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Wieland LS, Ludeman E, Chi Y, Feinberg TM, Chen IH, Chen KH, Zhu Y, Wolverson E, Amri H

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[Intervention Review]

# Ginkgo biloba for cognitive impairment and dementia

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## ABSTRACT

### Background

Dementia is a neurocognitive disorder that interferes with cognition and independent functioning. Common dementia subtypes include Alzheimer's disease, vascular dementia, and mixed type. Mild cognitive impairment (MCI) is a risk factor for dementia, and subjective cognitive complaints may be the earliest manifestation. Although cholinesterase inhibitors may help reduce some cognitive and behavioral symptoms, there is no established treatment that cures or slows dementia progression. *Ginkgo biloba* (ginkgo) is a popular herbal preparation that is used to improve brain and circulatory health, and neuroprotective effects are biologically plausible.

### Objectives

To assess the benefits and harms of *Ginkgo biloba* for the treatment of people with cognitive impairment or dementia.

### Search methods

We searched the Cochrane Dementia and Cognitive Improvement Group's register, MEDLINE, Embase, four other databases, and two trials registries on 8 December 2022. The search was updated in MEDLINE, Embase, CENTRAL, and the trials registers on 18 November 2024.

### Selection criteria

We included randomized controlled trials (RCTs) comparing ginkgo with placebo, usual treatment, or other treatments for cognitive problems in people with cognitive complaints or diagnoses of MCI or dementia.


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**Data collection and analysis**

Two review authors independently selected trials, extracted data, and assessed studies for risk of bias. Key outcomes were global clinical status, global cognitive function, activities of daily living (ADLs), adverse events (AEs), and serious adverse events (SAEs) at six months. When clinically appropriate, we pooled data using a random-effects model and expressed treatment effects as mean differences (MDs), standardized mean differences (SMDs), or risk ratios (RRs), each with its 95% confidence interval (CI). We used GRADE methods to assess the certainty of the evidence for each estimate.

**Main results**

We included 82 studies with 10,613 participants; 72 studies with 9783 participants provided extractable data. Four studies were at low risk of bias in all domains. Below we present data for the comparison of ginkgo versus placebo in people with different clinical conditions.

**Subjective cognitive impairment**

Three studies (597 participants) compared ginkgo with placebo for people with subjective cognitive complaints. Based on one study that lasted six months, it is uncertain whether ginkgo has any effect on global clinical status measured on a five-point Likert scale (MD 0.00, 95% CI −0.33 to 0.33; P = 1.00; 1 study, 197 participants; very low-certainty evidence). There were no data on cognition or ADLs. One study reported no difference in minor side effects between treatment groups and did not mention SAEs. A larger study lasting three months found that the risk of AEs may be higher with ginkgo versus placebo. It provided very uncertain evidence on the risk of SAEs.

**Multiple sclerosis and cognitive impairment**

Two studies (164 participants) tested ginkgo versus placebo over three months in people with multiple sclerosis and cognitive problems. Ginkgo probably has little or no effect on cognition measured on the Perceived Deficits Questionnaire (MD −0.09, 95% CI −0.41 to 0.22; P = 0.55, $I^2$ = 0%; 2 studies, 152 participants; moderate-certainty evidence). There were no data on global clinical status or ADLs. The studies suggested no important difference in numbers of AEs between groups, and there was no indication of SAEs due to ginkgo.

**Mild cognitive impairment**

Twelve studies (1913 participants) tested ginkgo against placebo in people with MCI. At six months, moderate-certainty evidence suggests that ginkgo probably has little to no effect on global clinical status measured on the Clinical Dementia Rating Scale (MD −0.03, 95% CI −0.06 to 0.01; 3 studies, 631 participants; $I^2$ = 0%), cognition measured on the Alzheimer's Disease Assessment Scale – cognition (MD −0.07, 95% CI −0.67 to 0.51; $I^2$ = 0%; 2 studies, 508 participants), and ADLs measured on the Instrumental ADL scale (MD −0.05, 95% CI −0.29 to 0.19; 1 study, 350 participants). There may be little or no difference between ginkgo and placebo at up to 12 months in the risk of AEs (RR 0.98, 95% CI 0.77 to 1.24; $I^2$ = 58%; 7 studies, 991 participants, 379 events; low-certainty evidence), and there is little or no difference in the risk of SAEs (RR 0.95, 95% CI 0.82 to 1.09; $I^2$ = 0%; 3 studies, 714 participants, 327 events; high-certainty evidence).

**Dementia**

Thirteen studies (3288 participants) compared ginkgo with placebo for dementia. At six months, low-certainty evidence suggests that people taking ginkgo may have better global clinical status on a six-point Likert scale (lower is better; MD −0.06, 95% CI −1.00 to −0.20; $I^2$ = 88%; 5 studies, 1359 participants), better cognition measured by decreases on a short cognitive performance test (*Syndrom-Kurztest*; MD −1.86, 95% CI −3.48 to −0.24; $I^2$ = 96%; 9 studies, 2801 participants), and slightly better ADLs measured on the ADL International Scale (MD −0.19, 95% CI −0.35 to −0.03; $I^2$ = 91%; 8 studies, 2571 participants). There is probably little or no difference between ginkgo and placebo in the risk of AEs at up to 12 months (RR 0.95, 95% CI 0.90 to 1.00; $I^2$ = 0%; 9 studies, 2746 participants, 1480 events; moderate-certainty evidence). There may be little or no difference in risk of SAEs at six months (RR 0.88, 95% CI 0.58 to 1.33; $I^2$ = 0%; 6 studies, 2463 participants, 89 events; low-certainty evidence).

**Authors' conclusions**

In people with cognitive complaints, we are unsure whether ginkgo improves global clinical status at six months, and it may be associated with an increased risk of AEs at three months. Ginkgo probably has no benefit at three months for cognition in multiple sclerosis; numeric data on AEs were unavailable, but studies did not suggest concerns. In people with MCI, ginkgo probably has little or no effect at six months on global status, cognition, or ADLS. There may be little or no difference in AEs, and there is little or no difference in SAEs, at up to 12 months. In people with dementia, there may be small to moderate benefits at six months for global status, cognition, and ADLs. There is probably little or no difference in AEs at up to 12 months, and there may be no difference in SAEs.

## PLAIN LANGUAGE SUMMARY

### What are the benefits and risks of *Ginkgo biloba* for cognitive impairment and dementia?

**Key messages**

• For people who are worried about their thinking or memory, it is uncertain whether ginkgo is better than placebo (dummy treatment) for improving their overall condition at six months.


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• For people with multiple sclerosis and problems with thinking or memory, ginkgo is probably not better than placebo for improving thinking at three months.
• For people diagnosed with mild cognitive impairment but not dementia, ginkgo is probably not better than placebo for improving their overall condition, thinking, or the skills needed to complete everyday tasks at six months.
• For people diagnosed with dementia, ginkgo may be better than placebo for improving their overall condition, overall thinking, and the skills needed to complete everyday tasks at six months. However, individual studies had very different estimates about the effects of ginkgo, making it difficult to form strong conclusions.
• Studies comparing ginkgo to placebo for mild cognitive impairment or dementia found that there is probably no increased risk of harm with ginkgo.

**What are cognitive impairment and dementia?**

Cognitive impairment is a pattern of problems with thinking, learning, remembering, or making decisions. It may also include changes in mood, behavior, or motivation. Dementia is an umbrella term for serious cognitive impairment that interferes with daily life and usual activities. Dementia risk increases with age, and the most common type of dementia diagnosed in older adults is Alzheimer's disease.

**How are cognitive impairment and dementia treated?**

No available treatments have been proven to stop or slow the progression of cognitive impairment or dementia. Medicines such as cholinesterase inhibitors may improve symptoms, and nonmedical therapies may also be helpful.

**What did we want to find out?**

We wanted to find out whether medicine based on the plant *Ginkgo biloba* (ginkgo) could help treat cognitive impairment or dementia, particularly whether it might help with thinking skills and the skills needed to complete everyday tasks. We also wanted to know whether ginkgo could help people who were worried about their thinking, or had problems with thinking that were related to multiple sclerosis.

**What did we do?**

We searched for studies testing ginkgo for people with thinking problems or diagnoses of mild cognitive impairment or dementia. People had to be treated for at least three months. We summarized the results of these studies separately for different types of thinking problems or diagnoses. We rated our confidence in the evidence based on factors such as how well the studies were carried out, how big the studies were, and whether different studies had similar or different results.

**What did we find?**

We found 82 studies including 10,613 people who were worried about problems with thinking, had problems with thinking associated with multiple sclerosis, or had diagnoses of mild cognitive impairment or dementia. Studies compared ginkgo to placebo (dummy treatment) or to other medicines, or they added ginkgo to other treatments. More than half the studies were conducted in China.

**Main results**

For people who are worried about their memory and thinking, it is uncertain whether ginkgo is better than placebo for improving their overall condition at six months. One study found no difference in harms between ginkgo and placebo at six months. However, another study lasting only three months found there may be more overall harms with ginkgo.

For people with cognitive problems associated with multiple sclerosis, treatment with ginkgo instead of placebo for three months probably makes little or no difference to thinking skills. No studies reported the total number of people experiencing harms. Two people in one study experienced serious harms that were probably unrelated to ginkgo.

For people diagnosed with mild cognitive impairment, treatment with ginkgo instead of placebo for six months probably makes little or no difference to their overall condition, thinking skills, or the skills needed to carry out everyday activities. There may be little or no difference between ginkgo and placebo in the risk of any harms up to 12 months, and there is little to no difference in the risk of serious harms.

For people diagnosed with dementia, treatment with ginkgo instead of a placebo for six months may lead to some improvements in their overall condition, thinking skills, and the skills needed to carry out everyday activities. There is probably little or no difference between ginkgo and placebo in the risk of any harms at up to 12 months, and there may be little to no difference in the risk of serious harms.

**What are the limitations of the evidence?**

Many studies had problems with their methods, and there were sometimes inconsistent findings between studies, which makes us less certain about the results. Few studies tested ginkgo for dementia beyond six months, so the potential benefits and harms of longer-term use for dementia are unknown.

**How up to date is this evidence?**


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The evidence is current to November 2024.


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**Summary of findings 1. *Ginkgo biloba* versus placebo for adults with subjective cognitive impairment**

**Patient or population:** adults with subjective cognitive impairment but no diagnosis of mild cognitive impairment or dementia

**Settings:** community

**Intervention:** *G biloba*

**Comparison:** placebo

| Outcomes | Illustrative comparative risks* (95% CI) | | Relative effect (95% CI) | No. of participants (studies) | Certainty of the evidence (GRADE) | Comments |
|---|---|---|---|---|---|---|
| | Risk with placebo | Risk with *G biloba* | | | | |
| **Global clinical status** measured on a Likert scale (1 = no complaints to 5 = very frequent complaints) at 6 months | The mean score in the placebo group at the end of treatment was 2.3 (from 2.1 to 2.6). | The mean score in the *G biloba* group was 0 points different (from 0.33 lower to 0.33 higher). | — | 197<br>(1 study) | ⊕⊖⊖⊖<br>**Very low**[a] | It is uncertain whether *G biloba* leads to any improvement in global clinical status at 6 months compared to placebo. |
| **Global cognitive function** | — | — | — | — | — | No studies reported global cognitive function. |
| **Activities of daily living (ADLs)** | — | — | — | — | — | No studies reported ADL outcomes. |
| **All adverse events** measured as the number of people who had an adverse event | — | — | — | — | — | Brautigam 1998 did not report the number of people with adverse events at 6 months, but reported that there was no difference in the number of side effects (primarily gastrointestinal upset and dizziness) in each treatment group. EUCTR2005-005765-11-EE, a larger study testing EGb for 3 months, found that the risk of adverse events may be higher with EGb 761 versus placebo (RR 1.33, 95% CI 0.92 to 1.93; P = 0.13; 1 study, 304 participants; low-certainty evidence due to very serious imprecision). |


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| **Serious adverse events** measured as the number of people who had a serious adverse event | — | — | — | — | — | Brautigam 1998 did not report whether any adverse events at 6 months were serious. EUCTR2005-005765-11-EE, a larger study testing EGb for 3 months, provided uncertain evidence on the relative risk of serious adverse events with *G biloba* versus placebo (RR 0.33, 95% CI 0.01 to 8.12; P = 0.50; 1 study, 304 participants; very low-certainty evidence due to extremely serious imprecision). |

*The **corresponding risk** (and its 95% CI) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

**Abbreviations: CI:** confidence interval; **RR:** risk ratio.

**GRADE Working Group grades of evidence**
**High certainty:** we are very confident that the true effect lies close to that of the estimate of the effect.
**Moderate certainty:** we are moderately confident in the effect estimate; the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
**Low certainty:** our confidence in the effect estimate is limited; the true effect may be substantially different from the estimate of the effect.
**Very low certainty:** we have very little confidence in the effect estimate; the true effect is likely to be substantially different from the estimate of effect.

[a] Downgraded one level for imprecision, because the study had fewer than 400 participants; one level for risk of bias, because there were problems with how the study was conducted, including possible problems with allocation concealment, attrition, and selection bias; and one level for indirectness, because the study may not have excluded people with MCI or mild dementia.

### Summary of findings 2. *Ginkgo biloba* versus placebo for adults with multiple sclerosis and cognitive impairment

**Patient or population:** adults with multiple sclerosis and cognitive impairment

**Settings:** community

**Intervention:** *G biloba*

**Comparison:** placebo

| **Outcomes** | **Illustrative comparative risks* (95% CI)** | | **Relative effect (95% CI)** | **No. of participants (studies)** | **Certainty** of the evidence (GRADE) | **Comments** |
|---|---|---|---|---|---|---|
| | **Risk with placebo** | **Risk with *G biloba*** | | | | |
| **Global clinical status** | — | — | — | — | — | No studies measured global clinical status. |


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| | | | | | | |
|---|---|---|---|---|---|---|
| **Global cognitive function** measured on the PDQ (range 0–80, lower scores are better) at 3 months | The mean score in the placebo group at the end of treatment ranged from 32.5 to 33.4 points. | The mean score in the *G biloba* group was 0.09 points lower (from 0.41 points lower to 0.22 points higher). | — | 152 (2 studies) | ⊕⊕⊕⊖ **Moderate**[a] | There is probably little or no difference in cognitive function with *G biloba* compared with placebo. |
| **Activities of daily living (ADLs)** | — | — | — | — | — | No studies measured ADL outcomes. |
| **All adverse events** measured as the number of people who had an adverse event | — | — | — | — | — | Neither study reported the total number of people with any adverse events. Lovera 2007 stated that 1 participant in the *G biloba* group had constipation that might have been related to the treatment. Lovera 2012 stated that both groups had a similar incidence of MS relapses (2/61 in the *G biloba* group and 3/59 in the placebo group). Urinary tract infections, dyspepsia, flu-like symptoms, back pain, infective conjunctivitis, headache, and worsening EDSS scores were more common in the *G biloba* group, but this difference was not statistically significant. |
| **Serious adverse events** measured as the number of people who had a serious adverse event | — | — | — | — | — | Lovera 2007 stated there were no serious adverse events at 3 months. Lovera 2012 stated that 2 participants in the *G biloba* group experienced serious adverse events over 3 months (severe depression and a myocardial infarction), but these were likely unrelated to the intervention. |

*The **corresponding risk** (and its 95% CI) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

**Abbreviations: CI:** confidence interval; **EDSS:** Expanded Disability Status Scale; **MS:** multiple sclerosis; **PDQ:** Perceived Deficits Questionnaire.

**GRADE Working Group grades of evidence**
**High certainty:** we are very confident that the true effect lies close to that of the estimate of the effect.
**Moderate certainty:** we are moderately confident in the effect estimate; the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
**Low certainty:** our confidence in the effect estimate is limited; the true effect may be substantially different from the estimate of the effect.
**Very low certainty:** we have very little confidence in the effect estimate; the true effect is likely to be substantially different from the estimate of effect.

[a] Downgraded one level for imprecision, because the study enrolled fewer than 400 people.


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**Summary of findings 3. *Ginkgo biloba* versus placebo for adults with mild cognitive impairment**

**Patient or population:** adults with mild cognitive impairment

**Settings:** outpatient

**Intervention:** *G biloba*

**Comparison:** placebo

| Outcomes | Illustrative comparative risks* (95% CI) | | Relative effect (95% CI) | No. of participants (studies) | Certainty of the evidence (GRADE) | Comments |
|---|---|---|---|---|---|---|
| | Risk with placebo | Risk with *G biloba* | | | | |
| **Global clinical status** measured on the CDR (range 0–3, lower scores are better) at 6 months[a] | The mean score in the placebo group at the end of treatment was 0.37. | The mean score in the *G biloba* group was 0.03 points lower (from 0.06 points lower to 0.01 points higher). | — | 631 (3 studies) | ⊕⊕⊕⊖ **Moderate**[b] | There is probably little or no difference in global clinical status with *G biloba* and placebo at 6 months based on data from 3 studies (SMD −0.12, 95% CI −0.28 to 0.04). When the analysis is restricted to the study at overall low risk of bias (GEM 2010), there is high-certainty evidence of little or no difference in global clinical status measured on the CDR (MD −0.04, 95% CI −0.08 to 0.00; 450 participants). |
| **Global cognitive function** measured on the ADAS-Cog (range 0–70, lower scores are better) at 6 months[c] | The mean score in the placebo group at the end of treatment was 8.4 points. | The mean score in the *G biloba* group was 0.07 points lower (from 0.67 points lower to 0.51 points higher). | — | 508 (2 studies) | ⊕⊕⊕⊖ **Moderate**[b] | There is probably little or no difference in cognition with *G biloba* and placebo at 6 months based on data from 2 studies (SMD −0.02, 95% CI −0.20 to 0.15). When the analysis is restricted to the study at overall low risk of bias (GEM 2010), there is high-certainty evidence of little or no difference in cognition measured on the ADAS-Cog (MD −0.10, 95% CI −0.71 to 0.51; 450 participants). |
| **Activities of daily living (ADLs)** measured on the IADL (range 0–8, higher scores are better) at 6 months[d] | The mean change in the placebo group at the end of treatment was 0.74 points. | The mean score in the *G biloba* group was 0.05 points lower (from 0.29 points lower to 0.19 points higher). | — | 350 (1 study) | ⊕⊕⊕⊖ **Moderate**[e] | There is probably little or no difference in ADLs with *G biloba* and placebo at 6 months. |


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| | | | | | | |
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| **All adverse events** measured as the number of people who had an adverse event at up to 12 months | 355 per 1000 | 348 per 1000 (274 to 441) | **RR** 0.98 (0.77 to 1.24) | 991 (7 studies) | ⊕⊕○○ **Low**[b,f] | There may be little or no difference in the risk of adverse events at up to 12 months' follow-up between *G biloba* and placebo. |
| **Serious adverse events** measured as the number of people who had a serious adverse event at up to 6 months | 528 per 1000 | 502 per 1000 (433 to 576) | **RR** 0.95 (0.82 to 1.09) | 714 (3 studies) | ⊕⊕⊕⊕ **High** | There is little or no difference in the risk of serious adverse events at up to 6 months' follow-up between *G biloba* and placebo. |

*The **corresponding risk** (and its 95% CI) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

**Abbreviations: ADAS-Cog:** Alzheimer's Disease Assessment Scale – cognition; **CDR:** Clinical Dementia Rating Scale; **CI:** confidence interval; **IADL:** Instrumental Activities of Daily Living Scale; **MD:** mean difference; **RR:** risk ratio; **SMD:** standardized mean difference.

**GRADE Working Group grades of evidence**
**High certainty:** we are very confident that the true effect lies close to that of the estimate of the effect.
**Moderate certainty:** we are moderately confident in the effect estimate; the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
**Low certainty:** our confidence in the effect estimate is limited; the true effect may be substantially different from the estimate of the effect.
**Very low certainty:** we have very little confidence in the effect estimate; the true effect is likely to be substantially different from the estimate of effect.

[a] Global clinical status was measured on the CDR in one large study at low risk of bias (GEM 2010), and on the Sandoz Clinical Assessment Geriatric Scale (SCAG) in two smaller studies with some risk of bias (Demarin 2017; van Dongen 2000). Because GEM 2010 was at low risk of bias and accounted for 77% of the weight of the meta-analysis, we re-expressed the SMD as MD on the CDR using the standard deviation of the placebo group from GEM 2010.
[b] Downgraded one level for risk of bias, because there were problems with how some of the studies were conducted.
[c] Cognition was measured on the ADAS-Cog in one large study at low risk of bias (GEM 2010), and on the Mattis Dementia Rating Scale (MDRS) in one smaller study with some risk of bias (Demarin 2017). Because GEM 2010 was at low risk of bias and accounted for 89.8% of the weight of the meta-analysis, we re-expressed the SMD as the MD on the ADAS-Cog using the standard deviation of the placebo group from GEM 2010.
[d] Activities of daily living were measured on the IADL in one large study at low risk of bias (GEM 2010), and on the *Nürnberger Alters Alltagsaktivitäten Skala* (NAI-NAA; Nuremberg gerontopsychological rating scale for activities of daily living) in one smaller study with some risk of bias (van Dongen 2000). We could not analyze the studies together because they used different scales, with endpoint values in one case and change values in the other. As GEM 2010 was large and at low risk of bias, we used the IADL and the results from GEM 2010.
[e] Downgraded one level for imprecision, because there were fewer than 400 people in the analysis.
[f] Downgraded one level for heterogeneity, because there was a lot of variation in effect estimates between studies.

### Summary of findings 4. *Ginkgo biloba* versus placebo for adults with dementia

**Patient or population:** adults with dementia


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**Settings:** outpatient

**Intervention:** *G biloba*

**Comparison:** placebo

| Outcomes | Illustrative comparative risks* (95% CI) | | Relative effect (95% CI) | No. of participants (studies) | Certainty of the evidence (GRADE) | Comments |
|---|---|---|---|---|---|---|
| | Risk with placebo | Risk with *G biloba* | | | | |
| **Global clinical status** measured on a Likert scale (range 1–7, lower scores are better) at 6 months | The mean score in the placebo group at the end of treatment ranged from 3.8 to 5.2 points. | The mean score in the *G biloba* group was 0.6 points lower (from 1.0 points lower to 0.2 points lower). | — | 1359 (5 studies) | ⊕⊕⊖⊖ **Low**[a] | There may be better global clinical status with *G biloba* versus placebo at 6 months (SMD −0.55, 95% CI −0.89 to −0.21). |
| **Global cognitive function** measured on the SKT (range 0–27, lower scores are better) at 6 months[b] | The mean change in the placebo group at the end of treatment ranged from an increase of 1.3 points to a decrease of 2.0 points. | The mean score in the *G biloba* group was 1.86 points lower (from 3.48 points lower to 0.24 points lower). | — | 2801 (9 studies) | ⊕⊕⊖⊖ **Low**[a] | There may be an improvement in cognition with *G biloba* versus placebo at 6 months (SMD −0.47, 95% CI −0.88 to −0.06). |
| **Activities of daily living (ADLs)** measured on the ADL-IS (lower scores are better) at 6 months[c] | The mean change in the placebo group at the end of treatment ranged from 0 points to an increase of 0.04 points. | The mean score in the *G biloba* group was 0.19 points lower (from 0.35 points lower to 0.03 points lower). | — | 2571 (8 studies) | ⊕⊕⊖⊖ **Low**[a] | There may be a slight improvement in ADLs with *G biloba* versus placebo at 6 months (SMD −0.32, 95% CI −0.59 to −0.05). |
| **All adverse events** measured as the number of people who had an adverse event at up to 12 months | 525 per 1000 | 499 per 1000 (472 to 525) | **RR** 0.95 (0.90 to 1.00) | 2746 (9 studies) | ⊕⊕⊕⊖ **Moderate**[d] | There is probably little or no difference at up to 12 months of follow-up in the risk of adverse events with *G biloba* versus placebo. |
| **Serious adverse events** measured as the number of people who had a serious adverse event at up to 6 months | 35 per 1000 | 31 per 1000 (21 to 47) | **RR** 0.88 (0.58 to 1.33) | 2463 people (6 studies) | ⊕⊕⊖⊖ **Low**[e] | There may be little or no difference between *G biloba* and placebo in the risk of serious adverse events. |

*The **corresponding risk** (and its 95% CI) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).


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**Abbreviations: ADL-IS:** Activities of Daily Living – International Scale; **CI:** confidence interval; **RR:** risk ratio; **SKT:** *Syndrom-Kurztest* (short cognitive performance test); **SMD:** standardized mean difference.

**GRADE Working Group grades of evidence**
**High certainty:** we are very confident that the true effect lies close to that of the estimate of the effect.
**Moderate certainty:** we are moderately confident in the effect estimate; the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
**Low certainty:** our confidence in the effect estimate is limited; the true effect may be substantially different from the estimate of the effect.
**Very low certainty:** we have very little confidence in the effect estimate; the true effect is likely to be substantially different from the estimate of effect.

[a] Downgraded one level for risk of bias, because there were problems with how the studies were conducted; and one level for heterogeneity, because there was considerable variation in effect estimates between studies.

[b] Three studies used the Alzheimer Disease Assessment Scale – cognition (ADAS-Cog), and six studies used the SKT (66% weight of the meta-analysis); therefore, we chose to report the risks using the SKT. The changes in the placebo groups ranged widely amongst the studies, and this may partly explain why the effect estimates at the end of treatment varied. To calculate the corresponding risk with *G biloba*, we used the standard deviation of GOT IT 2012, a large study at low risk of bias that used the SKT and had a placebo group change that was in the middle of the range.

[c] Two studies used the ADL-IS, two studies used the Geriatric Evaluation of Relative's Rating Instrument (GERRI), two studies used the Gottfries, Bråne and Steen ADL scale (GBS-ADL), one study used the *Nürnberger Alters Inventar-Beobachtungs-Skala* (NAB; Nuremberg gerontopsychological observation scale for activities of daily living), and one study used the Quality of Life – Alzheimer's Disease (QOL-AD) carer-rated scale. We chose to use the ADL-IS because it was used by two large studies that were at relatively low risk of bias. To calculate the corresponding risk with *G biloba, w*e used the standard deviation of GOT IT 2012, a large study at low risk of bias that used the ADL-IS.

[d] Downgraded one level for risk of bias, because there were problems with how the studies were conducted.

[e] Downgraded two levels for very serious imprecision, because there were few events (< 300), and the CI included both important risk reduction and important risk increase.


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# BACKGROUND

## Description of the condition

The number of persons aged 60 or above is expected to reach 1.4 billion by 2030, 2.1 billion by 2050, and 3.1 billion by 2100 (UN 2019; WHO 2024). While this represents a triumph for population health, it carries an inherent set of challenges related to adapting the current healthcare system to the needs of this burgeoning cohort. A key area of focus for policy, research, and care services is addressing the prevention and management of dementia and cognitive decline associated with aging.

Alzheimer's disease (AD) is the fifth leading cause of death among people aged over 65 years in the USA (Alzheimer's Association 2023), and dementia and AD currently constitute the second leading cause of death after ischemic heart disease in England and Wales (ONS 2023). The estimated USA prevalence is 6.7 million and is expected to increase to 13.8 million by 2060 (Alzheimer's Association 2023). The disease accounted for USD (US dollar) 305 billion of direct and indirect (foregone wage) costs in 2020, and this figure is expected to rise to USD 2.2 trillion by 2060 (Nandi 2024). More than 55 million people worldwide had the disease in 2020, and the predicted number for 2050 is 139 million people, most of whom will be living in low- and middle-income countries (Alzheimer's Disease International 2017).

Dementia is not a single entity. It encompasses a variety of clinical syndromes, which are most commonly due to progressive neurodegenerative diseases. The term used to define the condition in the *Diagnostic and Statistical Manual of Mental Disorders*, Fifth Edition (DSM-5) is 'major neurocognitive disorder'. Diagnosis requires evidence of cognitive decline that is not due to another mental disorder and is severe enough to interfere with independent functioning (APA 2013). The commonest subtype of dementia is that due to AD. Other common subtypes are vascular dementia (VD), dementia with Lewy bodies, dementia in Parkinson's disease, and frontotemporal dementia. A substantial percentage of cases are mixed type (Custodio 2017). There are some reversible dementia syndromes, for example, due to thyroid problems or vitamin deficiencies. However, none of the common neurodegenerative dementias have cures. Dementia is often preceded by a period of milder cognitive dysfunction. Mild cognitive impairment (MCI) is an intermediate condition between normal cognitive changes that may occur with age and more serious symptoms that indicate dementia. People with MCI have detectable cognitive decline, more than expected from age alone, but retain functional independence. MCI is a risk factor for eventually developing dementia (due to AD and other types), but does not always progress to dementia (NIH 2024).

The diagnosis of dementia is based on clinical assessment, including a history from an informant who knows the person well, neuropsychological tests, and functional assessment. Some cognitive changes are part of the normal aging process, which primarily involves some decreases in processing speed and working memory, while general knowledge and vocabulary remain stable (Loaiza 2024). Differentiating between these normal changes in functioning and MCI can be challenging and often focuses on greater than usual declines in memory or executive functioning (Grundman 2004; Moreira 2019). By definition, MCI does not impair everyday functioning, while dementia impacts an individual's ability to function independently. The later stages of dementia are associated with increased healthcare costs and eventually result in severe disability and death (Kosaner Kließ 2021).

Given the different clinical and pathological variants of dementia, it is evident that no single causal factor is sufficient and necessary to explain progression from normal age-related cognitive decline to dementia. Although the etiology of dementia due to AD remains uncertain, there are genetic factors, with genes for amyloid precursor protein (APP), presenilin 1 (PSEN1), and presenilin 2 (PSEN2) contributing to early-onset AD, and apolipoprotein E (APOE) E4 allele associated with an increased risk for late-onset AD (Elahi 2017). A review by the Lancet Commission also identified 14 health and lifestyle risk factors that, in combination, contribute to 50% of the risk for dementia (Livingston 2024). It is clear that the mechanisms responsible for dementia are complex and comprise numerous interactions between biological, psychological, and social factors that exert different effects at different stages of the disease process. However, there is currently no known effective treatment for most progressive forms of dementia.

## Description of the intervention

*Ginkgo biloba* (ginkgo) is the only surviving species of the plant division Ginkgophyta. It is an endangered non-flowering tree that can be traced back through the fossil record for over 200 million years (Camfield 2016; Isah 2015; Singh 2008). Although native to China, ginkgo is also cultivated elsewhere, and the fruits and leaves have been used since early human history as both a food and a traditional medicine (Camfield 2016; McKenna 2001). Ginkgo leaves and other aerial parts have been part of traditional East Asian medicine practices for at least the last 2000 years (Benzie 2011; Yang 1998). In addition to the ongoing empirical traditional use of the plant, numerous commercially prepared products containing ginkgo extractions (i.e. extracts) are currently available. Various parts of the ginkgo tree possess bioactive compounds, including ginkgolides and bilobalides (i.e. terpene trilactones unique to the plant), as well as flavonoids (flavones, biflavones, flavonols, tannins, and associated glycosides) (Isah 2015). Extracts of the dried green ginkgo leaves have been investigated for treating several medical conditions, particularly those related to diseases of the peripheral and cerebral circulation (Isah 2015; McKenna 2001). Many studies have investigated ginkgo-derived standardized extract EGb 761 (Camfield 2016). The makeup of this product includes flavone glycosides (22% to 27%); terpene lactones, including ginkgolides A, B, and C (2.8% to 3.4%) and bilobalide (2.6% to 3.2%); and less than 5 parts per million (ppm) ginkgolic acids, constituents of known allergic and cytotoxic potency (Baron-Ruppert 2001; Zuo 2017). Because ginkgo natural products encompass a variety of preparations and doses of active compounds, a comprehensive investigation of various ginkgo natural products is warranted to determine which, if any, may be beneficial for the treatment of cognitive impairment and dementia.

## How the intervention might work

For centuries, the raw material from ginkgo has been used for its broad medicinal efficacy in various parts of Asia. The most commonly investigated extract is EGb 761 and its major purified components, which include ginkgolides A, B, and C and bilobalide. Preclinical and clinical studies have investigated EGb 761 and its components for their beneficial effects on a wide range of pathological states, including vascular problems (Tian 2017; Wu 2019; Ye 2024), ischemic stroke (Feng 2019; Tulsulkar 2016; Zhang


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2023), diabetes-related health complications (Shi 2019; Zhao 2016), and neurodegenerative conditions leading to cognitive decline and dementia, including AD (Gauthier 2014; Morató 2023; Rapp 2018; Savaskan 2018). AD is characterized by the extracellular accumulation of amyloid-beta (Aβ) and hyperphosphorylated tau protein-based neurofibrillary tangles. Many of these pathologies have reasonably well-known etiologies involving oxidative stress, inflammation, and cell death. EGb 761 reportedly acts as an antioxidant in vitro and in vivo (Drieu 2000; Tunali-Akbay 2007), and this effect was recently confirmed in silico (Suárez-González 2023). Other studies have shown the extract prevents inflammation (Gargouri 2018; Jiang 2014), reduces stress (Amri 1996; Amri 2002), and exerts a neuroprotective effect (Montes 2015; Nabavi 2015; Singh 2019). However, the molecular mechanisms and pathways of AD are not completely understood, and identifying therapeutic targets and designing effective therapies remains very challenging.

The complexity of the pathophysiology combined with the challenge of using an herbal extract has, unsurprisingly, led to a multitude of potential pathways through which EGb 761 might act. Studies of EGb 761 have used established cell lines, primary cell cultures, and animal models. Gargouri 2018 showed the antineuroinflammatory effects of EGb 761 in lipopolysaccharide (LPS)-activated primary microglial cells by acting on the cyclooxygenase (COX)/prostaglandin $E_2$ ($PGE_2$) pathway. Similarly, Sun 2024 found that EGb 761 exerted an anti-inflammatory effect in LPS-activated BV2 microglial cells in vitro by inhibiting the expression and release of several inflammatory factors, cytokines, and chemokines and their ligands. The effects of EGb 761 on neurite growth have also been a subject of great interest, as neuroplasticity is significantly reduced in aging and neurodegenerative diseases. Lejri 2019a used SH-SY5Y neuroblastoma cell line in a 2D and 3D surface culture and found that EGb 761 stimulated neurite outgrowth by acting on the AKT/mTOR pathway. In a recent study, the neurite outgrowth effects in the PC12 cell line was attributed to the lactone moieties of bilobalide (Usuki 2020). Kuo 2019 conducted ex-vivo mouse model studies comparing ginkgolide A to memantine, a low-affinity antagonist of the N-methyl-D-aspartate (NMDA) glutamate receptor and a drug used clinically to treat the symptoms of dementia due to AD. They found that ginkgolide A inhibited NMDA receptors and prevented the neuronal Aβ-induced increase in c-Jun N-terminal kinase phosphorylation. Furthermore, behavioral changes, locomotor activity, and memory retention were assessed using the Y and Morris Water Maze and the Open Field test. The results showed that the treatment improved the memory of the wild-type mice, suggesting that ginkgolide A could be a phytomedicine-based drug acting similarly to memantine (Kuo 2019), with potential for fewer side effects.

Rats with homocysteinemia-induced amnesia that were treated with EGb 761 exhibited an improvement of their cognitive impairment and a reduction in the AD-like Tau hyperphosphorylation, attributable to the antioxidative activity of ginkgo (Zeng 2018). Long-term feeding (two or five months) of human P301S tau mutant-transgenic mice with EGb 761 resulted in a switch of the microglia from pro- to anti-inflammatory status, a decrease in the tau protein content, recovery of the CREB phosphorylation, inhibition of p38-MAPK and GSK-3β, and an amelioration of the decline in cognitive function. EGb 761 and its purified compounds ginkgolide A and bilobalide (not ginkgolides B or C) amplified autophagy and tau protein degradation in the neuronal lysosomes. This study demonstrated the molecular specificity of EGb 761 and its purified compounds in their ability to target various pathways, and the importance of the molecular synergy in herbal products (Qin 2018).

Using systems medicine and computer modeling approaches, Li and colleagues recently reported the top 30 putative AD target proteins, which were associated with multiple pathways, including antioxidation, anti-inflammation, antiapoptosis, mitochondrial protection, ion homeostasis, hormone synthesis, and neuroprotection via effects on amyloidogenesis and tau protein phosphorylation. These mechanisms may be at least partially responsible for the potential beneficial effects of ginkgo (Li 2018). Interestingly, Li and colleagues identified six putative AD-related proteins for which research is currently lacking (see Li 2018 for details). Those newly discovered represent additional potential therapeutic targets for neurodegenerative diseases and may represent potential targets to continue examining the effects of gingko and its components, in addition to the panoply of existing conventional cholinergic and antiglutamatergic agents as treatment.

Although EGb 761 is the most widely studied phytomedicinal extract, the molecular mechanisms underlying its potential positive health outcomes remain elusive. Furthermore, standardized EGb 761 is widely considered the 'gold standard' of ginkgo preparations, but there are many other ginkgo supplements or ginkgo-based medications on the international market that involve the whole herb or other extracts (e.g. LI 1370). These other preparations likely differ somewhat from EGb 761 in their pharmacological properties and mechanisms (Bader 2018). The complex synergistic effects of the various ginkgo compounds and the multifaceted disease processes in dementia make isolation of specific mechanisms difficult. Nevertheless, ginkgo compounds are the topic of ongoing research as potentially effective therapeutic agents offering dementia treatment with fewer or less severe side effects compared with alternative medications such as cholinesterase inhibitors, and research continues into potential mechanisms.

## Why it is important to do this review

Dementias such as those due to AD are an evolving public health issue, and there are no established cures or effective treatments to slow or reverse disease progression. Despite the absence of clear evidence from early randomized controlled trials (RCTs) for the effect of gingko in preventing or treating dementia, it remains a popular herbal remedy to mitigate cognitive decline. Its neuroprotective effects are biologically plausible, since studies have shown it can reduce Aβ aggregation and toxicity (Luo 2002; Wu 2006), and may also modulate vascular endothelial repair through activation of heme oxygenase-1 (Wu 2019). The last Cochrane review on this topic, from 2009, found no evidence for improvement in cognitive function with ginkgo versus placebo (Birks 2009). However, subsequent studies have shown a modest improvement in cognitive performance, ability to perform activities of daily living (ADLs), and global cognitive function (Savaskan 2018; Tan 2015; Yang 2016; Yuan 2017), and there is recent support for ginkgo from expert panels and guidelines. The Asian Clinical Expert Panel on Neurocognitive Disorders reached a consensus stating that there is an important role for ginkgo used alone or as an adjunctive therapy for MCI and dementia, especially in people who show limited benefit from conventional drugs (Kandiah 2019). The World Federation of Societies of Biological Psychiatry assessed ginkgo


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for the level of evidence as category B and grade 3, reflecting the growing confidence in the efficacy of this herbal extract (Lejri 2019b). Finally, although overall sales of ginkgo have declined in the USA since the mid-2000s, sales are predicted to increase in the near future (Future Market Insights 2025; IARC Working Group 2016). Given our evolving understanding of the complex disease process of dementia, a comprehensive review of the literature and a systematic assessment of all available studies for methodological rigor might lead to clearer conclusions about the potential effectiveness of a relatively cheap over-the-counter remedy. Even small improvements in cognitive function might improve quality of life for people with dementia and their carers. Furthermore, given its ubiquity, ease of access, and relatively benign side effect profile, treatment with ginkgo could lead to widespread cost savings if implemented at a large scale.

## OBJECTIVES

To assess the benefits and harms of *Ginkgo biloba* for the treatment of people with cognitive impairment or dementia.

## METHODS

### Criteria for considering studies for this review

#### Types of studies

We included RCTs. We excluded quasi-randomized trials, which we define as trials that allocated participants to treatment groups using methods that were not strictly random (e.g. alternation, medical record number). If the study report did not describe the method of randomization, we contacted the study authors for clarification. We did not restrict study eligibility by language or publication status.

#### Types of participants

We included trials in adults with existing cognitive impairment or dementia. To be inclusive of populations with cognitive impairment, we accepted trials including participants with diagnoses of MCI according to specific diagnostic criteria (e.g. the criteria for MCI proposed by the First Key Symposium in 2004 [Winblad 2004]) and trials with participants characterized as cognitively impaired according to more general criteria (e.g. age-related memory impairment, subjective cognitive complaints). To be inclusive of populations with dementia, we accepted trials with participants meeting formal diagnostic criteria for dementia (e.g. DSM-5 diagnosis of major neurocognitive disorder) and trials with participants identified with probable dementia based only on cognitive test scores or other clinical criteria. We excluded trials in people at high risk of cognitive problems (e.g. after a stroke) unless the study clearly indicated that participants had subjective or objective indications of cognitive problems at baseline.

We included studies that focused on both healthy participants and participants with cognitive impairment or dementia only if separate outcome data were available for participants with cognitive impairment or dementia.

#### Types of interventions

We included studies that evaluated ginkgo as an intervention for cognitive impairment or dementia, including any preparation or extract, at any dose, and by any route of administration (e.g. oral or intravenous).

The comparisons of interest were as follows.

- Ginkgo versus placebo.
- Ginkgo versus no treatment (e.g. wait list, no other specified active intervention).
- Ginkgo versus other active interventions.
- Ginkgo plus other active interventions versus the other active interventions alone.

For all comparisons involving ginkgo plus other active interventions, we grouped similar types of active interventions together (e.g. different types of conventional medications, or acupuncture plus Chinese herbal medicines), and used subgroup analyses to evaluate different interventions within that category (e.g. different conventional medications) when sufficient data were available.

We did not exclude studies due to lack of information about ginkgo preparation or dose. We allowed concomitant treatments, as long as they were given to both intervention groups.

#### Types of outcome measures

Because dementia is a chronic and progressive condition, we only included studies that followed participants for a minimum of three months. We extracted outcomes assessed in the short term (three to four months, and closest to three months), intermediate term (between four and 11 months, and closest to six months), and long term (at least 12 months, and closest to 12 months). We considered the intermediate-term outcomes (closest to six months) to be the outcomes of primary interest.

##### *Primary outcomes*

- Global clinical status (e.g. as measured on a continuous scale by tools such as the Clinician's Interview-Based Impression of Change [CIBIC] or the Clinical Dementia Rating Scale [CDR])
- Global cognitive function (e.g. as measured by tools such as the Mini Mental State Examination [MMSE] or the Alzheimer's Disease Assessment Scale – cognition [ADAS-Cog]). For each included study, we favored scales that were more comprehensive, where this could be distinguished. For example, we favored the ADAS-Cog over shorter scales such as the MMSE.
- Ability to perform ADLs (e.g. as measured by tools such as the Bristol Activities of Daily Living Scale [Bristol ADL] or the Disability Assessment for Dementia [DAD])
- All adverse events, including ginkgo-drug interactions when reported
- Serious adverse events, including ginkgo-drug interactions when reported

##### *Secondary outcomes*

- Memory, based on memory-specific cognitive measures (e.g. Logical Memory Test)
- Executive function, based on executive function-specific cognitive measures (e.g. Verbal Fluency Test)
- Quality of life (e.g. as measured by disease-specific tools such as the Cornell-Brown Scale for Quality of Life in Dementia [CBS], the Dementia Quality of Life Instrument [DEMQOL], or the Psychological Well-Being in Cognitively Impaired Persons tool [PWB-CIP]). We reported mental and physical life separately when they were assessed separately.


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- Neuropsychiatric outcomes (e.g. as measured on neuropsychiatric-specific tools such as the Neuropsychiatric Inventory [NPI], on scales measuring psychological well-being, or on scales of depression or anxiety such as the Geriatric Depression Scale [GDS] or the State-Trait Anxiety Inventory [STAI]). We reported anxiety, depression, mental well-being, and the NPI separately.

## Search methods for identification of studies

### Electronic searches

We searched the Cochrane Dementia and Cognitive Improvement Group (CDCIG) Specialized Register on 8 December 2022. The Register was maintained by the Information Specialists for the Cochrane Dementia and Cognitive Improvement Group until closure of the Group in 2023, and contained studies that fall within the areas of dementia prevention, dementia treatment and management, and cognitive enhancement in healthy older people. The studies were identified through a monthly search of the following sources.

- Databases:
  - Cochrane Central Register of Controlled Trials (CENTRAL) in the Cochrane Library
  - MEDLINE
  - Embase
  - CINAHL
  - PsycINFO
  - LILACS
  - Web of Science
- Trials registers:
  - ClinicalTrials.gov and the World Health Organization (WHO) International Clinical Trials Registry Platform (ICTRP) portal (www.who.int/ictrp/en)
  - ISRCTN
  - Australian and New Zealand Clinical Trial Registry
  - Chinese Clinical Trial Register
  - India Clinical Trials Registry
  - German Clinical Trials Register
  - Iranian Registry of Clinical trials
  - Sri Lanka Clinical Trials Registry
  - The Netherlands National Trial Register

We ran separate searches on 8 December 2022 in CENTRAL, MEDLINE, Embase, CINAHL, and PsycINFO.

### Latest search (November 2024)

To ensure comprehensive and up-to-date searches of the major databases for this review, we updated the search on 18 November 2024 in CENTRAL, MEDLINE, Embase, and clinical trials registers including ClinicalTrials.gov and the WHO ICTRP portal. We also searched the following sources.

- IndMED (medind.nic.in/imvw; inception to 18 November 2024).
- China Network Knowledge Infrastructure (CNKI; www.cnki.net; 1915 to 18 November 2024).
- Chinese Scientific Journals Database (VIP; www.cqvip.com; 1989 to 18 November 2024).
- Wan Fang data (www.wanfangdata.com.cn/index.html; 1985 to 18 November 2024).
- SinoMed (www.sinomed.ac.cn; 1978 to 18 November 2024).
- Korean Medicine Information System (Oriental Medicine Advanced Searching Integrated System [OASIS]; 1963 to 18 November 2024).
- KoreaMed (Korean Association of Medical Journal Editors; www.koreamed.org; 1958 to 18 November 2024).
- Korean Medical Database (KMbase; kmbase.medric.or.kr; 1958 to 18 November 2024).
- Research Information Service System (RISS; www.riss.kr; 1958 to 18 November 2024).
- The Town Society of Science Technology (TSSN; society.kisti.re.kr; 1963 to 18 November 2024).
- Korean Studies Information Service System (KISS; kisseng.kstudy.com; 1954 to 18 November 2024).
- Korean Traditional Knowledge Portal (KTKP; www.koreantk.com/ktkp2014; 1963 to 18 November 2024).

We conducted these searches to ensure the inclusion of relevant South Asian and East Asian trials.

The search strategies for all the databases and registers searched are available in Appendix 1.

### Searching other resources

We screened the references of included trials and relevant systematic reviews and practice guidelines identified during the screening process.

## Data collection and analysis

### Selection of studies

Two review authors (LSW and EL for non-Chinese studies; IC, YZ, KC, or YC for Chinese studies) independently screened the titles and abstracts of all retrieved citations and assessed the full text of all potentially eligible references. We recorded the reasons for exclusion at the full-text stage in the Characteristics of excluded studies table. We resolved disagreements by consensus or by involving a third review author (EW or HA).

### Data extraction and management

One review author (LSW) extracted the characteristics of each non-Chinese-language study, and a different review author (IC, YZ, KC, or YC) extracted the characteristics of each Chinese-language study. They used a prepiloted data extraction form and collected the following data.

- Methods: study design, study setting, recruitment method, inclusion and exclusion criteria.
- Participants: number of participants randomized and analyzed, age, sex, diagnostic criteria, baseline cognitive status.
- Interventions: detailed description of active interventions, including product preparation, standardization, dose, and total length of treatment period.
- Comparators: description of control conditions and presence of co-interventions.
- Outcomes: listing of all outcomes reported in the study.


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- Other: trial sponsorship, conflicts of interest, details of assessment of adverse effects (active or passive surveillance, whether and how authors defined serious adverse events).

A second review author (TMF or EL for non-Chinese-language studies; IC, YZ, KC, or YC for Chinese-language studies) checked the extracted data.

Two review authors (LSW, EL) independently extracted the outcome data from non-Chinese-language studies for our prespecified primary and secondary outcomes, using a standard prepiloted extraction form. They resolved any disagreements by consensus. Similarly, two review authors (IC, YZ, KC, or YC) independently extracted the outcome data from Chinese-language studies and resolved any disagreements by consensus.

When studies reported multiple measures of global status or overall cognitive function, we selected the measure that provided a more detailed and comprehensive assessment (e.g. we preferred the ADAS-Cog to the MMSE). When we were unable to choose between measures on this basis, we selected the measure that was most commonly used in other studies making the same comparison at the same time point (e.g. if most other studies used the MMSE, and we were unable to choose between the MMSE and another measure of cognitive function, we preferred the MMSE). When studies reported multiple measures of memory or executive function, we combined the multiple measures within the study using procedures described in Chapter 24 of Borenstein 2009. We used a correlation of 0.5 between outcome measures in our calculations, unless the study provided the correlations.

When both endpoint and change data were available in the study report, we used endpoint data in our primary analysis. In cases where study participants were lost to follow-up, and both available-case analyses and intention-to-treat analyses using imputation were presented, we used the imputed data for our primary analysis.

We had planned to use sensitivity analyses to observe whether our results were robust to decisions to use endpoint instead of change data, and intention-to-treat data with imputation instead of available-case data, but there were insufficient data to carry out these analyses (Sensitivity analysis).

### Assessment of risk of bias in included studies

Two review authors (LSW and EL for non-Chinese studies; IC, YZ, KC, or YC for Chinese-language studies) independently assessed the risk of bias for each included study using the Cochrane risk of bias tool RoB 1, as outlined in Chapter 8 of the *Cochrane Handbook for Systematic Reviews of Interventions* Version 5.2 (Higgins 2017). The review authors extracted information on risk of bias, including relevant quotations from the study and an explanation of each judgment, into a standard prepiloted form. They checked understanding and agreement for at least two studies before proceeding to evaluate the remaining studies. We resolved disagreements on risk of bias by consensus.

We assessed the risk of bias according to the following domains.

- Selection bias (random sequence generation, allocation concealment).
- Performance bias (blinding of participants, blinding of personnel or care providers).
- Detection bias (blinding of outcome assessors).
- Attrition bias (incomplete outcome data).
- Reporting bias (selective reporting of outcomes).
- Other bias (other sources of bias related to a particular trial design or specific circumstances, such as conflicts of interest).

We classified the risk of bias as low, high, or unclear in each domain (Higgins 2017). We considered trials that were at low risk of bias in each domain to be at overall low risk of bias, and carried out sensitivity analyses in which we omitted trials at overall higher risk of bias (Sensitivity analysis).

### Measures of treatment effect

We calculated risk ratios (RRs) and 95% confidence intervals (CIs) for dichotomous data, and mean differences (MDs) or standardized mean differences (SMDs) with 95% CIs for continuous data.

### Unit of analysis issues

We planned to follow the guidance on cluster-randomized trials and cross-over trials presented in Chapter 23 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2019). However, we found no eligible trials with these designs.

### Dealing with missing data

If primary outcome data or important study characteristics were missing from the study report, we emailed the contact author or the primary investigator to obtain the missing information. We noted this correspondence and the results in the Characteristics of included studies table.

### Assessment of heterogeneity

We assessed clinical heterogeneity between studies qualitatively. For studies that we considered sufficiently homogeneous with regard to participants, interventions, comparators, and outcomes to combine in a meta-analysis, we assessed the presence of statistical heterogeneity using the $Chi^2$ test. We considered a P value of less than 0.10 as evidence of statistically significant heterogeneity.

The $I^2$ statistic describes the percentage of variability in the overall effect that is due to heterogeneity rather than chance (Deeks 2019). The suggested thresholds for interpretation of $I^2$ percentages are as follows.

- 0% to 40%: might not be important.
- 30% to 60%: may represent moderate heterogeneity.
- 50% to 90%: may represent substantial heterogeneity.
- 75% to 100%: considerable heterogeneity.

We assessed the importance of the $I^2$ values in the context of the range and direction of effects as observed from the forest plots, and the strength of the evidence for heterogeneity based upon the $Chi^2$ test (Deeks 2019). We also used subgroup analyses to explore potential sources of clinical heterogeneity (see Subgroup analysis and investigation of heterogeneity).

### Assessment of reporting biases

We used Egger's test and a funnel plot to assess the potential for small-study bias in meta-analyses that included at least 10 studies (Egger 1997; Sterne 2011). Since the appropriateness of funnel plots for analyses using the SMD is unclear (Zwetsloot 2017), when an


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analysis had at least 10 studies, we first checked that there were sufficient studies using the same scale to permit use of the MD and, if so, we created a funnel plot based on the MD. We also evaluated the possibility of selective outcome reporting for each included study as part of the risk of bias assessment (Assessment of risk of bias in included studies).

### Data synthesis

We used meta-analysis to combine the outcome data across trials when there were available data and sufficient clinical similarity of trials in terms of population, interventions, comparators, outcomes, and timing of assessment.

We carried out separate analyses for participants with subjective cognitive problems, MCI, and dementia, as different degrees or types of impairment may respond differently to ginkgo. We also carried out a separate analysis for participants with cognitive problems associated with multiple sclerosis. We used a random-effects model for all analyses, because we expected some between-study variation, and we wished to generalize the study results beyond the specific studies included in the analyses. When it was not possible to carry out a meta-analysis, we provided a qualitative description of the results from clinically similar trials.

We summarized dichotomous data using the RR and 95% CI. We summarized continuous data using the MD and 95% CI when studies in the analysis used the same scale, and the SMD and 95% CI when studies used different scales to measure the same underlying concept (e.g. cognition). We did not specify the size of effects; however, according to traditional thresholds, SMD values below 0.5 are considered small, values of 0.5 to 0.8 are considered moderate, and values greater than 0.8 are considered large (Andrade 2020).

### Subgroup analysis and investigation of heterogeneity

When there were sufficient data, we carried out subgroup analyses based on factors that may cause the effect of the intervention to vary. We defined sufficient data as at least 10 studies overall and at least two studies in each subgroup (Deeks 2019). Subgroups included the following factors.

- Type of impairment (e.g. vascular impairment or VD versus non-vascular impairment or AD), as the mechanisms and effects of ginkgo may be different in different types of impairment.
- Type of ginkgo intervention (e.g. standardized extract EGb 761 versus other standardized extracts versus non-standardized ginkgo extracts versus traditional preparation types [i.e. decoction or tea, tincture]), as different types and preparations of ginkgo natural product may produce different effects.
- Different dosages of ginkgo (i.e. < 200 mg/day versus ≥ 200 mg/day), as some recent research suggests that doses of standardized extract over 200 mg/day are associated with greater efficacy (Yuan 2017).

We used the $I^2$ statistic to assess the percentage of the variability in effect estimates that was due to genuine subgroup differences rather than to chance. We were cautious about drawing conclusions about causality based on subgroup differences, as between-study comparisons provide observational evidence.

### Sensitivity analysis

We carried out sensitivity analyses to assess the robustness of results to risk of bias (as defined in Assessment of risk of bias in included studies), but we had insufficient available data to carry out our preplanned sensitivity analyses for endpoint versus change data, imputed versus available-case data, or adjusted versus unadjusted data.

### Summary of findings and assessment of the certainty of the evidence

We assessed the overall certainty of the evidence for each outcome, regardless of whether there were available quantitative data. We used the GRADE criteria outlined in Chapter 14 of the *Cochrane Handbook for Systematic Reviews of Interventions* to determine whether the evidence for each estimate was of high, moderate, low, or very low certainty (Schünemann 2019). The GRADE approach begins by considering evidence from RCTs to be high certainty. However, the certainty of evidence from RCTs may be downgraded by one or more levels for serious concerns in any of the following areas.

- Study limitations (risk of bias).
- Inconsistency (heterogeneity).
- Indirectness of evidence.
- Imprecision (insufficient sample size or a CI encompassing both important and null effects).
- Publication bias.

We downgraded the evidence once in the presence of serious risk of bias and twice when we judged the risk of bias to be very serious. We downgraded the evidence once for serious inconsistency (when the $I^2$value was50% or greater). We did not downgrade twice for very serious inconsistency unless the effect estimates were clearly a mix of benefit and harm. We downgraded the evidence once for serious imprecision when an analysis contained fewer than 400 participants or fewer than 300 events, and twice for very serious imprecision when an analysis contained fewer than 50 participants or fewer than 25 events. We also downgraded for imprecision when a CI included both important and null effects; evidence could be downgraded a maximum of three times for extremely serious imprecision. We downgraded the evidence once for publication bias when we judged there was evidence supporting a strong suspicion of publication bias.

One review author (LSW) applied the GRADE approach to each outcome, and one review author (EL) checked the assessments. If any disagreements arose, we reached consensus through discussion.

