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Chemistry, Pharmacology, and Medicinal Property of Sage (*Salvia*) to Prevent and Cure Illnesses such as Obesity, Diabetes, Depression, Dementia, Lupus, Autism, Heart Disease, and Cancer

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ABSTRACT

For a long time, sage (*Salvia*) species have been used in traditional medicine for the relief of pain, protecting the body against oxidative stress, free radical damages, angiogenesis, inflammation, bacterial and virus infection, etc., Several studies suggest that sage species can be considered for drug development because of their reported pharmacology and therapeutic activities in many countries of Asia and Middle East, especially China and India. These studies suggest that *Salvia* species, in addition to treating minor common illnesses, might potentially provide novel natural treatments for the relief or cure of many serious and life-threatening diseases such as depression, dementia, obesity, diabetes, lupus, heart disease, and cancer. This article presents a comprehensive analysis of the botanical, chemical, and pharmacological aspects of sage (*Saliva*).

Key words: Pharmacological property, Sage (*Salvia* species), Traditional remedies

INTRODUCTION

The genus *Salvia*, commonly known as sage, is the largest member of Lamiacea or mint family containing over 900 species throughout the world.[1,2] The plants are mostly aromatic and perennial [Figures 1 and 3], with flowers in different colors [Figure 2].[3] Many species of *Salvia*, including *Salvia officinalis* (common sage), are native to the Mediterranean region and some of the *Salvia* species have been used worldwide as flavoring spices as well as traditional herbal medicine.[3,4]

Sage tea has been traditionally used for the treatment of digestive and circulation disturbances, bronchitis, cough, asthma, angina, mouth and throat inflammations, depression, excessive sweating, skin diseases, and many other diseases.[5-7] *Salvia* essential oils have been used in the treatment of a wide range of diseases like those of the nervous system, heart and blood circulation, respiratory system, digestive system, and metabolic and endocrine diseases. In addition, sage essential oil has been shown to have carminative, antispasmodic, antiseptic, and astringent properties.[8,9]

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The essential oil of *Salvia* species has various compositions depending on the genetic, climatic, seasonal, and environmental factors.[10] Some chemical compounds like flavonoids, terpenoids, and essential oils are present in different species of *Salvia* [Figure 4].[3] Essential oils are very important sources for the screening of anticancer, antimicrobial, antioxidant, and free radical scavenging agents.[11] *S. officinalis* (common sage) is considered to have the highest amount of essential oil compared to the other species of *Salvia*.[5,12]

In all analyzed samples of *S. officinalis*, the major components, although present in different concentrations, are: 1,8-cineole, camphor, borneol, bornyl acetate, camphene, α- and β-thujone, linalool, α- and β-caryophyllene, α-humulene, α- and β-pinene, viridiflorol, pimaradiene, salvianolic acid, rosmarinic acid, carnosolic acid, ursolic acid, etc.[7,12] Studies have shown that some biological properties of the essential oil of *Salvia* depend on camphor, 1,8-cineole, α-thujone, and β-thujone.[9] The essential oil of sage contains about 20% camphor, and as the leaves expand, the camphor content also increases.[13] In a study, the most powerful scavenging compounds were reported to be α-thujone and β-thujone, bornyl acetate, camphor, menthone, and 1,8-cineol in the essential oil.[11] In the same study, the essential oil of *Melissa officinalis* and *S. officinalis* showed better antioxidant activities than some other Lamiaceae plants.[11]

Sage is also a natural source of flavonoids and polyphenolic compounds [Figure 5] (e.g., carnosic acid, rosmarinic acid and caffeic acid) possessing strong antioxidant, radical-scavenging, and antibacterial activities.[14] The majority of the phenolic acids in *Salvia* species are derivatives of caffeic acid which is the building block of a variety of plant metabolites.[15] Caffeic acid plays a central role in the biochemistry of the Lamiaceae plants, and occurs mainly in a dimer form as rosmarinic acid.[15] Carnosic acid and rosmarinic acid, which are present at high concentrations in the extract of sage plants, have shown strong antioxidant properties.[16] Ursolic acid, also a component of sage, has strong anti-inflammatory properties, and in sage preparations, it is considered as a quality control measurement for the anti-inflammatory effects of different solutions.[17]

COMMON NAMES

S. officinalis has numerous common names. Some of the best known names include sage, common sage, garden sage, golden sage, kitchen sage, true sage, culinary sage, dalmatian sage, and broadleaf sage. Cultivated forms include purple sage and red sage. In Turkey, *S. officinalis* is widely known as adaçayı, meaning "island tea." In the Levant, it is called maramia.

