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REVIEW

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Systematic Review of Clinical Trials Assessing Pharmacological Properties of *Salvia* Species on Memory, Cognitive Impairment and Alzheimer's Disease

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SUMMARY

Salvia officinalis L. and *Salvia lavandulaefolia* L. have a longstanding use as traditional herbal remedies that can enhance memory and improve cognitive functions. Pharmacological actions of *S. officinalis* and *S. lavandulaefolia* on healthy subjects and on patients suffering of cognitive decline have been investigated. Aim of this review was to summarize published clinical trials assessing effectiveness and safety of *S. officinalis* and *S. lavandulaefolia* in the enhancement of cognitive performance in healthy subjects and neurodegenerative illnesses. Furthermore, to purchase a more complete view on safety of *S. officinalis* and *S. lavandulaefolia,* we collected and discussed articles regarding toxicity and adverse reactions. Eight clinical studies investigating on acute effects of *S. officinalis* on healthy subjects were included in the review. Six studies investigated on the effects of *S. officinalis* and *S. lavandaeluaefolia* on cognitive performance in healthy subjects. The two remaining were carried out to study the effects of sage on Azheimer's disease. Our review shows that *S. officinalis* and *S. lavandulaefolia* exert beneficial effects by enhancing cognitive performance both in healthy subjects and patients with dementia or cognitive impairment and is safe for this indication. Unfortunately, promising beneficial effects are debased by methodological issues, use of different herbal preparations (extracts, essential oil, use of raw material), lack of details on herbal products used. We believe that sage promising effects need further higher methodological standard clinical trials.

Introduction and Background

The *Salvia* genus comprises about 900 species, of which, *Salvia officinalis* L. and *Salvia lavandulaefolia* L. have a longstanding reputation as traditional herbal remedies having been used by ancient Greek and Roman, Ayurvedic, Native American and Chinese folk medicines [1]. *S. officinalis* L. and *S. lavandulaefolia* L. belong to the Lamiaceae family and they are known with the English common names "common sage or sage" and "spanish sage," respectively.

Salvia officinalis is a perennial evergreen subshrub, with woody stems, grayish leaves, and blue to purplish flower, native to the Mediterranean area, and is cultivated in different European countries. Sage possesses well-known carminative, antispasmodic, antiseptic, astringent, and antihydrotic properties [1,2].

Salvia lavandulaefolia is a small woody herbaceous perennial plant native to Spain and southern France. This plant has been used for its reputed beneficial effects on behavioral function, including depression treatment [3]. According to folk medicine, *Salvias* herbal preparations are agents that can enhance memory and improve cognitive functions [4].

The treatment of deficits in memory and more generally of cognitive decline represents, on the light of their impact on global Public Health, a prominent challenge for modern medicine. Alzheimer's disease (AD) is a chronic progressive neurodegenerative disorder and is the most common cause for the development of progressive dementia in elderly. AD is characterized by the presence of amyloid plaques, neurofibrillary tangles and marked cholinergic degeneration clinically expressed through cognitive impairment. To explain the pathogenesis of AD, numerous processes have been involved, including free radical damage and inflammation [5]. To date, scientific research on AD has been partly successful in terms of effective therapies, a number of failures with regard to development of disease-modifying treatments occurred. Because a therapeutic

approach based on one-drug one-target paradigm revealed limited efficacy in the management of AD, it appears desirable using a multimodal approach implementing new integrated therapies including herbal medicine [5,6].

During last decades, several experimental studies explored the potential of medicinal plants in the management of memory disorders and to fight the age-related memory decline [7,8]. Among these plants, the pharmacological actions of *S. officinalis* and *S. lavandulaefolia* on healthy subjects and on patients suffering of cognitive decline have been also studied [9,10].

Aim of the Review

Aim of this review was to summarize previous published clinical trials assessing effectiveness and safety of *S. officinalis* and *S. lavandulaefolia* in the enhancement of cognitive performance in healthy subjects and as a treatment of cognitive decline linked to Alzheimer's disease or other neurodegenerative illnesses. The present work offers a critical view of methodologic accuracy and risk of bias analyzing the results from clinical studies. The review also suggests a possible perspective for future clinical research according to high methodological standards.

Research Method and Inclusion Criteria of Clinical Trials

A bibliographic research of scientific literature published prior December 2013 has been conducted independently by two researchers in the following scientific databases and search engines: Cochrane Library, Embase, Google Scholar, Pubmed, Scopus, SciFinder, and Web of Science.

The keywords used were as follows: *Salvia*, *Salvia officinalis*, *Salvia lavandulaefolia*, sage, Spanish sage, each combined with *memory*, *cognitive impairment*, *cognitive decline*, *Alzheimer's disease*, *neurodegeneration*, *dementia*, *anticholinesterase*, *beta-amyloid*. We collected all published clinical studies investigating effects of *S. officinalis and S. lavandulaefolia* on memory and cognitive impairment. We decided to include only articles written in English language published on peer reviewed scientific journals reporting clinical trials independently of the study design. We included clinical trials based on whole herbal extracts, consequently a study conducted with the isolated substance Salvinorina-A, contained in *Salvia divinorum* L., has been not included. Only studies in which sage was not used in combination were considered. In some studies collected for this review, *Helianthus annuus* L. (sun flower) oil was used as a carrier.

Two investigators independently extracted data from clinical studies using a standard data extraction form. To avoid the risk to include less accurate data, unpublished clinical trials were not considered. Methodologic quality was assessed using validated tools such as Jadad Scale, Cochrane Risk of Bias Assessment Tool, and Consort Statement in Reporting Clinical trials with Herbal Medicine Intervention (Section 4) [11–14]. To purchase a more complete view on safety of *S. officinalis* and *S. lavandulaefolia,* we collected and discussed articles regarding toxicity and adverse reactions linked to the use of these plants.

