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REVIEW ARTICLE

Salvia (Sage): A Review of its Potential Cognitive-Enhancing and Protective Effects

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Abstract Genus *Salvia*, commonly known as sage, is the largest genus in the Lamiaceae family. It comprises many species traditionally used as brain-enhancing tonics. In vitro and animal studies have confirmed that several *Salvia* species contain a large array of active compounds that may enhance cognitive activity and protect against neurodegenerative disease. In this review, the active constituents in plants belonging to the genus *Salvia* are summarised, and their influence on pharmacodynamics pertinent to cognitive activity are detailed. In particular, the effects of plants belonging to the genus *Salvia* and their constituents on cognitive skills including memory, attention and learning are detailed. Their potential effects in dementia, including Alzheimer's disease, are also examined. Completed human trials are summarised, and factors influencing the potency of *Salvia* plants are covered. Finally, directions for future research are proposed to enhance our understanding of the potential health benefits of *Salvia* plants.

Key Points

Salvia plants and their constituents can influence several biological mechanisms associated with cognition including their effects on amyloid-β, cholinergic activity, neurotrophins, oxidative stress, inflammation and anxiolytic/antidepressant behaviours.

Several studies have confirmed the many *Salvia* species have promising, cognitive-enhancing effects in human adults.

Further research is required to examine the longer-term cognitive-enhancing effects of *Salvia* species on cognition, memory and the treatment of neurodegenerative diseases such as Alzheimer's disease.

1 Introduction

Cognition refers to mental actions associated with acquiring knowledge. It encompasses processes associated with attention, memory, judgment and evaluation, reasoning, problem solving and decision making. Interest in herbal remedies as cognitive-enhancing agents (often referred to as nootropics) is on the increase with several promising compounds available, including curcumin, *Ginkgo biloba* and *Bacopa monnieri*. The genus *Salvia* (sage) is the largest genus of plants in the Lamiaceae family, comprising over 900 species distributed throughout the world.

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Common species include *S. officinalis* (common sage), *S. miltiorrhiza* (Chinese sage), *S. lavandulaefolia* (Spanish sage), *S. fruticose* (Greek sage), *S. sclarea* (clary sage) and *S. hispanica* (chia).

Salvia officinalis comes from the Latin word meaning 'to heal' and is widely used in both culinary and medicinal preparations. Many species of *Salvia* are native to Mediterranean Europe and have been traditionally used for the treatment of a range of problems including digestive and circulation disturbances, bronchitis, coughs, asthma, memory problems, angina, mouth and throat inflammation, depression and excessive sweating. *Salvia* plants are traditionally noted for their antioxidant effects and ability to enhance 'head and brain' function, improve memory, quicken the senses, and delay age-associated cognitive decline [1].

In this review, the active constituents in plants belonging to the genus *Salvia* are summarised, and their influence on pharmacodynamic activity pertinent to cognition are detailed. In particular, the effects of plants belonging to the genus *Salvia* and their constituents on cognitive skills including memory, attention and learning are detailed. Their potential effects in dementia, including Alzheimer's disease, are also reviewed. Completed human trials are summarised, and factors influencing the potency of *Salvia* plants are covered. Finally, directions for future research are proposed to enhance our understanding of the potential health benefits of *Salvia* plants.

2 Active Constituents in Salvia Species

As detailed in Table 1, *Salvia* plants are a rich source of polyphenol compounds with over 160 identified polyphenols, comprising an array of phenolic acids and flavonoids. These phenolic compounds include caffeic acid and its derivatives, rosmarinic acid, salvianolic acids, sagecoumarin, lithospermic acids, sagernic acid, and yunnaneic acids. The most prevalent flavonoids include luteolin, apigenin, hispidulin, kaempferol and quercetin [2]. Plants of the genus *Salvia* are also rich in essential oils, with a large array of terpenoids including α and β-thujone, camphor, 1,8-cineole, α-humulene, β-caryophyllene and viridiflorol. Moreover, they are rich sources of diterpenes and triterpenes such as carnosic acid, ursolic acid, carnosol and tanshinones.

The composition of the polyphenols and terpenoids can vary considerably across *Salvia* species. For example, rosmarinic acid is high in *S. officinalis* but low in *S. hypoleuka* [3]. Levels of thujone are also reported to be higher in *S. officinalis* compared with *S. lavandulaefolia* [4]. Tanshinones are found in *S. miltiorrhiza* [5], and varying forms of yunnaneic acids and salvianolic acids differ across *Salvia* species.