Figure 1. *Salvia officinalis*

Figure 2. *Salvia officinalis* "sage flowers"

Figure 3. *Salvia officinalis* "sage leaves"

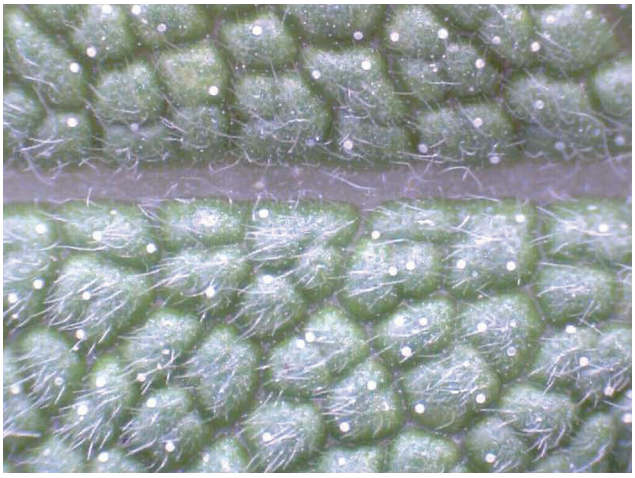

Figure 4. Sage leaf – trichomes are visible

CHEMICAL COMPOSITION

In the commonly known form sage of *S. officinalis*, a total of 28 components were identified [Table 1]. The principal components in the sage oil were 1,8-cineole, camphor, α-thujone, β-thujone, borneol, and viridiflorol. The chemotypes of sage were not determined in the investigated samples. The concentrations of the main compounds in the drugs obtained from different types of sage and at different locations varied about the same range as the concentrations of these compounds in the oils of drugs obtained from other countries. The comparatively high concentration of toxic thujones seems to be characteristic of sage leaves cultivated in different locations as well.

Table 1. Essential oil composition (% of major components) of sage *Salvia officinalis* collected as a sample[5]

Compound*	*S. officinalis***	*S. officinalis****
(1*R*)-(+)-α-Pinene	3.70	4.50
(−)-Camphene	2.60	5.00
β-Pinene	6.00	5.20
Sabinene	-	0.30
β-Myrcene	3.00	3.50
α-Terpinene	-	0.40
(*R*)-(+)-Limonene	-	-
1,8-Cineole	62.0	55.0
γ-Terpinene	0.30	0.50
P-Cymene	0.60	0.60
Terpinolene	-	0.20
(−)-α-Thujone	1.38	1.80
β-Thujone	0.72	1.50
Camphor	8.0	10.0
(−)-Linalool	0.80	0.80
Linalyl acetate	0.60	0.30
(−)-*Trans*-caryophyllene	2.00	1.00
Monoterpene	1.26	1.10
(+)-Menthol	-	-
Borneol	5.00	4.50
α-Terpineol	0.20	-
Geranyl acetate	0.30	-
Geraniol	0.10	0.25
Phytol	0.18	-
Thymol	0.80	0.70
Carvacrol	0.20	0.40
Farnesol	0.20	-
Trans, trans-Farnesol	0.06	0.15
Total components	45	30

*Compounds of essential oil extracted from fresh green leaves and flowering top; ***S. officinalis* L. collected at 100 m above the sea level; ****S. officinalis* L. collected at 500 m above the sea level

ANTIOXIDANT ACTIVITY

Antioxidants play a very important role in protecting the body against the oxidative stress and free radical induced damages which are the cause of various ailments such as diabetes, heart diseases, cancer, brain dysfunction, weakened immune system, etc.[18]