Phytochemistry of *Salvia officinalis* and *Salvia lavandulaefolia*

Chemical compositions of common sage and Spanish sage are far from being completely explored. Phytocomplex of *S. officinalis* contains monoterpenes with a broad range of carbon skeletons, including acyclic, monocyclic, and bicyclic compounds (e.g., thujone, 1,8-cineole, camphor), diterpenes (e.g., carnosic acid), triterpenes (e.g., oleanoic and ursolic acids), and phenolic compounds such as rosmarinic acid [15,16]. Chemical constituents of *S. lavandulaefolia* are similar to phytocomplex of *S. officinalis,* with the exception of the thujone content, a terpenoid ketone, which is considered toxic in large doses [17]. The majority of potentially bioactive hydrocarbons contained in *S. lavandulaefolia* herbal preparations, such as essential oils and extracts, seems to be terpenoids [18].

Preclinical Evidence

Several *Salvia* species and their isolated constituents possess significant antioxidant and antiinflammatory activities [19]. An ethanolic extract of *S. lavandulaefolia* showed to produce *in vitro* dose-dependent estrogenic activity [8]. Extracts of *Salvia* have been reported to have cholinergic activities relevant to the treatment of Alzheimer's disease. Inhibition of butyrylcholinesterase was also shown by individual constituents, such as 3-carene and beta-pinene [20]. It was shown that administration of extracts of *S. officinalis* or *S. lavandulaefolia* potentiate memory retention and also interact with muscarinic and nicotinic cholinergic systems that are involved in the cognitive and memory processes [21]. The supposed ability of *S. lavandulaefolia* to inhibit acetyl-cholinesterase (AChE) has been verified and confirmed in preclinical experiments [20,22]. On the light of preclinical results, it was assumed that the major monoterpenoid constituents present in essential oil of *Salvia* are responsible for anti-ChE activity [15,20,22,23].

Based on *in vitro* and *in vivo* data, *S. officinalis* and *S. lavandulaefolia* herbal preparations were selected for clinical trials to evaluate the potential beneficial actions on cognitive performance in healthy volunteers and in patients with cognitive impairment such as Alzheimer's disease.

Overview of the Clinical Studies with *Salvia officinalis* and *Salvia lavandulaefolia*

We took in consideration eight clinical studies investigating acute effects of *S. officinalis*. Six studies were carried out to assess the effects of *S. officinalis* and *S. lavandaeluaefolia* on cognitive performance in healthy subjects. One of the two remaining studies was conducted on subjects with probable diagnosis of Alzheimer's disease and the other on patients affected by mild-to-moderate Azheimer's disease. Table 1 summarized study design and results of all eight clinical trials.

Table 1 Summary of clinical trials reporting the effects of *Salvia* species on cognitive performance

Reference	Study design	Condition	Sample size of participants (treatment/control)	Age of patients (years)	Intervention	Control	Treatment duration	Tests/Outcomes	Main results
Akhondzadeh et al. [27]	DB RCT	Patients with: Probable Alzheimer's disease according to NINCDS/ADRDA. Mild-to-moderate dementia according to ADAS-cog and CDR	19 (12 males, seven females) 20 (12 males, eight females)	*S. officinalis* group: 71.78 ± 3.67 *Placebo* group 72.75 ± 3.43	60 drops daily of extract of *S. officinalis* dried leaf (1:1 in alcohol 45%)	*Placebo*	4 months	ADAS-cog/change of score at ADAS-cog. CDR-SB Clinical Dementia Rating Scale/change in CDR-SB Clinical Dementia Rating Scale	16-week administration of *S. officinalis* extract could be effective in the management of mild-to-moderate Alzheimer's disease. *Officinalis* extract group on both observed case and ITT analyses
Tildesley et al. [4] (two trials)	DB "pseudo randomized" CT	Healthy volunteers	20 (18 females, two males)	19.7 (range, 18–31)	1, 2 or 3 capsules containing 50 μL of *S.lavandulaefolia* essential oil + 50 μL sunflower oil per capsule daily (respectively, 50, 100, 150 μL daily)	100 μL Sunflower oil	Single administration	Cognitive Drug Research Battery modified version/ immediate and delayed word recall	Ingestion of single doses of *S. lavandulaefolia* can enhance memory in a dose-dependent manner
	DB "pseudo randomized" CT	Healthy volunteers	24 (16 females, eight males)	23.21 (range 18–37)	25 or 50 μL of *S.lavandulaefolia* essential oil + 50 μL sunflower oil	100 μL Sunflower oil	Single administration	Cognitive Drug Research Battery modified version/ immediate and delayed word recall	Ingestion of single doses of *S. lavandulaefolia* can enhance memory in a dose-dependent manner
Perry et al. [8]	Open-label CT	Mild-to-moderate probable Alzheimer's disease	11 (10 females, one male)	76–95 range	50 μL of *S.lavandulaefolia* essential oil + 50 μL Week: one capsule daily; Week 2: two capsules daily Weeks 3–6: three capsules daily	N/A	3 weeks	MMSE/change at MMSE. Cognitive Drug Research battery/ change of scoring at Cognitive Drug Research. NPI, developed to assess psychopathology in dementia patients/ change at NPI	Significant differences between baseline and 6-week treatment were a reduction in neuropsychiatric symptoms and an improvement in attention
Tildesley et al. [18]	DB RCT	Healthy volunteers	24 (16 females, eight males)	23.21 (range 18–37)	25 or 50 μL of *S.lavandulaefolia* essential oil + 50 μL sunflower oil	100 μL Sunflower oil	Single administration	Cognitive Drug Research modified version/change at Cognitive Drug Research. Bond–Lader Visual Analog Scale/change of score at Bond-Lader Visual Analog Scale	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 increased calmness following 25 μL

(continued)

Table 1 (Continued)