Table 1 Common compounds identified in *Salvia* species

Phenolic acids	Caffeic acid, rosmarinic acid, salvianolic acids, sagecoumarin, lithospermic acid, sagerinic acid, yunnaneic acids
Flavonoids	Luteolin, apigenin, hispidulin, kaempferol, quercetin
Terpenoids	α and β-Thujone, camphor, 1,8-cineole, α-humulene, β-caryophyllene, viridiflorol, carnosic acid, ursolic acid, carnosol, tanshinones
Polysaccharides	Arabinogalactans, pectin

3 Salvia and its Pharmacodynamic Influences on the Brain

Cognitive activity and performance can be influenced by an array of neurological and biochemical factors. Damage to specific neurological structures can be associated with specific cognitive deficits, and there is an increasing awareness of the influence of different hormones and neurotransmitters on cognitive activity. Because of its rich array of chemical constituents, plants of genus *Salvia* can influence multiple physiological pathways (summarised in Fig. 1). Those especially pertinent to cognition are summarised in the following sections.

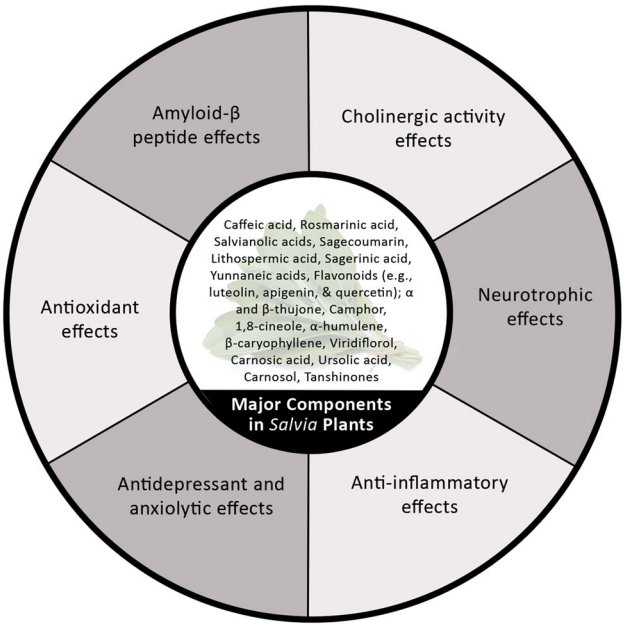

Fig. 1 Major components in *Salvia* species and their pharmacodynamic effects in the brain

3.1 Salvia and Amyloid-β

The accumulation of the amyloid-β peptide (Aβ) is a characteristic of Alzheimer's disease and its deposition is considered partially responsible for the cognitive dysfunction seen in Alzheimer's disease. It is theorised that aggregated Aβ is accountable for the progressive nature of the disease, as the unregulated build-up of aggregates are neurotoxic, causing dysfunction to cholinergic neurons and calcium homeostasis, and promoting the formation of reactive oxygen species (ROS) and pro-inflammatory responses. Aβ are known to cause specific learning and memory impairment and its administration has been renowned for inducing memory loss in animal models [6].

Salvia miltiorrhiza has been shown to protect mice from Aβ-induced neurotoxicity by inhibiting increases in tumour necrosis factor-α (TNF-α), interleukin-6 (IL-6) levels and acetylcholinesterase (AChE) activity [7]. Tanshinones from *S. miltiorrhiza* can also protect against Aβ-induced toxicity by ameliorating mRNA expression of inducible nitric oxide synthase (iNOS), matrix metalloproteinase 2 and nuclear transcription factor-κ [8].

Animal studies have demonstrated that supplementation with *S. sahendica* attenuated memory deficits, modulated cAMP response element binding protein and its downstream molecules and decreased apoptosis in Aβ-injected rats [9]. In mice exposed to an acute injection of Aβ, rosmarinic acid also prevented Aβ-induced nitration of proteins (an indirect indicator of peroxynitrite damage) in the hippocampus. Rosmarinic acid also prevented memory impairments induced by Aβ toxicity [10]. Protective effects from Aβ toxicity have also been observed following the administration of the *Salvia* constituents, salvianolic acid [11], carnosic acid [12] and quercetin [13].

3.2 Salvia and Cholinergic Activity

Central cholinergic signalling has long been associated with features of memory, motivation and mood. Acetylcholine (ACh), a neurotransmitter involved in cholinergic signalling, is believed to play an important role in several aspects of cognitive function and behaviour, including attention, learning, memory and motivation. Alterations in ACh signalling are involved in the pathophysiology of multiple neurodegenerative disorders including Alzheimer's disease [14]. Recent studies have also provided support for a role of cortical ACh in attentional effort, orientation and the detection of behaviourally significant stimuli [15].

