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• Meta-analysis •

Ginkgo biloba extract for dementia: a systematic review

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Background: Given the increasing burden of dementia internationally and the lack of effective treatments, several countries are already recommending the use of ginkgo biloba extract (GbE) in the treatment of dementia, despite the inconsistent research results about its effectiveness.

Aim: Conduct a meta-analysis of studies about the effect of GbE on cognition and daily functioning in persons with dementia.

Methods: Searches of various English and Chinese databases identified reports of placebo controlled, randomized trials of ginkgo biloba treatment (lasting a minimum of 22 weeks) for dementia that were published from January 1982 to September 2012. Data extraction and critical appraisal of studies were conducted using the GRADE system. Heterogeneity, sensitivity and potential publication bias of the studies were evaluated using RevMan 5.1. Pooled results of the meta-analysis were presented as forest plots using standardized mean differences (SMD) in scores for continuous variables and relative risk (RR) for categorical variables.

Results: Nine studies with a total of 2578 patients met the inclusion and exclusion criteria. Pooled results from the six studies that were included in the meta-analysis (total n=1917) found that GbE was superior to placebo in preventing deterioration in cognitive functioning and in activities of daily living, but these results were only valid for studies with younger subjects (with a mean age below 75). There were no significant differences in the dropout rates between groups or in the overall rates of adverse events during treatment. However, there was considerable heterogeneity in the results between the studies (primarily based on the age of the subjects) and there were several potential biases in the reports (most of which were supported by pharmaceutical firms), so the overall evidence was considered of 'low quality'.

Conclusion: This meta-analysis highlights serious weaknesses in the available studies about this important problem. GbE may be effective in persons under 75 years of age with dementia, but large, placebo controlled, randomized trials focused on milder forms of dementia (including mild cognitive impairment) that compare different doses of GbE and that follow subjects for prolonged periods (at least one year) are needed to confirm this result.

1. Background

Dementia, including Alzheimer's disease, vascular dementia, and Parkinson's disease, is a syndrome characterized by impaired memory and cognition associated with decrements in occupational and social functioning.[1,2] The prevalence of dementia, which increases with age, is between 0.46 to 7.0% in the elderly.[3] The etiology of dementia remains unknown. Despite decades of intensive research, there are still no effective treatments.[4,5]

The main active ingredients of ginkgo biloba extract (GbE) are flavonoids (including meletin, kaempferol and isorhamnetin) and laetones (including ginkgolides and bilobalide). GbE can remove free radicals, protect the endothelial cells of blood vessels, block platelet activating factors, and improve brain circulation.[6,7] GbE has been widely used in the treatment of dementia, cognitive impairment, peripheral nerve problems, and vascular tinnitus.[8] However, clinical studies about the efficacy of GbE in the treatment of dementia have been inconclusive: some studies report beneficial effects on cognition and functioning,[9,10] while others do not.[8,11,12] The current study aims to help resolve this issue by conducting a meta-analysis of all studies available in the international and Chinese literature that evaluate the effect of GbE on cognitive functioning and on daily functioning in persons with dementia.

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2. Methods

2.1 Search strategies

Studies on the treatment effect of GbE for dementia, published between January 1982 and September 2012, were searched for in the following databases: Pubmed, Embase, the Cochrane Library, ISI Web of science, Chinese Biological Medical Literature Database (CBM), Chinese National Knowledge Infrastructure (CNKI), Chinese Technical Periodicals (VIP) and Wanfang Database. Key words used for the search were 'ginkgo biloba', and 'dementia' in English and Chinese. We also used other terms for ginkgo biloba in the search, including 'EGb 761' and the commercial names 'Tanakan', 'Tebonin', 'Rokan', and 'Ginkoba'. The reference lists of identified articles were checked for other potential studies.

2.2 Inclusion and exclusion criteria

A study was included if it was a randomized controlled trial and study participants were diagnosed with Alzheimer's disease, vascular dementia, or mixed dementia according widely accepted criteria. (Acceptable diagnostic criteria were those specified by the International Classification of Diseases [ICD], the Diagnostic and Statistical Manual of Mental Disorders of the American Psychiatric Association [DSM], the National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association [NINCDS-ADRDA], the National Institute of Neurological Disorders and Stroke and Association Internationale pour la Recherché et l'Enseignement en Neurosciences [NINDS/AIREN], and the Chinese Classification of Mental Disorders [CCMD]).

Studies were excluded if: a) they were animal studies; b) they were reviews, conference presentations, or unpublished reports; c) they were duplicated reports; d) other cognitive boosting medications were used as adjunctive treatments; e) there was no placebo control; or f) there was no control group. There was no restriction on the dosage or method of administration for GbE. The control group had to receive some form of placebo. The minimum duration of treatment was set at 22 weeks because six months is a widely accepted observational period to assess the effect of treatments for dementia.[13]

Cognitive outcomes were assessed using the Syndrom-Kurz tests (SKT), the Mini-Mental State Examination (MMSE), and the Alzheimer Disease Assessment Scale-Cognitive (ADAS-cog). Daily functioning was assessed using the Activities of Daily Living scale (ADL). Secondary assessments included administration of the Neuropsychiatric Inventory (NPI), analysis of study dropouts, and recording of the prevalence, persistence and severity of adverse effects.

2.3 Evaluation of the quality of studies

We evaluated the quality of included studies based on criteria specified in the Cochrane handbook (5.1.0) [14] and GRADE.[15] Two researchers (JL and SL) extracted data independently from each included study and then compared their results. When discrepancies occurred, they discussed their differences and came to a consensus opinion; if necessary, a third researcher was asked to resolve any remaining differences. When possible, authors were contacted if the information was not clear or insufficient in the original article.

2.3.1 Evaluation of risk of biases

The risk of biases was assessed using the method recommended by the Cochrane Collaboration.[14] The characteristics evaluated included the following: a) randomization process; b) allocation concealment; c) use of blinding; d) completeness of results; e) selective reporting; and f) other potential risks that may harm the validity of the study. Based on all available information, each study was assigned to one of the three categories: 'low risk' when the risk of bias was low, 'high risk' when the risk of bias was high, or 'unclear risk' when the risk of bias was uncertain.

2.3.2 Evaluation of quality of evidence

The method recommended by GRADE[15] was used to categorize the quality of evidence provided in each report into one of four levels: a) 'high quality,' when further research will not change the validity of the current evaluation of the treatment; b) 'medium quality,' when further research will likely change the validity of the current evaluation of the treatment; c) 'low quality,' when further research is very likely to change the validity of the current evaluation of the treatment; and d) 'very low quality,' when the treatment effect is unclear. GRADEpro software was used to edit, analyze, and graph the level of evidence.[16]

Evidence from randomized controlled trials is initially considered of high quality but several factors can downgrade the quality of evidence: study limitations, inconsistent results, indirect evidence, imprecise results, and reporting bias.

