

# *Salvia officinalis* extract in the treatment of patients with mild to moderate Alzheimer's disease: a double blind, randomized and placebo-controlled trial

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## SUMMARY

**Background:** Alzheimer's disease is characterized by a slow, progressive decline in cognitive function and behaviour. Acetylcholine esterase inhibitors are the only agents approved by the Food and Drug Administration for the treatment of Alzheimer's disease. All other agents prescribed for the treatment of Alzheimer's disease are used on an off-label basis. Current research into new drugs is focused on agents that will prevent, slow down and/or halt the progress of the disease process. *Salvia officinalis* has been used in herbal medicine for many centuries. It has been suggested, on the basis of traditional medicine, its *in vitro* cholinergic binding properties and modulation of mood and cognitive performance in humans, that *Salvia officinalis* might potentially provide a novel natural treatment for Alzheimer's disease. The objective of this study was to assess the efficacy and safety of *Salvia officinalis* extract using a fixed dose (60 drops/day), in patients with mild to moderate Alzheimer's disease, over a 4-month period.

**Methods:** This was a 4-month, parallel group, placebo-controlled trial undertaken in three centres in Tehran, Iran. Patients with mild to moderate Alzheimer's disease aged between 65 and 80 years ( $n = 42$ , 18 women) with a score of  $\geq 12$  on the cognitive subscale of Alzheimer's Disease Assessment Scale (ADAS-cog) and  $\leq 2$  on the Clinical Dementia Rating (CDR) were randomized to placebo or fixed dose of *S. officinalis* extract. Over the 16 weeks, the main efficacy

measures were the change in the ADAS-cog and CDR-Sum of Boxes scores compared with baseline. In addition, side-effects were systematically recorded throughout the study using a checklist. **Results:** At 4 months, *S. officinalis* extract produced a significant better outcome on cognitive functions than placebo (ADAS-cog:  $F = 4.77$ , d.f. = 1,  $P = 0.03$ ) (CDR-SB:  $F = 10.84$ , d.f. = 1,  $P < 0.003$ ). There were no significant differences in the two groups in terms of observed side-effects except agitation that appears to be more frequent in the placebo group ( $P = 0.09$ ).

**Conclusions:** The results of this study indicate the efficacy of *S. officinalis* extract in the management of mild to moderate Alzheimer's disease. Moreover, *S. officinalis* may well reduce agitation of patients but this needs to be confirmed.

**Keywords:** Alzheimer's disease, herbal medicine, *Salvia officinalis*

## INTRODUCTION

Alzheimer's disease is characterized by profound memory loss sufficient to interface with social and occupational functioning. It is the most common form of dementia, affecting approximately 20 million people worldwide (1, 2). Alzheimer's disease is characterized by an insidious loss of memory, associated functional decline and behavioural disturbances. Patients may live for more than a decade after they are diagnosed with Alzheimer's disease, making it the leading cause of disability in the elderly. The prevalence and incidence of this disease and its cost to society, increase exponentially with age. The prevalence increases from 0.3% at 65 years of age to nearly 50% after 85 years. The incidence increases from 0.5% at 65 years of age to