AChE is an enzyme that catalyses the breakdown of acetylcholine and there are several AChE inhibitor drugs available to increase overall ACh concentration. These drugs are based on the premise that increasing the availability of ACh at acetylcholine receptors in the brain enhances neuron-to-neuron transport and ultimately improves cognitive function [16].

In vitro and animal studies have revealed that several *Salvia* species and their constituents are effective AChE inhibitors. An aqueous extract of *S. officinalis* lowered AChE activity in mice [17], and *in vitro* analyses revealed that ethanolic extracts of *S. officinalis* reduced AChE, with greater effects on butyrylcholinesterase [18, 19]. In mice subjected to Aβ peptide, pre-treatment with *S. sahendica* significantly ameliorated reductions in AChE activity and memory performance [20]. The essential oil of *S. fruticosa* also showed inhibition against AChE [21], and similar findings were revealed from the essential oil of *S. lavandulaefolia*, although AChE inhibiting activity occurred exclusively via the monoterpernoids [22]. AChE inhibition has also been observed from the phenolic diterpenes, 7a-methoxyrosmanol and isorosmanol, isolated from *S. officinalis*. [23]. The active constituents, rosmarinic acid, carnosic acid and quercetin, found in several *Salvia* species can also inhibit AChE activity [23–25]. The tanshinones from *S. miltiorrhiza* also inhibit both AChE and butyrylcholinesterase activity [26, 27].

3.3 Salvia and Neurotrophins

Neurotrophins are important regulators of neural survival, development, function and plasticity [28]. Brain-derived neurotrophic factor (BDNF) is one neutrophin that has received particular attention in cognitive and neurological research due to its role in supporting the survival of existing neurons, encouraging the growth and differentiation of new neurons and synapses, and enhancing learning and memory [29]. In a recent meta-analysis, peripheral BDNF levels were confirmed to be lower in patients with Alzheimer's disease and mild cognitive impairment [30].

In one study, the administration of *S. miltiorrhiza* to mice mitigated Aβ-induced reductions in BDNF [7]. Rosmarinic acid also protected against memory deficits induced by cerebral artery occlusion in mice. One mechanism of the neuroprotective effects of rosmarinic acid involved an increase in BDNF [31]. In rats exposed to chronic unpredictable stress, rosmarinic acid restored hippocampal BDNF. Moreover, in vitro experiments revealed that rosmarinic acid increased BDNF levels in cultured astrocytes [32].

Caffeic acid reduced immobility time of mice in the forced swim test and ameliorated stress-induced reductions in levels of BDNF mRNA in the frontal cortex. Caffeic acid did not modify the levels of BDNF in brain regions of naive mice, indicating that it primarily attenuates the down-regulation of BDNF transcription during stressful conditions [33].

The flavonoid luteolin was identified to be highly active in inducing the synthesis and secretion of neurotrophic factors, including nerve growth factor, glial-derived neurotrophic factor and BDNF in cultured astrocytes [34]. There have also been some reports that quercetin can increase BDNF levels in brain injury models [35]. The production of nerve growth factor, another neurotrophin important for the growth, maintenance and survival of neurons, has also been shown to be enhanced by carnosic acid, carnosol [36], tanshinones [37] and quercetin [38].

3.4 Salvia and Antioxidant Effects

Excess free radical activity and reduced antioxidant defences create a state of oxidative stress. Over time, oxidative stress can damage all body tissues, with the brain particularly susceptible. Oxidative stress has been implicated in many neurological disorders including Alzheimer's disease [39] and Parkinson's disease [40]. Oxidative stress is also elevated in many mental health disorders including major depressive disorder [41] and attention-deficit hyperactivity disorder (ADHD) [42]. Moreover, animal models of induced oxidative stress have confirmed that it can adversely influence memory and learning performance [43, 44].

Salvia plants and their individual constituents possess strong antioxidant activity. In an analysis of 10 *Salvia* species, it was confirmed that all species exhibited significant antioxidant activity as measured by oxygen radical absorbance capacity, radical scavenging capacity and total phenolic content. The extent of antioxidant activity varied across species and extraction methods used, the ethanolic extract of *S. officinalis* exhibited the highest activity [45].

It has been confirmed that *S. miltiorrhiza* can reduce the production of ROS by inhibiting oxidases, reducing the production of superoxide, inhibiting the oxidative modification of low-density lipoproteins and ameliorating mitochondrial oxidative stress. *S. miltiorrhiza* also increases the activities of catalase, manganese superoxide dismutase, glutathione peroxidase, and coupled endothelial nitric oxide synthase [46]. In an animal model, *S. officinalis* prevented diabetes-induced acquisition and memory deficits by inhibiting lipid peroxidation and enhancing antioxidant defence systems [47].