Reference	Study design	Condition	Sample size of participants (treatment/control)	Age of patients (years)	Intervention	Control	Treatment duration	Tests/Outcomes	Main results
Kennedy et al. [24]	DB, RCT	Healthy volunteers	30 (17 males, 13 females)	24.4 ± 4.4	300 or 600 mg *S. officinalis* dried leaf encapsulated	*Placebo*	Single administration	Defined Intensity Stressor Simulation (DISS) Computerized Battery/ change of score at DISS. State-Trait Anxiety Inventory (STAI)/mood change. Bond–Lader Visual Analog Scale/mood change	*S. officinalis*, and improved mood and cognitive performance following the administration of single doses
Scholey et al. [9]	DB, RCT, CR	Healthy volunteers	20 (11 males, nine females)	72.9 (range 65–90)	167, 333, 666 and 1332 mg of *S. officinalis* ethanolic (70%) extract of dried leaf. Each administration was separated by a week wash-out period	*Placebo*	Single administration	Cognitive Drug Research Battery tests/change of score at Cognitive Drug Research	*S. officinalis* administration has dose depending memory-enhancing effects on elder healthy volunteers
Moss et al. [26]	SB RCT	Healthy volunteers	135 (*S. officinalis* group: 37 females, 8 males; *S. lavandulaefolia* group: 36 females, nine males; control group: 36 females, nine males)	*S. officinalis* group: females 21.3 ± 3.6 males 22.4 ± 3.0; *S. lavandulaefolia* group: females 21.3 ± 4.9 males 23.1 ± 3.8 Control group: females 21.3 ± 4.4 males 23.9 ± 4.4	*S. officinalis* aroma *S. lavandulaefolia* aroma Each administration was separated by a week wash-out period	No aroma	Single administration	Cognitive Drug Research Battery tests/change of score at Cognitive Drug Research	*S. officinalis* aroma produced a significant enhancement of quality of memory, in particular long term or secondary memory with no impact on working memory. No significant effects were found for *S. lavandulaefolia*. Alert mood measure was affected by the presence of aroma. Aroma conditions increase alertness from pre- to post-testing compared to a the control condition
Kennedy et al. [25]	DB RCT CR	Healthy volunteers	36 (10 males 26 females)	23.8 ± 4.38	50 μL of *S. lavandulaefolia* essential oil + olive oil	Olive oil (considered as *placebo*)	Single administration in two occasions after 1-week wash-out	Computerized Mental Performance Assessment System(COMPASS)/number of items correctly recalled and average time to answer at Compass. Cognitive Demand Battery \ (CDB)/number of correct responses and average time to answer/of items correctly recalled and average time. Serial threes subtraction task/of items correctly recalled and average time.	Single dose of *S. lavandulaefolia* essential oil improves cognitive performance and mood in healthy volunteers

(continued)

Table 1 (Continued)

Reference	Study design	Condition	Sample size of participants (treatment/control)	Age of patients (years)	Intervention	Control	Treatment duration	Tests/Outcomes	Main results
								Serial sevens Subtraction Task. Rapid Visual Information Processing task (RVIP)/change of score. "Mental fatigue" Visual Analog Scale/change of score. Bond–Lader mood scales/change of mood at Bond–Lader. State-Trait Anxiety Inventory (STAI)/change of score at STAI	

RCT, randomized controlled trial; SB, single-blind; DB, double-blind; CR, crossover; N/A, not applicable; NINCDS/ADRDA, National Institute of Neurological and Communicative Disorders and Stroke and Alzheimer's Disease and Related Disorders Association; ADAS-cog, Score of 12 on the cognitive subscale of Alzheimer's Disease Assessment Scale; CDR, Clinical Dementia Rating Scale; ITT, Intention to Treat.

Clinical Studies with *Salvia officinalis* and *Salvia lavandulaefolia* on Healthy Subjects (Oral Administration)

In one article, results of two *placebo*-controlled, double-blind, balanced, crossover clinical trials (Trials 1 and 2) have been reported. The trial was performed by multidose, multiple-testing time regimes. In Trial 1, twenty mainly female healthy young subjects (mean age: 19.7; range 18–31) received 50, 100, and 150 μL of essential oil of *S. lavandulaefolia* and a *placebo*. In Trial 2, twenty-four participants (age: 23.21) received 25 and 50 μL of essential oil of *S. lavandulaefolia* and *placebo*. The administration of the different doses was separated by a 7-day washout interval. The cognitive performance was measured using Cognitive Drug Research computerized test battery prior to treatment and 1, 2.5, 4, and 6 h thereafter. The 50-μL dose of spanish sage essential oil significantly improved immediate word recall in both studies. The results led to the conclusion that assumption of single doses of *S. lavandulaefolia* can enhance memory in a dose-dependent manner in healthy young volunteers. In Trial 1, memory performance was enhanced for the 50 μL dose at 1- and 2.5-h time points. The effect was also evident following administration of the 100 μL dose at 2.5 h postdose sessions. A dose-specific enhancement on delayed word recall was also observed for the 50 μL dose at 1 and 2.5 h postdose. In Trial 2, the immediate word recall effect at 1 h was maintained, and this was coupled with improved memory performance at 4 h postdose testing session for the same dose. No significant enhancement on word recall was found for both the lowest (25 μL) and the highest (150 μL) dose of *Salvia* [4].

Another study recruited 24 subjects (23.21 years mean age) who received a single dose of *placebo*, 25 and 50 μL of a standardized essential oil of *S. lavandulaefolia* separated by a 7-day washout interval. Cognitive performance was assessed prior to the day's treatment and at 1, 2.5, 4, and 6 h thereafter using the Clinical Dementia Rating (CDR) computerized test suite. Further, subjective mood ratings were measured using Bond–Lader visual analog scales. The primary outcomes were scores on the five cognitive factors that can be derived by factor analysis of the task outcomes from the CDR battery. Results showed that administration of *S. lavandulaefolia* consistently improved the "Speed of Memory" factor with both the 25 and 50 μL dose. There was also an improvement in the "Secondary Memory" factor with the 25 μL dose. Mood was significantly enhanced, with increase in self-rated "alertness," "calmness," and "contentedness" following the 50-μL dose and increased "calmness" following 25 μL. Results suggested that Spanish sage acutely modulates mood and cognition in healthy young adults. Data also indicate that previous reports of memory enhancement determined by Spanish sage may be due to more efficient retrieval of target material [18].

