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REVIEW ARTICLE

The Effect of Complementary and Alternative Medicines on Cognitive Function in Alzheimer's Disease: A Systematic Review

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ABSTRACT

Considering the various symptoms of Alzheimer's disease patients, there are many treatments available but they are not for permanent care of the AD. To facilitate the better management of these chronic diseases, recent attention has focused on the use of complementary and alternative medicine, together with Oriental and traditional medicines. Many patients-especially elderly persons-independently use CAM for improving AD symptoms. There are still insufficient data on CAM treatments. The objective of this study is to evaluate the effect of CAM on cognitive outcomes in patients with AD. A total of 100 abstracts were identified from preliminary searching, a final sample of 13 articles regarding the effect of CAM use in AD patients for analysis. 5 studies report that herb therapy group was more effective in cognitive function than placebo group. In the methodological quality, 5 studies received 5 points as high quality in the assessment. In the risk of bias, 3 domains;allocation concealment, blinding of participants, personnel and outcome assessors, and incomplete outcome data were mostly rated as "High" or "Unclear". These results indicate that small systematic review demonstrates the effects of complementary and alternative medicines on cognitive function in AD.

＜Key-words＞
complementary and alternative medicines, cognitive function, Alzheimer's disease, non−pharmacological therapies

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Ⅰ. Background

Alzheimer's disease(AD) is a progressive disease of the brain. As the condition progresses, AD patients show lack of interest towards the environment, swallowing difficulties, uncontrolled bladder and bowel function, and decreased mobility(Hurley, Volicer, Narran, et al., 1992; Mitchell, Teno, Kiely, et al., 2009). Although AD has a great variety of symptoms, progressive memory loss and decline in other cognitive functions are its main characteristics(Talwalker, Overall, Srirama, et al., 1996). There is no cure for AD, but several drug treatments are effective that improve or stabilize symptoms. But medications given to patients with probable AD-related dementia increase the drugs' side effects. For example, the anti-convulsant drug phenytoin can cause gingival hyperplasia specially in the presence of plaque, while many antipsychotic agents such as phenothiazines used to control behavioral problems, especially aggression and emotional instability, can cause xerostomia, a lack of salive(Chiappelli, Navarro, Moradi, et al., 2006). Because AD is such a devastating illness, many patients and their families are desperate for any approaches to treatment that carry claims of potential help.

There are many treatments available for AD but they are not for permanent care of the AD. The symptoms of AD also differ between individual patients. At the onset of dementia in some patients, certain personality traits that had been well controlled in the past become accentuated, whereas in others there is a 'loss of personality', where the uniqueness of the patient's personality is lost. Some patients show a more rapid deterioration of cognitive function, whereas others show a slower rate of cognitive decline. Some patients exhibit various types of BPSD, whereas others exhibit few abnormal behaviors(Hamuro, Isono, Sugai, et al., 2008). Considering the difference in symptoms of dementia patients, a more individualized treatment and management program should be considered taking into account of the emotional and affective responses of each patient individually(Takeda, Hashimoto, Kudo, et al., 2010).

To facilitate the better management of these chronic diseases, recent attention has focused on the use of complementary and alternative medicine (CAM), together with Oriental and traditional medicines(Cooper, 2004). CAM is a set of varying health care systems, practices, and products that are not generally considered part of conventional medicine(National Center for Complementary and Alternative Medicine web site). Examples of CAM include music therapy, drama therapy, aromatherapy, animal-assisted therapy, gardening, horse riding, exercise, bathing, herbal medications, acupuncture, moxibustion, shiatsu, and yoga among others(Kawamura, Niiyama & Niiyama, 2007). Complementary interventions are used together with conventional treatments, whereas alternative interventions are used instead of them(Goldrosen & Straus, 2004). In recent years, CAM has been used together with drug therapy to help individuals to remain independent, including occupational therapy, physiotherapy, and psychological intervention. These CAM treatments have a common objective involving maintenance of

the functional abilities and independence of the individuals, particularly in ADLs, even if these aspects do not ultimately improve the disease condition(Littbrand, Rosendahl, Lindelof, et al., 2006).

Many patients-especially elderly persons-independently use CAM for improving AD symptoms(National Center for complementary and alternative medicine web site). But although the prevalence of the use of CAM throughout developed countries ranges from 9% of individuals to 65%(Ernst, 2000; Barnes, Powell-Griner, McFann, et al., 2004), there are still insufficient data on the prevalence, effectiveness, efficacy, safety and health economic benefits of most CAM treatments(Fischer, Lewith, Witt, et al., 2014).

Findings from numerous epidemiologic and clinical studies suggest that multiple biological, behavioral, social, and environmental factors may contribute to the risk for cognitive decline(Kverno, Black, Nolan, et al., 2009). However, few systematic reviews have examined the breadth of evidence on the wide range of factors that are potentially associated with cognitive decline or the evidence about interventions that may slow decline(Plassman, Williams, Burke, et al., 2010).

It is the objective of this review to evaluate the current evidence and investigate the effect of CAM on cognitive outcomes in patients with AD.

Ⅱ. Methods

1. Database Search

We searched MEDLINE(during January 2015, PubMed) and Google Scholar(during January 2015). The last research was performed in 10th January 2015.

