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Pharmacological Properties and Therapeutic Potential of *Salvia officinalis*

Research

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الآيـة

بسم الله الرحمن الرحيم

(وَلَقَدْ خَلَقْنَا الْإِنسَانَ مِن سُلَالَةٍ مِّن طِينٍ ، ثُمَّ جَعَلْنَاهُ نُطْفَةً فِي قَرَارٍ مَّكِينٍ)

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الى صاحب السيرة العطرة، والفكر المستنير؛ الذي له الفضل

الأول في بلوغي التعليم العالي (والدي الحبيب)

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إلى من وضعتني على طريق الحياة، وجعلتني رابط الجأش،

وراعتني حتـــى صرت كبيراً (أمي الغالية)

إلى إخوتي؛ من كان لهم بالغ الأثر في كثير من العقبـــات

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SUPERVISOR CERTIFICATION

Certify that this Project (Pharmacological Properties and Therapeutic Potential of *Salvia officinalis*) was prepared under our supervision at the College of Pharmacy, University of Misan, as graduation research

Supervisor

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Specific specialization: Medicinal plant

Date:

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Abstract:

Salvia officinalis (Sage) is a plant in the family of Labiate. It is native to the Middle East and Mediterranean areas, but today it has been naturalized throughout the world. In folk medicine, *S. officinalis* has been used for the treatment of different kinds of disorders, including seizures, 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*. These findings include anticancer, anti-inflammatory, antinociceptive, antioxidant, antimicrobial, antimutagenic, antidementia, hypoglycemic, and hypolipidemic effects commonly used for antioxidant, anticancer and anti-tumor, anti-stress and anti-anxiolytic and antidepressant, anti-Alzheimer, anti-cardiovascular diseases, memory improving, and concentration.

It was said to be good for insomnia and dysomnia. *Salvia officinalis* L. is widely used for therapeutic and non-therapeutic purposes that trigger its significant value. Also, chemical constituents responsible for the pharmacological effects of *S. officinalis* and the clinical studies on this plant are presented and discussed. Various combinations and numerous medicinal properties of its extract, oil, and leaves demand further and more studies about the other useful and unknown properties of this multipurpose plant.

1. Introduction:

Salvia officinalis L. is a plant in the mint family Lamiaceae, subfamily Nepetoideae, tribe Mentheae, and genus Salvia [1]. Salvia is the largest genus of the Lamiaceae family, containing around 1000 species [2], and can be found in Europe around the Mediterranean, in Southeast Asia, and Central and South America [3].

Historically, sage is known as the "Salvation Plant", originating from the old Latin word "salvarem", which means save or cure. It has been used to reduce perspiration, as a gargle for sore throat, to improve regularity of a menstrual cycle and to reduce hot flashes in menopause, to fight gastroenteritis and other infections, to improve lipid status and liver function in general, to improve appetite and digestion, and to improve mental capacity [4].

Salvia is extensively used in traditional medicine as an antiseptic, antiscabies, antibacterial, antisyphilis, and anti-inflammatory medication, and it was reportedly used to cure fever and some digestive disorders in several locations of the Middle East[5].

About 80% of rural people in developing countries use traditional medicine made from plants. Even people in developed countries are becoming more interested in medicinal plants [6].

Indeed, over 25% of medications used in the previous two decades are typically extracted from plants, while the remaining 25% are chemically altered natural substances. Despite this, only around 5%–15% of the roughly 250,000 higher plants have ever been studied for pharmacological activities [7].

Numerous studies conducted over the last few decades have shown that research on therapeutic plants is critical and bioactive phytochemicals or bionutrients are abundant in medicinal plants; these phytochemicals have a critical role in avoiding chronic illnesses such as cancer [8-10]diabetes [11-14]and coronary heart disease [15-17]. Dietary fiber, detoxifying agents, antioxidants, anticancer, neuropharmacological

agents, and immune-stimulating agents are the key groups of phytochemicals having disease-preventive properties [18].