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8% at 85 years (1–3). The first neurotransmitter defect discovered in Alzheimer's disease involved acetylcholine (ACh). As cholinergic function is required for short-term memory, the cholinergic deficit in Alzheimer's disease was also believed to be responsible for much of the short-term memory deficit (4). Clinical drug trials in patients with Alzheimer's disease have focused on drugs that augment levels of ACh in the brain to compensate for the loss of cholinergic function. These drugs have included ACh precursors, muscarinic agonists, nicotinic agonists and acetylcholine esterase inhibitors (AChEIs). The most highly developed and successful approaches to date have employed AChE inhibition (5). The first drug approved for general clinical use in Alzheimer's disease was tacrine, followed a few years later by donepezil. More recently, rivastigmine has been used in several countries around the world, and was launched in the US by June 2000 (6). Pharmacological treatment strategies in Alzheimer's disease include three classes of agents: (i) mechanism-based, disease-modifying therapies such as vitamin E and selegiline; (ii) mechanism-based therapies that compensate for transmitter deficits such as AChEIs, and (iii) psychotropic agents administered to relieve behavioural symptoms of Alzheimer's disease (7–10). Although two Food and Drug Administration approved drugs are available for the management of Alzheimer's disease, the outcomes are often unsatisfactory and there is a place for alternative medicine and in particular phytotherapy (3, 6, 10). It has been suggested, on the basis of a retrospective review of the historical role of a number of European herbs in the improvement of cognition and in particular, memory, that *S. officinalis* and another herb in the labiatae family, *Melissa officinalis*, might potentially provide natural treatment for Alzheimer's disease (11, 12). *Salvia officinalis* comes from Europe and is now grown all over the world. Just as mint, it is known for its soothing and carminative effects (13). In addition, it has been reported that *S. officinalis* exhibits CNS acetylcholine receptor activity, with demonstration of both nicotinic and muscarinic binding properties (14). Moreover, a recent study showed that *M. officinalis* another herb from this family with the same CNS acetylcholine receptor activity modulated mood and cognitive performance in acute administration in healthy young volunteers (15). No side-effects or

symptoms of toxicity were reported with the use of *S. officinalis* (13–15). The present study was undertaken to test the efficacy and safety of *S. officinalis* using a fixed dose, in patients with mild to moderate Alzheimer's disease, over 4 months in a double-blind, randomized and placebo-controlled trial for the first time.

## METHODS

### *Trial organization*

This was a 4-month, parallel group, placebo-controlled trial undertaken in three centres in Tehran, Iran during October 2000 to September 2002. Overall coordination of the trial was by the Institute of Medicinal Plants, Tehran, Iran. All centres were required to secure appropriate local ethics or research committee approval before recruitment could begin. The trial was approved by the National Research centre of Medical Sciences, Tehran, Iran.

### *Participants*

Eligible participations in the study were male and female outpatients, aged between 65 and 80 years. Patients with a history of cognitive decline that had been gradual in onset and progressive for at least 6 months were included. Other inclusion criteria were:

- A diagnosis of probable 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) (16).
- Presence of mild to moderate dementia (score of  $\geq 12$  on the cognitive subscale of Alzheimer's Disease Assessment Scale (ADAS-cog) and  $\leq 2$  on Clinical Dementia Rating Scale (CDR) (17, 18).

Patients also had to have regular contact with a responsible caregiver. Those with concomitant disease such as hypertension, congestive heart failure, non-insulin-dependent diabetes mellitus and hypothyroidism were included in the study, provided the disease was controlled. Patients were excluded from the study if they had evidence of other neurodegenerative disorders, any cardiovascular disease thought likely to prevent completion of the study, clinically significant psychiatric

diseases, urinary outflow obstruction, an active peptic ulcer, any history of epilepsy, or significant drug or alcohol misuse. Any other medication being taken to treat dementia had to be discontinued. The use of other concomitant medication was permitted, except that, where possible, drugs with a psychotropic action were discontinued 48 h before cognitive evaluation. Drugs with anticholinergic effects or cholinomimetic effects were avoided. The ADAS is a 21-item scale used to assess the severity of cognitive and non-cognitive impairments that has been validated for use in patient with Alzheimer's disease. ADAS-cog is a subscale of 11 items that evaluates selected aspects of attention, language, memory, orientation, praxis and reasoning. Score for ADAS-cog range from 0 to 70 (very severe) (17). Clinical Dementia Rating-Sum of the Boxes (CDR-SB) provides a consensus-based global clinical measure by summing the ratings from six domains: memory, orientation, judgement, problem-solving, community affairs, home and hobbies, and personal care. Ratings were assigned by the function in relation to cognitive ability and past performance, with an increase in score denoting deterioration (18). Patients were randomized to receive *S. officinalis* extract or placebo in a 1 : 1 ratio using a computer-generated code. The assignments were kept in sealed, opaque envelopes until the point of allocation. The randomization and allocation process was carried out by the pharmacist of the Roozbeh hospital. The trial was performed in accordance with the Declaration of Helsinki and subsequently revised and approved by ethics committee at National Research Center of Medical Sciences of Iran. The patient (or a representative), together with the carer, provided written informed consent to participate.