2.4 Data extraction

EndNote X5 software was used to manage the data extraction process. A data extraction table was constructed and two researchers extracted and double-checked the data from the included articles. Abstracted information included: a) general information about the article such as the title of the study, the first author, and the year of publication; b) demographic characteristics

of study participants such as mean age, sex ratio, inclusion and exclusion criteria, and so forth; and c) study methods such as the intervention, the baseline assessment, the duration of treatment, the number of participants in each group, and the main and secondary outcome variables.

2.5 Data analysis

RevMan 5.1 statistical software was used to conduct the meta-analysis. Quantitative variables were summarized via standardized mean differences (SMD); qualitative variables were summarized using relative risk (RR). Pooled results were presented using forest plots. Heterogeneity across studies was tested for each outcome measure to determine which model would be used to pool the results:[17] when I^2 was less than 50% and $p \geq 0.1$, studies were considered homogeneous and the fixed-effect model was used; in all other cases studies were considered heterogeneous so a random-effect model was used and the cause of the heterogeneity was investigated using subgroup analysis or meta-regression. Sensitivity analysis was conducted to assess the stability of the results and funnel plots were used to assess the possibility of publication bias.

3. Results

3.1 Results of literature search and characteristics of included studies

The study selection process is shown in Figure 1. A total of 1142 potentially relevant studies were identified, 331 (29%) of which came from China.

Nine studies published by October 2012 met our pre-defined inclusion and exclusion criteria. Three studies from Germany were excluded because the duration of treatment was less than 22 weeks: the 1997 study by Maurer and colleagues[18] treated 20 patients for 12 weeks; the 1996 study by Haase and colleagues[19] treated 40 patients for 4 weeks; and the 1991 study by Halama [20] treated 50 patients for 12 weeks. A 2009 study by Yancheva and colleagues[21] was excluded because it did not include a placebo control group. Among the 331 studies from China, only 22 were clinical studies and none of them met inclusion criteria for the meta-analysis: in 19 studies subjects were treated for less than 22 weeks, in 17 studies there was no placebo control group, and in 10 studies GbE was used in combination with some other medication. Of the 22 studies, 9 had all

