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Does herbal medicine have an effect on the cognitive function of patients with mild to moderate Alzheimer's disease over the age of 50?

Melissa Liebman
Philadelphia College of Osteopathic Medicine

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Melissa Liebman, PA-S

A SELECTIVE EVIDENCE BASED MEDICINE REVIEW

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ABSTRACT

OBJECTIVE: The objective of this selective evidence based medicine review is to determine whether or not "herbal medicine has an effect on the cognitive function of patients with mild to moderate Alzheimer's disease over the age of 50".

STUDY DESIGN: Review of three double-blind, randomized control trials published between 2003 and 2015. All studies were published in English language in peer reviewed journals.

DATA SOURCES: Three randomized control trials were found via PubMed.

OUTCOMES MEASURED: The outcomes measured include changes in Alzheimer's symptoms based upon a neurologist, improvement of Alzheimer's symptoms based on ADAS-cog and CDR-SOB clinical rating scale, and Alzheimer health related quality of life based on a 20-item questionnaire.

RESULTS: Akhondzadeh et al (2003) demonstrated a significant reduction in Alzheimer's symptom scores after treatment with herbal medicine, Salvia officinalis extract, with a p value of <0.0001. Tajadini et al (2005) demonstrated a significant reduction in Alzheimer's symptom scores after treatment with herbal medicine, Davaie Loban, with a p value of <0.001. Zhang et al (2015) demonstrated a significant reduction in Alzheimer's symptom scores after treatment with herbal formula, Yishen Huazbuo decoction, with a p value of <0.05.

CONCLUSIONS: Results of the three studies demonstrate that herbal medicine is an effective treatment in individuals over the age of 50 for the cognitive improvement of mild to moderate Alzheimer's disease. Two studies recommend that further studies should be done with longer follow-ups and larger sample sizes to more confidently confirm the findings.

KEY WORDS: Alzheimer's disease, herbal medicine, cognitive function

INTRODUCTION

Alzheimer's Disease is an irreversible and chronic brain disorder that occurs when brain tissue is changed and destroys memory and thinking skills. As the population living of the United States is continuing to age, Alzheimer's is becoming a more prevalent cause of death[5]. This decline happens because neurons that are involved in cognitive function slowly become damaged over time and do not function properly[4]. Alzheimer's is a common disease. Experts suggest that 5.5 million Americans have Alzheimer's disease and one in nine people age 65 and older are affected. It is estimated that the total annual healthcare cost for Alzheimer's disease is $259 billion dollars[5]. They even state that there are 780 hospital stays per 1,000 Medicare beneficiaries age 65 and older with Alzheimer's disease and other dementias[4].

The exact cause of Alzheimer's is unknown; however, it has been found that the symptoms it causes seem to come from nerve damage. Nerve cells get tangles called neurofibrillary tangles and protein deposits called beta-amyloid plaques that build up in the brain. These brain changes are believed to contribute to the development of Alzheimer's. Eventually, the number of synapses decrease, information transfer at synapses decline, and neurons begin to die[6]. The most common symptoms of Alzheimer's disease include memory loss that disrupts daily life, challenges in solving problems, confusion with time and place, trouble understanding visual images and relationship, and problem with words in both speaking and writing. There are numerous complications of Alzheimer's including immobility, swallowing disorders, malnutrition, and pneumonia[4].

There is no cure for Alzheimer's disease, but medications and sensory therapy can help its symptoms and slow the progression[4]. Non-pharmacologic therapies include music therapy and reminiscence therapy. Previous published research has shown that exercise, gardening, word

games, and listening to music can show assurance. Lifestyle modifications also include schedule toileting to reduce incontinence, daily routines, and encourage social interaction[4]. However, current pharmacologic therapies as well as non-pharmacologic therapies have not been shown to alter the viscous course of Alzheimer's disease. There are different types of drugs that can target treatment of memory loss, sleep problems, behavior changes, and other symptoms associated with Alzheimer's. It is recommended to treat depression and irritability with selective serotonin reuptake inhibitors (SSRI) such as citalopram (Celexa). For people experiencing anxiety, medicine such as alprazolam (Niravam, Xanax) may be beneficial. Cholinesterase inhibitors such as Donezepil (Aricept) are the treatment of choice for people experiencing mild to moderate symptoms of Alzheimer's. N-methyl-D-aspartate receptor blocker such as Memantine (Namenda) is offered to people experiencing more severe symptoms[6].