The majority of antioxidant effects are attributed to *Salvia* phenolic compounds such as rosmarinic acid, salvianolic acid, sagecoumarin and sagerinic acid as they exhibit strong radical scavenging activity with approximately 90% of 2,2-diphenylpicrylhydrazyl (DPPH) scavenged under the experimental conditions. In fact, their effects were substantially greater than the sage flavonoids, luteolin and apigenin [48]. In another in vitro study, salvianolic acid L showed potent free radical scavenging activities for DPPH and superoxide anion radicals. It was identified as a significantly better scavenger of these free radicals than trolox (a water-soluble analogue of vitamin E), caffeic acid and rosmarinic acid [49].

The monoterpenes 1,8-cineole and α-pinene identified in *S. lavandulaefolia* essential oil were also able to attenuate oxidative injury in astrocytes by inhibiting ROS production and increasing endogenous antioxidant compounds (e.g. glutathione, catalase, superoxide dismutase, heme oxygenase 1 activity and protein expression) [50]. Carnosic acid and ursolic acid are also powerful antioxidants [51, 52].

3.5 Salvia and Anti-Inflammatory Effects

Evidence for the influence of inflammation on cognitive function is accumulating. In animal models, the activation of the immune system with lipopolysaccharides (LPS) [44], a high-fat diet [53] or the non-invasive enteric pathogen, *Citrobacter rodentium* [54], induced memory impairments. In a meta-analysis, it was confirmed that an elevated level of C-reactive protein was associated with a 45% increased risk of all-cause dementia, and a higher level of IL-6 was associated with a 32% increased risk. In patients with Alzheimer's disease, the association remained significant but less pronounced for C-reactive protein, while there was no association with IL-6 [55]. However, in a meta-analysis on studies in people with mild cognitive impairment, no significant differences in inflammatory factors with healthy controls were identified [56]. Increased inflammation has been demonstrated in patients with ADHD [57], and increased inflammatory markers are associated with decreased psychomotor speed in patients with major depressive disorder [58], and reduced cognitive performance in adults suffering from acute-phase psychosis [59].

Findings from in vitro and animal studies have demonstrated that *Salvia* species and their constituents have anti-inflammatory effects. An examination of the essential oils in *S. officinalis* (mainly comprising 1,8-cineole and camphor) revealed that it significantly inhibited nitric oxide production stimulated by LPS in mouse macrophages [60]. Acute inflammation induced with intraperitoneal administration of turpentine oil in mice was significantly reduced by *S. officinalis* tincture, demonstrated by reductions in total leukocyte and monocyte percentages, and the activation of circulating phagocytes [61]. Phenolic diterpenes (carnosol and carnosic acid) present in *S. officinalis* reduced nitric oxide and prostaglandin E_2 (PGE_2) production in LPS-stimulated macrophages. They also significantly blunted gene expression levels of iNOS, cytokines/interleukins (IL-1α, IL-6) and chemokines including CCL5/RANTES and CXCL10/IP-10 [62].

A methalonic extract of *S. plebeian*, and several of its active components, significantly reduced inflammatory

processes induced by the in vivo exposure of 12-*O*-tetradecanoylphorbol-12-acetate, and in vitro exposure to LPS-activated macrophages. *S. plebeian* decreased the release of nitric oxide, cyclooxygenase-2 (COX-2), PGE_2 and the expression of iNOS [63].

Bioactive constituents contained in *S. miltiorrhiza* such as the tanshinones and salvianolic acids have also been shown to have anti-inflammatory mechanisms by influencing cytokine production and iNOS activity. They also inhibited COX-2, hypoxia-inducible factor-1α, and nuclear factor κβ activity [64]. Moreover, in one study, tanshinones isolated from *S. miltiorrhiza* significantly inhibited the mRNA and protein expression of TNF-α, IL-1β, and IL-8 in LPS-stimulated macrophages [65]. Investigations into the constituents of *Saliva* plants have also confirmed that caffeic acid, rosmarinic acid [66] and ursolic acid [51] have strong anti-inflammatory properties.

3.6 Salvia and Antidepressant and Anxiolytic Effects

Depression and chronic stress can have deleterious effects on cognitive performance. In fact, cognitive deficits including impairments in memory, attention and learning are common symptoms of major depressive disorder and most anxiety disorders [67]. Exposure to chronic and acute stress can adversely affect cognitive abilities. Alzheimer's disease also has a high comorbidity with major depression and it has been demonstrated that depressive symptoms can be a prodrome to this condition [68]. Interventions that have beneficial effects on depression and anxiety are therefore likely to have positive effects on cognitive performance.

