

Review

The Use of Herbal Medicine in Alzheimer's Disease—A Systematic Review

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The treatments of choice in Alzheimer's disease (AD) are cholinesterase inhibitors and NMDA-receptor antagonists, although doubts remain about the therapeutic effectiveness of these drugs. Herbal medicine products have been used in the treatment of Behavioral and Psychological Symptoms of Dementia (BPSD) but with various responses. The objective of this article was to review evidences from controlled studies in order to determine whether herbs can be useful in the treatment of cognitive disorders in the elderly. Randomized controlled studies assessing AD in individuals older than 65 years were identified through searches of MEDLINE, LILACS, Cochrane Library, dissertation Abstract (USA), ADEAR (Alzheimer's Disease Clinical Trials Database), National Research Register, Current Controlled trials, Centerwatch Trials Database and PsychINFO Journal Articles. The search combined the terms Alzheimer disease, dementia, cognition disorders, Herbal, Phytotherapy. The crossover results were evaluated by the Jadad's measurement scale. The systematic review identified two herbs and herbal formulations with therapeutic effects for the treatment of AD: *Melissa officinalis*, *Salvia officinalis* and Yi-Gan San and BDW (Ba Wei Di Huang Wan). *Ginkgo biloba* was identified in a meta-analysis study. All five herbs are useful for cognitive impairment of AD. *M. officinalis* and Yi-Gan San are also useful in agitation, for they have sedative effects. These herbs and formulations have demonstrated good therapeutic effectiveness but these results need to be compared with those of traditional drugs. Further large multicenter studies should be conducted in order to test the cost-effectiveness of these herbs for AD and the impact in the control of cognitive deterioration.

Keywords: Alzheimer's disease – cognitive impairment – dementia – elderly – herbs – randomized clinical trial – systematic review

Introduction

Alzheimer's disease (AD) is characterized as a progressive neurodegenerative disorder and considered as prominent cause of dementia in the elderly. The main characteristics of this disease are difficulties in household handling routine and cognitive and emotional disturbance in the elderly. The

treatment of AD is a clinical challenge. With the development of cholinesterase inhibitors and a *N*-methyl-D-aspartate antagonist (memantine), good perspectives have emerged in controlling the symptoms of AD. Therapeutic decisions have to be guided by clinical studies and should consider the physiopathogenesis and epidemiology of the disease.

The main objective of these clinical trials is to reduce the Behavioral and Psychological Symptoms of Dementia (BPSD) and to improve cognition and the functional activity status, thus reducing the impairment of instrumental activities of the daily living (IADLs) and to lower the institutionalization rates (nursing home placement). Unfortunately, only a limited

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number of trials have dealt with this topic and with follow-up periods shorter than two years. In spite of the absence of sufficient therapeutic effectiveness in mild and moderate AD, these drugs are still considered as the first line of treatment for AD (1). Studies of cost-effectiveness suggest that memantine (2,3) and donepezil (4) are useful in the reduction of institutionalized care and/or cognitive impairment in patients with AD. Recently, two clinical trials showed no improvement of the cognitive deficit (5,6) or reduction in the institutionalization rate (6).

Searching for alternatives, many herbal products have been tested and employed in the treatment of AD, but with different clinical responses (7). The assessment of these drugs through randomized controlled trials should be useful to identify effective products in the treatment of AD.

Methods

Searching at MEDLINE (during April 2006, PubMed), LILACS (Latin American and Caribbean Health Science Literature: 40th edition, May 2001, the last research was performed in April 2006); Cochrane Library (issue 1, 2006); Dissertation Abstract (USA, during April 2006); ADEAR (Alzheimer's Disease Clinical Trials Database, until April 2006); National Research Register (1/2006); Current Controlled trials (the last research was performed in October 2005); PsychINFO Journal Articles (during the year of 2006); relevant web sites; and scanning of reference list of relevant articles. There were no language or publication restrictions.