In another randomized, double-blind, *placebo*-controlled, crossover clinical trial, 30 young healthy volunteers (mean age 24 years) received a single dose of 300 mg or a single dose of 600 mg of dried *S. officinalis* leaves preparation or *placebo*, each one in three different days each one separated by

7-day intervals. Participants at predose time and at 1 and 4 h postdose underwent mood assessment, evaluated by Bond–Lader mood scales and the State-Trait Anxiety Inventory (STAI) before and after a 20-min performance on the Defined Intensity Stress Simulator (DISS) computerized multitasking battery. DISS is an experimental test consisting of a set of four cognitive and psychomotor tasks presented on a screen layout producing increases in self-ratings of negative mood, arousal, and stress-related physiological responses. Evaluation of the cumulative score reflects accuracy and speed of response to DISS. Both doses of *S. officinalis* leaves preparation led to postdose improved ratings of mood before performing on the DISS in the absence of stress. The lower dose reduced anxiety while the higher dose increased "alertness," "calmness," and "contentedness" on the Bond–Lader scales. However, the lower dose effect of anxiety reduction was abolished by DISS. The higher dose exerted an improvement at task performance on the DISS battery at both postdose sessions, but after the lower dose, task performance was decreased. On the basis of these results, authors concluded that single doses of sage leaf dose dependently can improve cognitive performance and mood in healthy young volunteers. In the same study, a cholinesterase assay was performed with an ethanolic extract from *S. officinalis* dried leaves showing a dose-dependent inhibitory effect on acetylcholinesterase activity. However, herbal preparations used for human treatment or *in vitro* experiments seem to be different (the first could be raw material and the second is certainly an ethanolic extract) because it is not cleared by authors [24].

In another randomized, *placebo*-controlled, double-blind, five-period crossover study, the acute effects on cognitive performance of a standardized extract of *S. officinalis* L. in elder adults were investigated. Each one of twenty healthy volunteers (>65 years of age, mean 72.95) received four doses of an ethanolic extract of dried leaves (167, 333, 666 and 1332 mg) and a *placebo* with a 7 days wash-out period between treatments. The investigators evaluated cognitive performance with CDR computerized assessment battery. On study days, treatments were administered immediately following a baseline assessment with further assessments at 1, 2.5, 4, and 6 h post-treatment. Authors reported that the 333-mg dose of sage was associated with significant enhancement of secondary memory performance at all testing times, *placebo* exhibited the characteristic performance decline over the day. Although to a lesser extent, similar effects were observed with the other doses. There also was a significant improvement to accuracy of attention following the 333-mg dose. Performance of *in vitro* analysis showed cholinesterase inhibiting properties of the extract. Results revealed a dose-related benefit to processes involved in efficient stimulus processing and/or memory consolidation rather than retrieval or working memory efficiency [9].

In a double-blind, *placebo*-controlled, crossover study, 36 healthy volunteers (mean age 23.4) received capsules containing either 50 μL of the essential oil of *S. lavandulaefolia* or *placebo* on separate occasions, 7 days apart. The essential oil used showed cholinesterase inhibitory properties in an experimental preclinical model performed before the clinical assessment. Effects on cognitive performance and mood were evaluated. All tasks were delivered within the Computerized Mental Performance Assessment System (COMPASS), a software application for the flexible delivery of randomly generated parallel versions of standard and novel cognitive assessment tasks. Outcome measures were a selection of computerized memory and attention tasks and the Cognitive Demand Battery (CDB) before the treatment and 1 and 4 h postdose. CDB evaluates the impact of treatment on speed/accuracy and mental fatigue during continuous performance of cognitively demanding tasks. Bond–Lader mood scales and STAI—"state" subscale were also administered. *S. officinalis* essential oil intake determined improved performance of secondary memory and attention tasks, most notably at the 1 h postdose testing session, and reduced mental fatigue and increased alertness, which were more pronounced 4 h postdose [25].

Clinical Study with *Salvia officinalis* and *Salvia lavandulaefolia* on Healthy Subjects (Inhalation of Aromas)

A single-blind randomized, controlled trial evaluated the putative action of the aromas of *S. officinalis* and *S. lavandulaefolia* essential oils on cognition and mood. One hundred and thirty-five healthy volunteers were recruited, 45 of them were assigned to each group. Authors reported an improvement in cognitive performance and mood measured through Cognitive

Table 2 Cochrane Collaboration's tool for assessing risk of bias in randomised trials

	Random sequence generation	Allocation concealment	Blinding of participants, personnel	Blinding of outcome assessors	Incomplete outcome data	Selective reporting
Akhondzadeh et al. [27]	L	L	L	U	H	U
Tildesley et al. [4]	H	U	U	U	H	U
Perry et al. [8]	H	H	H	H	L	U
Tildesley et al. [18]	L	U	U	U	U	U
Kennedy et al. [24]	L	L	U	U	L	U
Scholey et al. [9]	L	U	U	U	L	U
Moss et al. [26]	U	U	H	H	L	U
Kennedy et al. [25]	L	U	U	U	L	U

L, low risk of bias; U, unclear risk of bias; H, high risk of bias.

Drug Research (CDR) System and Bond–Lader mood scales, respectively. Five drops of the essential oil and 5 mL of water were placed on a stone and left to diffuse in a testing cubicle, as a result of a constant temperature warming provided by the stone, for 5 min prior to testing. Data collected revealed that the *S. officinalis* aroma group performed significantly better than the control group on the quality of memory outcome factors from the test battery. The Alert mood measure displayed significant differences between both aromas and the control condition. Results revealed that aromas of essential oils of *S. officinalis* reproduced a significant enhancement of quality of memory factor. This enhancement was restricted to long-term or secondary memory with no impact of working memory. No significant effects were found for *S. lavandulaefolia* [26].

Clinical Studies with *Salvia officinalis* and *Salvia lavandulaefolia* on Patients with Cognitive Impairment (Oral Administration)

The effect of a *S. officinalis* leaf liquid extract prepared as "1:1 in alcohol 45%" (1 kg dried herb (leaf) to 1 L of alcohol) has been evaluated in a randomized, double-blind, *placebo*-controlled study on 39 patients (aged 65–80 years). The eligible patients had a diagnosis of mild-to-moderate dementia according to the criteria of the cognitive subscale of Alzheimer's Disease Assessment Scale (ADAS-cog) and Clinical Dementia Rating Scale (CDR); or a probably Alzheimer's disease according to the criteria of National Institute of Neurological and Communicative Disorders and Stroke and Alzheimer's Disease and Related Disorders Association (NINCDS/ADRDA). The participants allocated to two groups received 60 drops daily of sage liquid extract or *placebo* for 16 weeks. Thirty patients completed the trial, in the *Salvia* extract and *placebo* group, the number of dropouts were four and five, respectively, accordingly to authors no significant difference are observed in the two groups in terms of dropout. Authors reported that, compared with the *placebo* group, patients who received *S. officinalis* experienced significant benefits in cognitive function by the end of the treatment, as indicated by improved scores in the Clinical Dementia Rating and the Alzheimer's Disease Assessment Scale [27].