The essential oil of Salvia species has various compositions depending on the genetic, climatic, seasonal, and environmental factors [19]. Essential oils are very important sources for the screening of anticancer, antimicrobial, antioxidant, and free radical scavenging agents [20]. *S. officinalis* (common sage) is considered to have the highest amount of essential oil compared to the other species of Salvia [21-22].

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 [22-23]. Studies have shown that some biological properties of the essential oil of Salvia depend on camphor, 1,8-cineole, α-thujone, and β-tthujone [24].

The essential oil of sage contains about 20% camphor, and as the leaves expand, the camphor content also increases [25]. Sage is also a natural source of flavonoids and polyphenolic compounds (carnosic acid, rosmarinic acid, and caffeic acid) possessing strong antioxidant,radical-scavenging, and antibacterial activities[26].

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. Caffeic acid plays a central role in the biochemistry of the Lamiaceae plants, and occurs mainly in a dimer form as rosmarinic acid [27].

Carnosic acid and rosmarinic acid, which are present at high concentrations in the extract of sage plants, have shown strong antioxidant properties [28]. Ursolic acid, also a component of sage, has strong anti-inflammatory properties, and in sage preparations, it is considered a quality control mea- measurement for the anti-inflammatory effects of different solutions [29].

Figure 1: ***Salvia officinalis***

2. Bioactive compounds of *S. officinalis*

The major phytochemicals in flowers, leaves, and stems of *S. officinalis* are well identified. A wide range of constituents, including alkaloids, carbohydrates, fatty acids, glycosidic derivatives (e.g., cardiac glycosides, flavonoid glycosides, saponins), phenolic compounds (e.g., coumarins, flavonoids, tannins), polyacetylenes, steroids, terpenes/terpenoids (e.g., monoterpenoids, diterpenoids, triterpenoids, sesquiterpenoids), and waxes are found in *S. officinalis*. [30-46] 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 [30,33,34]. 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*. [38] 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*. [36,47] Rosmarinic acid and ellagic acid are the most abundant flavonoids in *S. officinalis* infusion extract, followed by rutin, chlorogenic acid, and quercetin.[47] The most abounding carbohydrates described in this plant are arabinose, galactose, glucose, mannose, xylose, uronic acids and rrhamnose [31] 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 a-pinene and cineole; and bornyl acetate, camphene, camphor, humulene, limonene, and thujone are the most present phytochemicals in theofficial [43] However, it should be considered that, like other herbs, the chemical composition of S. official's would be varied depending on the environmental conditions such as climate, water availability, and altitude.[41]