### Interventions

Patients were randomized to receive *S. officinalis* extract 60 drops/day or placebo drop 60 drops/day. Throughout the study, the person who administrated the medications, rater and patients were blind to assignments.

### Extract preparation

*Salvia officinalis* was obtained from the farm of Institute of Medicinal Plants, Halejerd, Iran. The

taxonomic identity of the plants was confirmed by the botanist of the Department of Cultivation and Development of Institute of Medicinal Plants, Tehran, Iran. The plant extract was prepared as 1 : 1 in alcohol 45%. In other words, 1 kg dried herb (leaf) to 1 L of alcohol.

### Outcomes

The main efficacy measures were the ADAS-cog and CDR-SB and outcome measures were the change in ADAS-cog and CDR-SB scores over the trail. Patients were assessed by a neurologist at baseline and every 2 weeks after the medication started.

### Safety evaluations

All adverse events, reported, elicited or observed, were recorded at each visit. Routine physical examinations were conducted at each clinic visit. Complete physical examinations, including 12-lead electrocardiograph (ECG) recordings, were conducted at week 0, week 8 and week 16.

### Statistical analysis

Using data from pilot study and considering a five-point difference in the change in ADAS-cog score between patients treated with *Salvia* and placebo, we calculated that at least 15 patients were needed in each arm. A two-way repeated measures analysis of variance (time-treatment interaction) was used. The two groups as a between-subjects factor (group) and the nine measurements during treatment as the within-subjects factor (time) were considered. This was carried out for ADAS-cog and CDR-SB scores. In addition, a one-way repeated measures analysis of variance with a two-tailed *post hoc* Tukey mean comparison test were performed on the change in ADAS-cog and CDR-SB from baseline. To compare the reduction of score of ADAS-cog and CDR-SB scale at week 16 compared with baseline, an unpaired two-sided Student's *t*-test was used. Results are presented as mean  $\pm$  SEM differences and were considered significant at  $P \leq 0.05$ . To compare the baseline data and frequency of side-effects between the protocols, Fisher's exact test was performed. A traditional 'observed cases' (OC, the patients who completed

	Salvia extract	Placebo	<i>P</i> -value
Age (mean ± SD)	71.78 ± 3.67	72.75 ± 3.43	0.44
Gender	Male: 12, female: 7	Male: 12, female: 8	1.00

**Table 1.** Baseline characteristic

the trial) analysis at 16 weeks was the primary efficacy analysis. In addition, intention to treat (ITT) analysis with last observation carried forward (LOCF) procedure was also performed. All results discussed are based on OC analysis unless otherwise stated.

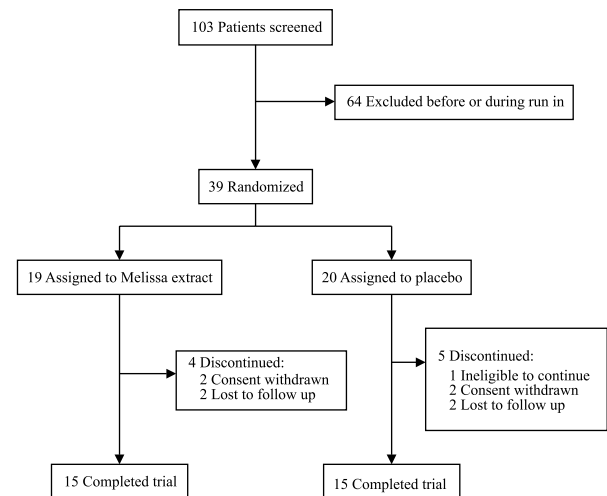
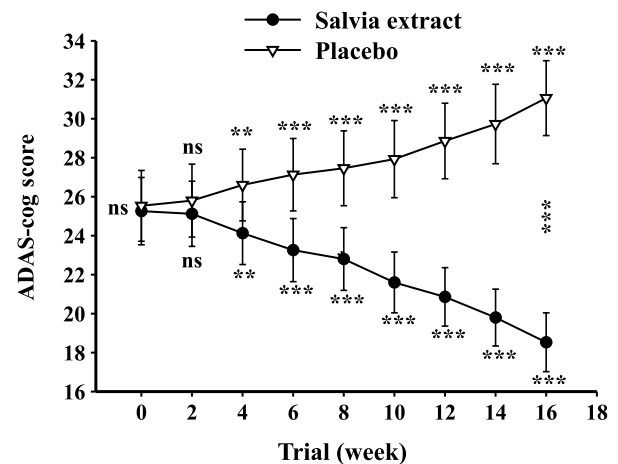
## RESULTS