Another study, designed as open-label, involved oral administration of a *S. lavandulaefolia* essential oil in the treatment of AD. Sample of patients was composed of eleven patients, aged 76–95 years, which have been diagnosed with mild-to-moderate probable Alzheimer's disease according to NINCDS/ADRDA criteria. Eligible patients obtained at Mini-Mental State Examination (MMSE), a score between 10 and 26 and Neuropsychiatric Inventory (NPI) scores for items 3 and 9 were 0 suggesting cognitive decline. Sage treatment consisted of one capsule daily containing 50 μL of *S. lavandulaefolia* essential oil +50 μL of sunflower oil as a carrier for 1 week, then two capsules daily and three capsules daily for other 3 weeks, in total 6 weeks. Endpoints were changes in scores obtained with MMSE, Cognitive Drug Research test, and Neuropsychiatric Inventory. At the end of the trial, the investigators observed a significant difference between baseline scores and 6 weeks treatment characterized by

Table 3 Quality assessment according to Jadad score

Reference	Was similarity between the two (or more) groups at baseline?	Was the trial described as randomized?	Was the randomization procedure described and appropriate?	Was the treatment allocation concealed?	Was the trial described as double-blind?	Was the method of double blinding described and appropriate?	Was the number of withdrawals/dropouts in each group mentioned?	Was an analysis conducted on the intention to treat sample?	Jadad score
Akhondzadeh et al. [27]	Yes	Yes	No	No	Yes	No	Yes	Yes	5
Tildesley et al. [4]	Yes	Yes	No	No	Yes	No	Yes	No	3
Perry et al. [8]	Yes	No	No	No	No	No	Yes	Yes	3
Tildesley et al. [18]	Yes	Yes	No	No	Yes	No	No	No	3
Kennedy et al. [24]	Yes	Yes	Yes	No	Yes	No	No	N/A	3
Scholey et al. [9]	Yes	Yes	Yes	No	Yes	No	No	No	4
Moss et al. [26]	Yes	Yes	No	No	No	No	No	No	2
Kennedy et al. [25]	Yes	Yes	No	Yes	Yes	Yes	No	No	5

reduction in neuropsychiatric symptoms and improvement in attention [8].

Safety Profile

Despite their widespread use, adverse reactions to common sage and Spanish sage have rarely been documented in scientific literature. In all the clinical trials included in the present review, these plants did not cause serious adverse reaction, in consequence of this being generally considered well-tolerated and safe. In the Perry et al.'s [8] clinical trial, a significant increase in diastolic and systolic blood pressure occurred in two patients; however, this medical event has been considered by authors as pre-existing hypertension.

Two articles reporting complexively three cases describing adverse reactions were published. A case report describes a cutaneous allergic reaction in an 83-year-old woman due to the application of a cosmetic cream containing *S. officinalis* [28]. An article reports two cases regarding a newborn and a toddler, respectively, who both experienced generalized tonic-clonic seizures after accidental oral exposure to *S. officinalis* oil, any other possible cause of seizure has been excluded [29].

Discussion

Salvia species effects were studied on cognitive performance and mood in healthy subjects and in subjects affected by mild-to-moderate dementia and by Alzheimer's disease. Complexively, analysis of results of clinical studies shows that intake of herbal preparations derived from *S. officinalis* and *S. lavandulaefolia* may produce positive effects on cognitive performance with improvement in memory. Some studies indicate secondary memory as the component that is more positively influenced by sages treatments. However, the clinical trials show different levels of methodological accuracy and different risk of biases (Table 2).

The most part of the studies (six out of eight) were randomized and controlled double-blinded studies, two of these were performed as crossover studies. One of the remaining was designed as a open-label study and the other one as a single-blind study (Tables 1, 3 and 2). Notoriously, these are points of weakness in clinical research as open-label clinical trials are not free from patients and investigators expectations, resulting in a possible overestimation of the results. For this reason, blinding is a prominent methodological feature of randomized clinical trials (RCTs) that can minimize bias and maximize the validity of the results [30,31].

Furthermore, only some of the included randomized clinical studies sufficiently describe the methods adopted to generate random allocation sequence (Tables 3 and 2). It has been proved that the lack of these details represents a common source of selection bias [32]. Only one clinical study [25] reports details regarding the allocation concealment process. This is a crucial point in a clinical trial, because it keeps investigators and patients unaware of upcoming assignments and prevents deciphering assigned treatments [33]. In addition, some studies (Table 1) suffer from the limited number of enrolled subjects, for example, only 11 subjects were enrolled in the Perry et al. [8] study (Table 1). Further, in anyone of the considered clinical trials is described how the sample size was calculated in accordance with power of sample analysis (Tables 3 and 2).

In the Tildesley et al. [4], an intention to treat (ITT) analysis is lacking, despite the occurrence of a drop-out (Table 3). In the Akhondzadeh et al.'s article, authors evaluated just the "'observed cases' (OC, patients who completed the trial)" and performed an ITT analysis based on "last observation carried forward (LOCF) procedure". Various evidences show that this method gives a biased estimation of the treatment effect and underestimates the variability of the result [34,35]. In clinical research, an analysis is considered adequate if all randomized patients are included in the analysis in the group they had been allocated (ITT). Moreover, in general lines a per-protocol analysis is commonly considered inadequate. In case of dropouts, it is desirable providing an explanation of the reasons of withdrawal, while the above cited study did not purchase any motivation [36].

