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Common Sage (*S. Officinalis*)- A Natural Medicine and Its Health Benefits

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ABSTRACT

Common Sage (*Salvia officinalis*) belongs to the Labiatae/Lamiaceae family Indigenous to the Middle East and Mediterranean regions but today has been world-widely revolutionized. *Salvia officinalis* exhibited an extensive array of functionally bioactive chemical constituents that have been employed in the treatment of multiple chronic health conditions and has been under primarily extensive research documenting its novel biological significance and exploring revolutionary biological impacts on well-being revealing an extensive range of pharmaceutical significance. These investigations demonstrated that besides curing relatively mild illnesses, *S. officinalis* possesses potentially revolutionary natural remedial treatment alleviating chronic health-related life-threatening conditions by possessing anti-carcinogenic, anti-depressive, and anti-diabetic efficacy. This review will shed light on *Salvia officinalis* pharmaco-medicinal biological properties signifying its anti-oxidative, immune-modulatory, anti-tumor, anti-hyperlipidemic, Neuro-cognitive efficacy, Microbicide activities, and its toxicological effects to preserve and restore health by highlighting the significance of this plant as a fantastic herb with multi-factorial health and wellness benefits.

INTRODUCTION

Salvia officinalis L. (Sage) is a perennial spherical shrub that belongs to the family of Labiatae/Lamiaceae containing approximately 900 species worldwide and the flowering plants are mostly aromatic with distinctive color variations [1] globally grown owing to its culinary, pharmacological, and flavour enhancing characteristics [2]. *S. officinalis*' customary application and traditional folk-medicinal utilization are globalized around the world, and the Latinian meaning of this plant *Salvia* is curative demonstrating health-promoting properties signifying the importance of this plant as a pharmacologically therapeutic herbal botanical [3]. The aerial plant parts are strategically employed against the therapeutic treatment of gouty arthritis, rheumatic arthritis, anti-hyperglycemic, and diarrhea throughout Asian and Northern American countries [4]. Additionally, *S. officinalis* possessively employed against the pharmacological treatment of digestive problems such as Indigestion, ulceration, cardialgia, and acid indigestion, along with upper airway complications such as pharygitis and inflammatory triggers [5]. Historically, *S. officinalis* tea infusions are traditionally utilized against treating gastrointestinal and cardiovascular diseases such as angina, chest cold, oral infections, Tonsilitis, depressive disorders, hyperhidrosis,

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skin inflammation, and multiple chronic conditions [6]. Additionally, Research investigations potentiated the utilization of *S. officinalis* oil as a therapeutic remedial approach as a de-flatulent agent, spasmolytic, skin disinfectant, and astringent [7]. *S. officinalis* vitally essential oil-based infusions is a mixture of volatile components utilized for therapeutic screening of anti-carcinogenic, microbicides, and free radical scavenging agents [8]. Sage also has noticeable beneficial effects in age-related cognitive disorders [9]. Investigational analysis exhibited the exploration of *S. officinalis* in inducing irritability, tranquillity, and explicit memory within Alzheimer's patients [10]. *S. officinalis* leafage is customarily utilized within the agri-food sector owing to its flavor enhancer, anti-oxidative, and micro-biocidal-related pharmacological health benefits [11]. Additionally, *S. officinalis* hepato-protection or anti-hepatotoxic remedial effects were outlined by investigational approaches as far as the herbal botanical exhibited therapeutically curative effects about anti-hepatotoxic efficacy and is currently employed as a conventional remedial medicinal approach with potentiated hepato-protective effects around the globe [12, 13].

Pharmacologically Functional Properties

Common Sage (*S. officinalis)* possesses an extensive range of functional bioactive constituents which through a diverse range of extensive investigatory techniques provide an enormous amount of physicochemical constituents which gradually becoming popular for its anti-oxidative, immune-modulatory, anti-tumor, anti-hyper-lipidemic, neuro-protective, microbicide and possessing no toxicological effects with extensive historical medicinally and culinary applications [14].