Figure 1. Identification of articles for inclusion

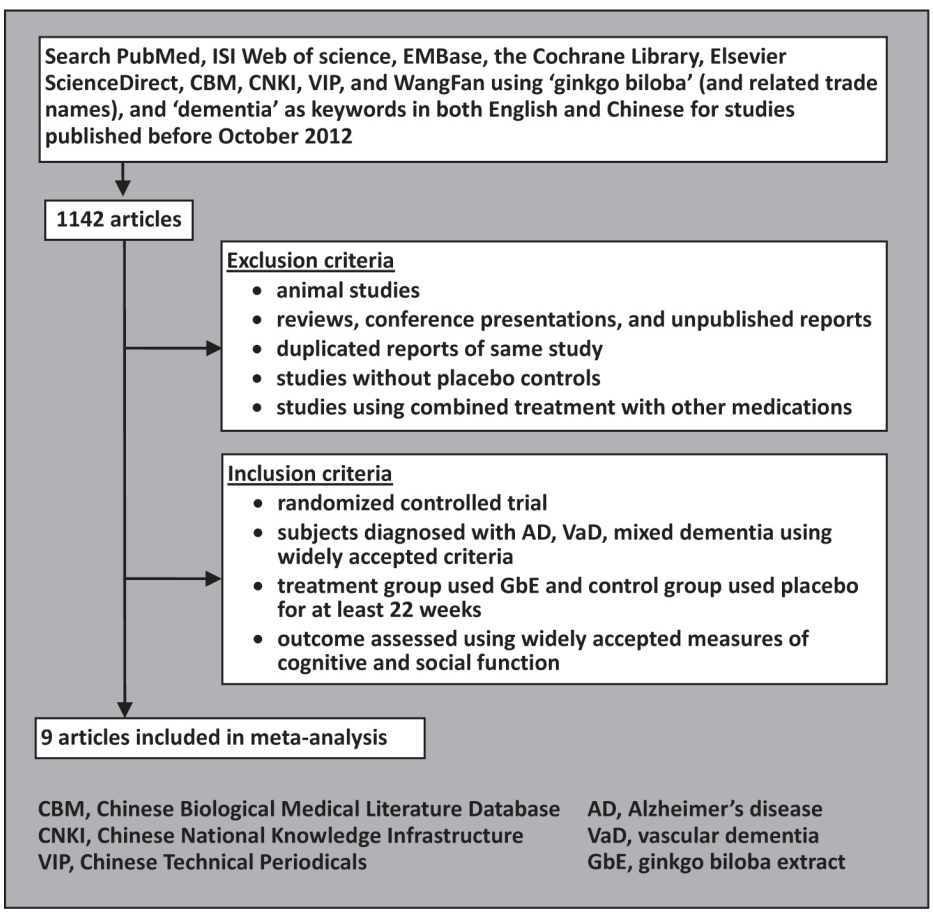

Table 1. Characteristics of the nine included studies

Study	Inclusion criteria	Duration (weeks)	Treatment method	n	Age mean (sd)	Sex Ratio (M/F)	Baseline value of primary outcome mean (sd)		
							MMSE	**ADAS-cog**	**ADL**
Le Bars 2000[24]	age>45; AD or MID by ICD-10 and DSM-III-R; MMSE=9-26; GDS=3-6	52	GbE 120mg/d	155	69 (10)	76/79	21.1 (5.8)	20.0 (16.0)	no report
			placebo	154	69 (10)	67/87	21.2 (5.5)	20.5 (14.7)	no report
							MMSE	**SKT**	**ADL**
Dongen 2003[30]	age≥50 years; AD, VaD, by DSM-III-R and ICD-10 or AAMI by Crook criteria; SKT= 8-23	24	GbE 160mg/d	40	82.6 (5.1)[a]	11/68[a]	18.0 (4.9)[a]	15.6 (4.1)[a]	44.3 (7.2)[a]
			GbE 240mg/d	39					
			placebo	44	82.5 (5.8)	8/36	18.7 (4.6)	14.1 (4.6)	42.0 (8.5)
							SKT	**ADL**	**----**
Kanowski 2003[28]	age>55; AD or MID by DSM-III-R; SKT=6-18; MMSE=13-25; MADRS<41	24	GbE 240mg/d	106	72 (10)	34/72	no report	21.5 (3.8)	
			placebo	99	72 (10)	29/70	no report	21.1 (3.7)	
							ADAS-cog	**ADL**	**----**
Schneider 2005[25]	age>60; AD by DSM-IV or probable AD by NINCDS/ADRDA; MSE=10-24; modified Hachinski Ischemic Score <4	26	GbE 120mg/d	169	78.6 (7.0)	85/84	24.7 (11.9)	2.4 (0.6)	
			GbE 240mg/d	170	78.1 (7.0)	74/96	24.8 (12.7)	2.4 (0.5)	
			placebo	174	77.5 (7.4)	85/90	25.0 (11.1)	2.4 (0.6)	
							MMSE	**SKT**	**----**
Mazza 2006[22]	50–80 years of age; AD by DSM-IV; Brief Cognitive Rating Scale=3-5; HIS<4; IQ>80; SKT=8-23; MMSE=13-25	24	GbE 160mg/d	25	66.2 (6.0)	12/13	18.8 (3.6)	16.5 (3.1)	
			placebo	26	69.8 (3.0)	10/16	18.8 (3.6)	15.9 (3.9)	
							SKT	**NPI-12**	**ADL**
Napryeyenko 2007[29]	age>50; mild to moderate AD with or without CVD or VaD using NINCDS/ADRDA and NINDS/AIREN; NPI-12>5; SKT=9-23; CDT<6; HAMD17<20	22	GbE 240mg/d	198	65 (8)	55/143	15.6 (3.9)	21.3 (9.5)	4.8 (3.9)
			placebo	197	63 (8)	55/142	15.4 (3.7)	21.6 (9.9)	4.9 (4.1)
							MMSE	**ADAS-cog**	**----**
McCarney 2008[23]	age>55; clinical diagnosis of dementia using DSM-IV; MMSE=12-26; care-giver available	24	GbE 120mg/d	88	79.3 (7.8)	37/51	23.0 (14.2)	20.4 (8.2)	
			placebo	88	79.7 (7.5)	32/56	22.0 (14.2)	25.0 (10.3)	
							SKT	**NPI-12**	**ADL**
Ihl 2011[27]	age>50; mild to moderate AD with or without CVD or VaD using NINCDS/ADRDA and NINDS/AIREN; NPI-12>5; SKT=9-23; CDT<6; HAMD17<20	24	GbE 240mg/d	202	65 (10)	63/139	16.7 (3.9)	16.4 (8.1)	1.9 (0.6)
			placebo	202	65 (9)	69/133	17.2 (3.7)	17.0 (8.2)	2.0 (0.5)
							SKT	**NPI-12**	**ADL**
Herrschaft 2012[26]	age>50; mild to moderate AD with or without CVD or VaD using NINCDS/ADRDA and NINDS/AIREN; NPI-12>5; SKT=9-23; CDT<6; HAMD17<20	24	GbE 240mg/d	200	65.1 (8.8)	61/139	15.1 (4.1)	16.8 (6.9)	1.7 (0.6)
			placebo	202	64.9 (9.4)	62/140	15.3 (4.2)	16.7 (6.4)	1.8 (0.6)

[a]combined value for low dosage and high dosage groups
AAMI, age associated memory impairment
AD, Alzheimer's disease
ADAS-cog, Alzheimer disease assessment scale (cognitive)
ADL, activities of daily living
CDT, clock drawing test
CVD, Cerebral Vascular Disease
DSM-III-R, Diagnostic and Statistical Manual (3rd edition, revised)
DSM-IV, Diagnostic and Statistical Manual (4th edition)
GbE, ginkgo biloba extract
GDS, Global Deterioration Scale
HAMD, Hamilton depression rating scale
HIS, Hachinski ischemic scale
ICD-10, International Classification of Diseases (10th edition)
IQ, Intelligence Quotient
MADRS, Montgomery-Asberg Depression Rating Scale
MID, multi-infarct dementia
MMSE, mini-mental state examination
NINCDS/ADRDA, National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association
NINDS/AIREN, National Institute of Neurological Disorders and Stroke and Association Internationale pour la Recherché et l'Enseignement en Neurosciences
no report, no baseline value provided
NPI-12, 12-item version of Neuropsychiatric Inventory
SKT, Syndrom-Kurz test
VaD, vascular dementia

three of these problems, 6 had two of these problems, and 7 had one of these problems.

A total of 2578 patients with dementia were enrolled in the nine identified studies,[22-30] including 1392 who received GbE and 1186 who received a placebo. In three studies[22-24] the daily dosage of GbE was under 200 mg, in four studies[26-29] it was over 200 mg, and two studies[25,30] had both a low-dose and a high-dose subgroup. The duration of treatment was 52 weeks in one study[24] and between 22 and 26 weeks in the other eight studies.[22,23,25-30] Table 1 provides a description of the sample size, inclusion criteria, duration of treatment, sex ratio, and outcome measures of all included studies.

3.2 Changes in cognitive functioning

For studies that assessed multiple measures of cognitive functioning, SKT was chosen as the outcome measure if it was assessed, if SKT was not assessed MMSE was chosen, and if neither SKT nor MMSE were assessed ADAS-cog was chosen. Eight of the nine studies provided before-versus-after changes in cognitive measures;[22,24-30] the 2008 McCarney study[23] only provided endpoint scores. The 2006 study by Mazza[22] had some apparent computational errors in the tables so it was excluded. And the result of the 2007 Napryeyenko study[29] was very different from that of the other studies so it was also excluded from the analysis; it had a SMD more than twice as large as that of the study with the next largest SMD (SMD=-1.91, 95%CI= -2.15, -1.67 and I^2 changed from 97% to 84% when the study was removed). This left the six studies shown in the forest plot of the results in Figure 2, subgrouped into four studies in which the mean age of subjects was under 75[24,26-28] and two studies in which the mean age of subjects was over 75.[25,30] The results showed that GbE was significantly better in improving cognitive function than placebo in the younger age group but not in the older age group. Within each of the age strata the results of the studies were homogeneous. When combining results from both age strata there was an overall beneficial effect for treatment with GbE, but there was significant heterogeneity across the six included studies due to significant differences between the two age strata.

A parallel analysis based on the same six studies of five groups of subjects that received high doses of GbE and three groups of subjects that received low doses of GbE (two studies had high-dose and low-dose subgroups) found that GbE was significantly better than placebo at improving cognitive functioning at higher doses but not at lower doses, though the differences in results between the high-dose and low-dose strata were not statistically significant (Figure 3). The results within both of the dosage strata were heterogeneous, possibly because each strata included samples with both high and low mean ages. The pooled effect in all eight samples included in the analysis showed a significant advantage for GbE, but the results for the eight samples were heterogeneous.

