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Original Article

Pharmacological properties of *Salvia officinalis* and its components

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ABSTRACT

Salvia officinalis (Sage) is a plant in the family of Labiatae/Lamiaceae. It is native to Middle East and Mediterranean areas, but today has been naturalized throughout the world. In folk medicine, *S. officinalis* has been used for the treatment of different kinds of disorders including seizure, ulcers, gout, rheumatism, inflammation, dizziness, tremor, paralysis, diarrhea, and hyperglycemia. In recent years, this plant has been a subject of intensive studies to document its traditional use and to find new biological effects. These studies have revealed a wide range of pharmacological activities for *S. officinalis.* Present review highlights the up-to-date information on the pharmacological findings that have been frequently reported for *S. officinalis*. These findings include anticancer, anti-inflammatory, antinociceptive, antioxidant, antimicrobial, antimutagenic, antidementia, hypoglycemic, and hypolipidemic effects. Also, chemical constituents responsible for pharmacological effects of *S. officinalis* and the clinical studies on this plant are presented and discussed.

1. Introduction

Salvia officinalis L. (Sage) is a perennial round shrub in the family of Labiatae/Lamiaceae (Fig. 1). Salvia is the largest genus of this family and includes near 900 species. Plants of this genus grow all over the world and the specie of *S. officinalis* is native to Middle East and Mediterranean areas. Today's, it has been naturalized throughout the world particularly in Europe and North America.[1–3] The aerial parts of *S. officinalis* shrub has a long history of use in cookery and traditional medicine. Because of its flavoring and seasoning properties, this plant has been widely used in preparation of many foods. In folk medicine of Asia and Latin America, it has been used for the treatment of different kinds of disorders including seizure, ulcers, gout, rheumatism, inflammation, dizziness, tremor, paralysis, diarrhea, and hyperglycemia.[4,5] In traditional medicine of Europe, *S. officinalis* has been used to treat mild dyspepsia (such as heartburn and bloating), excessive sweating, age-related cognitive disorders, and inflammations in the throat and skin.[6–8] German Commission E has accepted the use of *S. officinalis* for a number of medical applications included inflammation and dyspepsia.

In recent years, many research studies have been conducted to document the traditional uses of *S. officinalis* and to find new biological effects for this plant. These studies have revealed a wide range of pharmacological activities including anticancer, anti-inflammatory, anti-nociceptive, antioxidant, antimicrobial, antimutagenic, antidementia, hypoglycemic, and hypolipidemic, effects. In this review, effort has been made to discuss all pharmacological findings that have been frequently reported for *S. officinalis*. Also, chemical constituents responsible for the biological effects of this plant are presented and discussed. Some of the unwanted effects and toxicity of *S. officinalis* are briefly outlined.

2. Bioactive compounds of *S. officinalis*

The major phytochemicals in flowers, leaves, and stem of *S. officinalis* are well identified. A wide range of constituents include alkaloids, carbohydrate, fatty acids, glycosidic derivatives (e.g., cardiac glycosides, flavonoid glycosides, saponins), phenolic compounds (e.g., coumarins, flavonoids, tannins), poly acetylenes, steroids, terpenes/terpenoids (e.g., monoterpenoids, diterpenoids,

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Fig. 1. Arial parts of *Salvia officinalis* L.