In a study conducted on the antioxidant activity of many plant extracts, like sage (*S. officinalis*), it was found that the phenolic and flavonoid compounds are mainly responsible for the antioxidant and free radical scavenging effects of these plants.[18,19] Phenolic compounds such as carnosol, carnosic and rosmarinic acids, rosmadial, rosmanol, epirosmanol, methyl carnosate, and luteolin-7-*O*-β-glucopyranoside have a high antioxidative activity and are usually extracted from sage with ethanol.[20] The phenolic compounds can either stimulate endogenous antioxidant defense systems or scavenge reactive species.[21]

The antioxidant properties of sage have been studied intensively, and are found to be related to the presence of rosmarinic acid and carnosic acid.[22,23] In addition, salvianolic acid, which is a rosmarinic acid dimer isolated from the sage extract, showed a high antioxidant activity and is a very significant scavenger of free radicals [Figure 6].[23] The aqueous extract of *S. officinalis* has been shown to have antioxidant and antiviral effects. In a study, it was observed that after drinking sage tea (common sage) for 2 weeks, the liver antioxidant status improved.[24]

MEMORY

Amongst many herbal extracts, *Salvia* species are known for the beneficial effects on memory disorders, depression, and cerebral ischemia.[25,26] *S. officinalis* (common sage), *Salvia lavandulaefolia* (Spanish sage), and *Salvia miltiorrhiza* (Chinese sage) have been used for centuries as restoratives of lost or declining mental functions such as in Alzheimer's disease (AD).[25-27] In AD, the enzyme acetyl cholinesterase (AChE) is responsible for degrad-

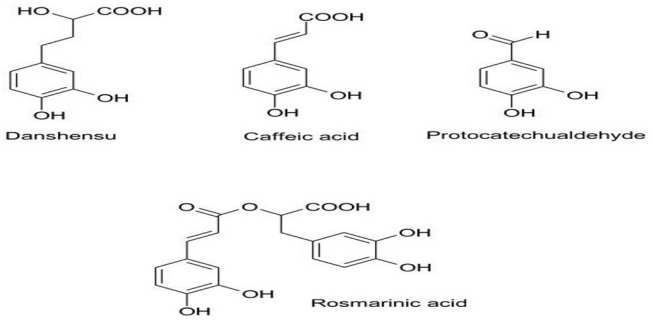

Figure 5. Danshensu and monoterpenoids from *Salvia miltiorrhiza*. All these compounds contain catechol functionalities

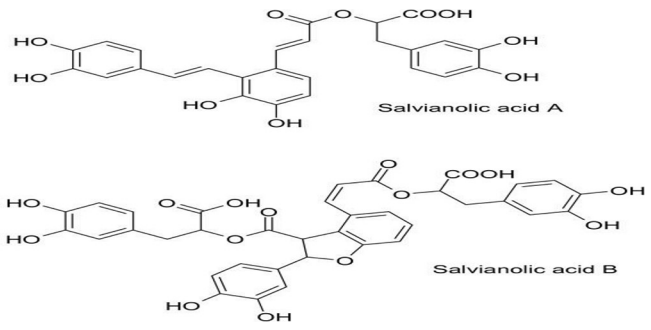

Figure 6. Salvianolic acids from *Salvia miltiorrhiza*. All these compounds contain catechol moieties

ing and inactivating acetylcholine, which is a neurotransmitter substance involved in the signal transferring between the synapses. AChE inhibitor drugs act by counteracting the acetylcholine deficit and enhancing the acetylcholine in the brain.[28] Essential oil of *S. officinalis* has been shown to inhibit 46% of AChE activity at a concentration of 0.5 mg/ml.[28]

A study shows that *S. officinalis* improves the memory and cognition, and with increasing dosage, the mood gets elevated as well as alertness, calmness, and contentedness increase.[29] A randomized, double-blind clinical study has shown that an ethanolic extract from common sage (*S. officinalis*) as well as Spanish sage (*S. lavandulaefolia*) is effective in the management of mild to moderate AD, and study on patients did not show any adverse effect on them on taking sage.[30,31] Administration of *S. lavandulaefolia* (Spanish sage) has been reported to be effective in improving the speed of memory and mood. *Salvia* essential oil also has been reported to improve immediate word recall.[27]