#### *Summary of findings table*

We created separate summary of findings tables presenting our main comparison (ginkgo versus placebo) for subjective cognitive impairment, multiple sclerosis and cognitive impairment, MCI, and dementia. We presented the estimates and certainty of the evidence for the primary outcomes of global clinical status, global cognitive function, ADLs, adverse events, and serious adverse events at the intermediate-term time point (six months) when this was available. When data at six months were not available, we used data at the closest available time point. For continuous outcomes, we presented the MD and scale from analyses including


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only one study, and we back-calculated the SMD to a commonly used measure (e.g. the MMSE) from analyses including multiple studies when possible.

# RESULTS

## Description of studies

See the Characteristics of included studies table and the Characteristics of excluded studies table.

### Results of the search

Electronic searches by the Cochrane Dementia and Cognitive Improvement Group Information Specialist in December 2022 were supplemented by searches of Chinese-language databases by YC. In November 2024, the search was updated by further searches of MEDLINE, Embase, CENTRAL, and the trials registers. The search retrieved 11,049 records; two additional studies were found from reference lists of relevant papers. After removing 7894 duplicates, we screened 3157 references for potential eligibility and excluded 2578 on the basis of their title and abstract. We assessed 579 full-text reports for eligibility, excluding 462 studies, listing 27 studies as awaiting classification, listing eight studies as ongoing, and including 82 studies (see Figure 1).


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**Figure 1. PRISMA flow diagram**

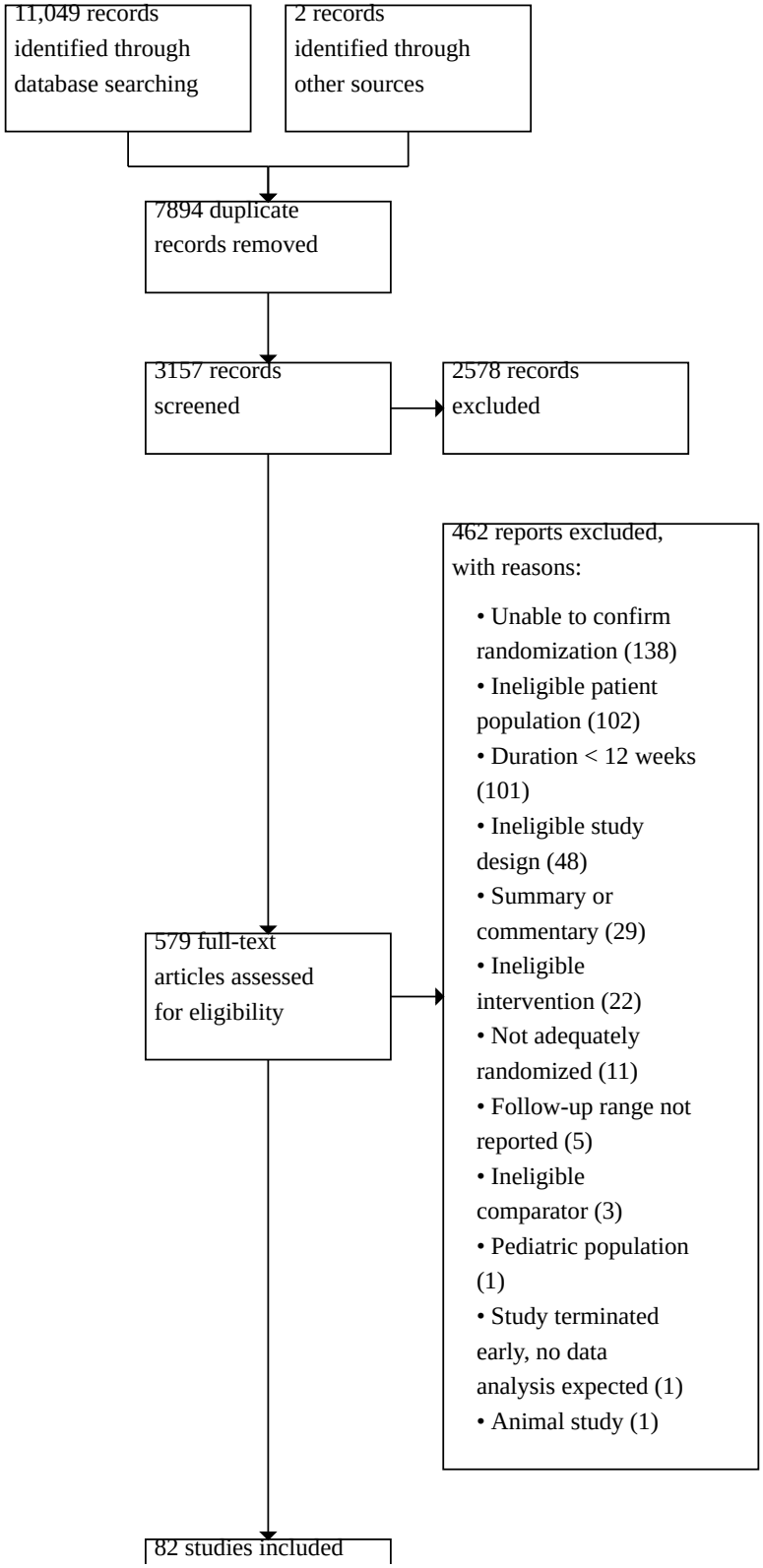



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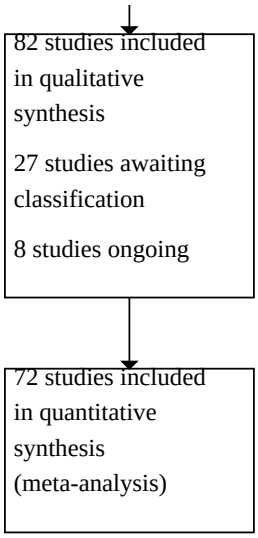
**Figure 1. (Continued)**




### Included studies

We included 82 RCTs with a total of 10,613 participants. Seventy-two RCTs (9783 participants) provided data. The studies were conducted in China (53 studies), Germany (six studies), the USA (five studies), the UK (three studies), Bulgaria (two studies), Croatia (two studies), France (two studies), the Netherlands (two studies), Ukraine (two studies), Estonia (one study), Italy (one study), Latvia (one study), Switzerland (one study), and Russia, Belarus, and Moldova (one study). Sample sizes ranged from 20 to 513 participants, with a median of 92 participants. Eighty-one studies were published between 1975 and 2022, while one study conducted in 2005 and 2006 had yet to be published at the time of writing of this review. Forty-one studies did not report their funding or have any apparent relationship with a funder. Of the remaining studies, 13 were funded by Dr. Willmar Schwabe GmbH & Co, the manufacturer of EGb 761 (a widely marketed extract of ginkgo), and four were funded by other companies. The remaining 24 studies were funded by government, non-profit, or academic institutions.

#### *Participants*

Mean participant ages ranged from 49 years to 84 years, and the percentage of female participants ranged from 24% to 92%.

Three studies recruited people with subjective cognitive problems but no diagnosis of impairment (Brautigam 1998; EUCTR2005-005765-11-EE; Gessner 1985; see Table 1), two studies recruited people with cognitive problems associated with multiple sclerosis (MS; Lovera 2007; Lovera 2012; see Table 2), 42 trials recruited people with diagnoses of MCI without dementia (see Table 3), and 35 trials recruited people with dementia diagnoses, primarily specified as mild to moderate in severity (see Table 4).

We classified study populations as people with subjective cognitive impairment if one or more subjective cognitive complaints were required for study inclusion, but objective cognitive impairment did not exist or was not assessed. We classified studies of cognitive impairment with MS as studies where study authors explicitly stated that the goal of the study was to treat existing cognitive problems in participants with MS. We considered study populations to have MCI based on statements by study authors that participants had some form of cognitive impairment or objective dysfunction, but dementia was either not mentioned or explicitly excluded. Likewise, we considered study populations to have dementia based on statements by study authors that participants met diagnostic criteria for definite or probable dementia. We did not use MMSE scores or other criteria to classify study populations ourselves. One study clearly included a mixed population of both mild-to-moderate dementia and age-associated memory impairment without dementia (van Dongen 2000). Data were not available by diagnostic category, so we classified this trial as an MCI trial because 70% of participants were diagnosed with age-associated memory impairment without dementia.

### Interventions and comparators

Seventy-two trials used EGb 761 and three trials used LI 1370, another commercially produced extract. Two placebo-controlled studies using LI 1370 tested 150 mg/day, and one placebo-controlled study using LI 1370 tested 240 mg/day. When reported, doses of EGb 761 ranged from 2.4 mg/day to 3 g/day, and placebo-controlled studies all tested doses between 60 mg/day and 240 mg/day. No other products were clearly used in more than one trial.

Seventy-two trials had two arms, and 10 trials had three arms. Four of the three-arm trials tested two doses of ginkgo against placebo (Brautigam 1998; Demarin 2017; Schneider 2005; van Dongen 2000), three tested ginkgo against both placebo and another medication (Gessner 1985; Mazza 2006; Tian 2019), two tested ginkgo alone against donepezil and the combination of donepezil and ginkgo (He 2016; Yancheva 2009), and one tested ginkgo against a pharmacological treatment and an herbal treatment (Tan 2016). Thirty studies tested ginkgo against placebo (Brautigam 1998; Demarin 2017; DIGGER 2008; EUCTR2005-005765-11-EE; Gavrilova 2014; GEM 2010; Gessner 1985; GINDEM-NP 2005; GOTADAY 2011; GOT IT 2012; Grass-Kapanke 2011; Gschwind 2017; Halama 1988; Halama 1991a; Israel 1987; Kanowski 1996; Le Bars 1997; Lovera 2007; Lovera 2012; Maurer 1997; Mazza 2006; Moreau 1975; PLAGIN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2013; Oswald 1997; Rai 1991; Schneider 2005; Tian 2019; van Dongen 2000; Vesper 1994; Wesnes 1987). No studies compared ginkgo to no treatment. Eighteen studies compared ginkgo alone to a pharmacological treatment, including butylphthalide (Yang 2020a; Yu 2021), donepezil (Deng 2021; He 2016; He 2018a; Ji 2020; Li 2016a; Mazza 2006; Yancheva 2009; Zhang 2019a), mecobalamin (Qu 2020), nicergoline (Gessner 1985), nimodipine (Gu 2017; He 2018b; Li 2015a; Tan 2016), oxiracetam (Xu 2021), and piracetam (Wang 2020a). Ten studies compared ginkgo alone to a traditional Chinese medicine intervention, either acupuncture or Chinese herbal medicine (Chen 2014a; Feng 2008; He 2005; Liao 2017a; Wang 2004; Wu 2017; Yang 2015a; Zhang 2022; Zhang 2016a; Zheng 2021).

Twenty-one studies tested the addition of ginkgo to a specific pharmacological intervention versus that same intervention alone; the pharmacological interventions were allopurinol (Li 2013a), butylphthalide (Huang 2017; Liu 2021; Xu 2017), citicoline sodium (Fang 2020), donepezil (Bu 2016; Gao 2019; Guan 2019; He 2016; Liu 2015a; Wang 2014a; Wu 2021a; Xu 2019a; Yancheva 2009; Yu 2014; Zheng 2020), idebenone (Dong 2021), memantine hydrochloride (Kang 2020; Li 2017a), and piracetam (Ma 2015; Meng 2012). Another seven trials examined the addition of ginkgo to a more diverse set of interventions, which were described as basic or conventional treatment and appeared to include medications together with other lifestyle approaches (Dong 2011; Han 2016; Jiang 2018; Li 2019a; Shi 2017; Xia 2013; Zhao 2020). One of these seven trials used placebo in testing ginkgo plus conventional vascular medications against placebo plus conventional vascular medications (Jiang 2018).

### Outcomes

Seventy-two studies reported at least one relevant usable outcome other than a statement of no adverse events. See Table 5 for a description of the scales used to measure the outcomes, including the direction of each scale.

Eleven studies reported global clinical status, using a global clinical impression rating scale (nine studies), the CDR (two studies), or the Sandoz Clinical Assessment Geriatric Scale (SCAG; two studies; used in conjunction with a global clinical status rating scale).

Sixty-two studies reported global cognition, using one or more scales. Forty-one studies used the MMSE, 18 used the Montreal Cognitive Assessment (MoCA), 12 used the ADAS-Cog, nine used the *Syndrom-Kurztest* (SKT; short cognitive performance test), three used the Hasegawa Dementia Scale (HDS), two used the Perceived Deficits Questionnaire (PDQ), and one each used the Function Independence Measure (FIM) cognitive items, Mattis Dementia Rating Scale (MDRS), Revised Mini Mental Status (3MSE), and Test for Early Detection of Dementia with Discrimination from Depression (TE4D).

Forty studies reported ADLs. Eighteen studies used an unnamed ADL rating scale, six used the Instrumental Activities of Daily Living (IADL) functional activities scale, four used the Barthel Index (Barthel), three used the Gottfries, Bråne and Steen ADL scale (GBS-ADL), three used the Geriatric Evaluation of Relative's Rating Instrument (GERRI), two used the Activities of Daily Living – International Scale (ADL-IS), and one each used the Alzheimer's Disease Cooperative Study – Activities of Daily Living – Mild Cognitive Impairment 24-items version (ADCS-ADL-MCI-24), *Nürnberger Alters Inventar-Beobachtungs-Skala* (NAB; Nuremberg gerontopsychological observation scale for activities of daily living), *Nürnberger Alters Alltagsaktivitäten Skala* (NAI-NAA; Nuremberg gerontopsychological rating scale for activities of daily living), and combined ADL and IADL.

Seventeen studies reported the secondary outcome memory, using one or more scales. Three studies used the Wechsler Memory Scale – Memory Quotient (MQ), two used the Benton, two used the California Verbal Learning Test (CVLT-II), and one each used the Adult Memory and Information Processing Battery – Delayed Story Recall (AMIPB-DSR), Digit Span Memory Test (digit span), *Fragebogen zur Erfassung alltäglicher Gedachtniserfahrungen* (FEAG; questionnaire for assessing subjectively experienced memory performance in everyday life), logical memory, MMSE memory subscale, MoCA memory subscale, Rey 1, Rey 2, *Termine Test* (appointments test) Immediate Recall (TT-immediate), *Termine Test* Delayed Recall (TT-delayed), verbal learning test, Wechsler Memory Scale (WMS) III Faces I or WMS III Faces II.

Fifteen studies reported executive function using one or more scales. Six studies used the Clock Drawing Test (CDT), five used verbal fluency, two each used the Trail Making Test part B (TMT B), Controlled Oral Word Association Test (COWAT), Paced Auditory Serial Addition Test (PASAT), and Stroop Test (Stroop), and one each used the Expanded Memory Control Test (EMCT), MoCA executive function subscale, Symbol Digit Modalities Test (SDMT), *Wien Test System – Arbeitsleistungsserie* (WTS-ALS; Vienna Test System – Work Performance Series), and *Wien Test System* – Determination Test (WTS-DT).

Five studies reported the secondary outcome quality of life. Two used the Dementia Quality of Life (DEMQOL), and one each used the Progressive Deterioration Scale (PDS), Quality of Life – Alzheimer's Disease (QOL-AD), or 36-item Short Form Health Survey (SF-36).

Twenty-one studies reported neuropsychological outcomes using one or more scales. Nine studies used the Neuropsychiatric Inventory (NPI), three used the Hamilton Rating Scale for Depression (HAM-D), two each used the *Befindlichkeitsskala* (BfS'; mental balance scale) and State-Trait Anxiety Inventory (STAI), and one each used the Geriatric Depression Scale (GDS), Beck Depressive Inventory (BDI), Center for Epidemiologic Studies Depression Scale (CESD), *Depressions-Skala* (D-S'; depression scale), and Montgomery Åsberg Depression Rating Scale (MADRS).

We obtained additional information on methods or outcomes from trialists for 10 studies (Bu 2016; Demarin 2017; EUCTR2005-005765-11-EE; GEM 2010; Gessner 1985; Mazza 2006; PLAGIN 2013; Tian 2019; Yancheva 2009; Zheng 2021). The Characteristics of included studies table includes details of this correspondence. All other data came from published reports.

### Excluded studies

We excluded 462 studies for the following reasons.

- Unable to confirm randomization (138 studies).
- Duration less than 12 weeks or follow-up time not reported (106 studies).
- Ineligible patient population (102 studies).
- Ineligible study design, including quasi-randomized studies (59 studies).


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- Not a primary study report (e.g. summary or commentary; 29 studies).
- Ineligible intervention (22 studies).
- Ineligible comparator (three studies).
- Pediatric population (one study).
- Study terminated early and no data analysis expected (one study).
- Animal study (one study).

See details in the Characteristics of excluded studies table for the 233 studies where we excluded the study on the basis of inadequate or unclear duration, ineligible patient population, ineligible intervention, or ineligible comparator.

### Risk of bias in included studies

Most studies were at unclear or high risk of bias in at least one domain. Four studies met our prespecified criteria for overall low risk of bias (EUCTR2005-005765-11-EE; GEM 2010; Grass-Kapanke 2011; Lovera 2012). The Characteristics of included studies table provides detailed information about the risk of bias in the included studies, and Figure 2 and Figure 3 provide a visual summary.

**Figure 2. Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies**

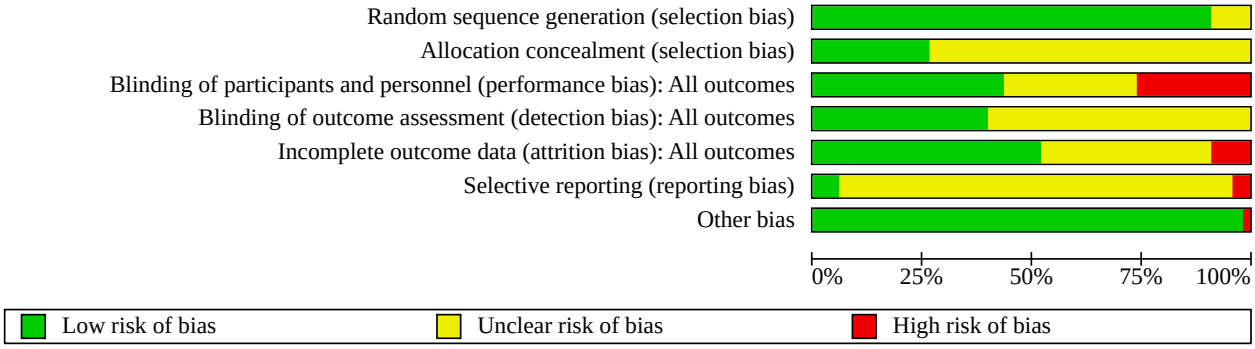



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**Figure 3. Risk of bias summary: review authors' judgements about each risk of bias item for each included study**

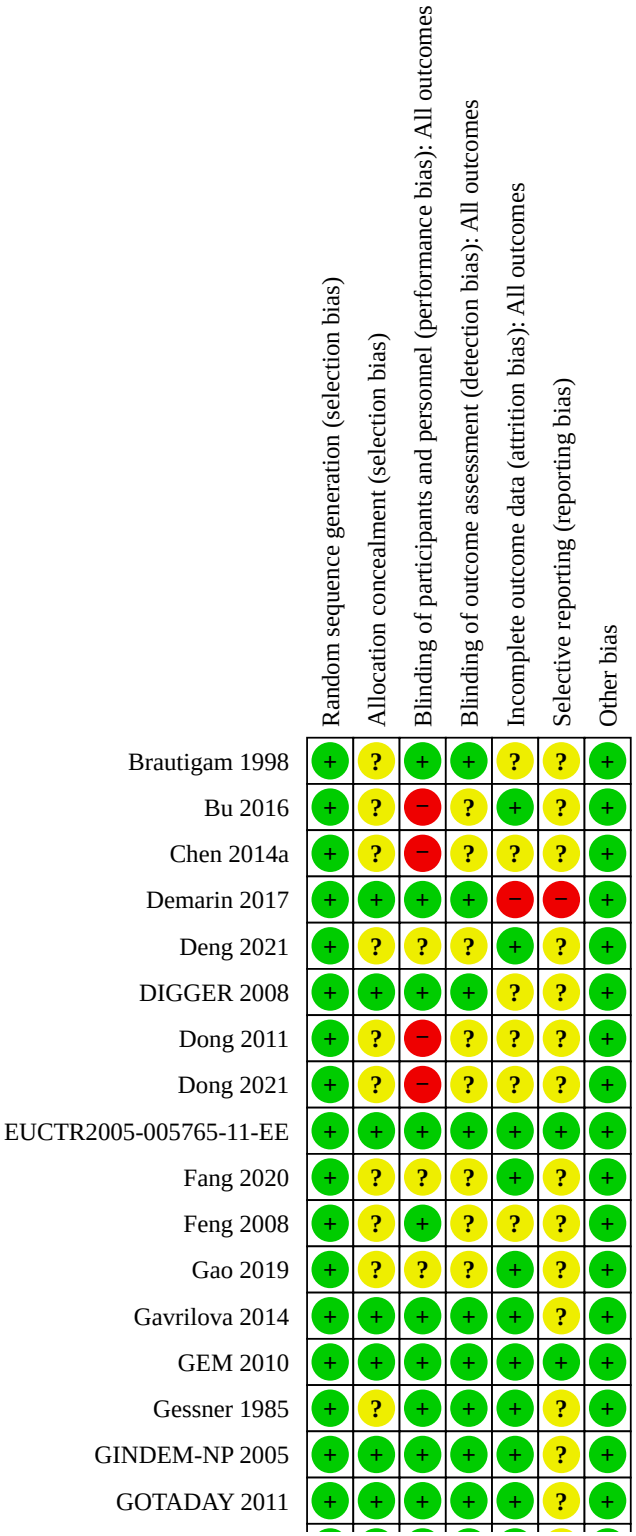



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**Figure 3. (Continued)**

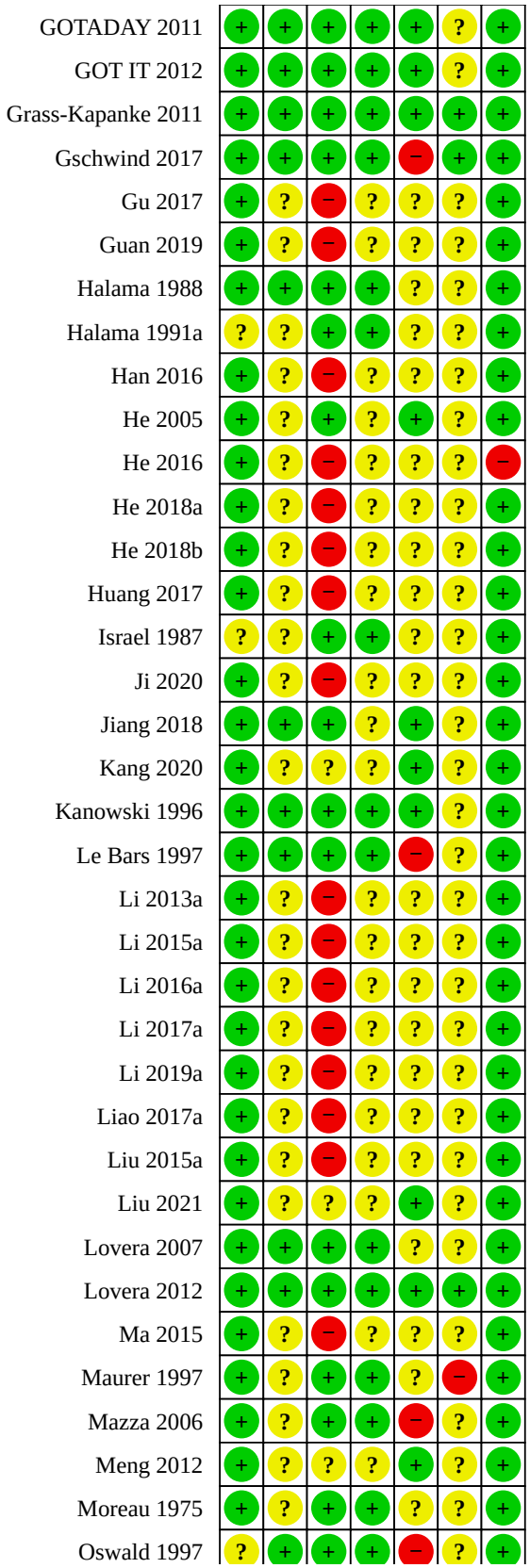



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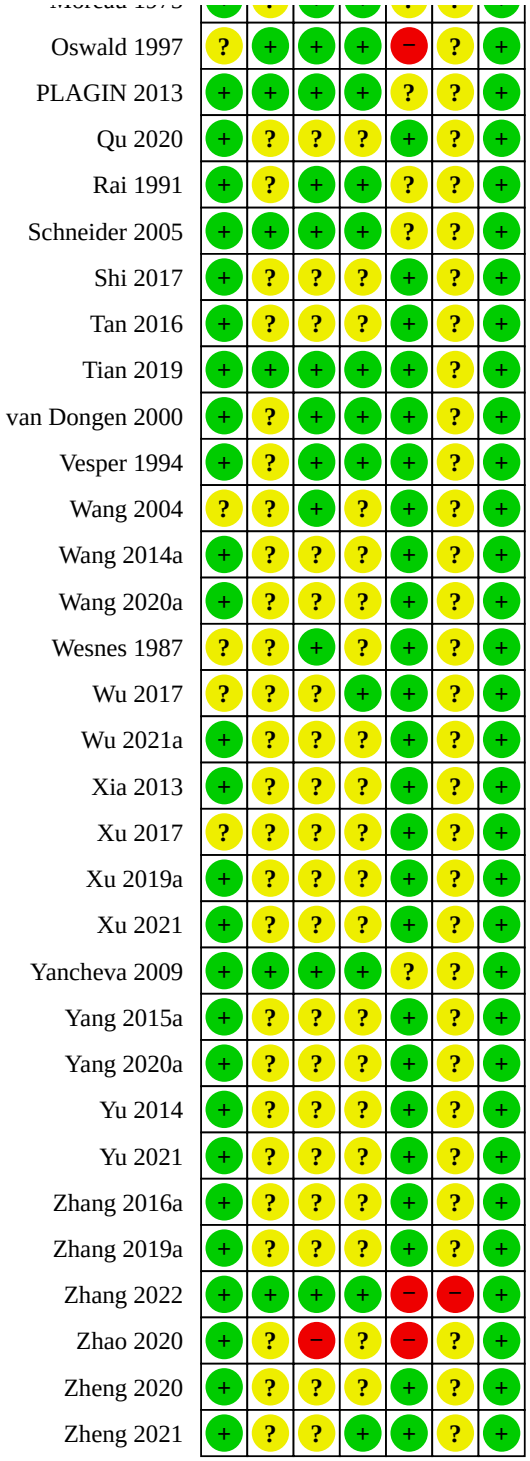
**Figure 3. (Continued)**




### Allocation

We considered 75 studies had used an adequate method of random sequence generation (low risk of bias). Four studies likely used adequate sequence generation, but the report was not fully explicit (Halama 1991a; Israel 1987; Oswald 1997; Wesnes 1987), and three studies described an appropriate method, but we felt the risk of misuse of the method was high (Wang 2004; Wu 2017; Xu 2017). We judged these seven studies at unclear risk of bias in this domain.

In contrast, we considered only 22 studies reported adequate allocation concealment (low risk of bias), while the remaining 60 studies provided insufficient information (unclear risk of bias).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### Blinding

We considered blinding of participants and personnel was adequate in 36 studies, unclear in 25 studies, and inadequate in 21 studies (Bu 2016; Chen 2014a; Dong 2011; Dong 2021; Gu 2017; Guan 2019; Han 2016; He 2016; He 2018b; He 2018a; Huang 2017; Ji 2020; Li 2017a; Li 2013a; Li 2015a; Li 2016a; Li 2019a; Liao 2017a; Liu 2015a; Ma 2015; Zhao 2020).

Slightly fewer than half of the studies adequately blinded outcome assessment, while the remaining studies provided insufficient information on blinding of outcome assessment (unclear risk of bias).

### Incomplete outcome data

Approximately half of the studies adequately reported outcome data. Seven studies had incomplete outcome data (Demarin 2017; Gschwind 2017; Le Bars 1997; Mazza 2006; Oswald 1997; Zhang 2022; Zhao 2020). Demarin 2017, Mazza 2006 and Oswald 1997 had high rates of loss to follow-up. Gschwind 2017 had a 28% dropout rate in the placebo group compared to only 4% in the ginkgo group. In Le Bars 1997, 50% of the EGb group completed the entire study compared with only 38% of the placebo group. Zhang 2022 had a 7% dropout rate in the ginkgo group compared to 30% in the control group. Zhao 2020 had unspecified attrition which appeared to be addressed by enrollment of additional participants. It was unclear if the rest of the studies reported all outcome data, so we judged them at unclear risk of attrition bias.

### Selective reporting

Protocols were not readily available for most studies. Therefore, insufficient information was available to make clear judgments about the risk of reporting bias. The study report of GEM 2010 stated that the investigators had administered the 3MSE and ADAS-Cog throughout, but it provided no data for these outcomes. We contacted the study authors, who shared the raw data. Therefore, we rated the study at low risk of selection bias. PLAGIN 2013 mentioned several outcomes in the Methods that were not reported in their Results (e.g. verbal fluency rest, CDT, HAM-D); however, we obtained the outcome data from the sponsor and therefore rated the risk of reporting bias as unclear. We rated three studies at high risk of reporting bias (Demarin 2017; GOTADAY 2011; Maurer 1997). Demarin 2017 did not report all the prespecified primary outcomes, and, while the protocol registration stated outcomes would be measured at six months, additional analyses were conducted and reported at three months. GOTADAY 2011 did not report all outcomes (e.g. according to one publication, TE4D was repeated at week 24, but the main study report did not mention this assessment). Maurer 1997 mentioned the TMT as a secondary outcome but reported no specific data, only mentioning that the result was nonsignificant. We rated five studies with trial registrations at low risk of reporting bias (EUCTR2005-005765-11-EE; GEM 2010; Grass-Kapanke 2011; Gschwind 2017; Lovera 2012).

### Other potential sources of bias

We judged one study to be at high risk of bias from other sources. He 2016 reported benefits for ginkgo on a scale not extracted for this review, and the data were outside the range of the reported scale. This raises concern that all data in the trial might be unreliable and biased.

## Effects of interventions

See: **Summary of findings 1** *Ginkgo biloba* versus placebo for adults with subjective cognitive impairment; **Summary of findings 2** *Ginkgo biloba* versus placebo for adults with multiple sclerosis and cognitive impairment; **Summary of findings 3** *Ginkgo biloba* versus placebo for adults with mild cognitive impairment; **Summary of findings 4** *Ginkgo biloba* versus placebo for adults with dementia

### Ginkgo for subjective cognitive impairment

Three studies with 597 participants tested ginkgo for people who reported subjective cognitive impairments but had no diagnosis of cognitive impairment or dementia (Brautigam 1998; EUCTR2005-005765-11-EE; Gessner 1985). Gessner 1985 compared ginkgo to placebo and nicergoline but contained no extractable information on outcome scales or adverse events; the other two studies compared ginkgo to placebo and randomized 537 participants. EUCTR2005-005765-11-EE met our prespecified criteria for overall low risk of bias. In Brautigam 1998, participants had memory or concentration complaints but did not have dementia according to the MMSE (no cutoff score given) or depression defined as a BDI score greater than 21. In EUCTR2005-005765-11-EE, all participants had subjective cognitive impairments for at least three months, together with an MMSE score above 23 and no indication of dementia. The issue of MCI was not explicitly addressed in either trial, and although an MMSE of 23 points or lower is commonly used to indicate dementia, the MMSE is not considered sensitive to milder cognitive impairment (Nyenhuis 2023). It is possible that participants in EUCTR2005-005765-11-EE had undiagnosed MCI and participants in Brautigam 1998 had undiagnosed MCI or mild dementia. Therefore, while both studies met our inclusion criterion of no diagnosed MCI or dementia, we downgraded the certainty of the evidence due to uncertainty about the true cognitive status of the participants.

#### *Ginkgo versus placebo*

Brautigam 1998 tested Geriaforce, a proprietary tincture of ginkgo, at doses of 5.6 mL and 2.8 mL, for 24 weeks. There was no evidence of a difference between Geriaforce doses in the trial, and we combined both doses for our analyses. EUCTR2005-005765-11-EE tested EGb 761 at a dose of 240 mg for 12 weeks. Both studies reported memory and executive function outcomes, Brautigam 1998 reported physician assessment of participant memory and concentration complaints, and EUCTR2005-005765-11-EE reported results for anxiety and depression. Because Geriaforce is known to provide markedly lower levels of flavone glycosides and terpene lactones (ginkgolides and bilobalide) than EGb 761, we did not consider the two trials to be testing a sufficiently similar intervention, and we analyzed them separately. Find GRADE assessments for primary outcomes in Summary of findings 1, along with all other outcomes in Appendix 2.

##### Global clinical status

Brautigam 1998 reported the physician assessment of overall status of memory and concentration complaints at three and six months on a five-point Likert scale (1 = no complaints, 5 = very frequent complaints). It is uncertain whether there is a difference on the Likert scale between Geriaforce and placebo at three months (MD 0.04, 95% CI −0.40 to 0.48; P = 0.86; 1 study, 197 participants; very low-certainty evidence; Analysis 1.1) and six months (MD 0.00,


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95% CI −0.33 to 0.33; P = 1.00; 1 study, 197 participants; very low-certainty evidence; Analysis 1.2). We downgraded the evidence certainty for serious risk of bias, serious indirectness, and serious imprecision.

#### Global cognitive function

Neither trial reported global cognitive function outcomes.

#### Ability to perform activities of daily living

Neither trial reported ADL outcomes.

#### Adverse events (all)

Brautigam 1998 reported side effects, primarily gastrointestinal upset and dizziness, in each treatment group, and stated that there were no differences in the number of these side effects between treatment groups at six months. However, the number of participants with adverse events in each group was not given. Results from EUCTR2005-005765-11-EE suggest that the risk of any adverse events may be higher with EGb 761 than with placebo at three months (RR 1.33, 95% CI 0.92 to 1.93; P = 0.13; 1 study, 304 participants, 84 events; low-certainty evidence; Analysis 1.3); however, the CI included the possibility of no effect. We downgraded the evidence certainty for very serious imprecision.

#### Serious adverse events

Brautigam 1998 did not report whether any adverse events at six months were serious. EUCTR2005-005765-11-EE reported one serious adverse event at three months, which occurred in the placebo group. It is uncertain whether there is a difference between ginkgo and placebo in the risk of serious adverse events (RR 0.33, 95% CI 0.01 to 8.12; P = 0.50; 1 study, 304 participants, 1 event; very low-certainty evidence; Analysis 1.4). The CI included the possibility of important effects and a null effect, and there was only one reported serious adverse event. Therefore, we downgraded the evidence certainty by three levels for extremely serious imprecision.

#### Memory

Brautigam 1998 measured memory at three and six months on the Benton, the Rey 1, and the Rey 2. We combined these measures following the model proposed in Borenstein 2009, and using the Pearson product-moment correlations given in Table 4 of the study report. Because this does not reflect a single scale, we reported the SMD. It is uncertain whether there is a difference between Geriaforce and placebo for memory at three months (SMD 0.01, 95% CI −0.28 to 0.30; P = 0.95; 1 study, 197 participants; very low-certainty evidence; Analysis 1.5) or six months (SMD 0.01, 95% CI −0.28 to 0.30; P = 0.95; 1 study, 197 participants; very low-certainty evidence; Analysis 1.6). We downgraded the evidence certainty for serious risk of bias, serious indirectness, and serious imprecision.

EUCTR2005-005765-11-EE measured memory at three months on the FEAG. There may be little or no difference between EGb 761 and placebo for memory at three months (MD 0.04, 95% CI −0.18 to 0.26; P = 0.72; 1 study, 296 participants; low-certainty evidence; Analysis 1.7). We downgraded the evidence certainty for serious indirectness and serious imprecision.

#### Executive function

Brautigam 1998 measured executive function at three and six months on the EMCT. It is uncertain if there is any difference between Geriaforce and placebo for executive function at three months (MD 0.05, 95% CI −1.06 to 1.16; P = 0.93; 1 study, 197 participants; very low-certainty evidence; Analysis 1.8) or six months (MD 0.09, 95% CI −0.83 to 1.01; P = 0.85; 1 study, 197 participants; very low-certainty evidence; Analysis 1.9). We downgraded the evidence certainty for serious risk of bias, serious indirectness, and serious imprecision.

EUCTR2005-005765-11-EE measured executive function at three months on the TMT B. There may be little or no difference between EGb 761 and placebo for executive function at three months (MD −1.10, 95% CI −5.78 to 3.58; P = 0.65; 1 study, 296 participants; low-certainty evidence; Analysis 1.10). We downgraded the evidence certainty for serious indirectness and serious imprecision.

#### Quality of life

Neither trial reported quality of life outcomes.

#### Neuropsychiatric outcomes

#### Anxiety

At three months, EUCTR2005-005765-11-EE measured anxiety using the state subscale of the STAI (STAI-X1). There may be little or no difference between EGb 761 and placebo for anxiety at three months (MD 0.40, 95% CI −1.69 to 2.49; P = 0.71; 1 study, 296 participants; low-certainty evidence; Analysis 1.11). We downgraded the evidence certainty for serious indirectness and serious imprecision.

#### Depression

Brautigam 1998 reported using the BDI at each study examination but provided no outcome data. At three months, EUCTR2005-005765-11-EE measured depression using the *Depression Skala* (version D-S'). There may be little or no difference between EGb 761 and placebo for depression at three months (MD 0.20, 95% CI −1.09 to 1.49; P = 0.76; 1 study, 296 participants; low-certainty evidence; Analysis 1.12). We downgraded the evidence certainty for serious indirectness and serious imprecision.

### Ginkgo for multiple sclerosis and cognitive impairment

Two studies, including 164 participants with MS tested whether ginkgo could improve cognition in this population (Lovera 2007; Lovera 2012). Lovera 2012 met our prespecified criteria for overall low risk of bias.

Both studies compared ginkgo to placebo and followed participants for three months. No studies compared ginkgo to no treatment or another treatment, or tested ginkgo as an adjunct to another treatment.

#### *Ginkgo versus placebo*

Participants in both trials had an MS diagnosis based on McDonald's criteria (McDonald 2001). They also met study criteria for cognitive impairment: a score between 0.5 and 2.5 standard deviations (SDs) below the normative mean on the PASAT or the CVLT-II (Lovera 2007), or at least 1 SD below the normative mean of the Stroop, CVLT-II, COWAT, or PASAT (Lovera 2012). The ginkgo product in the two studies was not identical but provided similar amounts of active ingredients: 240 mg of a product containing 31.4% flavonol-O-glycosides and 4.5% terpenoids by weight (Lovera 2007), and 240 mg of EGb 761 containing 29.7 mg of flavoglycosides and 7.3 mg of


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terpene lactones (Lovera 2012). We analyzed the studies together where possible. Find GRADE assessments for primary outcomes in Summary of findings 2, along with all other outcomes in Appendix 3.

#### Global clinical status

Neither study reported global clinical status outcomes.

#### Global cognitive function

Both trials assessed cognition at three months on the PDQ, a self-report instrument often used to measure cognitive function in MS. There is probably little or no difference in cognitive function at three months with ginkgo versus placebo (MD −0.09, 95% CI −0.41 to 0.22; P = 0.74; $I^2$ = 0%; 2 studies, 152 participants; moderate-certainty evidence; Analysis 2.1). We downgraded the evidence certainty for serious imprecision. When we carried out a sensitivity analysis by risk of bias, including only Lovera 2012, the findings were similar (MD −0.12, 95% CI −0.48 to 0.23; P = 0.50, 1 study, 120 participants; moderate-certainty evidence; see data for Lovera 2012 in Analysis 2.1). We downgraded the evidence certainty for serious imprecision.

#### Ability to perform activities of daily living

Neither study reported ADL outcomes.

#### Adverse events (all)

Neither trial provided the total number of participants in each group experiencing any adverse events at three months. Lovera 2007 stated that one participant in the ginkgo group had constipation that might have been related to the treatment. Lovera 2012 reported that both groups had a similar incidence of MS relapses (2/61 in the ginkgo group and 3/59 in the placebo group), and that while urinary tract infections, dyspepsia, flu-like symptoms, back pain, infective conjunctivitis, headache, and worsening Expanded Disability Status Scale (EDSS) scores were more common in the ginkgo group, this difference was not statistically significant.

#### Serious adverse events

Lovera 2007 stated that no serious adverse events occurred over three months. Lovera 2012 reported that two participants in the ginkgo group experienced serious adverse events (severe depression and a myocardial infarction), but they were probably unrelated to the intervention.

#### Memory

Both trials tested memory with the CVLT-II at three months. We were unable to combine the data because Lovera 2007 reported adjusted means and Lovera 2012 reported adjusted Z-scores. Based on information from Lovera 2007, it is uncertain whether there is a difference between ginkgo and placebo for memory (MD −0.38, 95% CI −1.01 to 0.25; P = 0.24; 1 study, 39 participants; very low-certainty evidence; Analysis 2.2). We downgraded the evidence certainty for serious risk of bias and extremely serious imprecision. Information from Lovera 2012 suggests there is probably little or no difference between ginkgo and placebo for memory (MD 0.00, 95% CI −0.36 to 0.36; P = 1.00; 1 study, 120 participants; moderate-certainty evidence; Analysis 2.3). We downgraded the evidence certainty for serious imprecision.

#### Executive function

Both trials measured executive function at three months on the PASAT, COWAT, and Stroop. Lovera 2007 also used the SDMT. We combined the scores from different instruments in each trial to calculate SMDs for composite executive function. We were unable to combine data from the two trials because Lovera 2007 reported adjusted means and Lovera 2012 reported adjusted Z-scores. Based on Lovera 2007, it is uncertain whether there is a difference between ginkgo and placebo for executive function (SMD −0.08, 95% CI −0.71 to 0.55; P = 0.80; 1 study, 39 participants; very low-certainty evidence; Analysis 2.4). We downgraded the evidence certainty for serious risk of bias and extremely serious imprecision. Information from Lovera 2012 suggests there is probably little or no difference (SMD −0.11, 95% CI −0.47 to 0.25; P = 0.55; 1 study, 120 participants; moderate-certainty evidence; Analysis 2.5). We downgraded the evidence certainty for serious imprecision.

#### Quality of life

Neither study reported quality of life outcomes.

#### Neuropsychiatric outcomes

#### Depression

Lovera 2012 measured depression at three months on the BDI-II. There may be little or no difference between ginkgo and placebo for depression at three months (MD −1.30, 95% CI −3.88 to 1.28; P = 0.32; 1 study, 120 participants; low-certainty evidence; Analysis 2.6). We downgraded the evidence certainty for very serious imprecision.

### Ginkgo for mild cognitive impairment

Forty-two studies with 4630 randomized participants tested ginkgo for people with MCI (Bu 2016; Demarin 2017; Deng 2021; Dong 2011; Feng 2008; Gavrilova 2014; GEM 2010; Grass-Kapanke 2011; Gschwind 2017; Gu 2017; Halama 1988; Han 2016; He 2016; He 2018b; He 2018a; He 2005; Israel 1987; Jiang 2018; Li 2013a; Li 2015a; Li 2016a; Li 2019a; Liu 2015a; Moreau 1975; Qu 2020; Rai 1991; Shi 2017; Tan 2016; Tian 2019; van Dongen 2000; Vesper 1994; Wang 2020a; Wang 2004; Xia 2013; Xu 2021; Yang 2020a; Yang 2015a; Yu 2021; Zhang 2022; Zhao 2020; Zhang 2019a; Zheng 2021). Participants in van Dongen 2000 were diagnosed with either dementia (30%) or age-associated memory impairment (70%); data were not available by diagnostic subgroups, but since most participants did not have dementia, we included the study in the MCI analyses. Six studies provided no usable data for our outcomes (Feng 2008; He 2005; Israel 1987; Moreau 1975; Rai 1991; Vesper 1994). The remaining 36 studies randomized 4278 participants. GEM 2010 and Grass-Kapanke 2011 met our prespecified criteria for low overall risk of bias.

Twelve studies compared ginkgo to placebo, and no studies compared ginkgo to no treatment. Three studies compared ginkgo to conventional pharmacological treatment, seven studies compared ginkgo to Chinese herbal medicine or acupuncture, and 22 studies tested ginkgo as an adjunct to another treatment.

#### *Ginkgo versus placebo*

Twelve studies (1913 participants) compared ginkgo to placebo and followed participants for three to 12 months or beyond (Demarin 2017; Gavrilova 2014; GEM 2010; Grass-Kapanke 2011; Gschwind 2017; Halama 1988; Israel 1987; Moreau 1975; Rai 1991; Tian 2019; van Dongen 2000; Vesper 1994). Four of these studies provided


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no usable data for our outcomes (Israel 1987; Moreau 1975; Rai 1991; Vesper 1994), leaving eight studies with 1594 participants for analysis.

Participants in Demarin 2017 and Halama 1988 were diagnosed with impairment of vascular origin, while participants in other studies were diagnosed with other types of impairment, or with impairment of mixed or unclear etiology. All studies with extractable data tested either LI 1370 (Gschwind 2017 used 240 mg/day) or an EGb 761 product (Gavrilova 2014 and Grass-Kapanke 2011 used 240 mg/day, while Demarin 2017, Halama 1988, and Tian 2019 used < 240 mg/day). Demarin 2017 tested EGb 761 at doses of 60 mg and 120 mg against placebo and reported no evidence of a difference between doses, so we combined the ginkgo intervention arms for our analyses. van Dongen 2000 tested EGb 761 at doses of 160 mg and 240 mg against placebo. We used the combined ginkgo data for our primary analyses and planned to use the individual study arm data (when available and when the total number of comparisons was at least 10) for subgroup analyses by EGb 761 dose. However, all analyses had fewer than 10 studies or comparison arms. See Table 3 for more details on diagnostic criteria and ginkgo interventions for all studies. Find GRADE assessments for primary outcomes in Summary of findings 3, along with all other outcomes in Appendix 4.

#### Global clinical status

Demarin 2017 measured global status on the SCAG and the Clinical Global Impression of Change (CGIC) at three and six months, GEM 2010 measured global status on the CDR at six and 12 months, Tian 2019 measured change in global status on the CDR – Sum of Boxes (CDR-SB) at 12 months, and van Dongen 2000 measured change in global status on the SCAG and global status on the CGIC at six months. When both the SCAG and the CGIC were appropriate for meta-analysis, we selected the SCAG as a more detailed assessment of global status.

At three months, it is uncertain whether there is a difference between ginkgo and placebo for global clinical status measured on the SCAG (MD 4.20, 95% CI −0.42 to 8.82; P = 0.07; 1 study, 58 participants; very low-certainty evidence; Analysis 3.1). We downgraded the evidence certainty for very serious risk of bias and very serious imprecision. At six months, there is probably little or no difference between ginkgo and placebo for global clinical status (SMD −0.12, 95% CI −0.28 to 0.04; P = 0.13; $I^2$ = 0%; 3 studies, 631 participants; moderate-certainty evidence; Analysis 3.2). We downgraded the evidence certainty for serious risk of bias. When we included only the study with low overall risk of bias in a sensitivity analysis (GEM 2010), the results showed little or no difference in global clinical status measured on the CDR at six months (MD −0.04, 95% CI −0.08 to 0.00; P = 0.08; 1 study, 450 participants; high-certainty evidence; Analysis 3.3). Data from GEM 2010 and Tian 2019 indicate that there is probably a slight benefit with ginkgo at 12 months (SMD −0.17, 95% CI −0.33 to −0.01; P = 0.04; $I^2$ = 0%; 2 studies, 604 participants; moderate-certainty evidence; Analysis 3.4). We downgraded the certainty of evidence for risk of bias. When we included only the study with low overall risk of bias in a sensitivity analysis (GEM 2010), the results showed little or no difference in global clinical status measured on the CDR at 12 months (MD −0.04, 95% CI −0.09 to 0.01; P = 0.10; 1 study, 430 participants; high-certainty evidence; Analysis 3.5).

#### Global cognitive function

Demarin 2017 measured cognition at three and six months on the MDRS and the MMSE, GEM 2010 measured cognition at six and 12 months on the ADAS-Cog and the 3MSE, Tian 2019 measured cognition at 12 months on the ADAS-Cog and the MMSE, and van Dongen 2000 measured change in cognition on the SKT at six months. We selected the ADAS-Cog and the MDRS for analyses when available. We used the MDRS at three months. At six months, we combined MDRS endpoints for Demarin 2017 and ADAS-Cog endpoints for GEM 2010, but we could not include SKT change scores from van Dongen 2000, which we analyzed separately. At 12 months, we combined the ADAS-Cog endpoints from GEM 2010 and the ADAS-Cog changes from Tian 2019.

It is uncertain whether there is any difference between ginkgo and placebo for cognition measured on the MDRS at three months (MD −0.20, 95% CI −7.44 to 7.04; P = 0.96; 1 study, 58 participants; very low-certainty evidence; Analysis 3.6). We downgraded the evidence certainty for very serious risk of bias and very serious imprecision. At six months, there is probably little or no difference between ginkgo and placebo for cognition (SMD −0.02, 95% CI −0.20 to 0.15; P = 0.79; $I^2$ = 0%; 2 studies, 508 participants; moderate-certainty evidence; Analysis 3.7). We downgraded the evidence certainty for serious risk of bias. When we included only the study at low risk of overall bias in a sensitivity analysis (GEM 2010), the results showed little or no difference between ginkgo and placebo for global cognitive function measured on the ADAS-Cog at six months (MD −0.10, 95% CI −0.71 to 0.51; P = 0.75; 1 study, 450 participants; high-certainty evidence; Analysis 3.8). An analysis using change scores at six months was consistent in showing there may be little or no difference in change in cognitive function measured on the SKT with ginkgo versus placebo (MD 0.40, 95% CI −1.04 to 1.84; P = 0.59; 1 study, 123 participants; low-certainty evidence; Analysis 3.9). We downgraded the evidence certainty for some risk of bias and indirectness (one level in total) and serious imprecision. At 12 months, there may be little or no difference in cognition measured on the ADAS-Cog with ginkgo versus placebo (MD −1.95, 95% CI −5.29 to 1.39; P = 0.25; $I^2$ = 97%; 2 studies, 604 participants; low-certainty evidence; Analysis 3.10). We downgraded the evidence certainty for serious inconsistency and serious imprecision. When we included only the study at low risk of overall bias in a sensitivity analysis (GEM 2010), the results suggested little or no effect of ginkgo versus placebo on cognition measured on the ADAS-Cog (MD −0.27, 95% CI −0.95 to 0.41; P = 0.43; 1 study, 430 participants; high-certainty evidence; Analysis 3.11).

#### Ability to perform activities of daily living

van Dongen 2000 measured ADLs at three and six months on the self-reported NAI-NAA and the staff-assessed NAI-NAA. When data were available for both self-reported and staff-assessed scores, we chose the evaluations by staff for analysis, to be consistent with other studies in the review. GEM 2010 measured IADLs at six months and 12 months, and Tian 2019 measured ADLs on the ADCS-ADL-MCI-24 at 12 months. We could not combine data from van Dongen 2000 and GEM 2010 at six months or from Tian 2019 and GEM 2010 at 12 months, because the three studies used different scales, and van Dongen 2000 and Tian 2019 reported changes, while GEM 2010 reported endpoint measures.

At three months, there may be little or no improvement on the NAI-NAA with ginkgo versus placebo (MD −1.35, 95% CI −2.88 to 0.18; P = 0.08; 1 study, 214 participants; low-certainty evidence;


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Analysis 3.12). We downgraded the evidence certainty for some risk of bias and indirectness (one level in total) and for serious imprecision. At six months, there is probably little or no difference in IADL endpoint scores between people receiving ginkgo and those receiving placebo (MD −0.05, 95% CI −0.29 to 0.19; P = 0.68; 1 study, 350 participants; moderate-certainty evidence; Analysis 3.13). We downgraded the evidence certainty for serious imprecision. There may be no difference between ginkgo and placebo in NAI-NAA change scores at six months (MD 0.00, 95% CI −1.94 to 1.94; P = 0.1.00; 1 study, 123 participants; low-certainty evidence; Analysis 3.14). We downgraded the evidence certainty for some risk of bias and indirectness (one level in total) and for serious imprecision. At 12 months, there is probably little or no difference in IADL endpoint scores between people receiving ginkgo and those receiving placebo (MD −0.07, 95% CI −0.31 to 0.17; P = 0.57; 1 study, 338 participants; moderate-certainty evidence; Analysis 3.15). We downgraded the evidence certainty for serious imprecision. However, changes on the ADCS-ADL-MCI-24 may be slightly better among people receiving ginkgo (MD 1.63, 95% CI 0.07 to 3.19; P = 0.04; 1 study, 174 participants; low-certainty evidence; Analysis 3.16). We downgraded the evidence certainty for serious risk of bias and serious imprecision.

#### Adverse events (all)

One study stated that no adverse events occurred (Vesper 1994), and seven studies reported the total number of participants experiencing adverse events (Demarin 2017; Gavrilova 2014; Grass-Kapanke 2011; Gschwind 2017; Halama 1988; Tian 2019; van Dongen 2000). There may be little or no difference at up to 12 months of follow-up in the risk of adverse events with ginkgo versus placebo (RR 0.98, 95% CI 0.77 to 1.24; P = 0.86; $I^2$= 58%; 7 studies, 991 participants, 379 events; low-certainty evidence; Analysis 3.17). We downgraded the evidence certainty for serious risk of bias and serious inconsistency. When we included only the study at low overall risk of bias in a sensitivity analysis (Grass-Kapanke 2011), the effect estimate was similar (RR 0.99, 95% CI 0.58 to 1.68; moderate-certainty evidence; see data for Grass-Kapanke 2011 in Analysis 3.17). We downgraded the evidence certainty for serious imprecision.

#### Serious adverse events

Two studies specified that no serious adverse events occurred during the trials (Gavrilova 2014; Grass-Kapanke 2011). Three studies reported numbers of serious adverse events at six months (GEM 2010; Gschwind 2017; van Dongen 2000), and one study reported the number of serious adverse events from six months to one year (GEM 2010). To avoid double-counting, we reported data separately for six months and for six months to one year.

There is little or no difference between ginkgo and placebo in the risk of serious adverse events at six months (RR 0.95, 95% CI 0.82 to 1.09; P = 0.44; 3 studies, 714 participants, 327 events; $I^2$= 0%; high-certainty evidence; Analysis 3.18), and between six months and one year (RR 0.96, 95% CI 0.83 to 1.11; P = 0.62; 1 study, 430 participants, 272 events; high-certainty evidence; Analysis 3.19).

#### Memory

Grass-Kapanke 2011 evaluated memory using the WMS III Faces I, WMS III Faces II, TT-Immediate, and TT-Delayed at three months; van Dongen 2000 used the digit span and the verbal learning test at three and six months; and Tian 2019 reported the AMIPB-DSR at 12 months. We combined the multiple memory assessments in Grass-Kapanke 2011 and van Dongen 2000 into composite measures for memory for each study and reported the SMD.

At three months, there is probably little or no difference between ginkgo and placebo for memory (SMD 0.06, 95% CI −0.12 to 0.25; P = 0.50; $I^2$ = 0%; 2 studies, 510 participants; moderate-certainty evidence; Analysis 3.20). We downgraded the evidence certainty by one level for some risk of bias and indirectness (one level in total). When we included only the study at low risk of bias in a sensitivity analysis (Grass-Kapanke 2011), the results were consistent in showing there is probably little or no effect of ginkgo on the composite memory outcome (SMD 0.13, 95% CI −0.10 to 0.35; P = 0.28; 1 study, 296 participants; moderate-certainty evidence; see data for Grass-Kapanke 2011 in Analysis 3.20). We downgraded the evidence certainty for serious imprecision. At six months, there may be little or no difference between ginkgo and placebo for a composite memory outcome (SMD 0.08, 95% CI −0.29 to 0.45; P = 0.67; 1 study, 123 participants; low-certainty evidence; Analysis 3.21). We downgraded the evidence certainty for some risk of bias and indirectness (one level in total) and for serious imprecision. At 12 months, there may be little or no difference between ginkgo and placebo for memory measured on the AMIPB-DSR (MD 1.17, 95% CI −0.39 to 2.73; P = 0.14; 1 study, 174 participants; low-certainty evidence; Analysis 3.22). We downgraded the evidence certainty for some risk of bias and very serious imprecision.