triterpenoids, sesquiterpenoids), and waxes are found in *S. officinalis*.[9–25] Structure of main flavonoids and terpenes/terpenoids isolated from *S. officinalis* is shown in Fig. 2 and Fig. 3, respectively. Most of the phytochemicals which are reported from *S. officinalis* have been isolated from its essential oil, alcoholic extract, aqueous extract, butanol fraction, and infusion preparation. More than 120 components have been characterized in the essential oil prepared from aerial parts of *S. officinalis*. The main components of the oil include borneol, camphor, caryophyllene, cineole, elemene, humulene, ledene, pinene, and thujone.[9,12,13] Alcoholic and aqueous extracts of *S. officinalis* are rich in flavonoids particularly rosmarinic acid and luteolin-7-glucoside. Also the phenolic acids such as caffeic acid and 3-Caffeoylquinic acid have been found in methanolic extract of *S. officinalis*.[17] Several flavonoids like chlorogenic acid, ellagic acid, epicatecin, epigallocatechin gallate, quercetin, rosmarinic acid, rutin, and luteolin-7-glucoside, as well as several volatile components such as borneol, cineole, camphor, and thujone have been identified in infusion prepared from *S. officinalis*.[15,26] Rosmarinic acid and ellagic acid are the most abundant flavonoids in *S. officinalis* infusion extract, followed by rutin, chlorogenic acid, and quercetin.[26] The most abounding carbohydrates described in this plant are arabinose, galactose, glucose, mannose, xylose, uronic acids and rhamnose.[10]

Comparing the phytochemicals in flowers, leaves, and stem of *S. officinalis*; linalool is the most present phytochemical in the stem; the flowers have the highest level of α-pinene and cineole; and bornyl acetate, camphene, camphor, humulene, limonene, and thujone are the most present phytochemicals in the leaves.[22] However, it should be considered that, like other herbs, the chemical composition of *S. officinalis* would be varied depending on the environmental conditions such as climate, water availability, and altitude.[20]

3. Pharmacological activities

Experimental and clinical studies on pharmacological properties of *S. officinalis* are presented and discussed in the following sections. Table 1 summarizes clinical studies on *S. officinalis*.

3.1. Anticancer and antimutagenic effects

Potential antitumor activity of *S. officinalis* has been studied on several cancerous cell lines and on animal models of cancer. It has

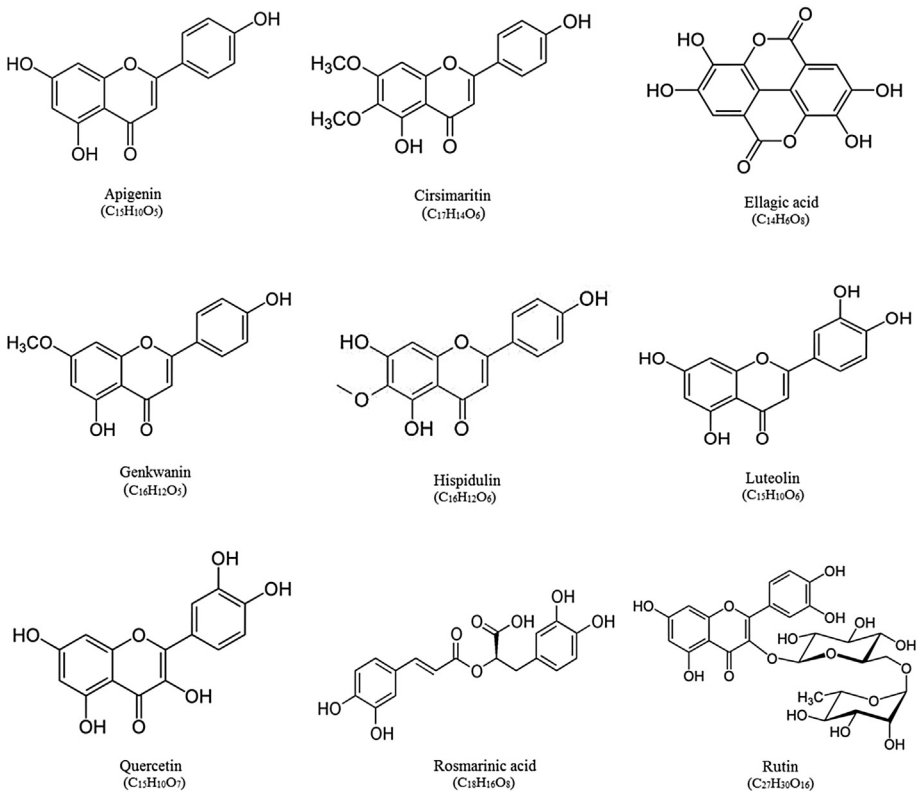

Fig. 2. Structure of main flavonoids isolated from *Salvia officinalis*.

