9, 21]. Rosmarinic acid significantly increased the activities of pancreatic catalase,

glutathione peroxidase, glutathione-S-transferase, and superoxide dismutase, which showed reduced insulin resistance in streptozotocin-induced diabetic rats [35]. Eight diterpenes were isolated and identified including a new abietane diterpene being the epirosmanol ester of 12-O-methyl carnosic acid and 20-hydroxyferruginol, which was isolated from *S. officinalis* for the first time, as well as viridiflorol, oleanolic acid, and α-linolenic acid. 12-O-methyl carnosic acid and α-linolenic acid were able to significantly activate peroxisome proliferator-activated receptor gamma (PPARγ) showing potential anti-diabetic activity [13]. Methanolic extract of sage improved insulin sensitivity, inhibited lipogenesis in adipocytes and reduced inflammation as judged by plasma cytokines. Hence it could be used as an alternative in pharmaceuticals for the treatment of diabetes and associated inflammation [11].

Anti-inflammatory effect

Sage essential oil exerted a topical anti-inflammatory effect by significantly inhibiting croton oil-induced ear edema, and sage essential oil doses tested significantly inhibited leukocyte chemotaxis induced by casein and reduced the number of rolling, adhesion and leukocytes migration to spermatic fascia after the inflammatory stimulus [65]. An investigation on anti-inflammatory activity of sage revealed that the presence of caffeic acid, rosmarinic acid and ursolic acid in sage oil were responsible for decreasing swelling and skin infections [51, 74]. Study on the intramammary infusion of sage essential oil to ewes affected with subclinical mastitis resulted in a significant decrease in mastitis, 24 h, and 48 h post-treatment. In addition, milk fat and lactose were increased in animals that received the essential oil [4].

Anti-cancer property

Sage has been used as a potential anti-cancer drug and research studies were reported on various cancer cell lines, *in-vitro* and animal models. Presence of *trans*-caryophyllene, which is the main component of the sesquiterpene fraction in *S. officinalis*, showed strong cytotoxic activity against the human melanotic melanoma and renal adenocarcinoma cells. Also, α-humulene, present in sage extract reported having a powerful cytotoxic effect on human prostate cancer LNCaP cells [37, 58].

Xavier *et al*. reported that the aqueous extract of Sage and rosmarinic acid inhibited cell proliferation and ERK phosphorylation in human colon carcinoma-derived cell lines due to the inhibition of MAPK/ERK pathway [98]. Several studies on inhibition of growth of various human cancer cells were demonstrated the reliable use of rosmarinic acid present in sage by suppression of small cell lung carcinoma, breast adenocarcinoma, colon carcinoma, chronic myeloid leukemia, prostate carcinoma, hepato-cellular carcinoma cells [100]. The potential pro-apoptotic activity of the sage essential oils from different regions related to the active α- and β-thujone isomers associated to the synergism of other compounds present in the essential oil such as camphor [86]. Anti-cancer property of sage was also reported in oral cavity squamous cell carcinoma cells, cell lines of cervix adeno carcinoma (HeLa), insulinoma (RINm5F), laryngeal carcinoma (Hep-2), lung carcinoma (A549), melanoma (A375, M14, A2058, B16) and breast cancer (MCF-7) [28, 48, 55, 90].

Hypo-lipidemic activity

Clinical and research studies have confirmed the use of sage extract for reducing blood cholesterol level. The extract of *S. officinalis* resulted in activation of peroxisome proliferator-activated receptor gamma (PPARγ), which helps for gene regulation of lipid peroxidation and energy metabolism. This, in turn, improved the high-density lipoprotein (HDL) content in the blood, and at the same time it reduced the low-density lipoproteins (LDL), and it also reduced the fat contents under the adipose tissue. Hence it could be effective in the prevention of cardiovascular disease due to the prevention of LDL cholesterol oxidation [13, 88]. Hernandez-Saavedra *et al*. (2016) reported that injection of sage leaf decoction reduced serum triglycerides, total cholesterol and low-density lipoproteins (LDL) levels in diet-induced obese rats and the hypolipidemic activity of garden sage was due to the activity of flavonoids, rosmarinic acid, and ellagic acid [43].

Cytotoxicity

Though the herb, *S. officinalis* has been used traditionally since ancient times, there were no reports of the adverse effects associated with intake of the herb extract and was found to be well tolerated by healthy adults [3, 79, 88]. The limited usage of sage for the household purpose was found very safe, and there were some side effects were noticed on using sage leaves an excessive amount or by usage of sage essential oils rich in thujone content [77, 97].

Conclusion

Sage (*S. officinalis*) has been conventionally used for the treatment of various ailments since ancient times at various parts of the world. Immense usage of sage including culinary, medicinal, aromatic and pharmaceutical makes it most popular among essential oil-bearing plants. With an increasing demand over good quality organically grown sage, there is a need for further research to standardize the organic cultivation techniques including seed priming to economically viable extraction and processing methods. The quality of the herb and essential oil content is highly variable depending on environmental conditions and harvesting time. Findings from *in-vitro* and several clinical studies supporting the evidence of its medicinal uses such as cognitive, anti-diabetic, hypo lipidemic, anti-cancer and anti-inflammatory properties. Though it is a very potential and commonly available herb for pharmaceutical industries, there is a need to develop extraction and isolation protocols for testing the efficacy of the herb. The various biologically active compounds in sage responsible for its pharmacological properties and the extent of cytotoxicity are still unknown and hence there is a lot of scope to conduct drug dosage studies in the future.

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