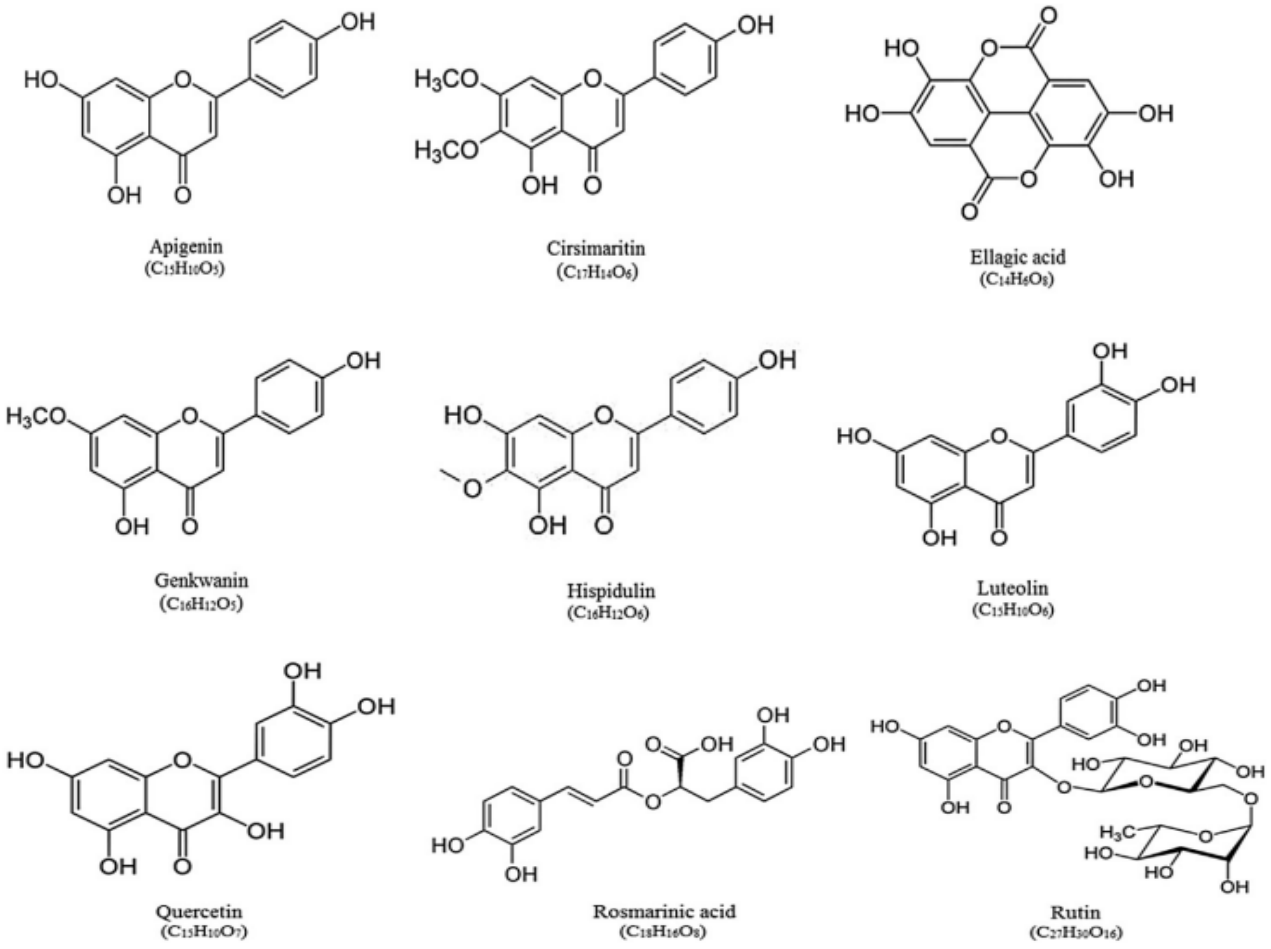

Figure 2: Structure of main flavonoids isolated from *Salvia officinalis*

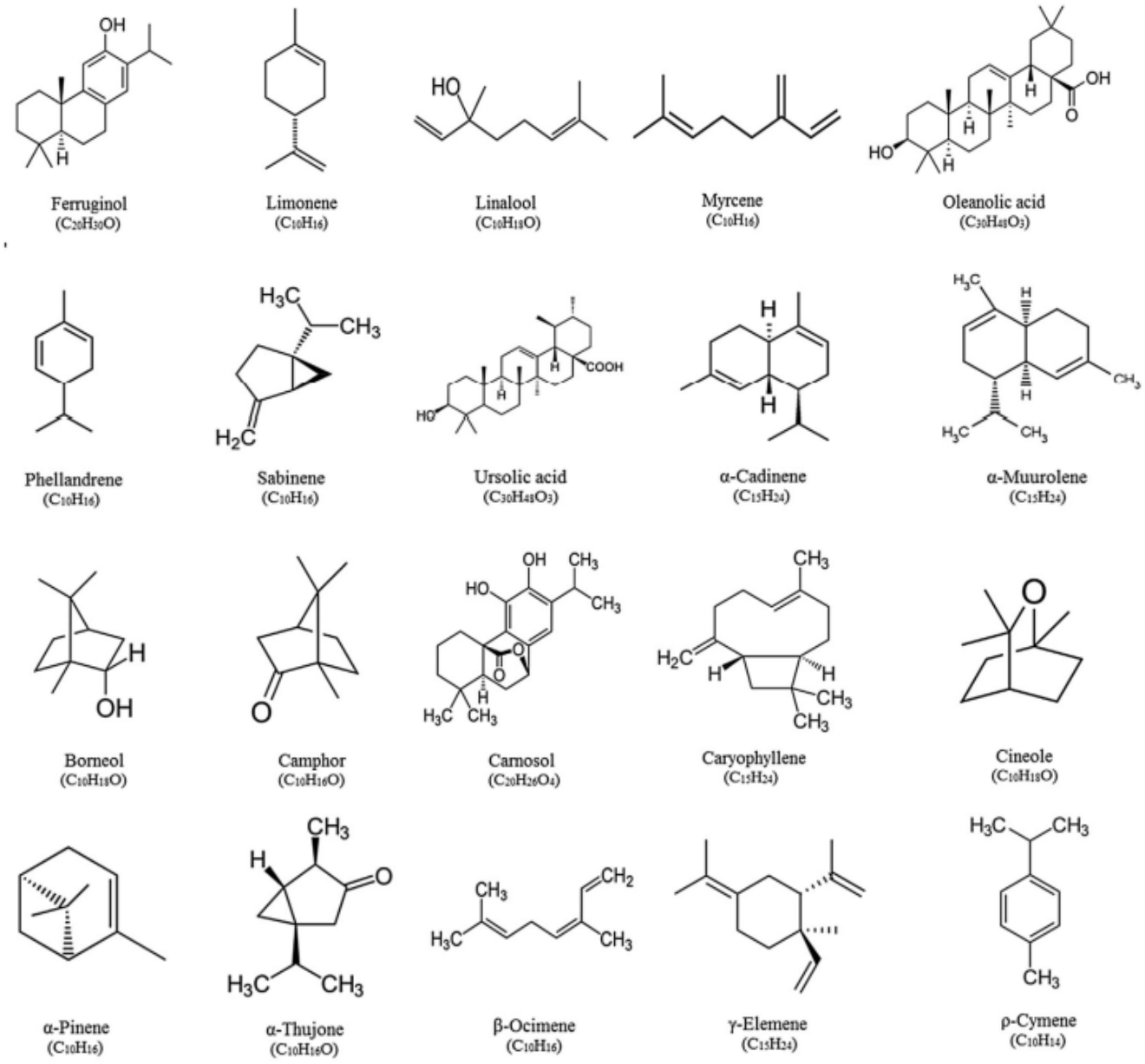

Figure 3: Structure of main terpenes and terpenoids isolated from *Salvia officinalis*

3. Pharmacologic properties:

3.1. Anticancer effects:

Cancer is characterized by the abnormal growth of cells that tend to proliferate in an uncontrolled way, and in some cases, spread to other parts of the body.[48] The important factor in proliferation and spreading of cancer cells is the ability of tumors to produce a large number of new blood vessels, which is known as angiogenesis.[49] Most primary solid tumors are dependent on angiogenesis for survival, growth, invasion, and metastasis.[49] 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.[48] 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.[50]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 into proliferating cells. [51] This study has shown that dietary compounds can change the epigenetic status. Many food plants are rich in bioactive compounds and have been shown to possess anticancer properties. [51] 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 H2O2-induced DNA damage in vitro. [51]

Extracts from this plant have demonstrated pro-apoptotic and growth-inhibitory effects on cell lines of breast cancer (MCF-7), cervical adenocarcinoma (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 [52-55]. In addition to its antiproliferative activity, *S. officinalis* exhibits antimigratory and antiangiogenic properties [56-58].