The administration of hydroalcoholic extracts of *S. elegans* [69] and *S. verticillata* [70] has been shown to produce antidepressant and anxiolytic-like effects via animal models of depression and anxiety. The same has been observed following the administration of essential oils of *S. sclarea* [71, 72] and *S. miltiorrhiza* [73]. In fact, the effects of *S. sclarea* were more pronounced than those obtained from the administration of essential oils of *Anthemis nobilis* (chamomile), *Rosmarinus officinalis* (rosemary), and *Lavandula angustifolia* (lavender). The anti-stressor effect of *S. sclarea* was significantly blocked by pretreatment with dopamine receptor antagonists, indicating its influences via dopaminergic activity [72]. Several constituents from *S. officinalis* also influence benzodiazepine receptor activity, including the flavones, apigenin, hispidulin and cirsimaritin; and the diterpenes, 7-methoxyrosmanol and galdosol [74].

The phenolic acids, rosmarinic acid and caffeic acid, also possess antidepressant and anxiolytic-like activity. In a neuropharmacological analysis, neither of these substances affected either the uptake of monoamines to synaptosomes or mitochondrial monoamine oxidase activity in the mouse brain, suggesting that they produce their antidepressant effects via mechanisms other than the inhibition of monoamine transporters and monoamine oxidase [75, 76]. Moreover, salvianolic acid B, a compound from *S. miltiorrhiza* [77], and salvinorin A from *S. divinorum* [78] exhibited antidepressant and anxiolytic effects in animals models.

4 Human Trials on the Brain-Enhancing Effects of Salvia

The cognitive-enhancing efficacy of plants of genus *Salvia* has been investigated in several human trials and are summarised in Table 2. There have been two trials undertaken in patients with Alzheimer's disease, both with preliminary, positive findings. In a pilot, open-label study, 11 patients with probable Alzheimer's disease were administered capsules containing 50 μL of *S. lavandulaefolia* essential oil, administered 1–3 times per day over a 3-week period. Capsule intake was well tolerated, although two patients with a history of hypertension experienced increases in blood pressure at the highest dose. There were statistically significant reductions in caregiver-rated neuropsychiatric symptoms, and improvements in attention over the 6-week period, although these findings were tempered by the open-label, no-placebo arm, and small sample size [79]. In a randomised, double-blind, placebo-controlled study, the efficacy of an ethanolic extract of *S. officinalis* was evaluated in patients with Alzheimer's disease. In this 4-month study, participants allocated to the active-drug condition (60 drops of *S. officinalis* daily) experienced significantly greater improvements in cognitive function as measured by the Alzheimer's Disease Assessment Scale, and the Clinical Dementia Rating Scale. *S. officinalis* administration was well tolerated with no differences in adverse effects across the active and placebo conditions [80].

The cognitive-enhancing effects of acute, single administration of different *Salvia* species has been investigated in six studies, five utilising randomised, double-blind, placebo-controlled designs. In five studies, the efficacy of *Salvia* plants in healthy young adults was investigated, while one was conducted on healthy, older-age volunteers. Positive cognitive (e.g. secondary memory, attention, word recall and speed of memory) and mood-enhancing (e.g. alertness, calmness and contentedness) effects from the single administration of differing dosages of essential oil of *S. lavandulaefolia* in healthy adults was demonstrated [22, 81, 82]. Improvements in mood (e.g. alertness, contentedness, and calmness) and cognition were

Table 2 Summary of human trials investigating the cognitive effects of plants of *Salvia* species

