Bulletin of Pharmaceutical Research 2020;10(1-3):170
An Official Publication of Association of Pharmacy Professionals
ISSN: 2249-6041 (Print); ISSN: 2249-9245 (Online)
DOI: 10.21276/bpr.2020.10.2

REVIEW ARTICLE

HERBAL MEDICINES FOR ALZHEIMER'S DISEASE: A TREATISE

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Received: Apr 07, 2020 / Revised: May 13, 2020 / Accepted: May 14, 2020

Alzheimer's disease (AD) is characterized by an menacing loss of recollection, connected purposeful refuse, and behavioral disorder. Patients may live for more than a decade after they are diagnosed with AD, making it the important cause of disability in the aged. The treatments of alternative in AD are cholinesterase inhibitors and NMDA-receptor antagonists. As cholinergic purpose is requisite for short-term memory, the cholinergic shortage in AD was also supposed to be accountable for much of the short-term memory shortage. Herbal medicine products have been used in the handling of Behavioral and Psychological Symptoms of Dementia (BPSD) but with different responses. Although some FDA-approved drugs are accessible for the treatment of AD, the outcomes are often insufficient, and there is always a place for herbal medicine. The prearranged assessment recognized two herbs and herbal formulations for the treatment of AD *viz. Melissa officinalis*, *Salvia officinalis*; Yi-Gan San and BDW (Ba Wei Di Huang Wan); *Ginkgo biloba*. All five herbs are useful for cognitive injury of AD. These herbs and formulations have confirmed good therapeutic usefulness but these results need to be compared with those of conventional drugs.

Key words: Alzheimer's disease, BPSD, NMDA-receptor antagonists, Yi-Gan San, Herbs.

INTRODUCTION

Alzheimer's disease (AD) is the most ordinary cause of relentless mental deterioration (dementia) in the elderly [1-3]. AD was known to occur sporadically in families but was not essentially thought to be related to the more normal happening of cognition impairment in late life. The latter condition was known as senile dementia [4]. The foremost characteristics of this ailment are difficulties in household treatment, routine, cognitive and affecting commotion in the elderly. When results of careful pathology studies emerged in the 1970s and 1980s showing that the pathology of the brains of patients with early-onset (before the age of 65 years) and late-onset AD was the same, research into the pathologic process as well as the clinical manifestations accelerated [1,3]. The occurrence and frequency of AD rose with escalating age, more than ever for those over the age of 65 years. The incidence of AD ranges from 1 to 4% of the inhabitants per year, getting higher from its buck level at ages 65 to 70 years to charge that may come up to 6% for those over the age of 85 years. With the development of cholinesterase inhibitors and a N-methyl-*d*-aspartate antagonist (memantine), good perspectives have emerged in scheming the symptoms of AD. The main aim of these experimental trials was to diminish the Behavioral and Psychological Symptoms of Dementia (BPSD) and to get better cognition and the purposeful activity position, thus dropping the mutilation of influential actions of the daily living (IADLs) and to lower the institutionalization rates (nursing home placement). Unfortunately, only a limited quantity of trials have dealt with this matter and with follow-up periods shorter than two years. In spite of the absence of adequate curative helpfulness in mild and restrained AD, these drugs are still considered as the first line of

treatment for AD [5,6]. Studies of cost-effectiveness suggest that memantine [7,8] and donepezil [9] are positive in the lessening of institutionalized care and/or cognitive destruction in patients with AD. Pervasiveness rates of AD also amplify by half a decade or decade; intelligence in the journalism of how many cases survive at any solitary phase vary. Estimates of the pervasiveness of AD range from 3% of the populace between the ages of 65 and 75 years to the chief reported estimate of 47% of people over the age of 85 years. In general, all studies report a progressive increase in the pervasiveness of dementia as a meaning of age between 65 and 85 years; more unadventurous estimates at the upper end are in the range of 30 to 35%, which is still a significant number. Whatever the current estimates, all researchers concur that the number of AD cases will in all chance triple over the next 30 to 40 years.

Recently, two clinical trials showed no improvement of the cognitive deficit [10,11] or lessening in the institutionalization rate [11]. While searching for alternatives, many herbal products have been experienced and working in the treatment of AD, but with different clinical responses [12]. The assessment of these drugs through randomized prescribed trials should be practical to recognize effectual products in the treatment of AD.

Definitions of AD

There are three generally used criteria-based approaches to the judgment of AD: The intercontinental categorization of Diseases, 10th review (ICD-10); the Diagnostic and Statistical Manual of Mental Disorders, fourth edition (DSM-IV); and the National Institute of Neurological and Communicative Disorders and Stroke (Alzheimer's Disease and Related Disorders Association [NINCDS-ADRDA]) work group criteria [13-15]. Not astonishingly, the three definitions contribute to many universal features. Three general misconceptions concerning AD are 1) it is a global disorder, 2) it is a diagnosis of exclusion, and 3) it can be a diagnosed only at autopsy.

