Complementary and alternative medicine for Alzheimer’s disease: an overview of systematic reviews

Paul Posadzki, Edzard Ernst, Myeong Soo Lee

Abstract
Aim The aim of this overview was to critically evaluate the literature on complementary and alternative medicine (CAM) for Alzheimer’s disease.
Method Four electronic databases were searched to identify all relevant systematic reviews of effectiveness of CAM for Alzheimer’s disease. Reviews were defined as systematic if they included explicit and repeatable criteria for the selection of primary studies. The methodological quality of reviews was assessed using the Oxman criteria for systematic reviews.
Results Six systematic reviews met the inclusion criteria. Most reviews were of high quality. Three reviews arrived at ambiguous conclusions, two arrived at positive conclusions and one reached a negative conclusion.
Conclusions Evidence supporting the effectiveness of CAM for the treatment of Alzheimer’s disease is ambiguous. Since some herbal medicines show promise in the management of Alzheimer’s disease, future research seems justified.

Keywords
Alzheimer’s disease • complementary and alternative medicine • effectiveness • systematic reviews

Introduction
Alzheimer’s disease (AD) is the most common cause of dementia; it is characterised by an insidious onset and slow deterioration of memory processes.1 The condition also causes severe debilitation, uncompro- misingly decreasing the QoL of both affected patients and their caregivers.2 The prevalence rates of AD vary between regions,3 with an estimated 81.1 million cases projected worldwide by 2040.4 To date, there has been inconsistent evidence supporting the use of dietary and nutritional interventions, such as B-vitamins and fatty acids, for the treatment or prevention of AD.5 The mainstream treatment of AD is drug therapy, with agents such as donepezil, rivastigmine, galantamine or memantine.2

Many AD patients use CAM.6 The reasons for this widespread use are complex but the notion that CAM is effective and safe play an important role. Some patients with AD might feel that their needs are not being met by mainstream medicine and, in turn, look for alternatives. Whatever the reasons are for CAM’s popularity, it is important to know whether CAM is a safe and effective treatment for AD.

Several trials of CAM for AD have been published; the results of many of these trials have been summarised in systematic reviews (SRs). The aim of this article is to provide an overview of the findings from SRs of any type of CAM for the treatment of AD.

Methods
An electronic search of the literature was conducted to identify SRs of CAM for AD. The search was conducted using the following electronic databases:
MEDLINE, EMBASE, AMED and The Cochrane Library, from their inception to May 2011. The following search terms were used: [Alzheimer’s disease*] AND [systematic ADJ review]. In addition, our own extensive departmental files were hand searched. No language barriers were imposed.

Abstracts of identified reviews were inspected; those appearing to meet the inclusion criteria were retrieved for further evaluation by two authors (PP, EE). Two authors independently extracted data from the identified articles according to predefined criteria (Table 1). The methodological quality of each SR was evaluated based on the criteria initially devised by Oxman and Guyatt.7 This validated tool assesses the quality of review articles across nine domains, including: reporting and comprehensiveness of searches, repeatable eligibility criteria, avoidance of selection bias, presence of a validity assessment tool, robustness of data analysis and supportiveness of conclusions. Each question is scored as 1 (fulfilled), 0 (partially fulfilled), or −1 (not fulfilled). The final result falls into one of four categories: 1 or below, 2–3, 4–5 and 6–9, meaning the review has extensive, major, minor and minimal or no flaws, respectively.8 Any disagreements throughout the review process were resolved by discussion.

For the purpose of this review, CAM was defined as: ‘diagnosis, treatment and/or prevention which complements mainstream medicine by contributing to a common whole, satisfying a demand not met by orthodoxy, or diversifying the conceptual framework of medicine’.9 The following CAM modalities were eligible for inclusion: acupuncture/acupressure, Alexander technique, aromatherapy, (Bach) flower remedies, chiropractic, herbal medicine, homeopathy, hypnosis, massage (of any form), naturopathy, osteopathy, spiritual healing, tai chi, TCM and yoga. Dietary supplements, vitamins and physical exercises were not considered a part of CAM and were therefore excluded.

Systematic reviews were defined as review articles that used explicit and repeatable criteria for the selection of primary studies. To be eligible for inclusion, SRs had to: (1) pertain to the effectiveness of CAM modalities; (2) focus specifically on AD; and (3) include evidence from at least two controlled clinical trials. The protocol stipulated that if multiple SRs were found for a single CAM modality, the most up-to-date, methodologically sound and independent review would be included. Systematic reviews of non-randomised clinical trials were excluded, as were non-SRs.10

Results
The search identified 225 articles, of which 219 were excluded (Figure 1). Six SRs met the inclusion criteria.6,11–15 Most reviews were of herbal medicines;6,12–15 one was of acupuncture11 (Table 1).

Methodological aspects of the included reviews
Two SRs were of low methodological quality6,12 (i.e. had extensive flaws). These reviews lacked a method for combining the included trials, as well as details of studies excluded. The other SRs were of high methodological quality11,13–15 (i.e. had minimal to no flaws), meaning that extensive and explicit literature searches, repeatable eligibility criteria, validity assessment and quantitative analyses had been used (Table 2).