Study	Duration	Study design	Participants	Intervention	Main results
Alzheimer's disease					
Akhondzadeh et al. [80]	4 months	Double-blind, placebo-controlled study	30 patients completed trial with average age of 72 years	*S. officinalis* extract 60 drops/day or placebo 60 drops/day. *Salvia* extract was prepared as 1:1 in alcohol 45%	Over a 4-month period, people taking *Salvia* liquid drops experienced significantly better cognitive function (as measured by the Alzheimer's Disease Assessment Scale, and Clinical Dementia Rating Scale) compared with adults taking placebo capsules
Perry et al. [79]	6 weeks	Open-label design	11 patients aged 76–95 years in whom a diagnosis of mild to moderate probable Alzheimer's disease was established	Capsules contained 50 μL essential oil of *S. lavandulaefolia* plus 50 μL of sunflower oil GC analysis demonstrated 94 peaks, the major peaks were of borneol, camphene, camphor, 1,8-cineole and α-terpineol, with only a trace of thujone. Dosage—Week 1: one capsule at 8 a.m.; Week 2: one capsule at 8 a.m. and one capsule at 7 p.m.; Weeks 3–6: as above with one additional capsule at 12:30 p.m.	There were statistically significant reductions in neuropsychiatric symptoms and an improvement in attention from baseline to 6 weeks
Acute cognitive and mood effects					
Tildesley et al. [82]	6 h	Double-blind, placebo-controlled study	Trial 1, 20 healthy adults with a mean age of 20 years; Trial 2, 24 healthy adults with a mean age of 23 years	In Trial 1, 20 participants received 50, 100 and 150 μL of a standardised essential oil extract of *S. lavandulaefolia* and placebo. In Trial 2, 24 participants received 25 and 50 μL of a standardised essential oil extract of *S. lavandulaefolia* and placebo GC-MS was performed and the terpene constituents were as follows (%): α-pinene, 6.5; camphene, 6.3; β-pinene, 5.4; myrlene, 1.9; limonene, 1.2; 1,8-cineole, 25.8; camphor, 24.4; caryophyllene, 1.2; terpinen-4-OL, 2.0; borneol, 3.3; α-terpineol, 2.8	In Trial 1, memory performance was enhanced for the 50-μL dose at 1- and 2.5-hour time points. The effect was also apparent following administration of the 100 μL dose at 2.5 h post-dose sessions. A dose-specific enhancement on delayed word recall was also observed for the 50 μL dose at 1 and 2.5 h post-dose In Trial 2, the immediate word recall effect at 1 hour was maintained, and this was coupled with improved memory performance at 4 h post-dose testing session for the same dose. No significant enhancement on either immediate or delayed word recall was found for either the lowest (25 μL) or the highest (150 μL) doses of *Salvia*
Tildesley et al. [81]	6 h	Double-blind, placebo-controlled study	24 healthy adults with a mean age of 23 years	Two identical capsules corresponding to a dose of either 0 (a sunflower oil placebo), 25 μL, or 50 μL of *S. lavandulaefolia* essential oil in sunflower oil	Administration of *S. lavandulaefolia* resulted in a consistent improvement for both the 25- and 50-μL dose on the 'Speed of Memory' factor. There was also an improvement on the 'Secondary Memory' factor for the 25-μL dose. Mood was consistently enhanced, with increases in self-rated 'alertness', 'calmness' and 'contentedness' following the 50-μL dose and elevated 'calmness' following 25 μL

Table 2 continued

Study	Duration	Study design	Participants	Intervention	Main results
Kennedy et al. [18]	4 h	Double-blind, placebo-controlled study	30 healthy adults with a mean age of 24 years	On each study day participants received 4 capsules of identical appearance, each containing either placebo or 150 mg of *S. officinalis* dried leaf. Drug dosages corresponded to either 0 mg (placebo), 300 or 600 mg of *S. officinalis* dried leaf	Both doses of *Salvia* led to improved ratings in mood in the absence of the stressor (that is, in pre-DISS mood scores) post-dose, with the lower dose reducing anxiety and the higher dose increasing 'alertness', 'calmness' and 'contentedness' on the Bond–Lader mood scales The reduced anxiety effect following the lower dose was, however, abolished by performing the DISS, with the same dose also being associated with a reduction of alertness during performance. Task performance on the DISS battery was improved for the higher dose at both post-dose sessions, but reduced for the lower dose at the later testing session
Scholey et al. [19]	6 h	Double-blind, placebo-controlled study	20 healthy, older-age adults with a mean age of 73 years	Each tablet contained either 167 or 333 mg of *S. officinalis* extract. Participants received oral doses of four pills, each combination of active and placebo pills corresponding to 0 (placebo), 167, 333, 666 or 1332 mg of the standardised sage extract depending on that day's treatment The *S. officinalis* for the study was a standardised ethanolic (70%) extract of dried *S. officinalis* in an approximate concentration ratio of 7.5:1 leaf/extract	Compared with the placebo condition, the 333-mg dose was associated with significant enhancement of secondary memory performance at all testing times. The same measure benefited to a lesser extent from other doses. There also were significant improvements to accuracy of attention following the 333-mg dose. In vitro analysis confirmed cholinesterase inhibiting properties for the extract
Moss et al. [83]	Not specified	Randomised, single-blinded study	135 healthy adults with a mean age of 22 years	*S. officinalis* aroma, *S. lavandulaefolia* aroma and no aroma (control). Five drops of the appropriate essential oil and 5 mL water were placed on the stone and left to diffuse into the testing cubicle	*S. officinalis* aroma group performed significantly better than the control group on the quality of memory and secondary memory primary outcome factors from the test battery. The Alert mood measure displayed significant differences between both aromas and the control condition
Kennedy et al. [22]	4 h	Double-blind, placebo-controlled study	36 healthy adults with a mean age of 24 years	A single soft gel capsule containing either 50 mL of *S. lavandulaefolia* essential oil plus olive oil, or a placebo capsule containing olive oil	The essential oil was a potent inhibitor of human AChE and consisted almost exclusively of monoterpenoids. Oral consumption led to improved performance of secondary memory and attention tasks, most notably at the 1-hour post-dose testing session, and reduced mental fatigue and increased alertness, which were more pronounced 4-hours post-dose