All are challenged by the three investigative frameworks that necessitate that concentration be satisfactorily integral to leave out hallucination as the grounds of the psychological status changes, while an international muddle would consist of attentional abnormality. All definitions are independent on the practicability of clinical diagnosis, and nearly everyone sequence find correctness charge of 85 to 90% based on these criteria. An indicative cultivate for AD should begin with comprehensive interviews of both the enduring and a stool pigeon who is memorable with the patient. The checkup history can endow with significant in sequence, such as the timing of onset of symptoms, level of purposeful destruction, rate of weakening, and any alterations in disposition [12,15]. A inclusive corporeal assessment should comprise an in-office cognitive estimation, such as the Mini Mental State inspection, and a brief neurological assessment [16]. The incidence of gloominess should also be evaluated; useful screens include the elderly hopelessness range and the Zung Self-Rating Scale for melancholy (16). Laboratory evaluations should include blood chemistries; a complete blood cell count; tests for neurosyphilis, thyroid, kidney, and liver function; and serum levels of vitamin B12. Computed tomography is usually satisfactory to eradicate subdural hematoma or tumors as a prospective grounds; however, magnetic resonance imaging (MRI) may be compulsory to distinguish the occurrence of white-matter ischemic lesions. Positron emission tomography (PET) or single photon emission computed tomography (SPECT) are constructive in characteristic AD from other dementias through quantifying metabolism or to evaluate general blood flow.

Pathophysiology of AD

Neuroimaging of the uncomplaining with AD or other dementias may disclose weaken of the brain, such as engorged ventricles and sulci and tapering gyri, although these features are not at all times there. Neuronal beating is the main neuropathologic feature fundamental symptoms of AD. Microscopically, AD is characterized by the incidence of senile plaques and neuro fibrillary tangles (NFTs). Plaques are extracellular deposits of filamentous beta-amyloid, a protease cleavage merchandise of amyloid forerunner protein [17,18].

NFTs are formed intracellularly by the abnormal rescheduling of microtubule-associated proteins, such as tau. Both NFTs and senile plaques, although analytical of AD when experiential in large numbers, are also nearby to various degree in the brains of standard elderly people. However, the plaques seen in ordinary brains or early-stage AD are distribute and moderately benevolent deposits of f-amyloid, whereas at later stages, the plaques assume a compact

β-pleated conformation and afterward turn into connected with dystrophic neuritis. These later-stage plaques are contemplation to symbolize a more neurotoxic form [17,18].

Cholinergic hypothesis

The first neurotransmitter imperfection naked in AD caught up acetylcholine (ACh). Because cholinergic purpose is compulsory for short-term recollection meaning, it was unwavering that cholinergic shortage in AD was also accountable for much of the short-term recollection shortage [19]. Markers for cholinergic neurons such as choline acetyltransferase (ChAT) and acetylcholine-sterase (AChE), which are enzymes accountable for fusion and dilapidation of ACh, correspondingly, are decreased in the cortex in adding to hippocampus areas of the brain concerned in cognition and recollection [19,20]. The most basic loss of neurons occurs in the nucleus basalis and the entorhinal cortex (EC), where cholinergic neurons are preferentially exaggerated. As the poor health progresses, up to 90 % of cholinergic neurons in the nucleus basalis of Meynert (NBM) may be lost [20,21]. Animal studies have established that loss of cholinergic meaning in these areas is connected with declines in knowledge capability in addition to recollection. The consequential diminish in ACh-dependent neurotransmission is contemplation to escort to the handy deficits of AD, much as dopaminergic deficits cause Parkinson's disease and its clinical manifestations [20,21]. Clinical drug trials in patients with AD have all ears on drugs that supplement levels of ACh in the brain to recompense for wounded of cholinergic meaning in the brain. These drugs have incorporated ACh precursors, muscarinic agonists, nicotinic agonists, and cholinesterase inhibitors [22,23]. The best-developed and most triumphant approaches to date have used cholinesterase reticence [24,25]. The primary drug permitted for universal clinical use in AD was tacrine. However, three new cholinesterase inhibitors available are donepezil (Aricept®), rivastigmine (Exelon®), and galantamine (Reminyl®) [26]. All of these drugs have been experienced first and foremost in patients with AD, with most trials studying conduct in patients with mild to reasonably ruthless illness. The latest drug for AD breaks out of the ACh-enhancing mode and focuses on a dissimilar receptor multifaceted. Memantine (Namenda®) was permitted for the US market in October 2003 and has been used in Europe for many existence. Memantine is marketed for patients at the reasonable to ruthless stages of the syndrome.

Pharmacological treatment

Many of today's imitation drugs originated from the plant kingdom, and only about two centuries ago the major pharmacopoeias were subjugated by herbal drugs. Herbal medicine ruthless stages went into rapid refuse when basic and clinical pharmacology recognized themselves as important brushwood of medicine. Nevertheless, herbal medicine is still of concentration in many diseases [27,28], in particular, psychiatric and neurological disorders [29]. There are some reasons for this issue including 1) patients are dissatisfied with conventional treatment, 2) patients want to have control over their healthcare decision, 3) patients see that herbal medicine is congruent with their philosophical values.