Search for keywords in MeSH (medical subject heading (MeSH) with the words 'Alzheimer disease, dementia, cognition disorders' was performed first. In the second part, the keywords were 'Herbal' and 'Phytotherapy'. The crossover results of the two searches were evaluated by the Jadad's measurement scale (8).

Inclusion criteria: Three investigators independently reviewed all of the articles found. The articles were selected using the criteria listed below:

- i. The studies should be randomized; double-blind and controlled (with a control group and a treatment group).
- ii. Studies should establish methodological procedures in the crossover or be conducted at the same time.
- iii. In the case of being crossover, a washout period of at least 7 days was required.
- iv. Patients included in the researches had their diagnosis rated into three degrees as follows: mild, moderate and severe forms of AD, according to the criteria from the National Institute of Neurological and Communicative Disorders and Stroke—AD and Related Disorders Association (NINCDS-ADRDA) (9). The models used were as follows: Mini-mental beginning values between 10 and 26 (initial and mild group) or <10 (initial group).
- v. Clinical trials should last for at least 1 month (4 weeks).

- vi. Detailed description of the herbal product used.
- vii. Neuropsychiatry symptoms progression should be measured with numerical score using the Assessment Scale (ADAS-noncog, range of score, 0–70), NPI (Neuropsychiatric Inventory, range of score 0–120), Clinical Global impression of change or Behavioral rating scale for Geriatric patients.
- viii. The final score should be quantified using a combination of ADL and IADL methodological procedures.

Exclusion criteria: The herbal product has already been target of a quantified systematic review study. In this case, only the results of the studies will be considered.

Jadad's measurement scale: Methodological quality was assessed using a scale developed and validated by Jadad *et al.* (8). This scale assesses the completeness of reporting using three items with a five points maximum score. If the allocation into groups is explicitly randomized, item 1 is scored. A bonus point is given if an adequate method to generate the random sequence is described. If there is an explicit statement that the study is double-blind Item 2 is scored. A bonus point is given if the method is described and adequate. Item 3 is scored if there is either an explicit statement that all patients included were also analyzed or if the number and reasons for dropouts in all groups are given separately. For being classified as adequately reported a trial should score at least three of five points, a cut-off point is recommended by the author of the scale (10).

All extraction and quality assessments were performed by at least two independent reviewers using standard forms developed for each review. Disagreements were documented and discussed with final decisions made by the principal reviewer.

Results

Two herbs and two herbal formulations were identified to have effectiveness in the treatment of cognitive disturbance of AD in the systematic review: *Salvia officinalis* (11), *Melissa officinalis* (12), and Yi-Gan San (13) and Ba Wei Di Huang Wan (BDW) (14). The main characteristics of the study are described in Table 1.

Ginkgo biloba was previously identified in one meta-analysis (15), and only the conclusions of the study will be considered. Another study will be conducted with huperzine A, a product derived from a Chinese herb *Huperzia serrata*, to evaluate the safety and efficacy in the treatment of AD in a multicenter randomized controlled trial of its effect on cognitive function (16).

The studies of *Salvia* (11), *Melissa* (12), Yi-Gan San (13) and BDW (14) have reached Jadad's measurement scale of ≥ 3 . The researches had a follow up of 1 month (Yi-Gan San) (13), 2 months (BDW) (14) and 4 months (*Salvia* and *Melissa*) (11,12). All samples studied were composed of patients with initial mild symptoms judged as AD. Two studies compared herbal medicines and control samples, using intention to treat [*Salvia* (11) and *Melissa* (12)].