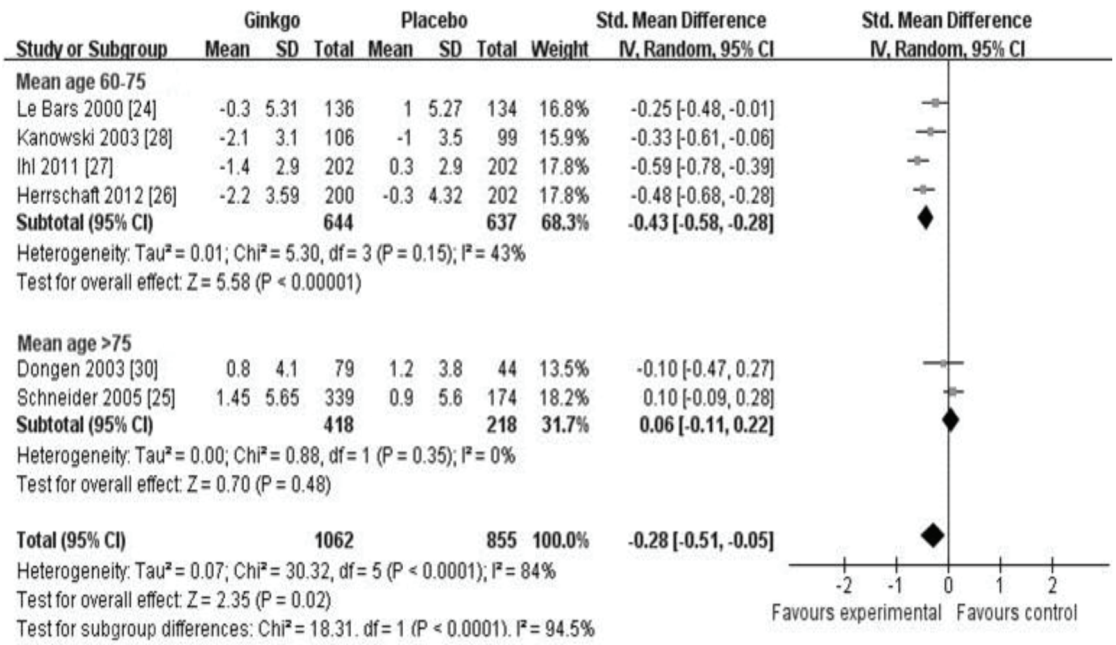

Figure 2. Comparison of the change in cognitive scores among patients with dementia after 22 to 52 weeks of treatment with ginkgo biloba extract versus placebo (subgroup analysis according to mean age of group members)

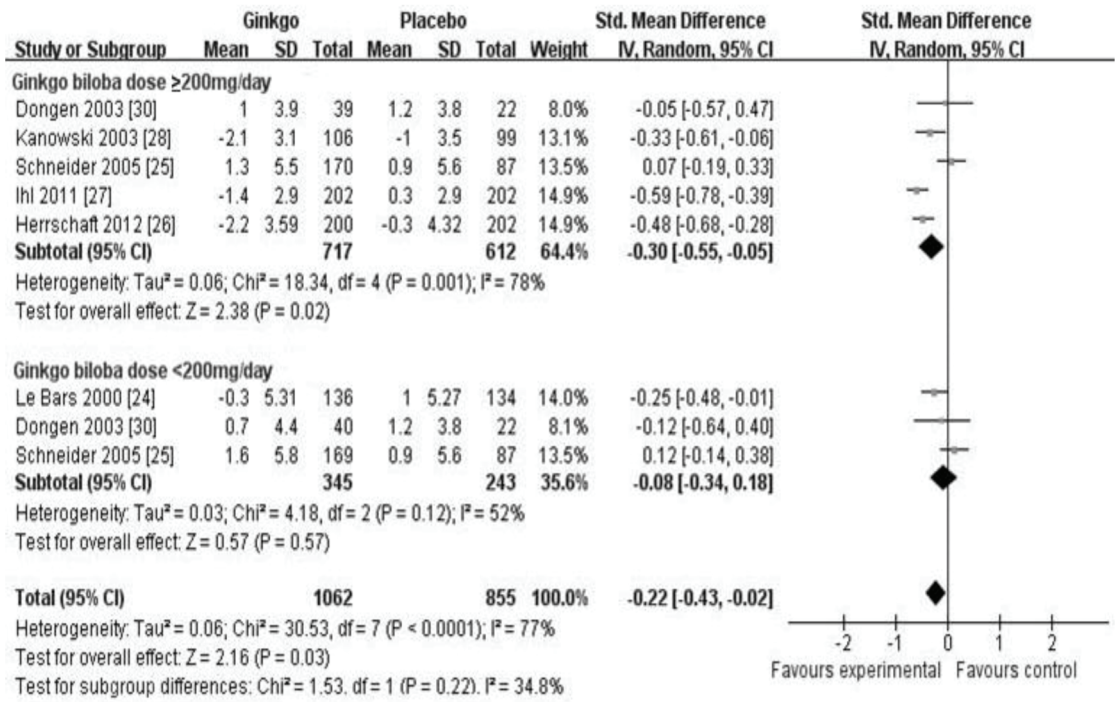

Figure 3. Comparison of the change in cognitive scores among patients with dementia after 22 to 52 weeks of treatment with ginkgo biloba extract versus placebo (subgroup analysis according to mean daily dose of ginkgo biloba extract)

3.3 Changes in activities of daily living

The results for the activities of daily living (ADL) measure were quite similar to those for cognitive functioning. Three studies were excluded from the final analysis: the 2008 McCarney study[23] did not provide before versus after change values, the 2006 Mazza study[22] had apparent computational errors, and the result of the 2007 Napryeyenko study[29] was quite different from that of the other studies resulting in high heterogeneity (SMD=-1.09, 95%CI=-1.31, -0.88 and I^2 changed from 91% to 62% when the study was removed). The remaining four studies with younger subjects (i.e., mean age under 75 years of age) showed significant improvement with GbE while the two studies with older subjects (i.e., mean age over 75 years of age) did not show improvement (Figure 4). Similar to the results for cognitive functioning, ADL results within each of the two age strata were homogenous but the results were significantly different between the two age strata. When pooling results from all six studies there was a significant advantage for treatment with GbE versus placebo, but the results were heterogeneous because of the differences by age. The five groups of subjects that received higher doses showed significant improvement in ADL, but the results were heterogeneous across the five groups, presumably because the high-dose strata included samples with both high and low mean ages. The results for the three groups of subjects receiving low doses were homogeneous but they did not show an advantage for treatment with GbE. There was no statistically significant difference in the results for the two dosage strata. The pooled results for the eight groups of subjects showed a significant advantage of GbE over placebo and the results for the eight groups of subjects were homogeneous (I^2=46%, p=0.07) (Figure 5).