Galantamine

An alkaloid cholinesterase inhibitor initially resultant from European daffodils or common snowdrops, this drug is a spirited and discriminatory acetylcholinesterase inhibitor (**Figure 1**). Galantamine also allosterically modifies nicotinic ACh receptors, potentiating the presynaptic rejoinder to ACh. Galantamine has a half-life of 5 to 6 hrs and is metabolized by CYP-450 enzymes as donepezil. Galantamine has not been linked with hepatotoxicity in clinical trials [29,30]. Pooled information from 4 randomized trials of patients with mild AD specify that patients who received conventional galantamine 24 mg/d for six months had enhanced cognition more often than those who received conventional placebo, and that a advanced quantity getting galantamine were internationally enhanced. This suggests that patients with mild AD advantage from galantamine management [29,30].

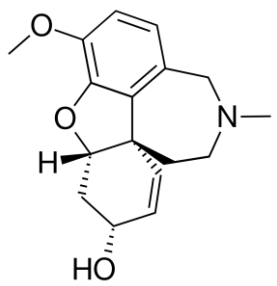

Fig. 1. Chemical structure of Galantamine

Ginkgo biloba

Ginkgo biloba is an herbal medicine that has been worn to treat a assortment of ailments for thousands of years in China (**Figure 2**). The patients were specified either 120 mg of *Ginkgo biloba* remove (GBE) or placebo each day for up to a year [31]. At the six-month point, 27% of those using *Ginkgo biloba* had reasonable development on a diversity of cognitive tests. Only 14% of those using placebo had an development on these tests. In a disconnect trial, 112 patients with chronic cerebral deficiency conventional 120 mg/d of GBE [32]. The researchers found the important improvements in blood and oxygen stream. Controlled blood and oxygen flow to the brain may be an important reason in the expansion of AD. GBE appears to be most successful in the early stages of AD. GBE has been shown to have the capacity to standardize the ACh receptors in the hippocampus area of the brain in elderly animals [33]. GBE has also established the capability to boost cholinergic movement and to present improvements in other aspects of the infection [34]. A double-blind study of 216 patients with AD or dementia caused by small strokes found that 240 mg of GBE daily led to important improvements in a assortment of clinical parameters when compared to placebo [35]. A study compared the efficiency of the most ordinary AD drug to *Ginkgo biloba* extract called EGb 761 [36]. A dissimilar study originate that EGb 761 prevents f-amyloid toxicity to brain cells, a key part of the progress of the syndrome [37]. All forms of *Ginkgo biloba* necessitate to be taken constantly for at least 12 weeks, a potentially difficult task for AD patients, to conclude whether the complement is functioning. A current double-blind placebo-controlled randomized study of patients with AD originate that EGb761 fashioned important improvements in cognitive purpose compared to a placebo collection. This study also confirmed that EGb 761 was as safe as placebo through the study episode [38]. Nevertheless, the experimental trial information for cholinesterase inhibitors, reported in reviews by the Cochrane Collaboration, materialize to be more constant and vigorous than those for *Ginkgo biloba*, and also show larger property on cognition.

Huperzine A

Huperzine A is a chemical consequent from a meticulous type of society moss (*Huperzia serrata*). Like caffeine and cocaine, huperzine A

Fig. 2. *Ginkgo biloba* (maidenhair) leaves

medicinally vigorous plant consequential substance that belongs to the class identified as alkaloids (**Figure 3**). This material is really additional a medicine than an herb, but it is sold over the contradict as a nutritional enhancement for memory loss and mental mutilation. According to three Chinese double-blind trials enrolling a total of more than 450 people, use of huperzine A can considerably recover symptoms of AD and other forms of dementia [39,40]. One double-blind trial failed to find confirmation of advantage, but it was comparatively small [41].

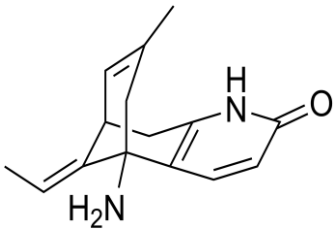

Fig. 3. Chemical structure of Huperzine A

Vinpocetine

Vinpocetine is a substance resulting from vincamine, a ingredient in the foliage of periwinkle (Vinca minor), the seeds of different African flora (**Figure 4**). It is used as a management for memory hammering and psychological mutilation. In the United States, it is obtainable as dietary supplement, although the material possibly does not fit that grouping by any coherent classification. Vinpocetine does not exist to any momentous amount in nature. Producing it requires momentous compound employment performed in the laboratory. A number of double-blind studies have evaluated vinpocetine for the management of AD and correlated environment [42]. A assessment of the writing set up three studies of satisfactory superiority, enrolling a total of 728 persons. Perhaps the best of these was a 16-week double-

blind placebo-controlled trial of 203 people with mild to reasonable dementia that found important advantage in the treated collection [42]. However, even this trial had several technological borders.