AChE acetylcholinesterase, *DISS* Daytime Insomnia Symptom Scale, *GC* gas chromatography, *GC-MS* gas chromatography-mass spectrometry

also identified following the single administration of a *S. officinalis* extract to healthy young adults [18], and enhancement in memory and attention were revealed following the single administration of *S. officinalis* to healthy, older-age adults [19]. In a randomised, single-blinded design (participant-masked), Moss et al. [83] also found positive cognitive and mood-enhancing effects from acute exposure to the aroma of *S. officinalis* and *S. lavandulaefolia*.

These studies provide preliminary support for the cognitive and mood-enhancing efficacy of some *Salvia* species. However, conclusions are tempered by the small sample sizes and short treatment duration. Treatment dose, *Salvia* species and extracts used have been variable, further limiting study conclusions. Additional research is required utilising larger populations, particularly in examining its efficacy for the treatment of patients with Alzheimer's disease. Furthermore, although *Salvia* seems to have positive, acute, cognitive-enhancing effects, its effects over longer-term ingestion require investigation.

5 Factors Influencing Biological Potency of Salvia

Although the influence of plants of different species of *Salvia* on cognition has been reviewed, differences in the active constituents across each species are likely to affect their influence on biological processes and therefore their therapeutic efficacy. Currently, the relative efficacy of different *Salvia* species on cognitive function is unknown. The influence of individual constituents also requires further investigation. Moreover, human studies on cognitive function have only been conducted using *S. officinalis* and *S. lavandulaefolia*. The extracts used also varied considerably as both essential oils and ethanolic extracts were examined.

Typical factors influencing the potency of herbal remedies include growing, harvesting, collection, drying, and extraction methods used. This requires consideration when evaluating the therapeutic efficacy of *Salvia* plants. For example, in an examination of the antioxidant capacity of *S. officinalis*, it was found that methanolic extract yielded the highest total phenolic compounds and antioxidant activity compared with aqueous and ethanol extracts [84]. An evaluation of antioxidant potential of 10 *Salvia* species demonstrated that ethanol extracts possessed significantly higher antioxidant capacity and total phenolic content compared with aqueous and CO_2 extraction [45]. Ratios of amount-to-solvent, solvent temperature and duration of immersion also influence extract potency [85]. Even the season of *Salvia* plant collection is important as the highest content of rosmarinic acid in *S. officinalis* leaves was detected when collections occurred in May, July and September [86].

6 Contraindications for the Use of Salvia

The acute administration of *Salvia* in healthy adults has confirmed that its single intake is well tolerated, with no reported adverse events. The safety profile of *Salvia* plants in longer-term, human trials are summarised in Table 3. Overall, all administered *Salvia* species were well tolerated, with only minor adverse events reported. Populations examined included patients with Alzheimer' disease, menopausal women suffering from hot flushes, older-age men undergoing treatment for prostate cancer and suffering from hot flushes, male and female adults with type 2 diabetes mellitus, and male and female patients with newly diagnosed primary hyperlipidaemia. Adverse events reported across all studies comprising approximately 140 adult participants taking different *Salvia* extracts included increased blood pressure in two patients with Alzheimer's disease and a history of hypertension (essential oil of *S. lavandulaefolia*), infrequent reports of mild gastrointestinal complaints (*S. officinalis* and *S. spissum,* extraction process not detailed), and one event of acneiform skin eruption (*S. officinalis,* extraction process not detailed).

The essential oils of *Salvia* plants do contain varying concentrations of α and β-thujone [87]. In animal studies it has been confirmed that thujone can be neurotoxic by inhibiting the γ-aminobutyric acid A ($GABA_A$) receptor, causing excitation and convulsions in a dose-dependent manner. Although its effect in humans is uncertain, cases of severe intoxication in humans have been reported after consumption of essential oils rich in thujone [87]. Consequently, the Committee on Herbal Medicinal Products/European Medicines Agency (HMPC/EMA) has recommended an upper daily thujone intake of 6 mg derived from products used for medicinal purposes [88].