Though there is no cure for Alzheimer's disease, effective control of the symptoms is an attainable goal. Despite the existence of effective treatments for sleep problems and behavior changes, there continues to be an effort to find an effective treatment to improve cognitive function. It is for this reason that several randomized control trials have been carried out in an attempt to scientifically show the effectiveness of improving cognitive function with herbal medicine.

OBJECTIVE

The objective of this selective evidence based medicine review is to determine whether or not "herbal medicine has an effect on the cognitive function of patients with mild to moderate Alzheimer's disease over the age of 50?"

METHODS

Criteria: This selective evidence based medicine review evaluates three randomized control trials chosen based on population, intervention, comparison group, and outcomes measures. The selected population of interest was patients 50 years or older with a diagnosis of mild to moderate Alzheimer's disease. The intervention in these three studies was the treatment of herbal medicines. The treatment group receiving Salvia Officinalis extract, Davaie Loban, or Chinese herbal formual Yishen Huazbuo decoction was compared to a group receiving a visually matched placebo or herbal formula donepezil hydrochloride. The outcomes measured in these studies included the effect on the patient's cognitive function and activities of daily living.

Data Sources: The key words "Alzheimer's disease", "herbal medicine", and "cognitive function" were searched on PubMed to find articles both relevant to the clinical question and ones that included patient oriented outcomes (POEMS: Patient Orientated Evidence that Matters). All articles were published in the English language between 2003 and 2015 in peer-reviewed journals. The inclusion criteria included double-blind studies published after 2000 and exclusion criteria included patients under 50 years old. The statistics used and reported in the selective based medicine review include p-value and change in mean from baseline with a standard deviation.

Table 1- Demographics & Characteristics of Included Studies

Study	Type	# Pts	Age (years)	Inclusion criteria	Exclusion criteria	W/D	Interventions
Akhondzadeh, 2003 (1)	Double-blind, RCT	39	Salvia extract: 71.78 ± 3.67 Placebo: 72.75 ± 3.43	Patients between 65 and 80, patients with a history of cognitive decline for at least 6 months, diagnosed with ALZ according to the NINCDS/ADRDA, ADAS-cog ≥12 and CDR-SOB ≤2, any other medication to treat dementia must be d/c,	Evidence of other neurodegenerative disorders, any cardiovascular disease, active peptic ulcer, urinary outflow obstruction, history of	9	Salvia officinalis extract delivered 60 drops/day for 4 months

				HTN, HF, DM were included provided the disease was controlled	epilepsy, drugs with anticholinergic effects		
Tajadini 2015 (2)	Double-blind, RCT	50	Davaie Loban 66.25 ± 6.25 Placebo : 67.65 ± 5.99	Patients older than 50, diagnosed with mild to moderate ALZ, ADAS-cog≥12 and CDR-SOB ≤2, brain CT or MRI were examined to rule out multi-infarct dementia or cerebrovascular diseases	Cardiovascular disease, illicit drug use, DM, epilepsy, cerebrovascular disease, neurodegenerative disorders, taking coagulants	6	Davaie Loban capsules (500g, three times daily, every 8 hours) for 3 months
Zhang, 2015 (3)	Double-blind, RCT	144	> 50 years old	Diagnosis of dementia of the Alzheimer's type according to the diagnostic and statistical manual, diagnosis was confirmed by image test (CT/MRI), women/men aged 50-85, Hachinski ischemic score ≤ 4, Hamilton depression rating ≤7, CDR=1	Vascular dementia or any neurological disorder other than AD that contributed to dementia, severe heart, liverm or kidney disease, use of drugs that may affect cognitive function 4 weeks prior to randomization, uncontrolled HTN, aphasia, hemiplegia	31	Chinese herbal formular Yishen Huaxhuo decoction (100 ml orally once a day, half an hour after breakfast) for 12 months