Acupuncture
Lee et al.11 assessed the evidence of effectiveness for acupuncture for the treatment of AD. The total number of patients with AD included in the review was 166. The authors concluded that ‘the existing evidence does not demonstrate the effectiveness of acupuncture for AD’. These conclusions were limited as they were based on three poor-quality trials.

Herbal medicine
Dos Santos-Neto et al.12 reviewed the evidence from controlled studies investigating the effectiveness of any type of herbal medicine for the treatment of AD. The total number of patients with AD included in the
### Table 1  Systematic reviews of CAM for Alzheimer's disease

<table>
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<tr>
<th>First author (year), country</th>
<th>Intervention evaluated</th>
<th>Number of primary studies</th>
<th>Quality of primary studies</th>
<th>Meta-analysis</th>
<th>Quality of SR (Oxman scale)&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Conclusion (quote)</th>
<th>Direction of conclusion</th>
<th>Mention of adverse effects</th>
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<tbody>
<tr>
<td>Dos Santos-Neto (2006),&lt;sup&gt;12&lt;/sup&gt; Brazil</td>
<td>All herbal medicines</td>
<td>Four</td>
<td>Not mentioned</td>
<td>No</td>
<td>One</td>
<td>‘These herbs and formulations have demonstrated good therapeutic effectiveness but these results need to be compared with those of traditional drugs.’</td>
<td>(+)</td>
<td>Yes</td>
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<tr>
<td>Fu (2009),&lt;sup&gt;6&lt;/sup&gt; USA</td>
<td>All Chinese herbs</td>
<td>Six</td>
<td>Various from low to high</td>
<td>No</td>
<td>One</td>
<td>‘the current evidence in support of their use is inconclusive or inadequate. Future research should place emphasis on herbs that can treat the root of the disease.’</td>
<td>(-/+)&lt;sup&gt;+&lt;/sup&gt;</td>
<td>Yes</td>
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<tr>
<td>Janssen (2010),&lt;sup&gt;13&lt;/sup&gt; Germany</td>
<td>Ginkgo</td>
<td>Six</td>
<td>High</td>
<td>Yes</td>
<td>Nine</td>
<td>‘For the outcome ADL, there is evidence of a benefit of high-dose (240 mg) Ginkgo. In patients taking this dose, there are also indications of a benefit for the outcomes cognition and accompanying psychopathological symptoms.’</td>
<td>(+)</td>
<td>Yes</td>
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<tr>
<td>Lee (2009),&lt;sup&gt;11&lt;/sup&gt; South Korea</td>
<td>Acupuncture</td>
<td>Three</td>
<td>Poor</td>
<td>Yes</td>
<td>Nine</td>
<td>‘the existing evidence does not demonstrate the effectiveness of acupuncture for AD.’</td>
<td>(-)&lt;sup&gt;+&lt;/sup&gt;</td>
<td>Yes</td>
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<tr>
<td>Lee (2009),&lt;sup&gt;14&lt;/sup&gt; South Korea</td>
<td>Ginseng</td>
<td>Two</td>
<td>Poor</td>
<td>Yes</td>
<td>Nine</td>
<td>‘the evidence for ginseng as a treatment of AD is scarce and inconclusive. Further rigorous trials seem warranted.’</td>
<td>(-/+)&lt;sup&gt;+&lt;/sup&gt;</td>
<td>Yes</td>
</tr>
<tr>
<td>Man (2008),&lt;sup&gt;15&lt;/sup&gt; China</td>
<td>All herbal medicines</td>
<td>16</td>
<td>Various; mostly poor</td>
<td>No</td>
<td>Eight</td>
<td>‘Further multi-center trials with large sample size, high methodological qualities and standardized HM ingredients are necessary for clinical recommendations on the use of HM in treating AD.’</td>
<td>(-/+)&lt;sup&gt;+&lt;/sup&gt;</td>
<td>Yes</td>
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<sup>a</sup>see Table 2 for more details.

AD, Alzheimer's disease; ADL, activities of daily living; HM, herbal medicine; SR, systematic review; (+), positive; (-), negative; (-/+), inconclusive.
The authors recommended the use of Melissa officinalis (lemon balm), Salvia officinalis (sage), Yi-Gan San and Ba Wei Di Huang Wan for patients with AD. However, none of the included studies compared herbal medicine with current drug therapy, such as acetyl-cholinesterase inhibitors or memantine. Three of the four included RCTs failed to provide details of a placebo arm or a reference to quantitative testing.

Fu and Li\(^6\) conducted a SR of the current evidence concerning the use of Chinese herbs for the treatment of AD. The total number of patients included in the review was 819. The authors reported that Ginkgo biloba (ginkgo), Lycopodium serratum (Huperzine A) and Panax ginseng (ginseng) show promise in the treatment of AD. Two of the three high-quality RCTs included in the review showed no difference between ginkgo and placebo for changes in AD assessment scale scores or Mini-Mental State Examination scores. The proposed mechanisms of action of single Chinese herbs in the treatment of AD were purely hypothetical.