Table 1. Phytotherapeutic interventions in the Alzheimer's disease—selected RCT

Reference number	No. of patients	Study and duration	Herbal medicinal product name	Composition	Dosage regimen and quantitative description	Qualitative testing	Placebo/control group	Cognitive outcome measurements	Inclusion/exclusion criteria	Adverse effects
11	30	Single blind, 4 months	<i>Salvia officinalis</i> extract manufactured by the Medicinal Plants Institute (Tehran)	Leaf extract containing essential oil: aldehydes, monoterpene, flavonoids, polyphenol (rosmarinic acid) and monoterpene glycosides	3000 mg of alcoholic solution (45%) per day, corresponding to 100 mg per ml per day in a dosage of 3 ml per day or 60 drops per day. There is no information on interval	There is no reference on the article	There is no reference on the placebo used	ADAS-cog CDR-SB	Cognitive deficit in the past 6 months. Mild to moderate dementia. Patients under ChE-I treatment were excluded	Not significant
12	30	Single blind, 4 months	<i>Melissa officinalis</i> extract, manufactured by the Department of Cultivation and Development of the Plants Institute (Tehran)	Hydroalcoholic leaf extract the containing 500 µg citral per ml	1500 mg of an alcoholic solution (45%) per day, corresponding to 500 mg per ml per day in a dosage of 3 ml per day or 60 drops per day	There is no reference on the article	There is no reference on the placebo used	ADAS-cog CDR-SB	Cognitive deficit in the past 6 months. Mild to moderate dementia. Patients under ChE-I treatment were excluded	Agitation occurred to 40% of individuals from placebo group versus 5% from the study group ($P = 00.3$)
13	52	Single-blind, 1 month	Yi-Gan-San formula*	Rootstock and branches lyophilized dry extract	2.5 g of YGS powder, corresponding to 1.5 g of the TTD extract before meals	3D-HPLC	There is no reference on the placebo used	NPI Barthel Index MMSE	Dementia with over than 12 month of diagnosis. 17.3% (9) presented some type of associated cerebral-vascular disease. Patients under ChE-I treatment were excluded	Not significant
14	50	Double-blind, 2 months	Ba Wei Di Huang Wan [†] . Product approved for use in Japan, manufactured by Uchida Wakanyaku Co. Ltd	Powder containing medicinal plants mixed with honey	20 cpr (2 g) of BDW or TTD placebo after meals	There is no reference on the article	Black face powder with Sepia sp.	MMSE Barthel Index	Dementia with over than 12 month of diagnosis. 17.3% (9) presented some type of associated cerebral-vascular disease. Patients under ChE-I treatment were excluded	Not significant

ADAS-cog, Alzheimer's disease assessment scale; CDR-SB, clinical dementia rating-sum of the boxes; ChE-I, acetyl cholinesterase inhibitor; MMSE, mini-mental state examination; NPI, neuropsychiatric inventory; HPLC, high-performance liquid chromatography.

*Formula containing 4 g of *Arctylodis Lanceaea* rootstock; 4.0 g of *Poria cocos* Wolf; 3.0 g of *Cnidium monnieri* rootstock; 3.0 g of *Urticaria* and *Angelica sinensis* root; 2.0 g of *Bupleuri* radix; 1.5 g of *Glycyrrhizae uralensis* rhizoma; and 3.0 g of *Uncariae ramulus* et Uncus.

[†]Formula containing 8 g of *Rehmannia glutinosa* Libosch. var. *purpurea* Makino (Scrophulariaceae); 4 g of *Cornus officinalis* Sieb et zucc (Cornaceae); 4 g of *Dioscorea batatas* Decne root (Dioscoreaceae); 3 g of *Alisma orientale* Juzep rhizome (Alimataceae); 3 g of *Poria cocos* Wolf (Poriacea); 3 g of *Paeonia suffruticosa* Andr. (Paeoniaceae); 1 g of *Cinnamomum cassia* Blume (Lauraceae); and 1 g of *Aconitum carmichaeli* Debx. (Ranunculaceae).

None of the studies evaluated the institutionalization rate or compared the active principle with the current therapies with Acetyl Cholinesterase Inhibitor or memantine.

Discussion

The results of this systematic review identified four studies with methodological quality assessing *S. officinalis* (11), *M. officinalis* (12), Yi-Gan San (13) and BDW (14). The last two are composed of formulations with different phytoactive agents. These herbs and formulations presented efficiency in reducing the mild and moderate symptoms of AD.