Search for keywords in MeSH(Medical subject heading; MeSH) with the words ‘Alzheimer’s disease, dementia, cognitive function’ was performed first. In the second part, the keywords were ‘complementary medicines, alternative medicines, randomized controlled’. All databases were restricted to those published in English between 1 January 2000 and 31 December 2014.

2. Inclusion criteria

1) Type of studies

All selected studies implemented complementary medicines or alternative medicines. Clinical trials should last for at least 1 month(4 weeks). The studies should be randomized; double-blind and controlled (with a control group and a treatment group).

There were no limitations to the measurements taken as long as quantitative and objective measures of cognition(e.g. executive function, learning, and memory) were recorded. All included studies had to be published and written in English.

2) Types of participants

All 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)(McKhann, Drachman, Folstein, et al., 1984). All patients scored between 10 and 24 on the Mini-Mental State Examination(MMSE)(Folstein, Folstein & McHugh, 1975). The age of participants in studies was not restricted.

3) Types of outcome measures

The outcome measure of interest was cognitive function. This included any neuropsychologic tests designed to detect a change in cognitive function in any domain-for example, executive function, memory, or learning, or MMSE score.

3. Exclusion criteria

Studies were excluded that: (i) non-randomized controlled trials including short communication, qualitative study, case report, note or letter; (ii) not translated with English; (iii) not having a control group or (iv) inappropriate control; (v) not examined the effect of CAM use for cognitive functions; (vi) short intervention period(<4 weeks); (vii) duplicate publications or methods.

4. Assessment of Methodological Quality

Methodological quality was assessed using a scale developed and validated by Jadad et al.(Jadad, Moore, Carroll, et al., 1996). The Jadad scale is sometimes described as a five-point scale, though there are only three items with five points maximum score. Either give a score of 1 point for each “Yes” or 0 points for each “No”. 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 good trial should score at least three of five points, a cut-off point is recommended by the author of the scale(Khan, Daya & Jadad, 1996). The following questions are (i) was the study described as randomized (this includes the use of words such as randomly, random, and randomization)? (ii) was the study described as double blind? (iii) was there a description of withdrawals and dropouts?.

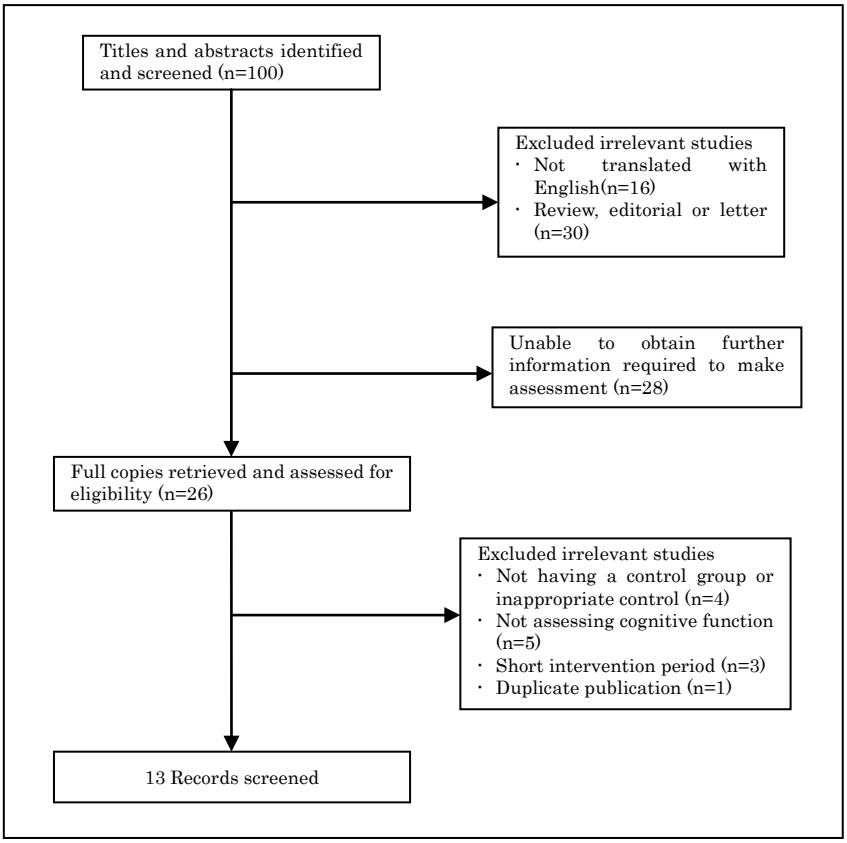
5. Risk of Bias Assessment

Risk of bias was evaluated in accordance with the Cochrane Handbook for Systematic Reviews of interventions, using the following parameters: adequacy of sequence generation; allocation concealment; blinding of participants, personnel and outcome assessors; incomplete outcome data; and selective outcome reporting(Higgins & Green, 2011).

Ⅲ. Results

1. Identification and selection of studies

A total of 100 abstracts were identified from preliminary searching. 46 abstracts were not original article or those that were not published in English. The full texts of the remaining 26 studies were then examined in detail to determine whether they met the study criteria. Exclusion of the 13 studies that did not meet the criteria resulted in a final sample of 13 articles regarding the effect of CAM use in AD patients for analysis(Figure 1).