A number of studies have investigated the effects of the aromas of plant essential oils on cognition and mood.[32] The aroma of *S. officinalis* produced significant enhancement effect in the quality of memory factor derived from Cognitive Drug Research (CDR) system.[32] The findings suggest that the aromas of essential oils of *Salvia* species have some, but not all the effects found following the oral consumption of the herb.[32] The antioxidant and anti-inflammatory properties of the *S. officinalis* or *S. lavandulaefolia* may offer a long-term protection in the pathogenesis of dementia.[29] Also, the mood-enhancing properties of the herb may have applications in the treatment of advanced dementia, in which disturbed mood and agitation feature as a major problem.[29] There is no report of negative side effects associated with *S. officinalis* or *S. lavandulaefolia* despite many years of usage.[29]

The cytoprotective effect of sage against Aβ (amyloid beta plaques) toxicity in neuronal cells has also been proven by the data presented in a study which provides the pharmacological basis for the traditional use of sage in the treatment of AD.[31] Rosmarinic acid as a component of sage has shown neuroprotective, antioxidative, and anti-apoptotic effects against Aβ toxicity, and this could contribute, at least in part, to the neuroprotective effect of sage. Therefore, it is possible that rosmarinic acid, the very low toxic natural compound, could be used as a therapeutic agent in the treatment of AD.[31]

DIABETES

S. officinalis has been used as a traditional remedy against diabetes in many countries and its glucose-lowering affects have been demonstrated in animal studies.[33] In a study, it was found that methanolic extracts of *S. officinalis* significantly decreased serum glucose in type I diabetic rats without affecting pancreatic insulin production.[33] An aqueous extract of *S. officinalis* has been found to exhibit insulin-like activities.[33]

In a study, drinking of sage tea (common sage) (300 ml, twice a day) showed increase in antioxidant defenses and improved the lipid profile, without causing any hepatotoxicity or inducing any adverse affects such as changes in blood pressure, heart rate, and body weight, which may indirectly improve the diabetic condition.[21] Tea infusions of *S. officinalis* have shown to be as effective as metformin, which is an oral anti-diabetic drug used for the treatment of type II diabetes, and act by reducing liver glucose production as well as increasing the action of insulin.[33] In many studies, the sage extract was found to have hypoglycemic effect in diabetic animals and further researches need to consider the additional therapeutic effects of this plant in future.[34]

CANCER

Cancer is characterized by abnormal growth of cells which tend to proliferate in an uncontrolled way, and in some cases, spread to other parts of the body.[35] The important factor in proliferating and spreading of cancer cells is the ability of tumors to produce a large number of new blood vessels, which is known as angiogenesis.[36] Most primary solid tumors are dependent on angiogenesis for survival, growth, invasion, and metastasis.[36] It was found in a study that *S. officinalis* extract at pharmacological concentrations inhibits angiogenesis *in vivo*, which could be a novel starting point for the development of a new anti-angiogenic drug.[35] Ursolic acid found in sage effectively inhibits angiogenesis, invasion of tumor cells, and metastasis, and suppresses the lung colonization of B16 melanoma cells *in vivo*.[37]

Colorectal cancer (CRC) is a common type of cancer and a significant cause of mortality in Western societies. It develops by genetic and epigenetic alterations which transfer normal colon cells to proliferating cells.[38] This study has shown that dietary compounds can change the epigenetic status. Many food plants are rich in bioactive compounds and have shown to possess anticancer properties.[38] The effect of drinking sage (*S. officinalis*) herbal tea was studied on the prevention of colon cancer in rats. It was found that *S. officinalis* water extract significantly decreased the oxidative H_2O_2-induced DNA damage *in vitro*.[38]