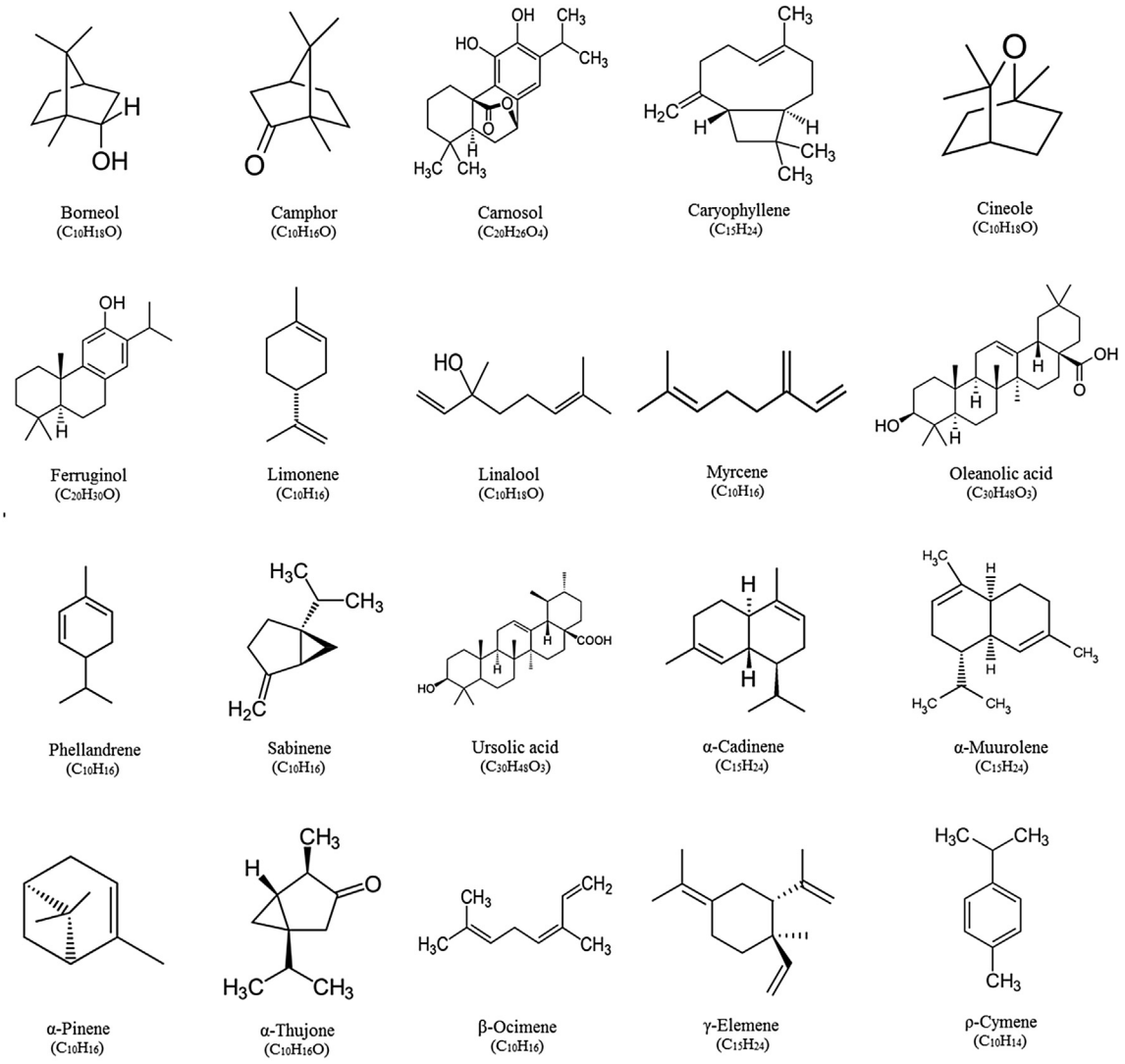

Fig. 3. Structure of main terpenes and terpenoids isolated from *Salvia officinalis*.