<Figure 1> Flowchart of study selection process

2. Characteristics of included studies

All studies were carried out between 2000 and 2014. The included studies employed therapies described as herb therapy (n=8)(Nasab, Bahrammi, Nikpour, et al., 2012; Herrschaft, Nacu, Likhachev, et al., 2012; Akhondzadeh, Sabet, Harirchian, et al., 2010; van Dongen, van Rossum, Kessels, et al., 2003; Akhondzadeh, Noroozian, Mohammadi, et al., 2003; Yakoot, Salem & Helmy, 2013; Snitz, O'Meara, Carlson, et al., 2009; Akhondzadeh, Noroozian, Mohammadi, et al., 2003), art therapy (n=1)(Hattori, Hattori, Hokao, et al., 2011), music therapy (n=2)(Bruer, Spitznagel & Cloninger, 2007; Sakamoto, Ando & Tsutou, 2013), horticultural therapy (n=1)(Jarrott & Gigliotti, 2010) and Multi-sensory stimulation (MSS) therapy (n=1)(Baker, Bell, Baker, et al., 2001). The severity of all report was between MMSE 0 and MMSE 26 inclusively. The most common therapy was herb therapy using with Ginkgo biloba(G. biloba), Saffron, Salvia officinalis(S. officinalis) and Melissa officinalis(M.officinalis). 5 studies reported that herb therapy group was more effective in cognitive function than placebo group (table 1).

<Table 1> A descriptive overview of cognitive function with AD patients

Study/ population	Severity of cognitive impairment	Treatment and comparison groups	Outcomes	Instruments
Nasab et al. (2012) 51 dementia	MMSE<17	G. biloba; n=25 Rivastigmine; n=26	Cognitive function	MMSE, SMT
Herrschaft et al. (2012), 402 AD or VaD	SKT<16 NPI<17	G. biloba; n=200 Placebo; n=202	Cognition, psychopathology, functional measures, and quality of life(QOL)	SKT,NPI,NPI caregiver distress score, ADCS-CGIC, ADL-IS, DEMQOL-Proxy, VFT, TE4D cognitive, 11-point box scale
Akhondzadeh et al. (2010) 46 AD	MMSE 15-26(inclusive)	Saffron group; n=23, Placebo group; n=23	Cognitive function	MMSE, ADAS-cog, CDR-SB
van Dongen et al. (2003) 214 AD or VaD	ADAS 6.5±2.7	G. group; n=79, Placebo group; n=44	Memory impairment	SKT,CGI-2, NAI-NAA
Akhondzadeh et al. (2003) 42 AD	ADAS-cog ≧ 12, CDR ≦ 2	S. officinalis group; n=15, Placebo group; n=15	Cognitive function, Agitation	ADAS-cog, CDR-SB
Yakoot et al. (2013) 60 MCI	Herb therapy group; MMSE 24.90±1.06 Control group; MMSE 24.87± 1.14	Herb therapy group; n=30, Control group; n=30	Cognitive decline	MMSE

Snitz et al. (2009) 3069 older adults and MCI	CDR ≦ 0.5	Herb therapy group; n=1545, Control group; n=1524	Cognitive decline	3MSE, ADAS-cog, CVLT, California verbal learning test, Rey-Osterrieth Figure Test, WAIS-R Digit Span Forward, Trail Making test Part A and B, Boston Naming Test, Semantic verbal fluency, Stroop color/word test
Akhondzadeh et al. (2003) 35 AD	ADAS-cog ≧ 12, CDR ≦ 2	Herb therapy group; n=20, Control group; n=15	Cognitive function, Agitation	ADAS-cog, CDR-SB
Hattori et al. (2011) 39 AD	MMSE<24	Art therapy; n=20, calculation; n=19	Cognitive function, Memory, Mood, Vitality, QOL, Behavioral abnormalities	MMSE, WMS-R, GDS, Apathy scale, SF-8, DBD, BI
Bruer et al. (2007) 28 elderly cognitively-impaired psychiatric inpatients	Unclear	Music therapy group; n=17, Control group; n=11	Cognitive function	MMSE
Sakamoto et al. (2013) 39 AD	Passive group MMSE 4.7±4.8 Interactive group MMSE 4.6±3.5 Control group MMSE 4.7±3.9	Music intervention groups(Passive or Interactive);n=13,n=13, Control group; n=13	Cognitive function, Emotional function	Short-term effects:autonomic nerve index, Faces scale, Long-term effects:BEHAVE-AD
Jarrott et al. (2010) 129 dementia	MMSE 9.62±7.76	Horticultural therapy group; n=75 Traditional activities group; n=54	Adaptive behavior, Affective states	MMSE, AARS,MPES
Baker et al. (2001) 50 AD, VaD or a mixed diagnosis	MMSE 0-17	MSS group; n=25, Control group; n=25	Behavior, mood and cognitive function	REHAB, BMD, BRS, MMSE, CAPE, CAS