#### Executive function

Grass-Kapanke 2011 assessed changes in executive function on the WTS-ALS and the WTS-DT at three months, and Gavrilova 2014 collected TMT B outcomes at six months. We combined the two executive function assessments in Grass-Kapanke 2011 into a summary measure for executive function.

Executive function may be slightly better at three months with ginkgo versus placebo (SMD 0.23, 95% CI 0.00 to −0.46; P = 0.05; 1 study, 296 participants; low-certainty evidence; Analysis 3.23). We downgraded the evidence certainty for very serious imprecision. At six months, the executive function measured on the TMT B may have improved by about 12 seconds with ginkgo versus placebo (MD −12.50, 95% CI −24.29 to −0.71; P = 0.04; 1 study, 159 participants; low-certainty evidence; Analysis 3.24). We downgraded the evidence certainty for some risk of bias and serious imprecision.

#### Quality of life

Grass-Kapanke 2011 assessed changes in SF-36 mental and physical quality of life at three months. At three months, there may be little or no difference between ginkgo and placebo for mental quality of life (MD 2.07, 95% CI −1.88 to 6.02; P = 0.30; 1 study, 296 participants; low-certainty evidence; Analysis 3.25) or physical quality of life (MD 3.32, 95% CI −0.39 to 7.03; P = 0.08; 1 study, 296 participants; low-certainty evidence; Analysis 3.26). Both estimates were downgraded for very serious imprecision.

#### Neuropsychiatric outcomes

##### Anxiety

Gavrilova 2014 measured state anxiety on the STAI-X1 at six months. There may be a slightly greater reduction in state anxiety with ginkgo versus placebo at six months (MD −2.80, 95% CI −5.16 to −0.44; P = 0.02; 1 study; 159 participants; low-certainty evidence;


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Analysis 3.27). We downgraded the evidence certainty for serious risk of bias and serious imprecision.

#### Depression

Three studies assessed depression. van Dongen 2000 measured changes on the GDS at three and six months, Gavrilova 2014 measured changes on the GDS at six months, and GEM 2010 measured depression symptoms on the CESD at six and 12 months. As we could not combine changes in the GDS with endpoints on the CESD, we reported changes and endpoints separately at six months.

At three months, there may be little or no difference between ginkgo and placebo in changes on the GDS (MD 0.58, 95% CI −0.53 to 1.69; P = 0.31; 1 study, 214 participants; low-certainty evidence; Analysis 3.28). We downgraded the evidence certainty for some risk of bias and indirectness (one level in total) and for serious imprecision. At six months, it is uncertain whether there is a difference in changes on the GDS (MD −0.04, 95% CI −0.46 to 0.38; P = 0.86; $I^2$ = 67%; 2 studies, 282 participants; very low-certainty evidence; Analysis 3.29). We downgraded the evidence certainty for serious risk of bias, serious inconsistency, some indirectness, and serious imprecision. There is little or no difference between ginkgo and placebo for CESD endpoints at six months (MD 0.11, 95% CI −0.70 to 0.92; P = 0.79; 1 study, 450 participants; high-certainty evidence; Analysis 3.30) or 12 months (MD 0.45, 95% CI −0.40 to 1.30; P = 0.30; 1 study, 430 participants; high-certainty evidence; Analysis 3.31).

#### Mental well-being

Grass-Kapanke 2011 used the BfS' to evaluate effects on mental well-being at three months. At three months, there is probably little or no difference between ginkgo and placebo for mental well-being measured on the BfS' (MD 1.78, 95% CI −0.70 to 4.26; P = 0.16; 1 study, 296 participants; moderate-certainty evidence; Analysis 3.32). We downgraded the evidence certainty for serious imprecision.

#### Neuropsychiatric Inventory

Gavrilova 2014 measured neuropsychiatric symptoms on the NPI at six months. There may be little or no difference between Gingko and placebo for NPI score at six months (MD −1.50, 95% CI −3.01 to 0.01; P = 0.05; 1 study; 159 participants; low-certainty evidence; Analysis 3.33). We downgraded the evidence certainty for some risk of bias and for very serious imprecision.

### *Ginkgo versus conventional medications*

Three studies including 266 participants with vascular cognitive impairment compared ginkgo to another medication for MCI (He 2016; Tan 2016; Yu 2021). He 2016 compared ginkgo to donepezil, Tan 2016 compared ginkgo to nimodipine, and Yu 2021 compared ginkgo to butylphthalide. Nimodipine is not commonly used in the West but is considered to be effective for VD in China (Yang 2022). Two studies (Tan 2016; Yu 2021) used EGb 761 and one study (Tan 2016) used EGb 761 at > 200 mg/day. Find GRADE assessments for all outcomes in Appendix 5.

#### Global clinical status

No studies reported continuous measures of global clinical status.

#### Global cognitive function

All three studies measured global cognitive function. He 2016 used the MMSE and MoCA at three months, Yu 2021 used the MoCA at three months, and Tan 2016 used the MMSE and MoCA at six months. We considered the MoCA to be a more detailed assessment of cognitive status than the MMSE and chose it for all analyses.

It is uncertain whether there is a difference between ginkgo and butylphthalide for cognition measured on the MoCA at three months (MD −3.16, 95% CI −4.55 to −1.77; P < 0.001; 1 study, 46 participants; very low-certainty evidence; Analysis 4.1), between ginkgo and donepezil for cognition measured on the MoCA at three months (MD −3.70, 95% CI −5.11 to −2.29; P < 0.001; 1 study, 100 participants; very low-certainty evidence; Analysis 4.2), or between ginkgo and nimodipine for cognition measured on the MoCA at six months (MD 0.40, 95% CI −1.11 to 1.91; P = 0.60; 1 study, 80 participants; very low-certainty evidence; Analysis 4.3). We downgraded the evidence certainty in all three analyses for serious or very serious risk of bias and for serious or very serious imprecision.

#### Ability to perform activities of daily living

Yu 2021 measured ADLs on the Lawton IADL scale, while He 2016 and Tan 2016 used unspecified continuous scales (with higher scores indicating better outcomes).

It is uncertain whether there is a difference on the Lawton IADL scale between ginkgo and butylphthalide at three months (MD −12.38, 95% CI −15.76 to −9.00; P < 0.001; 1 study, 46 participants; very low-certainty evidence; Analysis 4.4), on a 100-point scale between ginkgo and donepezil at three months (MD 5.40, 95% CI 1.19 to 9.61; P = 0.01; 1 study, 100 participants; very low-certainty evidence; Analysis 4.5), or on a 100-point scale between ginkgo and nimodipine at six months (MD 1.90, 95% CI −2.59 to 6.39; P = 0.41; 1 study, 80 participants; very low-certainty evidence; Analysis 4.6). We downgraded the evidence certainty in all three analyses for serious or very serious risk of bias and for serious or very serious imprecision.

#### Adverse events (all)

No studies reported all adverse events.

#### Serious adverse events

No studies reported serious adverse events.

#### Memory

He 2016 measured memory on the WMS. It is uncertain whether there is a difference between ginkgo and donepezil for memory at three months (MD −14.30, 95% CI −20.07 to −8.53; P < 0.001; 1 study, 100 participants; very low-certainty evidence; Analysis 4.7). We downgraded the evidence certainty for very serious risk of bias and serious imprecision.

#### Executive function

No studies reported executive function.

#### Quality of life

No studies reported quality of life.


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#### Neuropsychiatric outcomes

No studies reported neuropsychiatric outcomes.

### *Ginkgo versus Chinese herbal medicine or acupuncture*

Seven studies randomizing 769 participants tested ginkgo against Chinese herbal medicines (Feng 2008; He 2005; Tan 2016 Tian 2019; Wang 2004; Yang 2015a; Zhang 2022). The herbal medicines studied were Bu Shen Yi Nao, Compound xueshuantong capsule, Guilingji capsules, Jianpi Tianjing, Jiawei Wuzi Yanzong Particle, Qinggongshoutao, and Yi Zhi Ling. One study with 60 participants tested ginkgo against acupuncture (Zheng 2021). All studies were conducted in China. Participants in three trials had vascular impairment (Tan 2016; Yang 2015a; Zhang 2022). Six trials either clearly stated they used EGb 761 or provided information that indicated the product was EGb 761 (Feng 2008; He 2005; Tan 2016; Tian 2019; Wang 2004; Zheng 2021). The dose was lower than 200 mg/day in one trial (Tian 2019), above 200 mg/day in two trials (He 2005; Tan 2016), and reported as 28.8 g/day in two trials (Feng 2008; Wang 2004). The dose in Zheng 2021 was not stated. See Table 3 for a description of the type of and diagnostic criteria for cognitive impairment for each study, as well as a description of the ginkgo and comparator interventions. Two trials provided no usable data for our outcomes (Feng 2008; He 2005), leaving six studies with 736 participants comparing ginkgo to herbal medicine or acupuncture. Find GRADE assessments for all outcomes in Appendix 6.

#### Global clinical status

No studies reported continuous measures of global clinical status.

#### Global cognitive function

Five studies measured cognition at three, six, or 12 months using one or more of the MMSE, MoCA, or ADAS-Cog (Tan 2016; Tian 2019; Yang 2015a; Zhang 2022; Zheng 2021). We used the ADAS-Cog when available and preferred the MoCA to the MMSE.

At three months, it is uncertain whether there is a difference between ginkgo and acupuncture for cognition measured on the MoCA (MD −1.62, 95% CI −2.36 to −0.88; P < 0.001; 1 study, 57 participants; very low-certainty evidence; Analysis 5.1), between ginkgo and Guilingji capsule for cognition measured on the ADAS-Cog (MD −0.06, 95% CI −3.55 to 3.43; P = 0.97; 1 study, 82 participants; very low-certainty evidence; Analysis 5.2), between ginkgo and Yi Zhi Ling for cognition measured on the MMSE (MD −2.20, 95% CI −3.24 to −1.16; P < 0.001; 1 study, 66 participants; very low-certainty evidence; Analysis 5.3), or between ginkgo and Compound xueshuantong capsule for cognition measured on the MoCA (MD −3.70, 95% CI −5.21 to −2.19; P < 0.001; 1 study, 80 participants; very low-certainty evidence; Analysis 5.4). At six months, it is uncertain whether there is a difference between ginkgo and Guilingji capsule for cognition measured on the ADAS-Cog (MD 2.00, 95% CI −0.94 to 4.94; P = 0.18; 1 study, 82 participants; very low-certainty evidence; Analysis 5.5). For all estimates at three and six months, we downgraded the evidence certainty for very serious risk of bias and serious imprecision. There may be no difference between ginkgo and Qinggongshoutao for cognition measured on the ADAS-Cog at 12 months (MD −0.33, 95% CI −1.15 to 0.49; P = 0.43; 1 study, 278 participants; low-certainty evidence; Analysis 5.6). We downgraded the evidence certainty for serious risk of bias and serious imprecision.

#### Ability to perform activities of daily living

Tan 2016 measured ADLs at six months using an unspecified 100-point scale on which higher scores are better. It is uncertain whether ginkgo is worse than Compound xueshuantong capsule for ADLs at six months (MD −9.80, 95% CI −14.63 to −4.97; P < 0.001; 1 study, 80 participants; very low-certainty evidence; Analysis 5.7). We downgraded the evidence certainty for very serious risk of bias and serious imprecision.

#### Adverse events (all)

Tian 2019 reported numbers of all adverse events at 12 months. There may be little or no difference in the risk of adverse events with ginkgo versus Qinggongshoutao (RR 0.83, 95% CI 0.63 to 1.09; P = 0.17; 1 study, 278 participants, 130 events; low-certainty evidence; Analysis 5.8). We downgraded the evidence certainty for serious risk of bias and serious imprecision.

#### Serious adverse events

Tian 2019 reported six serious adverse events at the end of 12 months. It is uncertain whether there is any difference in the risk of serious adverse events with ginkgo versus Qinggongshoutao (RR 3.35, 95% CI 0.62 to 17.95; P = 0.16; 1 study, 278 participants, 6 events; very low-certainty evidence; Analysis 5.9). We downgraded the evidence certainty for extremely serious imprecision.

#### Memory

Wang 2004 reported memory on the MQ at three months. Due to very serious risk of bias and extremely serious imprecision, it is uncertain whether there is any difference between ginkgo and Jiawei Wuzi Yanzong Particle for memory at three months (MD −2.42, 95% CI −9.35 to 4.51; P = 0.49; 1 study, 43 participants; very low-certainty evidence; Analysis 5.10).

#### Executive function

No studies reported executive function.

#### Quality of life

No studies reported quality of life.

#### Neuropsychiatric outcomes

No studies reported neuropsychiatric outcomes.

### *Ginkgo plus other active treatments versus other active treatments alone*

Twenty-two studies randomizing 2192 participants compared the addition of ginkgo to a treatment regimen for MCI versus that treatment regimen alone (Bu 2016; Deng 2021; Dong 2011; Gu 2017; Han 2016; He 2016; He 2018b; He 2018a; Jiang 2018; Liu 2015a; Li 2013a; Li 2015a; Li 2016a; Li 2019a; Qu 2020; Shi 2017; Wang 2020a; Xia 2013; Xu 2021; Yang 2020a; Zhang 2019a; Zhao 2020). Seven studies added ginkgo to a basic or standard treatment that involved medications, but the reports did not provide a comprehensive description of the medications (Dong 2011; Han 2016; Jiang 2018; Li 2019a; Shi 2017; Xia 2013; Zhao 2020). Among the studies specifying a pharmacological treatment, one study added ginkgo to allopurinol and exercise (Li 2013a); one study added ginkgo to a regimen of aspirin, oral atorvastatin calcium, and donepezil (Bu 2016); one study added ginkgo to butylphthalide (Yang 2020a); six studies added ginkgo to donepezil (Deng 2021; He 2016; He 2018a; Li 2016a; Liu 2015a; Zhang 2019a); one study added


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ginkgo to mecobalamin (Qu 2020); three studies added ginkgo to nimodipine (Gu 2017; He 2018b; Li 2015a); one study added ginkgo to oxiracetam (Xu 2021); and one study added ginkgo to piracetam (Wang 2020a).

Participants were primarily diagnosed with MCI or vascular cognitive impairment (VCI)/vascular cognitive impairment, no dementia (VCIND), and all studies were conducted in China. Twenty studies (all except Deng 2021 and He 2016) stated that they used EGb 761, EGb, or a Dr. Willmar Schwabe product (presumably EGb 761) or used a product that appeared to be based on EGb 761. Of these, six studies used the product at a dose of more than 200 mg/day (Bu 2016; Dong 2011; Han 2016; Wang 2020a; Xu 2021; Yang 2020a), six studies used the product at less than 200 mg/day (Li 2015a; Li 2016a; Qu 2020; Shi 2017; Xia 2013; Zhao 2020), and the remaining studies were unclear about dose. See Table 3 for a description of the type of and diagnostic criteria for cognitive impairment for each study, as well as a description of the ginkgo and conventional treatments. Find GRADE assessments for all outcomes in Appendix 7.

#### Global clinical status

Jiang 2018 measured global clinical status on the CIBIC at three and six months. Adding ginkgo to treatment regimens may improve global clinical status at three months (MD −1.03, 95% CI −1.87 to −0.19; P = 0.02; 1 study, 68 participants; low-certainty evidence; Analysis 6.1). We downgraded the evidence certainty for serious risk of bias and serious imprecision. It is uncertain whether ginkgo has any effect on global clinical status at six months (MD −1.03, 95% CI −2.23 to 0.17; P = 0.09; 1 study, 68 participants; very low-certainty evidence; Analysis 6.2). We downgraded the evidence certainty for serious risk of bias and very serious imprecision.

#### Global cognitive status

Sixteen studies measured cognition at three, six, or 12 months on the ADAS-Cog, MoCA, MMSE, or HDS. (Bu 2016; Deng 2021; Dong 2011; Gu 2017; Han 2016; He 2016; Jiang 2018; Liu 2015a; Li 2013a; Li 2015a; Li 2016a; Li 2019a; Shi 2017; Xia 2013; Yang 2020a; Zhang 2019a). We used the ADAS-Cog when available. When the ADAS-Cog was not available but the MoCA was, we preferred the MoCA to the MMSE; otherwise, we used the MMSE in analyses.

It is uncertain whether there is a difference in global cognitive function with adjunctive ginkgo at three months (SMD 0.98, 95% CI 0.73 to 1.24; P < 0.001; $I^2$= 80%; 15 studies, 1339 participants; very low-certainty evidence; Analysis 6.3), six months (SMD 0.90, 95% CI 0.74 to 1.06; P < 0.001; $I^2$= 38%; 11 studies, 1160 participants; very low-certainty evidence; Analysis 6.4), or 12 months (SMD 0.97, 95% CI 0.70 to 1.24; P < 0.001; $I^2$= 56%; 4 studies, 578 participants; very low-certainty evidence; Analysis 6.5). We downgraded the evidence certainty for serious inconsistency at three and 12 months, and for very serious risk of bias and strong suspicion of publication bias at each time point (see Assessment of publication bias immediately below).

#### Assessment of publication bias

There were more than 10 studies in the analysis of cognition, and the MMSE was the most commonly used scale. Therefore, for each study in the analysis, we entered the MMSE (when available) at the longest time of follow-up and created a funnel plot (Analysis 6.6; Figure 4). The funnel plot suggests that publication bias may be present, and we therefore downgraded the certainty of evidence for each of the cognition outcomes by one level based on a strong suspicion of publication bias.


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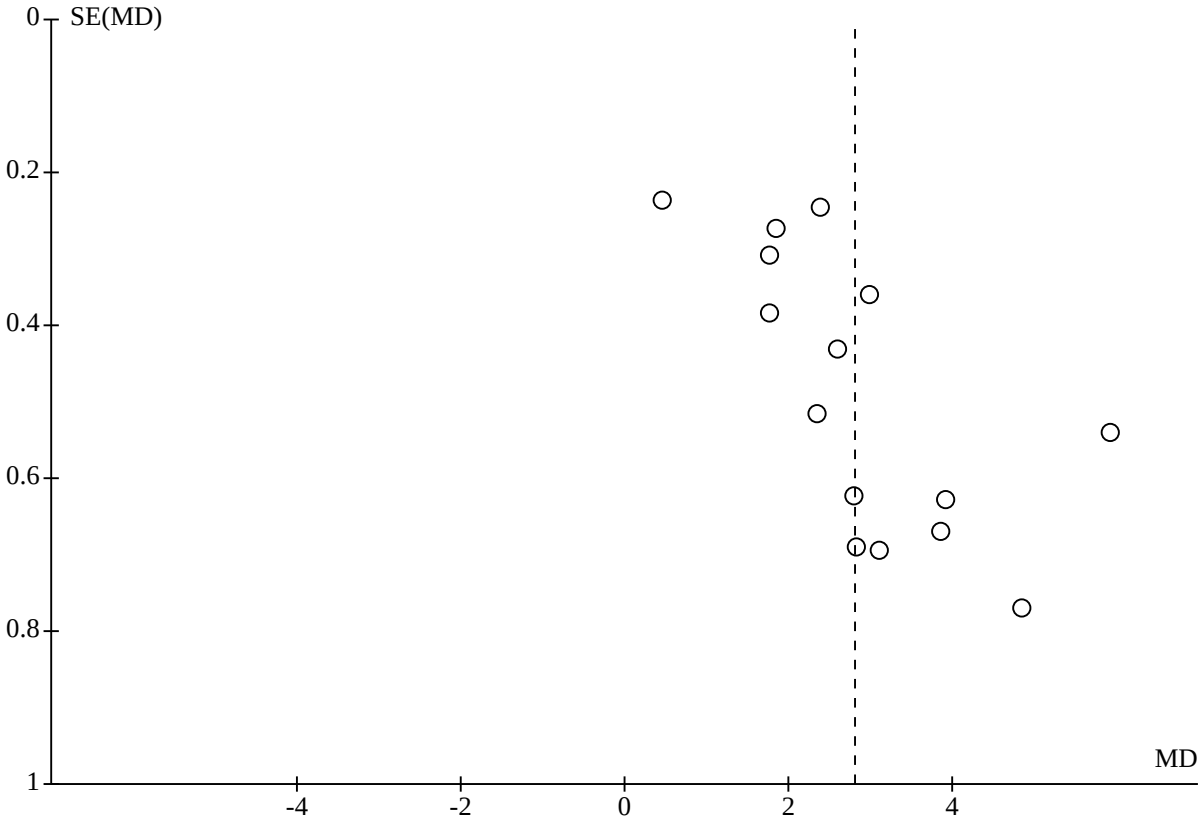
**Figure 4. Funnel plot of comparison: 5 Mild cognitive impairment - *Ginkgo biloba* added to conventional treatment, outcome: 5.27 Cognition - MMSE analysis at 3 to 12 months to check for publication bias**




#### Subgroup analyses

Since there were more than 10 studies in the analysis of global cognitive function at three and six months, we carried out subgroup analyses when there were at least two studies available in each subgroup.

When we compared study populations with and without a stated diagnosis of vascular impairment, we found no evidence of a subgroup difference for cognition at three months (Analysis 6.7; $I^2$ = 18.5%) or six months (Analysis 6.8; $I^2$ = 0%).

When we carried out a subgroup analysis by use of EGb 761 (versus other or unclear), we found no evidence of a subgroup difference between EGb 761 versus non-EGb 761 groups for cognition at three months (Analysis 6.9; $I^2$ = 0%). All studies with data at six months used EGb 761.

#### Ability to perform activities of daily living

Eight studies reported ADLs at three, six, or 12 months on unspecified continuous scales, with higher scores representing better outcomes (Bu 2016; Deng 2021; He 2016; Li 2016a; Wang 2020a; Xu 2021; Yang 2020a; Zhao 2020). Because the scales are unknown, we presented the SMD for each effect estimate.

It is uncertain whether there is a difference in ADLs with adjunctive ginkgo at three months (SMD 0.94, 95% CI 0.31 to 1.56; P < 0.003; $I^2$= 93%; 7 studies, 636 participants; very low-certainty evidence; Analysis 6.10), six months (SMD 1.07, 95% CI 0.43 to 1.71; P = 0.001; $I^2$= 75%; 2 studies, 180 participants; very low-certainty evidence; Analysis 6.11), or 12 months (SMD 0.76, 95% CI 0.35 to 1.17; P < 0.001; 1 study, 100 participants; very low-certainty evidence; Analysis 6.12). We downgraded the evidence certainty for very serious risk of bias at all time points, for serious inconsistency at three and six months, and for serious imprecision at six and 12 months.

#### Adverse events (all)

Seven studies stated that no adverse events occurred (Bu 2016; Dong 2011; Gu 2017; Han 2016; He 2016; Jiang 2018; Zhao 2020), and five studies reported the total number of participants experiencing adverse events at three or six months of follow-up (He 2018a; Li 2016a; Wang 2020a; Xu 2021; Zhang 2019a). It is uncertain whether there is a difference in the risk of adverse events with the addition of ginkgo to treatment at up to six months of follow-up (RR 1.08, 95% CI 0.62 to 1.87; $I^2$= 0%, P = 0.89; 5 studies, 430 participants, 46 events; very low-certainty evidence; Analysis 6.13). We downgraded the evidence certainty for serious or very serious risk of bias and for very serious imprecision.

#### Serious adverse events

Several studies mentioned that there were no serious adverse events, and no studies mentioned that serious adverse events occurred. It is therefore not possible to estimate the effect of ginkgo on the risk of serious adverse events.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#### Memory

Six studies measured memory using the WMS, MQ, logical memory (not further specified), or the memory subscale of the MoCA at three, six or 12 months (Dong 2011; Han 2016; He 2016; Shi 2017; Wang 2020a; Xu 2021). Dong 2011 reported both the MQ and logical memory, and we combined these outcomes into a single effect estimate for memory.

It is uncertain whether there is a benefit with adjunctive ginkgo for memory measured on the WMS at three months (MD 6.62, 95% CI 3.06 to 10.19; P < 0.001; $I^2$= 70%; 3 studies, 294 participants; very low-certainty evidence; Analysis 6.14). It is uncertain whether adjunctive ginkgo has an effect on memory measured on a combination of scales at six months (SMD 0.41, 95% CI 0.18 to 0.65; P < 0.001; $I^2$= 0%; 3 studies, 293 participants; very low-certainty evidence; Analysis 6.15) or 12 months (SMD 0.64, 95% CI 0.38 to 0.90; P < 0.001; $I^2$= 0%; 2 studies, 233 participants; very low-certainty evidence; Analysis 6.16). We downgraded the evidence certainty for very serious risk of bias and serious imprecision at each time point, and for serious inconsistency at three months.

#### Executive function

Three studies measured executive function with the CDT (Dong 2011; Li 2013a; Xia 2013), and Shi 2017 used the executive function subscale of the MoCA, at three, six, or 12 months.

It is uncertain whether adjunctive Gingko improves executive function measured on the CDT at three months (MD 0.56, 95% CI 0.15 to 0.97; P = 0.07; 1 study, 69 participants; very low-certainty evidence; Analysis 6.17) or 12 months (MD 0.57, 95% CI 0.39 to 0.75; P < 0.001; $I^2$= 0%; 2 studies 358 participants; very low-certainty evidence; Analysis 6.19). We downgraded the evidence certainty at both time points for very serious risk of bias and serious imprecision. There may be an improvement in executive function with adjunctive ginkgo at six months (SMD 0.57, 95% CI 0.37 to 0.77; 3 studies, 418 participants; P < 0.001; $I^2$= 0%; low-certainty evidence; Analysis 6.18). We downgraded the evidence certainty at six months for very serious risk of bias.

#### Quality of life

No studies reported quality of life.

#### Neuropsychiatric outcomes

No studies reported neuropsychiatric outcomes.

### Ginkgo for dementia

Thirty-five studies randomizing 5222 participants tested ginkgo for people diagnosed with dementia (Chen 2014a; DIGGER 2008; Dong 2021; Fang 2020; Gao 2019; GINDEM-NP 2005; GOTADAY 2011; GOT IT 2012; Guan 2019; Halama 1991a; Huang 2017; Ji 2020; Kang 2020; Kanowski 1996; Le Bars 1997; Liao 2017a; Li 2017a; Liu 2021; Ma 2015; Maurer 1997; Mazza 2006; Meng 2012; PLAGIN 2013; Oswald 1997; Schneider 2005; Wang 2014a; Wesnes 1987; Wu 2021a; Wu 2017; Xu 2017; Xu 2019a; Yancheva 2009; Yu 2014; Zhang 2016a; Zheng 2020). No studies met our prespecified criteria for overall low risk of bias. Three studies provided no usable data for our outcomes (Ji 2020; Ma 2015; Oswald 1997), leaving 32 studies with 4804 participants for analysis.

#### *Ginkgo versus placebo*

Thirteen studies with 3288 participants compared ginkgo to placebo in people with dementia (DIGGER 2008; GINDEM-NP 2005; GOTADAY 2011; GOT IT 2012; Halama 1991a; Kanowski 1996; Le Bars 1997; Maurer 1997; Mazza 2006; PLAGIN 2013; Oswald 1997; Schneider 2005; Wesnes 1987). We were unable to extract any relevant data from Oswald 1997, leaving 12 studies with 3062 participants for analysis. All studies except Halama 1991a used EGb 761, and seven of these studies used an EGb 761 dose of 240 mg/day (GINDEM-NP 2005; GOTADAY 2011; GOT IT 2012; Kanowski 1996; Maurer 1997; PLAGIN 2013). Find GRADE assessments for primary outcomes in Summary of findings 4, along with all other outcomes in Appendix 8.

#### Global clinical status

The trials used a Likert scale to assess global clinical change at three months (Maurer 1997), six months (GOTADAY 2011; GOT IT 2012, Kanowski 1996, Le Bars 1997; Mazza 2006), and one year (Le Bars 1997). The Likert scales varied, and effect estimates are presented as SMDs.

Due to serious risk of bias and extremely serious imprecision, the effects of ginkgo versus placebo on global clinical status are uncertain at three months (SMD −0.87, 95% CI −1.85 to 0.11; P = 0.08; 1 study, 18 participants; very low-certainty evidence; Analysis 7.1). At six months, there may be an improvement in clinical status with ginkgo versus placebo (SMD −0.55, 95% CI −0.89 to −0.21; P < 0.00; $I^2$= 88%; 5 studies, 1359 participants; low-certainty evidence; Analysis 7.2). We downgraded the evidence certainty for serious risk of bias and serious inconsistency. At 12 months, there may be little or no difference between ginkgo and placebo for global clinical status (SMD 0.00, 95% CI −0.22 to 0.22; P = 1.00; 1 study, 309 participants; low-certainty evidence; Analysis 7.3). We downgraded the evidence certainty for serious risk of bias and serious imprecision.

#### Exploration of heterogeneity

We did not conduct subgroup analyses because there were fewer than 10 studies. However, we explored the high heterogeneity in the primary analysis of global status at six months by carrying out a sensitivity analysis including only studies with the same eligibility criteria, doses of EGb 761, and outcome scales. We restricted the analysis to two studies which had similar inclusion criteria (National Institute of Neurological and Communicative Diseases and Stroke/Alzheimer's Disease and Related Disorders Association [NINCDS-ADRDA] and National Institute of Neurological Disorders and Stroke/*Association Internationale pour la Recherche et l'Enseignement en Neurosciences* [NINDS-AIREN] criteria for possible or probable AD or VD, together with a baseline NPI score of 5 or 6), tested 240 mg of EGb 761 against placebo, and measured global change on the CGI (GOTADAY 2011; GOT IT 2012). The heterogeneity for cognition at six months disappeared ($I^2$ = 0%; Analysis 7.4). If we were to apply the concept of qualitative conclusive effects (IQWiG 2022), we would say that there is clearly conclusive evidence of benefit.

#### Global cognitive function

Ten studies assessed cognition (DIGGER 2008; GINDEM-NP 2005; GOTADAY 2011; GOT IT 2012; Kanowski 1996; Le Bars 1997; Maurer 1997; Mazza 2006; PLAGIN 2013; Schneider 2005). Four studies used the ADAS-Cog at three, six, or 12 months (DIGGER 2008; Maurer


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1997; Le Bars 1997; Schneider 2005), and seven used the SKT at three or six months (GINDEM-NP 2005; GOTADAY 2011; GOT IT 2012; Kanowski 1996; Mazza 2006; Maurer 1997; PLAGIN 2013). All studies reported change values, with the possible exception of DIGGER 2008, which was unclear.

At three months, the effects of ginkgo versus placebo on cognition measured on the ADAS-Cog are uncertain (MD −5.80, 95% CI −19.82 to 8.22; P = 0.42; 1 study, 18 participants; very low-certainty evidence; Analysis 7.5) due to serious risk of bias and very serious imprecision. At six months, cognition may be better with ginkgo compared to placebo (SMD −0.47, 95% CI −0.88 to −0.06; 9 studies, 2801 participants; P = 0.02; $I^2$ = 96%; low-certainty evidence; Analysis 7.6). We downgraded the evidence certainty for serious risk of bias and serious inconsistency. Ginkgo compared to placebo may result in slight improvement in cognition measured on the ADAS-Cog at 12 months (MD −1.40, 95% CI −2.78 to −0.02; P = 0.05; 1 study, 274 participants; low-certainty evidence; Analysis 7.7). We downgraded the evidence certainty for serious risk of bias and serious imprecision.

#### Exploration of heterogeneity

We did not conduct subgroup analyses because there were fewer than 10 studies in each meta-analysis. However, we explored the high heterogeneity in the analysis of cognition at six months by carrying out a sensitivity analysis including only studies with the same eligibility criteria, doses of EGb 761, and outcome scales. We restricted the analysis to four studies that used similar inclusion criteria (NINCDS-ADRDA and NINDS-AIREN criteria for possible or probable AD or VD, together with a baseline NPI score of 5 or 6), tested 240 mg of EGb 761 against placebo, and measured cognition on the SKT (GINDEM-NP 2005; GOTADAY 2011; GOT IT 2012; PLAGIN 2013). The heterogeneity for cognition at six months remained high ($I^2$ = 97%; Analysis 7.8), possibly due to the extreme effects in GINDEM-NP 2005 and PLAGIN 2013. The placebo group in GINDEM-NP 2005 had a large worsening of cognition at the end of treatment, and the placebo group in PLAGIN 2013 had a large improvement in cognition at the end of treatment, and these differences in the placebo group outcomes may be driving the very different effect estimates, but we do not have an explanation for this. If we were to apply the concept of qualitative conclusive effects (IQWiG 2022), we would say that there is moderately conclusive evidence of benefit.

#### Assessment of publication bias

The analysis of cognition included 10 studies across all time points. However, the outcome was not measured on a common scale across studies, and funnel plots of the SMD against the standard error may be considered unsuitable for publication bias assessment (Zwetsloot 2017). Therefore, we did not construct such a plot.

#### Ability to perform activities of daily living

Eight studies assessed ADLs at six or 12 months using the ADL-IS, GBS-ADL, GERRI, or NAB (DIGGER 2008; GINDEM-NP 2005; GOTADAY 2011; GOT IT 2012; Kanowski 1996; Le Bars 1997; PLAGIN 2013; Schneider 2005).

There may be a slight improvement in ADLs with ginkgo versus placebo at six months (SMD −0.32, 95% CI −0.59 to −0.05; P = 0.02; $I^2$ = 91%; 8 studies, 2571 participants; low-certainty evidence; Analysis 7.9). We downgraded the evidence certainty for serious risk of bias and serious inconsistency. Ginkgo compared with placebo may result in a slight improvement in ADLs measured on the GERRI at 12 months (MD −0.14, 95% CI −0.23 to −0.05; P = 0.004; 1 study, 270 participants; low-certainty evidence; Analysis 7.10). We downgraded the evidence certainty for serious risk of bias and serious imprecision.

#### Exploration of heterogeneity

We did not conduct subgroup analyses because there were fewer than 10 studies in each meta-analysis. However, we explored the high heterogeneity in the primary analysis of ADLs at six months by carrying out a sensitivity analysis including only studies with the same eligibility criteria, doses of EGb 761, and outcome scales (Analysis 7.11). We restricted the analysis to two studies that used similar inclusion criteria (NINCDS-ADRDA and NINDS-AIREN criteria for possible or probable AD or VD, together with a baseline NPI score of 5 or 6), tested 240 mg of EGb 761 against placebo, and measured ADLs on the GBS (GINDEM-NP 2005; PLAGIN 2013). The heterogeneity for ADLs at six months did not change ($I^2$ = 98%). We also looked at two other studies that used similar inclusion criteria (NINCDS-ADRDA and NINDS-AIREN criteria for possible or probable AD or VD, together with a baseline NPI score of 5 or 6), tested 240 mg of EGb 761 against placebo, and measured ADLs on the ADL-IS (GOTADAY 2011; GOT IT 2012). In this case, the $I^2$ value was 5%. The heterogeneity in the primary analysis again appears to be driven by the extremes seen in GINDEM-NP 2005 and PLAGIN 2013, although they used an identical outcome scale, and we do not have an explanation for the differences between effects in these two trials.

#### Adverse events (all)

Two studies reported that no adverse events occurred (Maurer 1997; Mazza 2006), and nine studies reported numbers of adverse events (DIGGER 2008; GINDEM-NP 2005; GOTADAY 2011; GOT IT 2012; Halama 1991a; Le Bars 1997; PLAGIN 2013; Schneider 2005; Wesnes 1987). There is probably little or no difference between ginkgo and placebo in risk of adverse events at up to 12 months (RR 0.95, 95% CI 0.90 to 1.00; P = 0.06; $I^2$ = 0%; 9 studies, 2746 participants, 1480 events; moderate-certainty evidence; Analysis 7.12). We downgraded the evidence certainty for serious risk of bias.

#### Serious adverse events

There may be little or no difference between ginkgo and placebo in the risk of serious adverse events at up to six months (RR 0.88, 95% CI 0.58 to 1.33, P = 0.54; $I^2$ = 0%; 6 studies, 2463 participants, 89 events; low-certainty evidence; Analysis 7.13). We downgraded the evidence certainty for very serious imprecision.

#### Memory

To assess effects upon memory, Wesnes 1987 used the Benton at three months. Due to serious risk of bias and extremely serious imprecision, it is uncertain whether there is a difference in memory with ginkgo versus placebo at three months (MD 0.20, 95% CI −0.86 to 1.26; P = 0.71; 1 study, 47 participants; very low-certainty evidence; Analysis 7.14).

#### Executive function

Four studies assessed executive function at six months using a verbal fluency test (GINDEM-NP 2005; GOTADAY 2011; GOT IT 2012; PLAGIN 2013); two of these studies also used the CDT (GINDEM-NP 2005; PLAGIN 2013). For GINDEM-NP 2005 and PLAGIN 2013, we combined the verbal fluency test results and the CDT


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results to estimate a summary executive function outcome. Ginkgo compared with placebo may result in better executive function at six months (SMD 0.64, 95% CI 0.02 to 1.26; P = 0.04; $I^2$= 96%; 4 studies, 1598 participants; low-certainty evidence; Analysis 7.15). We were uncertain about the appropriateness of the combined executive function measure for GINDEM-NP 2005 and PLAGIN 2013, but because the combined measure incorporated the verbal fluency test, which was used by all studies, and we noted that removing the studies from the analysis did not substantially reduce heterogeneity ($I^2$ = 80%), we retained this outcome for the analysis. We downgraded the evidence certainty for serious risk of bias and serious inconsistency.

#### Quality of life

Four studies measured quality of life at six months using the PDS (Schneider 2005), the Carer-rated QOL-AD (DIGGER 2008), or the DEMQOL-Proxy-Carer (GOTADAY 2011; GOT IT 2012). There may be little or no difference in quality of life with ginkgo versus placebo at six months (SMD 0.11, 95% CI −0.06 to 0.28; P = 0.22; $I^2$= 60%; 4 studies, 1392 participants; low-certainty evidence; Analysis 7.16). We downgraded the evidence certainty for serious risk of bias and serious inconsistency.

#### Exploration of heterogeneity

We did not conduct subgroup analyses because the primary analyses included fewer than 10 studies. However, we explored the heterogeneity for quality of life by carrying out a sensitivity analysis including only studies with similar eligibility criteria and identical doses of EGb 761 and outcome measurement tools. We restricted the analysis to two trials which had similar inclusion criteria, tested 240 mg of EGb 761 against placebo, and measured quality of life on the DEMQOL-Proxy-Carer (GOTADAY 2011; GOT IT 2012). The heterogeneity for quality of life at six months was $I^2$ = 0% (Analysis 7.17).

#### Neuropsychiatric outcomes

#### Depression

Depression was measured at six months on the HAM-D (GINDEM-NP 2005; PLAGIN 2013) and the MADRS (Kanowski 1996). We could not combine change data on the HAM-D from GINDEM-NP 2005 and PLAGIN 2013 with endpoint data on the MADRS data from Kanowski 1996, so we analyzed the studies separately.

At six months, ginkgo may have little to no effect on depression assessed by the HAM-D (MD −2.31, 95% CI −6.03 to 1.42; P = 0.22; $I^2$= 99%; 2 studies, 792 participants; low-certainty evidence; Analysis 7.18), and there is probably little or no difference in depression with ginkgo on the MADRS (MD −0.40, 95% CI −2.57 to 1.77; P = 0.72; 1 study, 156 participants; moderate-certainty evidence; Analysis 7.19). For both analyses, we downgraded the evidence certainty for serious imprecision. For the HAM-D estimate, we also downgraded for serious inconsistency.

#### Neuropsychiatric Inventory

Five studies measured neuropsychiatric symptoms on the NPI at six months (DIGGER 2008; GINDEM-NP 2005; GOTADAY 2011; GOT IT 2012; PLAGIN 2013). Ginkgo compared with placebo may reduce neuropsychiatric symptoms at six months (MD −3.95, 95% CI −7.34 to −0.57; P = 0.02; $I^2$= 96%; 5 studies, 1686 participants; low-certainty evidence; Analysis 7.20). We downgraded the evidence certainty for serious risk of bias and serious inconsistency.

#### Exploration of heterogeneity

We did not carry out subgroup analyses because there were fewer than 10 studies. However, we explored the high heterogeneity in the analysis of neuropsychiatric symptoms by restricting the analysis to the four studies that had the same inclusion criteria and tested 240 mg of EGb 761 against placebo (GINDEM-NP 2005; GOTADAY 2011; GOT IT 2012; PLAGIN 2013). The heterogeneity for neuropsychiatric symptoms at six months remained high ($I^2$ = 97%; Analysis 7.21). If, in light of this heterogeneity, we were to apply the concept of qualitative conclusive effects (IQWiG 2022), we would say that there is moderately conclusive evidence of benefit.

### *Ginkgo versus conventional medications*

Three studies randomized 173 participants with AD to either ginkgo or donepezil and followed the participants for up to six months (Ji 2020; Mazza 2006; Yancheva 2009). Ji 2020 provided no usable data for our outcomes, leaving two studies with 113 participants for analysis. Both studies tested EGb 761; Mazza 2006 used a dose of 160 mg/day, and Yancheva 2009 used a dose of 240 mg/day. See Table 4 for details on interventions and participants. Find GRADE assessments for all outcomes in Appendix 9.

#### Global clinical status

Mazza 2006 measured global clinical status on the CGIC at six months. Due to serious risk of bias and extremely serious imprecision, the comparative effects of ginkgo and donepezil on global status are uncertain (MD 0.15, 95% CI −0.43 to 0.73; P = 0.61; 1 study, 41 participants; very low-certainty evidence; Analysis 8.1).

#### Global cognitive function

Mazza 2006 and Yancheva 2009 measured cognition on the SKT at six months, and Mazza 2006 also reported the MMSE. We chose to analyze the SKT so as to calculate the MD. Due to serious risk of bias and very serious imprecision, the comparative effects of ginkgo and donepezil on cognition measured on the SKT are uncertain (MD 1.03, 95% CI −0.29 to 2.36; P = 0.13; $I^2$ = 0%; 2 studies, 103 participants; very low-certainty evidence; Analysis 8.2).

#### Ability to perform activities of daily living

Yancheva 2009 measured ADLs on the GBS-ADL at six months. Due to serious risk of bias and very serious imprecision, the comparative effects of ginkgo and donepezil on the GBS-ADL are uncertain (MD −1.81, 95% CI −3.94 to 0.32; P = 0.10; 1 study, 62 participants; very low-certainty evidence; Analysis 8.3).

#### Adverse events (all)

Both Mazza 2006 and Yancheva 2009 reported the total number of participants experiencing adverse events at six months of follow-up. There may be a lower risk of adverse events with ginkgo than with donepezil (RR 0.42, 95% CI 0.25 to 0.72; P = 0.002; $I^2$= 0%; 2 studies, 112 participants, 38 events; low-certainty evidence; Analysis 8.4). We downgraded the evidence certainty for serious risk of bias and serious imprecision.

#### Serious adverse events

No adverse events described by Mazza 2006 were serious, but Yancheva 2009 reported a serious adverse event in the ginkgo arm, which appeared to be unrelated to the study treatment. Due to extremely serious imprecision, it is uncertain whether there are any differences in the risk of serious adverse events with ginkgo


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and donepezil (RR 3.19, 95% CI 0.14 to 75.49; P = 0.47; 1 study, 62 participants, 1 event; very low-certainty evidence; Analysis 8.5).

#### Memory

No studies reported memory.

#### Executive function

Yancheva 2009 reported executive function on the CDT and a verbal fluency test at six months. We combined the CDT and verbal fluency test outcomes to create a summary executive function outcome for the study, and we reported the SMD. The comparative effects of ginkgo and donepezil on executive function are uncertain due to serious risk of bias and very serious imprecision (SMD 0.31, 95% CI −0.19 to 0.82; P = 0.22; 1 study, 62 participants; very low-certainty evidence; Analysis 8.6).

#### Quality of life

No studies reported quality of life.

#### Neuropsychiatric outcomes

#### Depression

Yancheva 2009 measured depression on the HAM-D at six months. The comparative effects of ginkgo and donepezil on the HAM-D are uncertain due to serious risk of bias and very serious imprecision (MD 0.00, 95% CI −1.55 to 1.55; P = 1.00; 1 study, 62 participants; very low-certainty evidence; Analysis 8.7).

#### Neuropsychiatric Inventory

Yancheva 2009 measured neuropsychiatric symptoms on the NPI at six months. The comparative effects of ginkgo and donepezil on the NPI are uncertain due to serious risk of bias and very serious imprecision (MD 1.20, 95% CI −2.58 to 4.98; P = 0.53; 1 study, 62 participants; very low-certainty evidence; Analysis 8.8)

### *Ginkgo versus Chinese herbal medicine or acupuncture*

Four studies randomizing 380 participants compared ginkgo to Chinese herbal medicine (Chinese herbal decoction, Shenma Yizhi Recipe, or Tongxinluo capsule [Chen 2014a; Wu 2017; Zhang 2016a]) or to acupuncture plus cognitive rehabilitation (Liao 2017a) in people with dementia.

Participants in studies comparing ginkgo to Chinese herbal medicine were primarily diagnosed with VD, while the study comparing ginkgo to acupuncture enrolled participants diagnosed with AD. All studies were conducted in China, and no studies described using EGb 761. See Table 4 for a description of the type and diagnostic criteria for dementia for each study, as well as a description of the ginkgo and comparator treatments. We analyzed the comparisons between ginkgo and Chinese herbal medicine separately from the comparison between ginkgo and acupuncture. Find GRADE assessments for all outcomes in Appendix 10.

#### Global clinical status

No study reported continuous outcomes for global clinical status.

#### Global cognitive function

All four studies assessed cognition at three months. The study comparing ginkgo to acupuncture used the FIM cognitive items, where higher scores are better (Liao 2017a), and the studies comparing ginkgo to Chinese herbal medicine used the MMSE (Chen 2014a; Wu 2017; Zhang 2016a); Wu 2017 also used the MoCA, and we used the MoCA in preference to the MMSE.

At three months, it is uncertain whether there is a difference between ginkgo and acupuncture on the FIM cognitive items (MD −6.89, 95% CI −7.90 to −5.88; P < 0.001; 1 study, 100 participants; very low-certainty evidence; Analysis 9.1), between ginkgo and Chinese herbal decoction on the MMSE (MD −3.47, 95% CI −5.00 to −1.94; P < 0.001; 1 study, 96 participants; very low-certainty evidence; Analysis 9.2), between ginkgo and Shenma Yizhi Recipe on the MoCA (MD 0.34, 95% CI −1.79 to 2.47; P = 0.75; 1 study, 64 participants; very low-certainty evidence; Analysis 9.3), or between ginkgo and Tongxinluo capsule on the MMSE (MD −2.00, 95% CI −3.30 to −0.70; P = 0.003; 1 study, 120 participants; very low-certainty evidence; Analysis 9.4). All effect estimates were downgraded for very serious risk of bias and for serious or very serious imprecision.

#### Ability to perform activities of daily living

All studies assessed ADLs at three months. The study comparing ginkgo to acupuncture used an IADL functional activities questionnaire where lower scores are better (Liao 2017a), and the studies comparing ginkgo to Chinese herbal medicine used unspecified scales where higher scores are better (Chen 2014a; Wu 2017; Zhang 2016a). We used the SMD to estimate effects on unspecified scales.

At three months, it is uncertain whether there is a difference between ginkgo and acupuncture for ADLS measured on the IADL functional activities questionnaire (MD 7.40, 95% CI 5.53 to 9.27; P < 0.001; 1 study, 100 participants; very low-certainty evidence; Analysis 9.5). It is also uncertain whether there is a difference for ADLs when ginkgo is compared to Chinese herbal decoction (SMD −1.06, 95% CI −1.49 to −0.63; P < 0.001; 1 study, 96 participants; very low-certainty evidence; Analysis 9.6), Shenma Yizhi Recipe (SMD −0.55, 95% CI −1.05 to −0.05; P = 0.03; 1 study, 64 participants; very low-certainty evidence; Analysis 9.7), or Tongxinluo capsule (SMD −1.04, 95% CI −1.42 to −0.66; P < 0.001; 1 study, 120 participants; very low-certainty evidence; Analysis 9.8). All effect estimates were downgraded for very serious risk of bias and serious imprecision.

#### Adverse events

No studies mentioned adverse events.

#### Memory

No studies reported memory.

#### Executive function

No studies reported executive function.

#### Quality of life

No studies reported quality of life outcomes.

#### Neuropsychiatric outcomes

No studies reported neuropsychiatric outcomes.

### *Ginkgo plus other active treatments versus other active treatments alone*

Seventeen studies randomizing 1460 participants evaluated the addition of ginkgo to a pharmacological dementia treatment versus the same pharmacological treatment alone. Three studies


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compared ginkgo plus butylphthalide to butylphthalide alone (Huang 2017; Liu 2021; Xu 2017), one study compared ginkgo plus citicoline sodium to citicoline sodium alone (Fang 2020), eight studies compared ginkgo plus donepezil to donepezil alone (Gao 2019; Guan 2019; Wang 2014a; Wu 2021a; Xu 2019a; Yancheva 2009; Yu 2014; Zheng 2020), one study compared ginkgo plus idebenone to idebenone alone (Dong 2021), two studies compared ginkgo plus memantine hydrochloride to memantine hydrochloride alone (Kang 2020; Li 2017a), and two studies compared ginkgo plus piracetam to piracetam alone (Ma 2015; Meng 2012). Ma 2015 provided no usable data for our outcomes, leaving 16 studies with 1328 participants for analysis.

Participants in half the studies were diagnosed with VD, and all studies except Yancheva 2009 were conducted in China. All studies except Zheng 2020 stated they used EGb 761, EGb, or a Dr. Willmar Schwabe product (presumably EGb 761), or were otherwise determined to have likely used an EGb 761 product. Only Dong 2021 and Yancheva 2009 clearly stated that the dose was 240 mg/day or greater. See Table 4 for a description of the type and diagnostic criteria for dementia for each study, as well as a description of the ginkgo and pharmacological treatments. Find GRADE assessments for all outcomes in Appendix 11.

#### Global clinical status

Zheng 2020 measured global clinical status on the CDR at three months. There may be improved global clinical status at three months when ginkgo is added to donepezil (MD −0.40, 95% CI −0.49 to −0.31; P < 0.001; 1 study, 100 participants; low-certainty evidence; Analysis 10.1). We downgraded the evidence certainty for serious risk of bias and serious imprecision.

#### Global cognitive function

Fourteen studies measured cognition endpoints at three, six, or nine months on the ADAS-Cog, HDS, MMSE, or MoCA (Dong 2021; Fang 2020; Gao 2019; Guan 2019; Huang 2017; Kang 2020; Li 2017a; Liu 2021; Wang 2014a; Wu 2021a; Xu 2017; Xu 2019a; Yu 2014; Zheng 2020). We used the ADAS-Cog and MoCA in preference to the MMSE or HDS when available. Yancheva 2009 measured change in SKT score at six months. We were unable to combine SKT change data with endpoint data from other studies, and therefore analyzed Yancheva 2009 separately.

Due to very serious risk of bias, serious inconsistency, and suspicion of publication bias (see Assessment of publication bias below), it is uncertain whether adding ginkgo to butylphthalide, citicoline, donepezil, idebenone, or memantine hydrochloride improves cognition at three months (SMD 1.25, 95% CI 0.81 to 1.69; P < 0.001; $I^2$= 86%; 9 studies, 728 participants; very low-certainty evidence; Analysis 10.2) or six to nine months (SMD 1.63, 95% CI 0.92 to 2.34; P < 0.001; $I^2$= 93%; 7 studies, 585 participants; very low-certainty evidence; Analysis 10.3). Due to serious risk of bias and very serious imprecision, the effect of adjunctive ginkgo on cognition as measured by changes on the SKT at six months is also uncertain (MD −1.00, 95% CI −2.68 to 0.68; P = 0.24; 1 study, 63 participants; very low-certainty evidence; Analysis 10.4).

#### Subgroup analyses

We carried out a subgroup analysis by diagnosis (VD versus AD). Each time point had too few studies to test for heterogeneity, so we conducted a test across all time points, using the longest time of follow-up for each study. The heterogeneity between subgroups was nonsignificant at P < 0.05 ($I^2$ = 66.4%; P = 0.08; Analysis 10.5), and heterogeneity within each subgroup remained considerable.

We used subgroup analyses to evaluate whether there were different effects when ginkgo was added to different medications. Each time point had too few studies to test for heterogeneity. However, when we conducted a test across all time points for medications with at least two studies, using the longest time of follow-up for each study, we observed that between-subgroup heterogeneity seemed low ($I^2$ = 26.4%; Analysis 10.6), while within-subgroup heterogeneity remained very high.

#### Assessment of publication bias

There were more than 10 studies in the analysis of cognition, and the MMSE was the most commonly used scale. Therefore, for each study in the analysis, we entered the MMSE (when available) at the longest time of follow-up and created a funnel plot (Analysis 10.7; Figure 5). The funnel plot suggests that publication bias may be present, and we therefore downgraded the certainty of evidence for each of the cognition outcomes by one level due to strong suspicion of publication bias.


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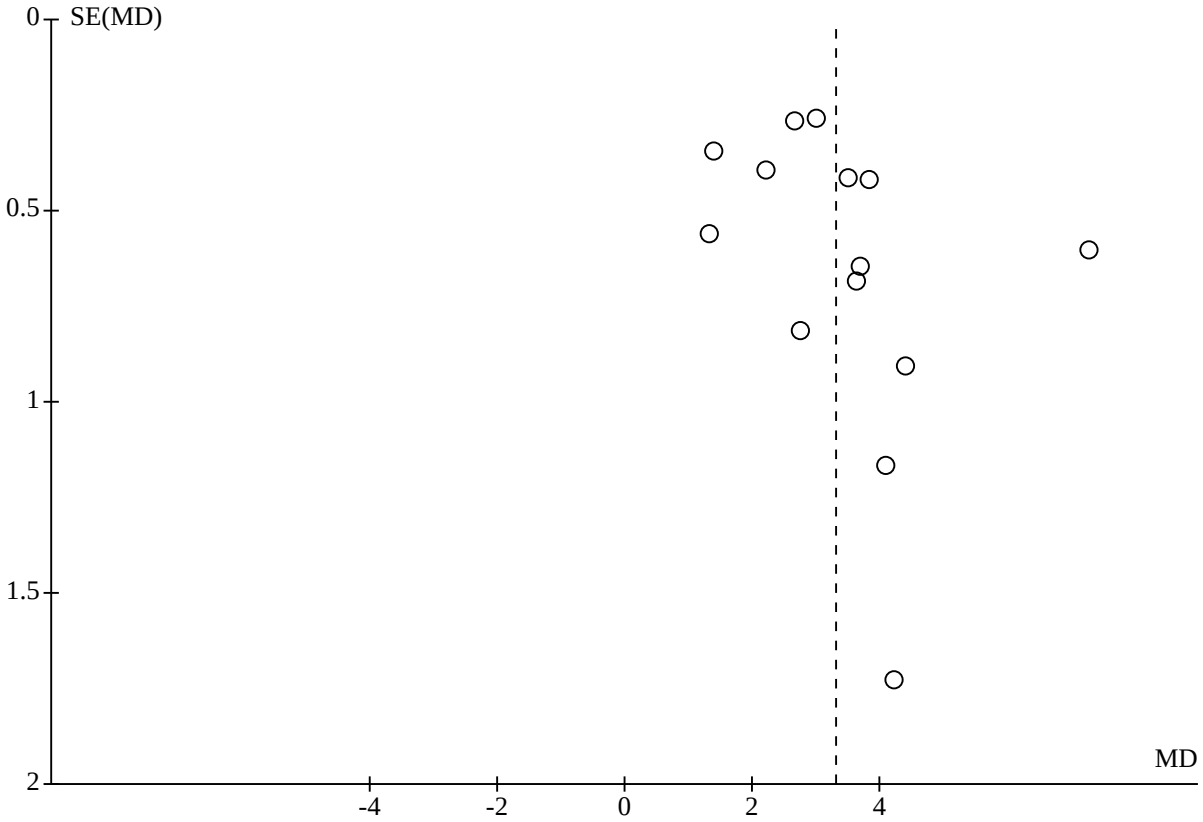
**Figure 5. Funnel plot of comparison: 9 Dementia - *Ginkgo biloba* added to conventional treatment, outcome: 9.24 Cognition - MMSE analysis at 3 to 9 months to check for publication bias**




#### Ability to perform activities of daily living

Fifteen studies measured ADLs at three months or six to nine months (Fang 2020; Gao 2019; Guan 2019; Huang 2017; Kang 2020; Li 2017a; Liu 2021; Meng 2012; Wang 2014a; Wu 2021a; Xu 2017; Xu 2019a; Yu 2014; Zheng 2020; Yancheva 2009). Four studies used the Barthel Index (Fang 2020; Kang 2020; Wu 2021a; Xu 2019a), and Yancheva 2009 measured ADLs on the GBS-ADL. Other studies did not specify the scale used, but we understood that higher scores were better.