OUTCOMES MEASURED

All of the outcomes measured in this selective evidence medicine based review include patient oriented evidence. The outcomes measured include changes in Alzheimer's symptoms based upon a neurologist, improvement of Alzheimer's symptoms based on ADAS-cog and CDR-SOB clinical rating scale, and Alzheimer health related quality of life based on a 20-item questionnaire. The ADAS-cog is a 21-item scale used to assess the severity of cognitive impairments in patients with Alzheimer's disease. It ranges from 0-70 (very severe) and evaluates selected aspects of attention, language, memory, orientation, praxis, and reasoning. The CDR-SOB sums up the ratings from six domains: memory, orientation, judgment, problem

solving, community affair, home and hobbies, and personal care. It ranges from 0-3 (3=severe dementia). The Akhondzadeh et al double-blind, randomized control trial measured improvement of cognitive function in patients with mild-to-moderate Alzheimer's disease prior to and four months after the treatment of herbal medicine Salvia officinalis extract. 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 4-month trial. Patients were evaluated by a neurologist at baseline and every 2 weeks after the Saliva officinalis extract was administered. The data was reported as a mean change in baseline with a standard deviation[1].

The Tajadini et al double- blind, randomized control trial measured improvement of cognitive function in patients with mild-to-moderate Alzheimer's disease prior to and three months after the treatment of herbal medicine Davaie Loban. This was assessed based on the ADAS-cog and CDR-SB clinical rating scale every 4 weeks during the study period of 12 weeks. This data was reported with statistical significant p values.

The Zhang et al double-blind, randomized control trial measured improvement of cognitive function in patient with mild Alzheimer's disease prior to and 6 months after the treatment of herbal formula, Yishen Huazhuo decoction. This was measured using the ADAS-cog and higher values indicating higher degree of deficit. The study also used a 20-item questionnaire designed to measure the patient's ability to carry out daily activities such as medication management, food preparation, personal hygiene and transportation utilization. Each of these items rating between 0 and 10, where higher values denote higher severity of symptom. The data was reported as a mean change in baseline with standard deviation[3].

RESULTS

This selective evidence based medicine review evaluates herbal medicine as a treatment for Alzheimer's disease. The results of these studies were all presented in continuous data. All three studies were randomized with concealment to randomization. All of the patients, clinicians, and study workers were kept blind to which patients were in the treatment group for the duration of the study.

Akhondzadeh et al is a double-blind, randomized control trial that assesses the improvement in cognitive function of herbal medicine Salvia officinalis extract in patients with mild-to-moderate Alzheimer's disease who are 50 years and older. The treatment group was compared to a visually matched placebo group. Thirty-nine participants were placed into one of the two groups: nineteen patients assigned to the herbal medicine group that received 60 drop/day of S. officinalis extract and twenty patients assigned to the placebo group that received 60 drops/day of placebo. The study measured improvement of cognitive function based on ADAS-cog and CDR-SOB scores over the trial at baseline and every 2 weeks after. Regarding both the ADAS-cog and CDR-SOB, there were no significant differences between the two groups in week 0 (baseline). The difference between the two protocols was significant at the end point (week 16). The changes at the endpoint compared with baseline for ADAS-cog were: -6.60 +/- 1.63 (mean +/- SD) and 5.53 +/- 1.12 for Salvia extract and placebo, respectively. The changes at the endpoint compared with baseline for CDR-SOB were: -1.60 +/- 1.35 (mean +/- SD) and 0.73 +/- 0.41 for Salvia extract and placebo, respectively. At the conclusion of the study, it was determined there was a significant increase in cognitive function in Alzheimer's patients with a statistically significant p-value of <0.0001[1].