Abbreviations: SMT=Seven Minute Test; SKT=Syndrome Kurz test; NPI=Neuropsychiatric Inventory; ADCS-CGIC=Alzheimer's Disease Cooperative Study-the Clinical Global Impression of Change; ADL-IS=the Alzheimer's Disease Activities of Daily Living International Scale; VFT=Verbal Fluency Test; TE4D=Test for Early Detection of Dementia with Discrimination from Depression; ADAS-cog=Alzheimer's disease assessment scale-cognitive subscale; CDR-SB=clinical dementia rating scale-sums of boxes; CGI-2=Clinical Global Impression of change; NAI-NAA=Nuremberg Gerontopsychological Rating Scale for Activities of Daily Living; 3MSE=Modified Mini-Mental State Examination, CVLT=California Verbal Learning Test; WAIS-R=Wechsler Adult Intelligence Scale-Revised; WMS-R=Wechsler Memory Scale revised; GDS=Geriatric Depression Scale; SF-8=Short Form-8; DBD=Dementia Behavior Disturbance Scale; BI=Barthel Index; BEHAVE-AD=Behavioral Pathology in Alzheimer's Disease Rating Scale; AARS=Apparent Affect Rating Scale; MPES=the Menorah Park Engagement Scale; BMD=Behaviour and Mood Disturbance Scale; BRS=Behaviour Rating Scale; CAPE=Clifton Assessment Procedures for the Elderly; CAS=Cognitive Assessment Scale

<Table 1> (continued)

Study/ population	Duration follow-up	Schedule	Results
Nasab et al. (2012) 51 dementia	Baseline, 24- week	G. biloba 120mg daily dose, Rivastigmine 4.5mg daily dose	MMSE and SMT both significantly improved in Rivastigmine group ($p<0.001$), but G. biloba groups showed no significant difference ($p>0.05$).
Herrschaft et al. (2012) 402 AD or VaD	Baseline, 24- week	G. biloba extract EGb 761 per tablet a once-daily dose of 240mg/weeks, Placebo once-daily	Patients treated with G. biloba improved by 2.2±3.5 points (mean± sd) on the SKT total score, whereas those receiving placebo changed only slightly by 0.3±3.7 points. The NPI composite score improved by 4.6±7.1 in the G. biloba group and by 2.1±6.5 in the placebo group. Both drug-placebo comparisons were significant at $p<0.001$.
Akhondzadeh et al. (2010) 46 AD	Baseline, 16-week	Saffron 30mg/day(15 mg twice per day) or placebo(two capsules per day) for a 16-week study	Saffron produced a significantly better outcome on cognitive function than placebo (ADAS-cog: F=4.12, df=1, P=0.04; CDR: F=4.12, df=1, P=0.04).
van Dongen et al. (2003) 214 AD or VaD	Baseline, 24-week	G. biloba 240 and 160 mg/d combined, 160mg/d, 240mg/d, Placebo	No statistically significant differences in mean change of scores between Ginkgo and placebo. The differences were SKT: ± 0.4 (90% confidence interval[CI]−0.9-1.7); CGI-2: ±0.1 (90% CI −0.3-0.4), and NAI-NAA: -0.4 (90% CI -1.9-1.2).
Akhondzadeh et al. (2003) 42 AD	Baseline and every 2 weeks after the medication started, total 18-week	S. officinalis extract 60 drops/day, Placebo drop 60 drops/day, over a 4-month period	S. officinalis extract produced a significant better outcome on cognitive functions than placebo (ADAS-cog: F=4.77, df=1, P<0.03) (CDR-SB: F=10.84, df=1, P<0.003). There were no significant differences in the two groups in terms of observed side effects except agitation that appears to be more frequent in the placebo group (P=0.09).
Yakoot et al. (2013) 60 MCI	Baseline, 4-week	Natural lyophilized royal jelly 750mg with two standardized herbal extracts(G. biloba 120mg, Panax ginseng 150mg) and placebo, at a dose of one capsule daily before breakfast	The mean change in MMSE score in the group treated with Memo for 4 weeks was significantly greater than in the control group (+2.07 versus +0.13, respectively) by the Student's t-test (t=6.485, P <0.0001).
Snitz et al. (2009) 3069 older adults and MCI	follow-up of 6.1 years	G. biloba extract EGb 761 per tablet twice-daily dose of 120mg/weeks or an identical-appearing placebo	Annual rates of decline in z scores did not differ between G biloba and placebo groups in any domains, including memory, attention, visuospatial abilities, language, and executive functions. For the 3MSE and ADAS-Cog, rates of change varied by baseline cognitive status (mild cognitive impairment), but there were no differences in rates of change between treatment groups (for 3MSE, P=0.71; for ADAS-Cog, P=0.97).

