



# Herbal medicine Davaie Loban in mild to moderate Alzheimer's disease: A 12-week randomized double-blind placebo-controlled clinical trial



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## ABSTRACT

**Objective:** In traditional texts on herbal medicines, various medicinal plants have been noted to have beneficial effects on dementia and Alzheimer's disease. According to the traditional books Herbal medicine Davaie Loban (DL) has beneficial effects in Alzheimer's disease. The study aim was to determine the clinical efficacy of DL in patients with mild-to-moderate Alzheimer's disease.

**Design:** Double blind randomized clinical trial.

**Setting:** Shahid Beheshti University of Medical Sciences.

**Interventions:** This included patients older than 50 years with mild to moderate Alzheimer's disease according to ADAS-cog (Alzheimer's Disease Assessment Scale-cognitive subscale;  $ADAS \geq 12$ ) and the Clinical Dementia Rating Scale Sum of Boxes (CDR-SOB;  $CDR \leq 2$ ). Twenty-four patients completed the study in DL group and 20 in placebo group.

**Main outcome measures:** ADAS-cog and CDR-SOB were filled out for patients to define the improvement in memory over the study period.

**Results:** At 4 weeks and 12 weeks there was significant difference in mean (SEM) ADAS-cog scores between DL and placebo groups and it was lower in DL group ( $p < 0.001$ ). At baseline, no significant difference was seen regarding mean (SEM) scores of CDR-SOB between DL and placebo groups ( $p = 0.096$ ). However, at 4 and 12 weeks there was significant difference in mean (SE) CDR-SOB scores between DL and placebo groups and it was lower in DL group ( $p < 0.001$ ).

**Conclusion:** Our findings suggest that DL may be effective in improvement of memory in patients with mild-to-moderate Alzheimer's disease.

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## 1. Introduction

Alzheimer's disease is a neurodegenerative disorder and is considered the most common form of dementia in the elderly people, especially those older than 60 years.<sup>1,2</sup> It is a chronic progressive disorder characterized by memory impairment, loss of visuospatial skills, language dysfunction, reduced insight into his or her deficits (anosognosia), dyspraxia, or difficulty in performing learned motor

tasks, and so on.<sup>3,4</sup> After age 65, the prevalence of Alzheimer's disease doubles every 5 years in a way that it is expected that 32% of those aged more than 85 years to have this condition.<sup>5</sup>

Various compounds have been used for Alzheimer's disease. Considering reduced level of brain choline acetyltransferase in the Alzheimer's disease, cholinesterase inhibitors such as donepezil and rivastigmine have been used widely in these patients and shown promising results.<sup>6,7</sup> Other pharmacologic agents such as memantine (an *N*-methyl-D-aspartate (NMDA) receptor antagonist) have been used in these patients, also.<sup>8</sup> Beside these agents, herbal medicines have also been studied in Alzheimer's disease.<sup>9</sup>

The concern remains among clinicians managing patients with Alzheimer's disease, is that many of the agents described above only have limited effects on cognitive dysfunction but not completely

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manage all aspects of the disease. Also, many pharmacologic agents are associated with some side effects on liver function.<sup>10</sup>

It seems that alternative and complimentary medicine especially herbal medicine has opened a new way for treatment of Alzheimer's disease.<sup>11</sup> There is some evidence about beneficial effects of herbal medicines such as *Ginkgo biloba* L. and *Mellisa officinalis* in the management of dementia.<sup>12,13</sup> However, the trials data about the efficacy of *ginkgo* in dementia is equivocal.<sup>14,15</sup>

Furthermore, in traditional texts on herbal medicines, various herbs have been noted to have beneficial effects on Alzheimer's disease. Beneficial effects of the herbs *Cyperus rotundus* L. (Nutt -grass), *Zingiber officinale* (ginger), *Acorus calamus* L. (Sweet-flag, Sweet sedge), *Piper nigrum* L. (black pepper), and *Boswellia carterii* (Incense) have been shown in Alzheimer's disease.<sup>16–18</sup>

Davaie Loban (DL) is one of the compounds that have been applied in traditional medicine for treatment of forgetfulness. Davaie Loban is an herbal medicine which contains all above-mentioned components and is widely used for Alzheimer's disease.<sup>19–21</sup>

In traditional medicine both DL and its components have been used for reinforcement of memory.<sup>16–21</sup> Various studies have investigated the efficacy of components of DL in the treatment of Alzheimer's disease<sup>22–27</sup> but there is no study about the efficacy of DL in treatment of Alzheimer's disease. So far, no study has been done to determine the clinical efficacy of DL in patients with Alzheimer's disease. Therefore, we intended to investigate the clinical efficacy of DL in Alzheimer's disease patients.