Anti-Oxidative Effects

Oxidative stress played a crucially pivotal role in the development, progression, and pathogenesis of many chronic illnesses disrupting the pathway between oxidative and anti-oxidative mechanisms within cells and tissues resulting in heart diseases, neurodegenerative disorders, mutagenesis, and metabolic abnormalities [15]. Oxidative stress resulted in Reactive oxygen species (ROS) production through mitochondrial-mediated electron transport chain (ETC) reactions, uncoupling of Nitric oxide synthase (NOS) enzymatic reactions, and Xanthine oxidoreductase activities. *S. officinalis* flavonoids and phenolic components are primarily responsible for its anti-oxidative potential and act as free radical scavengers by substantially improving anti-oxidative defensive activities owing to the presence of catalases, glutathione peroxidases, and superoxide dismutase activities [16, 17]. Multiple clinical analyses demonstrated *S. officinalis* potentiates anti-oxidative activities. *S. officinalis* enriched aqueous water enhances rats' hepatocyte cellular resistive action against oxidative damage [18]. Through an increase in glutathione peroxidase activity, it shielded and preserved hepatocytes' cellular activities by preventing hydrogen peroxide and dimethoxy-naphthoquinone-induced oxidative DNA damage [19]. *S. officinalis* isolated phenolic constituents such as carnosol, carnosic and rosmarinic acids, rosmadial, rosmanol, epirosmanol, methyl carnosate, and luteolin-7-O-β-glucopyranoside exhibited markable anti-oxidative activities [20]. *S. officinalis*-derived carnosol possesses radical scavenger activity comparable to that of alpha-tocopherol [21]. Within Streptozotocin (STZ)-induced diabetic rats rosmarinic acid exhibited demonstration of boosting pancreatic catalases, glutathione peroxidases, and SOD activities, radical scavenging activities are 15 to 20 times greater than the synthetically commercialized water-solubilized Vitamin E "trolox" [22]. Additionally, to the chemical component rosmarinic acid, other flavonoids majorly quercitin and rutin possess stronger anti-oxidative properties [23]. For instance, rutin reverses, suppresses, and mitigates elevated lipid peroxidation levels and causes a substantial reduction in the kidney's thiol concentration [24]. Aqueous isolated extract of *S. officinalis* possesses potent anti-oxidative and virucidal activities. An observational study analyzed that *S. officinalis* decoction tea administration to diabetic rats for fourteen days resulted in improving anti-oxidative defensive mechanisms, improves catalases and superoxide dismutase (SOD) activities [25].

Immune-Modulatory and Anti-Nociceptive Activities

Inflammation and pain are the two main symptoms in response to tissue damage. Non-steroidal anti-inflammatory drugs are the key pharmacological treatments. However, the clinical administration of these drugs is accompanied by unpleasant side effects such as gastrointestinal and cardiovascular complications [26]. Therefore, investigating new anti-inflammatory and antinociceptive with positive health implications remains an attractive subject. Pharmacological studies have exhibited that *S. officinalis* possesses stronger anti-inflammatory and anti-nociceptive effects [27, 28]. For example, it has been shown that this plant controls and mitigates neuropathic pain in chemotherapy-induced peripheral neuropathy. Among different extracts of *S. officinalis*, the chloroform exhibited potential anti-inflammatory action, while the methanol extract along with the essential oil demonstrated lower mechanistic action [29]. Flavonoids and terpenes potentially contribute to the anti-inflammatory and anti-nociceptive herbal action [30]. Mansourabadi et al reported that flavonoids extracted from *S. officinalis* reduce and mitigate inflammation in the

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mouse carrageenan model by inducing analgesic activities in a dose-dependent manner [28]. Topical application of rosmarinic acid inhibits epidermal inflammation. Manool, carnosol, and ursolic acid are of the terpenes/terpenoids with anti-inflammatory potential [30]. The anti-inflammatory action of ursolic acid is twofold more potent than an anti-inflammatory medication indomethacin [29]. This mechanistic action of *S. officinalis* constituents may also possess stronger anti-nociceptive efficacy in patients with pharyngitis [31]. However, this effect of *S. officinalis* is quite in line as compared to benzamine hydrochloride in controlling postoperative pain after tonsillectomy or adenoidectomy [32].