Figure 2: Mean +/- SEM scores of the two protocols on the ADAS-cog score. ns, non-significant

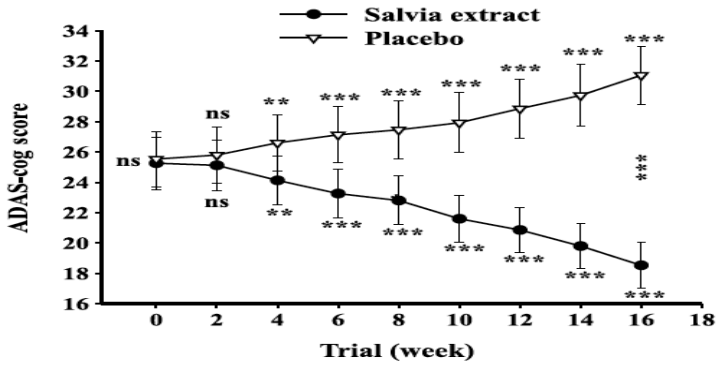
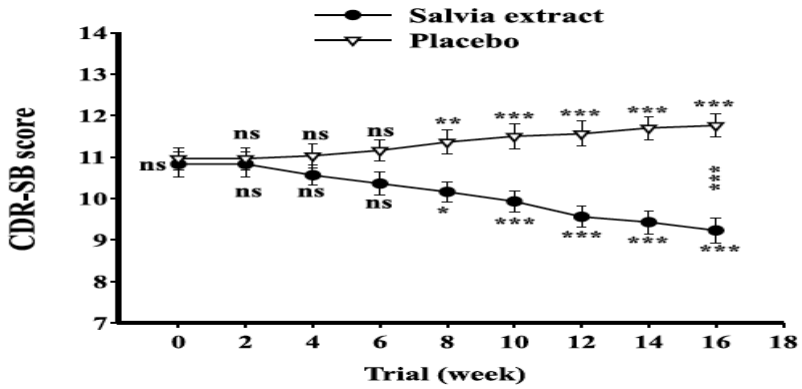


Figure 3: Mean +/- SEM scores of the two protocols on the CDR-SB score. ns, non significant



Tajadini et al is a double-blind, randomized control trial that assesses the improvement in cognitive function of herbal medicine Davaie Loban in patients with mild-to-moderate Alzheimer's disease who are 50 years and older. The treatment group was compared to a visually matched placebo group. Fifty participants were placed into one of the two groups: twenty-five patients assigned to the herbal medicine Davaie Loban received (500 mg three times daily) and twenty-five patients assigned to placebo group. The study measured improvement of cognitive function based on ADAS-cog and CDR-SOB scores over intervention that lasted for 12 weeks. Regarding the ADAS-cog, there were no significant difference between the two groups in week 0 (baseline) (p=0.751). However, after 4 and 12 weeks there was a significant difference in mean (SE) ADAS-cog scores between DL and placebo groups and it was lower in DL group

(p<0.001). Regarding the CDR-SOB, there was no significant decreases between the two groups in week 0 (baseline) (p=0.096). However, after 4 and 12 weeks there was a significant difference in mean (SE) CDR-SOB scores between DL and placebo groups and it was lower in DL group (p<0.001). At the conclusion of the study, it was determined there was a significant increase in cognitive function in Alzheimer's patients with a statistically significant p-value of <0.001[2].