## 2. Materials and methods

### 2.1. Setting and patients

This double-blind randomized clinical trial (registration No. IRCT2014010216028N1 at [www.irct.ir/www.irct.ir](http://www.irct.ir/www.irct.ir)) which lasted for 12 weeks included patients older than 50 years of age with MMSE scores between 15 and 26 and mild to moderate Alzheimer's disease. The probable diagnosis of Alzheimer's disease was made by a neurologist according to the criteria of the NINCDS-ADRDA Alzheimer's Criteria.<sup>28</sup> Brain CT or MRI reports of the patients at the time of the research or during the preceding year were examined to rule out the possibility of multi-infarct dementia or cerebrovascular diseases as the cause of dementia. The severity of Alzheimer's disease was determined using ADAS-cog (Alzheimer's Disease Assessment Scale-cognitive subscale)<sup>22</sup> and the Clinical Dementia Rating Scale Sum of Boxes (CDR-SOB).<sup>23</sup> The two assessment tools of study including ADAS-cog and CDR-SOB have been used previously and their good validity and reliability have been approved in several studies.<sup>29–31</sup>

Assessment of the patients with these scales was done every 4 weeks during the study period. Exclusion criteria were cardiovascular diseases, illicit drug abuse and alcohol dependence, diabetes mellitus, epilepsy, cerebrovascular diseases, neurodegenerative disorders, and taking anticoagulants. Initially 70 patients were screened and among them 50 patients were selected. Patients were randomly assigned into treatment and placebo groups (each 25 patients). Finally, 24 patients in herbal medicine group and 20 in placebo group completed the study to the end of 12 weeks follow-up (Fig. 1).

### 2.2. Preparation of Davaie Loban capsules

Firstly, medical plants including *C. rotundus* L. (Nutt -grass), *Z. officinale* (ginger), *A. calamus* L. (Sweet-flag, Sweet sedge), *P. nigrum* L. (black pepper), and *B. carterii* (Incense) were purchased from Medical Herbs Market in Kerman, Iran. Quality control was done in

all processes of the herbal medicine and microbial contamination of drug with Salmonella, Shigella, E. coli, and fungi was checked. The microbial and organoleptic properties were checked and verified by Karaj University Organization. The manufacture of the medicine was done by the traditional methods described in traditional texts. First the herbs were grinded and powder was formed. Then capsules in the form of 500 mg herbal medicine was prepared by taking into account of 35 gs of *C. rotundus* L. (Nutt -grass), *B. carterii* (Incense), and *A. calamus* L. (Sweet-flag, Sweet sedge) and 17.5 gs of *Z. officinale* (ginger) and *P. nigrum* L. (black pepper). The calculated dosage according to 1 g of herbal medicine was 1.5 g daily for each patient, which was prescribed three times daily in the form of 500 mg capsule.

### 2.3. Randomization and intervention

The patients were randomly assigned into two groups. One group received DL capsules (500 mg, three times daily, every 8 h). The placebo group received capsules similar in shape, color, and odour to DL capsules. This intervention was continued for 3 months.

### 2.4. Safety evaluation

In weekly visits done for the patients, any possible side effect of the herbal medicine was sought and if present, documented in a form. Routine physical examinations were also done at every visit.

### 2.5. Sample size

Having used Stata software version 13.00, the sample size was calculated based on the formula for comparing two means. The assumptions for this calculation was: type one error = 0.05, power = 0.8, and minimum importance difference ( $d$ ) = 0.4 of standard deviation.

### 2.6. Statistical analyses

The data gathered were entered into the SPSS software for Windows (ver. 20.0). Descriptive indices including frequency, percentage, mean, SD (standard deviation), and SEM (standard error of mean) were used to report the data. Comparisons of continuous variables between the two studied groups were done using the student *t*-test and one-way ANOVA (analysis of variance). Repeat measurement ANOVA was applied to find the trend of changes in variables over time.

### 2.7. Ethics

The study details were described for the patients prior to the study. Written informed consent was obtained and they were reassured about data confidentiality. The study protocol was in accordance to the ethical guidelines of the recent version of Declaration of Helsinki approved in October 2013.<sup>32</sup> The protocol was approved by ethics committee at Shahid Beheshti University of Medical Sciences with registration code 143.

## 3. Results

There were 12 males in herbal medicine group and 10 in placebo group. Mean (SD) age of patients in DL group was 66.25 (6.25) years and in placebo group it was 67.65 (5.99) years ( $P = 0.465$ ). Table 1 presents demographic characteristics in the study groups.