been reported that sage tea drinking prevented initiation phases of colon carcinogenesis.[27] Extracts of this plant showed pro-apoptotic and growth-inhibitory effects on cell lines of breast cancer (MCF-7), cervix adeno carcinoma (HeLa), colorectal cancer (HCT-116, HCT15, CO115, HT29), insulinoma (RINm5F), laryngeal carcinoma (Hep-2), lung carcinoma (A549), melanoma (A375, M14, A2058, B16), and oral cavity squamous cell carcinoma.[5,11,20,28–31] In addition to antiproliferative action, *S. officinalis* has antimigratory and anti-angiogenic effects.[32,33] The *S. officinalis* extract enhances TNF-α and nitric oxide release from macrophages therefore increasing its cytotoxic effect.[31] These effects may be related to the presence of several cytotoxic and anticancer compounds in *S. officinalis*. Among terpenes and terpenoids isolated from *S. officinalis*, the caryophyllene and α-humulene have been shown to inhibit growth of MCF-7 and HCT-116 tumor cells.[11] Manool, a diterpene, induces selective cytotoxicity on human cervical adenocarcinoma and human glioblastoma.[34] Also, ursolic acid, a pentacyclic triterpenoid, inhibits angiogenesis, neoplastic proteases, and invasion of melanoma cells.[35] Among flavonoids of *S. officinalis*, rosmarinic acid has been extensively studied for its anticancer effects. It inhibits the growth of various human cancer cells including breast adenocarcinoma, colon carcinoma, chronic myeloid leukemia, prostate carcinoma, hepatocellular carcinoma, and small cell lung carcinoma.[30,36] In animals studies, rosmarinic acid was able to prevent the formation of skin tumors in mice model of dimethylbenz(a) anthracene-induced skin carcinogenesis and to prevent bone metastasis from breast carcinoma.[37,38] The anticancer effects of this flavonoid seem to be due, at least in part, to the inhibition of Mitogen-Activated Protein Kinase/Extracellular Signal-regulated Kinase pathway, the suppression of reactive oxygen species (ROS) and nuclear transcription factor-kappa B, and the reduction of pro-inflammatory gene cyclooxygenase-2 expression.[36,39,40] It also inhibits several phases of angiogenesis (proliferation, migration, adhesion and tube formation) in endothelial cells.[41]

There is increasing evidence that *S. officinalis* can act as inhibitor of mutagenesis. Its essential oil has been shown to reduce UV-induced mutations in *Escherichia coli* and *Saccharomyces cerevisiae*.[42] Its tea infusion reduces the frequency of mutations induced by methyl methanesulphonate in *Drosophila melanogaster*.[43] Its methanolic extract shows protective effect against cyclophosphamide-induced genotoxicity in rats.[44] This plant also reduces hydrogen peroxide- and dimethoxy-1,4-naphthoquinone-induced oxidative DNA damage in HepG2 cells.[45] Antimutagenic effect of *S. officinalis* is mainly attributed to its monoterpene

Table 1
Clinical studies of the pharmacological effects of *S. officinalis*.