Akhondzadeh et al. (2003) 35 AD	At baseline and every 2 weeks after the treatment started, total 18 weeks	M. officinalis extract 60 drops/day or placebo 60 drops/day	At four months, M. officinalis extract produced a significantly better outcome on cognitive function than placebo (ADAS-cog: df = 1, F = 6.93, p=0.01; CDR: df=1, F=16.87, p<0.0001). There were no significant differences in the two groups in terms of observed side effects except agitation, which was more common in the placebo group (p=0.03).
Hattori et al. (2011) 39 AD	Baseline, 24 weeks	Coloring and drawings once a week/45-min training, Calculation	Between before and after therapy in each group showed significant improvement in the Apathy Scale in the art therapy group (P=0.014) and in the Mini-Mental State Examination score (P=0.015) in the calculation drill group, but no significant differences in the other items between the two groups. Significant improvement in the quality of life (QOL) was observed in the art therapy compared with the calculation training group (P=0.038, odds ratio, 5.54).
Bruer et al. (2007) 28 elderly cognitively-impaired psychiatric inpatients	3 times every week(prior to the intervention, immediately after intervention, and the morning following the intervention), total 8-week	Music therapy once a week, Control treatment(age-appropriate movie) once a week	Immediately after the intervention, MMSE scores in the music therapy group improved compared to the control group (p<0.05). Next-day MMSE test scores in the music therapy showed average improvements of 3.69 points compared to the control subjects (p<0.001). By the following week, no significant cognitive differences remained between the two groups.
Sakamoto et al. (2013) 39 AD	Before intervention, after 10th intervention, 3 weeks later	Each intervention was performed for 30 min once a week for 10 weeks	Passive and interactive music interventions caused short-term parasympathetic dominance (p<0.01). Interactive intervention caused the greatest improvement in emotional state (p<0.01). Greater long-term reduction in BPSD was observed following interactive intervention, compared with passive music intervention and a no-music control condition (p<0.025).
Jarrott et al. (2010) 129 dementia	6 weeks	Horticultural therapy twice weekly for 6 weeks, 1 session was 50 minutes.	No significant differences between the treatment and comparison groups on the 3 affective coding categories, including pleasure (P=0.123), anxiety (P=0.932), and interest (P=0.208).
Baker et al. (2001) 50 AD, VaD or a mixed diagnosis	Pre-trial, Mid-trial, Post-trial, Follow-up 1 month later	MSS sessions or eight Activity sessions over a 4-week trial(two 30-minute sessions a week)	The MSS group showed a significant improvement in mood (p=0.032) and behavior (p=0.037) at home compared to the Activity group whose behaviour deteriorated. No longer-term benefits were shown.

3. Assessment of methological quality

The methodological quality of included studies ranged from poor to high quality in the assessment with the majority scoring 5(Akhondzadeh, Sabet, Harirchian, et al., 2010; Akhondzadeh, Noroozian, Mohammadi, et al., 2003; Yakoot, Salem & Helmy, 2013; Snitz,

O'Meara, Carlson, et al., 2009; Akhondzadeh, Noroozian, Mohammadi, et al., 2003), one study received 1(Jarrott & Gigliotti, 2010), two studies 2(Akhondzadeh, Noroozian, Mohammadi, et al., 2003; Bruer, Spitznagel & Cloninger, 2007), four studies 3(Nasab, Bahrammi, Nikpour, et al., 2012; Hattori, Hattori, Hokao, et al., 2011; Sakamoto, Ando & Tsutou, 2013; Baker, Bell, Baker, et al., 2001), and two studies 4 points(Herrschaft, Nacu, Likhachev, et al., 2012; van Dongen, van Rossum, Kessels, et al., 2003) on the Jadad scale.

4. Risk of bias

In the sequence generation, 7 studies included the use of randomization such as computer random number generator, coin tossing, envelopes or minimization. In the allocation concealment, 6 studies adequately concealed allocation. In the blinding of participants, personnel and outcome assessors, 5 studies published descriptions of concealment procedures judged to be adequate. In the incomplete outcome data, 6 studies adequately addressed missing outcome data. In the selective outcome reporting, 11 studies were free of suggestion of selective outcome reporting. Finally, in the other sources of bias, 9 studies were apparently free of other bias(table 2).

<Table 2> The risk of bias of included RCT studies

	Sequence generation	Allocation concealment	Blinding of participants, personnel and outcome assessors	Incomplete outcome data	Selective outcome reporting	Other sources of bias
Nasab, et al. (2012)	Unclear	Low	Low	Low	Low	Low
Herrschaft, et al. (2012)	Low	Low	Low	Low	Low	Unclear
Akhondzadeh, et al. (2010)	Unclear	Low	Low	Low	High	Low
van Dongen, et al. (2003)	Low	Unclear	Unclear	High	Low	Low
Akhondzadeh, et al. (2003)	Low	Low	High	Unclear	Low	Low
Yakoot, et al. (2013)	Low	Low	Low	Low	Low	Low
Snitz, et al. (2009)	Unclear	Unclear	Low	Unclear	Low	Low
Akhondzadeh, et al. (2003)	Low	Low	Unclear	Unclear	Low	Low
Hattori, et al. (2011)	Low	Unclear	Unclear	Unclear	Low	Low
Bruer, et al. (2007)	Low	High	High	Unclear	Low	High
Sakamoto, et al. (2013)	Low	High	High	Low	Low	Low
Jarrott, et al. (2010)	High	High	High	Unclear	Unclear	High
Baker, et al. (2001)	Low	Unclear	Unclear	Low	Low	Low

Abbreviations: Low=low risk of bias; High=high risk of bias; Unclear=uncertain risk of bias

Ⅳ. Considerations and Conclusions

This systematic review examined published studies of CAM interventions aimed at reducing cognitive function in AD. 8 of 13 studies were reported the effect of CAM on cognitive function in AD. In the assessment of methodological quality, 5 studies rated as high quality. In the risk of bias, 3 domains;allocation concealment, blinding of participants, personnel and outcome assessors, and incomplete outcome data were mostly rated as “High” or “Unclear” because those were not described as double-blind or the absence of such a statement the use of identical placebos and missing outcome data is mentioned.