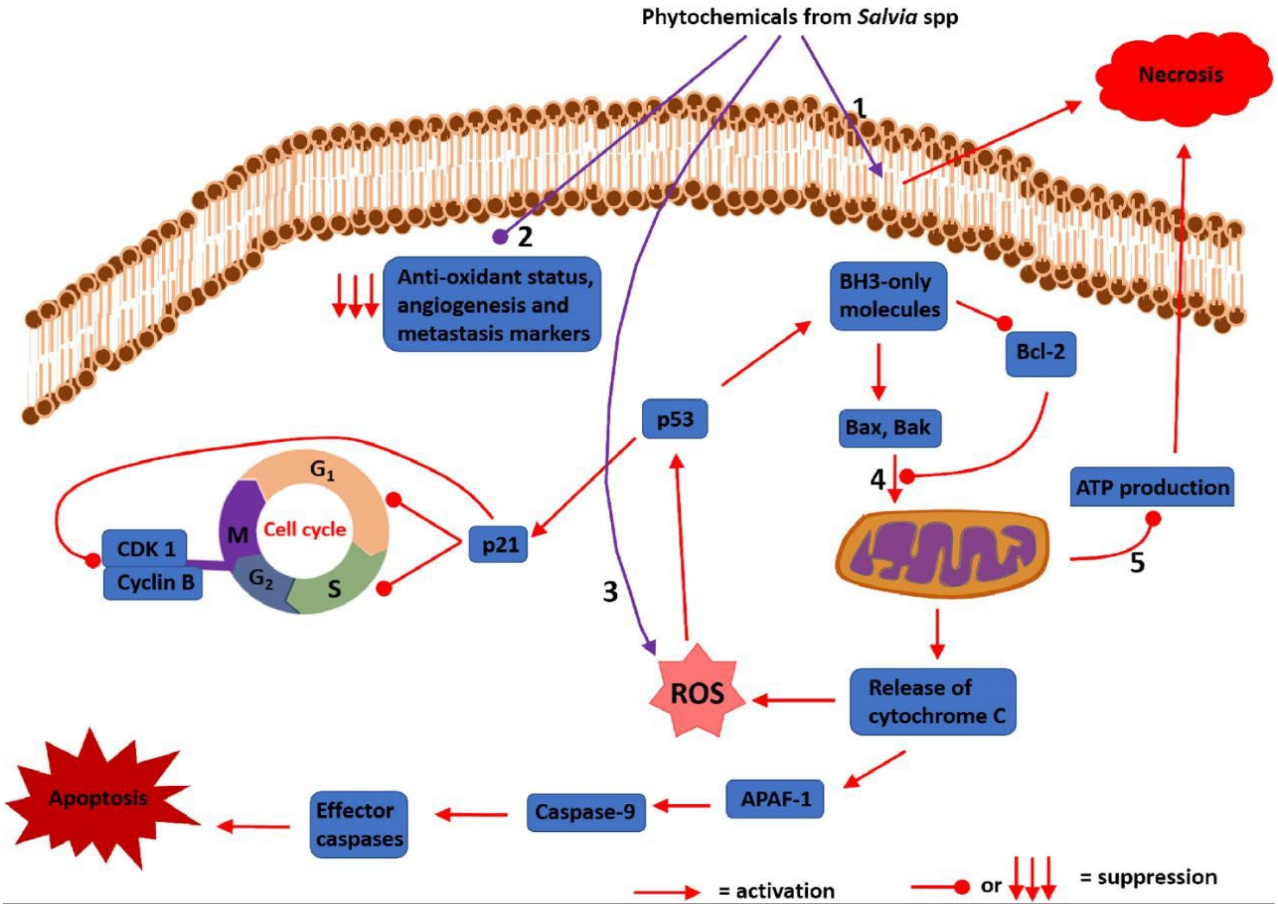

Figure 4: Anticancer effects of *Salvia officinalis*

3.2 Antibacterial effects:

There are studies that support the antibacterial properties of the plant [59]. The essential oil and ethanolic extract of *S.officinalis* exhibit strong bactericidal and bacteriostatic activities against both Gram-positive and Gram-negative bacteria [60]. Gram-positive pathogens such as Bacillus cereus, Bacillus megaterium, Bacillus subtilis, Enterococcus faecalis, Listeria monocytogenes, and Staphylococcus epidermidis have shown high susceptibility to *S. officinalis* [61-63].