Category	Study design	Subjects	Dosage	Effects	References
Effects on memory and cognitive functions	Randomized placebo-controlled trial	Patients with Alzheimer's disease	60 drops/day of alcoholic extract for week 16	Improvement of cognitive functions	88
	Randomized placebo-controlled trial	Healthy young participants	300–600 mg encapsulated dried leaf	Improvement of mood and cognitive functions after single dose	89
	Randomized placebo-controlled trial	Healthy old participants	167–1332 mg of ethanolic extract was administrated 1, 2.5, 4 and 6 h before assessment	Improvement of memory and attention	87
	Randomized controlled trial	Healthy adults participants	5 drops of essential oil were placed into the testing cubicle	Improvement of prospective memory and cognitive performance	85,86
Effects on pain	Randomized controlled trial	Patient with pharyngitis	15% spray containing 140 μl of the plant extract per dose	Reduction of the throat pain intensity	72
	Randomized controlled trial	Patients undergoing tonsillectomy or adenoidectomy	Infusion of the plant was administrated as an oral rinse 4–8 h following surgery and then 6 times a day	The antinociceptive effect was not more powerful than the benzydamine hydrochloride	73
Effects on glucose and lipids	Randomized placebo-controlled trial	Patients with newly diagnosed primary hyperlipidemia	500 mg encapsulated hydroalcoholic extract every 8 h for 2 months	Reduction of the blood levels of total cholesterol, triglyceride, LDL and VLDL; Increase of HDL level	102
	Randomized placebo-controlled trial	Hyperlipidemic type 2 diabetic patients	500 mg encapsulated hydroalcoholic extract every 8 h for 3 months	Reduction of the blood levels of glucose, HbA1c, total cholesterol, triglyceride, and LDL; Increase of HDL level	103
	Randomized placebo-controlled trial	Type 2 diabetic patients	150 mg sage extract 3 times a day for 3 months	Reduction of 2 h postprandial glucose and total cholesterol; No effect on fasting glucose, HbA1c, triglyceride, LDL and HDL	95
	A pilot study (non-randomized crossover trial)	Healthy female volunteers	300 mL of sage tea twice daily for 4 weeks	Reduction of total cholesterol and LDL; No effect on fasting glucose; Increase of HDL level	104

compounds such as thujone, camphor, limonene, and 1,8-cineole.[42,46–48] The protective effect of *S. officinalis* on DNA could be explained by its antioxidant activity.[44,45]

3.2. Antioxidant activities

Oxidative stress plays an important role in the initiation and progression of several diseases, such as cancer, cardiovascular disorders, diabetes, and neurological diseases.[49–52] Enhanced oxidative stress occurs when the generation of ROS by mitochondrial electron-transport chain, NADPH oxidase, uncoupled nitric oxide syntheses, and xanthine oxidase, exceeds the potential of antioxidant defenses including catalase, glutathione per oxidase, and superoxide dismutase activities.[51] Natural antioxidants protect cells against ROS over production and therefore can counteract oxidative stress-mediated tissue damage. Evidence from several studies suggests that *S. officinalis* has potent antioxidant activities. Enriching the drinking water of rats with *S. officinalis* extract increases resistance of rat hepatocytes against oxidative stress.[53] It protects hepatocytes against dimethoxy naphthoquinone- and hydrogen peroxide-induced DNA damage through elevation of glutathione peroxidase activity.[45] The most effective antioxidant constituents of *S. officinalis* are carnosol, rosmarinic acid, and carnosic acid, followed by caffeic acid, rosmanol, rosmadial, genkwanin, and cirsimaritin.[54] The radical scavenging effect of carnosol is comparable to that of α-tocopherol.[55,56] The superoxide scavenging activity of the rosmarinic acid derivatives are 15–20 times more than trolox, a synthetic water-soluble vitamin E. In streptozotocin-induced diabetic rats, rosmarinic acid increases activities of pancreatic catalase, glutathione peroxidase, glutathione-S-transferase, and superoxide dismutase.[57] In addition to rosmarinic acid, other flavonoids of *S. officinalis* particularly quercetin and rutin have strong antioxidant activities.[58] For example, in our previous work we showed that rutin reversed hexachlorobutadiene-induced elevation of lipid peroxidation and depletion of thiol content in the kidney.[59]