3.4 Secondary outcomes

3.4.1 Neuropsychiatric inventory (NPI) score

Three studies[26,27,29] reported changes in the NPI scores after treatment. Similar to the findings for the main outcome measures, sensitivity analysis found that the NPI result for the 2007 Napryreyenko study[29] was significantly different from those of the other two studies so it was excluded from the pooled analysis. The pooled results from the two remaining studies indicated that GbE resulted in significantly greater improvement in neuropsychiatric status than placebo (SMD= -0.44, 95% CI= -0.58 ~ -0.30, p<0.001, total n=806).

3.4.2 Loss to follow-up

Eight studies[22-29] reported loss to follow-up. No heterogeneity was found between the studies (p=0.84,

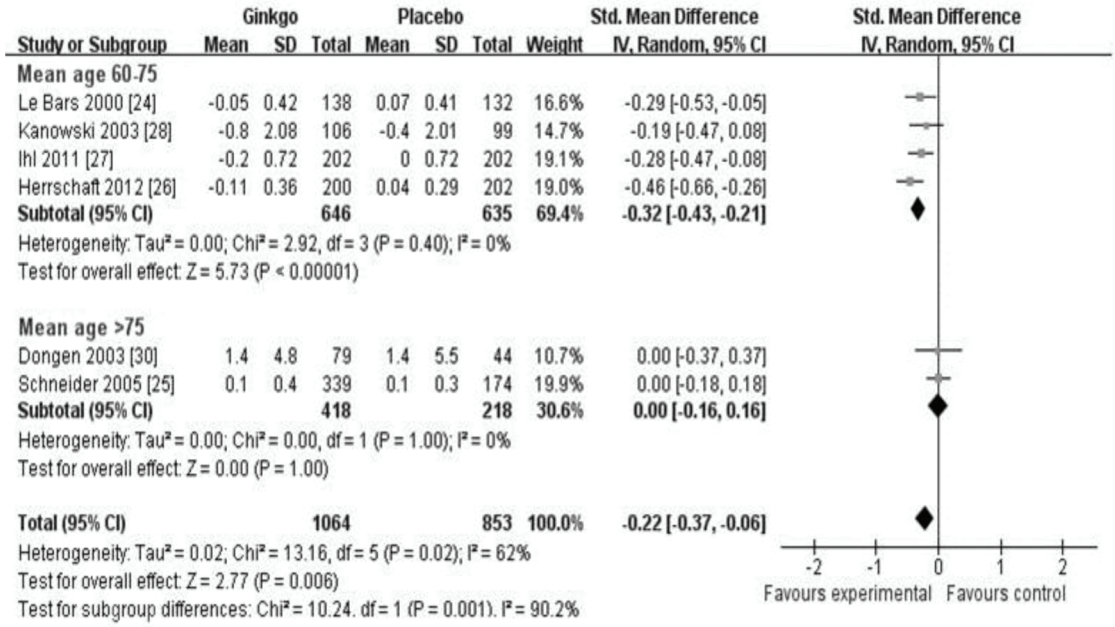

Figure 4. Comparison of the change in scores in activities of daily living (ADL) among patients with dementia after 22 to 52 weeks of treatment with ginkgo biloba extract versus placebo (subgroup analysis according to mean age of group members)

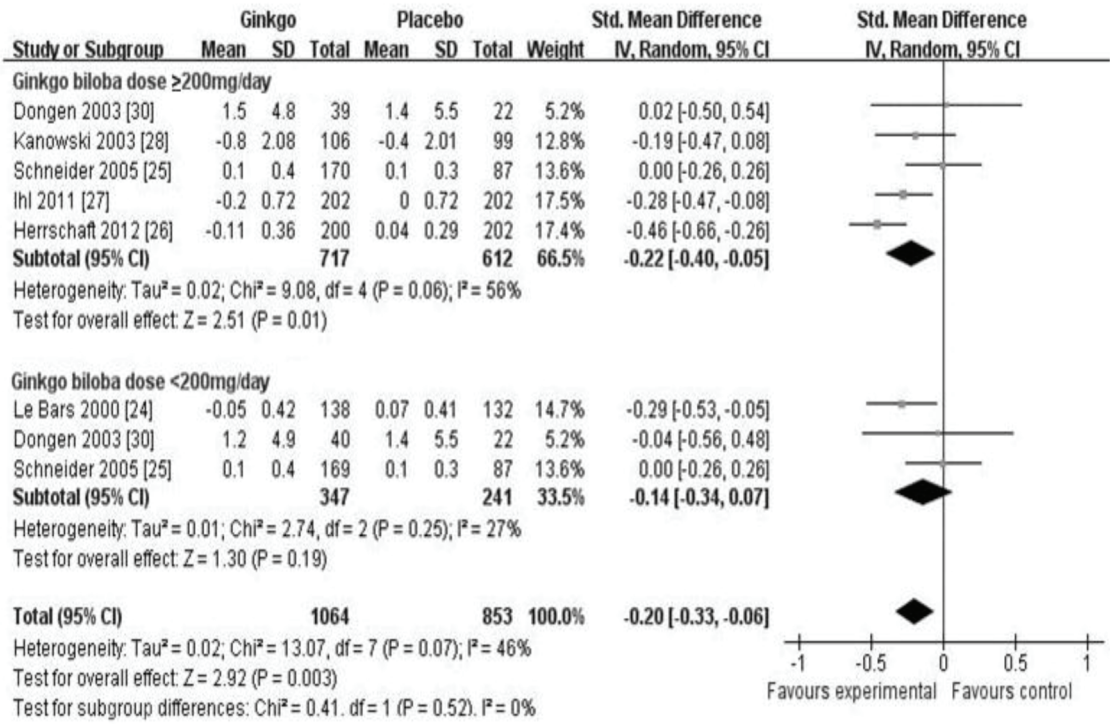

Figure 5. Comparison of the change in scores in activities of daily living (ADL) among patients with dementia after 22 to 52 weeks of treatment with ginkgo biloba extract versus placebo (subgroup analysis according to mean daily dose of ginkgo biloba extract)

I^2=0%). Pooled results from the fixed-effect model found no differences in loss to follow-up between the GbE group and the control group (RR=1.06, 95% CI=0.88-1.29, *p*=0.53, total n=2492).

3.4.3 Evaluation of the safety of GbE

The number of patients experiencing an adverse event during treatment was reported in six studies and the number experiencing a 'serious' adverse event was reported in three studies. A total of 57.6% (694/1204) of subjects in the GbE group and 57.8% (597/1032) in the control group experienced an adverse event; 5.2% (37/705) of those in the GbE group and 6.0% (32/535) in the control group experienced a serious adverse event. No heterogeneity was found across studies. Results from the fixed-effect model found no statistically significant difference in the occurrence of an adverse event (RR=0.97, 95% CI=0.91-1.04, *p*=0.38, total n=2236) or in the occurrence of a serious adverse events (RR=0.81, 95% CI= 0.51-1.29, *p*=0.36, total n=1240).