Although all studies correctly report the latin binomial names of the plants and the raw material used (Tables 1 and 4) to produce the herbal extracts, not all articles provide an exhaustive description of the Drug Extract Ratio and the procedure to obtain herbal preparations. High methodological standards in reporting herbal medicine strongly suggest to indicate the herbal medicinal product comprising crude herbal "type and concentration of solvent used and the ratio of herbal drug" for an extract. These data are

Table 4 Section 4 of elaborations of CONSORT items for randomized, controlled trials of herbal medicine interventions

Reference	Herbal medicinal product name	Characteristics of the herbal product	Dosage regimen and quantitative description	Qualitative testing	*Placebo*/control Group (rationale for control or *placebo* used)	Practitioner
Akhondzadeh et al. [27]	Yes	Yes	Yes	No	No	No
Tildesley et al. [4]	Yes	Yes	Yes	Yes	No	No
Perry et al. [8]	Yes	Yes	Yes	Yes	No	No
Tildesley et al. [18]	Yes	Yes	Yes	Yes	No	No
Kennedy et al. [24]	Yes	Yes	Yes	No	No	No
Scholey et al. [9]	Yes	Yes	Yes	Yes*	No	No
Moss et al. [26]	Yes	Yes	No	No	No	No
Kennedy et al. [25]	Yes	Yes	Yes	Yes	No	No

*Perry et al. declared to have performed qualitative testing, but they did not provide results in the article.

Table 5 Tests, scales, and tools to assess outcomes in the reviewed clinical trials

Reference	Scale and abbreviation	Description
Rosen et al. [37]	Alzheimer's Disease Assessment Scale—cognition (ADAS-cog)	ADAS-Cog comprises 11 individual tests, spoken language ability (0–5), comprehension of spoken language (0–5), recall of test instructions (0–5), word finding difficulty (0–5), following commands (0–5), naming object (0–5), construction drawing (0–5), ideational praxis (0–5), orientation (0–8), word recall (0–10) and word recognition (0–12). The total score ranges from 0 to 70, the high score indicating greater impairment
Bond et al. [38]	Bond and Lader's Visual Analog Scale	Bond and Lader's visual analog scales were used to assess mood. The scales consist of 15 horizontal lines, 100 mm in length, with antonymous adjectives (e.g., alert ± drowsy) on either pole. The mood scales have been validated. Each item was attributed to one of three factors: "alertness," "contentedness," and "calmness." Principal components analyses (with Varimax rotation) produced three components at each point, accounting for between 64.1 and 71.5% of the variance. All scales showed sufficient internal reliability (Cronbach's alphas = 0.77–0.93)
Simpson et al. [39]	Cognitive Drug Research (CDR) Battery Test	The CDR system is a series of brief neuropsychological testes that assess major aspects of cognitive function known to be influenced by a wide variety of factors including trauma, fatigue, stress, nutrition, aging, disease (both physical and mental), medicines, and drugs. The standard battery of cognitive tests in the CDR system includes immediate/delayed word recall, word recognition, picture recognition, simple reaction time, digit vigilance, choice reaction time, numeric working memory, and spatial working memory. Individual tests can be added to or removed from the battery to target specific cognitive domains. Examples of tests that can be added include measurements of executive function mood states, social cognition motor function, and postural stability. The standard battery of tests lasts 18 min. The CDR system tasks have proven validity in definitively measuring cognitive function in a variety of domains including attention, working memory episodic secondary memory, executive function, and motor skill
Hughes et al. [40]	Clinical Dementia Rating-Sum of the Boxes (CDR-SB)	The CDR-SB sums the ratings in each of six domains ("Boxes") of the CDR to provide a consensus-based global clinical measure, that is, the Sum of the Boxes. The domains assessed included three cognitive components (memory, orientation, judgment and problem solving) and three components related to Activities of Daily Living (ADL) (community affairs, home and hobbies, and personal care). The scores are: 0 = None, 0.5 = Questionable; Mild = 1, Moderate = 2, Severe = 3
Kennedy et al. [41]	Cognitive Demand Battery	Cognitive Demand Battery assesses the impact of treatment on speed/accuracy and mental fatigue during continuous performance of cognitively demanding tasks. The working hypothesis underlying this approach is that any psychoactive properties of a test substance are liable to be more readily apparent during a period of intense cognitive demand and the "mental fatigue" state elicited by this prolonged task performance. Participants complete the 10-min battery of tasks six times in immediate succession (i.e., for a continuous period of 60 min).
http://www.cognitivetesting.co.uk [42]	Computerized Mental Performance Assessment System (COMPASS)	The battery contains a wide range of standard and novel tasks that measure mood and cognitive performance across domains. Choosing an appropriate set of tasks is simplified by either looking at the full list of tasks or, alternatively, viewing all of the tasks that are thought to assess performance in a specific domain (e.g., "working memory," "attention," or "executive function"). Choosing and ordering tasks involves simply dragging and dropping them in to the "task order" tray. You can then customize selected parameters (e.g., specify the length of a task in seconds, or the number of stimuli presented) and once you are happy with your selection the system will generate your customized battery. Previous configurations are stored as simple files, so you can recall a previous study design that you want to rerun, or amend any of its parameters
Wetherell et al. [43]	Defined Intensity Stressor Simulation (DISS) Computerized Battery	The DISS computerized battery (Stress-Sim Ltd, The Coach House, Plymouth, www.stress-sim.co.uk) comprises a set of four concurrent cognitive and psychomotor tasks presented via a split screen. This newly developed instrument was chosen for several reasons. It has the advantage over other laboratory stressors of being both

(continued)

Table 5 (Continued)