Due to very serious risk of bias and serious inconsistency, it is uncertain whether adding ginkgo to conventional treatment has an effect on ADLs at three months (SMD 1.38, 95% CI 0.76 to 2.00; P < 0.001; $I^2$ = 93%; 9 studies, 728 participants; very low-certainty evidence; Analysis 10.8) or six to nine months (SMD 1.46, 95% CI 0.77 to 2.16; P < 0.001; $I^2$ = 94%; 8 studies, 678 participants; very low-certainty evidence; Analysis 10.9).

#### Subgroup analyses

We carried out a subgroup analysis by diagnosis (VD versus AD). Each time point had too few studies to test for heterogeneity, so we conducted a test across all time points, using the longest time of follow-up for each study. Heterogeneity within each subgroup was substantial, and there was no evidence of a difference in effects between subgroups ($I^2$ = 0%; Analysis 10.10).

We carried out a subgroup analysis by medications. Each time point had too few studies to test for heterogeneity, so we conducted a test across all time points, using the longest time of follow-up for each study and including all medications with at least two studies (butylphthalide, donepezil, and memantine hydrochloride). At three to nine months, heterogeneity within each subgroup was substantial, and there was no evidence of a difference in effects between subgroups ($I^2$ = 0%; Analysis 10.11).

#### Assessment of publication bias

While there were 14 studies in the analysis of ADLs, the outcome was not measured on a common scale across studies, and we decided not to create funnel plots based on the SMD (Zwetsloot 2017).

#### Adverse events (all)

Eight studies reported the total number of participants experiencing adverse events at three to six months of follow-up (Fang 2020; Guan 2019; Kang 2020; Li 2017a; Wu 2021a; Xu 2017; Xu 2019a; Yancheva 2009), and one study reported that there was no evidence of a difference in the incidence of adverse events in the two groups at nine months (Gao 2019). Adding ginkgo to conventional treatment may result in little or no difference in the risk of adverse events up to six months (RR 0.88, 95% 0.67 to 1.16; P = 0.36; $I^2$= 0%; 8 studies, 640 participants, 118 events; low-certainty evidence; Analysis 10.12). We downgraded the evidence certainty for serious risk of bias and serious imprecision.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#### Serious adverse events

Two studies reported that there were no serious adverse events (Guan 2019; Yancheva 2009), and one study reported serious adverse events only in the non-ginkgo arm (Li 2017a). Due to serious risk of bias and very serious imprecision, it is uncertain whether there is any difference in serious adverse events with the addition of ginkgo to other pharmacological treatment (RR 0.05, 95% CI 0.00 to 0.85; P = 0.04; 1 study, 77 participants, 9 events; very low-certainty evidence; Analysis 10.13).

#### Memory

Meng 2012 reported the memory subscale of the MMSE at six months. The addition of ginkgo to piracetam may improve memory at six months (MD 0.72, 95% CI 0.36 to 1.08; P < 0.001; 1 study, 104 participants; low-certainty evidence; Analysis 10.14). We downgraded the evidence certainty for serious risk of bias and serious imprecision.

#### Executive function

Yancheva 2009 reported executive function on the CDT and a verbal fluency test at six months. We combined the CDT and verbal fluency test outcomes to create a summary executive function outcome and reported the SMD for the composite measure. Due to serious risk of bias and very serious imprecision, it is uncertain whether the addition of ginkgo to donepezil improves executive function at six months (SMD 0.28, 95% CI −0.22 to 0.77; P = 0.28; 1 study, 63 participants; very low-certainty evidence; Analysis 10.15).

#### Quality of life

No studies reported quality of life.

#### Neuropsychiatric outcomes

#### Depression

Yancheva 2009 measured depression on the HAM-D at six months. Due to serious risk of bias and very serious imprecision, it is uncertain whether the addition of ginkgo to donepezil improves depression (MD −0.40, 95% CI −2.13 to 1.33; P = 0.65; 1 study, 63 participants; very low-certainty evidence; Analysis 10.16).

#### Neuropsychiatric Inventory

Three studies measured neuropsychiatric symptoms on the NPI at three to six months (Liu 2021; Wu 2021a; Yancheva 2009). The addition of ginkgo to butlyphthalide may improve neuropsychiatric symptoms at three months (MD −1.93, 95% CI −2.67 to −1.19; P < 0.001; 1 study, 92 participants; low-certainty evidence; Analysis 10.17). We downgraded the evidence certainty for serious risk of bias and serious imprecision. Due to serious risk of bias, serious inconsistency, and very serious imprecision, it is uncertain whether the addition of ginkgo to butylphthalide or donepezil improves neuropsychiatric symptoms at six months (MD −3.13, 95% CI −7.27 to 1.02; P = 0.14; $I^2$ = 69%; 2 studies, 161 participants; very low-certainty evidence; Analysis 10.18).

## DISCUSSION

We included 82 studies (10,613 randomized participants), of which 72 studies with 9783 participants provided data for analysis.

## Summary of main results

### Effect of ginkgo for people with subjective cognitive impairment

Three studies (597 participants) compared ginkgo with placebo for people with subjective cognitive complaints but no diagnosis of cognitive impairment or dementia. Two studies (537 participants) had available data.

- Based on one study testing Geriaforce (a non-EGb 761 product) against placebo and following participants for six months, it is uncertain if Gingko improves global clinical status, as the evidence is of very low certainty (Brautigam 1998).
- There were no data on global cognitive function or ADLs at six months.
- Brautigam 1998 reported that there was no difference in the number of side effects, primarily gastrointestinal upset and dizziness, in each treatment group, but did not report numbers of events or any information about serious adverse events. A larger study testing EGb 761 versus placebo for three months found that there may be more side effects with Gingko versus placebo (EUCTR2005-005765-11-EE). It found no difference between gingko and placebo in the risk of serious adverse events, but the evidence was very uncertain.

### Effect of ginkgo for people with multiple sclerosis and cognitive impairment

Two studies (164 participants) compared ginkgo to placebo in people with MS and cognitive impairment. Both studies tested EGb 761 at 240 mg or a similar form of ginkgo for three months.

- Ginkgo probably results in little to no difference in global cognitive function at three months.
- There were no data on global clinical function or ADLs.
- Neither study reported the total number of people experiencing adverse events, but there were no major concerns regarding this outcome. Two serious adverse events were reported in the ginkgo group, but they were judged to be unrelated to the intervention.

### Effect of ginkgo for people with mild cognitive impairment

Forty-two studies (4630 participants) tested the effects of ginkgo products in people diagnosed with MCI. Twelve studies (1913 participants) compared ginkgo to placebo, and data from eight studies with 1594 participants were available for analysis. All studies used EGb 761; however, only five used doses of 240 mg/day in some or all participants.

- Ginkgo probably results in little to no difference in global clinical status, global cognitive function, or ADLs at six months.
- There may be little or no difference in the risk of any adverse events with ginkgo versus placebo at up to 12 months of follow-up. There is little or no difference in the risk of serious adverse events with ginkgo versus placebo at up to six months of follow-up.

### Effect of ginkgo for people with dementia

Thirty-five studies randomizing 5222 participants tested ginkgo for people diagnosed with dementia. Thirteen studies (3263 participants) compared ginkgo to placebo in people diagnosed


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with dementia, and data from 12 studies (3037 participants) were available for analysis. Eleven studies used EGb 761, and of these, seven used doses of 240 mg/day.

- Ginkgo may lead to better global clinical status, better global cognitive function, and a slight improvement in ADLs at six months. However, all estimates had high heterogeneity.
- There is probably little or no difference between ginkgo and placebo in the risk of adverse events at up to 12 months, and there may be little or no difference between ginkgo and placebo in the risk of serious adverse events at up to six months.

### Overall completeness and applicability of evidence

For our prespecified primary outcome of cognitive function, we found data in most included trials. However, we found fewer data for our other primary outcomes. There was limited information on adverse events, and we found very little discussion of the possibility of interactions with other drugs, although 30 trials combined ginkgo with another specific drug as part of testing the ginkgo intervention, and a further eight trials included background use of drugs that might have a direct influence (e.g. nootropics) or an indirect influence (e.g. blood pressure treatment) on cognitive functioning. This is a major gap, given that standard treatment of dementia involves acetylcholine esterase inhibitors or other drugs. For secondary outcomes such as memory and executive function, we found data in many trials, but the outcomes were measured in multiple ways that captured slightly different constructs and did not lend themselves to meta-analysis. We also found little data on quality of life and limited information on neuropsychiatric outcomes. Limited data on outcomes led to low precision and downgrading of the evidence to low or very low certainty for many analyses.

We found few studies with people who had subjective complaints without a diagnosis of cognitive impairment or dementia, so we were unable to draw firm conclusions for our primary effectiveness outcomes at six months. We have yet to obtain data on cognitive testing during follow-up from GuidAge 2008, an Ipsen-funded study that tested EGb 761 against placebo in people with memory complaints for prevention of Alzheimer's dementia. However, the published main results of the study are that there was no reduction in the risk of developing Alzheimer's dementia over five years. This indicates no long-term benefit in reducing the risk of dementia and is consistent with findings from Brautigam 1998 and EUCTR2005-005765-11-EE. We will continue to pursue GuidAge 2008 data in the hope of improving the clarity and certainty of the evidence.

We believe that we found all relevant studies on the use of ginkgo for cognitive impairment with MS. We found two good-quality published studies, as well as one registered trial sponsored by Ipsen for which we have been unable to obtain data (NCT00276341). Although the overall sample size in the published studies was not large, we considered that ginkgo probably had little or no effect on cognition, memory, executive function, or depression. We will continue to pursue the data from NCT00276341; the lack of published or otherwise available data from the trial may indicate that this study also found little or no benefit for ginkgo.

For MCI and dementia, we found 77 studies testing different forms and doses of ginkgo. Studies were primarily conducted in China or Europe, included participants with MCI or mild-to-moderate dementia, and were published between 1985 and 2022. Although this covers a broad geographic range and time span, representing many different background approaches to treatment for cognitive impairment and dementia, different study populations and comparisons were characteristic of different settings. We noted that most placebo-controlled trials were conducted in Europe, while both direct comparisons to other treatments and tests of ginkgo as adjunct to other treatments were primarily conducted in China.

Seventy-three studies appear to have used EGb 761, and 29 of these studies included a dose of over 200 mg/day. However, some studies used other types of ginkgo interventions, and the intervention doses were often unclear in study reports. Taking both the clarity and completeness of information into account, the evidence from comparisons of EGb 761 at 240 mg/day versus placebo for treatment of outpatients with dementia in Europe between 1996 and 2013 is fairly complete, but placebo comparisons for other forms of ginkgo are limited. We do not know to what extent these results for EGb 761 at 240 mg/day apply to other forms and doses of ginkgo, or can be applied in the context of the most up-to-date treatment regimens for dementia.

We were unable to locate the full text of 17 Chinese-language studies and four non-Chinese-language studies from the 1980s or 1990s. Nevertheless, aside from the limitation of irretrievable data from GuidAge 2008 and NCT00276341, which affected the completeness of information on subjective cognitive complaints and MS with cognitive complaints, we do not believe we have missed data from any large, high-quality studies that would affect the completeness and relevance of our review findings. However, several studies on ginkgo are ongoing or awaiting assessment.

### Quality of the evidence

This review included 82 parallel-group RCTs, of which 72 provided usable outcome data, and four met our prespecified criteria for low overall risk of bias. Sample sizes ranged from 20 to 513 participants, with a median of 92 participants. However, variation between populations, interventions, and comparators, and lack of data for some outcomes, meant that many analyses included limited information. There was also high unexplained heterogeneity in larger analyses, particularly those testing the addition of ginkgo to other medications for MCI and those testing ginkgo versus placebo for dementia. It is possible that the heterogeneity in analyses testing the adjunctive use of ginkgo is partially due to the different treatments in different studies, but the presence of very high heterogeneity in analyses testing the same dose of the same product (EGb 761) against placebo for dementia is more difficult to explain. Finally, many studies were judged to be at high risk of bias in at least one domain. Using GRADE methods, we rated the certainty of evidence for primary outcomes as very low to moderate due to risk of bias, inconsistency, and imprecision of results.

### Potential biases in the review process

To be inclusive, we did not require trials to include only participants meeting formal diagnostic criteria for cognitive impairment or dementia. We classified levels of cognitive problems into subjective concerns without a diagnosis of cognitive impairment, MCI, and dementia. We also classified trials in MCI and dementia into VD or AD diagnoses. We did not use scores on tests (e.g. the MMSE) or contact study authors to systematically appraise these factors;


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instead, we relied upon descriptions in the study reports. However, trials varied in their descriptions of participant conditions, and this probably varied across time periods and countries. Furthermore, at least one trial included both MCI and dementia participants (van Dongen 2000). Taking all of these factors into account, we may not have classified trials into the correct levels or types of impairment, leading to difficulty in detecting exactly for whom ginkgo might or might not be helpful.

Most trials conducted in Europe and North America clearly specified the nature of the intervention (EGb 761 or another form of ginkgo) and the dose delivered. Many trials in China had less information, or mentioned a manufacturer or trade name that we could not easily confirm as EGb 761 or not. Although we searched online for further information on products, we did not contact trialists to clarify information on the type and dose of the intervention, and we may have misclassified these in some cases.

Trials used several different measures for effects on memory and executive function. We could not decide upon a hierarchy of effect measures, and we chose not to select outcome measures for analysis at random. Instead, we considered that outcomes measured broadly similar constructs, and we combined them into single outcome measures for either memory or executive function. We used correlations between measures when they were available from study reports, but when correlations were not available, we assumed a correlation of 0.5 and did not conduct sensitivity analyses using different correlations. The impact of this decision upon effect estimates was likely not important, because few studies reported memory or executive function outcomes, and most evidence on these outcomes was uncertain due to risk of bias and limited sample sizes.

Finally, although we followed recommended Cochrane methods for searching and probably found all published or registered trials, we cannot exclude the possibility of publication bias, and we strongly suspect publication bias in the assessment of cognition and ADLs in MCI when ginkgo is added to another medication regimen.

### Agreements and disagreements with other studies or reviews

The previous Cochrane review comparing ginkgo to placebo for cognitive impairment and dementia found no consistent and convincing evidence that ginkgo is beneficial in this population (Birks 2009). The current review included an additional 12 placebo-controlled studies, six of which had more than 200 participants each. We found there may be little or no benefit for subjective cognitive impairment (low-certainty evidence), there is probably little or no benefit for cognitive impairment in MS (moderate-certainty evidence), and there is little or no benefit for MCI (high-certainty evidence), except a small improvement in executive function at three and six months (low-certainty evidence). These findings are consistent with the previous review but have greater certainty. They are also consistent with the overall conclusions from two large randomized trials: that ginkgo does not prevent or delay progression from subjective complaints or MCI to dementia over five to six years of follow-up (GEM 2010; GuidAge 2008). With regard to the effects of ginkgo versus placebo for dementia, we found evidence of some benefit for global clinical status, cognition, and ADLs at six months, but the certainty of the evidence is low because of unexplained heterogeneity. These findings are based on the addition of new studies since the previous Cochrane review Birks 2009, and suggest that there is a need for further clarification about any effects of ginkgo for the treatment of dementia.

Our review findings are consistent with those of other recent systematic reviews of the effects of ginkgo versus placebo in dementia treatment. Several reviews have found that ginkgo, particularly EGb 761 at doses of 240 mg/day, has moderate to large benefits for cognition and ADLs in people with dementia, although these effect estimates have very high heterogeneity (Brondino 2013, Gauthier 2014; Hashiguchi 2015; Hyde 2017; Ihl 2013; Janssen 2010; Jiang 2013; Liao 2020; Savaskan 2018; von Gunten 2016; Weinmann 2010; Yang 2014). Some studies suggested that heterogeneity might be due to varying etiologies and pathologies of dementia (e.g. Gauthier 2014). In this review, there were insufficient data in the placebo-controlled trials to investigate effects by different types of dementia (i.e. AD versus VD). To date, there has been no systematic review of the effects of ginkgo versus placebo for dementia that has adequately explained the high heterogeneity which is present for cognition and other outcomes.

We found recent systematic reviews of ginkgo plus donepezil compared to donepezil alone for AD (Li 2023) and VD (Xiao 2024). Li 2023 assessed the included studies as having at least some risk of bias and detected possible publication bias for studies reporting the MMSE, while Xiao 2024 assessed all included studies at low risk of bias and did not detect publication bias for studies reporting the MMSE (but did suggest there could be publication bias for clinical effectiveness rate). Both reviews reported benefits of adjunctive ginkgo for cognition but observed high heterogeneity that could not be explained and suggested that additional high-quality, multicenter trials are required. This is consistent with our findings of positive effects with high heterogeneity and accompanied by suspicion of publication bias. We found no other systematic reviews examining the effectiveness of ginkgo compared to other medications or used as an adjunctive treatment to other medication regimens for MCI or dementia.

## AUTHORS' CONCLUSIONS

### Implications for practice

It is uncertain whether *Ginkgo biloba* compared to placebo improves global clinical status at six months in people with subjective cognitive impairment. Data on adverse events at six months were unavailable, but there may be an increased risk of overall adverse events at three months.

There is probably little or no difference between *Ginkgo biloba* and placebo for cognitive function at three months in people with multiple sclerosis and cognitive impairment. Data on adverse events could not be extracted, but studies did not suggest concerns.

In people with mild cognitive impairment, there is probably little or no difference between *Ginkgo biloba* and placebo for global clinical status, cognitive function, or ability to perform activities of daily living at six months. There may be little to no difference between *Ginkgo biloba* and placebo in the risk of adverse events up to 12 months, and there is little or no difference in the risk of serious adverse events up to six months.

In people with dementia, there may be small to moderate improvements in global clinical status, cognitive function, and


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ability to perform activities of daily living at six months with *Ginkgo biloba* compared to placebo. There is probably little or no difference in overall adverse events up to 12 months, and there may be little or no difference in the risk of serious adverse events up to six months.

### Implications for research

Further research on *Ginkgo biloba* in mild cognitive impairment and dementia is needed to clarify potential benefits and risks. Data on adverse events were frequently limited; these should be consistently measured and reported. Further large and well-conducted studies testing *Ginkgo biloba* as an adjunctive treatment for mild cognitive impairment or dementia, together with the most commonly used medications in these conditions, could clarify whether these combinations have potential benefits. Such studies should assess any interactions between *Ginkgo biloba* and other medications. The effects of *Ginkgo biloba* compared to placebo on cognition, activities of daily living, and other outcomes in people with dementia are variable. Future research should identify the sources of this heterogeneity and define which people are most likely to benefit, under which circumstances, and according to which specific measures. Before conducting further studies to compare *Ginkgo biloba* to placebo for dementia, it may be useful to carry out an individual participant data meta-analysis of previous studies.

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### Editorial and peer-reviewer contributions

The following people conducted the editorial process for this article.

- Sign-off Editor (final editorial decision): Dr Sarah Cullum MBChB, PhD, MRCPsych, Associate Professor/Consultant in Old Age Psychiatry, Department of Psychological Medicine, School of Medicine, Faculty of Medical and Health Sciences, The University of Auckland; Toby Lasserson, Cochrane Acting Editor-In-Chief.
- Managing Editor (selected peer reviewers, provided editorial guidance to authors, edited the article): Ben Ridley, Central Editorial Service.
- Editorial Assistant (conducted editorial policy checks, collated peer-reviewer comments and supported the editorial team): Jacob Hester, Central Editorial Service.
- Copy Editor (copy editing and production): Julia Turner, Deirdre Walshe, and Jenny Bellorini, Cochrane Central Production Service.
- Peer-reviewers (provided comments and recommended an editorial decision): Jiří Cerman, MD, PhD, Department of Neurology, Second Faculty of Medicine, Charles University and Motol University Hospital (clinical/content review); Brian Duncan (consumer review); Jennifer Hilgart, Evidence Production and Methods Directorate, Cochrane (methods review); Steve McDonald, Cochrane Australia (search review).


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* Indicates the major publication for the study

# CHARACTERISTICS OF STUDIES

## Characteristics of included studies *[ordered by study ID]*

### Brautigam 1998

| ***Study characteristics*** | |
|---|---|
| Methods | **Study design:** RCT<br><br>**Study grouping:** parallel group<br><br>**Duration of intervention:** 24 weeks treatment with ginkgo or placebo<br><br>**Duration of follow-up:** 24 weeks from initiation of treatment<br><br>**Washout or placebo run-in period:** washout of 4 weeks during which "patients stopped, wherever possible, medication which might influence memory and/or concentration." |
| Participants | **Baseline characteristics**<br><br>Geriaforce 5.7 mL<br><br>• Number randomized: 77<br>• MMSE (mean, SD): 26.30, 2.31<br>• Age (mean, SD): 69.45, 7.18<br>• % female: 59.7%<br><br>Geriaforce 2.85 mL<br><br>• Number randomized: 82<br>• MMSE (mean, SD): 26.01, 2.54<br>• Age (mean, SD): 68.6, 8.28<br>• % female: 61.0%<br><br>Placebo |


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**Brautigam 1998** *(Continued)*

- Number randomized: 82
- MMSE (mean, SD): 26.11, 2.35
- Age (mean, SD): 68.83, 7.86
- % female: 57.3

**Total number randomized:** 241

**Inclusion criteria:** "Male and female non-institutionalised patients in the age range 55-86 years were recruited from general practice populations. The physicians selected the patients on the basis of self-reported memory and/or concentration complaints."

**Exclusion criteria:** "Patients were excluded from the study in case of mild/serious cognitive insufficiency (Mini Mental State Examination: score < 20) and depressive mood (Beck Depression Inventory: score ≥ 21), memory loss of known origin, which can/must be treated in a different way, psychosis and secondary cerebral insufficiency (intoxication, metabolic). Other exclusion criteria were severe internal disorders (renal insufficiency, liver insufficiency, diabetes mellitus, gastrointestinal disorders and cardiac insufficiency), malignancies (relevant for efficacy and tolerance of test medication), alcohol and medication abuse. Patients taking medication with explicit anticholinergic effect and patients using Ginkgo products during the last 3 months were excluded as well."

**Country:** the Netherlands

**Setting:** outpatient

**Date recruitment began:** 1996

**Recruitment methods:** recruited from 22 general practices

**Diagnosis:** memory impairment with MMSE ≥ 20

**Diagnostic criteria:** self-reported memory or concentration complaint

Interventions

**Intervention characteristics**

Geriaforce 2.85 mL

- "The alcohol/water extract of fresh leaves of Ginkgo biloba (composition: Ginkgo biloba L. folium, ethanol 70%v/v, drug extract ratio 1:4, total flavone glycosides 0.20 mg/ml, total ginkgolides 0.34 mg/ml; trade name Geriaforcev)" was obtained from Biohorma B.V., Elburg, The Netherlands." "The following dosages were used (taken with some water): ... Low dose (LO): 40 drops (1.9 ml) (Ginkgo extract 1:1 with placebo), 3 times daily. Placebo (PL): 40 drops (1.9 ml), 3 times daily."

Geriaforce 5.7 mL

- "The alcohol/water extract of fresh leaves of Ginkgo biloba (composition: Ginkgo biloba L. folium, ethanol 70%v/v, drug extract ratio 1:4, total flavone glycosides 0.20 mg/ml, total ginkgolides 0.34 mg/ml; trade name Geriaforcev)" was obtained from Biohorma B.V., Elburg, The Netherlands." "The following dosages were used (taken with some water): high dose (HO): 40 drops (1.9 ml) undiluted Ginkgo extract (using a measuring cup), 3 times daily."

Placebo

- "Water-soluble chlorophyll powder (Merck 2468 ) was dissolved in an alcohol/water mixture (90% v/v). The water-insoluble chlorophyll (derived from gallnuts obtained from Omnichem, Belgium) was dissolved in alcohol (96% v/v). The two chlorophyll solutions were combined and stirred thoroughly. To adjust the colour, water-soluble caramel powder (Techno-color Holland) was added to the chlorophyll solution and filtered until a clear solution was obtained." "The following dosages were used (taken with some water): ... Placebo (PL): 40 drops (1.9 ml), 3 times daily. Taste and colour of the 3 dosages were compared and judged as similar by 30 volunteers."

Outcomes

**Outcomes collected**


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**Brautigam 1998** *(Continued)*

- Participant and physician subjective evaluation of memory, or concentration, or both (participant rated on Likert scale from 1 = very frequent, to 5 = no; and physician rated on Likert scale from 1 = no complaints to 5 = very frequent complaints)
- Participant and physician rating at end of treatment of efficacy and tolerance of treatment (Likert scales from 1–5)
- Beck Depressive Inventory (BDI)
- Expanded Mental Control Test (EMCT)
- Benton Test of Visual Retention – Revised
- 15 Words of Rey (part 1 and 2)
- Adverse events (total number of events)

| | |
|---|---|
| Notes | **Sponsorship source:** none reported. However, the address for the contact author is the company producing the test product (Biopharma BV) and therefore we believe that Biopharma BV is the sponsor and funder.<br><br>**Trial registration number:** none reported |

***Risk of bias***

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Random sequence generation (selection bias) | Low risk | After the wash-out period, the participants were randomly allocated using a computerized generator to receive either *G biloba* alcohol/water extract in a high dose (HD), a low dose (LD) or a placebo (PL). |
| Allocation concealment (selection bias) | Unclear risk | Delivery of assignments to participants is not described. |
| Blinding of participants and personnel (performance bias)<br>All outcomes | Low risk | Finally, the double-blind situation was checked by asking the participants in which treatment group they believed they were. |
| Blinding of outcome assessment (detection bias)<br>All outcomes | Low risk | Stated to be double-blind. Twenty-two general practitioners participated in this multicenter, randomized, double blind and placebo-controlled study. Two assistant psychologists were trained by a clinical psychologist to let the participants perform the psychometric test battery in a standard way. |
| Incomplete outcome data (attrition bias)<br>All outcomes | Unclear risk | Almost 20% lost to follow-up, although numbers and reasons seem equally divided between groups and the study authors state that complete cases were random. |
| Selective reporting (reporting bias) | Unclear risk | Although the outcomes corresponded between methods and results, there was no published protocol describing planned outcomes and analysis methods. |
| Other bias | Low risk | The study appears to be free of other sources of bias. |

**Bu 2016**

***Study characteristics***

| | |
|---|---|
| Methods | **Study design:** RCT<br><br>**Study grouping:** parallel group |


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**Bu 2016** *(Continued)*

**Duration of intervention:** 3 months

**Duration of follow-up:** 3 months

**Washout or placebo run-in period:** none reported

| | |
|---|---|
| Participants | **Baseline characteristics**<br><br>*G biloba* + donepezil + atorvastin + aspirin<br><br>• Number randomized: 47<br>• MMSE (mean, SD): NR<br>• Age (mean, SD): NR<br>• % female: NR<br><br>Donepezil + atorvastin + aspirin<br><br>• Number randomized: 40<br>• MMSE (mean, SD): NR<br>• Age (mean, SD): NR<br>• % female: NR<br><br>**Total number randomized:** 87<br><br>**Inclusion criteria**<br><br>• Diagnostic criteria for VCIND in DSM-V<br>• Brain CT or MRI examination confirmed cerebrovascular disease<br><br>**Exclusion criteria**<br><br>• Hypertension, diabetes, severe depression, anxiety, and other diseases<br>• Rankin Scale score > 4 or obvious aphasia and dysarthroscopy that affected the assessment of cognitive function<br><br>**Country:** China<br><br>**Setting:** hospital<br><br>**Date recruitment began:** 2015<br><br>**Recruitment methods:** a total of 87 people with VCIND admitted to the Affiliated Hospital of Inner Mongolia University for Nationalities from August 2015 to June 2016 were selected.<br><br>**Diagnosis:** VCIND<br><br>**Diagnostic criteria:** diagnostic criteria for VCIND in DSM-V |
| Interventions | **Intervention characteristics**<br><br>*G biloba* + donepezil + atorvastin + aspirin<br><br>For 3 consecutive months:<br><br>• aspirin enteric-coated tablet 100 mg, once a day;<br>• oral atorvastatin calcium tablet 20 mg once a day;<br>• donepezil hydrochloride tablets 5 mg 3 times/day; and<br>• *G biloba* soft capsule 0.9 g, 3 times/day.<br><br>Donepezil + atorvastin + aspirin<br><br>For 3 consecutive months: |


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**Bu 2016** *(Continued)*

- aspirin enteric-coated tablet 100 mg once a day;
- oral atorvastatin calcium tablet 20 mg once a day; and
- donepezil hydrochloride tablets 5 mg 3 times/day.

| | |
|---|---|
| Outcomes | **Outcomes collected**<br>• Montreal Cognitive Assessment (MoCA)<br>• ADL<br>• Laboratory tests<br>• Adverse events |
| Notes | **Sponsorship source:** Science and Technology Project of Inner Mongolia Autonomous Region (2015-2016)<br>**Trial registration number:** none reported<br>**Note:** we contacted the study author for details of randomization and coin flip was reported. |

***Risk of bias***

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Random sequence generation (selection bias) | Low risk | Coin flip (study author's reply on 5 May 2021). |
| Allocation concealment (selection bias) | Unclear risk | Not reported. |
| Blinding of participants and personnel (performance bias)<br>All outcomes | High risk | Not reported. However, since the treatment and drug delivery route in the treatment group are distinct from that in the control group, it is likely that the outcomes have been influenced by lack of blinding. |
| Blinding of outcome assessment (detection bias)<br>All outcomes | Unclear risk | Not reported. Unclear the extent the outcomes to be influenced by lack of blinding. |
| Incomplete outcome data (attrition bias)<br>All outcomes | Low risk | "During the 3 months of treatment, 3 cases in the observation group and 2 cases in the control group were lost to follow-up, and no adverse reactions were observed in the other patients." 3% dropout rate and numbers comparable between the groups. |
| Selective reporting (reporting bias) | Unclear risk | No protocol available. Insufficient information to permit judgment of 'low risk' or 'high risk'. |
| Other bias | Low risk | No other apparent sources of bias. |

**Chen 2014a**

***Study characteristics***

| | |
|---|---|
| Methods | **Study design:** RCT<br>**Study grouping:** parallel group<br>**Duration of intervention:** 3 months |


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**Chen 2014a** *(Continued)*

**Duration of follow-up:** 3 months

**Washout or placebo run-in period:** none reported

Participants

**Baseline characteristics**

*G biloba*

- Number randomized: 48
- MMSE (mean, SD): 18.49, 2.327
- Age (mean, SD): 49, 89
- % female: 43.75

Chinese herbal decoction

- Number randomized: 48
- MMSE (mean, SD): 18.25, 2.306
- Age (mean, SD): 52, 94
- % female: 47.92

**Total number randomized:** 96

**Inclusion criteria:** "referred to the fourth edition of the American Statistical and Diagnostic Manual of Mental Disorders (DSM-IV), the diagnostic criteria of dementia and the diagnostic criteria of dementia in the Internal Medicine of Traditional Chinese Medicine were comprehensively formulated. (1) Multiple cognitive deficits are manifested as memory deficits or at least one of the following cognitive impairments: aphasia, apraxia, agnosia, and impairment of executive management function. (2) These cognitive deficits lead to impairments in social or vocational functions, and these functions may be found to be significantly less than before. (3) Focal neurological signs and symptoms (e.g., pseudobulbar palsy, abnormal gait, weakness of a limb) or laboratory evidence suggesting cerebrovascular disease may be the cause of the disorder."

**Exclusion criteria**

- Disorders of consciousness
- Dementia caused by other neurological diseases (e.g. Alzheimer's disease)
- Dementia caused by systemic diseases
- Mental diseases

**Country:** China

**Setting:** outpatient

**Date recruitment began:** 2010

**Recruitment methods:** a total of 96 outpatients were selected from July 2010 to February 2014.

**Diagnosis:** VD

**Diagnostic criteria:** the DSM-IV, the diagnostic criteria of dementia and the diagnostic criteria of dementia in the Internal Medicine of Traditional Chinese Medicine

Interventions

**Intervention characteristics**

*G biloba*

- Ginkgo dispersible tablets produced by Shenyang Gelin Pharmaceutical Co, Ltd (national drug approval Z20060440, 0.5/tablet) 500 mg tablet 3 times/day (total 1500 mg/day)

Chinese herbal decoction

- "Yinyanghuo (Epimedii folium) 6 g, Nuzhenzi (Ligustri Lucidi Fructus) 6 g, Gouqizi (Lycii Fructus) 6 g, Zhiheshouwu (Polygoni Multiflori Radix Praeparata) 6 g, Tusizi (Cuscutae Semen) 12 g, Huangjing


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**Chen 2014a** *(Continued)*

| | |
|---|---|
| | (Polygonati Rhizoma) 12 g, Huangqi (Astragali Radix) 9 g, Danggui (Angelicae Sinensis Radix) 8 g, Danshen (Sal Viae Miltiorrhizae Radix et Rhizoma) 6 g, Shanzha (Crataegi Fructus) 9 g. 1 dose/day, morning and evening after each meal to take 200 mL (warm)." |
| Outcomes | **Outcomes collected**<br>• MMSE<br>• ADL<br>• Effective rate |
| Notes | **Sponsorship source:** not stated<br>**Trial registration number:** none reported<br>**Note:** information from internet indicates that each tablet weighed 0.5g (each tablet contained 19.2 mg of total flavonol glycosides and 4.8 mg of terpenoid lactones) |

***Risk of bias***

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Random sequence generation (selection bias) | Low risk | Random number table |
| Allocation concealment (selection bias) | Unclear risk | Not reported |
| Blinding of participants and personnel (performance bias)<br>All outcomes | High risk | Not reported. However, since the treatment and drug delivery route in the treatment group are distinct from that in the control group, it is likely that the outcomes have been influenced by lack of blinding. |
| Blinding of outcome assessment (detection bias)<br>All outcomes | Unclear risk | Not reported. Unclear the extent the outcomes to be influenced by lack of blinding. |
| Incomplete outcome data (attrition bias)<br>All outcomes | Unclear risk | Not reported |
| Selective reporting (reporting bias) | Unclear risk | No protocol available. Insufficient information to permit judgment of 'low risk' or 'high risk'. |
| Other bias | Low risk | No other apparent sources of bias. |

**Demarin 2017**

***Study characteristics***

| | |
|---|---|
| Methods | **Study design:** RCT<br>**Study grouping:** parallel group<br>**Duration of intervention:** 6 months<br>**Duration of follow-up:** 6 months |


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**Demarin 2017** *(Continued)*

| | |
|---|---|
| | **Washout or placebo run-in period:** no |
| Participants | **Baseline characteristics**<br><br>EGb 761 60 mg<br><br>• Number randomized: 19<br>• MMSE (mean, SD): 25.1, 2.3<br>• Age (mean, SD): NR<br>• % female: NR<br><br>EGb 761 120 mg<br><br>• Number randomized: 20<br>• MMSE (mean, SD): 26.0, 2.6<br>• Age (mean, SD): NR<br>• % female: NR<br><br>Placebo<br><br>• Number randomized: 19<br>• MMSE (mean, SD): 26.4, 2.3<br>• Age (mean, SD): NR<br>• % female: NR<br><br>**Total number randomized:** 58<br><br>**Inclusion criteria:** "age >=50 years; fulfilled VCI criteria based on cerebrovascular insufficiency and Folstein Mini-Mental State Examination (MMSE) score of >20 and ≤28; completed initial screening; for women, postmenopause or use of contraception"<br><br>**Exclusion criteria:** "symptoms caused by psychiatric, metabolic, endocrine, nutritional, or heart disease; epilepsy, liver or kidney failure, uncontrolled diabetes mellitus, or hypertension; malignancy; history of myocardial infarction in the previous 6 months; alcohol or drug abuse; use of the following drugs: ticlopidine, clopidogrel, pentoxifylline, acetylsalicylic acid, dihydroergotamine, warfarin, and/or etibiskumacetate; and a positive pregnancy test in women."<br><br>**Country:** Croatia<br><br>**Setting:** outpatient<br><br>**Date recruitment began:** 2007<br><br>**Recruitment methods:** "patients presenting with VCI symptoms at the Outpatient Clinic of the Department of Neurology of “Sestre Milosrdnice” University Hospital from May 2007 to April 2010"<br><br>**Diagnosis:** vascular cognitive impairment (VCI)<br><br>**Diagnostic criteria:** "VCI criteria based on cerebrovascular insufficiency [not further explained] and Folstein Mini-Mental State Examination (MMSE) score of >20 and ≤28" |
| Interventions | **Intervention characteristics**<br><br>EGb 761 60 mg<br><br>• 60 mg of standardized extract of *G biloba* dry leaf as EGb 761, containing 24% flavonol glycosides and 6% terpenes. Participants were randomly assigned to receive 1 placebo tablet and 1 *G biloba* tablet daily (a total of 60 mg of *G biloba* extract) for 6 months. Participants were instructed to swallow the tablets whole, without breaking them, after a meal every day.<br><br>EGb 761 120 mg |


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**Demarin 2017** *(Continued)*

- 120 mg of standardized extract of *G biloba* dry leaf as EGb 761, containing 24% flavonol glycosides and 6% terpenes. Participants were randomly assigned to receive two *G biloba* tablets daily (a total of 120 mg of *G biloba* extract) for 6 months. Participants were instructed to swallow the tablets whole, without breaking them, after a meal every day.

Placebo

- Participants were randomly assigned to receive 2 placebo tablets daily for 6 months. The placebo tablet was identical to the active tablet in size, color, and shape (white and round tablet). The odor and taste of tablets were masked. Participants were instructed to swallow the tablets whole, without breaking them, after a meal every day. Content NR

"As for concomitant therapy, medications for cardiovascular conditions, neurological conditions, and nonsteroidal anti-inflammatory drugs (except acetylsalicylic acid) were most frequently used among the subjects."

Outcomes

**Outcomes collected**

- Mattis Dementia Rating Scale (MDRS)
- Clinical Global Impression Scale (CGI)
- Sandoz Clinical Assessment Geriatric Scale (SCAG)
- Folstein Mini-Mental State Examination (MMSE)
- Transcranial duplex ultrasound
- Carotid and vertebral arteries ultrasound
- Laboratory tests (complete blood cell count, blood glucose, urea, creatinine, and others)

Notes

**Sponsorship source:** "The study was sponsored by Milsing d.o.o. The Ginkgo biloba standardized extract and placebo were donated by a company Milsing d.o.o."

**Trial registration number:** NCT00446485

**Note:** outcome data provided in email to EL by Dr Demarin on 15 November 2021

***Risk of bias***

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Random sequence generation (selection bias) | Low risk | "The block randomization was used to randomize subjects into three groups with equal sample sizes. Each box carried a unique drug number (code) that was generated and assigned to the active drug and placebo." |
| Allocation concealment (selection bias) | Low risk | "The randomization codes were stored in a locked compartment at the sponsors' office. The sealed envelopes were also given to the principal investigator and were inaccessible to other staff involved in the trial. The block length was not disclosed to the investigators or clinical staff. This procedure ensured both double-blinding and concealment of allocation sequence." |
| Blinding of participants and personnel (performance bias)<br>All outcomes | Low risk | Double-blinded, and participants and personnel unaware of treatment assignments. The placebo tablet was identical to the active tablet in size, color, and shape (white and round tablet). The odor and taste of tablets were masked. Participants were instructed to swallow the tablets whole, without breaking them, after a meal every day. |
| Blinding of outcome assessment (detection bias)<br>All outcomes | Low risk | Double-blinded, sealed envelopes inaccessible to investigators and clinical staff involved in trial. The randomization codes were stored in a locked compartment at the sponsors' office. The sealed envelopes were also given to the principal investigator and were inaccessible to other staff involved in the trial. |
| Incomplete outcome data (attrition bias) | High risk | Numbers and reasons for loss to follow-up were given, and the participants who completed and discontinued were similar, but the rate of loss to fol- |


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**Demarin 2017** *(Continued)*

| | | |
|---|---|---|
| All outcomes | | low-up was very high (28%). No ITT sensitivity analyses for treatment success or other outcomes. |
| Selective reporting (reporting bias) | High risk | Not all of the study's prespecified primary outcomes were reported; VFT not reported though was listed in trial protocol as a primary outcome measure. Protocol registration prespecified outcomes to be measured at 6 months but additional analyses done and reported at 3 months. |
| Other bias | Low risk | The study appears to be free of other sources of bias. |

**Deng 2021**

| | |
|---|---|
| ***Study characteristics*** | |
| Methods | **Study design:** RCT<br><br>**Study grouping:** parallel group<br><br>**Duration of intervention:** 3 months<br><br>**Duration of follow-up:** 3 months<br><br>**Washout or placebo run-in period:** no |
| Participants | **Baseline characteristics**<br><br>*G biloba* + donepezil<br><br>• Number randomized: 29<br>• MMSE (mean, SD): 16.34, 2.75<br>• Age (mean, SD): 65.63, 5.53<br>• % female: 37.9%<br><br>Donepezil<br><br>• Number randomized: 29<br>• MMSE (mean, SD): 16.54, 3.22<br>• Age (mean, SD): 64.63, 4.67<br>• % female: 41.4%<br><br>**Total number randomized:** 58<br><br>**Inclusion criteria:** cognitive impairment after infarction<br><br>**Exclusion criteria:** NR<br><br>**Country:** China<br><br>**Setting:** unclear, may be inpatient or outpatient<br><br>**Date recruitment began:** 2020<br><br>**Recruitment methods:** patients with cerebral infarction who visited the author's hospital from January 2020 to March 2021 were recruited<br><br>**Diagnosis:** cognitive impairment after infarction<br><br>**Diagnostic criteria:** NR |
| Interventions | **Intervention characteristics** |


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**Deng 2021** *(Continued)*

| | |
|---|---|
| | *G biloba* plus donepezil<br>• On the basis of the donepezil group, the group additionally received 19.2 mg of *G biloba* leaves, orally 3 times a day.<br>Donepezil<br>• Donepezil 5 mg, orally at night, once a day |
| Outcomes | **Outcomes collected**<br>• ADL<br>• MMSE<br>• Hasegawa Dementia Scale (HDS)<br>• Adverse reactions (no adverse reactions in the 2 groups during treatment) |
| Notes | **Sponsorship source:** none<br>**Trial registration number:** NR |

***Risk of bias***

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Random sequence generation (selection bias) | Low risk | Random number table. |
| Allocation concealment (selection bias) | Unclear risk | No mention of allocation concealment. |
| Blinding of participants and personnel (performance bias)<br>All outcomes | Unclear risk | No mention of blinding. |
| Blinding of outcome assessment (detection bias)<br>All outcomes | Unclear risk | No mention of blinding. |
| Incomplete outcome data (attrition bias)<br>All outcomes | Low risk | No attrition. |
| Selective reporting (reporting bias) | Unclear risk | No protocol or trial registration. |
| Other bias | Low risk | No other apparent sources of bias. |

**DIGGER 2008**

***Study characteristics***

| | |
|---|---|
| Methods | **Study design:** RCT<br>**Study grouping:** parallel group<br>**Duration of intervention:** 6 months |


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**DIGGER 2008** *(Continued)*

**Duration of follow-up:** 6 months

**Washout or placebo run-in period:** none

| | |
|---|---|
| Participants | **Baseline characteristics**<br><br>*G biloba*<br><br>• Number randomized: 88<br>• MMSE (mean, SD): median 23.0, 10th percentile to 90th percentile 16.9 to 26.0<br>• Age (mean, SD): 79.3, 7.77<br>• % female: 58.0<br><br>Placebo<br><br>• Number randomized: 88<br>• MMSE (mean, SD): median 22.0, 10th percentile to 90th percentile 13.0 to 25.1<br>• Age (mean, SD): 79.7, 7.53<br>• % female: 63.6<br><br>**Total number randomized:** 176<br><br>**Inclusion criteria:** "Inclusion criteria were: aged 55 years or over; presence of a carer; informed consent or if lacking capacity, their assent and the agreement of their nominated carer; sufficient command of English; clinical diagnosis of dementia (subsequently sub-classified using DSM-IV criteria)(American Psychiatric Association, 2000); a MiniMental State Examination (MMSE) (Folsteinet al.,1975) score of 12–26 inclusive; living in the community."<br><br>**Exclusion criteria:** "Exclusion criteria were: use of Ginkgo in 2 weeks prior to the baseline assessment; commencement of cholinesterase inhibiting drugs within 2 months of baseline or during follow-up; concomitant warfarin therapy; known bleeding abnormalities [a link has been suggested between life-threatening risk of haemorrhage (Vale, 1998; Kayne, 2001) and the ingestion of Ginkgo; therefore we considered a history of abnormal clotting or the use of anti-coagulation therapy grounds for exclusion]"<br><br>**Country:** UK<br><br>**Setting:** outpatient<br><br>**Date recruitment began:** 2003<br><br>**Recruitment methods:** "We recruited participants in Greater London (UK) and adjoining regions through referrals from general practices, old age psychiatrists and other health care professionals; and from direct responses to advertising in Alzheimer Society newsletters, London-based newspapers, and posters in Age Concern centres." "A total of 119 GP practices agreed to recruit participants for the trial (representing 388 individual GPs). One hundred and thirty-two participants (75%) were recruited through their GP; 29 (16%) through psychiatrists and 15 (9%) from other sources (mainly other health professionals and advertisements)."<br><br>**Diagnosis:** dementia<br><br>**Diagnostic criteria:** clinical diagnosis of referring physician |
| Interventions | **Intervention characteristics**<br><br>*G biloba*<br><br>• "Active treatment was a standardised, concentrated Ginkgo biloba extract (EGb 7611) containing 24% Ginkgo-flavone glycosides and 6% terpene lactones". Dose was 120 mg/day.<br><br>Placebo |


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**DIGGER 2008** *(Continued)*

- "To facilitate blinding, the lactose-based placebo were identically packaged and labelled, physically indistinguishable tablets containing traces of quinine hydrochloride to mimic the bitter taste of Ginkgo".

"In keeping with the pragmatic nature of the study, other interventions were allowed during the trial, but commencement of an AChI was grounds for withdrawal." At baseline 33% of each group was on AChI.

| | |
|---|---|
| Outcomes | **Outcomes collected**<br>• Cognitive functioning, as measured by the ADAS-Cog<br>• Quality of life, rated by the participant and their nominated carer, as measured by the QOL-AD<br>• Psycho-pathology and the resulting distress to the carer, as measured by the Neuro-Psychiatric Inventory with caregiver Distress scale (NPI-D)<br>• Caregiver-reported daily living and social behavior score, as measured by the Geriatric Evaluation by Relative's Rating Instrument (GERRI)<br>• Caregiver-reported burden of caring as measured by the 12-item Zarit Burden Interview (ZBI)<br>• A report of caregiver health, as measured by the visual analogue scale of the European Quality of Life Visual Analogue Scale (EQ-VAS)<br>• A caregiver-reported global measure of benefit, by asking at the final follow-up, 'If you could continue the medication the person you care for has been receiving in this trial, would you (do you feel that it has helped him/her)?'(Answer: yes or no)<br>• Blood coagulation times as measured by Activated Clotting Time (ACT) using near-patient testing with the Coaguchek Pro DM1(Roche Diagnostics, Germany<br>• Adverse events |
| Notes | **Sponsorship source:** Alzheimer's Society (grant ref: QRD/2001/01/07<br>**Trial registration number:** ISRCTN45577048<br>**Note:** outcomes all provided in McCarney 2008 Table 3 as adjusted difference with confidence intervals between groups. Positive values favor ginkgo (even if this is opposite to the scale direction). |

***Risk of bias***

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Random sequence generation (selection bias) | Low risk | The randomization codes were generated using the computer algorithm RCODE v.4.8 (Schwabe, 2002). |
| Allocation concealment (selection bias) | Low risk | Study medication was randomized in blocks of 2 and blocks were allocated to a general practice when a participant was recruited from that practice. Participants were allocated a code on entry into the trial by the researcher. |
| Blinding of participants and personnel (performance bias)<br>All outcomes | Low risk | Researchers undertaking the analysis and the trial statistician remained blind until completion of the analysis defined in the analysis protocol. Participants, their carers and clinicians responsible for the participant (GPs and consultants) remained blinded to the allocation during their participation. Success of blinding was tested by asking the researcher undertaking assessments and the carer to indicate whether they believed the participant had been taking ginkgo or placebo. |
| Blinding of outcome assessment (detection bias)<br>All outcomes | Low risk | Researchers undertaking the analysis and the trial statistician remained blinded until completion of the analysis defined in the analysis protocol. |
| Incomplete outcome data (attrition bias)<br>All outcomes | Unclear risk | Numbers of withdrawals with reasons documented for both groups, and numbers were similar (with exception of withdrawal due to treatment ineffective (n = 5) solely in ginkgo group) but overall very high (25%). Multiple imputation |


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**DIGGER 2008** *(Continued)*

| | | |
|---|---|---|
| | | assuming missing at random was carried out to allow intention-to-treat (ITT) analysis and this was compared to analyses with evaluable data and per protocol analyses. |
| Selective reporting (reporting bias) | Unclear risk | Study report was consistent with trial registration, with the exception of the version of the NPI (study report used both NPI and NPI-D but only NPI was mentioned in the registration, however only NPI was extracted for this review) and the caregiver-measured global report of benefit, which was not mentioned in the registration. Also, protocol and report list EQ-5D but reporting of outcomes reports EQ-VAS and it is not clear that these are identical. |
| Other bias | Low risk | The study appears to be free of other sources of bias. |

**Dong 2011**

| ***Study characteristics*** | |
|---|---|
| Methods | **Study design:** RCT<br><br>**Study grouping:** parallel group<br><br>**Duration of intervention:** 6 months and 12 months<br><br>**Duration of follow-up:** 12 months<br><br>**Washout or placebo run-in period:** none reported |
| Participants | **Baseline characteristics**<br><br>*G biloba* + basic treatment<br><br>• Number randomized: 58<br>• MMSE (mean, SD): 25.78, 1.20<br>• Age (mean, SD): 72.78, 5.03<br>• % female: 70.69<br><br>Basic treatment<br><br>• Number randomized: 55<br>• MMSE (mean, SD): 25.62, 1.24<br>• Age (mean, SD): 73.53, 5.97<br>• % female: 58.18<br><br>**Total number randomized:** 113<br><br>**Inclusion criteria**<br><br>• Memory decline complaint from participants themselves, families or relatives<br>• Memory test results 1.5 SD less than control group after control for age and education<br>• Global Deterioration Scale 2 to 3; or clinical dementia rating (CDR) 0.5<br>• Normal general cognitive function<br>• Normal ADL<br>• Not dementia nor any physical/mental disease which can result in brain disorder<br>• WMS-RC < 100 and MMSE between 24 to 27<br>• Age between 60 to 85<br>• Informed consent<br><br>**Exclusion criteria** |


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**Dong 2011** *(Continued)*

- Illiteracy
- Depression scale, HAM-D, ≥ 17
- Dementia or any physical/mental disease which can result in brain disorder
- Serious concurrent cardiovascular, liver, kidney or hematopoietic system disease

**Country:** China

**Setting:** outpatient

**Date recruitment began:** 2009

**Recruitment methods:** from September 2009 to February 2011, people with MCI who were treated in the TCM Cognitive Disorders Clinic of Huadong Hospital, Fudan University (58 cases), the TCM Cognitive Disorders Clinic of Dongfang Hospital, Tongji University (34 cases), and the Community Health Service Center, Fulin Street, Shanghai (21 cases)

**Diagnosis:** MCI

**Diagnostic criteria:** diagnosis of MCI based on relevant literature criteria: MMSE score of 24 to 27 points. Global Deterioration Scale 2–3, still maintains general function, may have increased difficulties in daily living, and ADL scale score < 26.

| | |
|---|---|
| Interventions | **Intervention characteristics**<br><br>*G biloba* + basic treatment<br><br>• Basic treatment [general health education (actively adjust and treat old diseases, keep mood relaxed), moderate exercise (walking: 1000 m, once in the morning and once in the evening), body exercise (handball: 30 min/day, twice a day), general reasonable nutritional support, etc.]. Oral administration of EGb Tablet (Si Tai Long, 80 mg/tablet, containing *G biloba* total flavonoid 9.6 mg, produced by Shanghai Xingling Technology Pharmaceutical Co., Ltd., batch number: 100509), 1 tablet each time, 3 times a day, for consecutive 1 year. Dose 240 mg/day.<br><br>Basic treatment<br><br>• Basic treatment [general health education (actively adjust and treat old diseases, keep mood relaxed), moderate exercise (walking: 1000 m, once in the morning and once in the evening), body exercise (handball: 30 min/day, twice a day), general reasonable nutritional support, etc.] |
| Outcomes | **Outcomes collected**<br><br>• MMSE<br>• Logical memory (LM)<br>• Clock drawing task (CDT)<br>• Prevalence of dementia<br>• Adverse events<br>• Distribution of TCM syndrome differentiation<br>• MQ measured by WMS-RC |
| Notes | **Sponsorship source:** Project of Shanghai Science and Technology Commission (No.08DZ1972600); Chinese Medicine Scientific Research Fund of Shanghai Health Bureau (No.2010J001A)<br><br>**Trial registration number:** none reported |

***Risk of bias***

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Random sequence generation (selection bias) | Low risk | Random number table. |


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**Dong 2011** *(Continued)*

| | | |
|---|---|---|
| Allocation concealment (selection bias) | Unclear risk | Not reported. |
| Blinding of participants and personnel (performance bias)<br>All outcomes | High risk | One group took the drug, while the other group did not. |
| Blinding of outcome assessment (detection bias)<br>All outcomes | Unclear risk | Not reported. |
| Incomplete outcome data (attrition bias)<br>All outcomes | Unclear risk | Not reported. |
| Selective reporting (reporting bias) | Unclear risk | No protocol. |
| Other bias | Low risk | No other apparent sources of bias. |

**Dong 2021**

| | |
|---|---|
| ***Study characteristics*** | |
| Methods | **Study design:** RCT<br><br>**Study grouping:** parallel group<br><br>**Duration of intervention:** 6 months<br><br>**Duration of follow-up:** 6 months<br><br>**Washout or placebo run-in period:** none reported |
| Participants | **Baseline characteristics**<br><br>*G biloba* + Idebenone<br><br>• Number randomized: 37<br>• MMSE (mean, SD): 16.14, 2.03<br>• Age (mean, SD): 65.45, 3.27<br>• % female: 27.0<br><br>Idebenone<br><br>• Number randomized: 37<br>• MMSE (mean, SD): 16.32, 2.11<br>• Age (mean, SD): 66.22, 3.42<br>• % female: 29.7<br><br>**Total number randomized:** 74<br><br>**Inclusion criteria:** consistent with the clinical symptoms of VaD; cognitive dysfunction and neurological dysfunction; pathological changes of cerebrovascular disease were confirmed by brain biopsy. There were no pathological neurofibrillary tangles and senile plaques. There were no other causes of pathological changes in dementia. Age ≥ 60 years old; can cooperate with clinical examination and complete follow-up observation; patients gave informed consent. |


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**Dong 2021** *(Continued)*

**Exclusion criteria**

- Mixed dementia
- History of carbon monoxide poisoning
- Severe mental disorders
- Serious heart, lung, liver, kidney, and other important organ diseases

**Country:** China

**Setting:** inpatient

**Date recruitment began:** 2017

**Recruitment methods:** not reported

**Diagnosis:** VD

**Diagnostic criteria:** consistent with the clinical symptoms of vascular dementia; cognitive dysfunction and neurological dysfunction; pathological changes of cerebrovascular disease were confirmed by brain biopsy. There were no pathological neurofibrillary tangles and senile plaques. There were no other causes of pathological changes in dementia.

| | |
|---|---|
| Interventions | **Intervention characteristics**<br><br>*G biloba* + Idebenone<br><br>• *G biloba* capsules (Guilin Honghui Pharmaceutical Co, Ltd, Z20026289, 0.25g/capsule). Take 2 capsules orally 3 times daily. Dose *G biloba* 1.5 g/day + Idebenone 90 mg/day.<br><br>Idebenone<br><br>• Idebenone (Qilu Pharmaceutical Co, Ltd, H10970137, 30 mg/tablet). Oral administration of 30 mg three times a day after meals. Dose 90 mg/day. |
| Outcomes | **Outcomes collected**<br><br>• MMSE<br>• HDS<br>• S-100b proteins<br>• Neuron-specific enolase |
| Notes | **Sponsorship source:** not reported<br><br>**Trial registration number:** none reported |

***Risk of bias***

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Random sequence generation (selection bias) | Low risk | Random number table. |
| Allocation concealment (selection bias) | Unclear risk | Not reported. |
| Blinding of participants and personnel (performance bias)<br>All outcomes | High risk | Not reported. However, since the treatment and drug delivery route in the treatment group are distinct from that in the control group, it is likely that the outcomes have been influenced by lack of blinding. |


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**Dong 2021** *(Continued)*

| | | |
|---|---|---|
| Blinding of outcome assessment (detection bias) All outcomes | Unclear risk | Not reported. Unclear to what extent the outcomes were influenced by lack of blinding. |
| Incomplete outcome data (attrition bias) All outcomes | Unclear risk | Not reported. |
| Selective reporting (reporting bias) | Unclear risk | No protocol available. Insufficient information to permit judgment. |
| Other bias | Low risk | No other apparent sources of bias. |

**EUCTR2005-005765-11-EE**

| ***Study characteristics*** | |
|---|---|
| Methods | **Study design:** RCT<br><br>**Study grouping:** parallel group<br><br>**Duration of intervention:** 12 weeks<br><br>**Duration of follow-up:** 12 weeks<br><br>**Washout or placebo run-in period:** none |
| Participants | **Baseline characteristics**<br><br>EGb 761<br><br>• Number randomized: 149<br>• MMSE (mean, SD): 29, 1.29<br>• Age (mean, SD): 54, 6<br>• % female: 74.5%<br><br>Placebo<br><br>• Number randomized: 147<br>• MMSE (mean, SD): 29, 1.29<br>• Age (mean, SD): 55, 6<br>• % female: 78.2%<br><br>**Total number randomized:** 296<br><br>**Inclusion criteria:** "Patients included were men or women (aged 45 to 65 years) who had a subjectively perceived mental impairment present for at least 3 months. In order to be eligible for study inclusion, all patients were required to have a widely preserved general cognitive functioning, as evidenced by a total score above 23 in the Mini-Mental Status Examination (MMSE) without an indication of dementia. The patients were included into this study on the grounds that they subjectively perceived some mild cognitive decline and some slight affective-emotional disturbance."<br><br>**Exclusion criteria:** any "indication of dementia"<br><br>**Country:** Estonia<br><br>**Setting:** outpatient<br><br>**Date recruitment began:** 2006 |


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**EUCTR2005-005765-11-EE** *(Continued)*

**Recruitment methods:** "The study was conducted in 10 study centres in Estonia."

**Diagnosis:** subjectively perceived mental impairment present for at least 3 months.

**Diagnostic criteria:** ascertained by subjective complaints together with MMSE > 23 and no indication of dementia

Interventions

**Intervention characteristics**

EGb 761

- "One tablet contains: 240 mg dry extract from Ginkgo biloba leaves (35-67:1), extraction solvent: acetone 60% (w/w). The extract is adjusted to 22.0 – 27.0 % ginkgo flavonoids calculated as ginkgo flavone glycosides and 5.0 – 7.0 % terpene lactones consisting of 2.8 – 3.4 % ginkgolides A, B, C and 2.6 – 3.2 % bilobalide and contains less than 5 ppm ginkgolic acids." "One film-coated tablet of 240 mg EGb 761® or matching placebo once per day."