3.3 Hypoglycemic effect:

S. officinalis has been used as a traditional remedy against diabetes in many countries, and its glucose-lowering effects have been demonstrated in animal studies.[67] Recent pharmacological investigations demonstrated that different extracts of the aerial parts of *S. officinal* can decrease blood glucose in normal and diabetic conditions.[68-72] 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.[73]. The mechanisms suggested for the hypoglycemic effect of *S. officinalis* include an inhibition of hepatocyte gluconeogenesis and a decrease of insulin resistance through stimulation of peroxisome proliferator-activated receptor. [74-75].

Recently, one study group reported that *S. officinalis* extract increased plasma insulin in streptozotocin-induced diabetic rats. [76] However, in their previous work, they observed that the extract did not affect insulin release from the pancreas of normal or diabetic rats. [77]

3.4. Hypolipidemic effects:

S. officinalis has been shown to improve lipid profiles and reduce the risk of associated complications, such as cardiovascular diseases [78, 79].

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 tri glycerides, total cholesterol, and low density lipoproteins (LDL) levels in diet-induced obese rats.[80] 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.[81]

3.5 Obesity:

Overweight and obesity are recognized to cause several abnormalities, including Type II diabetes, dyslipidemia, hypertension, etc., which are all important risk factors in developing serious diseases such as cardiovascular diseases, chronic kidney diseases, and many others. [82] To regulate fat absorption, the effective way is to reduce body weight and obesity. [83]

Pancreatic lipase is well known to play an important role in lipid digestion.[83] In several studies on anti-obesity components from natural medicine, the effects of *S. officinalis* and its active components on the pancreatic lipase activity and lipid digestion were investigated.[84] 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.[84] Carnosic acid and carnosol are two of the diterpenes isolated from the methanolic extract of *S. officinalis* with 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. [84] 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 was eventually effective in reducing body weight and obesity. [84]

3.6 Antidiarrheal effects:

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 due to the presence of some gut relaxant components.[85] 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.[85] Therefore, this study provides a pharmacological basis for the medicinal use of *S. officinalis* in hyperactive gut disorders such as abdominal colic and diarrhea.[85]

3.7 Antioxidant effects:

Oxidative stress plays an important role in the initiation and progression of several diseases, such as cancer, cardiovascular disorders, diabetes, and neurological diseases. [86-89]. Natural antioxidants protect cells against ROS overproduction 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 the resistance of rat hepatocytes against oxidative stress. [90]. The most effective antioxidant constituents of S. officinalis are carnosol, rosmarinic acid, and carnosic acid, followed by caffeic acid, rosmanol, rosmadial, genkwa nin, and cirsimaritin.[91]. In addition to rosmarinic acid, other flavonoids of *S. officinalis*, particularly quercetin and rutin, have strong antioxidant activities. [92]