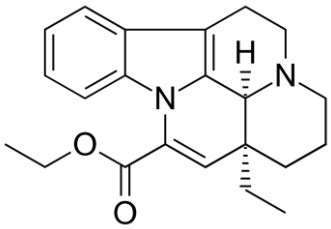

Fig. 4. Chemical structure of Vinpocetine

Melissa officinalis and Salvia officinalis

It has been reported that *Melissa officinalis* (lemon balm) improves cognitive purpose and reduces demonstration in patients with mild to reasonable AD. *M. officinalis* is recognized to have ACh receptor movement in the middle nervous organization with both nicotinic and muscarinic obligatory properties [43,44]. A current study has revealed that this plant modulates character and cognitive presentation when administered to young, vigorous volunteers [45]. In addition, a parallel, randomized, placebo-controlled study assessed the effectiveness and security of *M. officinalis* in 51 patients with kind to reasonable AD [46]. Subjects were treated for four months. The main effectiveness events were the cognitive subscale of the Alzheimer's Disease Assessment Scale (ADAS-cog) and the Clinical Dementia Rating-Sum of the Boxes (CDR-SB) scores. The CDR-SB provides a consensus-based global clinical compute by summing the ratings from six domains *viz.* memory, direction, judgment, problem solving, community affairs, home and hobbies, and individual care. The results exposed that patients getting *M. officinalis* extract practiced noteworthy improvements in cognition after 16 weeks of handling. Improvements were seen on both the ADAS-cog and CDR-SB scores. The researchers experimental no important distinction in the occurrence of side effects sandwiched between the placebo group and those getting the herb extort. However, the frequency of campaigning was higher in the placebo group compared to those getting active management [46].

The clinical application of these result was emphasized by the improvements seen in both the ADAS-cog and CDR-SB measures in the *S. officinalis* extract group on both experimental case and intention-to-treat analyses. The changes at the endpoint compared to baseline (mean SD) were -1.60 (1.35) and 0.73 (0.41) for Salvia extort and placebo, respectively, on the CDR-SB scores. The side effects connected with Salvia in this study were generally those probable from cholinergic encouragement and were similar to those reported with cholinesterase inhibitors [47].

Frequency of campaigning appeared higher in the placebo collection, and this may point toward an supplementary benefit for *M. officinalis* in the organization of patients with AD. In termination, healing strategies will have to comprise a assortment of interventions heading for at numerous targets. So far, the outcomes with obtainable FDA-approved medications for AD are often unsatisfactory, and there is a place for substitute medicine, in meticulous herbal medicine [48].

As described for many of these herbs, there is, in fact, a supposed pharmacological objective such as a receptor or neurotransmitter; none of the herbs can be said to treat the "whole disorder".

Fig. 5. *Melissa officinalis* (lemon balm) and *Salvia officinalis* (common sage)

Yi-Gan San

Yi-Gan San is an herbal formulation used in traditional East Asian medicine. Yi-Gan San is composed of a ratio of 4:4:3:3:3:2:1.5 of the following 7 dried medicinal herbs: Atractylodis Lanceae Rhizoma (rhizome of *A. lancea* De

Candolle, Compositae), Poria (sclelrotium of *P. cocos* Wolf, Polyporaceae), Cnidii Rhizoma (rhizome of *C. officinale* Makino, Umbelliferae), Angelicae Radix (root of *A. acutiloba* Kitagawa, Umbelliferae), Uncaria Uncis Cum Ramulus (hook of *U. rhynchophilla* Miquel, Rubiaceae), Bupleuri Radix (root of *B. falcatum* Linne, Umbelliferae), and Glycyrrhizae radix (root and stolon of *G. uralensis* Fisher, Leguminosae). Increasingly, yi-gan san is being used for a variety of psychological and psychiatric conditions associated with dementia, personality disorder, schizophrenia, sleep disorders, traumatic brain injury, and Charles Bonnet syndrome. There is limited clinical data indicating its usefulness in chronic urticaria and tardive dyskinesia. The mechanisms of action related to yi-gan san's calming effects are related to the attenuation of glutamate release, uptake, and transport, as well as the inhibition of N-methyl-D-aspartate (NMDA) receptors. Yi-gan san also activates the gamma-aminobutyric acid-A (GABA-A) receptor, which accounts for its use for management of insomnia. Actions related to signal mediation of G protein–coupled receptors lead to pharmacological uses related to aggressive behavior, memory disturbance, and head twitch. These effects result from actions on 5-HT and muscarinic receptors. A randomized, observer-blind, controlled trial of the 'Yi-Gan San' was carried out to examine the efficacy and safety of this traditional Chinese herbal medicine in the improvement of behavioral and psychological symptoms of dementia (BPSD) and activities of daily living (ADL). Fifty-two patients with mild-to-severe dementia (24 men and 28 women, mean +/- SD age = 80.3 +/- 9.0 years) according to DSM-IV criteria were investigated. Participants were randomly assigned to the YGS group (N = 27) or control (drug-free) group (N = 25) and treated for 4 weeks. The Neuropsychiatric Inventory (NPI) for the assessment of BPSD, the Mini-Mental State Examination (MMSE) for cognitive function, and the Barthel Index for ADL were administered at baseline and the end of the treatment. The frequency of extrapyramidal symptoms (EPS) and other adverse events was recorded. If patients showed insufficient response to treatment after 1 week, tiapride hydrochloride, a dopamine D(1) selective neuroleptic, was added to the regimen. Data were collected from January 2004 to March 2004. All participants in both groups completed the trial. In the control group, 11 patients required treatment with tiapride hydrochloride. Significant improvements in mean +/- SD NPI (from 37.9 +/- 16.1 to 19.5 +/- 15.6) and Barthel Index (from 56.4 +/- 34.2 to 62.9 +/- 35.2) scores were observed in the YGS group, but not in the control group. MMSE results were unchanged in both groups. EPS were not observed in either group, but dizziness and impaired postural sway were observed in 6 patients treated with tiapride hydrochloride. Yi-Gan San improves BPSD and ADL. Follow-up studies using a double-blinded, placebo-controlled design are recommended [49].