Placebo

- "One film-coated tablet of 240 mg EGb 761® or matching placebo once per day." "twelve weeks of double-blind treatment, according to the protocol."

Outcomes

**Outcomes collected**

- Questionnaire for Assessing Subjectively Experienced Memory Performance in Everyday Life (*Fragebogen zur Erfassung alltäglicher Gedächtniserfahrungen* [FEAG])
- Trail-Making Test (TMT)
- Change in dimensions of wellbeing (Multidimensional Wellbeing Questionnaire [MDBF])
- Depression Scale (D-S')
- State-Trait Anxiety Inventory-X1 (STAI-X1)
- Adverse events

Notes

**Sponsorship source:** Dr Willmar Schwabe GmbH & Co

**Trial registration number(s)**: EudraCT No. 2005-005765-11

**Note:** outcome data provided in email to LSW by Dr Hörr on 12 November 2021, and clarification of methods provided by Dr Hörr on 14 March 2022

***Risk of bias***

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Random sequence generation (selection bias) | Low risk | "Randomised, double-blind, placebo-controlled, parallel-group trial". Description from study protocol e-mailed to LSW by Dr Robert Hörr on 14 March 2022: "Randomisation (1:1, active drug - placebo ratio), stratified by centres, was performed by the sponsor's biometrics unit using a validated computer program (RCODE). A randomization list was generated in which each drug number was assigned a treatment. The length of the balanced blocks was described in a separate document that was withheld from the study sites. Drug boxes containing active drug or placebo were labelled uniformly and numbered in accordance with the randomisation list." |
| Allocation concealment (selection bias) | Low risk | Description from study protocol emailed by Robert Hörr to LSW on 14 March 2022: "Random treatment allocation was performed by handing each patient at a clinical site the drug box with the lowest yet unassigned number. The investigators received sealed emergency-envelopes for individual patients, all of which returned unopened after completion of the trial." |


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**EUCTR2005-005765-11-EE** *(Continued)*

| | | |
|---|---|---|
| Blinding of participants and personnel (performance bias)<br>All outcomes | Low risk | Double-blind trial without details about blinding. However, given the limitations of the study report format (clinical registration report) and other studies conducted by the same study, it is likely that participants and personnel were blinded. |
| Blinding of outcome assessment (detection bias)<br>All outcomes | Low risk | Described as a double-blind study. Although no details are given on outcome assessment, likely due to the format of the study report, it is very likely that outcome assessment was blinded. |
| Incomplete outcome data (attrition bias)<br>All outcomes | Low risk | "All 304 randomised patients were included in the safety analysis set (SAS) (EGb 761®: 152 patients, placebo: 152 patients). Eight patients of the safety analysis set could not be included in the FAS due to missing post treatment measurements (EGb 761®: 3 patients, placebo: 5 patients). Thus, the FAS consisted of 296 patients, 149 and 147 patients in the EGb 761® and the placebo group, respectively." Roughly equal small proportion of missing outcome data in each group. Last observation carried forward is used in the full analysis set. |
| Selective reporting (reporting bias) | Low risk | The outcomes are consistent with the outcomes listed in the trial registration. |
| Other bias | Low risk | No other apparent sources of bias. |

**Fang 2020**

| | |
|---|---|
| ***Study characteristics*** | |
| Methods | **Study design:** RCT<br><br>**Study grouping:** parallel group<br><br>**Duration of intervention:** 3 months<br><br>**Duration of follow-up:** 3 months<br><br>**Washout or placebo run-in period:** no |
| Participants | **Baseline characteristics**<br><br>*G biloba* plus citicoline sodium tablets<br><br>• Number randomized: 30<br>• MMSE (mean, SD): 15.8, 3.8<br>• Age (mean, SD): 63.51, 10.96<br>• % female: 40%<br><br>Citicoline sodium tablets<br><br>• Number randomized: 30<br>• MMSE (mean, SD): 16.3, 4.4<br>• Age (mean, SD): 63.61, 11.09<br>• % female: 43.3%<br><br>**Total number randomized:** 60<br><br>**Inclusion criteria**<br><br>• Vascular dementia Western medicine diagnosis and TCM syndrome differentiation criteria<br>• Age 50 to 75 years |


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**Fang 2020** *(Continued)*

- No other treatment received before admission, or influence of other treatment removed after a washout period
- Approved by the Medical Ethics Committee of our hospital
- Informed consent

**Exclusion criteria**

- Other disturbances of consciousness, epilepsy, delirium, or mental illness
- Severe aphasia
- Severe heart, liver, kidney insufficiency, drug metabolism dysfunction
- Life-threatening diseases such as malignant tumors
- Inability to guarantee medication compliance

**Country:** China

**Setting:** inpatient

**Date recruitment began:** 2017

**Recruitment methods:** recruitment of people with vascular dementia who were diagnosed and treated in the author's hospital from 10 April 2017 to 10 April 2018

**Diagnosis:** VD

**Diagnostic criteria:** the diagnosis of dementia refers to the relevant diagnostic criteria in the American Psychiatric Association's Diagnostic and Statistical Manual of Mental Disorders:

- Cognitive dysfunction includes memory impairment and cognitive function (language ability, abstract thinking or judgment) impairment, and obviously interferes with occupation and social activities, or significantly decreased compared with the individual in the past.
- The above-mentioned disorders cannot be explained by other primary mental and emotional diseases such as depression and schizophrenia. Diagnosis of cerebrovascular disease is based on the presence of cerebrovascular pathology (such as large vessel infarction, lacunar infarction, multiple cerebral infarction, and periventricular white matter lesions) confirmed by imaging examination CT or MRI. Determination of causality: dementia occurs within 3 months after definite stroke, with sudden decline in cognitive function, or fluctuation-like or step-like impairment of cognitive function The syndrome differentiation standard conforms to the "Vascular Dementia Diagnosis, Syndrome Differentiation and Curative Effect Judgment Criteria" in the fluctuating period of vascular dementia, common wind-phlegm stasis, liver and kidney yin deficiency, turbid phlegm stasis, spleen and kidney deficiency, phlegm-fire disturbing the heart, heart and kidney insufficiency Syndromes such as handover, specifically: obvious sluggishness, dizziness, drowsiness, laziness, excessive phlegm, salivation and bad breath, dry stool, white or yellow greasy fur, slippery pulse, etc. Anger, strong tongue, dizzy speech, dizziness, limb numbness, sticky phlegm, salivation, slippery pulse, and greasy fur.

Interventions

**Intervention characteristics**

*G biloba* plus citicoline sodium tablets

- On the basis of the control group, *G biloba* leaves (produced by Nanjing Yiheng Pharmaceutical Co, Ltd, Z20063958), 1 tablet each time, 3 times a day. Dose NR.

Citicoline sodium tablets

- Citicoline sodium tablets (China Resources Double-Crane Limin Pharmaceutical [Jinan] Co, Ltd, permission H20080745) taken orally, 2 tablets each time, 3 times a day, for 3 months. Dose 0.6 g/day.

Outcomes

**Outcomes collected**

- MMSE
- ADL (Barthel index)
- Curative effect
- Homocystine (Hcy)


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**Fang 2020** *(Continued)*

| | |
|---|---|
| | • Adverse events |
| Notes | **Sponsorship source:** none<br>**Trial registration number:** none reported |

***Risk of bias***

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Random sequence generation (selection bias) | Low risk | Random number table. |
| Allocation concealment (selection bias) | Unclear risk | Not reported. |
| Blinding of participants and personnel (performance bias)<br>All outcomes | Unclear risk | Blinding not reported. |
| Blinding of outcome assessment (detection bias)<br>All outcomes | Unclear risk | Blinding not reported. |
| Incomplete outcome data (attrition bias)<br>All outcomes | Low risk | No attrition. |
| Selective reporting (reporting bias) | Unclear risk | No trial registration or protocol available. |
| Other bias | Low risk | No other apparent source of bias. |

**Feng 2008**

***Study characteristics***

| | |
|---|---|
| Methods | **Study design:** RCT<br>**Study grouping:** parallel group<br>**Duration of intervention:** 3 months<br>**Duration of follow-up:** 3 months<br>**Washout or placebo run-in period:** no |
| Participants | **Baseline characteristics**<br>*G biloba*<br>• Number randomized: 25<br>• MMSE (mean, SD): NR<br>• Age (mean, SD): 71.3, 4.2<br>• % female: 28<br>Bu Shen Yi Nao |


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**Feng 2008** *(Continued)*

- Number randomized: 25
- MMSE (mean, SD): NR
- Age (mean, SD): 70.5, 3.4
- % female: 20

**Total number randomized:** 50

**Inclusion criteria**

- Diagnostic criteria of MCI
- Age 55 to 80 years
- No functional failure of important organs such as heart, brain and kidney
- No neuropsychiatric disorder
- Voluntary participation in trial, informed consent

**Exclusion criteria**

- Prone to allergies, or allergy to drug components
- Serious primary diseases (e.g. cardiovascular, liver, kidney, hematopoietic system)
- Mental illness

**Country:** China

**Setting:** NR

**Date recruitment began:** NR

**Recruitment methods:** NR

**Diagnosis:** MCI

**Diagnostic criteria:** Guiding Principles for Clinical Research of New Drugs of Traditional Chinese Medicine and Diagnostic and Statistical Manual of Mental Disorders (version 3)

| | |
|---|---|
| Interventions | **Intervention characteristics**<br><br>Bu Shen Yi Nao<br><br>• Bu Shen Yi Nao capsule (composition is traditional Chinese medicine; 0.3 g per capsule; produced by pharmacy preparation department of the hospital). 3 capsules each time, 3 times a day (total of 9 capsules per day). In addition, placebo of *G biloba* capsule (component of placebo is starch).<br><br>*G biloba*<br><br>• *G biloba* capsule (produced by Jiang Yin Tian Jiang Pharmaceuticals in Jiang Yin, Jiang Su province; every capsule contains 9.6 g flavonoid). 1 capsule each time, 3 times a day (total of 3 capsules per day). In addition, placebo of Bu Shen Yi Nao capsule (component of placebo is starch). |
| Outcomes | **Outcomes collected**<br><br>• Clinical memory scale<br>• Lab result of SOD, MDA and AchE |
| Notes | **Sponsorship source:** NR<br><br>**Trial registration number:** NR<br><br>No outcome data relevant to this review could be extracted from the study. |

***Risk of bias***


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**Feng 2008** *(Continued)*

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Random sequence generation (selection bias) | Low risk | Random number table. |
| Allocation concealment (selection bias) | Unclear risk | Not reported. |
| Blinding of participants and personnel (performance bias)<br>All outcomes | Low risk | Placebo in use. |
| Blinding of outcome assessment (detection bias)<br>All outcomes | Unclear risk | Not reported. Unclear to what extent the outcomes were influenced by lack of blinding. |
| Incomplete outcome data (attrition bias)<br>All outcomes | Unclear risk | Exclusion not reported. |
| Selective reporting (reporting bias) | Unclear risk | No protocol available. Insufficient information to permit judgment. |
| Other bias | Low risk | No other apparent sources of bias. |

**Gao 2019**

| ***Study characteristics*** | |
|---|---|
| Methods | **Study design:** RCT<br>**Study grouping:** parallel group<br>**Duration of intervention:** 9 months<br>**Duration of follow-up:** 9 months<br>**Washout or placebo run-in period:** none |
| Participants | **Baseline characteristics**<br>Donepezil<br>• Number randomized: 58<br>• MMSE (mean, SD): 15.41, 2.03<br>• Age (mean, SD): 70.6, 8.8<br>• % female: 53.4<br>*G biloba*<br>• Number randomized: 58<br>• MMSE (mean, SD): 15.43, 2.06<br>• Age (mean, SD): 71.0, 8.3<br>• % female: 44.8<br>**Total number randomized:** 116 |


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**Gao 2019** *(Continued)*

**Inclusion criteria**

- Age 55 to 85 years old
- Course of illness ≥ 6 months
- Support of family members to adhere to treatment
- Ability to complete relevant scale tests
- Informed consent

**Exclusion criteria**

- Severe AD
- Recent use of treatment drugs
- Vascular and other types of dementia
- Mental disorders caused by external stimuli
- Allergy to study drugs
- Underlying diseases such as liver, kidney, and lung
- Severe depression
- Brain tumors and organic brain disease

**Country:** China

**Setting:** inpatient

**Date recruitment began:** 2014

**Recruitment methods:** selected 116 people with AD who were diagnosed and treated in the hospital from May 2014 to March 2016.

**Diagnosis:** AD

**Diagnostic criteria:**

- Western medicine diagnostic criteria: refer to the *Guidelines for the diagnosis and treatment of dementia in China*:
  - memory impairment symptoms ≥ 6 months, and progressive decline;
  - abnormal behavior, decreased living ability, communication disorders, and progressive deterioration;
  - imaging showed different degrees of brain atrophy, degenerative lesions of brain microvessels, and decreased blood flow speed;
  - the level of cerebrospinal fluid β amyloid 1∼42 decreased; and
  - mental abnormalities caused by brain tumors, cerebral infarction and epilepsy were excluded.
- Diagnostic criteria of traditional Chinese medicine: refer to the *Guiding Principles of Clinical Research on New Chinese Medicines*: blood stasis internal resistance type: slow expression, unfavorable speech, forgetfulness, easy to panic, abnormal thinking, strange behavior, with wrong skin, dry mouth, the dull eyes, the dark tongue and the thin and astringent pulse.

Interventions

**Intervention characteristics**

Donepezil

- Donepezil hydrochloride tablets (Eisai [China] Pharmaceutical, 5 mg/s, lot number 131009), orally, 5 mg/day in the 1st month and 10 mg/day thereafter for a total of 9 months.

*G biloba*

- *G biloba* extract tablets (Dr Willmar Schwabe GmbH & Co. KG, 40 mg/s, lot number 13904) on the basis of the treatment of the control group, orally, 80 mg/time, 2 times/day, for a total of 9 months

Outcomes

**Outcomes collected**

- ADAS-cog


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**Gao 2019** *(Continued)*

- MMSE
- ADL
- Levels of cerebrospinal fluid acetylcholine (ACh)
- Serum malondialdehyde (MDA), and nitric oxide (NO)
- Total efficiency of treatment

| | |
|---|---|
| Notes | **Sponsorship source:** not reported<br>**Trial registration number(s)**: none reported |

***Risk of bias***

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Random sequence generation (selection bias) | Low risk | Random number table. |
| Allocation concealment (selection bias) | Unclear risk | Allocation process not described. |
| Blinding of participants and personnel (performance bias)<br>All outcomes | Unclear risk | Blinding not mentioned. |
| Blinding of outcome assessment (detection bias)<br>All outcomes | Unclear risk | Blinding of outcome assessors not mentioned. |
| Incomplete outcome data (attrition bias)<br>All outcomes | Low risk | No apparent loss to follow-up. |
| Selective reporting (reporting bias) | Unclear risk | No protocol available. |
| Other bias | Low risk | No other apparent risk of bias. |

**Gavrilova 2014**

***Study characteristics***

| | |
|---|---|
| Methods | **Study design:** RCT<br>**Study grouping:** parallel group<br>**Duration of intervention:** 24 weeks<br>**Duration of follow-up:** 24 weeks<br>**Washout or placebo run-in period:** no, although a run-in period of up to 4 weeks was permitted to complete electrocardiogram and MRI examinations and obtain all information required. |
| Participants | **Baseline characteristics**<br>*G biloba* |


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**Gavrilova 2014** *(Continued)*

- Number randomized: 80
- MMSE (mean, SD): 25.6, 1.3
- Age (mean, SD): 65, 7
- % female: 73%

Placebo

- Number randomized: 79
- MMSE (mean, SD): 25.7, 1.5
- Age (mean, SD): 63, 7
- % female: 84%

**Total number randomized:** 160 (baseline characteristics not provided for all participants randomized)

**Inclusion criteria**

- Age ≥ 55 years
- MCI
  - Cognitive complaints corroborated by informant
  - CAMCOG < 10th percentile for age, sex, and education
  - CAMCOG combined memory score ≤ 20 for people < 80 years and ≤ 17 for people ≥ 80 years
  - Decline from a former level of functioning
  - Mean score < 4 on the short form of the Informant Questionnaire on Cognitive Decline in the Elderly (Jorm, 1994)
  - MMSE ≥ 24
  - DSM-IV criteria for dementia not fulfilled
  - Cognitive complaints present for at least 6 months
- Total score ≥ 6 on the 12-item NPI, with at least 1 of the item scores for "depression/dysphoria," "anxiety," "apathy/indifference," "agitation," or "irritability/lability" being at least 4
- MRI taken no more than 1 year prior to screening consistent with the diagnosis of MCI
- No major depression

**Exclusion criteria:** "Patients with any type of neurological disorder, namely stroke with sequelae within the last 3 months or hemorrhagic stroke within the last 12 months before enrolment or dementia; current or recurrent psychiatric disorder; severe or insufficiently controlled cardiovascular disorder or insulin-dependent diabetes mellitus; severe hepatic or renal dysfunction, clinically significant anemia, thyroid dysfunction, or vitamin deficiency; gastrointestinal disorders with uncertain absorption; alcohol or substance abuse; active malignant disease; or severe and insufficiently corrected impairment in vision or hearing were excluded from the study. Participation in another clinical drug trial within 4 weeks before enrolment, previous participation in any trial of a G. biloba product, female patients of child-bearing age and no contraception, and intake of any medication that could interfere with the efficacy assessment were also grounds for exclusion."

**Country:** Russia

**Setting:** outpatient

**Date recruitment began:** NR (prior to 2014)

**Recruitment methods:** "Patients were enrolled by the psychiatric or neurologic outpatient departments of seven academic hospitals in Russia."

**Diagnosis:** MCI

**Diagnostic criteria:** international consensus criteria (cited Winblad 2004 report of the International Working Group on MCI)

| | |
|---|---|
| Interventions | **Intervention characteristics**<br><br>*G biloba* |


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**Gavrilova 2014** *(Continued)*

- "During the treatment period, patients were instructed to take one tablet of the study preparation, active drug or placebo, every morning. Active treatment consisted of tablets containing 240 mg of EGb 761. EGb 761 is a dry extract from G. biloba leaves (35–67:1); extraction solvent: acetone 60% (w/w). The extract is adjusted to 22.0–27.0% ginkgo flavonoids calculated as ginkgo flavone glycosides and 5.0–7.0% terpene lactones consisting of 2.8–3.4% ginkgolides A, B, and C and 2.6–3.2% bilobalide and contains less than 5 ppm ginkgolic acids."

Placebo

- Drug and placebo tablets were indistinguishable in appearance, packaging, and labeling. During the treatment period, participants were instructed to take 1 tablet of the study preparation (placebo) every morning. Placebo composition not described.

| | |
|---|---|
| Outcomes | **Outcomes collected**<br>• 12-item NPI (without caregiver distress rating)<br>• Geriatric Depression Scale (GDS)<br>• State-Trait Anxiety Inventory (STAI-X1) state subscale<br>• CGI (rated by participants and caregivers; much improved or very much improved was considered 'improved')<br>• Trail-Making Test (TMT) forms A and B<br>• Adverse events. |
| Notes | **Sponsorship source:** "This work was sponsored by Dr. Willmar Schwabe, GmbH & Co. KG, Karlsruhe, Germany."<br>**Trial registration number(s)**: none reported |

***Risk of bias***

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Random sequence generation (selection bias) | Low risk | "Randomization in blocks, with equal probabilities for active drug and placebo and stratified by centers, was performed by the sponsor's biometrics group using a validated computer program." |
| Allocation concealment (selection bias) | Low risk | "The randomization code was stored in a locked compartment at the sponsor's offices inaccessible to all persons involved in the trial; the block length was not disclosed to investigators or clinical staff. This procedure ensured both double blinding and concealment of allocation sequence." |
| Blinding of participants and personnel (performance bias)<br>All outcomes | Low risk | "Drug and placebo tablets were indistinguishable in appearance, packaging, and labeling. Each box carried a unique drug number that was generated and assigned to active drug or placebo by the randomization program." Double blinding ensured. |
| Blinding of outcome assessment (detection bias)<br>All outcomes | Low risk | "The block length was not disclosed to investigators or clinical staff. This procedure ensured both double blinding..." |
| Incomplete outcome data (attrition bias)<br>All outcomes | Low risk | Two dropouts in intervention group due to adverse events (0 excluded from analysis). Three dropouts in placebo group (1 withdrawal of consent, 1 lack of efficacy, 1 lost to follow-up); 1 excluded from analysis. Very few dropouts (n = 5; 3%), and all but one participant were included in the analysis. |
| Selective reporting (reporting bias) | Unclear risk | Study protocol unavailable. Insufficient information available to permit a judgment. |
| Other bias | Low risk | No other apparent sources of bias. |


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**GEM 2010**

| ***Study characteristics*** | |
|---|---|
| Methods | **Study design:** RCT<br><br>**Study grouping:** parallel group<br><br>**Duration of intervention:** 5 years then additional retention until sufficient dementia cases accumulated (median 6.1 years)<br><br>**Duration of follow-up:** 5 years then additional follow-up until sufficient dementia cases accumulated, resulting in median 6.1 years (maximum, 7.3 years)<br><br>**Washout or placebo run-in period:** no |
| Participants | **Baseline characteristics**<br><br>*G biloba*<br><br>• Number randomized: 256<br>• 3MSE (mean, SD): 90, 5.28<br>• Age (mean, SD): 79.75, 3.78<br>• % female: 48%<br><br>Placebo<br><br>• Number randomized: 226<br>• 3MSE (mean, SD): 89.5, 5.51<br>• Age (mean, SD): 79.7, 3.63<br>• % female: 50%<br><br>**Total number randomized:** 3072, of whom 482 had MCI at baseline.<br><br>**Inclusion criteria:** "non-demented or MCI; willing to participate in a 5-year follow-up trial of *G biloba* versus placebo; at least 75 years of age; English is their usual language; identify a person who will serve as a proxy" [Table 3, DeKosky et al Contemp Clin Trials 2006]<br><br>**Exclusion criteria:** "currently taking the anti-coagulant warfarin (Coumadin); current use of antipsychotic agents; currently being treated with tricyclic antidepressants b; taking donepezil (or similar agents) for cognitive problems or dementia; use of greater than 400 IU vitamin E/day; unwilling to discontinue taking over-the-counter (OTC) *G biloba*, beginning at screening visit and for the duration of the study; history of bleeding disorders; history of Parkinson's disease or taking carbidopa/levodopa or other antiParkinson's medications (e.g. dopaminergic receptor agonists); any cancer diagnosed and treated within the past 5 years; congestive heart failure with disability; acute medical condition based on review by physician of the baseline ECG; hospitalized for depression within the last year or ECT within last 10 years; baseline blood creatinine: > 2.0 mg/dL; baseline gamma gGT, ALT and AST U/L (2 × ULN = 90 IU); abnormal thyroid studies (TSH uIU/mL); B12 levels ≤ 210 pg/mL; baseline hematocrit < 30%; baseline white blood count < 3000 or > 15,000/cmm; platelet count < 100,000 or > 600,000 K/cmm; any condition that, in the judgment of clinical study staff, would preclude full participation in the study; participation in any other prevention or treatment trial or at discretion of principal investigator; participation in a clinical trial involving an intervention that could affect the GEM study outcomes" [Table 3, DeKosky et al Contemp Clin Trials 2006]<br><br>**Country:** USA<br><br>**Setting:** outpatient<br><br>**Date recruitment began:** 2000<br><br>**Recruitment methods:** "Using targeted mailing lists, an estimated 243,400 study brochures were mailed out to potential participants. Subsequent attempts were made to reach 14,603 households by |


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**GEM 2010** *(Continued)*

| | |
|---|---|
| | telephone, from which 12,186 (83.4%) successful contacts were made." "The vast majority of participants were recruited via mass mailings based on voter registration lists, commercially purchased mailing lists and university lists."<br><br>**Diagnosis:** non-demented or MCI; this extraction focuses on MCI<br><br>**Diagnostic criteria:** "The Modified Mini Mental State Examination (3MSE) administered to the participant and Dementia Questionnaire (DQ) completed by the proxy [were administered at the screening visit. A passing score on both instruments [>=80 on 3MSE] gained entry to the more detailed NPB. If participants achieved passing scores in all or all but one cognitive domain ("normal" and "mild cognitive impairment", respectively), they were eligible for entry to the study assuming that they met all the other criteria." |
| Interventions | **Intervention characteristics**<br><br>*G biloba*<br><br>• "Participants were randomized to twice-daily doses of 120 mg (a total of 240 mg per day) *G biloba* extract (EGb 761; Schwabe Pharmaceuticals, Karlsruhe, Germany). The formulation EGb 761 is issued in many of the branded ginkgo products sold in the USA. Selection of the specific formulation of *G biloba* to be used in the study was made following a separate NCCAM "Request for Product" for a company to provide *G biloba* product of consistent prespecified composition in blister pack format with equal amounts of identically packaged, identically appearing placebo tablets, sufficient to complete the study. The composition of EGb 761 as tested in this trial was described in detail previously." The preparation was "standardized to its major constituents, approximately 24% ginkgo-specific flavone glycosides and 6% terpene lactones, such that 120-mg dried extract of G. biloba leaves (plant raw material: extract ratio, 35–67:1) contains 28.8-mg ginkgo-flavone glycosides and 7.2-mg terpene lactones. Impurities are minimal with ginkgolic acid less than 5 ppm and heavy metal less than 10 ppm. These values were confirmed by an independent analytical laboratory for each batch of product used in GEM. NCCAM submitted and holds the IND for GEM. The IND cross-references a Drug Master File previously submitted to the FDA by Schwabe." "The 240-mg dose of EGb761 was chosen based on information from prior clinical studies suggesting a dose-response relationship up to 240 mg. Moreover, this dose is commonly used. The composition of the placebo and active tablets was confirmed by independent laboratory analysis for each lot of tablets used during the trial." Content included: "Ginkgo extract EGb 761, Lactose monohydrate, Silicon dioxide, colloidal Microcrystalline cellulose, Maize starch, Croscarmellose sodium, Magnesium stearate, Methylhydroxypropyl cellulose, Macrogol, Titanium dioxide, Iron oxide hydrate, E 172 red, and Talc."<br><br>Placebo<br><br>• "Participants were randomized to twice-daily doses of ... an identically appearing placebo." "The composition of the placebo and active tablets was confirmed by independent laboratory analysis for each lot of tablets used during the trial." Content included: "lactose monohydrate, silicon dioxide, colloidal microcrystalline cellulose, maize starch, croscarmellose sodium, magnesium stearate, methylhydroxypropyl cellulose, Macrogol, titanium dioxide, iron oxide hydrate, E 172 red, talc, and iron oxide yellow (0.2mg), iron oxide brown (0.1 mg) and quinine (2 mg) added for blinding purposes." |
| Outcomes | **Outcomes collected:** DSM-IV diagnosis of dementia using clinical criteria and results of a full neuropsychiatric battery (California Verbal Learning Test – long delayed free recall, 24-point modified Rey Osterrieth figure – delayed recall, 24-point modified ReyOsterrieth figure – copy condition, 24-point modified Wechsler Adult Intelligence Scale – Revised [WAIS-R] block design, 30-item Boston Naming Test, Animal fluency, WAIS-R digit span forward [total score], Trail Making Test A [time in seconds], Trail Making Test B [time in seconds], Stroop color/word test – interference condition [number of colors named], National Adult Reading Test – American version, Raven's Coloured Progressive Matrices), resulting in classification with specific dementia diagnosis according to NINCDS/ADRDA/NINDS-AIREN/ACCTC criteria.<br><br>Note: according to Snitz JAMA 2009, the 3MSE and ADAS-Cog were administered throughout the study; however, published results of these outcome values could not be found. We obtained unpublished data for these outcomes. |
| Notes | The trial had a mixed population of participants without cognitive issues and participants with MCI. |


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**GEM 2010** *(Continued)*

**Sponsorship source:** "This study was supported by grant U01 AT000162 from the National Center for Complementary and Alternative Medicine (NCCAM) and the Office of Dietary Supplements and National Institute on Aging; National Heart, Lung, and Blood Institute; University of Pittsburgh Alzheimer's Disease Research Center (P50AG05133); Roena Kulynych Center for Memory and Cognition Research; Wake Forest University School of Medicine; and National Institute of Neurological Disorders and Stroke. Schwabe Pharmaceuticals, Karlsruhe, Germany, donated the Gbiloba tablets and identical placebos in blister packs for the study."

**Trial registration number(s):** NCT00010803

**Note:** raw outcome data provided to TF and LSW by Dr Richard Nahin on 01 February 2023

***Risk of bias***

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Random sequence generation (selection bias) | Low risk | "Randomization was done separately for each clinical site using a computer-generated, randomly permuted list maintained at the data co-ordinating center at the University of Washington in Seattle, and each participant was assigned a batch number used throughout the study."<br><br>Assignment to *G biloba* or placebo was determined by permuted block design by site to ensure that allocation between treatment groups was well balanced. Randomization was done separately for each clinical site using a computer-generated, randomly permuted list. |
| Allocation concealment (selection bias) | Low risk | Randomization was done separately for each clinical site using a computer-generated, randomly permuted list maintained at the data co-ordinating center at the University of Washington in Seattle, and each participant was assigned a batch number used throughout the study. |
| Blinding of participants and personnel (performance bias)<br>All outcomes | Low risk | All clinical center and co-ordinating center personnel and participants were blinded to treatment assignment for the duration of the study. Only the study pharmacist who allocated the medication into batches, as well as 2 data coordinating center personnel responsible for monitoring serious adverse events and reporting to the study data and safety monitoring board (DSMB), knew which medication was active, but all of these personnel were unaware of participant information. |
| Blinding of outcome assessment (detection bias)<br>All outcomes | Low risk | All clinical center and co-ordinating center personnel and participants were blinded to treatment assignment for the duration of the study. Only the study pharmacist who allocated the medication into batches, as well as 2 data coordinating center personnel responsible for monitoring serious adverse events and reporting to the study DSMB, knew which medication was active, but all of these personnel were unaware of participant information. |
| Incomplete outcome data (attrition bias)<br>All outcomes | Low risk | There were 379 deaths from any cause. Cognitive status was known for 93.6% of all participants at trial end. There were 195 individuals (6.3%) who were either lost to follow-up or withdrew consent (97 in the *G biloba* group and 98 in the placebo group). The proportion was small and distributed evenly between ginkgo and placebo. The 195 participants who declined to continue the study after randomization did not differ from the 2874 who remained in the study. |
| Selective reporting (reporting bias) | Low risk | All preplanned study outcomes in the trial registration were reported either in publications or at https://clinicaltrials.gov/ct2/show/results/NCT00010803 or both. |
| Other bias | Low risk | Study appears to be free of other sources of bias. |


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**Gessner 1985**

| ***Study characteristics*** | |
|---|---|
| Methods | **Study design:** RCT<br><br>**Study grouping:** parallel group<br><br>**Duration of intervention:** 12 weeks<br><br>**Duration of follow-up:** 12 weeks<br><br>**Washout or placebo run-in period:** 2-week wash out period during which all psychoactive medications were excluded |
| Participants | **Baseline characteristics**<br><br>*G biloba*<br><br>• Number randomized: 20<br>• MMSE (mean, SD): NR<br>• Age (mean, SD): NR<br>• % female: NR<br><br>Nicergoline<br><br>• Number randomized: 20<br>• MMSE (mean, SD): NR<br>• Age (mean, SD): NR<br>• % female: NR<br><br>Placebo<br><br>• Number randomized: 20<br>• MMSE (mean, SD): NR<br>• Age (mean, SD): NR<br>• % female: NR<br><br>**Total number randomized:** 60<br><br>**Inclusion criteria:** volunteers of either sex, healthy for their age but reporting symptoms of cerebral deterioration<br><br>**Exclusion criteria:** none<br><br>**Country:** Germany<br><br>**Setting:** community<br><br>**Date recruitment began:** NR (prior to 1985)<br><br>**Recruitment methods:** not reported<br><br>**Diagnosis:** symptoms of cerebral deterioration (not specified). Classified as subjective cognitive impairment, in absence of specific information other than self-report.<br><br>**Diagnostic criteria:** self-report |
| Interventions | **Intervention characteristics**<br><br>*G biloba* |


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**Gessner 1985** *(Continued)*

- "Ginkgo biloba extract (G.B.E.) is a concentrated standardized extract of Ginkgo biloba leaves marketed under the trade name Tanakan (France) and rökan (Germany). The dosage was 3 x 40 mg/day."

Nicergoline

- "Nicergoline is marketed in Germany and it was administered at a dose rate of 3 x 5 mg/day."

Placebo

- "Placebo: a sugar preparation without pharmacological action was used as the placebo acting as a reference substance. Administration was again t.i.d. Placebo appearance was similar to the active drugs (one half similar to G.B.E., the other half similar to nicergoline)."

| | |
|---|---|
| Outcomes | **Outcomes collected**<br>• EEG<br>• Simple reaction time<br>• Multiple choice reaction test<br>• Flicker fusion frequency<br>• Pursuit tracking test<br>• Pauli Test<br>• d2 test<br>• Subjective evaluation of drug by participant and examiner |
| Notes | **Sponsorship source:** none stated; however, the study authors are from the drug company Bio-Data Gesellschaft für biomedizinische Datenverarbeitung mb. Therefore, we believe that the company is the sponsor and funder.<br>**Trial registration number(s)**: none reported<br>**Note:** email from Dr Andreas Völp, Dipl. Psych. to EL on 16 Feb 2021 specified randomization method. No outcome data relevant to this review could be extracted from the study. |

***Risk of bias***

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Random sequence generation (selection bias) | Low risk | Not reported and we emailed the study investigators. Reply from Dr Andreas Völp, Dipl. Psych. on 16 Feb 2021 to Emilie Ludeman: "As far as I recall, the randomization list was generated using a FORTRAN program written by one of the programmers of Bio-Data GmbH". |
| Allocation concealment (selection bias) | Unclear risk | Insufficient information available to permit a judgment. |
| Blinding of participants and personnel (performance bias)<br>All outcomes | Low risk | Placebo appearance was similar to active drugs. |
| Blinding of outcome assessment (detection bias)<br>All outcomes | Low risk | Double-blind trial; unlikely blinding was broken. |
| Incomplete outcome data (attrition bias)<br>All outcomes | Low risk | While the specific reasons were not given, only 3/60 (5%) participants dropped out and the number was the same across intervention groups. |


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**Gessner 1985** *(Continued)*

| | | |
|---|---|---|
| Selective reporting (reporting bias) | Unclear risk | Study protocol not available. Insufficient information available to permit a judgment. |
| Other bias | Low risk | Study appears to be free of other sources of bias. |

**GINDEM-NP 2005**

| ***Study characteristics*** | |
|---|---|
| Methods | **Study design:** RCT<br><br>**Study grouping:** parallel group<br><br>**Duration of intervention:** 22 weeks<br><br>**Duration of follow-up:** 22 weeks<br><br>**Washout or placebo run-in period:** yes, "a medication-free screening period of up to four weeks". In addition, "Treatment with other anti-dementia drugs, cognitive enhancers, cholinergic, anti-cholinergic, or hemorheologically active drugs, anti-Parkinson drugs or Ginkgo biloba supplements were prohibited during the study and at least 8 weeks before randomization." |
| Participants | **Baseline characteristics**<br><br>*G biloba*<br><br>• Number randomized: 198<br>• MMSE (mean, SD): NR<br>• Age (mean, SD): 65, 8<br>• % female: 72%<br><br>Placebo<br><br>• Number randomized: 197<br>• MMSE (mean, SD): NR<br>• Age (mean, SD): 63, 8<br>• % female: 72%<br><br>**Total number randomized:** 400 (baseline characteristics not provided for all participants randomized)<br><br>**Inclusion criteria**<br><br>• Age ≥ 50 years<br>• Diagnosis of probable AD (NINCDS/ADRDA criteria), possible AD with CVD (NINCDS/ADRDA and NINDS/AIREN criteria), or probable VD (NINDS/AIREN criteria)<br>• CT or MRI within the past year consistent with diagnosis and showing no evidence of other brain lesions<br>• Verification of cognitive impairment on at least 2 domains through the TE4D, with a total error score of 35 or less<br>• Baseline SKT test score of 9 to 23, CDT test score below 6, and score of at least 5 on the 12-item NPI with at least 1 item score (other than delusions or hallucinations) of at least 3<br>• Score below 20 on the HAM-D<br><br>**Exclusion criteria**<br><br>• Other types of dementia or neurological disorders<br>• Current or recent major depression or other psychiatric disorder<br>• Severe or insufficiently controlled cardiovascular, renal, or hepatic disorder |


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**GINDEM-NP 2005** *(Continued)*

- Diabetes
- Anemia
- Thyroid dysfunction
- Active cancer, HIV or Iues [sic] infection, or GI disease with problems of uncertain absorption

**Country:** Ukraine

**Setting:** outpatient

**Date recruitment began:** NR (prior to 2005)

**Recruitment methods:** outpatient clinics of 16 psychiatric or neurological hospitals

**Diagnosis:** probable AD, possible AD with CVD, or probable VD

**Diagnostic criteria:** probable AD criteria were NINCDS/ADRDA, possible AD with CVD were NINCDS/ADRDA and NINDS/AIREN, probable VaD was NINDS/AIREN.

Interventions

**Intervention Characteristics**

*G biloba*

- "The investigational produce, EGb 761 is a dry extract from Ginkgo biloba leaves (35-67:1), adjusted to 22.0-27.0% Ginkgo flavonoids and 5.0-7.0% terpene lactones consisting of 2.8-3.4% ginkgolic acids below 5 ppm. Patients had to take two tablets per day, i.e. 2 x 120 mg EGb 761 or placebo."

Placebo

- "Drug and placebo tablets were indistinguishable by appearance, packaging and labelling."

"Treatment with other anti-dementia drugs, cognitive enhancers, cholinergic, anti-cholinergic or haemorheologically active drugs ... was prohibited."

Outcomes

**Outcomes collected**

- SKT
- 12-item NPI composite score
- NPI distress
- Gottfries-Brane-Steen (GBS) total score
- ADL subscale of the GBS
- Clinically meaningful response
- Verbal Fluency Test
- CDT
- HAM-D
- Participant self-ratings of dizziness and tinnitus

Notes

**Sponsorship source:** Dr Willmar Schwabe GmbH

**Trial registration number(s)**: none reported

***Risk of bias***

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Random sequence generation (selection bias) | Low risk | "Randomisation (1:1, stratified by centres and in blocks of our), was performed with the aid of a validated computer program that linked ascending drug numbers to drug or placebo, respectively." |
| Allocation concealment (selection bias) | Low risk | "The sealed randomisation code was stored safely at the sponsor's biometrics unit, and block length was not disclosed to investigators. Upon successful |


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**GINDEM-NP 2005** *(Continued)*

| | | |
|---|---|---|
| | | screening, each patient was allocated the drug package with the lowest drug number still available at a site." |
| Blinding of participants and personnel (performance bias)<br>All outcomes | Low risk | "Drug and placebo tablets were indistinguishable by appearance, packaging and labelling." |
| Blinding of outcome assessment (detection bias)<br>All outcomes | Low risk | Participants and investigators were blinded to treatment group. |
| Incomplete outcome data (attrition bias)<br>All outcomes | Low risk | "Of the 400 patients who were randomised and received drug, 395 patients who had data for the primary outcome variable at week 12 or later make up the full analysis set for intention-to-treat (ITT) analysis." No mention of missing outcome data for specific outcomes. |
| Selective reporting (reporting bias) | Unclear risk | Protocol not available. Insufficient information available to permit a judgment. |
| Other bias | Low risk | No other apparent sources of bias. |

**GOTADAY 2011**

| ***Study characteristics*** | |
|---|---|
| Methods | **Study design:** RCT<br>**Study grouping:** parallel group<br>**Duration of intervention:** 24 weeks<br>**Duration of follow-up:** 24 weeks<br>**Washout or placebo run-in period:** washout of up to 4 weeks for discontinued medications |
| Participants | **Baseline characteristics**<br>*G biloba*<br>• Number randomized: 202<br>• MMSE (mean, SD): NR<br>• Age (mean, SD): 65, 10<br>• % female: 69%<br>Placebo<br>• Number randomized: 202<br>• MMSE (mean, SD): NR<br>• Age (mean, SD): 65, 9<br>• % female: 66%<br>**Total number randomized:** 410 (baseline characteristics not provided for all participants randomized)<br>**Inclusion criteria**<br>• Age 50 years or more |


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**GOTADAY 2011** *(Continued)*

- Probable Alzheimer's disease (AD) or possible AD with cardiovascular disease or probable vascular dementia
- Symptoms present at least 6 months
- MRI scan consistent with diagnosis and not showing other brain lesion
- Score of 35 or below on the Test for Early Detection of Dementia with Discrimination from Depression (TE4D)
- Score from 9 to 23 on the Syndrom-Kurztest (SKT), indicating mild to moderate dementia
- Score < 6 on the CDT
- Score ≥ 6 on the NPI, with at least one item score (other than delusion or hallucination) being 3 or higher
- Score < 20 on the Hamilton Rating Scale for Depression (HAMD) with item 1 rated no higher than 3
- Presence of caregiver/close relative who was willing to ensure that the participant complied with all aspects of the protocol

**Exclusion criteria**

- Other type of dementia or neurological disorder
- Major short-term fluctuations in symptom severity
- Current or recent major depression or other psychiatric disorder
- Severe or insufficiently controlled cardiovascular, renal, or hepatic disorder, diabetes, anemia, or thyroid dysfunction
- Active malignant disease, HIV, syphilis infection or gastrointestinal disease with uncertain absorption
- Ongoing treatment with other anti-dementia drugs, cognitive enhancers, cholinergic, anticholinergic or hemorheologically active drugs, anti-Parkinson drugs or ginkgo products (must be discontinued at least 8 weeks preceding randomization)

**Country:** Ukraine

**Setting:** outpatient

**Date recruitment began:** 2006

**Recruitment methods:** "Patients were recruited at 20 outpatient clinics of psychiatric or neurological hospitals in Ukraine." Additional methods not specified.

**Diagnosis:** possible or probable AD or probable VaD

**Diagnostic criteria:** NINCDS-ADRDA criteria for probable AD, NINDS-AIREN criteria for possible AD with CVD, and NINDS-AIREN criteria for probable VaD

Interventions

**Intervention characteristics**

*G biloba*

- "The investigational product, EGb 761, is a dry extract from Ginkgo biloba leaves (drug-extract ratio 35-67:1), adjusted to 22.0–27.0% ginkgo flavonoids and 5.0–7.0% terpene lactones consisting of 2.8–3.4% ginkgolides A, B, C and 2.6–3.2% bilobalide, with a content of ginkgolic acids below 5 ppm. In this trial, a once-daily formulation containing 240 mg of EGb 761 was used. Patients had to take one tablet in the morning."

Placebo

- "Drug and placebo tablets were indistinguishable by appearance, packaging and labelling. Patients had to take one tablet in the morning."

"Treatment with other antidementia drugs, cognitive enhancers, cholinergic, anti-cholinergic or haemorheologically active drugs, anti-Parkinson drugs or Ginkgo supplements was prohibited during the study and for at least 8 weeks preceding randomization."

Outcomes

**Outcomes collected**


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**GOTADAY 2011** *(Continued)*

- SKT
- NPI
- NPI caregiver distress
- CGIC
- ADAL-IS
- DEMQOL-Proxy
- TE4D
- Verbal Fluency Test

| | |
|---|---|
| Notes | **Sponsorship source:** Dr Willmar Schwabe GmbH<br><br>**Trial registration number(s)**: none reported |

***Risk of bias***

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Random sequence generation (selection bias) | Low risk | "Randomization (1:1, stratified by centres and in blocks of four) was performed with the aid of a validated computer program that linked random numbers to drug or placebo, respectively. The sealed randomization code was stored safely at the biometrics unit, and the length of randomization blocks within which numbers of drug and placebo were balanced was not disclosed to investigators." |
| Allocation concealment (selection bias) | Low risk | "Upon successful screening, each patient was assigned the lowest medication number still available at the site and handed over the corresponding drug package." The sealed randomization code was stored safely at the biometrics unit, and the length of randomization blocks within which numbers of drug and placebo were balanced was not disclosed to investigators. |
| Blinding of participants and personnel (performance bias)<br>All outcomes | Low risk | "Upon successful screening, each patient was assigned the lowest medication number still available at the site and handed over the corresponding drug package." Drug and placebo tablets were indistinguishable by appearance, packaging and labelling. Participants had to take one tablet in the morning. Drug dispensation and return was handled by persons not involved otherwise in the conduct of the trial, usually the hospital pharmacists. |
| Blinding of outcome assessment (detection bias)<br>All outcomes | Low risk | No indication of unblinding during trial. Statement that investigators were blinded to treatment assignment. |
| Incomplete outcome data (attrition bias)<br>All outcomes | Low risk | Numbers and reasons for losses were described and did not appear different between groups. There were no substantial numbers of people discontinuing or dropped from analysis, and both ITT and per-protocol analyses were done. |
| Selective reporting (reporting bias) | Unclear risk | No protocol or registration and unclear whether all outcomes were reported (e.g. TE4D was stated to have been repeated at week 24 in one of the papers, but this assessment was not mentioned in the main study report). We rated as unclear risk of bias given that this is likely an issue related to reporting across multiple papers and any requested data has previously been available from the sponsor. |
| Other bias | Low risk | No other evident sources of bias. |


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**GOT IT 2012**

| ***Study characteristics*** | |
|---|---|
| Methods | **Study design:** RCT<br><br>**Study grouping:** parallel group<br><br>**Duration of intervention:** 24 weeks<br><br>**Duration of follow-up:** 24 weeks<br><br>**Washout or placebo run-in period:** washout of discontinued medications for up to 4 weeks |
| Participants | **Baseline characteristics**<br><br>*G biloba*<br><br>• Number randomized: 200<br>• MMSE (mean, SD): NR<br>• Age (mean, SD): 65.1, 8.8<br>• % female: 69.5%<br><br>Placebo<br><br>• Number randomized: 202<br>• MMSE (mean, SD): NR<br>• Age (mean, SD): 64.9, 9.4<br>• % female: 69.3%<br><br>**Total number randomized:** 410 (baseline characteristics not provided for all participants randomized)<br><br>**Inclusion criteria**<br><br>• Age 50 years or more<br>• Mild to moderate AD or vascular dementia<br>• Symptoms present at least 6 months<br>• MRI scan consistent with diagnosis and not showing other brain lesions<br>• Score of 35 or below on the Test for Early Detection of Dementia with Discrimination from Depression (TE4D)<br>• Score from 9 to 23 on the Syndrom-Kurztest (SKT)<br>• Score below 6 on the CDT<br>• Score of 6 or greater on the NPI, with at least one of the items "anxiety", "apathy/indifference", "irritability/lability", or "depression/dysphoria" rated 4 or higher<br>• Score below 20 on the HAMD with item 1 rated no higher than 3<br>• Presence of caregiver/close relative who was willing to ensure that the participant complied with all aspects of the protocol<br><br>**Exclusion criteria**<br><br>• Other type of dementia or neurological disorder<br>• Major short-term fluctuations in symptom severity<br>• Current or recent major depression or other psychiatric disorder<br>• Severe or insufficiently controlled cardiovascular, renal, or hepatic disorder, diabetes, anemia, or thyroid dysfunction. People suffering from active malignant disease, HIV, syphilis infection or gastrointestinal disease with uncertain absorption<br>• Ongoing treatment with other anti-dementia drugs, cognitive enhancers, cholinergic, anticholinergic or hemorheologically active drugs, anti-Parkinson drugs or ginkgo products (must be discontinued at least 8 weeks preceding randomization).<br><br>**Countries:** Russian Federation, Republic of Belarus, Republic of Moldova |


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**GOT IT 2012** *(Continued)*

**Setting:** outpatient

**Date recruitment began:** 2008

**Recruitment source/methods:** "Outpatients were recruited at 17 psychiatry or neurology clinics in three countries with Russian-speaking populations (Republic of Belarus, Republic of Moldova, and Russian Federation). These countries were chosen, because cholinesterase inhibitor use was not common and the quick recruitment of untreated patients with dementia speaking the same language to a placebo-controlled study was possible."

**Diagnosis:** mild to moderate AD or vascular dementia (VaD)

**Diagnostic criteria:** NINCDS-ADRDA criteria for probable AD, NINDS-AIREN criteria for possible AD with CVD, and NINDS-AIREN criteria for VD

Interventions

**Intervention characteristics**

*G biloba*

- *G biloba* extract EGb 761® (Dr Willmar Schwabe GmbH& Co. KG, Karlsruhe, Germany [EGb 761® is a registered trademark of Dr Willmar Schwabe GmbH & Co. KG]) at a daily dose of 240 mg tablets for 24 weeks. EGb 761® is a dry extract from *G biloba* leaves (35 to 67:1), extraction solvent: acetone 60% (w/w). The extract is adjusted to 22.0% to 27.0% ginkgo flavonoids calculated as ginkgo flavone glycosides and 5.0% to 7.0% terpene lactones consisting of 2.8% to 3.4% ginkgolides A,B,C, and 2.6% to 3.2% bilobalide, and contains less than 5 ppm ginkgolic acids. Participants were requested to take 1 tablet in the morning.

Placebo

- Participants received matching placebo tablets for 24 weeks. Cited literature stated that active drug and placebo tablets were indistinguishable in appearance, packaging and labeling. Participants were requested to take 1 tablet in the morning. Content of placebo NR.

"Treatment with other anti-dementia drugs, cognitive enhancers, cholinergic, anticholinergic or haemorheologically active drugs, anti-Parkinson drugs or Ginkgo products was prohibited during the clinical trial and for at least 8 weeks preceding randomisation."

Outcomes

**Outcomes collected**

- SKT
- NPI
- NPI caregiver distress
- CGIC
- ADAL-IS
- DEMQOL-Proxy
- Verbal Fluency Test
- TE4D

Notes

**Sponsorship source:** "Dr. Willmar Schwabe GmbH & Co. KG Pharmaceuticals was the sponsor of the clinical trial."

**Trial registration number(s)**: Clinical-Trials.ru 390378

***Risk of bias***

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Random sequence generation (selection bias) | Low risk | "Randomisation (1:1, stratified by centre and in blocks of four), was performed with the aid of a validated computer program that linked random numbers to drug or placebo treatment, respectively." |


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**GOT IT 2012** *(Continued)*

| | | |
|---|---|---|
| Allocation concealment (selection bias) | Low risk | "The sealed randomisation code was stored safely at the biometrics unit, and the length of randomisation blocks within which numbers of drug and placebo were balanced was not disclosed to investigators. Upon successful screening, each patient was assigned the treatment package with the lowest drug number still available at a site." |
| Blinding of participants and personnel (performance bias)<br>All outcomes | Low risk | "Active drug and placebo tablets were indistinguishable in appearance, packaging and labelling." "Drug dispensation and returnwas handled by persons not involved otherwise in the conduct of the clinical trial, usually the hospital pharmacists." |
| Blinding of outcome assessment (detection bias)<br>All outcomes | Low risk | Investigators carried out assessments and were blinded to treatment. "All cognitive tests and all interviews, except the ADCSCGIC, were administered by the investigators and sub-investigators all of whom were psychiatrists or neurologists. The ADCS-CGIC ratings were done by independent physicians or psychologists who were not otherwise involved in the trial or the treatment of the patients and who had no knowledge of the results of other ratings and cognitive tests." |
| Incomplete outcome data (attrition bias)<br>All outcomes | Low risk | Numbers and reasons for losses were reported. Overall numbers of losses were small, and the numbers and reasons did not appear different between groups. EGb 761 n = 7 discontinued (withdrawal of consent: 4; adverse event: 2; lost to follow-up: 1). Completed trial n = 198. Analyzed for efficacy n = 200. Excluded from analysis n = 5 (no efficacy data after baseline; withdrawal of consent: 3; adverse event: 2). Placebo n = 5 discontinued (withdrawal of consent: 4; adverse event: 1). Completed trial n = 200. Analyzed for efficacy n = 202. Excluded from analysis n = 3 (no efficacy data after baseline; withdrawal of consent: 2; adverse event: 1). No missing outcome data. |
| Selective reporting (reporting bias) | Unclear risk | Although trial was stated to be registered, we could not find it in Clinical-Trials.ru. No published protocol listing outcomes and methods of analyses was available; however the methods and results were consistent in terms of outcomes collected and reported. |
| Other bias | Low risk | The study appears to be free of other sources of bias. |

**Grass-Kapanke 2011**

| | |
|---|---|
| ***Study characteristics*** | |
| Methods | **Study design:** RCT<br>**Study grouping:** parallel group<br>**Duration of intervention:** 12 weeks<br>**Duration of follow-up:** 12 weeks<br>**Washout or placebo run-in period:** no |
| Participants | **Baseline characteristics**<br>*G biloba*<br>• Number randomized: 149<br>• MMSE (mean, SD): 27.8, 1.5<br>• Age (mean, SD): 55.3, 5.7 |


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**Grass-Kapanke 2011** *(Continued)*

- % female: 81.2%

Placebo

- Number randomized: 147
- MMSE (mean, SD): 27.9, 1.4
- Age (mean, SD): 54.5, 6.1
- % female: 83.6%

**Total number randomized:** 300 (baseline characteristics not provided for all participants randomized)

**Inclusion criteria**

- Either sex
- Outpatients
- Age 45 to 65
- Very mild cognitive impairment as defined by subjective complaints of impairment, perceived to be present ≥ 3 months, MMSE > 23, intact activities of daily living, no dementia

**Exclusion criteria**

- Ischemic stroke with sequelae within past 3 months
- Cognitive impairment due to neurological or psychiatric disorder
- History of recurrent major depression or anxiety
- Severe somatic disease
- Impaired vision or hearing compromising neuropsychological testing

**Country:** Latvia

**Setting:** outpatient

**Date recruitment began:** NR (prior to 2011)

**Recruitment methods:** "Most subjects were recruited by general practitioners, a small proportion by neurologists." No further details.