Reference	Scale and abbreviation	Description
		automated (thus essentially eliminating experimenter effects) and drawing on random stimuli for each test, allowing for multiple testing sessions of the same participant. All responses are made with an external mouse
Folstein et al. [44]	Mini-Mental State Examination (MMSE)	The MMSE was developed as a short test suitable for the elderly with dementia. The test includes questions and tasks in a number of different areas: the time and place of the test, repeating lists of words, arithmetic such as the serial seven, language use and comprehension, and basic motor skills. It concentrates on the cognitive aspects of mental function, the five sections cover orientation, immediate recall, attention and calculation, delayed recall and language. A maximum score of 30 indicates no impairment
Cummings et al. [45]	Neuropsychiatric Inventory (NPI)	The NPI assesses 10 behavioral disturbances occurring in dementia patients: delusions, hallucinations, dysphoria, anxiety, agitation/aggression, euphoria, disinhibition, irritability/lability, apathy, and aberrant motor activity. Both the frequency (rarely, sometimes, often, very often) and the severity (mild, moderate and severe) of each behavior are determined. Information for the NPI is obtained from a caregiver familiar with the patient's behavior
Spielberger et al. [46]	State-Trait Anxiety Inventory (STAI)	The STAI "State" subscale is a widely used instrument for measuring fluctuating levels of anxiety. The subscale contains 20 statements (e.g., "I am calm") each with a 4-point Likert scale. Participants rate how much they feel like each statement at the time of making the response. Scores on the STAI range from 20 to 80, with higher scores representing higher levels of anxiety

fundamental to link the putative pharmacological effectiveness with a well-defined herbal product [13]. Only in this way physicians can identify what particular preparation derived from *S. officinalis* and *S. lavandulaefolia* can be effective in clinical practice. In four clinical trials, investigators administered *S. lavandulaefolia* essential oils (Table 1), in one ethanolic extract (1:1 in alcohol 45%) *of S. officinalis* dried leaf (Table 1), in another a *S. officinalis* ethanolic (70%) extract of dried *S. officinalis* leaf, and in a clinical trial encapsulated dried leaf of *S. officinalis.* In all the included studies, products were orally administered, only the Moss et al.'s study tested by inhalation aromas of *Salvia* species (Table 1), this kind of intervention is characterized by fugacity and absence of pharmacokinetics data. A major limitation of some study consisting of the lack of qualitative testing producing chemical fingerprint of herbal products (Table 4). Heterogeneity of herbal products used in studies represents an additional problem for the evaluation and comparison of clinical effectiveness of *S. officinalis* and *S. lavandulaefolia*. Additionally, some study presents as limitation a short duration of the treatment (e.g., single administration on healthy volunteers) and a short period of follow-up, only a study achieved a treatment lasting 16 weeks (on patients suffering from Alzheimer's disease) (Table 1). Unfortunately, none of the studies compared the effects of *Salvia* species against well-established drugs prescribed in the treatment of cognitive impairment such as anticholinesterase drugs.

Additional issues might be related to the different tests adopted by authors to evaluate the outcomes such as cognitive performance and mood (Table 5). The variability of aspects evaluated through various tests and scales may affect the comparability of results between the considered clinical trials.

Conclusion

This systematic review of scientific literature shows that *S. officinalis* and *S. lavandulaefolia* exert beneficial effects by enhancing cognitive performance both in healthy subjects and patients with dementia or cognitive impairment. Furthermore, *S. officinalis* and *S. lavandulaefolia* show to be safe for this indication with no serious adverse effects compared with *placebo*. Unfortunately, promising beneficial effects showed in clinical studies are debased by methodological issues, use of different herbal preparations (extracts, essential oil, use of raw material), lack of details on herbal products used, which together prevent to reach definitive conclusions on sage effectiveness in producing positive effects in healthy subjects or patients affected by cognitive impairment. On the light of these considerations, we believe that sage promising effects need further higher methodological standard clinical trials taking into account gaps raised by this review.

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Conflict of Interest

The authors declare no conflict of interest.