3.3. Anti-inflammatory and antinociceptive properties

Inflammation and pain are the two main symptoms which are occur in response to tissue damage. Non-steroidal anti-inflammatory drugs are still a key component of the pharmacological treatment of these symptoms. However, the clinical uses of these drugs are accompanied with unpleasant side effects such as gastrointestinal and cardiovascular complications.[60] Therefore, the search for new anti-inflammatory and antinociceptive agents with lesser unwanted actions remains an attractive subject. Pharmacological studies have shown that *S. officinalis* has anti-inflammatory and antinociceptive effects.[61–69] For example, it has been shown that this plant helps to control neuropathic pain in chemotherapy-induced peripheral neuropathy.[61] Among different extracts of *S. officinalis*, the chloroform one shows more anti-inflammatory action, while the methanolic extract and essential oil demonstrate low action.[70] Flavonoids and terpenes are the compounds that most likely contribute to the anti-inflammatory and antinociceptive actions of the herb.[58,64,67,70] Mansourabadi et al reported that flavonoids extracted from *S. officinalis* reduce inflammation in the mouse carrageenan model and induce analgesic effect in a dose-dependent manner.[64] Osakabe et al showed that topical application of rosmarinic acid inhibits epidermal inflammation.[71] Manool, carnosol, and ursolic acid are of the terpenes/terpenoids with anti-inflammatory potential.[65,67,70] The anti-inflammatory action of ursolic acid is twofold more potent than that of indomethacin.[70] This action of *S. officinalis* constituents

may be responsible for its antinociceptive effect in patient with pharyngitis.[72] However, this effect of *S. officinalis* is not more powerful than the benzydamine hydrochloride in controlling postoperative pain after tonsillectomy or adenoidectomy.[73]

3.4. Antiseptic effects

Several lines of evidence support antimicrobial effects of *S. officinalis*. The essential oil and ethanolic extract of *S. officinalis* show strong bactericidal and bacteriostatic effects against both Gram-positive and Gram-negative bacteria. Among Gram-positive pathogens, *Bacillus cereus*, *Bacillus megaterium*, *Bacillus subtilis*, *Enterococcus faecalis*, *Listeria monocytogenes*, and *Staphylococcus epidermidis* show high sensitivity to *S. officinalis*.[12,19,22,74,75] Effects of *S. officinalis* on Gram-negative bacteria depend on the type of extract used. While essential oil of *S. officinalis* has significant inhibitory effect on the growth of *Aeromonashydrophila*, *Aeromonassobria*, *E. coli*, *Klebsiella oxytoca, Klebsiella pneumonia*, *Pseudomonas morgani*, *Salmonella anatum*, *Salmonella enteritidis*, *Salmonella typhi*, and *Shigellasonei*, effect of ethanolic extract on *E. coli*, *Pseudomonas aeruginosa*, and *S. enteritidis* is weak.[12,19,22,74,75]

In addition to antibacterial action, *S. officinalis* has been reported to induce antifungal, antiviral and anti-malarial effects.[9,76–78] The antifungal activity has been reported against *Botrytis cinerea*, *Candida glabrata*, *Candida albicans, Candida krusei*, and *Candida parapsilosis*.[9,78] Antimicrobial effects of *S. officinalis* are attributed to terpens and terpenoids compounds found in this plant. It has been shown that camphor, thujone, and 1,8-cineole have antibacterial effects against *Aeromonas hydrophila*, *Aeromonas sobria, B. megatherium*, *B. subtilis*, *B. cereus*, and *Klebsiella oxytoca*.[75] Also, oleanolic acid and ursolic acid, two triterpenoids of *S. officinalis*, have inhibitory action on growth of multidrug-resistant bacteria such as vancomycin-resistant enterococci, penicillin-resistant *Streptococcus pneumonia*, and methicillin-resistant *Staphylococcus aureus*. The effect of ursolic acid on *Enterococcus faecium* and multidrug-resistant bacteria is stronger than that of ampicillin.[79] Carnosol, a diterpenoid, and its related compound carnosic acid are two other antibacterial compounds obtained from *S. officinalis*. These compounds potentiate the effects of aminoglycosides on methicillin-resistant *S. aureus*.[80] The antiviral activity of *S. officinalis* is most probably is mediated by safficinolide and sage one, two diterpenoids which are found in its aerial parts.[77]