**Diagnosis:** very mild cognitive impairment

**Diagnostic criteria:** subjective complaints and low functioning in at least 1 screening test, but MMSE > 23 and no indication of dementia.

| | |
|---|---|
| Interventions | **Intervention characteristics**<br><br>*G biloba*<br><br>• "Patients were instructed to take one tablet containing 240 mg of EGb 761® or placebo every morning for a period of 12 weeks. EGb 761® is a dry extract from Ginkgo biloba leaves (35-67:1), extraction solvent: acetone 60% (w/w). The extract is adjusted to 22.0 -27.0% ginkgo flavonoids calculated as ginkgo flavone glycosides and 5.0-7.0% terpene lactones consisting of 2.8-3.4% ginkgolides A, B, C and 2.6-3.2% bilobalide and contains less than 5 ppm ginkgolic acids. Active drug and placebo were of identical appearance."<br><br>Placebo<br><br>• "Patients were instructed to take one tablet containing 240 mg of EGb 761® or placebo every morning for a period of 12 weeks. " "Active drug and placebo were of identical appearance."<br><br>"Patients were not allowed to take any psychoactive drugs, cognition-enhancing drugs or drugs acting on haemorrheology." |
| Outcomes | **Outcomes collected**<br><br>• Wechsler Memory Scale III—Faces I |


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**Grass-Kapanke 2011** *(Continued)*

- Wechsler Memory Scale III—Faces II
- Vienna Test System—Work Performance Series (*Arbeitsleistungsserie*, WTS-ALS)
- Vienna Test System—Determination Test (WTS-DT)
- Appointments Test (*Termine Test*, TT)
- Mental Balance Scale (*Befindlichkeitsskala*, BfS')
- SF-36 Health Survey

| | |
|---|---|
| Notes | **Sponsorship source:** NR; however, corresponding author is a Dr Willmar Schwabe employee. Therefore we believe that the company was the sponsor and funder.<br><br>**Trial registration number(s)**: EUCTR2005-003747-31-LV 2005 |

***Risk of bias***

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Random sequence generation (selection bias) | Low risk | Randomization, stratified by centers, was performed by the sponsor's biometrics unit using a validated computer program. |
| Allocation concealment (selection bias) | Low risk | "The length of the balanced blocks was described in a separate document that was withheld from the study sites. Drug boxes containing active drug or placebo were labelled uniformly and numbered in accordance with the randomisation list. Random treatment allocation was performed by handing each patient the drug box with the lowest yet unassigned number. The investigators received sealed emergency-envelopes for individual patients, all of which returned unopened after completion of the trial." |
| Blinding of participants and personnel (performance bias)<br>All outcomes | Low risk | "Active drug and placebo were of identical appearance."<br><br>Drug boxes containing active drug or placebo were labeled uniformly and numbered in accordance with the randomization list. Random treatment allocation was performed by handing each participant the drug box with the lowest yet unassigned number. The investigators received sealed emergency envelopes for individual participants, all of which were returned unopened after completion of the trial. Participants and personnel were blinded to treatment group. |
| Blinding of outcome assessment (detection bias)<br>All outcomes | Low risk | Appears that everyone in the study was blinded to treatment assignment. |
| Incomplete outcome data (attrition bias)<br>All outcomes | Low risk | Although reasons for loss to follow-up were not given, loss was very small (1% to 2%) and similar between groups. 300 participants were randomized. 149 from EGb and 147 from placebo were included in ITT analysis. |
| Selective reporting (reporting bias) | Low risk | All outcomes mentioned in Methods were reported in Results, and there was a trial registration (EUCTR2005-003747-31-LV 2005) prior to date of first enrolment that was consistent with the measurement and reporting of outcomes. |
| Other bias | Low risk | No other apparent sources of bias. |

**Gschwind 2017**

***Study characteristics***

| | |
|---|---|
| Methods | **Study design:** RCT |


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**Gschwind 2017** *(Continued)*

**Study grouping:** parallel group

**Duration of intervention:** 12 months (after 6 months all participants were given open-label *G biloba*)

**Duration of follow-up:** 12 months

**Washout or placebo run-in period:** none reported

| | |
|---|---|
| Participants | **Baseline characteristics**<br><br>*G biloba*<br><br>• Number randomized: 25<br>• MMSE (mean, SD): NR<br>• Age (mean, SD): 67.8, 8.3<br>• % female: 60%<br><br>Placebo<br><br>• Number randomized: 25<br>• MMSE (mean, SD): NR<br>• Age (mean, SD): 69.2, 8.6<br>• % female: 40%<br><br>**Total number randomized:** 50<br><br>**Inclusion criteria:** "(1) aged 50–85 years, (2) German-speaking, (3) completed elementary school, (4) impaired executive functions defined as a reduction in gait velocity of ≥10% during dual-task compared to single-task walking [15 ], (5) no dementia according to International Classifications of Diseases 10 and Diagnostic and Statistical Manual of Mental Disorders IV, (6) MCI according to Winblad et al. [12 ], (7) written informed consent prior to inclusion, and (8) nihil obstat from the participants' private physician."<br><br>**Exclusion criteria:** "(1) current drug treatment with antipsychotic or warfarin-like drugs, (2) intake of GBE currently or during the last 6 months, (3) known hypersensitivity to GBE or its constituents, (4) diagnosed psychiatric disorders such as severe clinical depression, (5) impaired gait due to orthopaedic (e.g. hip joint replacement) or neurologic disorders (e.g. Parkinson's disease), (6) severe medical conditions (i.e. chronic renal insufficiency), (7) participation in a clinical intervention study within the previous 2 months, (8) use of a walking aid, and (9) habitual gait velocity <100 cm/s."<br><br>**Country:** Switzerland<br><br>**Setting:** outpatient<br><br>**Date recruitment began:** 2010<br><br>**Recruitment methods:** "This single-centre study took place at the University of Basel Hospital, Division of Acute Geriatrics, Switzerland. Patient recruitment occurred between January 2010 and February 2014."<br><br>**Diagnosis:** MCI<br><br>**Diagnostic criteria:** Winblad 2004 MCI consensus |
| Interventions | **Intervention characteristics**<br><br>*G biloba*<br><br>• *G biloba* extract (GBE); (Symfona® forte 120 mg) was given twice-daily for 6 months. The intervention contained 25% standardized flavone glycoside and 6% terpene lactone content. GBE was produced and supplied by Vifor SA, Villars-sur-Glâne, Switzerland, and repacked, labeled and stored at the University of Basel Hospital pharmacy according to Good Manufacturing Practice annex. At Visits 1 and 2, participants received enough study medication for 3 months plus a reserve (19 blisters, 190 tablets). |


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**Gschwind 2017** *(Continued)*

After Visit 3, a 6-month open-label phase with identical GBE dosage (36 blisters, 360 tablets) in both groups followed. The study medication dose was 1 capsule taken twice daily with meals. Omitted morning and evening doses were allowed to be taken until noon and midnight, respectively.

Placebo

- The control group (CG) participants received placebo capsules. These comprised the same pharmaceutical excipients, color and size of intervention capsules. The placebo was produced and supplied by Vifor SA, Villars-sur-Glâne, Switzerland, and repacked, labeled and stored at the University of Basel Hospital pharmacy according to Good Manufacturing Practice annex. At Visits 1 and 2, participants received enough study medication for 3 months plus a reserve (19 blisters, 190 tablets). After Visit 3, a 6-month open-label phase with identical GBE dosage (36 blisters, 360 tablets) in both groups followed. The study medication dose was 1 capsule taken twice daily with meals. Omitted morning and evening doses were allowed to be taken until noon and midnight, respectively.

Treatment with antipsychotics or warfarin-like drugs not allowed.

| | |
|---|---|
| Outcomes | **Outcomes collected**<br>• gait analysis |
| Notes | **Sponsorship source:** "The presented research was funded by the Acute Geriatric Clinic of the University of Basel Hospital, and supported by an unrestricted research grant from Vifor SA, Villars-sur-Glâne, Switzerland. The production and supply of GBE and placebo was organised by Vifor SA."<br>**Trial registration number(s)**: NCT01046292<br>**Note:** Dr Yves J Gschwind was emailed on 24 February 2021 regarding adverse events, but there was no reply. |

***Risk of bias***

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Random sequence generation (selection bias) | Low risk | The randomization was conducted independently by an experienced study pharmacist at the University of Basel Hospital pharmacy to ensure that all investigators and participants remained blinded. Permuted block randomization (block sizes 2n = 5) were used to ensure numbers were evenly distributed among groups. |
| Allocation concealment (selection bias) | Low risk | Process of allocation not described. However, the randomization was conducted independently by an experienced study pharmacist at the University of Basel Hospital pharmacy to ensure that all investigators and participants remained blinded. |
| Blinding of participants and personnel (performance bias)<br>All outcomes | Low risk | Blinding of participants and key study personnel ensured, and unlikely that the blinding could have been broken. |
| Blinding of outcome assessment (detection bias)<br>All outcomes | Low risk | Although blinded outcome assessment was not explicitly mentioned, participants and investigators were blinded. |
| Incomplete outcome data (attrition bias)<br>All outcomes | High risk | Reasons were given for the 8 dropouts from the trial. All dropouts but 1 were from the placebo group; therefore, the placebo group had a high dropout rate (7/25; 28%) while the ginkgo group did not (1/25; 4%). |


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**Gschwind 2017** *(Continued)*

| | | |
|---|---|---|
| Selective reporting (reporting bias) | Low risk | The study was registered during the same month that the study began (NCT01046292), and the study's prespecified primary and secondary outcomes have been reported in the prespecified way. |
| Other bias | Low risk | Study appears to be free from other sources of bias. |

**Gu 2017**

| | |
|---|---|
| ***Study characteristics*** | |
| Methods | **Study design:** RCT<br><br>**Study grouping:** parallel group<br><br>**Duration of intervention:** 24 weeks<br><br>**Duration of follow-up:** 24 weeks<br><br>**Washout or placebo run-in period:** none reported |
| Participants | **Baseline characteristics**<br><br>*G biloba* + Nimodipine<br><br>• Number randomized: 62<br>• MMSE (mean, SD): 26.17, 1.45<br>• Age (mean, SD): 59.39, 4.91<br>• % female: 38.71<br><br>Nimodipine<br><br>• Number randomized: 62<br>• MMSE (mean, SD26.29, 1.51<br>• Age (mean, SD): 60.45, 4.32<br>• % female: 41.94<br><br>**Total number randomized:** 124<br><br>**Inclusion criteria**<br><br>• Amnestic mild cognitive impairment<br>  ◦ Chief complaint of memory decline confirmed by the informed person<br>  ◦ Junior high school education or above<br>  ◦ Memory test was abnormal. In the control group with normal education matching, the logical memory delayed recall score was < 1.5D, and the AVLT delayed recall score was < 4 points.<br>  ◦ Comprehensive cognitive function and independence in ADLs<br>  ◦ No clinical diagnosis of dementia according to the diagnostic criteria of the National Institute of Neurology, Speech Communication Disorders and Stroke/Alzheimer's Disease and Related Disorders<br>• Age 40 to 75<br>• MMSE 24–30 points<br>• Vision and hearing meeting requirements of neuropsychological examination<br>• Normal blood vitamin B12 level and thyroid function<br>• Negative serological reaction of syphilis<br>• Normal ECG<br>• Clinical Dementia Scale (CDR) score of 0.5. |


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**Gu 2017** *(Continued)*

- Caregiver support
- Ethics committee approval and informed consent

**Exclusion criteria**

- Cerebrovascular disease and Hachinski ischemia score > 4
- Depression (HAM-D > 12 points)
- Head CT or MR showing infarction, infection, or focal lesion of the central nervous system
- Internal or mental diseases that could affect study participation
- Concurrent use of cholinergic or anticholinergic drugs and other drugs with adverse effects on cognitive function

**Country:** China

**Setting:** outpatient

**Date recruitment began:** 2014

**Recruitment methods:** not reported

**Diagnosis:** aMCI

**Diagnostic criteria:** according to the diagnostic criteria of the National Institute of Neurology, Speech Communication Disorders and Stroke/Alzheimer's Disease and Related Disorders

| | |
|---|---|
| Interventions | **Intervention characteristics**<br><br>*G biloba* plus Nimodipine<br><br>• On the basis of the control group, combined with *G biloba* Tablets (Manufacture: Beijing Wanhui Double Crane Pharmaceutical Co, Ltd; Specifications: each tablet contains total flavonoglycoside 9.6 mg, terpene lactone 2.4 mg; Approval Number: National Drug Approval Z20043536) 1 tablet/time, 3 times/day. The treatment course of both groups was 24 weeks.<br><br>Nimodipine<br><br>• Oral Nimodipine Tablets (Manufacturer: Shandong Oriental Furuida Pharmaceutical Co, Ltd; Specifications: 30 mg; Approval Number: National Drug Approval H37022796) 30 mg/time, 3 times /day. The treatment course of both groups was 24 weeks.<br><br>Taking cholinergic or anticholinergic drugs or other drugs with adverse effects on cognitive function was not allowed. |
| Outcomes | **Outcomes collected**<br><br>• MMSE<br>• MoCA<br>• sRAGE<br>• sLRP-1<br>• Adverse events |
| Notes | **Sponsorship source:** Jiangsu Province Yangzhou City Key Research and Development Program – Social Development Project (No. YZ2015051)<br><br>**Trial registration number(s)**: none reported<br><br>We contacted the study author for 6-month adverse event rates, but received no reply. |

***Risk of bias***

| Bias | Authors' judgement | Support for judgement |
|---|---|---|


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**Gu 2017** *(Continued)*

| | | |
|---|---|---|
| Random sequence generation (selection bias) | Low risk | Random number table. |
| Allocation concealment (selection bias) | Unclear risk | Allocation process not reported. |
| Blinding of participants and personnel (performance bias)<br>All outcomes | High risk | Not reported. However, since the treatment in the treatment group is distinct from that in the control group, it is likely that the outcomes have been influenced by lack of blinding. |
| Blinding of outcome assessment (detection bias)<br>All outcomes | Unclear risk | Not reported. Unclear the extent to which the outcomes were influenced by lack of blinding. |
| Incomplete outcome data (attrition bias)<br>All outcomes | Unclear risk | Not reported. |
| Selective reporting (reporting bias) | Unclear risk | No protocol available. Insufficient information to permit judgment. |
| Other bias | Low risk | No other apparent sources of bias. |

**Guan 2019**

| | |
|---|---|
| ***Study characteristics*** | |
| Methods | **Study design:** RCT<br><br>**Study grouping:** parallel group<br><br>**Duration of intervention:** 90 days<br><br>**Duration of follow-up:** 90 days<br><br>**Washout or placebo run-in period:** none reported |
| Participants | **Baseline characteristics**<br><br>*G biloba* plus donepezil<br><br>• Number randomized: 46<br>• MMSE (mean, SD): 13.78, 4.11<br>• Age (mean, SD): 63.59, 4.04<br>• % female: 36.96<br><br>Donepezil<br><br>• Number randomized: 46<br>• MMSE (mean, SD): 14.03, 4.02<br>• Age (mean, SD): 64.05, 3.81<br>• % female: 32.61<br><br>**Total number randomized:** 92<br><br>**Inclusion criteria:** the family members of the participants knew about the study and signed the consent form. |


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**Guan 2019** *(Continued)*

**Exclusion criteria**

- Renal and liver dysfunction
- History of allergy and allergic constitution to the study drug
- Other cardiovascular and cerebrovascular diseases
- Dementia caused by other factors

**Country:** China

**Setting:** inpatient

**Date recruitment began:** 2016

**Recruitment methods:** not reported

**Diagnosis:** VD

**Diagnostic criteria:** not reported

| | |
|---|---|
| Interventions | **Intervention characteristics**<br><br>*G biloba* + donepezil<br><br>• After admission, the 2 groups were given interventions such as antiplatelet accumulation and lowering blood lipid, etc. On this basis, the control group was given donepezil hydrochloride tablets (Jiangsu Hausen Pharmaceutical Co, Ltd, national drug approval H20030472), orally 5 mg/time, once a day, for 3 months. On the basis of the treatment in the control group, the research group added *G biloba* leaf extract injection (Yuekang Pharmaceutical Group Co, Ltd, H20070226), intravenously dripping 20 mL *G biloba* leaf extract injection + 200 mL normal saline, twice a day, 10 days after continuous use, and then rest for 5 days, then start the next course of treatment.<br><br>Donepezil<br><br>• After admission, the 2 groups were given interventions such as antiplatelet accumulation and lowering blood lipid, etc. On this basis, the control group was given donepezil hydrochloride tablets (Jiangsu Hausen Pharmaceutical Co, Ltd, national drug approval H20030472), orally 5 mg/time, once a day, for 3 months. |
| Outcomes | **Outcomes collected**<br><br>• MMSE<br>• ADLs<br>• Adverse events |
| Notes | **Sponsorship source:** none reported<br><br>**Trial registration number(s)**: none reported |

***Risk of bias***

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Random sequence generation (selection bias) | Low risk | Random number table. |
| Allocation concealment (selection bias) | Unclear risk | Not reported. |
| Blinding of participants and personnel (performance bias) | High risk | Not reported. However, since the treatment and drug delivery route in the treatment group are distinct from that in the control group, it is likely that the outcomes were influenced by lack of blinding. |


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**Guan 2019** *(Continued)*

| | | |
|---|---|---|
| All outcomes | | |
| Blinding of outcome assessment (detection bias)<br>All outcomes | Unclear risk | Not reported. Unclear the extent to which the outcomes might be influenced by lack of blinding. |
| Incomplete outcome data (attrition bias)<br>All outcomes | Unclear risk | Not reported. |
| Selective reporting (reporting bias) | Unclear risk | No protocol available. Insufficient information to permit judgment. |
| Other bias | Low risk | No other apparent sources of bias. |

**Halama 1988**

| ***Study characteristics*** | |
|---|---|
| Methods | **Study design:** RCT<br>**Study grouping:** parallel group<br>**Duration of intervention:** 12 weeks<br>**Duration of follow-up:** 12 weeks<br>**Washout or placebo run-in period:** none reported |
| Participants | **Baseline characteristics**<br>*G biloba*<br>• Number randomized: 20<br>• MMSE (mean, SD): NR<br>• Age (mean, SD): 65.2, 6.96<br>• % female: 60%<br>Placebo<br>• Number randomized: 20<br>• MMSE (mean, SD): NR<br>• Age (mean, SD): 66.6, 9.43<br>• % female: 25%<br>**Total number randomized:** 40<br>**Inclusion criteria**<br>• Diagnosis of "slight to moderate cerebral insufficiency of vascular origin" with Hachinski > 7 and Crichton 1 to 3<br>**Exclusion criteria**<br>• Primary degenerative dementia or any of the following conditions<br>  ◦ Psychoses or neuroses<br>  ◦ Secondary brain impairment (treatable underlying disease, e.g. intoxication, metabolic disorder, alcoholism) |


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**Halama 1988** *(Continued)*

- Epilepsy or other serious diseases (e.g. myocardial infarction in the last 6 months; severe renal insufficiency; severe, life-threatening cardiac arrhythmias; malignancy)
- Use of clonidine, reserpine, antihistamines, anti-Parkinson drugs, anticoagulants, platelet aggregation inhibitors, psychotropic drugs, centrally acting stimulants, or drugs that affect the brain metabolism or blood flow

**Country:** Germany

**Setting:** outpatient

**Date recruitment began:** NR (prior to 1988)

**Recruitment methods:** neurologist's practice (no further details)

**Diagnosis:** cerebral insufficiency of vascular origin

**Diagnostic criteria:** the diagnosis was made on the basis of the clinical findings and the results of the psychometric tests carried out and scale assessments (Hachinski: > 7, Crichton: levels 1 to 3).

Interventions

**Intervention characteristics**

*G biloba*

- Tebonin forte, film-coated tablets (3 × 1 per day, corresponding to a daily dose of 120 mg *G biloba* extract) for 12 weeks

Placebo

- Placebo film-coated tablets that could not be distinguished from the Tebonin forte tablets

Treatment with psychotropic drugs or nootropics was not allowed either during a 3-week washout phase before the start of the study or during the study.

Outcomes

**Outcomes collected**

- SCAG
- Crichton Scale
- *Hintergrund-Interferenz-Verfahren*
- SKT
- Cariocorporgraphy
- Symptoms of dizziness, ringing in the ears, headache, and hearing loss

Notes

**Sponsorship source:** none reported

**Trial registration number(s)**: none reported

Only the adverse event data were extractable.

***Risk of bias***

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Random sequence generation (selection bias) | Low risk | "*Den Patienten wurde eine Nummber in der Reihenfolge ihrer Aufnahme zugeteilt. Diese Nummern waren zuvor mit Hilfe eines EDV-Programmes den beiden Behandlungsgruppen je zur Haelfte randomisiert zugeordnet worden*." Patients were assigned a number in the order in which they were enrolled. These numbers had previously been randomly assigned to half of the 2 treatment groups with the help of a computer program. |


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**Halama 1988** *(Continued)*

| | | |
|---|---|---|
| Allocation concealment (selection bias) | Low risk | Neither the participants nor the examining doctor knew this assignment; the code was only opened after the data acquisition was completed at the beginning of the evaluation. |
| Blinding of participants and personnel (performance bias)<br>All outcomes | Low risk | The placebo tablet was film coated and could not be distinguished from the *G biloba* tablets. Neither participants nor doctors knew the assignment. "Neither the patient nor the examining doctor knew this assignment..." Tebonin "could not be distinguished from" placebo. |
| Blinding of outcome assessment (detection bias)<br>All outcomes | Low risk | "Neither the patient nor the examining doctor knew this assignment..." The code was opened after data acquisition. |
| Incomplete outcome data (attrition bias)<br>All outcomes | Unclear risk | No participants were described as lost to follow-up. However, the numbers initially randomized, lost (or not lost), and analyzed were not explicit. |
| Selective reporting (reporting bias) | Unclear risk | No protocol or other document that permitted a judgment of high or low risk of bias. |
| Other bias | Low risk | No other apparent source of bias. |

**Halama 1991a**

| | |
|---|---|
| ***Study characteristics*** | |
| Methods | **Study design:** RCT<br><br>**Study grouping:** parallel group<br><br>**Duration of intervention:** 12 weeks<br><br>**Duration of follow-up:** 12 weeks<br><br>**Washout or placebo run-in period:** 3-week washout period for nootropics and psychotropics |
| Participants | **Baseline characteristics**<br><br>*G biloba*<br><br>• Number randomized: 20<br>• MMSE (mean, SD): NR<br>• Age (mean, SD): 61 (range 46 to 83)<br>• % female: 75%<br><br>Placebo<br><br>• Number randomized: 22<br>• MMSE (mean, SD): NR<br>• Age (mean, SD): 61 (range 35 to 85)<br>• % female: 55%<br><br>**Total number randomized:** 50 (baseline characteristics not provided for all participants randomized)<br><br>**Inclusion criteria:** diagnosis of "presenile, simple senile or arteriosclerotic dementia"<br><br>**Exclusion criteria:** none reported |


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**Halama 1991a** *(Continued)*

| | |
|---|---|
| | **Country:** Germany<br><br>**Setting:** outpatient<br><br>**Date recruitment began:** NR (prior to 1991)<br><br>**Recruitment methods:** outpatients were enrolled from a neurological practice. No other description.<br><br>**Diagnosis:** "presenile, simple senile or arteriosclerotic dementia"<br><br>**Diagnostic criteria:** none reported |
| Interventions | **Intervention characteristics**<br><br>*G biloba*<br><br>• The treatment took place over 12 weeks with 3 × 50 mg *G biloba* special extract (LI 1370, standardized to 25% flavone glycosides and 6% terpene lactones) daily.<br><br>Placebo<br><br>• Not described |
| Outcomes | **Outcomes collected**<br><br>• *Syndrom-Kurztest* (SKT)<br>• *Zahlenverbindungstest* (ZVT)<br>• Symptom scores (not present, light, moderate, severe) for each of dizziness, headache, tinnitus, memory deficiency, concentration, anxiety, forgetfulness, tiredness, motivation, depression, and function<br>• Physician rating of effectiveness<br>• Participant rating of effectiveness |
| Notes | **Sponsorship source:** none reported<br><br>**Trial registration number(s)**: none reported<br><br>Only the adverse event data was extractable. |

***Risk of bias***

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Random sequence generation (selection bias) | Unclear risk | The author stated the study was randomized but did not describe the methods. Since the same author published a previous randomized trial in which randomization methods were stated, it is likely that the trial was randomized, but the procedures remain unclear. |
| Allocation concealment (selection bias) | Unclear risk | No mention of allocation procedures. |
| Blinding of participants and personnel (performance bias)<br>All outcomes | Low risk | Double-blind study. |
| Blinding of outcome assessment (detection bias)<br>All outcomes | Low risk | Double-blind study. |
| Incomplete outcome data (attrition bias) | Unclear risk | Of the original 50 participants enrolled, 42 could be evaluated. The reasons for discontinuation or exclusion were: concomitant medication with psychotropic |


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**Halama 1991a** *(Continued)*

| | | |
|---|---|---|
| All outcomes | | drugs (n = 2), non-compliance with follow-up times or dropout from the study (n = 5), and discontinuation of the medication due do allergy (n = 1). More participants dropped out of the *G biloba* group, and many of the reasons were vague. |
| Selective reporting (reporting bias) | Unclear risk | No protocol available. The outcomes in the Methods were reported in Results, but the correspondence with preplanned outcomes and analyses cannot be judged as there is no protocol. |
| Other bias | Low risk | No other apparent source of bias. |

**Han 2016**

| | |
|---|---|
| ***Study characteristics*** | |
| Methods | **Study design:** RCT<br><br>**Study grouping:** parallel group<br><br>**Duration of intervention:** 12 months<br><br>**Duration of follow-up:** 12 months<br><br>**Washout or placebo run-in period:** none reported |
| Participants | **Baseline characteristics**<br><br>*G biloba* + basic treatment<br><br>• Number randomized: 60<br>• MMSE (mean, SD): 20.05, 3.12<br>• Age (mean, SD): 72.3, 5.3<br>• % female: 68.33<br><br>Basic treatment<br><br>• Number randomized: 60<br>• MMSE (mean, SD): 20.14, 3.20<br>• Age (mean, SD): 71.7, 4.9<br>• % female: 63.33<br><br>**Total number randomized:** 120<br><br>**Inclusion criteria**<br><br>• MCI outpatients<br>• Age 60 to 80 years<br><br>**Exclusion criteria**<br><br>• Cognitive impairment caused by traumatic brain injury, depression, medications, thyroid disease, alcoholism, etc.<br>• Complicated cerebrovascular disease and impairment of heart, liver, lung, and kidney function<br>• Use of drugs affecting nerve and brain function in the past 3 months<br><br>**Country:** China<br><br>**Setting:** outpatient |


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**Han 2016** *(Continued)*

**Date recruitment began:** 2014

**Recruitment source/methods:** not reported

**Diagnosis:** MCI

**Diagnostic criteria:** referring to the MCI International Working Group's 2004 Diagnostic Criteria for Mild Cognitive Impairment:

- Chief complaint was memory impairment.
- Objective examination evidence of memory loss (memory test scores were more than 1.5 SDs lower than those of age-and culture-matched controls).
- The Global Deterioration Scale grade is 2–3, that is, the overall cognitive function is mildly abnormal.
- Normal general cognitive function and daily living ability.
- Exclude other diseases that may cause the decline of brain function and nerve function.

If the above conditions are met, MCI is diagnosed.

| | |
|---|---|
| Interventions | **Intervention characteristics**<br><br>*G biloba* + basic treatment<br><br>• "Patients in both groups received the following basic treatments, including: (1) Health publicity and education to guide patients to maintain a comfortable mood and actively treat basic diseases, such as hypertension and diabetes. (2) Moderate walking, handball, square dancing and other sports (walking: 20 ~ 30 min in the morning and about 1 000 min the evening;Handball:30 min/d, 1 time in the morning and 1 time in the evening;Square dance: at night, 30 min/time). (3) Nutrition support: Supplement protein and vitamins according to the basic situation of the patient to enhance the body immunity. On the basis of basic treatment, EGb Tablet (trade name: Si Tai Long, manufacturer: Shanghai Xingling Technology Pharmaceutical Co., Ltd., specifications: 80mg/tablet) were added for treatment, 1 tablet/time, 3 times/d, for 12 months."<br><br>Basic treatment<br><br>• "Patients in both groups received the following basic treatments, including: (1) Health publicity and education to guide patients to maintain a comfortable mood and actively treat basic diseases, such as hypertension and diabetes. (2) Moderate walking, handball, square dancing and other sports (walking: 20 ~ 30 min in the morning and about 1 000 min the evening;Handball:30 min/d, 1 time in the morning and 1 time in the evening;Square dance: at night, 30 min/time). (3) Nutrition support: Supplement protein and vitamins according to the basic situation of the patient to enhance the body immunity." |
| Outcomes | **Outcomes collected**<br><br>• Clinical effect<br>• Incidence of dementia<br>• Lab tests<br>• MQ (Memory Quotient)<br>• MMSE<br>• Adverse events |
| Notes | **Sponsorship source:** none reported<br><br>**Trial registration number(s)**: none reported |

***Risk of bias***

| Bias | Authors' judgement | Support for judgement |
|---|---|---|


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**Han 2016** *(Continued)*

| | | |
|---|---|---|
| Random sequence generation (selection bias) | Low risk | Random number table. |
| Allocation concealment (selection bias) | Unclear risk | Not reported. |
| Blinding of participants and personnel (performance bias)<br>All outcomes | High risk | Not reported, but since the treatment and drug delivery route in the treatment group are distinct from that in the control group, it is likely that the outcomes were influenced by lack of blinding. |
| Blinding of outcome assessment (detection bias)<br>All outcomes | Unclear risk | Not reported. Unclear the extent to which outcomes were influenced by lack of blinding. |
| Incomplete outcome data (attrition bias)<br>All outcomes | Unclear risk | Loss to follow-up not reported. |
| Selective reporting (reporting bias) | Unclear risk | No protocol available. Insufficient information to permit judgment. |
| Other bias | Low risk | No other apparent sources of bias. |

**He 2005**

| ***Study characteristics*** | |
|---|---|
| Methods | **Study design:** RCT<br>**Study grouping:** parallel group<br>**Duration of intervention:** 3 months<br>**Duration of follow-up:** 3 months<br>**Washout or placebo run-in period:** none reported |
| Participants | **Baseline characteristics**<br>*G biloba* + placebo Jianpi Tianjing<br>• Number randomized: 21<br>• MMSE (mean, SD): NR<br>• Age (mean, SD): 72.1, 3.9<br>• % female: 33.33<br>Jianpi Tianjing + placebo *G biloba*<br>• Number randomized: 22<br>• MMSE (mean, SD): NR<br>• Age (mean, SD): 71.5, 4.2<br>• % female: 27.27<br>**Total number randomized:** 43<br>**Inclusion criteria** |


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**He 2005** *(Continued)*

- Diagnostic criteria of MCI
- Age 60 to 85 years
- No heart, brain, kidney, or other important organ failure
- No neuropsychiatric disorders
- Informed consent

**Exclusion criteria**

- Allergic constitution or allergy to the ingredients of the study medicine
- Severe primary diseases, such as cardiovascular, liver, kidney, and hematopoietic disease, or mental illness.

**Country:** China

**Setting:** outpatient

**Date recruitment began:** NR (prior to 2005)

**Recruitment methods:** from the Affiliated Hospital of Northwest University for Nationalities Medical School and the Affiliated Hospital of Lanzhou Medical College

**Diagnosis:** MCI

**Diagnostic criteria:** formulated with reference to the relevant contents of *Guiding Principles for Clinical Research of New Chinese Medicine*, *Internal Medicine of Traditional Chinese Medicine* and *Diagnostic and Statistical Manual of Mental Disorders of the United States*.

- Chief complaint of memory loss
- Evidence of objective examination of memory decline (degree of memory decline defined as at least 1.5 criteria below the age- and education-matched control)
- Preservation of general cognitive function and daily living ability
- Simple Mental State Checklist (MMSE) score ≥ 24
- Insufficient damage to diagnose dementia

| | |
|---|---|
| Interventions | **Intervention characteristics**<br><br>*G biloba* + placebo Jianpi Tianjing<br><br>• *G biloba* capsules (produced by Beijing Shuguang Pharmaceutical Co, Ltd, each containing acetamide pyrrolidone 0.4g) were taken for continuous treatment 3 times a day. Placebo Jianpi Tianjing capsules also taken.<br><br>Jianpi Tianjing + placebo *G biloba*<br><br>• Jianpi Tianjing capsule: each capsule was 0.35 g, equivalent to crude drug 4.4 g, 3 tablets at a time, 3 times a day, with warm water. Placebo *G biloba* capsules also taken. |
| Outcomes | **Outcomes collected**<br><br>• CMS (clinical memory scale)<br>• Adverse events |
| Notes | **Sponsorship source:** none reported<br><br>**Trial registration number(s)**: none reported<br><br>No outcome data relevant to this review could be extracted from the study. The study reported that no adverse events occurred. |

***Risk of bias***


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**He 2005** *(Continued)*

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Random sequence generation (selection bias) | Low risk | Random number table. |
| Allocation concealment (selection bias) | Unclear risk | Not reported. |
| Blinding of participants and personnel (performance bias)<br>All outcomes | Low risk | "Double blind and double simulation method was adopted." |
| Blinding of outcome assessment (detection bias)<br>All outcomes | Unclear risk | Not reported. Unclear to what extent the outcomes were influenced by lack of blinding. |
| Incomplete outcome data (attrition bias)<br>All outcomes | Low risk | "One case in the treatment group did not take the medicine on time, which was counted as the dropout case. One case in the control group dropped out midway and was counted as the dropout case." Comparable with detail. |
| Selective reporting (reporting bias) | Unclear risk | No protocol available. Insufficient information to permit judgment. |
| Other bias | Low risk | No other apparent sources of bias. |

**He 2016**

| ***Study characteristics*** | |
|---|---|
| Methods | **Study design:** RCT<br>**Study grouping:** parallel group<br>**Duration of intervention:** 12 weeks<br>**Duration of follow-up:** 12 weeks<br>**Washout or placebo run-in period:** NR |
| Participants | **Baseline characteristics**<br>*G biloba*<br>• Number randomized: 50<br>• MMSE (mean, SD): 25.4, 3.2<br>• Age (mean, SD): 68.2, 3.2<br>• % female: 42<br>Donepezil<br>• Number randomized: 50<br>• MMSE (mean, SD): 24.9, 3.3<br>• Age (mean, SD): 67.1, 2.9<br>• % female: 40<br>*G biloba* + donepezil |


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**He 2016** *(Continued)*

- Number randomized: 50
- MMSE (mean, SD): 25.6, 3.1
- Age (mean, SD): 67.8, 3.0
- % female: 36

**Total number randomized:** 150

**Inclusion criteria**

- Rockwood clinical diagnostic criteria for VCI
- Age > 60 years
- Acquired cognitive impairment
- Vascular etiology confirmed by imaging examination
- Hachinski score < 4
- HAM-D score < 17

**Exclusion criteria:** NR

**Country:** China

**Setting:** inpatient

**Date recruitment began**: 2014

**Recruitment methods:** people with VCI who visited Aerospace Center Hospital from June 2014 to June 2015

**Diagnosis:** VCI

**Diagnostic criteria:** clinical diagnostic criteria for VCI established by Rockwood

| | |
|---|---|
| Interventions | **Intervention characteristics**<br>*G biloba*<br>• Single oral treatment of *G biloba* leaf extract tablets 3 times a day, 2 tablets each time (total 6 tablets per day)<br>Donepezil<br>• Single oral treatment of Aricept Tablets once a day, 1 tablet each time<br>*G biloba* + donepezil<br>• Single oral treatment of *G biloba* leaf extract tablets combined with Aricept tablets. Dosage were the same as the other groups. |
| Outcomes | **Outcomes collected**<br>• **T**otal effective rate<br>• MMSE<br>• MoCA<br>• WMS<br>• ADLs |
| Notes | **Sponsorship source:** NR<br>**Trial registration number:** NR |
| ***Risk of bias*** | |


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**He 2016** *(Continued)*

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Random sequence generation (selection bias) | Low risk | Random number table. |
| Allocation concealment (selection bias) | Unclear risk | Not reported. |
| Blinding of participants and personnel (performance bias)<br>All outcomes | High risk | Different medications and dosages across groups and no mention of blinding. |
| Blinding of outcome assessment (detection bias)<br>All outcomes | Unclear risk | Not reported. |
| Incomplete outcome data (attrition bias)<br>All outcomes | Unclear risk | No apparent attrition. |
| Selective reporting (reporting bias) | Unclear risk | No protocol available. Insufficient information to permit judgment. |
| Other bias | High risk | Some data for an outcome not extracted in this review were outside the range of the reported scale. This raises concerns that the data in the trial might be unreliable overall. |

**He 2018a**

| ***Study characteristics*** | |
|---|---|
| Methods | **Study design:** RCT<br>**Study grouping:** parallel group<br>**Duration of intervention:** 3 months<br>**Duration of follow-up:** 3 months<br>**Washout or placebo run-in period:** none reported |
| Participants | **Baseline characteristics**<br>*G biloba* + donepezil<br>• Number randomized: 42<br>• MMSE (mean, SD): 16.52, 3.30<br>• Age (mean, SD): 65.4, 3.5<br>• % female: 40.48<br>Donepezil<br>• Number randomized: 42<br>• MMSE (mean, SD): 16.83, 3.16<br>• Age (mean, SD): 65.8, 3.1<br>• % female: 38.10 |


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**He 2018a** *(Continued)*

| | |
|---|---|
| | **Total number randomized:** 84<br><br>**Inclusion criteria**<br><br>• Cognitive dysfunction after cerebral infarction and diagnosis of mild to moderate cognitive impairment through specialized evaluation<br>• No recent use of cholinesterase inhibitors<br>• Hospitalization within 24 hours after onset<br><br>**Exclusion criteria**<br><br>• Liver and kidney insufficiency<br>• Heart disease<br>• Craniocerebral tumor<br>• Disturbance of consciousness<br>• Dementia<br>• Craniocerebral trauma<br><br>**Country:** China<br><br>**Setting:** hospital<br><br>**Date recruitment began:** 2016<br><br>**Recruitment methods:** admitted to the Department of Neurology of our hospital from February 2016 to February 2017<br><br>**Diagnosis:** cognitive dysfunction after cerebral infarction<br><br>**Diagnostic criteria:** not reported |
| Interventions | **Intervention characteristics**<br><br>*G biloba* + donepezil<br><br>• Donepezil (Eisai Pharmaceutical Co, Ltd, National Drug Approval No. H20050978: 5 mg × 7 tablets), 5 mg/time, once a day, taken with warm water before bed. EGb Tablet (Jiangsu Chenpai Pharmaceutical Group Co, Ltd, National Drug Approval Z20027948 Specification: 9.6 mg：2.4mg × 12s × 4 plates), 1 tablet/time, 3 times/day, taken with warm water after meals<br><br>Donepezil<br><br>• Donepezil (Eisai Pharmaceutical Co, Ltd, National Drug Approval No. H20050978: 5 mg × 7 tablets), 5 mg/time, once a day, taken with warm water before bed |
| Outcomes | **Outcomes collected**<br><br>• MoCA<br>• MMSE<br>• Effective rate<br>• Adverse event |
| Notes | **Sponsorship source:** none reported<br><br>**Trial registration number(s)**: none reported |

***Risk of bias***

| Bias | Authors' judgement | Support for judgement |
|---|---|---|


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**He 2018a** *(Continued)*

| | | |
|---|---|---|
| Random sequence generation (selection bias) | Low risk | Random number table. |
| Allocation concealment (selection bias) | Unclear risk | Allocation process not reported. |
| Blinding of participants and personnel (performance bias)<br>All outcomes | High risk | Not reported. However, since the treatment (in the treatment group) is distinct from that in the control group, it is likely that the outcomes were influenced by lack of blinding. |
| Blinding of outcome assessment (detection bias)<br>All outcomes | Unclear risk | Not reported. Unclear the extent to which outcomes might be influenced by lack of blinding. |
| Incomplete outcome data (attrition bias)<br>All outcomes | Unclear risk | Attrition not reported. |
| Selective reporting (reporting bias) | Unclear risk | No protocol available. Insufficient information to permit judgment. |
| Other bias | Low risk | No other apparent sources of bias. |

**He 2018b**

| ***Study characteristics*** | |
|---|---|
| Methods | **Study design:** RCT<br>**Study grouping:** parallel group<br>**Duration of intervention:** 3 months<br>**Duration of follow-up:** 3 months<br>**Washout or placebo run-in period:** none reported |
| Participants | **Baseline characteristics**<br>*G biloba* + nimodipine<br>• Number randomized: 48<br>• MMSE (mean, SD): 19.15, 2.43<br>• Age (mean, SD): 65.79, 7.91<br>• % female: 43.75<br>Nimodipine<br>• Number randomized: 48<br>• MMSE (mean, SD): 19.28, 2.53<br>• Age (mean, SD): 65.27, 7.67<br>• % female: 39.58<br>**Total number randomized:** 96<br>**Inclusion criteria** |


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**He 2018b** *(Continued)*

- Diagnosis of cognitive dysfunction due to CSVD
- Blood stasis syndrome diagnosis
- Age 50 to 70 years
- Primary school education or above
- Clear consciousness and ability to cooperate with treatment
- Informed consent

**Exclusion criteria**

- Heart, liver, kidney, and other severe dysfunction
- Head trauma or other cognitive disorders
- Senile dementia
- Past abuse of psychiatric drugs
- Physical allergy

**Country:** China

**Setting:** hospital

**Date recruitment began:** 2015

**Recruitment methods:** not reported

**Diagnosis:** cognitive impairment due to CSVD

**Diagnostic criteria:** the diagnostic criteria of CSVD were formulated according to the Expert Consensus on Diagnosis and Treatment of Cerebrovascular Diseases.

- MRI confirmed the presence of CSVD, number of lacunar cerebral infarction ≥ 1, diameter 2–15 mm.
- MRI angiography showed no subcortical or watershed infarcts, no > 15 mm lesions, and no intracranial great artery occlusion.
- Cervical vascular ultrasound did not show carotid artery stenosis.
- Cerebrovascular disease risk factors, such as hypertension, diabetes, coronary heart disease, etc.
- Visual and hearing abilities and ability to cooperate with examination. The diagnostic criteria of cognitive impairment were determined by MMSE and MoCA scores. The MMSE score includes orientation, attention and calculation, memory, recall and language skills, with a score of 0 to 30, and < 25 for cognitive impairment. MoCA scores included visuospatial and executive ability, attention, language expression, naming, delayed recall, abstract thinking, and orientation, with scores ranging from 0 to 30, and < 26 for cognitive impairment.

Interventions

**Intervention characteristics**

*G biloba* + nimodipine

- Oral administration of Nimotop tablet (Bayer Medical Care Co, Ltd, National Drug License 2000H0031), 30 mg each time, 3 times a day, plus oral administration of Gingko Leaf capsules (Hangzhou KangEnBei Pharmaceutical Co, Ltd, National Drug License Z20063069), 3 times per day, 2 capsules per time

Nimodipine

- Oral administration of Nimotop tablet (Bayer Medical Care Co, Ltd, National Drug License 2000H0031), 30 mg each time, 3 times a day

Outcomes

**Outcomes collected**

- MMSE
- MoCA
- TCM score
- Lab tests


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**He 2018b** *(Continued)*

| | |
|---|---|
| Notes | **Sponsorship source:** none reported<br>**Trial registration number(s)**: none reported |

***Risk of bias***

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Random sequence generation (selection bias) | Low risk | Random number table. |
| Allocation concealment (selection bias) | Unclear risk | Not reported. |
| Blinding of participants and personnel (performance bias)<br>All outcomes | High risk | Different interventions in 2 groups. No placebo used. |
| Blinding of outcome assessment (detection bias)<br>All outcomes | Unclear risk | Not reported. Unclear the extent to which outcomes might be influenced by lack of blinding. |
| Incomplete outcome data (attrition bias)<br>All outcomes | Unclear risk | Lost to follow-up not reported. |
| Selective reporting (reporting bias) | Unclear risk | No protocol available. Insufficient information to permit judgment. |
| Other bias | Low risk | No other apparent sources of bias. |

**Huang 2017**

***Study characteristics***

| | |
|---|---|
| Methods | **Study design:** RCT<br>**Study grouping:** parallel group<br>**Duration of intervention:** 6 months<br>**Duration of follow-up:** 6 months<br>**Washout or placebo run-in period:** none reported |
| Participants | **Baseline characteristics**<br>*G biloba* + butylphthalide<br>• Number randomized: 40<br>• MMSE (mean, SD): 14.31, 1.05<br>• Age (mean, SD): 70.05, 11.38<br>• % female: 45<br>Butylphthalide<br>• Number randomized: 40 |


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**Huang 2017** *(Continued)*

- MMSE (mean, SD): 14.27, 1.08
- Age (mean, SD): 69.93, 12.04
- % female: 47.5

**Total number randomized:** 80

**Inclusion criteria**

- Conformity with diagnosis
- Mild to moderate disease
- Informed consent (family members)
- Age 50 to 80 years
- Supervision of adherence to the drug by family members
- TCM syndrome is "deficiency of liver and kidney Yin, phlegm and blood stasis blocking collaterals".

**Exclusion criteria**

- Secondary AD caused by other primary diseases
- Use of relevant therapeutic drugs within half a year
- Serious diseases of the heart, kidney, and other tissues and the blood system
- Mental abnormalities due to stimulation
- Traumatic brain injury and brain surgery

**Country:** China

**Setting:** hospital

**Date recruitment began:** 2014

**Recruitment methods:** people admitted to our hospital from October 2014 to August 2016

**Diagnosis:** AD

**Diagnostic criteria:** referring to the Diagnostic and Statistical Manual of Mental Disorders.

- The participants were found to have memory impairment symptoms for 6 months or more continuously by means of cue recall test.
- Abnormal behavior, uncontrolled, communication disorders, accompanied by aphasia symptoms, cognitive and living ability progressive decline
- The level of β-amyloid 1-42 in cerebrospinal fluid was decreased by laboratory examination; autosomal dominant mutation in AD.
- CT/MRI examination of the head showed different degrees of brain atrophy, the volume of hippocampus, entorhinal cortex, amygdala decreased, microvascular degeneration, cerebral blood flow decreased.
- Behavior changes or dementia caused by epilepsy, stroke, depression, vascular dementia, poisoning, cerebral ischemia, and hypoxia were excluded.

Interventions

**Intervention characteristics**

*G biloba* + butylphthalide

- Butylphthalide soft capsule (Shiyao Group Enbipu Pharmaceutical Co, Ltd, specifications 0.1 g* 24s, Batch No. 140903), taken orally on an empty stomach, twice a time, 3 times a day, for 6 consecutive months. EGb extract tablets (German Dr Willmar Schwabe GmbH & Co KG, 40 mg* 20s, Batch No. 141003), taken orally, 2 tablets/time, twice a day, for 6 consecutive months (total *G biloba* dose 160 mg/day).

Butylphthalide


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**Huang 2017** *(Continued)*

| | |
|---|---|
| | • Butylphthalide soft capsule (Shiyao Group Enbipu Pharmaceutical Co, Ltd, specifications 0.1g* 24s, Batch No. 140903), taken orally on an empty stomach, twice a time, 3 times a day, for 6 consecutive months. |
| Outcomes | **Outcomes collected**<br>• MMSE<br>• ADAS-cog<br>• ADLs<br>• Laboratory tests<br>• Effective rate<br>• Adverse event (no extractable information on events) |
| Notes | **Sponsorship source:** none reported<br>**Trial registration number(s)**: none reported |

***Risk of bias***

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Random sequence generation (selection bias) | Low risk | The study authors drew lots. |
| Allocation concealment (selection bias) | Unclear risk | Allocation process not reported. |
| Blinding of participants and personnel (performance bias)<br>All outcomes | High risk | Not reported. But since the dosage form in the treatment group is distinct from that in the control group, it is likely that the self-reported outcomes were influenced by lack of blinding. |
| Blinding of outcome assessment (detection bias)<br>All outcomes | Unclear risk | Blinding of outcome assessment not reported. |
| Incomplete outcome data (attrition bias)<br>All outcomes | Unclear risk | Loss to follow-up not reported. |
| Selective reporting (reporting bias) | Unclear risk | No protocol available. Insufficient information to permit judgment. |
| Other bias | Low risk | No other apparent sources of bias. |

**Israel 1987**

***Study characteristics***

| | |
|---|---|
| Methods | **Study design:** RCT<br>**Study grouping:** parallel group<br>**Duration of intervention:** 3 months<br>**Duration of follow-up:** 3 months |


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**Israel 1987** *(Continued)*

**Washout or placebo run-in period:** none reported

| | |
|---|---|
| Participants | **Baseline characteristics**<br><br>*G biloba*<br><br>• Number randomized: 40<br>• MMSE (mean, SD): NR<br>• Age (mean, SD): NR<br>• % female: NR<br><br>Placebo<br><br>• Number randomized: 40<br>• MMSE (mean, SD): NR<br>• Age (mean, SD): NR<br>• % female: NR<br><br>**Total number randomized:** 80<br><br>**Inclusion criteria**<br><br>• Age over 55 years<br>• Complaint of age-related memory impairment<br>• MMSE score between 20 and 26 inclusive<br>• Score < 18 on the Geriatric Depression Scale (GDS)<br><br>**Exclusion criteria**<br><br>• Severe acute or chronic illness<br>• History of depression<br>• Use of vasoregulatory or cerebral metabolic treatment that could not be suspended during the study<br><br>**Country:** France<br><br>**Setting:** outpatient<br><br>**Date recruitment began:** 1985<br><br>**Recruitment methods:** recruited through a Pension Fund (MGEN), a local pension association (AVAG), or presented themselves spontaneously to the Consultation of the Department of Clinical Gerontology of the CHU of Grenoble.<br><br>**Diagnosis:** age-related memory impairment<br><br>**Diagnostic criteria:** MMSE score between 20 and 26 |
| Interventions | **Intervention characteristics**<br><br>*G biloba*<br><br>• EGb at a dose of 2 mL morning and evening (160 mg/day of EGb) for 3 months. EGb 761 is made available to the Medical Corps in France under the name TANAKAN by the IPSEN Institute, 30 rue Cambronne, 75015 PARIS.<br><br>Placebo<br><br>• Placebo of the same presentation, at a dose of 2 mL morning and evening for 3 months |
| Outcomes | **Outcomes collected**<br><br>• Outpatient memory battery *(La batterie de mémoire pour personnes agées ambulatoires de L Israel)* |


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**Israel 1987** *(Continued)*

- Intellectual dynamism (*L'Echelle de dynamisme intellectuel de L Israel*)
- Questionnaire on impact of symptoms on daily life
- Geriatric Depression Scale (GDS)
- Self-assessment of cognitive deficits
- Satisfaction

| | |
|---|---|
| Notes | **Sponsorship source:** none reported<br>**Trial registration number(s)**: none reported<br>No outcome data relevant to this review could be extracted from the study. |

***Risk of bias***

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Random sequence generation (selection bias) | Unclear risk | Statement that randomization was pre-established means that true randomization was likely; however, there was no explicit description of the methodology. |
| Allocation concealment (selection bias) | Unclear risk | Randomization list is mentioned, but with no other details describing allocation procedures. |
| Blinding of participants and personnel (performance bias)<br>All outcomes | Low risk | Double-blind study. |
| Blinding of outcome assessment (detection bias)<br>All outcomes | Low risk | "It is important to underline that, so that the final evaluator is in ignorance of the protocol followed, the psychologists in charge of the final assessment were different from those in charge of the exercise sessions." |
| Incomplete outcome data (attrition bias)<br>All outcomes | Unclear risk | 94% follow-up (5/80 persons excluded from follow-up). Two were excluded for failing to adhere to medication, and it is unclear what groups any of the excluded participants belonged to. |
| Selective reporting (reporting bias) | Unclear risk | No protocol available. Insufficient information to permit judgment. |
| Other bias | Low risk | No other apparent sources of bias. |

**Ji 2020**

***Study characteristics***

| | |
|---|---|
| Methods | **Study design:** RCT<br>**Study grouping:** parallel group<br>**Duration of intervention:** 3 months<br>**Duration of follow-up:** 3 months<br>**Washout or placebo run-in period:** none reported |
| Participants | **Baseline characteristics** |


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**Ji 2020** *(Continued)*

*G biloba*

- Number randomized: 30
- MMSE (mean, SD): NR
- Age (mean, SD): 70.5, 3.2
- % female: 40%

Donepezil

- Number randomized: 30
- MMSE (mean, SD): NR
- Age (mean, SD): 71.8, 3.9
- % female: 43%

**Total number randomized:** 60

**Inclusion criteria**

- Meeting the diagnostic criteria formulated by the Chinese Medical Association in 1989
- Informed consent from family members

**Exclusion criteria**

- Severe heart, liver and kidney function diseases
- Epilepsy, asthma or obstructive diseases
- Anticoagulant therapy
- Poor compliance
- Allergy to study drugs

**Country:** China

**Setting:** Hospital

**Date recruitment began:** 2017

**Recruitment:** NR

**Diagnosis:** AD

**Diagnostic criteria:** diagnostic criteria formulated by the Chinese Medical Association in 1989

| | |
|---|---|
| Interventions | **Intervention characteristics**<br>*G biloba*<br>• *G biloba* leaf tablet (Nanjing Yiheng Pharmaceutical Co, Ltd, Chinese Medicine approval Z20063958, 0.1 g *24 s). 3 times a day, 2 tablets per time. Dosage reported as 600 mg/day.<br>Donepezil<br>• Donepezil hydrochloride (Weicai (China) Pharmaceutical Co, Ltd, Sinophamedo approval number H20070181). Take orally before sleep. Once per day, 2.5 mg every time. Dose 2.5 mg/day. |
| Outcomes | **Outcomes collected**: overall effective rate |
| Notes | **Sponsorship source:** not reported<br>**Trial registration number:** none reported<br>**Note:** according to the paper, the dosage was 0.1 g/tablet × 6 tablet/day = 0.6 g/day = 600 mg/day. However, the drug information was checked online and the weight for each tablet may in fact be 9.6 mg (roughly 0.01 g instead of 0.1 g per tablet). |


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**Ji 2020** *(Continued)*

No outcome data relevant to this review could be extracted from the study.

***Risk of bias***

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Random sequence generation (selection bias) | Low risk | Random number table. |
| Allocation concealment (selection bias) | Unclear risk | Not reported. |
| Blinding of participants and personnel (performance bias)<br>All outcomes | High risk | Not reported. However, since the dosage form in the treatment group is distinct from that in the control group, it is likely that the outcomes were influenced by lack of blinding. |
| Blinding of outcome assessment (detection bias)<br>All outcomes | Unclear risk | Not reported. Unclear to what extent the outcomes might be influenced by lack of blinding. |
| Incomplete outcome data (attrition bias)<br>All outcomes | Unclear risk | Not reported. |
| Selective reporting (reporting bias) | Unclear risk | No protocol available. Insufficient information to permit judgment. |
| Other bias | Low risk | No other apparent sources of bias. |

**Jiang 2018**

***Study characteristics***

Methods

**Study design:** RCT

**Study grouping:** parallel group

**Duration of intervention:** 24 weeks

**Duration of follow-up:** 24 weeks

**Washout or placebo run-in period:** none reported

Participants

**Baseline characteristics**

*G biloba* + conventional medications

- Number randomized: 34
- MMSE (mean, SD): 24.44, 1.52
- Age (mean, SD): NR
- % female: NR

Placebo + conventional medications

- Number randomized: 34
- MMSE (mean, SD): 24.09, 1.29
- Age (mean, SD): NR


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**Jiang 2018** *(Continued)*

- % female: NR

**Total number randomized:** 68

**Inclusion criteria**

- Met the above diagnostic criteria
- 50 to 70 years old
- MMSE score ≥ 20 (primary school) or ≥ 24 (middle school or above), or MRI suggesting subcortical ischemic cerebrovascular disease
- Informed consent

**Exclusion criteria:**

- Other diseases causing dementia such as multiple sclerosis, cerebral hemorrhage, watershed infarction, hippocampus or olfactory nucleus atrophy
- Hamilton Depression Scale score > 17 points
- Severe neurological deficits, such as all kinds of aphasia, apraxia, and severe partial paralysis
- Severe heart, liver, kidney, endocrine system and hematopoietic system and other primary diseases
- Mental illness and severe epilepsy
- Allergic constitution or allergy to study medicine

**Country:** China

**Setting:** inpatient and outpatient

**Date recruitment began:** 1985

**Recruitment methods:** inpatient or outpatient of Department of Neurology, Shuguang Hospital Affiliated to Shanghai University of Traditional Chinese Medicine from October 2015 to March 2017.