Ba Wei Di Huang Wan

Ba Wei Di Huang Wan is also termed as 'Rehmannia Eight' that contains herbs like Poria, Paeony Root Bark, Alisma Tuber, Prepared Rehmannia, Comus Fruit, Chinese Yam, Prepared Aconite Root, Cinnamon Bark. An 8-week randomized, double-blind, placebo-controlled clinical trial of 'Ba Wei Di Huang Wan' was carried out to evaluate whether this traditional Chinese herbal medicine "BDW" improves cognitive and physical functioning in dementia patients. Thirty-three patients with mild to severe dementia (7 men and 26 women; mean age +/- standard deviation=84.4 +/- 7.8) were recruited and enrolled from May 2002 through September 2002. Participants were randomly assigned to the active drug (BDW) group (n=16) or the placebo group (n=17) and treated for 8 weeks. Cognitive function and activities of daily living (ADLs); palsatility index were measured. After the trial, cognitive function as assessed using the Mini-Mental State Examination (MMSE) significantly improved from 13.5 +/- 8.5 to 16.3 +/- 7.7 (P<.01, 95% confidence interval (CI)=-4.1 to -1.4) in the BDW group. The ADL score in the Barthel Index also significantly changed, from 61.8 +/- 34.6 to 78.9 +/- 21.1 (P<.01, 95% CI=-26.2 to -7.9). In contrast, MMSE and Barthel Index scores of the placebo group showed no significant change. Eight weeks after the end of the administration, MMSE and Barthel Index scores of the BDW group declined to the baseline level. The pulsatility index in the internal carotid artery as measured using Doppler sonography significantly decreased in the BDW group (2.5 +/- 1.7 to 1.9 +/- 0.5, P<.05) but not in the placebo group. These results argue the benefits of BDW in the treatment of dementia [50].

METHODS

Penetrating at MEDLINE (during April 2006,

PubMed), LILACS (Latin American and Caribbean Health Science Literature: 40th edition, May 2001, the last explore 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); Psych INFO Journal Articles (during the year of 2006); relevant web sites; and scanning of suggestion list of related articles. There were no words or periodical limits. Search for keywords in MeSH (medical subject heading) with the words 'Alzheimer disease, dementia, cognition disorders' was performed first. In the second part, the keywords were 'Herbal' and 'Phytotherapy'. The intersect results of the two searches were evaluated by the Jadad's capacity level [51].

Inclusion criteria

Three investigators autonomously reviewed all of the articles originate. The articles were preferred using the criteria: 1) The studies should be randomized; double-blind and prohibited (with a control group and a treatment group), 2) Studies should institute mechanical measures in the crossover or be conducted at the same time, 3) In the case of being crossover, a disappointment phase of at least 7 days was obligatory, 4) Patients incorporated in the researches had their judgment rated into three degrees as follows: mild, sensible and ruthless 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) [15]. The models used were as follows: Mini-mental commencement principles between 10 and 26 (initial and mild group) or <10 (initial group), 5) Clinical trials be supposed to last for at least 1 month (4 weeks), 6) Detailed narrative of the herbal product used, 7) Neuropsychiatry symptoms development should be considered with numerical score using the consideration Scale (ADAS-noncog, range of score, 0-70), NPI (Neuropsychiatric Inventory, range of score 0-120), Clinical Global inkling of change or Behavioral rating scale for elderly patients, 8) The final score should be quantified using amalgamation of ADL & IADL procedural actions.

Exclusion criteria

The herbal produce has previously been aim of a quantified organized assessment study. In this case, only the fallout of the studies will be well thought-out Jadad's dimension scale: Methodological quality was assessed using a scale urbanized and validated [51]. This scale assesses the totality of treatment using three matter with a five points highest score. If the allotment into groups is overtly randomized, item 1 is scored. A bonus point is agreed if an enough method to produce the random progression is described. If there is an explicit announcement that the study is double-blind, item 2 is scored. A bonus point is given if the scheme is described and insufficient. Item 3 is scored if there is whichever an explicit proclamation that all patients built-in were also analyzed or if the number and reasons for dropouts in all groups are given independently. For being top clandestine as tolerably reported, a experiment should attain at least three of five points, a cut-off point is not compulsory by the novelist of the scale [52].