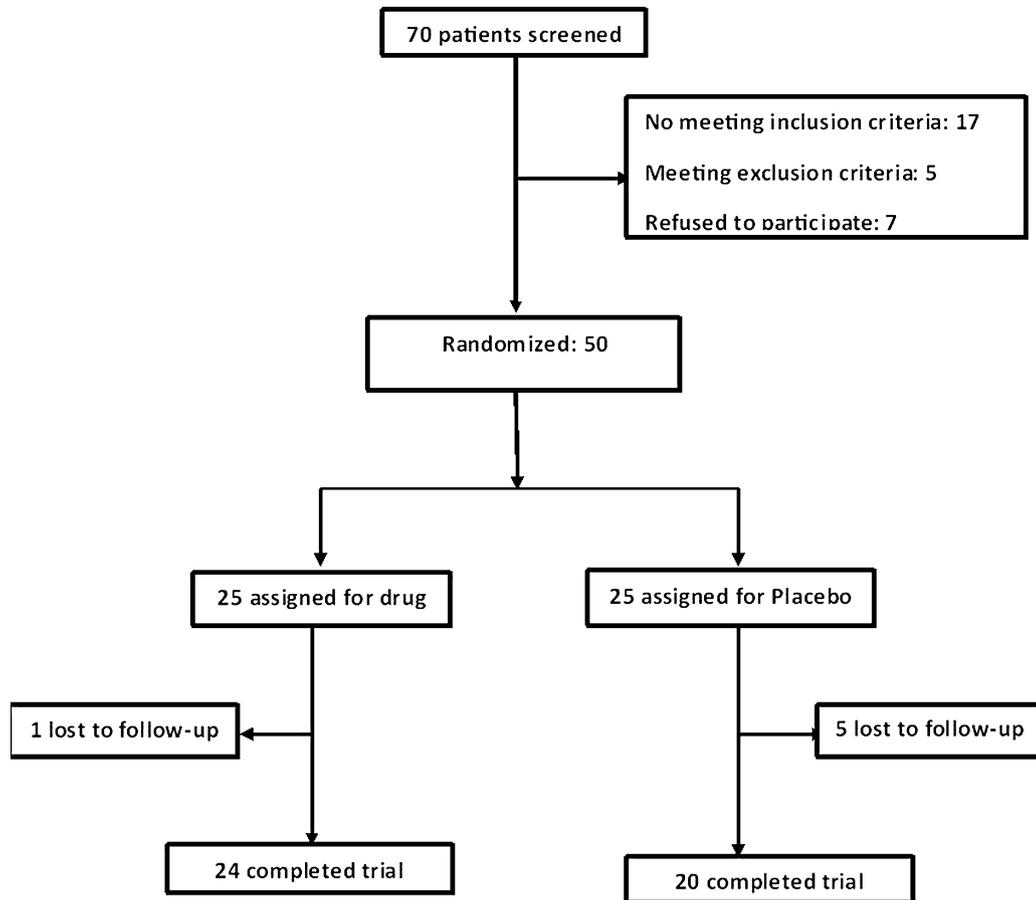


Fig. 1. The study flow chart.

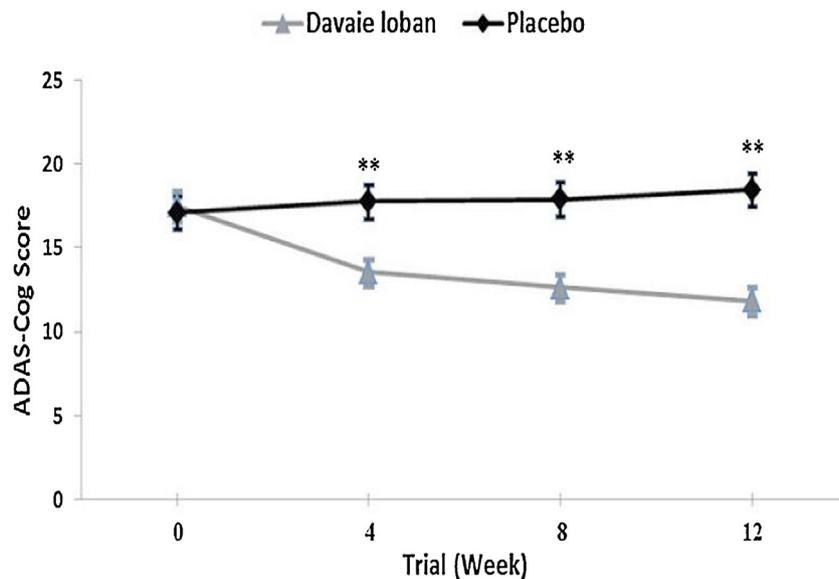


Fig. 2. Mean (SE) scores of ADAS-cog (Alzheimer’s Disease Assessment Scale–cognitive subscale) in Davaie loban and placebo groups at different time points throughout the study period.