Fig 2. Mean (SE) scores of ADAS-cog in DL and placebo group throughout study

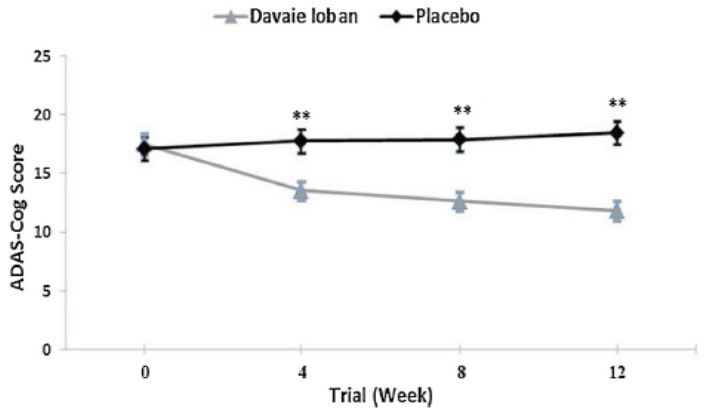
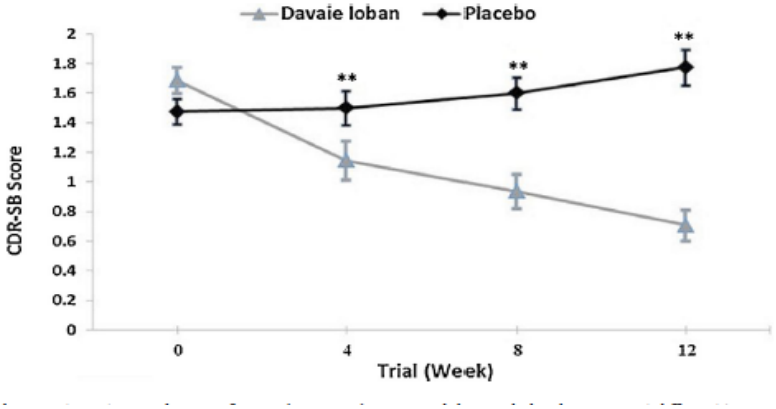


Fig 3. Mean (SE) scores of CDR-SOB in DL and placebo group throughout study



Zhang et al is a double-blind, randomized control trial that assesses the improvement in cognitive function of herbal formula Yishen Huazbuo decoction (YHD) in patients with mild Alzheimer's disease who are 50 years and older. The treatment group was compared to donepezil hydrochloride (DH). 144 participants were place into one of the two groups: seventy-two patients

were assigned to the herbal formula YHD and seventy-two patients were assigned to the DH group. The study measured improvement of cognitive function based on ADAS-cog and ADL scores over the intervention that lasted for 24 weeks. The scores in YHD group significantly reduced in week 12 and 24, while the scores of DH group declined in week 24. The mean scores of ADAS-cog showed a decreased of 3.10 +/- 4.55 in YHD group and a decrease of 1.22 +/- 4.99 in DH group during the 24 weeks treatment, with statistical significance of p-value <0.05[3]. Both YHD and DH could improve scores of ADL, but without statistically significant difference between groups. At the conclusion of the study, it was determined there was a significant increase in cognitive function in Alzheimer's patients with a statistically significant p-value of <0.05[3].