Anti-tumor and Anti-Mutagenic Effects

Carcinogenesis is characterized by aberrant cellular growth which possesses a propensity to propagate uncontrollably as well as in some instances metastasis spread to various bodily organs. The key component in the development, proliferation, and propagation of cancerous cells is the ability of the tumors to produce a significant proportion of new blood vessels collectively manifested as angiogenesis. Angiogenesis played a significant triggering factor in the development, invasion, and metastasis of the vast majority of primary solid tumors [33]. Investigational research hypothesized that *S. officinalis* extract suppresses angiogenesis within in-vivo analysis at therapeutically pharmacological concentrations which act as a novel innovative strategy that possesses anti-angiogenic mechanisms [34]. *S. officinalis* extracted isolates uphold caspase-mediated cell death and exhibited growth-inhibitory activities on cell lines of Invasive ductal carcinoma (Michigan Cancer Foundation-7 (MCF-7)), mesonephric (HeLa), colon and rectal carcinoma (hematocrit test (HCT)-116, HCT15, CO115, HT29), Islets carcinoma (RINm5F), squamous cell carcinoma (Hep-2), Squamous cell carcinoma (A549), malignant melanoma (A375, M14, A2058, B16) and oropharyngeal carcinoma [35, 36]. Sage's ursolic acid significantly prevents angiogenesis, metastases, and cellular invasion of cancerous cells by preventing pulmonary colonization of B16 melanocytic carcinoma within in-vivo investigational analysis [37]. Macro-phagocytic releasing of Nitric oxidases and Tumor Necrosis factor-alpha is triggered by *S. officinalis* administration owing to the presence of several cytotoxic and anti-carcinogenic components. [38] Metastatic colorectal cancer (CRC) significantly contributes towards mortalities within the Western countries developed as a result of genetic and epi-genetically modifications verily signifying potential capabilities of *S. officinalis* dietary components to viably alter the epigenetic state and playing a significant role in preventing colonic metastatic oncogenes within experimental rats [39]. Another study hypothesized the experimental demonstration of substantially reducing the oxidative H2O2-induced DNA destruction through *S. officinalis* aqueous extract supplementation within in-vitro analysis. A few isolated diterpenoids from the *S. officinalis* roots were found to possess chemotherapeutic and DNA degradation activities within human colonic carcinoma cells Caco-2 and within hepatic cells HepG2 as analyzed through in-vitro analysis [40]. *S. officinalis* driven sesquiterpenoidal proportion encompasses alpha-humelene exhibited stronger cytotoxicity within human prostate cancerous LNCaP cells [40]. Trans-caryophyllene isolated from sesquiterpene fraction from *S. officinalis* possesses stronger cytotoxicity against melanotic malignancy and renal adenocarcinoma cells within human prostate carcinoma LNCaP cells [41]. A diterpenoidal manool causes cytotoxic effects within human cervical mesonephric and Grade IV astrocytoma [42]. Flavonoids such as rosmaricin acid potentially exhibited anti-cancerous protective effects by inhibiting or preventing the growth of skin carcinoma cells within a rat model of dimethyl Benz (a) anthracene and also prevented bone metastasis due to breast carcinoma [43, 44]. Anti-carcinogenic effect of flavonoids possesses inhibitory activity on key signalling pathways involved in the regulation of G1 Phase Progression within proliferating hepatocytes, reactive oxygen species (ROS) generation, NF-κB factor, and exempted probable reduction within pro-inflammatory cyclo-oxygenase genetic expression [45, 46]. *S. officinalis* supplementation potentially inhibited various angiogenic stages (proliferators, migratory, adhesion, and tubular formation phase) within endothelium cells [47]. *S. officinalis* essential oil possesses demonstrated anti-mutagenic action by reducing or preventing UV-induced mutations within *E. coli* and S. cerevisiae [48]. Methyl methane-sulphonate mutations were inhibited and mitigated through the use of S. officinalis infusion tea [49]. *S. officinalis* methanolic isolate exhibited preventative effects against cyclophosphamide-induced gene toxicity within rat models [50, 51]. Anti-mutagenic efficacy of *S. officinalis* is strongly attributable to its mono-terpenoidal components such as thujone, camphor, limonene, and 1,8-cineole potentially exhibiting anti-carcinogenic and anti-mutagenic effects [48].