Based on the results of five studies, 10.9% (122/1116) of patients in the GbE group experienced headaches during treatment and 6.0% (67/1116) experienced dizziness; in the control group 16.5% (156/944) experienced headaches and 10.3% (97/944) experienced dizziness. Based on the results of three studies, 3.1% (23/745) of patients in the GbE group and 7.8% (45/578) of patients in the control group experienced tinnitus during treatment. There was no heterogeneity in these results between studies so a fixed-effect model was used to compare the pooled prevalence of these adverse events in the two groups. All three adverse events were reported significantly *less* frequently in the GbE group than in the control group: headaches (RR=0.74, 95% CI=0.60-0.92, *p*<0.01, total n=2060); dizziness (RR=0.54, 95% CI=0.30-0.97, *p*=0.04, total n=2060), and tinnitus (RR=0.39, 95% CI= 0.24-0.65, *p*<0.01, total n=1323).

There were no statistically significant differences between the GbE group and the control group in the occurrence of respiratory tract infections (RR=1.09, 95% CI= 0.78-1.52, *p*=0.62, from 4 RCT, total n=1733), diarrhea (RR=0.93, 95% CI=0.56-1.54, *p*=0.77, from 2 RCT, total n=810), or increased blood pressure (RR=0.73, 95% CI=0.47-1.15, *p*=0.17, from 3 RCT, total n=1220).

3.5 Publication bias

The funnel plots for the results of the seven studies (including the 2007 Napryeyenko study[29]) that reported before versus after change scores in cognitive functioning and in activities of daily living are shown in Figure 6. Both funnel plots are clearly imbalanced, suggesting a publication bias in favor of positive results. However, it is usually recommended that ten or more studies be available before a definitive conclusion about publication bias can be made, so this result may be considered suggestive of publication bias, not definitive evidence of publication bias.

3.6 Quality of the studies

As shown in Table 2, one of the nine studies did not describe the process of randomization, three studies did not describe how assignment was concealed, one study did not explain the blinding procedures, four studies did not describe cases lost to follow-up, six studies were sponsored by pharmaceutical companies, and the authors of two studies were employees of the sponsor. Overall, all the studies were considered at 'high risk' of bias.

The quality of the evidence for the two main outcomes – change in cognitive functioning and change in activities of daily living – was evaluated using data from the seven studies (total n=2312) that provided before versus after change values for each outcome.[24-30] (The

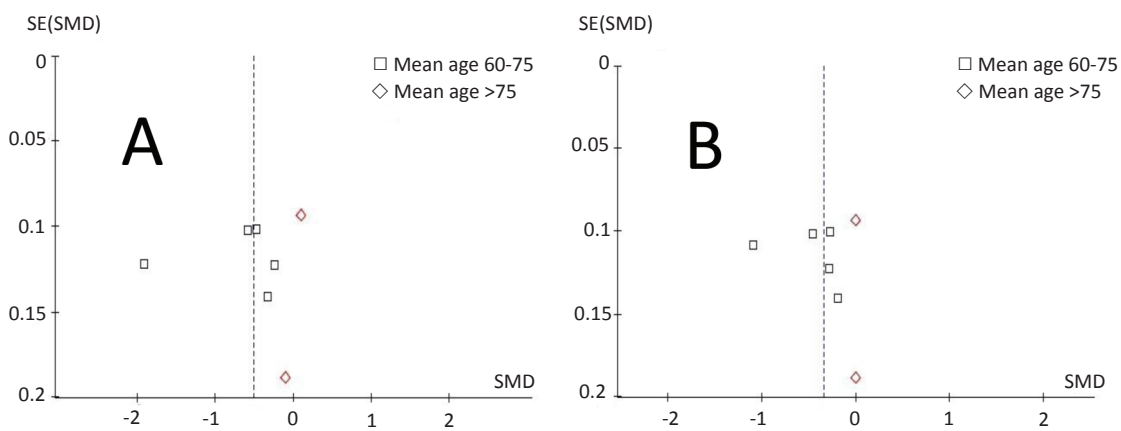

Figure 6. Funnel plots of results from seven studies that compare changes in cognitive functioning (A) and changes in activities of daily living (B) among patients with dementia receiving ginkgo biloba extract or placebo for 22 to 52 weeks

Table 2. Risk of different types of biases in the nine included studies

	Le Bars 2000[24]	Dongen 2003[30]	Kanowski 2003[28]	Schneider 2005[25]	Mazza 2006[22]	Napryeyenko 2007[29]	McCarney 2008[23]	Ihl 2011[27]	Herrschaft 2012[26]
Random sequence generation (selection bias)	?	low	low	low	low	low	low	low	low
Allocation concealment (selection bias)	?	low	low	?	?	low	low	low	low
Blinding (performance bias and detection bias)	?	low	low	low	low	low	low	low	low
Incomplete outcome data (attrition bias)	high	low	high	low	high	low	high	low	low
Selective reporting (reporting bias)	low	low	low	low	low	low	low	low	low
Other bias	?	high[a]	high[a,b]	high[a]	?	high[a]	?	high[a]	high[a,b]
OVERALL RISK OF BIAS CLASSIFICATION	high	high	high	high	high	high	high	high	high

[a] trial was sponsored by a pharmaceutical company
[b] one or more authors were employees of the sponsoring pharmaceutical company

other two studies[22,23] only provided scale scores at the conclusion of the intervention.) In these seven studies the standard mean difference (SMD) between the intervention and control group for the cognitive outcome measure was -0.51 (95% CI= -0.02 ~ -0.99) and the SMD for the activities of daily living outcome measure was -0.34 (95% CI= -0.05 ~ -0.63). Using the GRADE criteria[15] to assess the quality of the evidence, the evidence supporting both outcomes were considered 'low quality' for the following reasons: the heterogeneity of the results across studies, the opposite results for younger subjects (mean age 60-75) versus older subjects (mean age >75), the trend towards a publication bias, and the high risk of bias.