3.1. ADAS-cog

At baseline (start point of the study) no significant difference was seen regarding mean (SEM) scores of ADAS-cog between DL and placebo groups ( $p=0.751$ ). However, at 4th and 12th weeks there was significant difference in mean (SE) ADAS-cog scores between DL and placebo groups and it was lower in DL group

( $p<0.001$ ). Mean changes in ADAS-cog scores showed no difference between genders ( $p=0.728$ ). Likewise, no difference was seen in mean ADAS-cog scores between different categories of educational level ( $p=0.868$ ). Also, no difference was seen with regard to ADAS-cog scores between singles and married subjects ( $p=0.193$ ) (Fig. 2).

**Table 1**  
Demographic characteristics in the studied groups.

		Davaie Loban	Placebo
Gender	Male	12 (50%)	10 (50%)
	Female	12 (50%)	10 (50%)
Educational level	Junior school	16 (66.7%)	13 (65%)
	High school diploma	7 (29.2%)	6 (30%)
	Higher than high school diploma	1 (4.1%)	1 (5%)
Marital status	Single	5 (20.8%)	4 (20%)
	Married	19 (79.2%)	16 (80%)

### 3.2. CDR-SOB

At time zero no significant difference was seen regarding mean (SEM) scores of CDR-SOB between DL and placebo groups ( $p=0.096$ ). However, after 4 and 12 weeks there was significant difference in mean (SE) CDR-SOB scores between DL and placebo groups and it was lower in DL group ( $p<0.001$ ). Mean changes in CDR-SOB scores showed no difference between genders ( $p=0.915$ ). Likewise, no difference was seen in mean CDR-SOB scores between different categories of educational level ( $p=0.573$ ). Also, no difference was seen with regard to ADAS-cog scores between singles and married subjects ( $p=0.540$ ) (Fig. 3).

### 3.3. Side effects

One patient died in placebo group due to femoral neck fracture. Besides, two patients reported side effects. One of them in DL group complained of stomach burning pain and one case reported nausea in placebo group. No other side effects were reported.

## 4. Discussion

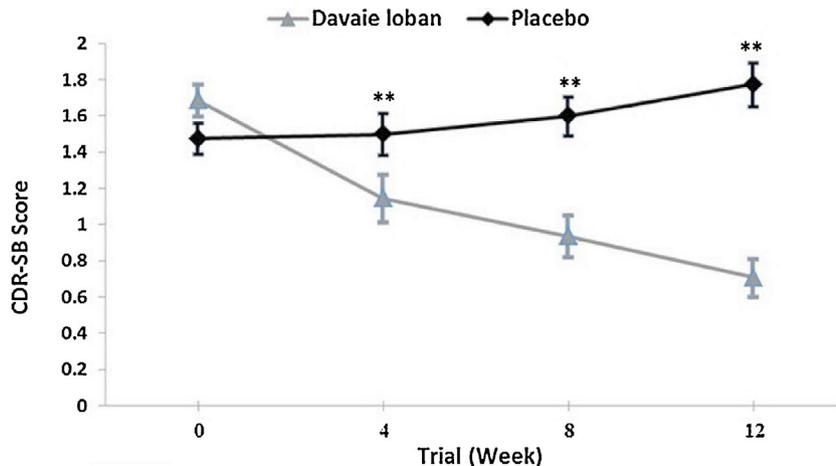
The obtained findings show that DL is effective in improving ADAS-cog and CDR-SOB scores. This is the first study to investigate the clinical efficacy of DL in patients with mild-to-moderate Alzheimer's disease. Hence, we are not able to compare the result we faced here with other studies. About each individual herbal plant, which DL contains, some evidence exists about their effect on cognition and memory, in particular in animal models. Rabiei et al.<sup>24</sup> studied the influence of *C. rotundus* L. (Cyperaceae) tubers ethanolic extract on learning and memory in the rat model of Alzheimer's and intact rats. They randomly divided 49 male Wistar rats into seven groups. Wistar rats received bilateral electric