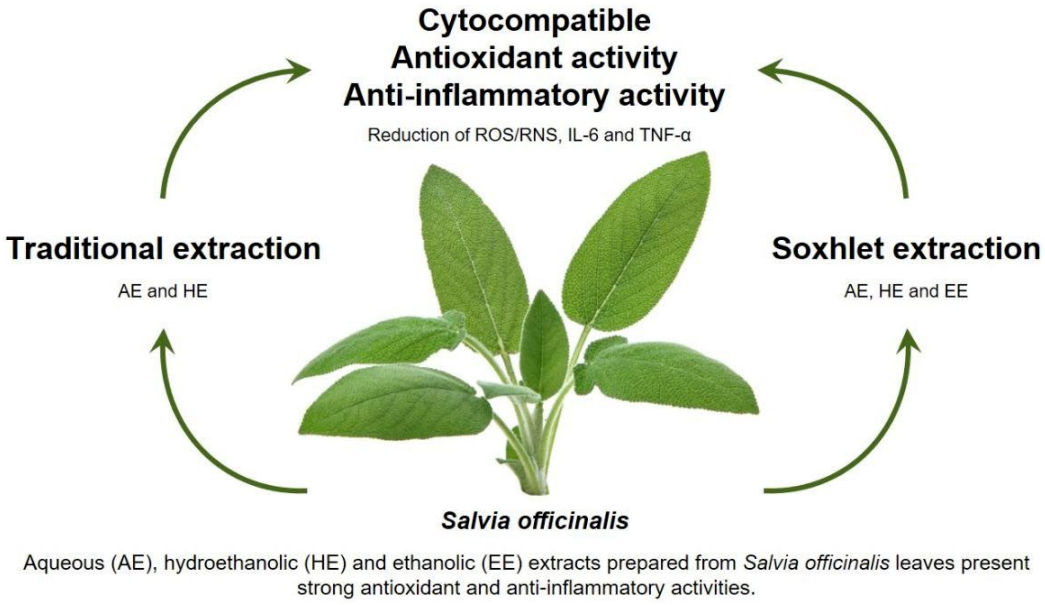

Figure 5: antioxidant effects of *Salvia officinalis*

3.8 Anti-inflammatory effects:

Inflammation and pain are the two main symptoms that occur in response to tissue damage. There are drug groups used to treat these symptoms, but they may be accompanied by side effects such as cardiovascular and Gastrointestinal complications. [93] Therefore, it was necessary to search for an agent with fewer side effects. An analysis of sage's chemistry and pharmacology indicated that ursolic acid is the primary ingredient responsible for its anti-inflammatory properties [94]. For quality control purposes, the determination of ursolic acid content in sage and sage-based therapies for the topical treatment of inflammatory diseases is recommended [95]. For example, it has been shown that this plant helps to control neuropathic pain in chemotherapy-induced peripheral neuropathy [96]. Flavonoids and terpenes are also compounds present in plants that have anti-inflammatory and anti-nociceptive actions of the herb [97,98,99,100]. This action of *S. officinalis* constituents may be responsible for its anti-nociceptive effect in patients with pharyngitis. [101]

3.9 Neuroprotective effects:

Several studies have investigated the neuroprotective potential of *S. officinalis*. One study demonstrated that the ethanolic extract of S. *officinalis* could protect neuronal cells from oxidative stress-induced cytotoxicity in vitro [102]. Another study reported that sage extract exhibited an inhibitory effect on acetylcholinesterase activity, suggesting its potential use in the treatment of Alzheimer's disease [103]. It has an interaction with muscarinic and nicotinic cholinergic systems that is involved in the memory retention process [104].

A study shows that *S. officinal* is improves memory and cognition, and with increasing dosage, the mood gets elevated as well as alertness, calmness, and contentedness iincrease.105]

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. [106]

4. Toxicity:

Several clinical trials have reported that consumption of *S. officinalis* does not induce severe side effects. [107,108,109] However, in the case of prolonged use or following overdose of ethanolic extract and volatile oil of *S. officinalis*, some unwanted effects such as vomiting, salivation, tachycardia, vertigo, hot flushes, allergic reactions, tongue swelling, cyanosis, and even convulsions may occur.[110,111,112]

Thujone, it is one of the *S. officinalis* constituents, a monoterpene ketone, has been associated with neurotoxicity and convulsions at high doses.[113] However, the levels of thujone present in culinary and medicinal preparations of *S. officinalis* are generally considered safe for consumption [114,115] 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.[116]

5. Conclusion:

Today, there is a lot of interest in 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 to update and integrate the findings. 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 are 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.

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