Anti-Hyperlipidemic Effects

The beneficial effects of various herbal medicinal plants influence regulatory effects on the body's metabolism majorly on adipogenesis, lipolysis, and serum lipids [52]. Pancreatic lipase plays a significant role in lipid degradation with a regulatory effect on fat absorption and metabolism [53]. Various studies on anti-obesity compounds from natural medicine, *S. officinalis*

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characteristics of its natural components, and its mechanistic action on pancreatic lipases and fats digestion were outlined. *S. officinalis* methanol extract signified inhibitory activity on pancreatic lipases and suppressed serum triglyceride elevation within an olive-oil-supplemented rat model [54]. Two diterpenoids such as carnosol and carnosic acid isolated from the methanol extract of *S. officinalis* possess inhibitory action on pancreatic lipases. Moreover, carnosic acid considerably decreased TG percentiles within the olive oil-loaded rat model by reducing body weight gain and accumulation of epididymal fat within the high fat-fed mice model after fourteen days [54]. *S. Officinalis*-derived carnosic acid substantially decreased triglycerides (TG) spike, total cholesterol, low-density lipoprotein (LDL) levels, excess body weight, and abdominal fat mass within diet-supplemented obese rats. *S. officinalis* investigational analysis possesses a beneficial effect on serum lipid profile with hyperglycemic animals which probably exhibited low levels of triglycerides, creatinine, urea, aspartate aminotransferase (AST) and alanine aminotransferase (ALT) levels within Streptozotocin (STZ)-induced diabetic rats [55]. *S. officinalis* investigational analysis hypothesized significant improvement in TG, total cholesterol, LDL, very-low-density lipoprotein (VLDL), and 2 hours' post-prandial blood glucose levels within hyper-lipidemic and hyper-glycaemic patients [56]. *S. officinalis* flavonoid content has also been shown to exhibit therapeutically advantageous effects in managing dyslipidemia within hyper-glycaemic and hyper-cholesterolemic patients [22]. *S. officinalis* isolated rutin fraction decreases adiposity and body weight gain within high fat diet-induced obese rat model further improving mitochondrial DNA composition and mitochondrial biogenesis-related genetic expression. (e.g., Peroxisome proliferator-activated receptor-gamma coactivator (PGC)-1α, Nuclear respiratory factor (NRF-1), transcription factor A, and nicotinamide adenine dinucleotide-dependent deacetylase) within skeletal muscles [57].

Neurocognitive Development

Several plant-derived botanical extracts from *S. officinalis* are widely recognized for their beneficial effects in treating memory disorders and in ameliorating depressive symptoms [58]. Increasingly supportive evidence apprehended *S. officinali's* potential neuro-cognitive and memory-boosting effects. In the experimental model, it has been demonstrated that ethanolic extract from *S. officinalis* enhances and improves cognitive and passive memory retention learning within rats. Garden Sage (*S. officinalis*) has been prescribed for ages to restore lost or deteriorating mental abilities, such as those triggered by Alzheimer's disease (AD), and boosts immediate world recall efficiency [59]. In AD, the enzyme acetylcholinesterase is degraded and inactivated acetylcholine, which is a neurotransmitter associated with the transmission of signals between synapses. Anti-AChE inhibiting drugs function by counteracting acetyl-choline depletion and enhancing acetylcholine content within the brain cells. *S. officinalis*-derived essential oil inhibited 46% of AChE activities at the concentration range of 0.5mg/ml [60]. *S. officinalis*-derived hydro-alcoholic extract and its main flavonoid rosmarinic acid enhance cognitive learning within healthy rats by preventing diabetes-related memory impairments [61]. *S. officinalis*-derived hydro-alcoholic isolate attenuated morphine-induced memory impairments [62, 63]. Additionally, *S. officinalis* supplementation enhances cognitive learning and memory retention and possesses positive effects on mood disorders with an increase in alertness, peace, and contentment levels with an increase in significant dosage relationship [64]. Ethanol-extracted isolates of this plant enhance and boost cognitive memory and ameliorate attention deficits within over-aged participants [65]. Plant essential oil aromas possess positive effects on neuro-cognitive development and mood disorders as investigated through experimental analysis. Moss *et al*, in the year 2010 analyzed that *S. officinalis* essential oil supplementation enhanced and improved long-term memory restoration and word recall possessing a noticeable improvement that influenced memory recollection as analyzed through the Cognitive Drug Research (CDR) Systematic Approach within healthy individuals [66]. *S. officinalis* supplementation benefited long-term protective effects against the emergence and progression of dementia by possessing long-term anti-oxidative and anti-inflammatory mechanisms [64] Sage's probable cytoprotective effect against amyloid beta plaques toxicity within nerve cells provides a pharmacological framework for conventionally using S. officinalis against Alzheimer disease. *S. officinalis*-derived rosmaricin acid exhibits neuroprotection, and antioxidant activities and causes caspase-mediated cell death which enhances its utilization in the treatment of AD [67, 68]. By demonstrated experimental trials, *S. officinalis* therapeutically supplementation exhibited potentially protective neurocognitive and memory-enhancing effects by acting as a promising therapeutically herbal remedial approach against Alzheimer's disease.