Ginkgo biloba presented statistically significant mild effectiveness in the treatment of cognitive deficit in AD. The meta-analysis study of Cochrane (13) concluded that additional controlled studies would be necessary in order to recognize cognitive improvement with the use of *ginkgo*. There is still need of a prospective study with an appropriate duration and representative sample to identify if *G. biloba* reduces the development of AD (17). Another plant with a large application perspective is *H. serrata*, after multicenter trial confirmation underway (16).

Melissa and Yi-Gan San showed reduction in the cognitive deficits and a good sedative effect in patients with AD (12,13). Previous clinical studies showed that the extract of *M. officinalis* reduces laboratory-induced stress (18) and might have benefits in mood improvement (19–21). The use of these herbs and formulations should be well tolerated, (22) and adverse effects have not yet been reported (23). Further studies should be conducted to compare the current therapies for AD and the use of these herbal remedies in controlling the symptoms of AD.

The action mechanisms of these herbs and formulations are not well known. It has been suggested that the chemical composition of the essential oil of the Melissa and Salvia leaf extracts are monoterpene aldehydes, polyphenol flavonoids (including rosmarinic acid) (24) and monoterpene glycosides (25). All of these components have many observable effects *in vitro*, which include powerful anti-oxidative activity (26,27) and an affinity to nicotinic and muscarinic receptor in the human cerebral cortex (28). This last mechanism is of special interest, as modulation of cholinergic systems should play a role in improving the cognitive function, especially in AD.

Yi-Gan San and BDW are mixes of many herbal ingredients. Yi-Gan San is a mixture of 7 different dried plants, many of them (*Uticariae sinensis* and *Angelicae root*) with possible actions in the serotonergic and gaba system. BDW consists of 8 herbs: *Rehmannia glutinosa* Libosh. var *purpurea* Makino, *Cornus officinalis* Sieb et Zucc (Cornaceae), *Dioscorea batatas* Decne root (Dioscoreaceae), *Alisma orientale* Juzep rhizome (Alimatacaceae), *Poria cocos* Wolf, *Paeonia suffruticosa* Andr. (Paeoniaceae), *Cinnamomum cassia* Blume (Lauraceae) and *Aconitum carmichaeli* Debx. (Ranunculaceae). Studies have suggested that BDW enhances the choline acetyltransferase activity and increases the acetylcholine content of the frontal cortex in a murine model (29,30).

Major methodological limitations of the four studies are small size of samples and short-term duration. There is no description of the chemical composition and/or possible active principles of the different products employed in studies Involving Yi-Gan San (13) and BDW (14) formulation (Table 1). In the study with BDW (13), Sepia sp. and face powder were used as placebo; however, the way that the shellfish formulation was performed was not described. In the control group of the study using the Yi-Gan-San (14) formulation, 25 mg per day of tiapride hydrochloride were introduced. This drug is a substituted derivative with selective dopamine D2-receptor antagonist properties. This intervention (contamination) occurred in 44% of the individuals and was responsible for the symptoms, among them dizziness.

Generally, crude herbal drugs are natural products and their chemical composition depends on several factors such as geographic source of the plant material, climate in which it was grown, and time of harvest. Commercially available herbal medicinal products also vary in their content and concentration of chemical constituents from batch to batch and when products containing the same herbal ingredient are compared between manufacturers. Even when herbal products are standardized for content of known active or marker compounds to achieve more consistent pharmaceutical quality, variations in the concentrations of other constituents can be observed. The use of a protocol such as the Consolidated Standards of Reporting Trials (CONSORT), composed of 22 items, will probably minimize the limitations of RTC with phytotherapeutic agents (31).

The use of herbal medicines in the treatment of AD should be compared with the pharmacological treatment currently in use. Such studies should include the identification of the active principle in order to improve the validation of the clinical trial. Further large-scale, multicenter studies are necessary to determine the effectiveness of these substances in the cognitive deterioration of AD. Until then, this review provides some evidence of the benefit of Melissa, Salvia, Yi-Gan San and BDW in the treatment of AD.

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