7 Conclusion and Directions for Future Research

Salvia plants have historically been used for the treatment of several ailments, with traditional knowledge suggesting they have benefits for cognitive and neurological conditions. From this review it seems that the knowledge passed on by our ancestors may have merit. Findings from research confirm that many *Salvia* species and their individual active constituents influence several biological processes that may impact on neurological and cognitive function. In vitro, animal and preliminary human studies have supported the evidence of *Salvia* plants to enhance cognitive skills and guard against neurodegenerative disorders. However, further research is required in several areas.

Presently, the majority of human studies have used *S. officinalis* and *S. lavandulaefolia* species, so the efficacy of

Table 3 Safety of *Saliva* plant administration in chronic human trials

Study	Study design	Population	*Salvia* treatment	Adverse events
Akhondzadeh et al. [80]	4-month, double-blind, placebo-controlled study	30 patients with Alzheimer's disease with an average age of 72 years	Ethanolic extract of *S. officinalis*, 60 drops daily	No difference in adverse events between *Salvia* and placebo conditions over the 4-month trial, except for near-statistically significant reductions in agitation ($p = 0.09$) in *Salvia*-treated patients
Perry et al. [79]	6-week, open-label design	11 patients aged 76–95 years with probable Alzheimer's disease	50 μL essential oil of *S. lavandulaefolia*, titrated to 3 capsules daily over 3 weeks	Increased blood pressure in two patients with a history of hypertension
Bommer et al. [89]	8-week, open-label design	69 women aged between 50 and 65 years (mean age 56 years), at least 12 months since last menstruation, at least five hot flushes daily	Once daily, 280-mg *S. spissum* tablet. Extract was thujone-free. Extraction process not detailed	10 adverse events among 6 patients, of which 2 were related to study medication (mild abdominal pain and mild diarrhoea in one patient)
Vandecasteele et al. [90]	8-week, open-label design	10 prostate cancer patients (median age 68) receiving androgen deprivation therapy and experiencing hot flashes	One 150-mg *S. officinalis* capsule, 3 times daily. Extract was thujone-free. Extraction process not detailed	Non-significant decrease in luteinising hormone and follicular stimulating hormone. One patient experienced acneiform skin eruption after 6 weeks on *Salvia*. Causal connection with sage could not be ruled out
Behradmanesh et al. [91]	12-week, double-blind, placebo-controlled study	80 type II diabetic patients (average age 52 years) who had not reached the ideal control of the disease	One, 150-mg *S. officinalis* tablet, 3 times daily. Extraction process not detailed	2 patients on active treatment reported mild gastrointestinal complaints, but did not require withdrawal from study
Kianbakht et al. [92]	8-week, double-blind, placebo-controlled study	67 patients aged 20–60 years with newly diagnosed primary hyperlipidaemia	One, 500-mg ethanolic/aqueous extract of *S. officinalis* tablet, 3 times daily	No reported adverse events

other *Salvia* species is uncertain. Moreover, the extracts used have varied considerably across studies. Ethanolic, methanolic and aqueous extracts have been used, along with the essential oils of *S. officinalis* and *S. lavandulaefolia*. The potency and pharmacodynamic effects of these differing extracts are likely to vary considerably, potentially impacting on their therapeutic efficacy. This is a matter that requires consideration in research as the extracts used are likely to influence outcomes. A common issue in herbal medicine relates to differences in the quality of extracts, making generalised conclusions about a medicinal herb difficult. It is important that standardised, replicable extracts be developed that include some measure of potency and purity.

Although there have been two studies conducted on patients with Alzheimer's disease for a period up to 3 months, the majority of research has evaluated the efficacy of a single administration of *Salvia* plants. The efficacy of longer term intake of different *Salvia* species on cognition therefore requires examination. Larger scale clinical studies are also essential, particularly given the initial promising findings in Alzheimer's disease.

Several species of *Salvia* are commonly ingested across numerous cultures, which increases confidence about its safety. However, further confirmation about its safety is necessary, particularly when ingested at higher doses. Given the potential of neurotoxic effects from the *Salvia* constituent thujone, further investigation is warranted, and/or extracts containing little or no thujone may be prudent.

Overall, evidence for the cognitive-enhancing and protective effects of *Salvia* plants is promising. However, greater investigation is essential to help us elucidate the potential of this commonly ingested herb to enhance cognitive health and wellbeing.

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Compliance with Ethical Standards

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