**Diagnosis:** VCIND

**Diagnostic criteria:** referred to the diagnostic criteria of VCIND developed by Ingles et al, and combined with the suggestions of domestic expert Jia Jianping, the following criteria were formulated.

- Cerebrovascular disease or risk factors of cerebrovascular disease
- Fluctuating course of cognitive impairment
- No damage or less damage to memory;
- Causal relationship between cognitive impairment and cerebrovascular disease, in addition to other diseases
- Normal ability of daily living
- Diagnostic criteria for dementia not met

Interventions

**Intervention characteristics**

*G biloba* + conventional medications

- Ginkgo ketone ester tablet (Shanghai Shangyao Xingling Technology Pharmaceutical Co, Ltd), 1 tablet each time, 3 times a day
- Basic treatment measures for vascular risk factor
  - Anti-platelet aggregation drugs for participants with cerebral infarction
  - Calcium antagonists, beta receptor inhibitors, angiotensin converting enzyme inhibitors, angiotensin Ⅱ receptor blockers and other drugs for those with hypertension
  - Insulin secretants, biguanides, α-glucosidase inhibitors, insulin sensitizers, insulin and other drugs for those with diabetes
  - Statins or fibrates for those with hyperlipidemia

Placebo + conventional medications

- Placebo with the same shape as ginkgo ester tablet was given 1 tablet each time, 3 times a day.


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**Jiang 2018** *(Continued)*

- Basic treatment measures for vascular risk factor:
  - Anti-platelet aggregation drugs for participants with cerebral infarction
  - Calcium antagonists, beta receptor inhibitors, angiotensin converting enzyme inhibitors, angiotensin Ⅱ receptor blockers and other drugs for those with hypertension
  - Insulin secretants, biguanides, α-glucosidase inhibitors, insulin sensitizers, insulin and other drugs for those with diabetes
  - Statins or fibrates for those with hyperlipidemia

| | |
|---|---|
| Outcomes | **Outcomes collected**<br>• MMSE<br>• ADAS-Cog<br>• CIBIC-PLUS<br>• Laboratory tests<br>• Adverse events |
| Notes | **Sponsorship source:** National Natural Science Foundation of China (81373619)<br>**Trial registration number(s)**: none reported<br>**Note:** "Shanghai Shangyao Xingling Technology Pharmaceutical Co., Ltd was entrusted to make the corresponding drugs and placebo according to the group numbers." The Pharmaceutical Co, Ltd is also the trial EGb provider. Potential conflict of interest. |

***Risk of bias***

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Random sequence generation (selection bias) | Low risk | Random number table. "SPSS20.0 software was used to generate a random number table in a ratio of 1 : 1 according to the completely random grouping method, and the group numbers were numbered. Shanghai Shangyao Xingling Technology Pharmaceutical Co., Ltd was entrusted to make the corresponding drugs and placebo according to the group numbers. Subjects were given experimental drugs with corresponding number according to the order of entering clinical observation. Neither clinical observer nor patient knew the grouping of drugs." |
| Allocation concealment (selection bias) | Low risk | Third party prepare intervention and placebo. "Shanghai Shangyao Xingling Technology Pharmaceutical Co., Ltd was entrusted to make the corresponding drugs and placebo according to the group numbers. Subjects were given experimental drugs with corresponding number according to the order of entering clinical observation. Neither clinical observer nor patient knew the grouping of drugs." |
| Blinding of participants and personnel (performance bias)<br>All outcomes | Low risk | Blinded, placebo used. "SPSS20.0 software was used to generate a random number table in a ratio of 1 : 1 according to the completely random grouping method, and the group numbers were numbered. Shanghai Shangyao Xingling Technology Pharmaceutical Co., Ltd was entrusted to make the corresponding drugs and placebo according to the group numbers. Subjects were given experimental drugs with corresponding number according to the order of entering clinical observation. Neither clinical observer nor patient knew the grouping of drugs." |
| Blinding of outcome assessment (detection bias)<br>All outcomes | Unclear risk | Not reported. Unclear the extent to which outcomes might be influenced by lack of blinding. |
| Incomplete outcome data (attrition bias) | Low risk | No loss to follow-up. |


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**Jiang 2018** *(Continued)*
All outcomes

| | | |
|---|---|---|
| Selective reporting (reporting bias) | Unclear risk | No protocol available. Insufficient information to permit judgment. |
| Other bias | Low risk | No other apparent risks of bias. |

**Kang 2020**

| ***Study characteristics*** | |
|---|---|
| Methods | **Study design:** RCT<br><br>**Study grouping:** parallel group<br><br>**Duration of intervention:** 6 months<br><br>**Duration of follow-up:** 6 months<br><br>**Washout or placebo run-in period:** no |
| Participants | **Baseline characteristics**<br><br>*G biloba* + memantine hydrochloride<br><br>• Number randomized: 43<br>• MMSE (mean, SD): 15.13, 2.85<br>• Age (mean, SD): 68.64, 7.02<br>• % female: 60.5%<br><br>Memantine hydrochloride<br><br>• Number randomized: 49<br>• MMSE (mean, SD): 15.87, 2.33<br>• Age (mean, SD): 67.91, 7.53<br>• % female: 59.2%<br><br>**Total number randomized:** 92<br><br>**Inclusion criteria**<br><br>• Diagnostic criteria for AD by Shaw LM, Arias J, Blennow K, et al (2018)<br>• No obvious abnormalities of the heart, liver, kidney, and other organs<br>• No nootropic drug treatment in the past 2 weeks<br>• Age 63 to 77 years<br><br>**Exclusion criteria**<br><br>• Sudden onset, early onset of seizures, gait disturbance, and behavioral changes<br>• Focal neurological symptoms such as visual field defect, sensory loss, hemiparesis, or early extrapyramidal symptoms<br>• Other medical diseases that might affect memory and related symptoms<br>• History of drug or alcohol abuse<br>• Contraindications to study drugs<br><br>**Country:** China<br><br>**Setting:** inpatient |


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**Kang 2020** *(Continued)*

**Date recruitment began:** 2017

**Recruitment methods:** people with AD were admitted to the hospital where the author worked from June 2017 to July 2018.

**Diagnosis:** AD

**Diagnostic criteria:** diagnostic criteria for AD by Shaw LM, Arias J, Blennow K, et al. (2018). Baseline characteristics, number randomized, MMSE (mean, SD), age (mean, SD), female (%)

| | |
|---|---|
| Interventions | **Intervention characteristics**<br><br>Memantine hydrochloride<br><br>• Using Lingbei Pharmaceutical (Tianjin) Co, Ltd, specification: 10 mg/tablet, lot number 20170102, taking 5 mg orally in the morning of the 1st week, taking 5 mg in the morning and evening of the 2nd week, and taking 15 mg orally in the 3rd week (10 mg in the morning, 5 mg in the evening), taking 10 mg in the morning and evening in the 4th week, and using this dose for maintenance treatment.<br><br>*G biloba* + Memantine hydrochloride<br><br>• On the basis of the memantine hydrochloride group, the *G biloba* extract group used Dr Willmar Schwabe GmbH & Co KG, specification: 40 mg/tablet, lot number: 20161014, 0.8 mg orally, 3 times a day. From the description, it is unclear whether *G biloba* dose is 120 mg/day or 2.4 mg/day. |
| Outcomes | **Outcomes collected**<br><br>• MMSE<br>• ADLs (Barthel index)<br>• Curative effect<br>• Serum BDMF<br>• NGF<br>• DA<br>• Adverse events |
| Notes | **Sponsorship source:** Hainan Provincial Natural Science Foundation General Project (818MS129)<br><br>**Trial registration number:** none reported |

***Risk of bias***

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Random sequence generation (selection bias) | Low risk | Random number table. |
| Allocation concealment (selection bias) | Unclear risk | No description. |
| Blinding of participants and personnel (performance bias)<br>All outcomes | Unclear risk | No description of blinding. |
| Blinding of outcome assessment (detection bias)<br>All outcomes | Unclear risk | No description of blinding. |
| Incomplete outcome data (attrition bias) | Low risk | No attrition. |


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**Kang 2020** *(Continued)*
All outcomes

| | | |
|---|---|---|
| Selective reporting (reporting bias) | Unclear risk | No protocol. |
| Other bias | Low risk | No other apparent source of bias. |

**Kanowski 1996**

| ***Study characteristics*** | |
|---|---|
| Methods | **Study design:** RCT<br><br>**Study grouping:** parallel group<br><br>**Duration of intervention:** 24 weeks<br><br>**Duration of follow-up:** 24 weeks<br><br>**Washout or placebo run-in period:** "Single-blind 4-week run-in period [during which] all patients received exclusively placebo" |
| Participants | **Baseline characteristics**<br><br>*G biloba*<br><br>• Number randomized: 106<br>• MMSE (mean, SD): 21.6, 2.6<br>• Age (mean, SD): 72, 10<br>• % female: 68%<br><br>Placebo<br><br>• Number randomized: 99<br>• MMSE (mean, SD): 21.5, 2.4<br>• Age (mean, SD): 72, 10<br>• % female: 71%<br><br>**Total number randomized:** 222 (baseline characteristics not provided for all participants randomized)<br><br>**Inclusion criteria:** "At least 55 years of age and suffered from either DAT or MID of mild to moderate severity. The clinical diagnosis was carried out by the investigating physician in accordance with DSM-III-R criteria (American Psychiatric Association, 1987)." "Only those patients who had a minimum score of 6 but not more than 18 points in the SKT whilst reaching a score of at least 13 but not more than 25 points in the MMSE were considered for study participation."<br><br>**Exclusion criteria:** "Patients with disturbance of consciousness and patients suffering from other cerebral diseases, in particular depression, psychosis, disorders due to cerebral ischemia or hemorrhage, epilepsy, and dementia of an origin other than those defined in the inclusion criteria, were excluded. Patients with a metabolism unstable due to severe cardiovascular insufficiency, non-compensated arrhythmia, severe chronic pulmonary diseases, hepatic and renal disorders, hyper- or dehydration, malign hypertension or pronounced hypotension, or gastro-intestinal disorders leading to uncertain resorption of the investigational drug were not to be enrolled." Patients who were unable to discontinue "drugs which might have interfered with the assessment of efficacy, such as psychostimulants, nootropics, centrally acting vasoactive substances, psychotropic substances, and reserpine" and patients abusing "alcohol, drugs, or narcotics" were excluded. "Diseases that prevented adequate test performance (e. g. non-compensated dysopia and defective hearing), lack of co-operation, and the inability to comprehend the instructions led to exclusion from the study." |


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**Kanowski 1996** *(Continued)*

| | |
|---|---|
| | **Country:** Germany<br><br>**Setting:** outpatient<br><br>**Date recruitment began:** 1992<br><br>**Recruitment methods:** recruitment from "41 study centers in Berlin, around Freiburg, and in Karlsruhe in 1992. These study centers comprised practices of neurologists, psychiatrists, internists, and general practitioners."<br><br>**Diagnosis:** dementia of Alzheimer's type (DAT) or multi-infarct dementia (MID) of mild to moderate severity<br><br>**Diagnostic criteria:** DSM-III-R criteria |
| Interventions | **Intervention characteristics**<br><br>*G biloba*<br><br>• "The investigational drug EGb 761 (manufacturer: Dr. Willmar Schwabe Arzneimittel, Karlsruhe, ER.G.) is a standardized mono-extract from dried leaves of the ginkgo biloba tree (50:1) synthesized by means of a multiple-step extraction procedure; it consists of 24 % ginkgo flavone glycosides and 6% terpene lactones (ginkgolides, bilobalide). The study drug was available in the form of capsules containing 120 mg of active substance." "One capsule taken in the morning and evening, before meals." Total daily dose of *G biloba* 240 mg.<br><br>Placebo<br><br>• "placebo capsules (reference formulation) did not differ from the active drug with regard to appearance, smell, or taste." One capsule of placebo had to be taken daily in the morning and in the evening, prior to meals.<br><br>"drugs which might have interfered with the assessment of efficacy, such as psychostimulants, nootropics, centrally acting vasoactive substances, psychotropic substances, and reserpine" were not allowed. |
| Outcomes | **Outcomes collected**<br><br>• SKT<br>• *Nuernberger Alters-Beobachtungsskala* (NAB)<br>• Montgomery-Asberg Depression Rating Scale (MADRS)<br>• Adverse events (total numbers of participants in each group could not be extracted) |
| Notes | **Sponsorship source:** none reported. However, the corresponding author is a Dr Wilmar Schwabe GmbH & Co employee, and we therefore believe that the company is the sponsor and funder.<br><br>**Trial registration number(s)**: none reported |

***Risk of bias***

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Random sequence generation (selection bias) | Low risk | Randomization into blocks of 4 participants per subgroup was done by the biometrics working group of Dr Willmar Schwabe Company by means of an EDP program which randomly allocated the predefined numbers of participants to the 2 treatment groups. |
| Allocation concealment (selection bias) | Low risk | Allocation was most likely concealed. "Patient number blocks, together with the respective drug/placebo, were assigned to the investigators, who allocated them to their patients in ascending sequence." |


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**Kanowski 1996** *(Continued)*

| | | |
|---|---|---|
| Blinding of participants and personnel (performance bias)<br>All outcomes | Low risk | "The placebo capsules (reference formulation) did not differ from the active drug with regard to appearance, smell, or taste." "In case of emergency, the investigators were provided with decoding envelopes, allowing them to break the random code for individual patients without endangering the double-blind conditions of the trial as a whole." Blinding of participants and key study personnel ensured. |
| Blinding of outcome assessment (detection bias)<br>All outcomes | Low risk | It was not explicitly stated that outcome assessors were blinded. However, the trial was double-blinded. Since the number of personnel at the study centers was limited, the recommendations given later by the advisory committees of the German Federal Health Office (Kern and Menges, 1992), according to which the primary outcome variables should be assessed by three independent raters, were only partly fulfilled in this study. The CGI and SKT were both administered by the investigating physicians. The NAB rating scale was completed by relatives in all cases where relatives were available. |
| Incomplete outcome data (attrition bias)<br>All outcomes | Low risk | Numbers and reasons for dropouts and protocol violations were given, and data for 205/216 participants were used for main efficacy analyses. |
| Selective reporting (reporting bias) | Unclear risk | Many mentions of study protocol, but no publication or other accessible protocol. It seems that the study was carried out and reported in accordance with protocol, but we cannot be certain. |
| Other bias | Low risk | No other apparent sources of bias. |

**Le Bars 1997**

| ***Study characteristics*** | |
|---|---|
| Methods | **Study design:** RCT<br>**Study grouping:** parallel group<br>**Duration of intervention:** 52 weeks<br>**Duration of follow-up:** 52 weeks<br>**Washout or placebo run-in period:** single-blind 14-day run-in period on placebo |
| Participants | **Baseline characteristics**<br>*G biloba*<br>• Number randomized: 155<br>• MMSE (mean, SD): 21.1, 5.8<br>• Age (mean, SD): 69, 10<br>• % female: 51%<br>Placebo<br>• Number randomized: 154<br>• MMSE (mean, SD): 21.2, 5.5<br>• Age (mean, SD): 69, 10<br>• % female: 56%<br>**Total number randomized:** 327 (baseline data not presented for all randomized participants) |


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**Le Bars 1997** *(Continued)*

| | |
|---|---|
| | **Inclusion criteria:** "Patients of both sexes, 45 years of age or older, with a diagnosis of uncomplicated dementia according to Diagnostic and Statistical Manual of Mental Disorders, Third Edition, Revised (DSM-III-R) and International Statistical Classification of Diseases, 10th Revision (ICD-10) criteria, either Alzheimer type (AD) or MID, were enrolled in the study. The severity of the dementia at screening was mild to moderately severe as assessed by a Mini-Mental State Examination score of 9 to 26 (inclusive) and a Global Deterioration Scale score of 3 to 6 (inclusive)."<br><br>**Exclusion criteria:** "To be eligible, patients had to have no other significant medical conditions including cardiac disease, insulin-dependent diabetes, liver disease, chronic renal insufficiency, or another psychiatric disorder as a primary diagnosis. Patients with brain mass or intracranial hemorrhage determined by computed tomography or magnetic resonance imaging were excluded."<br><br>**Country:** USA<br><br>**Setting:** outpatient<br><br>**Date recruitment began:** NR (prior to 1997)<br><br>**Recruitment methods:** recruited from 6 research centers in the USA, which were where the study was conducted. Methods not described.<br><br>**Diagnosis:** uncomplicated AD or MID<br><br>**Diagnostic criteria:** Diagnostic and Statistical Manual of Mental Disorders, Third Edition, Revised (DSM-III-R) and International Statistical Classification of Diseases, 10th Revision (ICD-10) criteria |
| Interventions | **Intervention characteristics**<br><br>*G biloba*<br><br>• "EGb had the identical formulation and chemical composition as the product used in Germany (Tebonin forte, Dr. Willmar Schwabe Pharmaceuticals, Karlsruhe). The study drugs were made by a standard method and came from the same batch of Ginkgo extract. EGb is a standardized concentrated extract from the dried leaves of the Ginkgo biloba tree, specially produced by means of a multiple step extraction procedure and consisting of 24% Ginkgo-flavone glycosides and 6% terpene lactones (3.1% ginkgolides A, B,and C, 2.9% bilobalide)." "EGb was supplied as a 40-mg tablet to be swallowed before each of the 3 principal daily meals, for a total daily dose of 120 mg."<br><br>Placebo<br><br>• "The EGb and the matched placebo tablets did not differ in their appearance and were film coated to ensure a similar smell and taste."<br><br>"The use of medications for preexisting conditions was not discontinued at screening, but change in regimen or prescription of new concomitant medications known to affect cognitive function was not permitted during the study." |
| Outcomes | **Outcomes collected**<br><br>• Cognitive impairment (ADAS-Cog)<br>• Daily living and social behavior (GERRI)<br>• Clinical Global Impression of Change (CGIC) |
| Notes | **Sponsorship source:** "Dr. Willmar Schwabe Pharmaceuticals"<br><br>**Trial registration number(s)**: none reported |

***Risk of bias***

| Bias | Authors' judgement | Support for judgement |
|---|---|---|


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**Le Bars 1997** *(Continued)*

| | | |
|---|---|---|
| Random sequence generation (selection bias) | Low risk | "Patients were consecutively assigned to EGb or to placebo following a predetermined order based on separate randomization schedules for each center using balanced blocks of 10 patients" |
| Allocation concealment (selection bias) | Low risk | "Patients were consecutively assigned to EGb or to placebo following a predetermined order based on separate randomization schedules for each center using balanced blocks of 10 patients. Consecutive numbers were printed on each drug study pack, and randomization codes, stored in sealed envelopes, were exclusively retained by International Drug Development Corporation independently from sponsor and investigating centers." |
| Blinding of participants and personnel (performance bias)<br>All outcomes | Low risk | "The EGb and the matched placebo tables did not differ in their appearance and were film coated to ensure a similar smell and tase." |
| Blinding of outcome assessment (detection bias)<br>All outcomes | Low risk | Participants and study staff blinded to treatment assignment. |
| Incomplete outcome data (attrition bias)<br>All outcomes | High risk | Although a similar proportion of participants withdrew from each treatment group before 26 weeks (33/155 for the EGb group and 33/154 for the placebo group), 28% (44/155) of the EGb group vs 40% (62/154) of the placebo group dropped out between 26 and 52 weeks. Consequently, 50% (78/155) of the EGb group completed the entire study compared with only 38% (59/154) of the placebo group. ITT analysis was performed using last observations after baseline carried forward, and the time points for this were on average later for the ginkgo group than for the placebo group. |
| Selective reporting (reporting bias) | Unclear risk | The study protocol is not available. Insufficient information available to permit a judgment. |
| Other bias | Low risk | The study appears to be free of other sources of bias. |

**Li 2013a**

| | |
|---|---|
| ***Study characteristics*** | |
| Methods | **Study design:** RCT<br>**Study grouping:** parallel group<br>**Duration of intervention:** 3 months<br>**Duration of follow-up:** 3 months<br>**Washout or placebo run-in period:** none reported |
| Participants | **Baseline characteristics**<br>*G biloba* + Allopurinol<br>• Number randomized: 35<br>• MMSE (mean, SD): 26.18,1.41<br>• Age (mean, SD): 71.36,4.97<br>• % female: 60<br>Allopurinol |


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**Li 2013a** *(Continued)*

- Number randomized: 34
- MMSE (mean, SD): 25.57, 1.26
- Age (mean, SD): 72.58, 5.09
- % female: 52.94

**Total number randomized:** 69

**Inclusion criteria**

- Diagnosis of MCI
- MMSE: 24 to 27
- Global Deterioration Scale: 2 to 3
- Increased difficulty in daily life, ADL < 26
- Age 60 to 80
- Signed consent form

**Exclusion criteria**

- Illiteracy
- HAMD score ≥ 17
- Concurrent serious primary diseases such as cardiovascular, cerebrovascular, liver, kidney, and hematopoietic system, inflammation, tumors, etc.

**Country:** China

**Setting:** inpatient and outpatient

**Date recruitment began:** 2010

**Recruitment methods:** MCI patients with hyperuricemia among people with coronary heart disease who were admitted to the outpatient department or inpatient department from September 2010 to October 2012.

**Diagnosis:** MCI

**Diagnostic criteria:** MMSE score 24 to 27 points. The Global Deterioration Scale was 2 to 3. General functions are still maintained. Difficulty in daily living may increase. ADL score < 26.

| | |
|---|---|
| Interventions | **Intervention characteristics**<br><br>*G biloba* + Allopurinol<br><br>• Basic treatment (allopurinol 0.1 g/time, 3 times/day, oral administration, moderate exercise [walking: 30 min in the morning and 30 min in the evening]). *G biloba* leaves (Ekangning, each tablet containing flavonol glucoside 9.6 mg and terpenoid lactone 2.4 mg, Yangzijiang Pharmaceutical Co, Ltd, national medicine permission Z20027949) were taken orally 1 tablet/time, 3 times/day for consecutive 3 months.<br><br>Allopurinol<br><br>• Basic treatment includes Zyloric, 0.1 g per time, 3 times a day and 30 mins of exercise. |
| Outcomes | **Outcomes collected**<br><br>• MMSE<br>• CDT<br>• Effective rate |
| Notes | **Sponsorship source:** Mandatory Project of Hebei Provincial Science and Technology Commission (10276105D-25) |


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**Li 2013a** *(Continued)*

**Trial registration number(s)**: none reported

***Risk of bias***

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Random sequence generation (selection bias) | Low risk | Random number table. |
| Allocation concealment (selection bias) | Unclear risk | Allocation process not reported. |
| Blinding of participants and personnel (performance bias)<br>All outcomes | High risk | Not reported. However, since the treatment and drug delivery route in the treatment group are distinct from that in the control group, it is likely that the outcomes have been influenced by lack of blinding. |
| Blinding of outcome assessment (detection bias)<br>All outcomes | Unclear risk | Not reported. Unclear the extent to which outcomes were influenced by lack of blinding. |
| Incomplete outcome data (attrition bias)<br>All outcomes | Unclear risk | Loss to follow-up not reported. |
| Selective reporting (reporting bias) | Unclear risk | No protocol available. Insufficient information to permit judgment. |
| Other bias | Low risk | No other apparent sources of bias. |

**Li 2015a**

***Study characteristics***

Methods

**Study design:** RCT

**Study grouping:** parallel group

**Duration of intervention:** 3 months

**Duration of follow-up:** 6 months

**Washout or placebo run-in period:** none reported

Participants

**Baseline characteristics**

*G biloba* + Nimodipine

- Number randomized: 60
- MMSE (mean, SD): NR
- Age (mean, SD): 71.5, 8.2
- % female: 46.7

Nimodipine

- Number randomized: 60
- MMSE (mean, SD): NR
- Age (mean, SD): 72.1, 8.6


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**Li 2015a** *(Continued)*

- % female: 43.3

**Total number randomized:** 120

**Inclusion criteria:** VCIND

**Exclusion criteria:** none reported

**Country:** China

**Setting:** Hospital

**Date recruitment began:** 2012

**Recruitment methods:** a total of 120 patients with non-dementia VCI admitted to our hospital from October 2012 to January 2014 were selected as the research subjects.

**Diagnosis:** VCIND

**Diagnostic criteria:** the 4th National Conference on Cerebrovascular Diseases

| | |
|---|---|
| Interventions | **Intervention characteristics**<br>*G biloba* + Nimodipine<br>• On the basis of the control group treatment, the intervention group took ginkgo leaves orally (Guizhou Xinbang Pharmaceutical), 19.2 mg/time, 3 times/day.<br>Nimodipine<br>• The control group used oral nimodipine tablets (Bayer), 30 mg/time, 3 times/day. |
| Outcomes | **Outcomes collected**<br>• MoCA<br>• Laboratory tests |
| Notes | **Sponsorship source:** none reported<br>**Trial registration number(s)**: none reported |

***Risk of bias***

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Random sequence generation (selection bias) | Low risk | Random number table. |
| Allocation concealment (selection bias) | Unclear risk | Allocation process not reported. |
| Blinding of participants and personnel (performance bias)<br>All outcomes | High risk | Not reported. However, since the number of drugs in the treatment group is distinct from that in the control group, it is likely the outcomes were influenced by lack of blinding. |
| Blinding of outcome assessment (detection bias)<br>All outcomes | Unclear risk | Not reported. It is unclear the extent to which outcomes were influenced by lack of blinding. |
| Incomplete outcome data (attrition bias) | Unclear risk | Number lost to follow-up not reported. |


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**Li 2015a** *(Continued)*
All outcomes

| | | |
|---|---|---|
| Selective reporting (reporting bias) | Unclear risk | No protocol available. Insufficient information to permit judgment. |
| Other bias | Low risk | No other apparent sources of bias. |

**Li 2016a**

| ***Study characteristics*** | |
|---|---|
| Methods | **Study design:** RCT<br><br>**Study grouping:** parallel group<br><br>**Duration of intervention:** 6 months<br><br>**Duration of follow-up:** 6 months<br><br>**Washout or placebo run-in period:** none reported |
| Participants | **Baseline characteristics**<br><br>*G biloba* + Donepezil<br><br>• Number randomized: 40<br>• MMSE (mean, SD): 22.12, 3.65<br>• Age (mean, SD): 67.4, 6.3<br>• % female: 55<br><br>Donepezil<br><br>• Number randomized: 40<br>• MMSE (mean, SD): 22.03, 2.99<br>• Age (mean, SD): 65.4, 6.8<br>• % female: 50<br><br>**Total number randomized:** 80<br><br>**Inclusion criteria**<br><br>• Diagnostic criteria of cognitive dysfunction in the elderly<br>• Age 60 to 80 years<br>• Certain degree of auditory perception and visual discrimination, and ability to cooperate with the completion of relevant neuropsychological tests<br>• Ability to adhere to all treatments<br>• Informed consent for diagnosis and treatment<br><br>**Exclusion criteria**<br><br>• Cognitive impairment due to other causes, such as schizophrenia, reactive psychosis, paranoid psychosis, mania, and manic depression<br>• Severe illness that was difficult to control<br>• Use of *G biloba* or similar preparations<br><br>**Country:** China<br><br>**Setting:** inpatient and outpatient |


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**Li 2016a** *(Continued)*

| | |
|---|---|
| | **Date recruitment began:** 2013<br><br>**Recruitment methods:** 80 elderly patients with cognitive dysfunction were recruited from the outpatient and inpatient departments of geriatrics department of our hospital from October 2013 to April 2015.<br><br>**Diagnosis:** cognitive dysfunction<br><br>**Diagnostic criteria:** none reported |
| Interventions | **Intervention characteristics**<br><br>*G biloba* + Donepezil<br><br>• *G biloba* leaf extract (Dr Willmar Schwabe GmbH & Co KG, 40 mg × 20 tablets) orally, 40 mg daily, twice a day<br><br>Donepezil<br><br>• Donepezil Hydrochloride Tablets (Eisai Pharmaceutical Co, Ltd, 5 mg × 7 tablets), 5 to 10 mg each time, once a day, orally |
| Outcomes | **Outcomes collected**<br><br>• MMSE<br>• MoCA<br>• ADL<br>• Effective rate<br>• Adverse events |
| Notes | **Sponsorship source:** none reported<br><br>**Trial registration number(s)**: none reported |

***Risk of bias***

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Random sequence generation (selection bias) | Low risk | Random number table. |
| Allocation concealment (selection bias) | Unclear risk | Not reported. |
| Blinding of participants and personnel (performance bias)<br>All outcomes | High risk | Not reported. However, since the treatment (in the treatment group) is distinct from that in the control group, it is likely that the outcomes were influenced by lack of blinding. |
| Blinding of outcome assessment (detection bias)<br>All outcomes | Unclear risk | Not reported. It is unclear the extent to which outcomes were influenced by lack of blinding. |
| Incomplete outcome data (attrition bias)<br>All outcomes | Unclear risk | Not reported. |
| Selective reporting (reporting bias) | Unclear risk | No protocol available. Insufficient information to permit judgment. |


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**Li 2016a** *(Continued)*

| | | |
|---|---|---|
| Other bias | Low risk | No other apparent risk of bias. |

**Li 2017a**

***Study characteristics***

| | |
|---|---|
| Methods | **Study design:** RCT<br><br>**Study grouping:** parallel group<br><br>**Duration of intervention:** 3 months<br><br>**Duration of follow-up:** 3 months<br><br>**Washout or placebo run-in period:** none reported |
| Participants | **Baseline characteristics**<br><br>*G biloba* + memantine hydrochloride<br><br>• Number randomized: 39<br>• MMSE (mean, SD): 19.62, 2.32<br>• Age (mean, SD): 74.77, 5.20<br>• % female: 48.72<br><br>Memantine hydrochloride<br><br>• Number randomized: 38<br>• MMSE (mean, SD): 18.80, 2.46<br>• Age (mean, SD): 73.81, 5.37<br>• % female: 44.7<br><br>**Total number randomized:** 77<br><br>**Inclusion criteria**<br><br>• DSM-IV criteria for the clinical diagnosis of AD<br>• Informed consent<br><br>**Exclusion criteria**<br><br>• Pseudo-dementia, vascular dementia, and other types of dementia<br>• Severe coronary heart disease, history of severe stroke and other diseases<br>• Allergy to the study interventions<br>• Concurrent hematopoietic system diseases<br>• Epilepsy or malignant tumors<br>• Dysfunction of the heart, liver, kidney or other important organs<br>• Long-term drug abuse, alcohol addiction, or neurological drug abuse<br>• Severe visual or hearing impairments or other factors that could prevent study completion<br><br>**Country:** China<br><br>**Setting:** hospital<br><br>**Date recruitment began:** 2014<br><br>**Recruitment methods:** people with AD who visited the hospital<br><br>**Diagnosis:** AD |


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**Li 2017a** *(Continued)*

| | |
|---|---|
| | **Diagnostic criteria:** DSM-IV |
| Interventions | **Intervention characteristics**<br><br>*G biloba* + memantine hydrochloride<br><br>• On the basis of the treatment of the control group, 20 mL of Shuxuening injection (manufacturer: Beijing China Resources High-tech Natural Medicine Co, Ltd) + 250 mL of normal saline was injected intravenously, once daily, for 3 months.<br><br>Memantine hydrochloride<br><br>• In the 1st week, memantine hydrochloride oral 5 mg (manufacturer: Zhuhai United Laboratories Co, Ltd, Zhongshan Branch) every morning; in the 2nd week, the dose was changed to 10 mg/day (5 mg in the morning and evening); in the 3rd week, the dose was increased to 15 mg/day (10 mg in the morning, 5 mg in the evening); 20 mg/day orally every day (10 mg in the morning and evening) from the 4th week, continuous treatment for 3 months. |
| Outcomes | **Outcomes collected**<br><br>• Effective rate<br>• MMSE<br>• ADL<br>• Laboratory tests<br>• Adverse events |
| Notes | **Sponsorship source:** none reported<br><br>**Trial registration number(s)**: none reported |

***Risk of bias***

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Random sequence generation (selection bias) | Low risk | Random number table. |
| Allocation concealment (selection bias) | Unclear risk | Not reported. |
| Blinding of participants and personnel (performance bias)<br>All outcomes | High risk | Not reported. But since the treatment and drug delivery route in the treatment group are distinct from that in the control group, it is likely the outcomes were influenced by lack of blinding. |
| Blinding of outcome assessment (detection bias)<br>All outcomes | Unclear risk | Not reported. Unclear the extent to which outcomes were influenced by lack of blinding. |
| Incomplete outcome data (attrition bias)<br>All outcomes | Unclear risk | Not reported. |
| Selective reporting (reporting bias) | Unclear risk | No protocol available. Insufficient information to permit judgment. |
| Other bias | Low risk | No other apparent sources of bias. |


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### Li 2019a

| *Study characteristics* | |
|---|---|
| Methods | **Study design:** RCT<br><br>**Study grouping:** parallel group<br><br>**Duration of intervention:** 24 weeks<br><br>**Duration of follow-up:** 24 weeks<br><br>**Washout or placebo run-in period:** none reported |
| Participants | **Baseline characteristics**<br><br>*G biloba* + conventional medications<br><br>• Number randomized: 28<br>• MMSE (mean, SD): NR<br>• Age (mean, SD): 74.5, 5.2<br>• % female: 35.7<br><br>Conventional medications<br><br>• Number randomized: 28<br>• MMSE (mean, SD): NR<br>• Age (mean, SD): 74.3, 5.5<br>• % female: 39.3<br><br>**Total number randomized:** 56<br><br>**Inclusion criteria**<br><br>• Relevant diagnostic criteria of vascular cognitive impairment<br>• Diagnosis confirmed by imaging tests<br>• Cognitive impairment for > 3 months according to patient's own description or confirmation by his or her family<br>• Normal intelligence, ability to cooperate with the relevant measurement scales involved in the study<br><br>**Exclusion criteria**<br><br>• Cognitive impairment due to other non-vascular related factors<br>• Physical disabilities and aphasia<br>• Mental diseases or other more serious systemic diseases<br>• Score of > 17 on the Hamilton Depression Scale or schizophrenia<br>• Stroke or some small vessel disease within 3 months prior to beginning of study<br>• Conditions in which the use of related drugs such as sedatives may have a definite effect on cognitive function<br><br>**Country:** China<br><br>**Setting:** hospital<br><br>**Date recruitment began:** 2016<br><br>**Recruitment methods:** a total of 56 patients with vascular cognitive impairment who received treatment in the Department of Neurology of Liulin County People's Hospital from February 2016 to June 2018 were selected as the research subjects.<br><br>**Diagnosis:** VCI |


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**Li 2019a** *(Continued)*

| | |
|---|---|
| | **Diagnostic criteria:** not reported |
| Interventions | **Intervention characteristics**<br>*G biloba* + conventional medications<br>• On the basis of treatment in control group, EGb tablets (Yangzijiang Pharmaceutical Group Co, Ltd, national medicine permission Z20027949, each tablet containing 19.3 mg total flavonol glycoside and 4.8 mg terpenoid lactone) were given orally, 1 tablet each time, 3 times a day. Treatment for 24 weeks.<br>Conventional medications<br>• Conventional therapy, which mainly included lipid-lowering, antiplatelet, and neurotrophic processes. Treatment for 24 weeks. |
| Outcomes | **Outcomes collected:** MoCA |
| Notes | **Sponsorship source:** none reported<br>**Trial registration number(s)**: none reported |

***Risk of bias***

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Random sequence generation (selection bias) | Low risk | Random number table. |
| Allocation concealment (selection bias) | Unclear risk | Allocation process not described. |
| Blinding of participants and personnel (performance bias)<br>All outcomes | High risk | Not reported. However, since the treatment and drug delivery route in the treatment group are distinct from that in the control group, it is likely the outcomes were influenced by lack of blinding. |
| Blinding of outcome assessment (detection bias)<br>All outcomes | Unclear risk | Not reported. Unclear the extent to which outcomes were influenced by lack of blinding. |
| Incomplete outcome data (attrition bias)<br>All outcomes | Unclear risk | Loss to follow-up not reported. |
| Selective reporting (reporting bias) | Unclear risk | No protocol available. Insufficient information to permit judgment. |
| Other bias | Low risk | No other apparent sources of bias. |

**Liao 2017a**

***Study characteristics***

| | |
|---|---|
| Methods | **Study design:** RCT<br>**Study grouping:** parallel group<br>**Duration of intervention:** 3 months |


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**Liao 2017a** *(Continued)*

**Duration of follow-up:** 3 months

**Washout or placebo run-in period:** none reported

| | |
|---|---|
| Participants | **Baseline characteristics**<br><br>*G biloba*<br><br>• Number randomized: 50<br>• MMSE (mean, SD): NR<br>• Age (mean, SD): 69.25, 7.91<br>• % female: 60<br><br>Acupuncture + cognitive rehabilitation<br><br>• Number randomized: 50<br>• MMSE (mean, SD): NR<br>• Age (mean, SD): 68.27, 8.19<br>• % female: 58<br><br>**Total number randomized:** 100<br><br>**Inclusion criteria:** AD<br><br>**Exclusion criteria**<br><br>• Other severe cerebrovascular disease diagnosed by brain CT or MRI<br>• Inability to undergo simple verbal communication<br>• Inability to adhere to treatment observation for 3 consecutive months<br>• Serious complications and underlying diseases of other organs<br>• Hachinski ischemic total score ≥ 7 (vascular dementia)<br>• Intolerance of scalp acupuncture<br>• Severe blood diseases<br>• Epilepsy or other mental illness<br><br>**Country:** China<br><br>**Setting:** inpatient<br><br>**Date recruitment began:** 2013<br><br>**Recruitment methods:** AD patients admitted to the Eighth People's Hospital of Nanning City from December 2013 to March 2016<br><br>**Diagnosis:** AD<br><br>**Diagnostic criteria:** ICD-10 |
| Interventions | **Intervention characteristics**<br><br>*G biloba*<br><br>• Both groups received treatment for the primary disease. The control group was treated with *G biloba* extract tablets, 3 tablets each time, 3 times per day (9 tablets per day, 5 days per week).<br><br>Acupuncture + cognitive rehabilitation<br><br>• Both groups received treatment for the primary disease. The treatment group was given scalp acupuncture plus real-time cognitive training. |
| Outcomes | **Outcomes collected** |


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**Liao 2017a** *(Continued)*

- Functional independence measure (FIM, FIM: Citation: Wang Xinde, Zhu Yonglian, Wang Ruihua, et al [2003] Neurology [M]. Beijing: People's Military Medical Press:181-5)
- Cognitive items
- IADL functional activities questionnaire (FAQ)
- Western aphasia battery (WAB)
- Effective rate
- Laboratory tests

| | |
|---|---|
| Notes | **Sponsorship source:** scientific research project of Guangxi Zhuang Autonomous Region Health and Family Planning Commission (Z2014453); Scientific Research and Technological Development Project of Xixiangtang District, Nanning City (2014801)<br><br>**Trial registration number(s)**: none reported |

***Risk of bias***

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Random sequence generation (selection bias) | Low risk | Random number table. |
| Allocation concealment (selection bias) | Unclear risk | Not reported. |
| Blinding of participants and personnel (performance bias)<br>All outcomes | High risk | Not reported. However, since the treatment and drug delivery route in the treatment group are distinct from that in the control group, it is likely the outcomes were influenced by lack of blinding. |
| Blinding of outcome assessment (detection bias)<br>All outcomes | Unclear risk | Not reported. Unclear the extent to which outcomes were influenced by lack of blinding. |
| Incomplete outcome data (attrition bias)<br>All outcomes | Unclear risk | Loss to follow-up not reported. |
| Selective reporting (reporting bias) | Unclear risk | No protocol available. Insufficient information to permit judgment. |
| Other bias | Low risk | No other apparent sources of bias. |

**Liu 2015a**

***Study characteristics***

| | |
|---|---|
| Methods | **Study design:** RCT<br><br>**Study grouping:** parallel group<br><br>**Duration of intervention:** 8 weeks<br><br>**Duration of follow-up:** 9 months<br><br>**Washout or placebo run-in period:** none reported |
| Participants | **Baseline characteristics** |


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**Liu 2015a** *(Continued)*

*G biloba* + donepezil

- Number randomized: 50
- MMSE (mean, SD): 18.31, 3.22
- Age (mean, SD): 71.05, 6.83
- % female: 48

Donepezil

- Number randomized: 50
- MMSE (mean, SD): 18.42, 3.28
- Age (mean, SD): 72.32, 5.30
- % female: 40

**Total number randomized:** 100

**Inclusion criteria**

- Diagnostic criteria of MCI in the *Guidelines for the Diagnosis and Treatment of Dementia and Cognitive Disorders in China*
- MMSE score < 24
- No AD

**Exclusion criteria**

- Mental disorders
- Age < 18 years
- Pregnancy
- Liver, kidney and other major organ insufficiency and vascular lesions
- Use of drugs affecting brain dysfunction
- Cognitive impairment caused by swelling, epilepsy, infection, Parkinson's syndrome, brain trauma, etc.

**Country:** China

**Setting:** outpatient

**Date recruitment began:** 2011

**Recruitment methods:** a total of 100 elderly patients with MCI were selected from the outpatient department of Haikou City People's Hospital from August 2011 to August 2013.

**Diagnosis:** MCI

**Diagnostic criteria:** *Guidelines for the Diagnosis and Treatment of Dementia and Cognitive Disorders in China*

| | |
|---|---|
| Interventions | **Intervention characteristics**<br><br>*G biloba* + donepezil<br><br>• Donepezil salate (national medicine approval H20030106), 5 mg/time, once/day, for 8 weeks. Ginkgo leaves tablet (national medicine standard word Z20027956) oral administration treatment, 1 ~ 2 tablets, 3 times a day, continuous administration for 8 weeks.<br><br>Donepezil<br><br>• Donepezil salate (national medicine approval H20030106), 5 mg/time, once/day, for 8 weeks. |
| Outcomes | **Outcomes collected**<br><br>• MMSE |


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**Liu 2015a** *(Continued)*

- Effective rate
- EEG

| | |
|---|---|
| Notes | **Sponsorship source:** none reported<br>**Trial registration number(s)**: none reported |

***Risk of bias***

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Random sequence generation (selection bias) | Low risk | Random number table. |
| Allocation concealment (selection bias) | Unclear risk | Not reported. |
| Blinding of participants and personnel (performance bias)<br>All outcomes | High risk | Patients from 2 groups took different interventions. No placebos were used. |
| Blinding of outcome assessment (detection bias)<br>All outcomes | Unclear risk | Not reported. |
| Incomplete outcome data (attrition bias)<br>All outcomes | Unclear risk | Loss to follow-up not reported. |
| Selective reporting (reporting bias) | Unclear risk | No protocol available. Insufficient information to permit judgment. |
| Other bias | Low risk | No other apparent sources of bias. |

**Liu 2021**

***Study characteristics***

| | |
|---|---|
| Methods | **Study design:** RCT<br>**Study grouping:** parallel group<br>**Duration of intervention:** 3 months<br>**Duration of follow-up:** 3 months<br>**Washout or placebo run-in period:** no |
| Participants | **Baseline characteristics**<br>*G biloba* plus butylphthalide<br>• Number randomized: 46<br>• MMSE (mean, SD): 16.23, 3.65<br>• Age (mean, SD): 72.15, 5.74<br>• % female: 39% |


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**Liu 2021** *(Continued)*

Butylphthalide

- Number randomized: 46
- MMSE (mean, SD): 16.41, 3.71
- Age (mean, SD): 72.84, 6.16
- % female: 43%

**Total number randomized:** 92

**Inclusion criteria**

- Diagnostic criteria for VD in the Diagnostic and Statistical Manual of Mental Disorders
- Diagnosis confirmed by cranial CT or MRI
- TCM criteria for phlegm turbidity obstructing orifices and score of ≥ 7 points on the Vascular Dementia Scale (DSVD)
- Hachinski ischemia score (HIS) > 4 points
- ≥ 1 stroke, VD onset after stroke, VD course > 3 months
- Age ≥ 55 years

**Exclusion criteria**

- Cerebrovascular disease diagnosed by cranial CT or MRI
- Severe dementia or end-stage dementia
- Auditory and visual dysfunction
- Severe complications
- Mental illness
- Malignant tumors
- Depression
- Other cerebrovascular diseases
- Active pulmonary tuberculosis
- Elderly benign amnesia
- Parkinson's disease or epilepsy
- Thyroid dysfunction
- Organic diseases of important organs
- Cognitive impairment caused by other diseases
- Poor compliance with doctor's orders
- Severe hypertension, diabetes, coronary heart disease, and other diseases

**Country:** China

**Setting:** hospital

**Date recruitment began:** 2017

**Recruitment methods:** people admitted to the Neurology Department of Xianyang Hospital of Yan'an University from December 2017 to December 2019

**Diagnosis:** VD

**Diagnostic criteria:** DSM-IV, 1994

Interventions

**Intervention characteristics**

*G biloba* plus butylphthalide capsule

- *G biloba* extract injection (produced in Taiwan ZhongHao International Co, Ltd, registration number: HC20090014, specification: 5 mL) 20 mL/time + 0.9% sodium chloride solution 500 mL/time intravenous drip treatment, 2 times/day, 10 days as a treatment cycle, stop the drug for 5 days after 1 cy-


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**Liu 2021** *(Continued)*

| | |
|---|---|
| | cle of treatment and then start the next cycle of treatment for 3 months. Dose *G biloba* 40 mL/day + butylphthalide 0.6 g/day.<br><br>Butylphthalide<br><br>• Butylphthalide capsules (manufactured by CSPC Enbipu Pharmaceutical Co, Ltd, approved by the nation H20050299, specification: 0.1 g) 0.2 g orally, 3 times a day, for 3 months. Dose 0.6 g/day. |
| Outcomes | **Outcomes collected**<br><br>• MMSE<br>• ADL/IADL<br>• NPI<br>• Curative effect |
| Notes | **Sponsorship source:** Project of Shaanxi Science and Technology Department (No.: 2018SF-131)<br><br>**Trial registration number:** none reported |

***Risk of bias***

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Random sequence generation (selection bias) | Low risk | Random number table. |
| Allocation concealment (selection bias) | Unclear risk | Not mentioned. |
| Blinding of participants and personnel (performance bias)<br>All outcomes | Unclear risk | Blinding not mentioned. |
| Blinding of outcome assessment (detection bias)<br>All outcomes | Unclear risk | Blinding not mentioned. |
| Incomplete outcome data (attrition bias)<br>All outcomes | Low risk | No attrition. |
| Selective reporting (reporting bias) | Unclear risk | No protocol. |
| Other bias | Low risk | No other apparent source of bias. |

**Lovera 2007**

***Study characteristics***

| | |
|---|---|
| Methods | **Study design:** RCT<br><br>**Study grouping:** parallel group<br><br>**Duration of intervention:** 12 weeks<br><br>**Duration of follow-up:** 12 weeks (from beginning of treatment) |


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**Lovera 2007** *(Continued)*

**Washout or placebo run-in period:** no

| | |
|---|---|
| Participants | **Baseline characteristics**<br><br>*G biloba*<br><br>• Number randomized: 21<br>• MMSE (mean, SD): NR<br>• Age (mean, SD): 47.8, 6.7<br>• % female: 70%<br><br>Placebo<br><br>• Number randomized: 22<br>• MMSE (mean, SD): NR<br>• Age (mean, SD): 50.2, 8.0<br>• % female: 68%<br><br>**Total number randomized:** 43<br><br>**Inclusion criteria**<br><br>• Diagnosis of MS by McDonald's criteria<br>• Age 18 to 60 years<br>• Score between 0.5 and 2.5 SDs below the mean on the Paced Auditory Serial Addition Test (PASAT) or the California Verbal Learning Test II (CVLT-II) total score<br><br>**Exclusion criteria**<br><br>• History of alcoholism, drug abuse, psychosis, major depression, or a score on the Beck Depression Inventory IA >19<br>• Severe cognitive impairment and need for a permanent caregiver<br>• Any significant medical problem, including insulin-dependent diabetes, uncontrolled hypertension, uncontrolled hypothyroidism, hepatic disease, renal disease, pulmonary disease, congestive heart failure, angina, valvular disease, or abnormalities of coagulation<br>• Significant MS exacerbation within the 30 days before screening<br>• Current use of anticoagulants<br>• Pregnancy<br>• Any visual problem that would interfere with testing, such as corrected binocular visual acuity worse than 20/50, nystagmus on primary gaze, or impaired color vision<br>• Not speaking English as the native language<br>• Any other condition that the investigator thought would make them unsuitable for the study<br><br>**Country:** USA<br><br>**Setting:** outpatient<br><br>**Date recruitment began:** 2002<br><br>**Recruitment methods:** "We recruited subjects from the OHSU MS Center of Oregon clinic, and the public. The MS Center of Oregon is a tertiary referral center that serves patients in Oregon and Washington. We advertised the study through the local newspaper and direct mailings, sent with the Oregon chapter of the National MS Society quarterly newsletter."<br><br>**Diagnosis:** MS with cognitive impairment<br><br>**Diagnostic criteria:** 0.5 to 2.5 SDs below mean on the CVLT-II or PASAT |
| Interventions | **Intervention characteristics**<br><br>*G biloba* |


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**Lovera 2007** *(Continued)*

- *G biloba* (GB; 120 mg) twice a day. The capsules were opaque and were provided by ThorneResearch Inc. (Dover, ID, USA). "The capsules were stored at room temperature in a dry location throughout the study. ChromaDex Inc. (Santa Ana, CA, USA) conducted a high performance liquid chromatography analysis of a sample of 20 GB capsules at the end of the study. The analysis showed that the product had 31.4% flavonol-O-glycosides and 4.5% terpenoids by weight. The coefficient of variation of the weight of the capsules was 0.44%."

Placebo

- "The GB (120 mg) and placebo capsules were opaque and of the same color and were provided by Thorne Research Inc. (Dover, ID, USA). The placebo powder consisted of 150 mg of powdered cellulose (Solka Floc† 300, International Fiber Corporation, North Tonawanda, NY, USA) and 13.5 mg of powdered brown food coloring (05135 Brown Shade 'R', Seltzer Chemical, Carlsbad, CA, USA), and was visually identical to the content of the GB capsules."

| | |
|---|---|
| Outcomes | **Outcomes collected**<br>• 3-second version of the PASAT<br>• Controlled Oral Word Association Test (COWAT)<br>• Symbol Digit Modalities Test (SDMT)<br>• Adapted version of the Useful Field of View Test (UFOV)<br>• Victoria version of the Stroop Color and Word Test (Stroop)<br>• Perceived Deficits Questionnaire (PDQ)<br>• Multiple Sclerosis Quality of Life Inventory (MSQLI) |
| Notes | **Sponsorship source:** "This study was supported by the National MS Society (PP0921), the NIH (P50AT00066-01), the Department of Veterans Affairs and the Nancy Davis Center Without Walls."<br><br>**Trial registration number(s)**: none reported |

***Risk of bias***

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Random sequence generation (selection bias) | Low risk | "The staff at the OHSU Medical Informatics and Clinical Epidemiology Department generated the allocation sequence, and numbered sequentially the containers provided by the manufacturer accordingly. The rest of the study personnel did not have access to the allocation sequence until the study was completed. The allocation sequence was generated using a random number generator. The sequence was stratified by age and had a block size of six." |
| Allocation concealment (selection bias) | Low risk | "The staff at the OHSU Medical Informatics and Clinical Epidemiology Department generated the allocation sequence, and numbered sequentially the containers provided by the manufacturer accordingly. The rest of the study personnel did not have access to the allocation sequence until the study was completed." |
| Blinding of participants and personnel (performance bias)<br>All outcomes | Low risk | "The blinding was implemented by using identical containers, instructions and labels. The subjects, physicians and research assistants did not know the treatment allocation at any point until the data analysis was completed. To evaluate the blinding, the subjects and the research assistant, who administered the neuropsychological testing, indicated at the exit visit what treatment they thought the subject received." |
| Blinding of outcome assessment (detection bias)<br>All outcomes | Low risk | "The blinding was implemented by using identical containers, instructions and labels. The subjects, physicians and research assistants did not know the treatment allocation at any point until the data analysis was completed." |


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**Lovera 2007** *(Continued)*

| | | |
|---|---|---|
| Incomplete outcome data (attrition bias)<br>All outcomes | Unclear risk | Although reasons were given for losses to follow-up and they did not appear related to interventions, the overall loss to follow-up was over 10% in the placebo group and 5% in the ginkgo group. |
| Selective reporting (reporting bias) | Unclear risk | All outcomes mentioned in the Methods were reported in the Results; however, no protocol or trial registration was available. |
| Other bias | Low risk | No other apparent source of bias. |

**Lovera 2012**

| ***Study characteristics*** | |
|---|---|
| Methods | **Study design:** RCT<br><br>**Study grouping:** parallel group<br><br>**Duration of intervention:** 12 weeks<br><br>**Duration of follow-up:** 12 weeks<br><br>**Washout or placebo run-in period:** no |
| Participants | **Baseline characteristics**<br><br>*G biloba*<br><br>• Number randomized: 61<br>• MMSE (mean, SD): NR<br>• Age (mean, SD): 51.3, 8.6<br>• % female: 48%<br><br>Placebo<br><br>• Number randomized: 59<br>• MMSE (mean, SD): NR<br>• Age (mean, SD): 53, 9.5<br>• % female: 63%<br><br>**Total number randomized:** 121 (baseline data not provided for all randomized participants)<br><br>**Inclusion criteria**<br><br>• Age 18 to 65 years<br>• MS by McDonald's criteria (Expanded Disability Status Scale [EDSS] score 0-7.5) and stable for at least 30 days<br>• Score of 1 SD or more below the mean of established normative samples on one or more of the 4 tests in the neuropsychological test battery (Stroop Color-Word Test Victoria version, California Verbal Learning Test II, Controlled Oral Word Association Test, 2-second version of the PASAT)<br>• No ginkgo use in preceding 30 days<br>• Native English speaker<br><br>**Exclusion criteria**<br><br>• Substance abuse, psychosis, or significant depression (BDI-II > 28)<br>• Any uncontrolled medical problem such as unstable angina, stage IV hypertension, cancer undergoing chemotherapy<br>• MS relapse within 30 days prior to screening |


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**Lovera 2012** *(Continued)*

- Abnormalities of coagulation or current use of drugs that affect coagulation except for aspirin and other NSAIDs
- Surgery planned for 4 months after screening
- Epilepsy
- Use of nifedipine, nicardipine, Saint John's Wort, papaverine, or mono-amino oxidase inhibitors
- Pregnancy
- Women not using reliable contraception
- Corrected binocular visual acuity worse than 20/50
- More than 1 error on binocular color vision testing
- Sustained nystagmus or diplopia on primary gaze
- Inability to complete the neuropsychological test battery at screening

**Country:** USA

**Setting:** outpatient

**Date recruitment began:** 2009

**Recruitment methods:** "The study was performed at 2 sites, the Portland and Seattle VA Medical Centers. We recruited from both sites' MS clinics, from their affiliated university's MS clinics, and from their communities. Enrollment started on January 2009 and ended in November 2010."