Herbal medicine uses plants to restore or maintain health. It is estimated that approximately half of all pharmaceuticals are derived from natural products, including morphine, digitalis, quinine, vincristine, taxol and artemisinin(Newman, Cragg & Snader, 2003). G.biloba is a plant whose herbal extracts(mainly EGb761) are often used as an alternative treatment to improve cognitive function. Extracts of G.biloba include several components, such as the flavonols quercetin and kaempferol as well as terpenoid lactones that are considered to be responsible for the neuroprotectvive functions of G.biloba(Rendeiro, Guerreiro, Williams, et al., 2012). Three RCTs on the use of G.biloba(Nasab, Bahrammi, Nikpour, et al., 2012; van Dongen, van Rossum, Kessels, et al., 2003; Snitz, O'Meara. Carlson, et al., 2009) did not show less cognitive decline over time in older adults with normal cognition or MCI taking G.biloba than those assuming placebo. Also, G.biloba showed no effects in reducing either the overall incidence rate of dementia or AD in old age individuals with normal cognition or MCI(DeKosky, Williamson, Fitzpatrick, et al., 2008).

Art therapy for dementia is typically provided by art therapists, artists, or facilitators to small groups of patients in a clinical or care setting(Chancellor, Duncan & Chatterjee, 2014). Art therapy engages attention, provides pleasure, and improves behavior and affect in patients with dementia(Safar & Press, 2011; Peisah, Lawrence & Reutens, 2011). Other studies show that the benefits of anxiety, agitation, and depression(Stewart , 2004). In this review, one study showed improved apathy, cognitive function and QOL(Hattori, Hattori, Hokao, et al., 2011). Chancellor reported that carefully designed clinical studies are desperately needed if arts programs tailored to patients’ talents and symptoms are to be common in the treatment armamentarium for AD(Chancellor, Duncan & Chatterjee, 2014).

Music therapy, of which traditional forms consist of basic active(e.g., instrument playing, singing) or passive(e.g., listening) music engagement, represents a low cost intervention with a wide range of benefits(Simmons-Stern, Deason, Brandler, et al., 2012). These benefits include improvements on measures of anxiety and depression(Guétin, Portet, Picot, et al., 2009), agitation(Svansdottir & Snaedal, 2006), autobiographical memory recall(Foster & Valentine, 2001), and apathy(Holmes, Knights,

Dean, et al., 2006). In this review, two studies were improved cognitive impairment after short term intervention(Bruer, Spitznagel & Cloninger, 2007; Sakamoto, Ando & Tsutou, 2013). There is limited but good quality evidence supporting the use of music therapy for the short-term reduction of cognitive function.

Gardening can be part of a rehabilitation programme aimed at improving motor skills, speech skills, and/or cognitive skills after debilitating illness or traumas such as strokes(Organic, Davies, Devereaux, et al., 2014). Detweiler et al.(2012) concluded that many preliminary studies have reported benefits of horticultural therapy and garden settings in reduction of pain, improvement in attention, lessening of stress, modulation of agitation, lowering of as need medications, and antipsychotics and reduction in falls(Detweiler, Sharma, Detweiler, et al., 2012). In this review, one study implemented horticultural therapy, but no significant differences between treatment group and control group(Jarrott & Gigliotti, 2010).

Multi-sensory stimulation therapy stimulates the senses through the provision of unpatterned visual, auditory, olfactory, and tactile stimuli. Individuals are given the opportunity to explore a variety of stimuli in a specially prepared room. In this review, one study by Baker et al.(Baker, Bell, Baker, et al., 2001) examined the effects of MSS on participants with moderately severe to severe dementia. But still MSS therapy is high quality, but very limited, evidence suggesting that non-verbal MSS is more effective that intellectual interventions for reducing apathy in individuals with severe dementia(Kverno, Black, Nolan, et al., 2009).

In Our review, all of the studies did not support the claim that CAM is effective in cognitive function. But mostly studies are rated as good methodological quality and low risk of bias that mean CAM is possibly effective in AD.

Our systematic review has several limitations. First, the number of RCTs is insufficient. Second, we acknowledge a publication bias in that studies with positive outcomes are more likely than negative studies to be reported in the medical literature. A third limitation of the literature on clinical decision; methodological quality and risk of bias is supported by one reviewer.

In conclusion, this small systematic review demonstrates the effect of complementary and alternative medicines on cognitive function in Alzheimer's disease. Although some important studies have been carried out on these topics, systematic approaches for several factors are still lacking. For improving evidence about CAM study, not only further large systematic review but also good quality clinical trials are needed.