All withdrawal and quality assessments were performed by at slightest two sovereign reviewers using typical forms residential for each review. Disagreements were predictable and discussed with final decisions made by the chief commentator.

RESULTS AND DISCUSSION

Two herbs and two herbal formulations were acknowledged to have efficiency in the behavior of cognitive annoyance of AD in the efficient review: *Salvia officinalis* [53], *Melissa officinalis* [46], and Yi-Gan San [49] and Ba Wei Di Huang Wan (BDW) [50]. *Gingko biloba* was until that time known in one metaanalysis [54], and only the conclusions of the study will be well thought-out. Another study is conducted with huperzine A, a product derivative from a Chinese parsley *Huperzia serrata*, to calculate the protection and efficiency in the handling of AD in a multicenter randomized prohibited trial of its consequence on cognitive purpose [55]. The studies of Salvia, Melissa, Yi-Gan San and BDW have reached Jadad's dimension scale of > 3. The researches had a follow up of 1 month (Yi-Gan San), 2 months (BDW) and 4 months (Salvia and Melissa). All samples calculated were collected of patients with preliminary mild symptoms judged as AD. Two studies compared herbal medicines and organize samples, using objective to treat the use of herbal drug in Alzheimer's disease. None of the studies evaluated the institutionalization rate or compared the active

attitude with the in progress therapy with acetyl cholinesterase Inhibitor or memantine.