Some diterpenoids isolated from the roots of *S. officinalis* have been found to have cytotoxic and DNA-damaging activity in human colon carcinoma Caco-2 cells and human hepatoma HepG2 cells in *in vitro* conditions.[10] The sesquiterpene fraction of *S. officinalis* containing α-humulene demonstrated a strong cytotoxic activity in human prostate carcinoma LNCaP cells.[10] Also, *trans*-caryophyllene, which is the main component of the sesquiterpene fraction in *S. officinalis*, shows high cytotoxic activity against the melanotic melanoma and renal adenocarcinoma cells.[8] Presence of α-humulene as a component of *S. officinalis* demonstrated a strong cytotoxic activity on the human prostate carcinoma LNCaP cells.[8]

Salvia libanotica (Lebanese sage) is one of the largely used sage species in traditional medicine, which has been used for many years to cure diseases such as abdominal pains, headaches, indigestion, and heart disorders.[2] The oil extract of this species was shown to possess strong antimicrobial and antitumor effects.[2] The components of Lebanese sage essential oil were identified by gas chromatography, and three of the components which contain on average 9.1% camphor (Ca), 1.3% α-terpineol (Te), and 1.1% linalyl acetate (Ly) were found to be responsible for the oil's antibacterial, antifungal,

anti-inflammatory, and antitumor effects.[2] In this study, Ly, Te, and Ca synergistically induced cell cycle arrest and apoptosis resulting in the inhibition of the growth of human colon cancer cell lines, HCT-116 (p53+/+ and p53−/−), without any effect on the growth of normal human intestinal cell lines.[2]

CHOLESTEROL

The metabolite profile of *S. miltiorrhiza* (SM) or Chinese sage is similar to that of common sage, and recently, it was shown that an extract of SM was able to lower the plasma cholesterol, low density lipoprotein (LDL), and triglycerides (TGs), as well as increase the high density lipoprotein (HDL) levels in lipidemic rats.[33]

The extract of *S. officinalis* is found to activate peroxisome proliferator-activated receptor gamma (PPARγ) which is a regulator of genes involved in energy spending as well as lipid and glucose metabolism, and its activation improves the HDL/LDL ratio and lowers TGs in serum, reduces insulin resistance, and reduces the size of adipose (fat) tissue.[33]

Extracts from some sage species have been shown to be effective in the prevention of cardiovascular disease due to, at least in part, prevention of LDL-cholesterol oxidation.[21]

OBESITY

Overweight and obesity are recognized to cause a number of abnormalities including Type II diabetes, dylipidemia, hypertension, etc., which are all important risk factors in developing serious diseases such as cardiovascular diseases, chronic kidney diseases, and many others.[39] To regulate fat absorption, the effective way is to reduce body weight and obesity.[40]

Pancreatic lipase is well known to play an important role in lipid digestion.[40] In several studies on anti-obese components from natural medicine, the effects of *S. officinalis* and its active components on the pancreatic lipase activity and lipid digestion were investigated.[41] The methanolic (MeOH) extract from the leaves of *S. officinalis* L. significantly inhibited the pancreatic lipase activity and suppressed serum TG elevation in olive oil–loaded mice.[41] Carnosic acid and carnosol are two of the diterpenes isolated from the methanolic extract of *S. officinalis* with an inhibitory activity on pancreatic lipase. Carnosic acid also significantly inhibited TG elevation in olive oil–loaded mice and reduced the gain of body weight and the accumulation of epididymal fat weight in high fat diet–fed mice after 14 days.[41] In the course of several studies on anti-obese components from natural medicine, the extract of *S. officinalis* leaves showed inhibitory effect against the pancreatic lipase activity and eventually was effective in reducing body weight and obesity.[41]

HOT FLASHES

Menopause is considered as a physiological adjustment process to an altered hormonal balance.[42] Menopausal symptoms include hot flashes, insomnia, night-time sweating, dizziness, headaches, and palpitations. These symptoms reflect adaptation of the body to estrogen deprivation which affects various central neurotransmitters.[42]