4. Discussion

4.1 Main findings

This systematic review identified nine studies with a total of 2578 patients with mild to moderate dementia, 1392 of whom were treated with ginkgo biloba extract (GbE) for 22 to 52 weeks and 1186 of whom were treated with a placebo. Meta-analysis of six of the studies found that GbE was superior to placebo in preventing deterioration in cognitive functioning and in activities of daily living, but these results were only valid for studies with younger subjects (with a mean age below 75). This age-based difference in effectiveness parallels two previous studies: our own previous work[31] found that community-based elderly under 75 years of age were most susceptible to the effects of cognitive aging and a large 2008 randomized controlled trial found that GbE was not effective in preventing dementia in the very old (i.e., over 75 years of age) with normal cognition or mild cognitive impairment.[11]

We found no significant differences in treatment outcome by dosage of GbE and we were unable to determine the potential effect of different durations of treatment, but these negative results may be because the small number of included studies made it impossible to distinguish the independent effects of age, dosage and duration of treatment.

There were no significant differences in the dropout rates between groups or in the overall rates of adverse events during treatment (though headaches, dizziness and tinnitus were *less* common in the GbE group than in the control group). However, there was considerable heterogeneity in the results between the studies (primarily based on the age of the subjects) and there were several potential biases in the reports, so the overall evidence was considered of 'low quality'.

4.2 Limitations

Our decision to limit included studies to placebo-controlled randomized controlled trials of persons with dementia that lasted for a minimum of 22 weeks allowed us to focus on the efficacy of GbE for dementia but it lead to the exclusion of several studies that lasted for shorter periods, that used active controls, and that included patients with mild cognitive impairment. This resulted in the exclusion of all potential studies conducted in China, where GbE treatment typically lasts for three months and where GbE is often used in combination with other medications. The small number of included

studies made it difficult to conduct subgroup analyses that may have identified the most effective dosage and duration of treatment for GbE. However, loosening the inclusion criteria of studies would probably increase the heterogeneity between the studies and, thus, increase the difficulty of interpreting the results.

4.3 Significance

Rapid aging of the population in many countries, including China, has increased the perceived importance of the prevention and treatment of dementia, both by the public and by the medical community. Several pharmacological approaches have been tested including antioxidants such as GbE, nonsteroidal anti-inflammatory agents and others.[32,33] But the studies that assess these agents often use different doses of the target agent, include various adjunctive treatments, use different measures of outcome, are subject to a variety of biases (strong financial incentives have resulted in the heavy involvement of pharmaceutical companies) and rarely last longer than six months. Partly due to these limitations, there is, as yet, no convincing scientific evidence for the efficacy of any agent in the prevention and treatment of this devastating condition. Despite the lack of definitive scientific evidence, the urgency of the clinical need has led many countries to prematurely approve GbE for the treatment of dementia:[34-36] GbE is widely available as a prescription drug in Germany and France and as a nonprescription food supplement in the United States, the United Kingdom and Canada.

This meta-analysis has highlighted serious weaknesses in the available studies about this important problem. It is certainly possible that GbE is effective for some subgroups of individuals with cognitive decline when used at appropriate times, at appropriate doses, and for appropriate intervals, but the currently available studies are too heterogeneous to differentiate individuals for whom GbE may be useful from those for whom it is not.

The one 'signal' that appears from our analysis is that GbE may be effective in younger persons with dementia. It is possible that younger age is simply a marker for less severe dementia so one interpretation of the result could be that GbE is more effective for milder forms of cognitive impairment or at earlier stages of the dementing process. Further large, placebo controlled, randomized trials focused on the effectiveness of GbE for milder forms of dementia (including mild cognitive impairment) that compare different doses of GbE and that follow subjects for prolonged periods (at least one year) are urgently needed.

Conflict of interest

The authors report no conflict of interest related to this manuscript.

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References

1. Cummings JL. Alzheimer's disease. *N Engl J Med* 2004; **351**(1): 56-67.
2. Aguero-Torres H, Fratiglioni L, Guo Z, Viitanen M, von Strauss E, Winblad B. Dementia is the major cause of functional dependence in the elderly: 3-year follow-up data from a population-based study. *Am J Public Health* 1998; **88**(10): 1452-1456.
3. Chiu HFK, Zhang M. Dementia research in China. *Int J Geriatr Psychiatry* 2000; **15**: 947-953.
4. Chu LW. Alzheimer's disease: early diagnosis and treatment. *Hong Kong Med J* 2012; **18**(3): 228-237.
5. Igoumenou A, Ebmeier KP. Diagnosing and managing vascular dementia. *Practitioner* 2012; **256**(1747): 13-16.
6. Ahlemeyer B, Krieglstein J. Neuroprotective effects of Ginkgo biloba extract. *Cell Mol Life Sci* 2003; **60**(9): 1779-1792.
7. Augustin S, Rimbach G, Augustin IL, Schliebs R, Wolffram S, Cermak R. Effect of a short-and long-term treatment with Ginkgo biloba extract on amyloid precursor protein levels in a transgenic mouse model relevant to Alzheimer's disease. *Arch Biochem Biophys* 2009; **481**(2): 177-1782.
8. Birks J, Grimley Evans J. Ginkgo biloba for cognitive impairment and dementia. Cochrane Database of Systematic Reviews 2009; (1): CD003120.
9. Ernst E, Pittler MH. Ginkgo biloba for vascular dementia and Alzheimer's disease: updated systematic review of double-blind, placebo-controlled, randomized trials. *Perfusion* 2005; **18**: 388–392.
10. Bomhofi G, Maxion-Bergemann S, Matthiessen PF. External validity of clinical trials for treatment of dementia with ginkgo biloba extracts. *Z Gerontol Geriatr* 2008; **41**(4): 298-312.
11. DeKosky ST, Williamson JD, Fitzpatrick AL, Kronmal RA, Ives DG, Saxton JA, et al. Ginkgo biloba for prevention of dementia: a randomized controlled trial. *JAMA* 2008; **300**(19): 2253-2262.
12. Schreiter Gasser U, Gasser T. A comparison of cholinesterase inhibitors and ginkgo extract in treatment of Alzheimer dementia. *Fortschr Med Orig* 2001; **119**: 135-138.
13. Kurz A, Van Baelen B. Ginkgo biloba compared with cholinesterase Inhibitors in the treatment of dementia: a review based on meta-analyses by the Cochrane collaboration. *Dement Geriatr Cogn Disord* 2004; **18**: 217-226.
14. Higgins JPT, Green S (eds). *Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0* [updated March 2011]. *The Cochrane Collaboration* 2011; Available from www.cochrane-handbook.org.
15. Guyatt GH, Oxman AD, Vist GE, Kunz R, Falck-Ytter Y, Alonso-Coello P, et al. GRADE: an emerging consensus on rating quality of evidence and strength of recommendations. *BMJ* 2008; **336**(7650): 924-926.