Microbicide Activity

S. officinalis potential anti-microbial and microbicide implications were supported through a wide array of experimental trials. *S. officinalis* derived ethanolic essential oil exhibited potential germicidal anti-septic and possesses high sensitivity as a bacteriostatic agent

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against gram-negative and gram-positive bacterial pathogenic strains (*B.cerus*, *L.monocytogens*, and *S. auerus*) and its mechanistic action primarily dependent on the type of extract used *S.officinalis* essential oil exhibited a substantial inhibitory effect on the growth of bacterium hydrophilum, Aeromonas Septicemia (MAS), Burkholderia pseudomallei and "Group D Shigella" possessing a weaker attraction for *E.coli* and *S. enteriditis* [69]. Furthermore, the bactericidal effect of *S. officinalis* has reportedly been claimed to induce fungicidal, and viricidal and act as an anti-parasitic chemical agent [56]. *S. officinalis* exhibited anti-fungicidal activity against *B.cinera*, *C.albicans*, and *C.parapsilosis* as analyzed through experimental analysis [70]. The bactericidal activity of *S. officinalis*-derived water-based extract within *in-vitro* analysis against specific food-decomposing bacterial species indicated substantial bactericidal effects against *B. mycoides*, *B. subtilis*, and *Proteus spp* [71]. The experimental analysis demonstrated that *S. officinalis* extracted essential oil acts as a potential substitute in line with alternative therapeutically anti-bacterial [72]. *S. officinalis*-driven terpenoidals, camphor, and thujonoic acid also exhibited substantial microbicide activities against *A. hydrophila*, *A. sobria*, *B subtilis*, and *klebsiella oxytoca* as analyzed through experimental trials [73]. Another analysis by Horiuchi K *et al.*, in the year 2007 hypothesized that oleanic acid and ursolic acid derived from *S. officinalis* exhibited growth inhibitory action against antibiotic-resistive microscopic bacteria such as enterococcus exhibited resistive action against vancomycin drug, Penicillium resistive *S. pnuemonia* and methicilin resistive *S. aureus*. The experimental analysis demonstrated that urosolic acid derived from *S. officinalis* exhibited stronger microbicidal activity against entero-bacterial *E. faceium* and multi-drug resistive bacterial species in comparison with ampicillin. Another experimental analysis showed that carnosolic acid, a dieterpenoidal from *S. officinalis* exhibited bactericidal properties potentiating the mechanistic action of antibiotic aminoglycosides within methicilin resistive *S. aureus* [74]. *S. officinalis* viricidal activity is probably intervened by safficinolide content which primarily features in its aerial sections [75]. Experimental analysis hypothesized probable efficacy and growth-inhibiting action of a hydro-alcoholic isolate from *S. officinalis* against certain dental diseases aggravated by *S. mutans*, *L. rhamnosus*, and *A. viscosus*. Given replacing herbal therapeutically conventional treatment with pharmacological therapies, *S. officinalis* anti-bacterial properties might be an alternative remedial approach for treating multiple diseases, particularly affecting the oral cavity [76]. Research revealed that Common Sage (*S. officinalis*) in combination with certain other herbal botanicals was analogous to synthetic preservative agents thereby demonstrating that water-soluble isolated extract can be employed in biotechnological research as a natural preservative component within the food sector [71].