3.5. Cognitive- and memory-enhancing effects

There is increasing evidence to suggest that *S. officinalis* has cognitive- and memory-enhancing effects. In animal studies, it has been shown that ethanoic extract of *S. officinalis* increases memory retention of passive avoidance learning in rats.[81] Hydroalcoholic extract from *S. officinalis* and its main flavonoid rosmarinic acid improve cognition in healthy rats and prevent learning and memory deficits induced by diabetes.[82] Also, *S. officinalis* hydroalcoholic extract attenuates morphine-induced memory impairment.[83]

Clinical trials confirm the results of animal studies and demonstrated that *S. officinalis* enhances cognitive performance both in healthy participants and patients with cognitive impairment or dementia.[84] Moss et al reported that the aroma of *S. officinalis* essential oil could enhance prospective memory performance in healthy adults.[85,86] Also, Scholey et al showed that ethanolic extract of this plant improved memory and attention in healthy older subjects.[87] A randomized controlled trial by Akhondzadeh et al showed that a 4-month treatment with hydroalcoholic extract of *S. officinalis* improved cognitive functions in patients with mild to moderate Alzheimer's disease.[88]

With regards the mechanisms responsible for cognitive- and memory-enhancing effects of *S. officinalis*, a potential interaction with cholinergic system has been suggested. Eidi and coworkers found that activation of muscarinic and nicotinic receptors by pilocarpine and nicotine, respectively, potentiated memory-enhancing effects of *S. officinalis*. On the other hand, blockade of muscarinic and nicotinic receptors by scopolamine and mecamylamine, respectively, attenuated this effect.[81] In addition, *S. officinalis* has been reported to inhibit acetylcholinesterase activity.[89,90] To date, inhibitors of acetylcholinesterase are the leading therapeutics of Alzheimer's disease and *S. officinalis* might be a promising source for developing therapeutic agents for this disease.

3.6. Metabolic effects

Experimental and clinical studies have confirmed the beneficial effects of some medicinal plants on body metabolism particularly glycemic status, serum lipids, lipolysis, and adipogenesis.[26,91–94] Recent pharmacological investigations demonstrated that different extracts of aerial parts of *S. officinalis* are able to decrease blood glucose in normal and diabetic conditions.[95–99] The mechanisms suggested for hypoglycemic effect of *S. officinalis* include an inhibition of hepatocyte gluconeogenesis and decrease of insulin resistance through stimulation of peroxisome proliferator-activated receptor γ (PPARγ).[100,101] Recently, one study group reported that *S. officinalis* extract increased plasma insulin in streptozotocin-induced diabetic rats.[97] However, in their previous work they observed that the extract did not affect insulin releasing from the pancreas of normal or diabetic rats.[96] Therefore further studies required to elucidate whether stimulation of insulin release mediates hypoglycemic effect of *S. officinalis*.