Sage (*S. officinalis*) has been traditionally used to treat sweating and menopausal hot flashes, as well as to alleviate the associated menopausal symptoms.[42] The efficacy of sage for the treatment of hot flashes during menopause was proven by a multi-center open clinical trial.[6] A fresh sage preparation demonstrated clinical value in the treatment of hot flashes and associated menopausal symptoms.[42] Once-daily application of the fresh sage extract demonstrated good clinical value in terms of safety, efficacy, and tolerability in the treatment of menopausal hot flashes and climacteric symptoms, validated by statistical analysis and the clinically relevant verdict of patients and physicians.[42] The study findings provide a scientific rationale for sage's use in folk medicine, offering a valuable option for patients and healthcare providers seeking alternative approaches for the treatment of menopausal hot flashes and climacteric complaints.[42]

ANTIBACTERIAL ACTIVITY

A study conducted on the antibacterial effect of sage against selected food spoiling bacteria *in vitro* indicates that the sage aqueous extract exerted significant antibacterial activity and it was most effective against *Bacillus mycoides, Bacillus subtilis, Enterobacter cloacae,* and *Proteus* sp.[24] This has made sage essential oil a good alternative to the traditional antibiotics as well as food preservatives.[5]

The findings of a study support the view that the hydroalcoholic extract of *S. officinalis* has growth inhibitory effect on some dental caries causing bacteria such as *Streptococcus mutans, Lactobacillus rhamnosus*, and *Actinomyces viscosus*. Based on this study and the global interest in using traditional treatments instead of chemical solutions, *S. officinalis* with its bactericidal effect could be a natural remedy for the treatment of diseases affecting mouth and teeth.[43]

A study showed that sage, along with different plant extracts was comparable to synthetic preservatives, and the result confirmed that the aqueous extract of *S. officinalis* can be used in biotechnology as a natural preservative ingredient in food industry.[24]

A study of the antibacterial activities of the essential oil of *S. officinalis* proved that sage essential oil in higher concentration exhibited a better efficiency than antibiotics.[5]

ANTI-DIARRHEAL ACTIVITY

Based on the medicinal use of sage in diarrhea and abdominal spasm, the crude extract of sage was tested for its anti-diarrheal and antispasmodic activities using the *in vitro* and *in vivo* assays. A study demonstrated that the crude extract provides protection against diarrhea through its inhibitory effect on gut motility by the presence of some gut relaxant components.[7] The data of a study suggest that the crude extract of *S. officinalis* possesses anti-diarrheal and antispasmodic activities, mediated possibly through activation of voltage-sensitive K^+ channels, together with a weak Ca^{++} antagonist effect.[7] Therefore, this study provides pharmacological basis for the medicinal use of *S. officinalis* in hyperactive gut disorders such as abdominal colic and diarrhea.[7]

TOXICITY OF SAGE

As far as we know, there are no reports of the negative side effects associated with *S. lavandulaefolia* or *S. officinalis* despite their usage for many centuries.[29] The normal usage of sage is very safe; however, there might be an adverse effect on using *S. officinalis* in excessive amount, which can be caused by the high content of thujone.[6] A study has shown that *S. lavandulaefolia* (Spanish sage), compared to *S. officinalis* (common sage), has similar compositions without the thujone content, which makes it more suitable for those concerned about the excessive usage of sage as a treatment.[40]

CONCLUSION

The objective of this paper is to review the recent advancements in the exploration of sage (*Salvia* species) as phytotherapy and to illustrate its potential as a therapeutic agent. *Salvia* species may represent a natural, safe, and effective treatment for many diseases and their symptoms. In recent decades, with the increase in pharmacological knowledge about the beneficial effects of sage, especially *S. officinalis*, these herbal medicines with antibacterial, antioxidant, anti-inflammatory, free radical scavenging, and antitumor activities have been found to be very effective in the development of novel natural drugs to prevent, control, and treat many minor health problems as well as more serious and complicated diseases such as diabetes, Alzheimer's, and cancer. It must be kept in mind that clinicians should remain cautious until more definite studies demonstrate the safety, quality, and efficacy of *S. officinalis*. For these reasons, extensive pharmacological and chemical experiments, together with human metabolic studies should be the focus of our future studies, and further potential of *S. officinalis* has to be employed in new therapeutic drugs and provide a basis for future research on the application of medicinal plants.

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