16. Schünemann H, Brożek J, Oxman A (eds). *GRADE handbook for grading quality of evidence and strength of recommendation.* Version 3.2 [updated March 2009]. The GRADE Working Group 2009; Available from http://www.cc-ims.net /gradepro. [accessed 7 October 2012]
17. Egger M, Davey Smith G, Schneider M, Minder C. Bias in meta-analysis detected by a simple, graphical test. *BMJ* 1997; **315**(7109): 629-634.
18. Maurer K, Ihl R, Dierks T, Frölich L. Clinical efficacy of Ginkgo biloba special extract EGb 761 in dementia of the Alzheimer type. *J Psychiatr Res* 1997; **31**: 645-655.
19. Haase J, Halama P, Horr R. Effectiveness of brief infusions with Ginkgo biloba special extract EGb 761 in dementia of the vascular and Alzheimer type. *Z Gerontol Geriatr* 1996; **29**(4): 302–309.
20. Halama P. Ginkgo biloba.The effectiveness of a special extract for patient with cerebral insufficiency. *Munch med Wschr* 1991; **133**: 190–194.
21. Yancheva S, Ihl R, Nikolova G, Panayotov P, Schlaefke S, Hoerr R, et al. Ginkgo bilobaextract EGb 761®, donepezil or both combined in the treatment of Alzheimer's disease with neuropsychiatric features: A randomised, double-blind, exploratory trial. *Aging Ment Health* 2009; **13**(2): 183-190.
22. Mazza M, Capuano A, Bria P, Mazza S. Ginkgo biloba and donepezil: a comparison in the treatment of Alzheimer's dementia in a randomized placebo-controlled double-blind study. *Eur J Neurol* 2006; **13**(9): 981-985.
23. McCarney R, Fisher P, Iliffe S, van Haselen R, Griffin M, van der Meulen J, et al: Ginkgo biloba for mild to moderate dementia in a community setting: a pragmatic, randomised, parallel-group, double-blind, placebo-controlled trial. *Int J Geriatr Psychiatry* 2008; **23**(12): 1222-1230.
24. Le Bars PL, Kieser M, Itil K. A 26-week analysis of a double-blind, placebo-controlled trial of the Ginkgo biloba extract EGb 761 in dementia. *Dement Geriatr Cogn Disord* 2000; **11**: 230-237.
25. Schneider LS, DeKosky ST, Farlow MR, Tariot PN, Hoerr R, Kieser M. A randomized, double-blind, placebo-controlled trial of two doses of Ginkgo biloba extract in dementia of the Alzheimer's type. *Curr Alzheimer Res* 2005; **2**: 541-551.
26. Herrschaft H, Nacu A, Likhachev S, Sholomov I, Hoerr R, Schlaefke S. 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* 2012; **46**(6): 716-723.
27. Ihl R, Bachinskaya N, Korczyn AD, Vakhapova V, Tribanek M, Hoerr R, et al: Efficacy and safety of a once-daily formulation of Ginkgo biloba extract EGb 761 in dementia with neuropsychiatric features: a randomized controlled trial. *Int J Geriatr Psychiatry* 2011; **26**: 1186-1194.
28. Kanowski S, Hoerr R. Ginkgo biloba extract EGb 761 in dementia_ intent-to-treat analyses of a 24-week, multi-center, double-blind,placebo-controlled, randomized trial. *Pharmacopsychiatry* 2003; **36**: 297-303.
29. Napryeyenko O, Borzenko I, Group G-NS. Ginkgo biloba special extract in dementia with neuropsychiatric features. A randomised, placebo-controlled, double-blind clinical trial. *Arzneimittel-Forschung* 2007; **57**(1): 4-11.
30. Dongen M. Ginkgo for elderly people with dementia and age-associated memory impairment: a randomized clinical trial. *J Clin Epidemiol* 2003; **56**(4): 367-376.
31. Li CB, Wu WY, Zhang MY, Xiao SF, Fang F, He YL, et al. Serial study on the mechanism of successful aging-analysis of follow-up data. *Chin J Psychiatry* 2007; **40**(2): 104-108. (in Chinese)
32. Doraiswamy PM. Non-cholinergic strategies for treating and preventing Alzheimer's Disease. *CNS Drug* 2002; **16**: 811-824.
33. Cui H., Ren J Sheng J, Li C. The pro-cognitive treatment of Alzheimer's disease. *World Clinical Medication* 2010; **31**(7): 399-403. (in Chinese)
34. Mckenna DJ, Jones K, Hughes K. Efficacy, safety, and use of ginkgo biloba in clinical and preclinical applications. *Altern Ther Health Med* 2001; **7**: 70-90.
35. Yoshikawa T, Naito Y, Kondo M: Ginkgo biloba leaf extract: Review of biological actions and clinical applications. *Antioxid Redox Signal* 1999; **1**: 469-480.
36. Watkins RW: Herbal therapeutics: The top 12 remedies. *Emerg Med* 2002; **34**:12-19.

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• Meta分析 •

银杏叶提取物治疗痴呆的系统综述

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摘要

背景 痴呆的疾病负担不断增加，而且缺乏有效的治疗方法，因此有些国家就推荐使用银杏叶提取物（ginkgo biloba extract, GbE）来治疗痴呆，虽然有关 GbE 疗效的研究结果尚不一致。

目的 就银杏叶提取物对痴呆患者认知功能和日常生活能力改善作用的研究进行meta分析。

方法 检索国内外数据库，找出 1982 年 1 月— 2012 年 9 月发表的关于银杏叶提取物治疗（不少于 22 周）痴呆患者的随机安慰剂对照研究的文献报告。根据 GRADE 系统推荐的方法进行文献质量评估并提取资料。采用 RevMan 5.1 软件进行异质性检验、敏感性分析并评估发表偏倚。对连续性变量的合并效应值采用标准均差（Standardized mean differences, SMD）表示，对分类变量则采用相对危险度（relative risk, RR）表示， meta 分析的合并结果采用森林图显示。

结果 有 9 项研究共计 2578 例患者符合入组和排除标准。其中 6 项研究共计 1917 例患者纳入 meta 分析，结果发现仅在样本年龄相对较低（平均年龄 75 岁以下）的研究中 GbE 在延缓认知功能衰退和防止日常活动能力下降方面优于安慰剂。组间脱落率以及治疗中总的不良事件发生率均无显著差异。然而，不同研究结果间存在明显的异质性（主要是因为研究对象的年龄差异），文献存在可能的发表性偏倚（大多数是医药公司资助的），因此总体证据强度属于“低”。

结论 这一 meta 分析表明，现有对此重要问题的研究证据依然极其薄弱。GbE 对 75 岁以下存在痴呆的人群可能有效。需要大样本、安慰剂对照的随机研究来验证上述结果，今后的研究应当聚焦于程度较轻的痴呆（包括轻度认知功能障碍），比较不同剂量 GbE 的效果，并且随访更长的时间（至少 1 年）。