REFERENCES

1. Akhondzadeh S, Abbasi SH. Herbal medicine in the treatment of Alzheimer's disease. *Am J Alzheimers Dis Other Demen*. 2006;21(2):113-118. doi:10.1177/1533175060210021
2. Katzman R. Editorial: The prevalence and malignancy of Alzheimer disease. A major killer. *Arch. Neurol.* 1976;33(4):217-218. doi:10.1001/archneur.1976.00500040001001
3. Evans DA, Funkenstein HH, Albert MS, et al. Prevalence of Alzheimer's disease in a community population of older persons. Higher than previously reported. *JAMA.* 1989;262(18):2551-2556.
4. Geldmacher DS, Whitehouse PJ Jr. Differential diagnosis of Alzheimer's disease. *Neurology*. 1997;48(5 Suppl 6):S2-S9. doi:10.1212/wnl.48.5_suppl_6.2s
5. Dos Santos-Neto LL, de Vilhena Toledo MA, Medeiros-Souza P, de Souza GA. The use of herbal medicine in Alzheimer's disease-a systematic review. *Evid Based Complement Alternat Med*. 2006;3(4):441-445. doi:10.1093/ecam/nel071
6. Doody RS, Stevens JC, Beck C, et al. Practice parameter: management of dementia (an evidence-based review). Report of the Quality Standards Subcommittee of the American Academy of Neurology. *Neurology*. 2001;56(9):1154-1166. doi:10.1212/wnl.56.9.1154
7. Jones RW, McCrone P, Guilhaume C. Cost effectiveness of memantine in Alzheimer's disease: an analysis based on a probabilistic Markov model from a UK perspective. *Drugs Aging*. 2004;21(9):607-620. doi:10.2165/00002512-200421090-00005
8. François C, Sintonen H, Sulkava R, Rive B. Cost effectiveness of memantine in moderately severe to severe Alzheimer's disease : a markov model in Finland. *Clin Drug Investig*. 2004;24(7):373-384. doi:10.2165/00044011-200424070-00001
9. Feldman H, Gauthier S, Hecker J, et al. Economic evaluation of donepezil in moderate to severe Alzheimer disease. *Neurology*. 2004;63(4):644-650. doi:10.1212/01.wnl.0000134663.79663.6e
10. Salloway S, Ferris S, Kluger A, et al. Efficacy of donepezil in mild cognitive impairment: a randomized placebo-controlled trial. *Neurology*. 2004;63(4):651-657. doi:10.1212/01.wnl.0000134664.80320.92
11. Courtney C, Farrell D, Gray R, et al. Long-term donepezil treatment in 565 patients with Alzheimer's disease (AD2000): randomised double-blind trial. *Lancet*. 2004;363(9427):2105-2115. doi:10.1016/S0140-6736(04)16499-4
12. Mantle D, Pickering AT, Perry EK. Medicinal plant extracts for the treatment of dementia. *Mol Diag Ther*. 2000;13(3):201-213. doi:10.2165/00023210-200013030-00006
13. World Health Organization: The ICD-JIO Classification of Mental and Behavioral Disorders. Geneva: World Health Organization,1992.
14. American Psychiatric Association: Diagnostic and Statistical Manual of Mental Disorders, 4th ed. Washington, DC: American Psychiatric Association, 1994.
15. McKhann G, Drachman D, Folstein M, Katzman R, Price D, Stadlan EM. Clinical diagnosis of Alzheimer's disease: report of the NINCDS-ADRDA Work Group under the auspices of Department of Health and Human Services Task Force on Alzheimer's Disease. *Neurology*. 1984;34(7):939-944. doi:10.1212/wnl.34.7.939
16. Schneiders LS. An overview of rating scales used in dementia. *Alzheimer Insights*. 1996;2:1-7.
17. Selkoe DJ. Amyloid beta-protein and the genetics of Alzheimer's disease. *J Biol Chem*. 1996;271(31):18295-18298. doi:10.1074/jbc.271.31.18295
18. Lue LF, Kuo YM, Roher AE, et al. Soluble amyloid beta peptide concentration as a predictor of synaptic change in Alzheimer's disease. *Am J Pathol*. 1999;155(3):853-862. doi:10.1016/s0002-9440(10)65184-x
19. Francis PT, Palmer AM, Snape M, Wilcock GK. The cholinergic hypothesis of Alzheimer's disease: a review of progress. *J Neurol Neurosurg Psychiatry*. 1999;66(2):137-147. doi:10.1136/jnnp.66.2.137
20. Wright CI, Geula C, Mesulam MM. Neurological cholinesterases in the normal brain and in Alzheimer's disease: relationship to plaques, tangles, and patterns of selective vulnerability. *Ann Neurol*. 1993;34(3):373-384. doi:10.1002/ana.410340312
21. Davies P, Maloney AJ. Selective loss of central cholinergic neurons in Alzheimer's disease. *Lancet*. 1976;2(8000):1403. doi:10.1016/s0140-6736(76)91936-x
22. Livingston G, Katona C. How useful are cholinesterase inhibitors in the treatment of Alzheimer's disease? A number needed to treat analysis. *Int J Geriatr Psychiatry*. 2000;15(3):203-207. doi:10.1002/(sici)1099-1166(200003)15:3<203::aid-gps100>3.0.co;2-9
23. Giacobini E. Cholinesterase inhibitor therapy stabilizes symptoms of Alzheimer disease. *Alzheimer Dis Assoc Disord*. 2000;14(Suppl 1):S3-S10. doi:10.1097/00002093-200000001-00002
24. Nordberg A, Svensson AL. Cholinesterase inhibitors in the treatment of Alzheimer's disease: a comparison of tolerability and pharmacology. *Drug Saf*. 1998;19(6):465-480. doi:10.2165/00002018-199819060-00004
25. Weinstock M: Selectivity of cholinesterase inhibition: Clinical implication for the treatment of Alzheimer's disease. *CNS Drugs*. 1999;12:307-323. doi:10.2165/00023210-199912040-00005
26. Bullock R. New drugs for Alzheimer's disease and other dementias. *Br J Psychiatry*. 2002;180:135-139. doi:10.1192/bjp.180.2.135
27. Solanki M, Jain N, Koshta A, Malviya S, Kharia A. Formulation and evaluation of antifungal cream using Nelumbo nucifera and Azadirachta indica leaves extracts. *Bull Pharm Res*. 2019;9(1-3):167. doi:10.21276/bpr.2019.9.8
28. Dahiya R, Singh S, Kaur K, Kaur R. Total synthesis of a natural cyclooligopeptide from fruits of sugar-apple. *Bull Pharm Res*. 2017;7(3):151. doi:10.21276/bpr.2017.7.3.4
29. Akhondzadeh S, Noroozian M. Alzheimer's disease: pathophysiology and pharmacotherapy. *IDrugs*. 2002;5(11):1062-1069.
30. Raskind MA, Peskind ER, Wessel T, Yuan W. Galantamine in AD: A 6-month randomized, placebo-controlled trial with a 6-month extension. The Galantamine USA-1 Study Group. *Neurology*. 2000;54(12):2261-2268. doi:10.1212/wnl.54.12.2261
31. Kanowski S, Herrmann WM, Stephan K, Wierich W, Hörr R. Proof of efficacy of the Ginkgo biloba special extract EGb 761 in outpatients suffering from mild to moderate primary degenerative dementia of the Alzheimer