A total of 103 patients were screened for the study and 39 were randomized to trial medication. No significant differences were identified between patients randomly assigned to the group 1 or 2 conditions with regard to basic demographic data including age and gender (Table 1). Thirty patients completed the trial. In the Salvia extract and placebo group, the number of drop-outs were four, and five, respectively. No significant difference was observed in the two groups in terms of drop-out ( $P = 1.00$ ) (Fig. 1).

### Efficacy

*ADAS-cog.* The mean ± SEM scores of two groups of patients are shown in Fig. 2. There were no significant differences between two groups in week 0 (baseline) on the ADAS-cog rating scale ( $t = 0.10$ , d.f. = 28,  $P = 0.91$ ). The difference between the two protocols was significant as indicated by the effect of group, the between-subjects factor ( $F = 4.77$ , d.f. = 1,  $P = 0.03$  and  $F = 4.92$ , d.f. = 1,  $P = 0.03$  for OC and LOCF analyses, respectively). The behaviour of the two treatments was not homogeneous across the time (groups-by-time interaction, Greenhouse × Geisser correction;  $F = 245.37$ , d.f. = 2.71,  $P < 0.0001$ ). In addition, a one-way repeated measures analysis of variance showed a significant effect of both protocols on the ADAS-cog rating scale scores ( $P < 0.0001$ ). In both groups *post hoc* comparisons showed a significant change from week 4 on the ADAS-cog rating scale scores. The difference between the two protocols was significant at the endpoint (week 16) ( $t = 5.12$ ,

d.f. = 28,  $P < 0.0001$  and  $t = 4.64$ , d.f. = 37,  $P < 0.0001$  for OC and LOCF analyses, respectively). The changes at the endpoint compared with baseline were:  $-6.60 \pm 1.63$  (mean ± SD) and  $5.53 \pm 1.12$  for Salvia extract and placebo, respectively. A significant difference was observed on the change of scores of the ADAS-cog rating scale at week 16 compared with baseline in the two groups

**Fig. 1.** Trial profile.**Fig. 2.** Mean ± SEM scores of the two protocols on the ADAS-cog score. ns, non-significant.

( $t = 23.63$ , d.f. = 28,  $P < 0.0001$  and  $t = 14.72$ , d.f. = 37,  $P < 0.0001$  for OC and LOCF analyses, respectively).

### CDR-SB

The mean  $\pm$  SEM scores of two groups of patients are shown in Fig. 3. There were no significant differences between two groups in week 0 (baseline) on the CDR-SB ( $t = 0.32$ , d.f. = 28,  $P = 0.75$ ). The difference between the two protocols was significant as indicated by the effect of group, the between-subjects factor ( $F = 10.84$ , d.f. = 1,  $P < 0.003$  and  $F = 13.10$ , d.f. = 1,  $P < 0.001$  for OC and LOCF analyses, respectively). The behaviour of the two treatments was not homogeneous across the time (groups-by-time interaction,  $F = 31.64$ , d.f. = 8,  $P < 0.0001$ ). In addition, a one-way repeated measures analysis of variance showed a significant effect of both protocols on the CDR-SB scores ( $P < 0.0001$ ). In both groups *post hoc* comparisons showed a significant change from week 8 on the CDR-SB scores. The difference between the two protocols was significant at the endpoint (week 16) ( $t = 6.13$ , d.f. = 28,  $P < 0.0001$  and  $t = 6.27$ , d.f. = 37,  $P < 0.0001$  for OC and LOCF analyses, respectively). The changes at the endpoint compared with baseline were:  $-1.60 \pm 1.35$  (mean  $\pm$  SD) and  $0.73 \pm 0.41$  for Salvia extract and placebo, respectively. A significant difference was observed on the change of scores of the CDR-SB at week 16 compared with baseline in the two groups ( $t = 6.38$ , d.f. = 28,  $P < 0.0001$  and