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Reference

1) Hurley AC, Volicer BJ, Narran PA, Houde S & Volicer L(1992) Assessment of discomfort in advanced Alzheimer patients. *Res Nurs Health*, 15(5), 369-377.
2) Mitchell SL, Teno JM, Kiely DK, et al.(2009) The clinical course of advanced dementia. *N Engl J Med*, 361(16), 1529-1538.
3) Talwalker S, Overall JE, Srirama MK & Gracon SI(1996) Cardinal features of cognitive dysfunction in Alzheimer's disease: a factor-analytic study of the Alzheimer's Disease Assessment Scale. *Journal of Geriatric Psychiatry and Neurology*, 9, 39-46.
4) Chiappelli F, Navarro AM, Moradi DR, Manfrini E & Prolo P(2006) Evidence-Based Research in Complementary and Alternative Medicine III: Treatment of Patients with Alzheimer's Disease. *Evid Based Complement Alternat Med.*, 3(4), 411-424.
5) Hamuro A, Isono H, Sugai Y, Mimura M & Kamijima(2008) Characteristics of behavioral and psychological symptoms of dementia in untreated oldest old Alzheimer's disease. *Psychogeriatrics*, 8, 8-11.
6) Takeda M, Hashimoto R, Kudo T, Okochi M, Tagami S, Morihara T, et al.(2010) Laughter and humor as complementary and alternative medicines for dementia patients. *BMC Complement Altern Med.*, 10(28), 1-7.
7) Cooper EL(2004) Complementary and Alternative Medicine, When Rigorous, can be Science. *Evid Based Complement Alternat Med*, 1(1), 1-4.
8) National Center for Complementary and Alternative Medicine. What is complementary and alternative medicine?
http://nccam.nih.gov/health/whatiscam/ (Accessed December 31, 2014).
9) Kawamura N, Niiyama M & Niiyama H(2007) Long-term evaluation of animal-assisted therapy for institutionalized elderly people: A preliminary result. *Psychogeriatrics*, 7, 8-13.
10) Goldrosen MH & Straus SE(2004) Complementary and alternative medicine: assessing the evidence for immunological benefits. *Nat Rev Immunol.*, 4(11), 912-921.
11) Littbrand H, Rosendahl E, Lindelof N, Lundin-Olsson L, Gustafson Y & Nyberg L (2006) A high-intensity functional weight-bearing exercise program for older people dependent in activities of daily living and living in residential care facilities: evaluation of the applicability with focus on cognitive function. *Phys Ther*, 86(4), 489-498.
12) National Center for complementary and alternative medicine web site.
http://nccam.nih.gov. (Accessed December 31, 2014).

13) Ernst E(2000) Prevalence of use of complementary/alternative medicine: a systematic review. *Bull. World Health Organ*, 78, 252–257.

14) Barnes PM, Powell-Griner E, McFann K & Nahin RL(2004) Complementary and alternative medicine use among adults: United States, 2002. *Adv. Data*, 343, 1–19.

15) Fischer FH, Lewith G, Witt CM, Linde K, von Ammon K, Cardini F, et al.(2014) High prevalence but limited evidence in complementary and alternative medicine: guidelines for future research. *BMC Complement Altern Med*, 6, 14-46.

16) Kverno KS, Black BS, Nolan MT & Rabins PV(2009) Research on treating neuropsychiatric symptoms of advanced dementia with non-pharmacological strategies, 1998-2008: a systematic literature review. *Int Psychogeriatr.*, 21(5), 825-43.

17) Plassman BL, Williams JW Jr, Burke JR, Holsinger T & Benjamin S(2010) Systematic review: factors associated with risk for and possible prevention of cognitive decline in later life. *Ann Intern Med*, 153(3), 182-93.

18) McKhann G, Drachman D, Folstein M, Katzman R, Price D & Stadlan EM(1984) 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*, 34, 939-44.

19) Folstein MF, Folstein SE & McHugh PR(1975) Mini-mental state: a practicalmethod for grading the cognitive state of patients for the clinician. *Journal of Psychiatric Research*, 12, 189-198.

20) Jadad AR, Moore RA, Carroll D, Jenkinson C, Reynolds DJ, Gavaghan DJ, et al. (1996) Assessing quality of reports of randomized clinical trials: is blinding necessary?. *Control Clin Trials*, 17, 1-12.

21) Khan KS, Daya S & Jadad AR(1996) The importance of quality of primary studies in producing unbiased systematic reviews. *Arch Intern Med*, 156, 661-6.

22) Higgins JPT & Green S(2011) Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0, The Cochrane Collaboration.

23) Nasab NM, Bahrammi MA, Nikpour MR, Rahim F & Naghibis SN(2012) Efficacy of rivastigmine in comparison to ginkgo for treating Alzheimer's dementia. *J Pak Med Assoc.*, 62(7), 677-80.

24) Herrschaft H, Nacu A, Likhachev S, Sholomov I, Hoerr R & Schlaefke S(2012) Ginkgo biloba extract EGb 761® in dementia with neuropsychiatric features: a randomised, placebo-controlled trial to confirm the efficacy and safety of a daily dose of 240 mg. *J Psychiatr Res*, 46(6), 716-23.

25) Akhondzadeh S, Sabet MS, Harirchian MH, Togha M, Cheraghmakani H, Razeghi S, et al.(2010) Saffron in the treatment of patients with mild to moderate Alzheimer's disease: a 16-week, randomized and placebo-controlled trial. *J Clin Pharm Ther*, 35(5), 581-8.

26) van Dongen M, van Rossum E, Kessels A, Sielhorst H & Knipschild P(2003) Ginkgo for elderly people with dementia and age-associated memory impairment: a randomized clinical trial. *J Clin Epidemiol.*, 56(4), 367-76.