type or multi-infarct dementia. *Pharmacopsychiatry*. 1996;29(2):47-56. doi:10.1055/s-2007-979544
32. Le Bars PL, Katz MM, Berman N, Itil TM, Freedman AM, Schatzberg AF. A placebo-controlled, double-blind, randomized trial of an extract of Ginkgo biloba for dementia. North American EGb Study Group. *JAMA*. 1997;278(16):1327-1332. doi:10.1001/jama.278.16.1327
33. De Feudis FV. Ginkgo biloba Extract EGb761. Pharmacological Activities and Clinical Applications. Elsevier: Paris, 1991.
34. Kleijnen J, Knipschild, P. Ginkgo biloba. *Lancet*. 1992;340(8828):1136-1139. doi:10.1016/0140-6736(92)93158-J
35. Wettstein A. Cholinesterase inhibitors and Gingko extracts--are they comparable in the treatment of dementia? Comparison of published placebo-controlled efficacy studies of at least six months' duration. *Phytomedicine*. 2000;6(6):393-401.
36. Doré S, Bastianetto S, Kar S, Quirion R. Protective and rescuing abilities of IGF-I and some putative free radical scavengers against beta-amyloid-inducing toxicity in neurons. *Ann N Y Acad Sci*. 1999;890:356-364. doi:10.1111/j.1749-6632.1999.tb08015.x
37. Mayeux R, Sano M. Treatment of Alzheimer's disease. N *Engl J Med*. 1999;341(22):1670-1679. doi:10.1056/NEJM199911253412207
38. Schulz V. Ginkgo extract or cholinesterase inhibitors in patients with dementia: what clinical trials and guidelines fail to consider. *Phytomedicine*. 2003;10(Suppl 4):74-79. doi:10.1078/1433-187x-00302
39. Xu SS, Gao ZX, Weng Z, et al. Efficacy of tablet huperzine-A on memory, cognition, and behavior in Alzheimer's disease. *Zhongguo Yao Li Xue Bao*. 1995;16(5):391-395.
40. Zhang Z, Wang X, Chen Q, Shu L, Wang J, Shan G. Clinical efficacy and safety of huperzine alpha in treatment of mild to moderate Alzheimer disease: A placebo-controlled, double-blind, randomized trial. *Zhonghua Yi Xue Za Zhi*. 2002;82(14):941-944.
41. Xu SS, Cai ZY, Qu ZW, et al. Huperzine-A in capsules and tablets for treating patients with Alzheimer disease. *Zhongguo Yao Li Xue Bao*. 1999;20(6):486-490.
42. Szatmari SZ, Whitehouse PJ. Vinpocetine for cognitive impairment and dementia. *Cochrane Database Syst Rev*. 2003;(1):CD003119. doi:10.1002/14651858.CD003119
43. Perry EK, Pickering AT, Wang WW, Houghton P, Perry NS. Medicinal plants and Alzheimer's disease: Integrating ethnobotanical and contemporary scientific evidence. *J Altern Complement Med*. 1998;4(4):419-428. doi:10.1089/acm.1998.4.419
44. Perry EK, Pickering AT, Wang WW, Houghton PJ, Perry NS. Medicinal plants and Alzheimer's disease: from ethnobotany to phytotherapy. *J Pharm Pharmacol*. 1999;51(5):527-534. doi:10.1211/0022357991772808
45. Kennedy DO, Scholey AB, Tildesley NT, Perry EK, Wesnes KA. Modulation of mood and cognitive performance following acute administration of Melissa officinalis (lemon balm). *Pharmacol Biochem Behav*. 2002;72(4):953-964. doi:10.1016/s0091-3057(02)00777-3
46. Akhondzadeh S, Noroozian M, Mohammadi M, Ohadinia S, Jamshidi AH, Khani M. Melissa officinalis extract in the treatment of patients with mild to moderate Alzheimer's disease: a double blind, randomised, placebo controlled trial. *J Neurol Neurosurg Psychiatry*. 2003;74(7):863-866. doi:10.1136/jnnp.74.7.863
47. Wake G, Court J, Pickering A, Lewis R, Wilkins R, Perry E. CNS acetylcholine receptor activity in European medicinal plants traditionally used to improve failing memory. *J Ethnopharmacol*. 2000;69(2):105-114. doi:10.1016/s0378-8741(99)00113-0
48. Schulz V, Hansel R, Tyler VE. Rational Phytotherapy. A Physicians' Guide to Herbal Medicine, 3rd edition, Springer- Verlag: Berlin, 1998.
49. Iwasaki K, Satoh-Nakagawa T, Maruyama M, et al. A randomized, observer-blind, controlled trial of the traditional Chinese medicine Yi-Gan San for improvement of behavioral and psychological symptoms and activities of daily living in dementia patients. *J Clin Psychiatry*. 2005;66(2):248-252. doi:10.4088/jcp.v66n0214
50. Iwasaki K, Kobayashi S, Chimura Y, et al. A randomized, double-blind, placebo-controlled clinical trial of the Chinese herbal medicine "ba wei di huang wan" in the treatment of dementia. *J Am Geriatr Soc*. 2004;52(9):1518-1521. doi:10.1111/j.1532-5415.2004.52415.x
51. 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):1-12. doi:10.1016/0197-2456(95)00134-4
52. Khan KS, Daya S, Jadad A. The importance of quality of primary studies in producing unbiased systematic reviews. *Arch Intern Med*. 1996;156(6):661-666.
53. Akhondzadeh S, Noroozian M, Mohammadi M, Ohadinia S, Jamshidi AH, Khani M. 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(1):53-59. doi:10.1046/j.1365-2710.2003.004 63.x
54. Birks J, Grimley EJ. Ginkgo biloba for cognitive impairment and dementia. The Cochrane Library, Issue 2, 2004.
55. http://clinicaltrials.gov/ct/how/NCT00083590

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