Janssen \(^{13}\) reviewed the evidence for ginkgo for AD. The review only included placebo-controlled RCTs of ginkgo for AD with a follow-up of 16 weeks or more. The total number of patients included in the review was 739. The authors suggested that there was evidence that high-dose ginkgo (240 mg) may improve QoL and cognition in patients with AD. However, none of the included studies compared herbal medicine with current drug therapy. There was also vast heterogeneity of the data analysed.

Lee \(^{14}\) assessed the evidence for ginseng for the treatment of AD. The total number of patients included in the review was 158. The authors reported that few RCTs have tested the effects of ginseng for AD. Two of the included RCTs favoured ginseng over donepezil, galantamine, memantine and rivastigmine for changes in AD assessment scale scores or Mini-Mental State Examination scores. However, the quantity and quality of primary studies included in the review limited the conclusions.

Man \(^{15}\) assessed the efficacy and safety of herbal medicines, as either monotherapy or adjunct therapy to orthodox medication, for AD. The total number of patients included in the review was 1320. The authors reported that herbal medicine can be a safe and effective treatment for AD, either alone or in conjunction with orthodox medicine. However, most of the 16 trials included in the review used herbal formulae instead of standardised extracts. Also, all 16 trials failed to adhere to CONSORT guidelines, which raises doubts about internal validity of these trials. There was also wide variation in terms of the length of AD treatment, the length of the follow-up period, the number of patients included in the trials, and the quality of the primary outcome measures used and the duration of the trials.

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<tr>
<td>Dos Santos-Neto et al.(^{12}) (2006)</td>
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<td>0</td>
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<td>Fu and Li(^6) (2009)</td>
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<td>Janssen et al.(^{13}) (2010)</td>
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<td>Lee et al.(^{11}) (2009)</td>
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<td>Man et al.(^{15}) (2008)</td>
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\(^{a}\) Each question is scored as 1, 0, or -1:
1 means that: (a) the review states the databases used, date of most recent searches and some mention of search terms; (b) the review searches at least two databases and looks at other sources; (c) the review states the criteria used for deciding which studies to include in the overview; (d) the review reports how many studies were identified by searches, numbers excluded and appropriate reasons for excluding them; (e) the review states the criteria used for assessing the validity of the included studies; (f) the review reports validity assessment and did some type of analysis with it; (g) the report mentions that quantitative analysis was not possible and reasons that it could not be done; (h) the review performs a test for heterogeneity before pooling or does appropriate subgroup testing, appropriate sensitivity analysis, or other such analysis; (i) the conclusions made by the author(s) are supported by the data and/or analysis reported in the review.

0 means that the above mentioned criteria were partially fulfilled.

-1 means that none of the above criteria were fulfilled.

A score of 1 or below means the review has extensible flaws, 2–3 major flaws, 4–5 minor flaws and 6–9 minimal or no flaws. This is an operationalisation of the Oxman criteria, adapted from elsewhere.8
of the therapeutic intervention, which limits the conclusions made.

**Discussion**

This overview aimed to summarise and critically evaluate the evidence from SRs of CAM for AD. Six SRs were included.\(^6,11–15\) The reviews investigated the effectiveness of acupuncture and several herbal medicines. There was some evidence to support ginseng and ginkgo. There was no evidence to support acupuncture and little quality-evidence to support the effectiveness of lemon balm, sage, Yi-Gan San, Ba Wei Di Huang Wan or Huperzine A.

We adapted Oxman and Guyatt criteria\(^7\) to evaluate the methodological quality of SRs (Table 2). Four SRs were of high quality and two were of low quality. The low-quality SRs recommended the use of lemon balm, sage, ginkgo and ginseng for AD. In our view, these recommendations are debatable.

All SRs mentioned adverse effects (AEs). In the majority of SRs that mentioned AEs, the incidence of AEs was low. However, in one of the RCTs reviewed by Fu and Li, 13% of patients experienced nausea or fever after ginseng.

Our analysis points out that there is a limited number of high-quality RCTs investigating the effectiveness of CAM for AD. Despite the large number of methodological obstacles that CAM research is facing, such as the use of placebo controls or double-blindness, future studies of CAM are considered feasible. Such studies of mind–body modalities or other CAM treatments should use adequate sample sizes based on suitable power calculations, use validated outcome measures, appropriately describe sequence generation and allocation concealment and analyse data based on the ITT principle.

The present analysis has limitations that should be kept in mind when interpreting the conclusions. In particular, all SRs are prone to publication bias within the primary research data that they include and, therefore, any such bias may have been inherited in our review.

**Conclusion**

The evidence to support the effectiveness of CAM as a treatment option for AD is ambiguous. Some herbal medicines hold promise in the management of AD; therefore, future research in this area seems justified.

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