lesions of the nucleus basalis of Meynert. The NBM-lesioned rats received *C. rotundus* L. (Cyperaceae) tubers ethanolic extract (100 and 200 mg/kg) for 15 days while distilled water was used for control group. By applying passive avoidance paradigm, passive avoidance learning and memory performance were assessed, and Morris water maze test was used for spatial learning and memory evaluation. They reported that *C. rotundus* L. (Cyperaceae) tubers ethanolic extract yielded some repairing effects on the memory and behavioral disorders in rats for which bilateral electric lesions of the nucleus basalis of Meynert had been done. Jebasingh et al.<sup>25</sup> in their study on the protective effect of ethanol extract of *C. rotundus* L. (Cyperaceae) (400 mg/kg) (a medicinal plant used in Ayurvedic traditional medicine against sodium nitrite-induced hypoxia) in rats found that *C. rotundus* L. (Cyperaceae) was associated with protective effects in this kind of cell injury in the brain. Also, CNS depressant activity of ethanol extract of *C. rotundus* in mice has been noted in the literature.<sup>26</sup>

Khalili et al.<sup>27</sup> reported that oral and intraperitoneal administration of the extract of *A. calamus* L. in higher dose increased spatial recognition and recalling the data in mice. In their study, rats for which *A. calamus* L. was used received this herb in oral route (plant/food ratio = 6.25%) for two weeks and in injection groups the plant extract were applied to rat in 25, 50 and 100 mg/kg dosages. Rats were conducted to Y maze and shuttle box tests in order to obtain spatial recognition and acquisition, and recalling data, respectively. It has been noted that *A. calamus* L. by anti-oxidant property and inhibition of acetylcholine esterase, has beneficial effects in improving memory.<sup>33</sup> In a study, the effects of Zingicomb, a mixture of *Z. officinale* and *G. biloba* extracts, on memory and learning of older (24 months) rats was assessed by Morris water maze. The authors reported that Zingicomb might also facilitate spatial learning in older rats and reduces oxidative stress in the brain after chronic administration.<sup>34</sup> *P. nigrum* has also been implicated in animal studies to decrease oxidative stress in the brain tissue and improving neurodegenerative condition.<sup>35</sup>

The above mentioned studies indicate the positive effect of each of the herbal medicines used in DL on memory. In addition, traditional books have emphasized on the effectiveness of DL on dementia, which is similar to Alzheimer's disease. Since our results indicate that DL was effective on mild-to-moderate Alzheimer's disease, it seems that this herbal medicine can be transformed to one of the effective medicines for Alzheimer's patients, after enough additional studies are done.

*P. nigrum* L. posses its effect by inhibition of cholinesterase activity and via antioxidant activity and protection against amyloid



**Fig. 3.** Mean (SE) scores of Clinical Dementia Rating Scale Sum of Boxes (CDR-SOB) in Davaie loban and placebo groups at different time points throughout the study period.

toxicity.<sup>36,37</sup> *C. rotundus* L. functions through anticholinesterase effect.<sup>38</sup> *Zingiber* also effects on Alzheimer's disease through antioxidant property, inhibition of cholinesterase activity and protection against amyloid toxicity.<sup>39</sup> *A. calamus* L. acts via cholinergic effects and antioxidant activity.<sup>40,41</sup> Effects of *B. carterii* in Alzheimer's disease is exerted by antioxidant and cholinergic effects.<sup>42,43</sup>

As the components of DL mainly effects through anti-cholinesterase and antioxidant activity and protection against amyloid toxicity, it seems that the main mechanisms of action of DL in Alzheimer's disease is cholinergic effect, antioxidant activity and reduction of amyloid toxicity. One of the main strengths of DL is its 'multi-component, multi-target action. These components may exert additive or over additive pharmacological synergic effects.

The anti-dementia effect of DL is moderate without any adverse drug reaction.

Limitations we faced here are short-term follow-up of patients and relatively low sample size of the groups. Using a valid questionnaire and few number of lost to follow-up are among the strengths of our study.

Future studies with greater sample size and longer follow-up period and taking to account the limitation of our study are recommended to confirm our study findings. Also, future studies are recommended for comparison of the effect of DL with other drugs like donepezil.

## 5. Conclusion

The study findings suggest that DL may be effective in improving memory in patients with mild to moderate Alzheimer's disease. Three-month administration of DL (*C. rotundus* L., *Z. officinale*, *A. calamus* L., *P. nigrum*, and *B. carterii*) associated with improved ADAS-cog and CDR-SOB scores without any serious side effects in patients with mild-to-moderate Alzheimer's disease. We recommend further studies on human subjects with longer follow-ups and comparison to chemical drugs currently used for Alzheimer's diseases to find any advantage or disadvantage of this herbal medicine.

## Conflict of interest

There is no conflict of interest.

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