Toxicological Effects

Multiple sub-clinical research investigations on animal trials have hypothesized that *S. officinalis* administration possesses no adverse consequences and does not trigger any negative adverse reactions [77]. However, prolonger administration and subsequent over-dosage of isolated ethanol extract and volatile oil (equivalent to greater than 15 g of the leaf), several undesirable outcomes including acro-cyanosis, sputum production, arrhythmias, light-headedness, vasomotor symptoms, hyper-sensitivity and in extreme condition seizures might occur. *S. officinalis* oil's mediated pro-convulsion action is possibly owing to its immediate effect on the peripheral neurological nerves [78]. Research trials hypothesized that *S. officinalis*-derived terpenoidal ketones such as camphor and thujonoic acid when taken in extremely high dosages might considered a potentially hazardous compound that could pose detrimental effects on fetuses and newly born infants. Consequently, *S. officinalis* consumption is not recommended for pregnant and lactating mothers [79]. Experimental research trials within animals demonstrated that the LD50 value for *S. officinalis oil* (oral administration) and methanol's isolated extract (intraperitoneal administration) is considered to be 2.6g/kg and 4g/kg correspondingly [59].

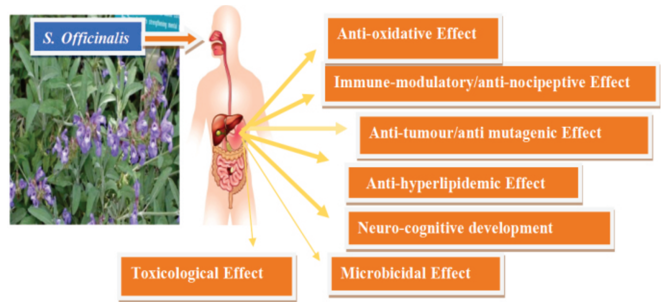

Figure 1: Pharmacological Beneficial Functional Properties of Common Sage (*Salvia Officinalis*)

CONCLUSIONS

The objective of this article is to undermine and explore the current advancements by probing the therapeutic significance and pharmacological effectiveness of Common Sage (*S. officinalis*) as a conventional medicinal herb gaining a lot of popularity in Today's World. Common Sage (*S. officinalis*) is rich in phytochemicals and antioxidants and possesses a wide range of bioactive components such as alkaloids, carbohydrates, fatty acids, glycosides derivatives, phenolic compounds, and poly-acetylenes exhibiting extensive biological effects, have proven to be exceptionally effective in the development of

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innovative natural pharmaceuticals regulating and preventing a variety of acute medical health problems as well as more serious and chronic health problems exhibiting anti-oxidative, immune-modulatory, anti-nociceptive activities, anti-tumor, anti-mutagenic effects, anti-hyperlipidemia effect, neurocognitive development, microbicide activities alongside toxicological investigational analysis of *S. officinalis* exhibited LD50 dosage for oral administration and methanol isolated extract (intraperitoneal administration) considered to be 2.6g/kg and 4g/kg respectively. Owing to *S. officinalis* therapeutically pharmacological significance, probable biochemical and medicinal experimentation along with human metabolically investigations ought to be the primary objective of our forth-coming studies and the prospective potential of *S. officinalis* has to be used in novel therapeutic medications.

Authors Contribution

Conceptualization: SI
Methodology: NA, SH, FH, SR, WA, AUK
Formal analysis: SI
Writing review and editing: SI, MKN

All authors have read and agreed to the published version of the manuscript.

Conflicts of Interest

All the authors declare no conflict of interest.

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