References

1. Blumenthal M, Goldberg A, Brinckmann J. *Herbal medicine: Expanded commission E monographs*. Boston, MA: American Botanical Council, 2000.
2. Barnes J, Phillipson DJ. *Sage. Herbal medicines,* 3rd edn. London: The Pharmaceutical Press, 2007.
3. Clebsch B. *The new book of salvias: Sages for every garden*. Portland, OR: Timber Press, 2008.
4. Tildesley N, Kennedy D, Perry E, et al. *Salvia lavandulaefolia* (Spanish Sage) enhances memory in healthy young volunteers. *Pharmacol Biochem Behav* 2003;**75**:669–674.
5. DeFina PA, Moser RS, Glenn M, Lichtenstein JD, Fellus J. Alzheimer's disease clinical and research update for health care practitioners. *J Aging Res* 2013;**2013**:207178.
6. May BH, Lit M, Xue CC, et al. Herbal medicine for dementia: A systematic review. *Phytother Res* 2009;**23**:447–459.
7. Howes MJR, Perry NS, Houghton PJ. Plants with traditional uses and activities, relevant to the management of Alzheimer's disease and other cognitive disorders. *Phytother Res* 2003;**17**:1–18.
8. Perry NS, Bollen C, Perry EK, Ballard C. *Salvia* for dementia therapy: Review of pharmacological activity and pilot tolerability clinical trial. *Pharmacol Biochem Behav* 2003;**75**:651–659.
9. Scholey AB, Tildesley NT, Ballard CG, et al. An extract of *Salvia* (sage) with anticholinesterase properties improves memory and attention in healthy older volunteers. *Psychopharmacology* 2008;**198**:127–139.
10. Imanshahidi M, Hosseinzadeh H. The pharmacological effects of *Salvia* species on the central nervous system. *Phytother Res* 2006;**20**:427–437.
11. Jadad AR, Moore RA, Carroll D, et al. Assessing the quality of reports of randomized clinical trials: Is blinding necessary? *Control Clin Trials* 1996;**17**:1–12.
12. Clark HD, Wells GA, Huët C, et al. Assessing the quality of randomized trials: Reliability of the Jadad scale. *Control Clin Trials* 1999;**20**:448–452.
13. Gagnier JJ, Boon H, Rochon P, et al. Reporting randomized, controlled trials of herbal interventions: An elaborated CONSORT statement. *Ann Intern Med* 2006;**144**:364–367.
14. Higgins JP, Altman DG, Gøtzsche PC, et al. The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. *BMJ* 2011; **343**: d5928.
15. Perry NB, Anderson RE, Brennan NJ, et al. Essential oils from dalmatian sage (*Salvia officinalis* L.): Variations among individuals, plant parts, seasons, and sites. *J Agric Food Chem* 1999;**47**:2048–2054.
16. Abu-Darwish M, Cabral C, Ferreira I, et al. Essential oil of common sage (*Salvia officinalis* L.) from Jordan: Assessment of safety in mammalian cells and its antifungal and anti-inflammatory potential. *Biomed Res Int* 2013;**2013**:538940.
17. Leung Albert Y, Foster S. *Encyclopedia of common natural ingredients*. New York: John Wiley & Sons Inc., 1996.
18. Tildesley N, Kennedy D, Perry E, et al. Positive modulation of mood and cognitive performance following administration of acute doses of *Salvia lavandulaefolia* essential oil to healthy young volunteers. *Physiol Behav* 2005;**83**:699–709.
19. Zupkó I, Hohmann J, Rédei D, et al. Antioxidant activity of leaves of *Salvia* species in enzyme-dependent and enzyme-independent systems of lipid peroxidation and their phenolic constituents. *Planta Med* 2001;**67**:366–368.
20. Savelev S, Okello E, Perry N, Wilkins R, Perry E. Synergistic and antagonistic interactions of anticholinesterase terpenoids in *Salvia lavandulaefolia* essential oil. *Pharmacol Biochem Behav* 2003;**75**: 661–668.
21. Eidi M, Eidi A, Bahar M. Effects of *Salvia officinalis* L. (sage) leaves on memory retention and its interaction with the cholinergic system in rats. *Nutrition* 2006;**22**:321–326.
22. Perry NS, Houghton PJ, Theobald A, Jenner P, Perry EK. *In vitro* inhibition of human erythrocyte acetylcholinesterase by *Salvia lavandulaefolia* essential oil and constituent terpenes. *J Pharm Pharmacol* 2000;**52**:895–902.
23. Perry N, Houghton P, Jenner P, Keith A, Perry E. *Salvia lavandulaefolia* essential oil inhibits cholinesterase *in vivo*. *Phytomedicine* 2002;**9**:48–51.
24. Kennedy DO, Pace S, Haskell C, Okello EJ, Milne A, Scholey AB. Effects of cholinesterase inhibiting sage (*Salvia officinalis*) on mood, anxiety and performance on a psychological stressor battery. *Neuropsychopharmacology* 2006;**31**:845–852.
25. Kennedy DO, Dodd FL, Robertson BC, et al. Monoterpenoid extract of sage (*Salvia lavandulaefolia*) with cholinesterase inhibiting properties improves cognitive performance and mood in healthy adults. *J Psychopharmacol* 2010;**25**:1088–1100.
26. Moss L, Rouse M, Wesnes KA, Moss M. Differential effects of the aromas of *Salvia* species on memory and mood. *Hum Psychopharmacol* 2010;**25**:388–396.
27. Akhondzadeh S, Noroozian M, Mohammadi M, et al. *Salvia officinalis* extract in the treatment of patients with mild to moderate Alzheimer's disease: A double blind, randomized and *placebo*, controlled trial. *J Clin Pharm Ther* 2003;**28**:53–59.
28. Mayer E, Gescheidt-Shoshany H, Weltfriend S. Allergic contact dermatitis caused by *Salvia officinalis* extract. *Contact Derm* 2011; **64**:237–238.
29. Halicioglu O, Astarcioglu G, Yaprak I, Aydinlioglu H. Toxicity of *Salvia officinalis* in a newborn and a child: An alarming report. *Pediatr Neurol* 2011;**45**:259–260.
30. Schulz KF, Grimes DA. Blinding in randomised trials: Hiding who got what. *Lancet* 2002;**359**:696–700.
31. Karanicolas PJ, Farrokhyar F, Bhandari M. Blinding: Who, what, when, why, how? *Can J Surg* 2010;**53**:345.
32. Miller KD, Rahman ZU, Sledge GW Jr. Selection bias in clinical trials. *Breast Dis* 2001;**14**:31–40.
33. Viera AJ, Bangdiwala SI. Eliminating bias in randomized controlled trials: Importance of allocation concealment and masking. *Fam Med* 2007;**39**:132.
34. Council PoHMDiCTNR. *The prevention and treatment of missing data in clinical trials. Panel on handling missing data in clinical trials*. Committee on National Statistics, Division of Behavioral and Social Sciences and Education. Washington, DC: The National Academies Press, 2010.
35. Little RJ, D'Agostino R, Cohen ML, et al. The prevention and treatment of missing data in clinical trials. *N Engl J Med* 2012;**367**:1355–1360.
36. Huwiler-Müntener KJP, Junker C, Egger M. Quality of reporting of randomized trials as a measure of methodologic quality. *JAMA* 2002;**287**:2801–2804.
37. Rosen WG, Mohs RC, Davis KL. A new rating scale for Alzheimer's disease. *Am J Psychiatry* 1984;**141**:1356–1364.
38. Bond A, Lader M. The use of analog scales in rating subjective feelings. *Br J Med Psychol* 1974;**47**:211–218.
39. Simpson PM, Surmon D, Wesnes KA, Wilcock G. The cognitive drug research computerized assessment system for demented patients: A validation study. *Int Psychogeriatr* 1991;**6**:95–102.
40. Hughes CP, Berg L, Danziger WL, Coben LA, Martin RL. A new clinical scale for the staging of dementia. *Br J Psychiatry* 1982;**140**:566–572.
41. Kennedy DO, Scholey AB. A glucose-caffeine, energy drink, ameliorates subjective and performance deficits during prolonged cognitive demand. *Appetite* 2004;**42**:331–333.
42. Brain, Performance and Nutrition Research Centre. Compass Cognitive System (2013). http://www.cognitivetesting.co.uk.
43. Wetherell MA, Sidgreaves MC. Secretory immunoglobulin-A reactivity following increases in workload intensity using the Defined Intensity Stressor Simulation (DISS). *Stress Health* 2002;**21**:99–106.
44. Folstein MF, Folstein SE, McHugh PR. Mini-mental state: A practical method for grading the cognitive state of patients for the clinician. *J Psychiatr Res* 1975;**12**:189–198.
45. Cummings JL, Mega M, Gray K, et al. The Neuropsychiatric inventory comprehensive assessment of psychopathology in dementia. *Neurology* 1994;**44**:2308.
46. Spielberger CD. *State-trait anxiety inventory. The Corsini encyclopedia of psychology*. New York, NY: John Wiley & Sons Inc., 2010.