27) Akhondzadeh S, Noroozian M, Mohammadi M, Ohadinia S, Jamshidi AH & Khani M (2003) 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*, 28(1), 53-9.

28) Yakoot M, Salem A & Helmy S(2013) Effect of Memo®, a natural formula combination, on Mini-Mental State Examination scores in patients with mild cognitive impairment. *Clin Interv Aging.*, 8, 975-81.

29) Snitz BE, O'Meara ES, Carlson MC, Arnold AM, Ives DG, Rapp SR, et al.; Ginkgo Evaluation of Memory (GEM) Study Investigators(2009) Ginkgo biloba for preventing cognitive decline in older adults: a randomized trial. *JAMA.*, 302(24), 2663-70.

30) Akhondzadeh S, Noroozian M, Mohammadi M, Ohadinia S, Jamshidi AH & Khani M (2003) 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*, 74(7), 863-6.

31) Hattori H, Hattori C, Hokao C, Mizushima K & Mase T(2011) Controlled study on the cognitive and psychological effect of coloring and drawing in mild Alzheimer's disease patients. *Geriatr Gerontol Int.*, 11(4), 431-7.

32) Bruer RA, Spitznagel E & Cloninger CR(2007) The temporal limits of cognitive change from music therapy in elderly persons with dementia or dementia-like cognitive impairment: a randomized controlled trial. *J Music Ther.*, 44(4), 308-28.

33) Sakamoto M, Ando H & Tsutou A(2013) Comparing the effects of different individualized music interventions for elderly individuals with severe dementia. *Int Psychogeriatr.*, 25(5), 775-84.

34) Jarrott SE & Gigliotti CM(2010) Comparing responses to horticultural-based and traditional activities in dementia care programs. A*m J Alzheimers Dis Other Demen.*, 25(8), 657-65.

35) Baker R, Bell S, Baker E, Gibson S, Holloway J, Pearce R, et al.(2001) A randomized controlled trial of the effects of multi-sensory stimulation (MSS) for people with dementia. *Br J Clin Psychol.*, 40(Pt 1), 81-96.

36) Newman DJ, Cragg GM & Snader KM(2003) Natural products as sources of new drugs over the period 1981–2002. *J. Nat. Prod.*, 66, 1022–1037.

37) Rendeiro C, Guerreiro JD, Williams CM & Spencer JP(2012) Flavonoids as modulators of memory and learning: molecular interactions resulting in behavioural effects. *Proc. Nutr. Soc.*, 71, 246–262.

38) DeKosky ST, Williamson JD, Fitzpatrick AL, Kronmal RA, Ives DG, Saxton JA, et al.; Ginkgo Evaluation of Memory (GEM) Study Investigators (2008) Ginkgo biloba for prevention of dementia: a randomized controlled trial. *JAMA*, 300, 2253–2262.

39) Chancellor B, Duncan A & Chatterjee A(2014) Art therapy for Alzheimer's disease and other dementias. *J Alzheimers Dis.*, 39(1), 1-11.

40) Safar LT & Press DZ(2011) Art and the brain: Effects of dementia on art production in art therapy. *Art Therapy*, 28, 96-103.

41) Peisah C, Lawrence G & Reutens S(2011) Creative solutions for severe dementia with BPSD: A case of art therapy used in an inpatient and residential care setting. *Int Psychogeriatrics*, 23, 1011-1013.

42) Stewart EG(2004) Art therapy and neuroscience blend: Working with patients who have dementia. *Art Ther J Am Art Ther Assoc*, 21, 148-155.

43) Simmons-Stern NR, Deason RG, Brandler BJ, Frustace BS, O'Connor MK, Ally BA, et al.(2012) Music-based memory enhancement in Alzheimer's disease: promise and limitations. *Neuropsychologia*, 50(14), 3295-303.

44) Guétin S, Portet F, Picot MC, Pommié C, Messaoudi M, Djabelkir L, et al.(2009) Effect of music therapy on anxiety and depression in patients with Alzheimer's type dementia: randomised, controlled study. *Dement Geriatr Cogn Disord.*, 28(1), 36-46.

45) Svansdottir HB & Snaedal J(2006) Music therapy in moderate and severe dementia of Alzheimer's type: a case-control study.*International Psychogeriatrics*, 18, 613–621.

46) Foster NA & Valentine ER(2001) The effect of auditory stimulation on autobiographical recall in dementia. *Exp Aging Res.*, 27(3), 215-28.

47) Holmes C, Knights A, Dean C, Hodkinson S & Hopkins V(2006) Keep music live: music and the alleviation of apathy in dementia subjects. *International Psychogeriatrics*, 18, 623-630.

48) Organic G, Davies SG, Devereaux M, Lennartsson M, Schmutz U & Williams S(2014) The benefits of gardening and food growing for health and wellbeing. Available from: http://bosf.org.uk/birmingham-open-spaces-forum/wp-content/uploads/2014/04/GrowingHealth_BenefitsReport.pdf (Accessed January 19, 2015)

49) Detweiler MB, Sharma T, Detweiler JG, Murphy PF, Lane S, Carman J, et al.(2012) What is the evidence to support the use of therapeutic gardens for the elderly? *Psychiatry Investig.*, 9(2), 100-10.

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