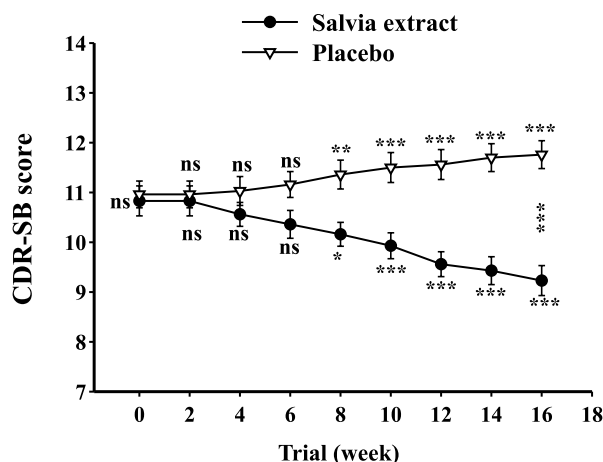


Fig. 3. Mean  $\pm$  SEM scores of the two protocols on the CDR-SB score. ns, non-significant.

Table 2. Observed side-effects over the trial

Side-effects	Salvia extract	Placebo	P-value
Vomiting	3	1	0.34
Dizziness	2	2	1.00
Wheezing	2	0	0.23
Agitation	1	6	0.09
Abdominal pain	2	0	0.23
Nausea	1	0	0.48

$t = 6.95$ , d.f. = 37,  $P < 0.0001$  for OC and LOCF analyses, respectively).

### Clinical complications and side-effects

Six cases of side-effects were observed over the trial. The difference between the Salvia extract and placebo in the frequency of side-effects was not significant except for agitation ( $P = 0.09$ ) (Table 2).

### DISCUSSION

This study showed that patients with mild to moderate Alzheimer's disease receiving *S. officinalis* extract experienced statistically significant benefits in cognition after 16 weeks treatment. The clinical relevance of these findings was emphasized by the improvements seen in both the ADAS-cog and CDR-SB measures in the *S. officinalis* extract group on both observed case and ITT analyses. To the best of our knowledge, this study is the first clinical trial of *S. officinalis* extract in the treatment of Alzheimer's disease. There is increasing evidence to indicate the possible efficacy of *S. officinalis* and *Melissa officinalis* in the management of Alzheimer's disease (11, 12). Indeed, a couple of recent reports indicated the CNS acetylcholine receptor activity of *M. officinalis* and *S. officinalis* and modulation of mood and cognitive performance following acute administration of *M. officinalis* that are in agreement with the findings of the present study (14, 15).

The side-effects associated with Salvia in this study were generally those expected from cholinergic stimulation, and similar to those reported with cholinesterase inhibitors (6, 10). Although, we cannot consider agitation as a side-effect, frequency of agitation appeared higher in the placebo group and this may indicate an additional advantage for

*Salvia officinalis* in the management of patients with Alzheimer's disease.

### Implications for research

The limitations of present study including the small number of patients and a relatively short period of follow-up should be taken into account. Further research is therefore needed.

### CONCLUSIONS

The results of this study indicate the efficacy of *Salvia officinalis* extract in the management of mild to moderate Alzheimer's disease. Moreover *Salvia officinalis* may reduce agitation in patients with Alzheimer's disease. Further investigations to validate the results are necessary.

### The trial group

Shahin Akhondzadeh (principal investigator and statistical support, clinical neuropsychopharmacologist from October 2000 to September 2002)

Mohammad Reza Mohammadi (clinical coordinator, psychiatrist from October 2000 to September 2002)

Maryam Noroozian (trial programmer, neurologist from October 2000 to September 2002)

Sina Ohadinia (trialist, medical doctor from October 2000 to September 2002)

Amir Hossein Jamshidi (pharmacognosist from October 2000 to September 2002)

Mousa Khani (botanist from October 2000 to September 2002)

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