Pharmacological studies also revealed that different extracts of *S. officinalis* reduces serum lipids. Hernandez-Saavedra et al Reported that infusion prepared from this plant reduced serum triglycerides, total cholesterol, and low density lipoproteins (LDL) levels in diet-induced obese rats.[26] It also decreased body weight and abdominal fat mass in these animals. The beneficial effects of *S. officinalis* on lipid profile have been also shown in diabetic animals. It could decrease the level of triglyceride, cholesterol, urea, uric acid, creatinine, aspartate amino transferase (AST), and alanine amino transferase (ALT) in streptozotocin-induced diabetic rats.[97,98] In clinical trials, extract of *S. officinalis* leaf could lower the blood levels of triglyceride, total cholesterol, LDL, very low density lipoproteins (VLDL) and 2 h postprandial glucose in patients with hyperlipidemia and diabetes.[95,102,103] The beneficial properties of *S. officinalis* tea consumption on serum lipid profile have been also reported on non-diabetic healthy volunteers.[104] Because hyperlipidemia is a common metabolic disorder contributing to mortalities and morbidities due to cerebrovascular and cardiovascular diseases, *S. officinalis* may be valuable for the management of dyslipidemia in high risk patients like those with diabetes mellitus or hypercholesterinemia. The beneficial action of *S. officinalis* on dyslipidemia may be related to flavonoids present in the plant. For example, rosmarinic acid treatment reduces the levels of triglycerides and cholesterol in serum of high fat diet- and streptozotocin-induced type 2 diabetic rats.[57] Also, administration of rutin reduces adipose tissue mass and body weight in high-fat diet-induced obese rats. In addition, this flavonoid increases mitochondrial size, mitochondrial DNA content, and gene expression related to mitochondrial biogenesis (e.g., PPARγ coactivator-1α, nuclear respiratory factor-1, transcription factor A, and nicotinamide adenine dinucleotide-dependent deacetylase) in skeletal muscle.[105]

4. Toxicological studies

A number of clinical trials have reported that consumption of *S. officinalis* does not induce severe side effects.[88,102,104] However, in the case of prolonged use or following overdose of ethanolic extract and volatile oil of *S. officinalis* (corresponding to more than 15 g of the leaves) some unwanted effects such as vomiting, salivation, tachycardia, vertigo, hot flushes, allergic reactions, tongue swallowing, cyanosis, and even convulsion may occur.[1,3,106] The proconvulsant action of *S. officinalis* oil is due to its direct effect (at doses more than 0.5 g/kg) on nervous system.[106] Camphor, thujone, and terpene ketones are considered as the most toxic compounds in *S. officinalis*. These compounds may induce toxic effects on the fetus and newborn. Therefore consumption of *S. officinalis* is not recommended in pregnancy and lactation.[1,3,106,107] Results from animal studies have demonstrated that the LD_{50} of *S. officinalis* oil (when consumed orally) and the methanolic extract (when injected intraperitoneally) is 2.6 g/kg and 4 g/kg, respectively.[96,106] It has been reported that *S. officinalis* tea enhances CCl4-induced hepatotoxicity in mice.[16] However, in clinical studies no hepatotoxic effects were reported.[102,104]

5. Conclusion

Today, there is lot of interest towards traditional medicines and herbal-based treatment all over the world. Therefore numerous experimental and clinical studies are being undertaken on medicinal plants and there is a need for updating and integrating the findings. In this article effort has been made to discuss available pharmacological findings that have been frequently reported for *S. officinalis*. On the basis of the available literature evidence, this plant shows anticancer, anti-inflammatory, antinociceptive, antioxidant, antimicrobial, hypoglycemic, hypolipidemic, and memory-enhancing effects. The effectiveness of *S. officinalis* as an antinociceptive, hypolipidemic, and memory-enhancing medicinal plant has been confirmed with clinical trials. In addition to the above mentioned effects, a number of other biological actions such as activating benzodiazepine receptors and inhibiting pentylenetetrazole-induced seizure have been shown for *S. officinalis* in literature.[63,108] The possible therapeutic applications for these effects of *S. officinalis* need to be elucidated in future studies. Also, future works is necessary to understand the exact molecular mechanisms responsible for *S. officinalis* effects, its toxicity, and drug-drug interactions.

Conflict of interest statement

The authors declare that there is no conflict of interest.

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