Fig 2. Scores of ADAS-cog and ADL in YHD and DH group

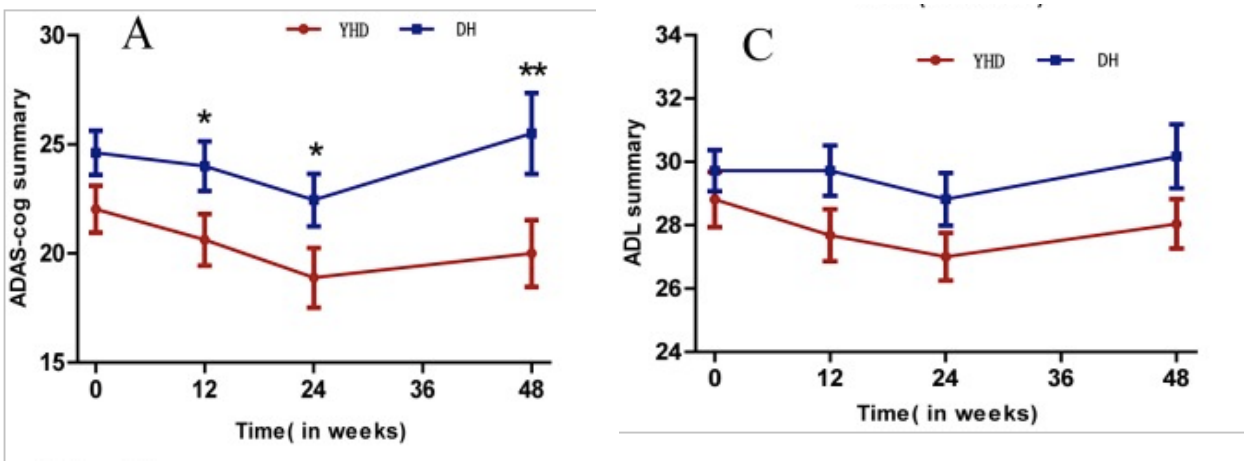


Table 2. Mean efficacy scores at all time points and change at week 24, 48 (Mean+/-SD)

	Group	Baseline	12weeks	24weeks	48weeks	Change 24 weeks	Change 48 weeks
ADAS-cog	YHD	22.03±9.14	20.63±9.37*	18.18±9.79*	19.65±10.62*	-3.10±4.55*	1.45±3.74*
	DH	24.62±8.57	24.01±8.64	22.24±8.89	25.16±11.21	-1.22±4.99	4.13±8.62
ADL	YHD	28.81±7.36	27.68±6.48	27.00±5.68	28.00±5.35	-1.12±3.16	1.36±3.60
	DH	29.72±5.56	29.46±5.96	28.82±6.14	30.46±6.75	-1.07±3.86	2.38±5.08

DISCUSSION

The three randomized controlled trials discussed in this review suggest that herbal medicine is an effective alternative treatment for Alzheimer's disease. All three studies demonstrated a statistically significant improvement in the cognitive function measured with a statistical significance threshold set a $p<0.05$. This study showed that the herbal medicines was above all else in terms of word recall task, following commands, orientation, word recognition task, remembering test direction, spoken language, comprehension, and word-finding difficulty.

All three studies in this selective evidence based medicine review demonstrated limitations. For two of the studies, sample size was the main limitation. Akhondzadeh et al had a sample size of thirty-nine and Tajadini et al had a sample size of fifty[1,2]. Another limitation was a moderate dropout rate. For instance, Akhondzadeh began their study with thirty-nine patients and ended with thirty[1]. In the treatment group, 4 discontinued (2 consent withdraw and 2 lost to follow up) and in the control group, 5 discontinued (1 ineligible to continue, 2 consent withdraw, 2 lost to follow up) thus the outcomes from these people that were not included in the analysis might have affected the significant of the results[1]. Tajadini began their study with fifty and ended with forty-four[2]. In the treatment group, 1 was lost due to follow up and in the control group, 5 were lost due to follow up, thus the outcomes from these people that were not included in the analysis might have affected the significance of the results[2].

CONCLUSION

All three studies successfully demonstrated that there is a significant improvement in cognitive function of patients 50 years and older with mild-to-moderate Alzheimer's disease following treatment with herbal medicine. Therefore, herbal medicine is an effective alternative

treatment for improving the cognitive function and reducing the symptoms of Alzheimer's disease in patients 50 years and older.

Despite this convincing evidence, further studies on human subjects with longer follow-ups, larger sample sizes, and comparison to chemical drugs currently used for Alzheimer's disease should be conducted. It would be important to create a study comparing herbal medicine to cholinesterase inhibitors or N-methyl-D-aspartate receptor blockers to see which method of treatment would be superior for treating symptoms of Alzheimer's disease.

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