**Diagnosis:** MS with cognitive impairment

**Diagnostic criteria:** ≥ 1 SD below mean on the Strop, CVLT-II, COWAT, or PASAT

| | |
|---|---|
| Interventions | **Intervention Characteristics**<br><br>*G biloba*<br><br>• "ginkgo 120 mg twice a day (EGb-761; Willmar Schwabe GmbH & Co, Germany)". "Our ginkgo tablets contained 29.7 mg of flavoglycosides and 7.3 mg of terpene lactones measured by high-performance liquid chromatography".<br><br>Placebo<br><br>• Participants were assigned 1 placebo tablet twice a day. Placebo tablets were dispensed in matching identical containers to intervention. Full protocol was cited in non-working hyperlink. Placebo content was NR. |
| Outcomes | **Outcomes collected**<br><br>• Stroop Color-Word Test Victoria version (Stroop)<br>• California Verbal Learning Test II (CVLT-II)<br>• Controlled Oral Word Association Test (COWAT)<br>• 2-second version of the PASAT<br>• Perceived Deficits Questionnaire (PDQ)<br>• Multiple Sclerosis Neuropsychological Screening Questionnaire (MSNSQ)<br>• Community Integration Questionnaire (CIQ)<br>• Modified Fatigue Impact Scale (MFIS)<br>• Beck Depression Inventory-II (BDI-II) |
| Notes | **Sponsorship source:** Department of Veterans Affair, Office of Research and Development, Rehabilitation Research and Development<br><br>**Trial registration number(s)**: NCT00841321<br><br>**Note:** the data in this trial was reported only as Z-scores. We emailed the author for additional data so that we could calculate the mean scores and carry out a meta-analysis, but we received no reply. |


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**Lovera 2012** *(Continued)*

***Risk of bias***

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Random sequence generation (selection bias) | Low risk | "The Portland VA research pharmacist generated the allocation sequence in Excel with alternating random blocks of 4 or 6 subjects stratified by disease duration and study site and a 1:1 ratio." |
| Allocation concealment (selection bias) | Low risk | "Only the research pharmacists had access to the allocation sequence. They assigned the participants to either ginkgo or matching placebo tablets and dispensed the tablets to them in matching identical containers." The process of allocation is not entirely clear but it appears that it was concealed. |
| Blinding of participants and personnel (performance bias)<br>All outcomes | Low risk | Placebo-controlled for participants and investigators. |
| Blinding of outcome assessment (detection bias)<br>All outcomes | Low risk | "One research assistant assessed adverse events and another administered the neuropsychological tests. They were instructed not to discuss adverse events (AEs) between them to ensure that the cognitive test assessments would be masked." Study personnel collecting outcome data were masked to intervention and to adverse events. |
| Incomplete outcome data (attrition bias)<br>All outcomes | Low risk | Reasons given for loss to follow-up did not appear related to the intervention and overall loss to follow-up and replacement by LOCF as planned in protocol was low. Placebo group had 1 participant lost to follow-up; 0 excluded from analysis. Ginkgo had 3 participants lost to follow-up; 0 excluded from analysis. |
| Selective reporting (reporting bias) | Low risk | Trial was registered 1 month after study start (NCT00841321) and prior to completion of study by any participants. Outcomes planned in NCT00841321 were reported consistently in the publication. |
| Other bias | Low risk | No other apparent source of bias. |

**Ma 2015**

***Study characteristics***

| | |
|---|---|
| Methods | **Study design:** RCT<br>**Study grouping:** parallel group<br>**Duration of intervention:** 3 months<br>**Duration of follow-up:** 3 months<br>**Washout or placebo run-in period:** none reported |
| Participants | **Baseline characteristics**<br>*G biloba* + piracetam<br>• Number randomized: 66<br>• MMSE (mean, SD): NR<br>• Age (mean, SD): 57.6, 7.3<br>• % female: 45.5 |


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**Ma 2015** *(Continued)*

| | |
|---|---|
| | Piracetam<br>• Number randomized: 66<br>• MMSE (mean, SD): NR<br>• Age (mean, SD): 62.6, 7.8<br>• % female: 48.5<br><br>**Total number randomized:** 132<br><br>**Inclusion criteria:** vascular dementia<br><br>**Exclusion criteria:** none reported<br><br>**Country:** China<br><br>**Setting:** community health center<br><br>**Date recruitment began:** 2011<br><br>**Recruitment source/methods:** people with vascular dementia who visited the hospital from January 2011 to February 2014<br><br>**Diagnosis:** vascular dementia<br><br>**Diagnostic criteria:** NR |
| Interventions | **Intervention characteristics**<br><br>*G biloba* + piracetam<br>• Besides routine therapy to control against blood glucose, blood pressure, coronary heart disease, and anemia, participants also took 3 Piracetam tablets per time, 3 times per day. In addition, participant took 1 GBT tablet per time, 3 times per day.<br><br>Piracetam<br>• Besides routine therapy to control against blood glucose, blood pressure, coronary heart disease and anemia, participants also took 3 Piracetam tablets per time, 3 times per day. |
| Outcomes | **Outcomes collected**<br>• MMSE<br>• HDS<br>• Effective rate |
| Notes | **Sponsorship source:** none reported<br><br>**Trial registration number(s)**: none reported<br><br>No outcome data relevant to this review could be extracted from the study. |

***Risk of bias***

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Random sequence generation (selection bias) | Low risk | Random number table. |
| Allocation concealment (selection bias) | Unclear risk | Allocation process not reported. |


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**Ma 2015** *(Continued)*

| | | |
|---|---|---|
| Blinding of participants and personnel (performance bias)<br>All outcomes | High risk | Not reported. However, since the number of drugs in the treatment group are distinct from that in the control group, it is likely the outcomes were influenced by lack of blinding. |
| Blinding of outcome assessment (detection bias)<br>All outcomes | Unclear risk | Not reported. Unclear the extent to which outcomes were influenced by lack of blinding. |
| Incomplete outcome data (attrition bias)<br>All outcomes | Unclear risk | Loss to follow-up not reported. |
| Selective reporting (reporting bias) | Unclear risk | No protocol available. Insufficient information to permit judgment. |
| Other bias | Low risk | No other apparent sources of bias. |

**Maurer 1997**

| ***Study characteristics*** | |
|---|---|
| Methods | **Study design:** RCT<br><br>**Study grouping:** parallel group<br><br>**Duration of follow-up:** 3 months<br><br>**Duration of intervention:** 3 months<br><br>**Washout or placebo run-in period:** unclear. 7-day run-in period but no placebo and no mention of wash out. |
| Participants | **Baseline characteristics**<br><br>*G biloba*<br><br>• Number randomized: 9<br>• MMSE (mean, SD): NR<br>• Age (mean, SD): 68.5, 6.0<br>• % female: 56%<br><br>Placebo<br><br>• Number randomized: 9<br>• MMSE (mean, SD): NR<br>• Age (mean, SD): 60.6, 8.82<br>• % female: 44%<br><br>**Total number randomized:** 20 (baseline data not provided for all randomized participants)<br><br>**Inclusion criteria**<br><br>• Age 50 to 80 years<br>• Hachinski Ischemic Score 4 or less<br>• Mild-moderate Alzheimer-type dementia (mean BCRS score 3–5)<br>• Normal CT finding or diffuse possibly asymmetric atrophy |


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**Maurer 1997** *(Continued)*

**Exclusion criteria**

- Advanced Alzheimer's dementia
- Intellectual degeneration
- Confusion or dementia of other origin such as multi-infarct dementia
- Pseudodementia
- Aphasia or sensory, motor, or visual disturbances that could interfere with testing
- Severe organic disease
- Neoplasia, epilepsy, cerebrovascular malformation, alcohol or drug abuse
- Vasoactive drugs, nootropics, or long-term treatment with other drugs proscribed during the study
- Non-cooperation during run-in phase

**Country:** Germany

**Setting:** outpatient

**Date recruitment began:** NR (prior to 1996)

**Recruitment methods:** not described

**Diagnosis:** mild to moderate Alzheimer's dementia

**Diagnostic criteria:** DSM-III-R and NINCDS/ADRDA criteria

| | |
|---|---|
| Interventions | **Intervention characteristics**<br>*G biloba*<br>• "Participants took 240 mg/day of Ginkgo biloba special extract EGb 761(Tebonin "" forte, manufactured by Dr. Willmar Schwabe, Karlsruhe)(three times with two film-coated tablets). A film-coated tablet of the active product contains 40 mg of dry extract of Ginkgo biloba leaves(35-67:1), adjusted to 9.6mg Ginkgo flavone glycosides and 2.4mg terpene lactones (ginkgolides,bilobalide)."<br>Placebo<br>• Participants took an identical placebo (3 times with 2 film-coated tablets). Content of placebo NR. |
| Outcomes | **Outcomes collected**<br>• Multiple-choice vocabulary test (MWT-B)<br>• SKT<br>• Trailmaking test (ZVT)<br>• ADAS-Cog<br>• CGI Item 2 |
| Notes | **Sponsorship source:** none reported<br>**Trial registration number(s)**: none reported |

***Risk of bias***

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Random sequence generation (selection bias) | Low risk | "Randomization numbers that had been allocated by a random generator to either active treatment or placebo were assigned to the patients strictly according to the sequence of their enrolment." |
| Allocation concealment (selection bias) | Unclear risk | Insufficient information available to permit a judgment. |


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**Maurer 1997** *(Continued)*

| | | |
|---|---|---|
| Blinding of participants and personnel (performance bias)<br>All outcomes | Low risk | Participants treated with a daily dose of 240 mg EGb 761 (3 times with 2 film-coated tablets) or with an identical placebo for 3 months (10 participants/group). |
| Blinding of outcome assessment (detection bias)<br>All outcomes | Low risk | Double-blind study and no mention that participants or personnel were unblinded during the study. |
| Incomplete outcome data (attrition bias)<br>All outcomes | Unclear risk | Although the loss to follow-up was not great (10%) and was the same in each group, 1 participant was excluded from analysis due to non-compliance, and another was excluded due to inability to measure the P300, and it is unclear which group each person belonged to. Given the very small size of the study, it is unclear whether this poses a risk of bias. |
| Selective reporting (reporting bias) | High risk | Protocol not available. Note that the trailmaking test (ZVT) was mentioned as a secondary outcome collected throughout the study, but specific outcome data was not reported (other than not significant), which leads to greater suspicion about reporting bias overall. |
| Other bias | Low risk | The study appears to be free of other sources of bias. |

**Mazza 2006**

| | |
|---|---|
| ***Study characteristics*** | |
| Methods | **Study design:** RCT<br><br>**Study grouping:** parallel group<br><br>**Duration of intervention:** 24 weeks<br><br>**Duration of follow-up:** 24 weeks<br><br>**Washout or placebo run-in period:** "A single-blind placebo 4-week run-in period was included to exclude placebo responders." |
| Participants | **Baseline characteristics**<br><br>*G biloba*<br><br>• Number randomized: 25<br>• MMSE (mean, SD): 18.80, 3.62<br>• Age (mean, SD): 66.2, 6<br>• % female: 52%<br><br>Donepezil<br><br>• Number randomized: 25<br>• MMSE (mean, SD): 18.55, 3.47<br>• Age (mean, SD): 64.5, 6<br>• % female: 48%<br><br>Placebo<br><br>• Number randomized: 26<br>• MMSE (mean, SD): 18.80, 3.63<br>• Age (mean, SD): 69.8, 3 |


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**Mazza 2006** *(Continued)*

| | |
|---|---|
| | • % female: 61%<br><br>**Total number randomized:** 76<br><br>**Inclusion criteria:** "All participants received a diagnosis of primary degenerative dementia of the Alzheimer type according to the criteria of DSM-IV. Inclusion criteria were: (i) a mean score of 3–5 on the Brief Cognitive Rating Scale, a Hachinski Ischemic Score of <4 and the presence of an adequate level of premorbid intelligence (IQ > 80, global assessment)." "The degree of severity of dementia had to be mild to moderate as assessed by a score between 8 and 23 on the Syndrom Kurz test (SKT)" "Another baseline and outcome measure was Mini-Mental State Examination (MMSE): subjects who reached a score of at least 13 but no more than 25 on the MMSE were considered for study participation."<br><br>**Exclusion criteria:** "Patients were excluded if they had dementia of other etiology, severe organic diseases (tumors, severe infectious diseases, brain trauma, epilepsy, cerebrovascular malformations, alcohol or drug abuse), pseudodementia or a history of schizophrenic or affective psychoses (Geriatric Depression Scale, 15-item version, total score <11)"<br><br>**Country:** Italy<br><br>**Setting:** outpatient<br><br>**Date recruitment began:** 2003<br><br>**Recruitment source/methods:** not reported<br><br>**Diagnosis:** primary degenerative dementia of the Alzheimer type<br><br>**Diagnostic criteria:** DSM-IV |
| Interventions | **Intervention characteristics**<br><br>*G biloba*<br><br>• "Ginkgo biloba (160 mg daily dose EGb761)"<br><br>Donepezil<br><br>• Donepezil (5 mg daily dose)<br><br>Placebo<br><br>• Not described<br><br>"Vasoactive drugs, nootropics and long-term treatment with other drugs were proscribed during the study, with the exception of low doses of benzodiazepines and neuroleptics in the treatment of behavioral disturbances." |
| Outcomes | **Outcomes collected**<br><br>• MMSE<br>• SKT<br>• CGI (item 2) |
| Notes | **Sponsorship source:** none reported<br><br>**Trial registration number(s)**: none reported<br><br>**Note:** clarifications on outcome data provided in email to LSW by Dr Mazza on 8 June 2021. Dr Mazza confirmed that the ITT analysis included only completers and the CIs for Table 2 are symmetrical around means in the other direction (CIs should be changed). |
| ***Risk of bias*** | |


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**Mazza 2006** *(Continued)*

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Random sequence generation (selection bias) | Low risk | "For randomization procedure we used a computer-generated random sample set." |
| Allocation concealment (selection bias) | Unclear risk | Insufficient information available to permit a judgment. |
| Blinding of participants and personnel (performance bias)<br>All outcomes | Low risk | Study is described as double-blinded. |
| Blinding of outcome assessment (detection bias)<br>All outcomes | Low risk | "The researchers who provided the pills to the study participants were different from those who conducted the neuropsychological evaluations, in order to guarantee the blinding." Study is double-blinded and extra precautions were taken for evaluators to be different from the researchers who provided pills. |
| Incomplete outcome data (attrition bias)<br>All outcomes | High risk | Numbers and reasons for loss to follow-up are given, and the numbers are similar across groups; however, the overall loss to follow-up is greater than 20%. Of 76 participants randomized for the study, 15 were withdrawn: 5 in the EGb group (20%), 4 in the donepezil group (16%), and 6 in the placebo group (23%). |
| Selective reporting (reporting bias) | Unclear risk | No protocol available. Insufficient information to permit judgment. |
| Other bias | Low risk | No other apparent sources of bias. |

**Meng 2012**

| ***Study characteristics*** | |
|---|---|
| Methods | **Study design:** RCT<br>**Study grouping:** parallel group<br>**Duration of intervention:** 6 months<br>**Duration of follow-up:** 6 months<br>**Washout or placebo run-in period:** none reported |
| Participants | **Baseline characteristics**<br>*G biloba* + Piracetam<br>• Number randomized: 52<br>• MMSE (mean, SD): NR<br>• Age (mean, SD): 67.6, 7.5<br>• % female: 44.2<br>Piracetam<br>• Number randomized: 52<br>• MMSE (mean, SD): NR<br>• Age (mean, SD): 68.7, 7.9<br>• % female: 38.5 |


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**Meng 2012** *(Continued)*

**Total number randomized:** 104

**Inclusion criteria**

- Diagnosis of vascular dementia according to DSM-3
- MMSE score 12-24
- Informed consent

**Exclusion criteria:** none reported

**Country:** China

**Setting:** outpatient

**Date recruitment began:** 2009

**Recruitment methods:** outpatients were diagnosed with vascular dementia in community health service center, Hutang street Shaoxing County Zhejiang Province, during 2009/12–2010/12.

**Diagnosis:** vascular dementia

**Diagnostic criteria:** in accordance with the diagnostic criteria of DSM-3 and the MMSE score was 12 - 24.

| | |
|---|---|
| Interventions | **Intervention characteristics**<br>*G biloba* + Piracetam<br>• 1 tablet of EGb per time, 3 times per day, plus 3 tablets of Piracetam per time, 3 times per day<br>Piracetam<br>• 3 tablets of Piracetam per time, 3 times per day |
| Outcomes | **Outcomes collected**<br>• ADL<br>• MMSE<br>• MMSE as efficacy index (MMSE score after treatment − MMSE score before treatment)/MMSE score before treatment × 100%) |
| Notes | **Sponsorship source:** none reported<br>**Trial registration number(s)**: none reported |

***Risk of bias***

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Random sequence generation (selection bias) | Low risk | Random number table. |
| Allocation concealment (selection bias) | Unclear risk | Allocation process not reported. |
| Blinding of participants and personnel (performance bias)<br>All outcomes | Unclear risk | Blinding not reported. |
| Blinding of outcome assessment (detection bias) | Unclear risk | Blinding of outcome assessment not reported. |


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**Meng 2012** *(Continued)*

| | | |
|---|---|---|
| All outcomes | | |
| Incomplete outcome data (attrition bias) All outcomes | Low risk | No attrition/exclusion. |
| Selective reporting (reporting bias) | Unclear risk | No protocol available. Insufficient information to permit judgment. |
| Other bias | Low risk | No other apparent risk of bias. |

**Moreau 1975**

| | |
|---|---|
| ***Study characteristics*** | |
| Methods | **Study design:** RCT<br>**Study grouping:** parallel group<br>**Duration of intervention:** 3 months<br>**Duration of follow-up:** 3 months<br>**Washout or placebo run-in period:** NR |
| Participants | **Baseline characteristics**<br>*G biloba*<br>• Number randomized: 30<br>• MMSE (mean, SD): NR<br>• Age (mean, SD): NR<br>• % female: NR<br>Placebo<br>• Number randomized: 30<br>• MMSE (mean, SD): NR<br>• Age (mean, SD): NR<br>• % female: NR<br>**Total number randomized:** 60<br>**Inclusion criteria:** NR<br>**Exclusion criteria:** NR<br>**Country:** France<br>**Setting:** NR<br>**Date recruitment began:** NR<br>**Recruitment methods:** NR<br>**Diagnosis:** NR. For the purposes of this review, we classified this study participants as exhibiting VCI.<br>**Diagnostic criteria:** NR |
| Interventions | **Intervention characteristics** |


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**Moreau 1975** *(Continued)*

| | |
|---|---|
| | *G biloba*<br>• Tanaken (Ipsen 225) 120 mg or 3 mL per day, divided into 3 doses, for 3 months<br>Placebo<br>• Identical placebo 120 mg or 3 mL per day, divided into 3 doses, for 3 months |
| Outcomes | **Outcomes collected**<br>• Examination signs and functional symptoms<br>• General activity, assessed by studying codified parameters<br>• Psychometric tests<br>• Tolerance of the therapy |
| Notes | Sponsorship source: NR<br>Trial registration number: NR<br>No indication of what scales were used, and based upon the names of the concepts, it is unclear how to allocate them against review outcomes. No outcome data relevant to this review could be extracted from the study. |

***Risk of bias***

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Random sequence generation (selection bias) | Low risk | "*en fonction d'un tirage au sort prealable*". Review author and French speaker (HA) advises that allocation was done by drawing of lots. "...according to a preliminary drawing of lots." |
| Allocation concealment (selection bias) | Unclear risk | No information about procedures surrounding allocation. |
| Blinding of participants and personnel (performance bias)<br>All outcomes | Low risk | Double-blinded study with no indication that blinding was broken. "The decoding, at the end of the double-blind study..." |
| Blinding of outcome assessment (detection bias)<br>All outcomes | Low risk | "The decoding, at the end of the double-blind study..." |
| Incomplete outcome data (attrition bias)<br>All outcomes | Unclear risk | 29 participants with outcome data in Ipsen group and 28 participants with outcomes in placebo group. No discussion of what happened to the 3 participants with no data. Although 10% loss is low, it is unclear what the reasons were, and bias is possible. |
| Selective reporting (reporting bias) | Unclear risk | No protocol or other pre-established documentation of trial methods. |
| Other bias | Low risk | No other apparent sources of bias. |

**Oswald 1997**

***Study characteristics***


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**Oswald 1997** *(Continued)*

| | |
|---|---|
| Methods | **Study design:** RCT<br><br>**Study grouping:** parallel group<br><br>**Duration of intervention:** 12 weeks<br><br>**Duration of follow-up:** 12 weeks<br><br>**Washout or placebo run-in period:** 2-week washout period |
| Participants | **Baseline characteristics**<br><br>*G biloba*<br><br>• Number randomized: 103<br>• MMSE (mean, SD): NR<br>• Age (mean, SD): 70.5, 7.8<br>• % female: 65%<br><br>Placebo<br><br>• Number randomized: 92<br>• MMSE (mean, SD): NR<br>• Age (mean, SD): 71.4, 7.9<br>• % female: 63%<br><br>**Total number randomized:** 226 (baseline data not provided for all randomized participants)<br><br>**Inclusion criteria**<br><br>• Age ≥ 60 years<br>• Mild to moderate brain impairment in old age (DSM-III, Cat 1 or ICD-9 No. 290) with SCAG 40 to 90 and an average value of at least 3.5 on SCAG items 2, 3, 6, and 8 and a total point value of 24 on SCAG items 1 to 8, but no point value of 7 on any of these items<br><br>**Exclusion criteria**<br><br>• **U**ncompensated cardiac, hepatic, pulmonary or renal insufficiency<br>• Brain impairment due to chronic alcoholism, brain trauma, or hemodynamically effective stenoses of the large cerebral arteries<br>• Apopleptic insult less than 6 months previously<br>• Suspected endogenous psychosis or organic depression<br>• History of cerebral convulsions<br>• Other severe acute or chronic illnesses<br>• Inability to do without treatment with antidepressants, neuroleptics, blood-circulating enhancing medications, or other nootropics during the trial<br>• Inability to take part in study tests (e.g. NAI)<br>• Suicidal tendencies<br><br>**Country:** Germany<br><br>**Setting:** outpatient<br><br>**Date recruitment began:** 1989<br><br>**Recruitment methods:** study carried out in 2 medical practices. 18.6% (42) of participant lived in a nearby senior citizens' home, 81.4% (184) in their own household in the vicinity of the doctor's office. No other details about source or recruitment.<br><br>**Diagnosis:** mild to moderate organic brain syndrome |


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**Oswald 1997** *(Continued)*

| | |
|---|---|
| | **Diagnostic criteria:** DSM-III, ICD-9 |
| Interventions | **Intervention Characteristics**<br><br>*G biloba*<br><br>• The *G biloba* special extract EGb 761 is a dry extract from *G biloba* leaves, which is adjusted to a content of 24% ginkgo flavone glycosides and 6% terpene lactones (ginkgolide, bilobalide). The standardization of the ingredients that determine the effectiveness ensures a constant extract quality. Accompanying substances in the extract make the lipophilic flavonoids and terpene lactones soluble in water and thus increase their absorption and bioavailability. EGb 761 is a standardized monoextract made from the dried leaves of the *G biloba* tree using a special multi-stage process. The highly purified and concentrated *G biloba* dry extract EGb 761 is standardized to ginkgo-specific flavone glycosides and terpene lactones, the active components, for quality assurance. One verum film-coated tablet contained 40 mg EGB dry extract from *G biloba* leaves, adjusted to 9.6 mg ginkgo flavone glycosides and 2.4 mg terpene lactones (ginkgolide, bilobalide). The dose was 3 film-coated tablets per day. The film-coated tablets were swallowed whole with meals. All film-coated tablets contained 3.0 mg riboflavin as a marker substance (for compliance measurement).<br><br>Placebo<br><br>• The dose was 3 film-coated placebo tablets per day. The film-coated tablets were swallowed whole with meals. Verum and placebo were of the same shape and identical film coating, indistinguishable externally and in terms of taste. All film-coated tablets contained 3.0 mg riboflavin as a marker substance (for compliance measurement).<br><br>Participants not allowed to take antidepressants, neuroleptics, blood-circulation-enhancing medications or other nootropics. |
| Outcomes | **Outcomes collected**<br><br>• Number-Symbol-Test (*Zahlen-Symbol-Test*; ZS-G)<br>• Labyrinth-Test (LT-G)<br>• Number-Connection-Test (*Zahlen-Verbindungs-Test*; ZVT-G)<br>• Condition and overall psychological assessment rated on 4 scales from the *Nürnberger-Alters-Inventar* (NAI), including:<br>  ◦ *Nürnberger-Alters-Selbstbeurteilungs-Skala* (NAS)<br>  ◦ *Nürnberger-Alters-Alltagsaktivitäten-Skala* (NAA)<br>  ◦ *Nürnberger-Selbsteinschätzungs-Liste* (NSL)<br>  ◦ *Nürnberger-Alters-Rating* (NAR) |
| Notes | **Sponsorship source:** sponsorship is not explicit; however, a Schwabe scientist (R Hoerr) is a co-author, and "the sponsor" is referred to with regard to randomization, and we believe that the company was the sponsor and funder.<br><br>**Trial registration number(s)**: none reported<br><br>No outcome data relevant to this review could be extracted from the study. |

***Risk of bias***

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Random sequence generation (selection bias) | Unclear risk | The randomization plan was deposited with the client so that none of those directly involved (doctor, psychologist, nursing staff, statistician, participant) knew which of the 2 preparations was administered in each individual case (double-blind condition). This means that true randomization was likely done; however, the method of sequence generation is not specified. |


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**Oswald 1997** *(Continued)*

| | | |
|---|---|---|
| Allocation concealment (selection bias) | Low risk | The randomization plan was deposited with the client so that none of those directly involved (doctor, psychologist, nursing staff, statistician, participant) knew which of the 2 preparations was administered in each individual case (double-blind condition). It is very likely that the allocation was blinded and, based on other studies conducted by this company, that the randomization scheme was not disclosed until after the end of the trial. |
| Blinding of participants and personnel (performance bias)<br>All outcomes | Low risk | Double-blinded trial. The randomization plan was deposited with the client so that none of those directly involved (doctor, psychologist, nursing staff, statistician, participant) knew which of the 2 preparations was administered in each individual case (double-blind condition). |
| Blinding of outcome assessment (detection bias)<br>All outcomes | Low risk | The randomization plan was deposited with the client so that none of those directly involved (doctor, psychologist, nursing staff, statistician, participant) knew which of the two preparations was administered in each individual case (double blind condition). All those directly involved with the trial were double-blinded. |
| Incomplete outcome data (attrition bias)<br>All outcomes | High risk | A total of 226 participants were included in the study. Of these, 31 participants dropped out for reasons unrelated to the medication: 22 participants dropped out of the study during the washout period. Three participants dropped out of their own free will in the course of the study, 2 because of a stay at a spa, 1 because of weight gain, 1 because of inadmissible concomitant medication by the ENT doctor, 1 because of pneumonia, and 1 participant died. Since these reasons for termination were not related to the treatment, the last-value option was not used. 103 participants remained in the treatment group and 92 participants in the placebo group, for a total of 195 participants. High numbers of loss to follow-up (43/226), of which 31 were classified as unrelated to medication (of which 22 dropped out during washout period), and 12 as related to medication and thus included in analyses using last-value option, for a total of 195 participants included in the analysis. |
| Selective reporting (reporting bias) | Unclear risk | No protocol available. |
| Other bias | Low risk | No other apparent sources of bias. |

**PLAGIN 2013**

| | |
|---|---|
| ***Study characteristics*** | |
| Methods | **Study design:** RCT<br>**Study grouping:** parallel group<br>**Duration of intervention:** 22 weeks<br>**Duration of follow-up:** 22 weeks<br>**Washout or placebo run-in period:** a drug-free run-in period of up to 4 weeks prior to randomization |
| Participants | **Baseline characteristics**<br>*G biloba*<br>• Number randomized: 196<br>• MMSE (mean, SD): NR<br>• Age (mean, SD): NR |


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**PLAGIN 2013** *(Continued)*

- % female: NR

Placebo

- Number randomized: 201
- MMSE (mean, SD): NR
- Age (mean, SD): NR
- % female: NR

**Total number randomized:** 408 (baseline data not provided for all randomized participants)

**Inclusion criteria:** "Patients with mild to moderate dementia (probable AD, possible AD with CVD or probable VaD, as described above) were enrolled, if they scored 35 or lower in the Test for the Early Detection of Dementia with Discrimination from Depression (TE4D) (Mahoney et al. 2005), between 9 and 22 on the SKT and 5 or higher on the NPI composite." Stated to be same as GINDEM-NP study with regard to participant selection.

**Exclusion criteria:** "other forms of dementia, neurological or psychiatric disorders, patients taking other anti-dementia agents, cholinergic or anticholinergic drugs, as well as patients with severe physical, in particular cardiac or pulmonary diseases were excluded."

**Country:** Bulgaria

**Setting:** outpatient

**Date recruitment began:** NR (prior to 2013)

**Recruitment methods:** not reported

**Diagnosis:** probable AD, possible AD with CVD, or probable VaD

**Diagnostic criteria:** probable AD criteria were NINCDS/ADRDA, possible AD with CVD were NINCDS/ADRDA and NINDS/AIREN, probable VD was NINDS/AIREN.

| | |
|---|---|
| Interventions | **Intervention Characteristics**<br><br>*G biloba*<br><br>• "Participants took 120 mg EGb 761® twice daily. EGb 761® is a dry extract from Ginkgo biloba leaves (35-67:1), made by an extraction solvent of acetone 60% (w/w). The extract is adjusted to 22.0 - 27.0% ginkgo flavonoids calculated as ginkgo flavone glycosides and 5.0 - 7.0% terpene lactones consisting of 2.8 - 3.4% ginkgolides A, B, Cand 2.6 - 3.2% bilobalide, and contains less than 5 ppm ginkgolic acids. The drug was manufactured and provided by Dr. Willmar Schwabe GmbH & Co. KG, Karlsruhe, Germany."<br><br>Placebo<br><br>• Participants took placebo twice daily. Content not reported.<br><br>As in GINDEM-NP, treatment with other antidementia drugs, cognitive enhancers, cholinergic, anticholinergic or hemorheologically active drugs was prohibited. |
| Outcomes | **Outcomes collected**<br><br>• SKT<br>• NPI composite and caregiver distress scores<br>• GBS total and ADL scores<br>• Verbal Fluency Test<br>• CDT<br>• HAM-D<br>• 11-point box scales for concomitant neurosensory symptoms (dizziness, tinnitus) |


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**PLAGIN 2013** *(Continued)*

| | |
|---|---|
| Notes | **Sponsorship source:** "Dr. Willmar Schwabe GmbH & Co. KG, Karlsruhe, Germany, was the sponsor of the study."<br><br>**Trial registration number(s)**: none reported<br><br>**Note:** sponsor contacted in July 2021 to verify methods. English translation states that "The present trial (PLAGIN Study) was identical to the GINDEM-NP Study (Napryeyenko et al. 2007) with respect to patient selection, study design and treatment." |

***Risk of bias***

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Random sequence generation (selection bias) | Low risk | Email from Dr Robert Hoerr on 15 July 2021 stated that "randomization was performed by the sponsor's biometrics department, using a validated computer program. Drug numbers were allocated to the treatments, active drug or placebo, by the randomization program, stratified by centers. As patients were enrolled, each patient was assigned the box of tablets with the lowest drug number still available at the site. EGb 761® and placebo tablets were indistinguishable by appearance. Boxes and labels were identical, except for the drug number. The sealed randomization list was kept at the sponsor's biometrics department, inaccessible to all persons involved in the study." |
| Allocation concealment (selection bias) | Low risk | Centralized randomization and sealed randomization list was kept at the sponsor's biometrics department, inaccessible to all persons involved in the study. |
| Blinding of participants and personnel (performance bias)<br>All outcomes | Low risk | All participants and personnel were blinded to treatment. "EGb 761® and placebo tablets were indistinguishable by appearance. Boxes and labels were identical, except for the drug number." |
| Blinding of outcome assessment (detection bias)<br>All outcomes | Low risk | Personnel and participants were blinded to treatment group. As participants were enrolled, each was assigned the box of tablets with the lowest drug number still available at the site. EGb 761® and placebo tablets were indistinguishable by appearance. Boxes and labels were identical, except for the drug number. |
| Incomplete outcome data (attrition bias)<br>All outcomes | Unclear risk | "Of 449 patients screened, 408 met all inclusion criteria and none of the exclusion criteria and were therefore randomized to EGb 761 ® (n = 203) or placebo (n = 205). For seven patients of the active treatment group and four patients of the placebo group no post-baseline efficacy data were available. Hence, the full analysis set for efficacy analysis consisted of 397 patients (EGb 761 ®: 196; placebo: 201)." Although the numbers lost to follow-up were different between groups and no reasons were given, efficacy data were available for 97% of participants. |
| Selective reporting (reporting bias) | Unclear risk | No available registration or protocol against which to check outcomes. Several outcomes in Methods that are relevant to this review are not mentioned in Results (verbal fluency test; CDT; HAM-D); however, we obtained them from the sponsor on request. |
| Other bias | Low risk | No other apparent sources of bias. |

**Qu 2020**

***Study characteristics***


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**Qu 2020** *(Continued)*

| | |
|---|---|
| Methods | **Study design:** RCT<br><br>**Study grouping:** parallel group<br><br>**Duration of intervention:** 4 months<br><br>**Duration of follow-up:** 6 months<br><br>**Washout or placebo run-in period:** no |
| Participants | **Baseline characteristics**<br><br>*G biloba* + Mecobalamin<br><br>• Number randomized: 47<br>• MMSE (mean, SD): nil<br>• Age (mean, SD): 63.06, 5.28<br>• % female: 40.4%<br><br>Mecobalamin<br><br>• Number randomized: 47<br>• MMSE (mean, SD): nil<br>• Age (mean, SD): 62.95, 5.39<br>• % female: 42.6%<br><br>**Total number randomized:** 94<br><br>**Inclusion criteria**<br><br>• Clinical diagnostic criteria of CSVCL<br>• MMSE score < 27 points<br>• Informed consent<br>• Complete clinical data and no drug contraindications<br><br>**Exclusion criteria**<br><br>• Cognitive impairment not caused by CSVD<br>• Other brain organic diseases<br>• Heart, liver, kidney, and other important organ dysfunction<br>• Mental abnormalities or cognitive impairments due to other reasons<br>• Incomplete clinical data<br>• Allergy to the drugs used in this study<br><br>**Country:** China<br><br>**Setting:** inpatient<br><br>**Date recruitment began:** 2018<br><br>**Recruitment source/methods:** people with CSVCL admitted to the Ninth People's Hospital of Nanning, Guangxi from May 2018 to May 2019 were recruited.<br><br>**Diagnosis:** cognitive impairment caused by CSVD<br><br>**Diagnostic criteria:** clinical diagnostic criteria of cognitive impairment caused by CSVD |
| Interventions | **Intervention characteristics**<br><br>*G biloba* + Mecobalamin |


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**Qu 2020** *(Continued)*

| | |
|---|---|
| | • On the basis of the control group, oral administration of Ginkgo leaf capsules (Shanghai Xinyi Paluda Pharmaceutical Co, Ltd, Z20010169, specifications: each tablet contains 9.6 mg of total flavonol glycosides and 2.4 mg of terpene lactones) 3 times/day, 1 tablet/time, for 16 weeks. Dose *G biloba* NR + Mecobalamin 1.5 mg/day.<br><br>Mecobalamin<br><br>• Description of intervention from report (both the product and administration): oral treatment with methylcobalamin tablets (Chenxin Pharmaceutical Co, Ltd, Sinopharm Zhun H20051425, specifications: 0.5 mg/tablet), 3 times/day, 1 tablet/time, for 16 weeks. Dose 1.5 mg/day. |
| Outcomes | **Outcomes collected**<br><br>• ADAS-Cog<br>• MoCA<br>• Curative effect<br>• Homocysteine and β-amyloid 1-40 |
| Notes | **Sponsorship source:** Nanning Scientific Research and Technology Development Plan Project (No.: 20183042-4)<br><br>**Trial registration number(s)**: none reported |

***Risk of bias***

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Random sequence generation (selection bias) | Low risk | Random number table. |
| Allocation concealment (selection bias) | Unclear risk | Not reported. |
| Blinding of participants and personnel (performance bias)<br>All outcomes | Unclear risk | Not reported. |
| Blinding of outcome assessment (detection bias)<br>All outcomes | Unclear risk | Not reported. |
| Incomplete outcome data (attrition bias)<br>All outcomes | Low risk | No loss to follow-up. |
| Selective reporting (reporting bias) | Unclear risk | No trial registration or protocol available. |
| Other bias | Low risk | No other apparent risks of bias. |

**Rai 1991**

***Study characteristics***

| | |
|---|---|
| Methods | **Study design:** RCT |


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**Rai 1991** *(Continued)*

**Study grouping:** parallel group

**Duration of intervention:** 24 weeks

**Duration of follow-up:** 24 weeks

**Washout or placebo run-in period:** no

| | |
|---|---|
| Participants | **Baseline characteristics**<br><br>G biloba<br><br>• Number randomized: 12<br>• MMSE (mean, SD): 26.8<br>• Age (mean, SD): 73.4, 7.25<br>• % female: 67%<br><br>Placebo<br><br>• Number randomized: 15<br>• MMSE (mean, SD): 24.3<br>• Age (mean, SD): 78.3, 5.93<br>• % female: 80%<br><br>**Total number randomized:** 31 (baseline data not provided for all randomized participants)<br><br>**Inclusion criteria**<br><br>• Age ≥ 50 years<br>• Mild to moderate memory impairment of organic origin as classified by NINCDS-ADRDA for ≥ 3 months<br><br>**Exclusion criteria**<br><br>• Memory problems due to physical illness<br>• Metabolic, endocrine, nutritional, neurological, or cardiac disease<br>• Previous functional disorder such as depression<br>• Evidence of renal or hepatic failure<br>• Presence of severe cardiac disease<br>• Myocardial infarction within the preceding 6 months<br>• Poorly controlled diabetes, epilepsy or malignant disease<br>• Use of drugs acting on cerebral metabolism or cerebral blood flow<br>• History of drug or alcohol abuse<br><br>**Country:** UK<br><br>**Setting:** outpatient<br><br>**Date recruitment began:** NR (prior to 1991)<br><br>**Recruitment methods:** NR<br><br>**Diagnosis:** mild to moderate memory impairment of organic origin<br><br>**Diagnostic criteria:** NINCDS-ADRDA |
| Interventions | **Intervention characteristics**<br><br>*G biloba*<br><br>• 40 mg *G biloba* extract ('Tanakan') tablets taken 3 times daily as appropriate. This standardized extract contained 24% flavonoid glycosides and 6% terpenes. |


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**Rai 1991** *(Continued)*

| | |
|---|---|
| | Placebo<br>• Identical placebo tablets 3 times daily as appropriate<br>Participants not allowed to take drugs acting on cerebral metabolism or cerebral blood flow. |
| Outcomes | **Outcomes collected**<br>• MMSE<br>• Kendrick Battery<br>• Digital recall task<br>• Classification task<br>• Latency of auditory event related potential<br>• EEG |
| Notes | **Sponsorship source:** none reported<br>**Trial registration number(s)**: none reported<br>**Note:** SDs are not given, and number of participants with data at endpoints is unclear. No outcome data relevant to this review could be extracted from the study. |

***Risk of bias***

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Random sequence generation (selection bias) | Low risk | "Treatment was allocated to the study numbers according to a computer generated randomization code". |
| Allocation concealment (selection bias) | Unclear risk | "Patients were allocated study numbers sequentially in the order in which they entered the study". Insufficient information about allocation process. |
| Blinding of participants and personnel (performance bias)<br>All outcomes | Low risk | Described as double-blind using identical placebo, and no reason to believe that participants or personnel were unblinded. |
| Blinding of outcome assessment (detection bias)<br>All outcomes | Low risk | Double-blind study with no reason to believe that outcome assessors were unblinded. |
| Incomplete outcome data (attrition bias)<br>All outcomes | Unclear risk | Numbers lost to follow-up were clearly described for each group. Reasons were given for active treatment group but not placebo group. When participants completed at least 12 weeks, they were included in the analysis. Data for 27/31 participants was included. Data omitted for 3 participants from ginkgo group and 1 from placebo group. |
| Selective reporting (reporting bias) | Unclear risk | Study protocol not available. Insufficient information available to permit a judgment. |
| Other bias | Low risk | No other apparent sources of bias. |

**Schneider 2005**

***Study characteristics***

| | |
|---|---|
| Methods | **Study design:** RCT |


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**Schneider 2005** *(Continued)*

**Study grouping:** parallel group

**Duration of intervention:** 26 weeks

**Duration of follow-up:** 26 weeks

**Washout or placebo run-in period:** "Anticholinergic drugs had to be discontinued at least 4 weeks prior to randomization and were not allowed during the study."

Participants

**Baseline characteristics**

EGb 761 120 mg

- Number randomized: 169
- MMSE (mean, SD): 18.2, 4.1
- Age (mean, SD): 78.6, 7.0
- % female: 50%

EGb 761 240 mg

- Number randomized: 170
- MMSE (mean, SD): 17.9, 4.0
- Age (mean, SD): 78.1, 7.0
- % female: 56%

Placebo

- Number randomized: 174
- MMSE (mean, SD): 18.2, 4.1
- Age (mean, SD): 77.5, 7.4
- % female: 52%

**Total number randomized:** 513

**Inclusion criteria:** "Outpatients were included if they were at least 60 years of age and met each of the following criteria: a diagnosis of Dementia of the Alzheimer's Type (Diagnostic and Statistical Manual of Mental Disorders, fourth edition); probable Alzheimer's disease (National Institute of Neurological and Communicative Disorders and Stroke and Alzheimer's Disease and Related Disorders Association, NINCDS/ADRDA); duration of dementia symptoms at least 6 months; Modified Hachinski Ischemic Score less than 4; and a Mini-Mental State Examination (MMSE) score of 10 to 24." "At inclusion, a CT or MRI scan performed within 1 year of study entry, had to be available, consistent with a diagnosis of Alzheimer's disease, and not having infarctions or other focal lesions."

**Exclusion criteria:** "Patients were excluded from the trial if they had any other type of dementia or central nervous system disorder; a recent history of major depression, current major depression or clinically significant depression as defined by a total score equal to or above 15 or an item score above 2 in item 1 (depressed mood) on the Hamilton Rating Scale for Depression (HAMD); any other current psychiatric disorder; severe, uncontrolled cardiovascular disease; severe renal or hepatic dysfunction; insufficiently controlled insulin-dependent diabetes mellitus; significant deficiency of vitamin B12 or folic acid; abnormal thyroid function; any active malignant disease; peptic ulcer or any other gastrointestinal disorder associated with impairment of drug absorption; or insufficiently corrected loss of vision or hearing." "Patients who had taken antidementia drugs, including cholinesterase inhibitors or cognition-enhancing substances within 6 weeks before planned randomization were excluded from study participation." "patients who had been receiving psychoactive drugs during the three months preceding randomization were excluded as well."

**Country:** USA

**Setting:** outpatient

**Date recruitment began:** 1999


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**Schneider 2005** *(Continued)*

| | |
|---|---|
| | **Recruitment methods:** "From March 1999 to May 2000, 701 patients were screened by 44 centers in the United States...."<br><br>**Diagnosis:** AD<br><br>**Diagnostic criteria:** DSM-IV, NINCDS-ADRDA |
| Interventions | **Intervention characteristics**<br><br>EGb 761 120 mg<br><br>• "The GbE used was Ginkgo special extract EGb 761® (manufacturer:Dr. Willmar Schwabe Pharmaceuticals, Karlsruhe,Germany). The preparation was standardized to contain 22-27% of flavonoids, 5-7% terpene lactones (ginkgolides, bilobalide) and no more than 5 ppm alkylphenols (ginkgolicacids)." (60 mg twice daily) [Citation provided which could not be located: DeFeudis FV. 'Ginkgo biloba extract (EGb 761). From chemistry to the clinic'. Ullstein Medical, Wiesbaden, p. 7-15 (1998)]<br><br>EGb 761 240 mg<br><br>• "The GbE used was Ginkgo special extract EGb 761® (manufacturer:Dr. Willmar Schwabe Pharmaceuticals, Karlsruhe,Germany). The preparation was standardized to contain 22-27% of flavonoids, 5-7% terpene lactones (ginkgolides, bilobalide) and no more than 5 ppm alkylphenols (ginkgolicacids)." (120 mg twice daily)<br><br>Placebo<br><br>• "identically appearing placebo"<br><br>Antidementia drugs (including cholinesterase inhibitors or cognition-enhancing substances) and psychoactive drugs were prohibited. |
| Outcomes | **Outcomes collected**<br><br>• ADAS-cog<br>• Clinical Global Impression of Change, a Clinicians Interview-Based Impression of Change with caregivers input (a CIBIC+) as devised by the Alzheimer's Disease Cooperative Study (ADCS-CGIC)<br>• Progressive Deterioration Scale (PDS)<br>• Geriatric Evaluation by Relative's Rating Instrument (GERRI)<br>• ADAS-noncognitive subscale<br>• HAM-D<br>• 11-point box scales for the rating of presence and severity of dizziness and tinnitus (Concomitant Symptoms Scale) were secondary outcomes. |
| Notes | **Sponsorship source:** Dr Willmar Schwabe GmbH<br><br>**Trial registration number(s)**: none reported |

***Risk of bias***

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Random sequence generation (selection bias) | Low risk | "Randomization in blocks of six was prepared at Schwabe Pharmaceuticals with a validated computer program (RCODE version 4.9) [52]." |
| Allocation concealment (selection bias) | Low risk | "the investigators as well as the whole study team remained blinded with respect to the treatment assignment until final lock of the database." Randomization prepared offsite and it is likely that the investigators did not know treatment assignments at the time of allocation. |


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**Schneider 2005** *(Continued)*

| | | |
|---|---|---|
| Blinding of participants and personnel (performance bias)<br>All outcomes | Low risk | The study drug and identically appearing placebo were packed and labeled according to the randomization list, and the investigators as well as the whole study team remained blinded with respect to the treatment assignment until final lock of the database. |
| Blinding of outcome assessment (detection bias)<br>All outcomes | Low risk | Placebo-controlled trial. "the investigators as well as the whole study team remained blinded with respect to the treatment assignment until final lock of the database." |
| Incomplete outcome data (attrition bias)<br>All outcomes | Unclear risk | "principle including all randomized patients. The applied imputation techniques for missing values included the last-observation-carried-forward (LOCF) method and various alternative strategies to assess the robustness of the results. An observed-cases analysis was also".<br><br>Reasons for dropout varied between groups (Figure 1). Multiple approaches to missing data were used, including LOCF and "various alternative strategies". |
| Selective reporting (reporting bias) | Unclear risk | Study protocol not available; insufficient information available to permit a judgment. |
| Other bias | Low risk | No other apparent source of bias. |

**Shi 2017**

| | |
|---|---|
| ***Study characteristics*** | |
| Methods | **Study design:** RCT<br><br>**Study grouping:** parallel group<br><br>**Duration of intervention:** 24 weeks<br><br>**Duration of follow-up:** 24 weeks<br><br>**Washout or placebo run-in period:** none reported |
| Participants | **Baseline characteristics**<br><br>*G biloba* + conventional medications<br><br>• Number randomized: 30<br>• MMSE (mean, SD): NR<br>• Age (mean, SD): 75.0, 5.3<br>• % female: 40<br><br>Conventional medications<br><br>• Number randomized: 30<br>• MMSE (mean, SD): NR<br>• Age (mean, SD): 74.0, 5.8<br>• % female: 43.3<br><br>**Total number randomized:** 60<br><br>**Inclusion criteria**<br><br>• VCI consistent with diagnostic criteria for vascular cognitive disorder (a VASCOG statement) by CT/ MRI |


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**Shi 2017** *(Continued)*

- VCI matched with standard of VCIND from *Guidelines for diagnosis and treatment of vascular cognitive impairment* (Chinese Medical Association publishing in 2011): having capacity to do daily activities; slightly impaired to do complex daily activities; not aligned with the criteria of dementia
- Memory and others cognitive impairment over 3 months, validated by participants or family members
- Primary school education or above, no aphasia, no mental abnormality, ability to cooperate with all kinds of scales
- No organic lesions in important organs

**Exclusion criteria**

- Cognitive impairment caused by exact non-vascular factors
- Severe aphasia, physical disability, or any other factor that may prevent the completion of neuropsychological tests
- History of mental illness, or depression and other mental diseases a short time after stroke
- Other serious systemic diseases
- HAM-D score > 17 or schizophrenia
- New stroke, hereditary or inflammatory small vessel disease within 3 months after enrollment
- Use of drugs that may affect cognitive function, including sedatives, antianxiety drugs, hypnotics, Nootropics, and choline mimics

**Country:** China

**Setting:** inpatient

**Date recruitment began:** 2014

**Recruitment methods:** people with VCIND in Affiliated Hospital of Nanjing University of traditional Chinese Medicine from July 2013 to September 2015

**Diagnosis:** VCIND

**Diagnostic criteria**

- VCI was consistent with diagnostic criteria for vascular cognitive disorder (a VASCOG statement) by CT/MRI.
- VCI matched standard of VCIND from *Guidelines for diagnosis and treatment of vascular cognitive impairment* (Chinese Medical Association publishing in 2011).

| | |
|---|---|
| Interventions | **Intervention characteristics**<br><br>*G biloba* + conventional medications<br><br>• In addition to receiving routine treatment, participants had *G biloba* leaves (Tanakang), 3 times a day, 40 mg each time (120 mg/day).<br><br>Conventional medications<br><br>• Routine treatment of cerebrovascular diseases, including antiplatelet, lipid-lowering, and nerve nutrition<br><br>Use of sedatives, antianxiety drugs, hypnotics, Nootropics, and choline mimics was not allowed. |
| Outcomes | **Outcomes collected**<br><br>• MoCA<br>• Subscales for memory, executive function, and other subscales |
| Notes | **Sponsorship source:** none reported<br><br>**Trial registration number(s)**: none reported |


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**Shi 2017** *(Continued)*

Shi YF is the primary author of the cited Master's Thesis.

***Risk of bias***

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Random sequence generation (selection bias) | Low risk | According to the random number table method, participants were divided into a control group and an experimental group, with 30 in each group. |
| Allocation concealment (selection bias) | Unclear risk | Process of allocation not described. |
| Blinding of participants and personnel (performance bias)<br>All outcomes | Unclear risk | Blinding not described. |
| Blinding of outcome assessment (detection bias)<br>All outcomes | Unclear risk | Blinding of outcome assessment not described. |
| Incomplete outcome data (attrition bias)<br>All outcomes | Low risk | No apparent loss to follow-up. |
| Selective reporting (reporting bias) | Unclear risk | There was no registration or trial protocol. |
| Other bias | Low risk | No other apparent sources of bias. |

**Tan 2016**

***Study characteristics***

Methods

**Study design:** RCT

**Study grouping:** parallel group

**Duration of intervention:** 10 weeks

**Duration of follow-up:** 6 months

**Wash out or placebo run-in period:** none reported

Participants

**Baseline characteristics**

*G biloba*

- Number randomized: 40
- MMSE (mean, SD): 13.8, 2.5
- Age (mean, SD): 62.1, 5.2
- % female: 35

Nimodipine

- Number randomized: 40
- MMSE (mean, SD): 13.4, 2.6
- Age (mean, SD): 62.8, 5.4


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**Tan 2016** *(Continued)*

- % female: 30

Compound xueshuantong capsule

- Number randomized: 40
- MMSE (mean, SD): 13.5, 2.8
- Age (mean, SD): 63.1, 5.1
- % female: 32.5

**Total number randomized:** 120

**Inclusion criteria**

- Voluntary participation in study and informed consent
- Development of cognitive impairment within 6 months of stroke
- No dementia

**Exclusion criteria**

- Allergy to research medications
- Cognitive dysfunction caused by medications, systematic diseases, and non-vascular factors
- No cerebrovascular disease on imaging examination
- Severe liver and kidney dysfunction, as well as cardiac insufficiency or secondary diseases
- Elderly people with depression, hearing impairment, visual impairment, and severe mental illness

**Country:** China

**Setting:** hospital inpatient

**Date recruitment began:** 2014

**Recruitment source/methods:** not reported

**Diagnosis:** VCIND

**Diagnostic criteria:** CT and MRI

Interventions

**Intervention characteristics**

*G biloba*

- Ginkgo leaf dripping pills (specification: 60 mg/capsule, lot number: Z20040071) produced by Zhejiang Wanbang Pharmaceutical, 5 capsules/time, 3 times/day (total dose calculated as 900 mg/day)

Nimodipine

- Nimodipine (specification: 20 mg/tablet, lot number: H44025019) from Guangdong Huanan Pharmaceutical Production Co, Ltd, 1 tablet/time, 3 times/day (total dose calculated as 60 mg/day)

Compound xueshuantong capsule

- Compound thrombosis tablets (specification drug: 0.4 g/pill lot: Z20050188) produced by Yangzhou Chinese Pharmaceutical Co, Ltd, 2 pills/time, 3 times/day (total dose calculated as 2.4 g/day)

Outcomes

**Outcomes collected**

- High-sensitivity C-reactive protein (hs-CRP; mg/L)
- Blood flow velocity (anterior cerebral artery, middle cerebral artery, posterior cerebral artery; vertebral artery, and basilar artery; cm/s)
- MoCA
- MMSE
- ADLs


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**Tan 2016** *(Continued)*

| | |
|---|---|
| Notes | **Sponsorship source:** none reported<br>**Trial registration number(s)**: none reported |

***Risk of bias***

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Random sequence generation (selection bias) | Low risk | According to the random number table method, they were divided into three groups, A, B, and C, with 40 cases in each group. |
| Allocation concealment (selection bias) | Unclear risk | Allocation process not reported. |
| Blinding of participants and personnel (performance bias)<br>All outcomes | Unclear risk | Blinding was not reported, but it was probably a participant-blinded study. |
| Blinding of outcome assessment (detection bias)<br>All outcomes | Unclear risk | Blinding of outcome assessment not reported. |
| Incomplete outcome data (attrition bias)<br>All outcomes | Low risk | There was no apparent loss to follow-up in the study. |
| Selective reporting (reporting bias) | Unclear risk | There was no protocol. |
| Other bias | Low risk | No other apparent source of bias. |

**Tian 2019**

***Study characteristics***

| | |
|---|---|
| Methods | **Study design:** RCT<br>**Study grouping:** parallel group<br>**Duration of intervention:** 52 weeks<br>**Duration of follow-up:** 52 weeks<br>**Washout or placebo run-in period:** 2-week placebo run-in period |
| Participants | **Baseline characteristics**<br>Ginkgo<br>• Number randomized: 104<br>• MMSE (mean, SD): 27.74, 1.47<br>• Age (mean, SD): 64.43, 7.72<br>• % female: 58%<br>Qinggongshoutao<br>• Number randomized: 174 |


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**Tian 2019** *(Continued)*

- MMSE (mean, SD): 27.60, 1.41
- Age (mean, SD): 63.17, 6.59
- % female: 49%

Placebo

- Number randomized: 70
- MMSE (mean, SD): 27.51, 1.59
- Age (mean, SD): 64.15, 7.25
- % female: 47%

**Total number randomized:** 350 (baseline data not provided for all randomized participants)

**Inclusion criteria:** "(1) memory complaints that were corroborated by an informant; (2) abnormal memory function as assessed by the Chinese version of the Adult Memory and Information Processing Battery Logical Memory Delayed Story Recall (AMIPB-DSR) subtest score of <15.5 for age (age 50-64 years < 15.5, 65-74 years ,<12.5, and over 75 years,<10) ; (3) normal general cognitive function as determined by a clinician's judgment based on a structured interview with the patients, a Mini–Mental State Examination (MMSE) score of 24 to30 for education, and Clinical Dementia Rating (CDR) Scale score 5=0.5, with the memory domain = 0.5 or 1, and no other domain greater than 1; (4) no or minimal impairments in activities of daily living as determined by a clinical interview with the patient and an informant, a score of 38 to 52 on the Alzheimer's Disease Cooperative Study–Activities of Daily Living Scale for patients with MCI (ADCS-ADL-MCI-24 items); (5) absence of dementia judged by an experienced clinician, including no impairment of cognitive function that would meet the core clinical criteria of the National Institute on Aging–Alzheimer's Association workgroups; (6) the patients were required to have adequate vision and hearing to participate in the study assessments; (7) all patients and legal guardians should provide written consent; and (8) deficiency of kidney essence to be confirmed using the kidney deficiency scale from the pattern elements scale >=7 points."

**Exclusion criteria:** "(1) nonamnestic MCI; (2) meeting the diagnostic criteria for dementia; (3) cognitive impairment resulting from conditions, such as acute cerebral trauma, cerebral damage due to a lack of oxygen, epilepsy vitamin deficiency, infections such as meningitis or AIDS, significant endocrine or metabolic disease, mental retardation, a brain tumor, or drug abuse or alcohol abuse; (4) having significant psychiatric disease, depression, the Hamilton Depression Scale.12; (5) magnetic resonance imaging scan having showed cerebral infarction, hemorrhage or focal lesions, and infections within 12 months; (6) accompanying poorly controlled diabetes or hypertension or severe arrhythmias; (7) having suffered from heart infarction within 3 months; (8) severe asthma or chronic obstructive pulmonary disease; (9) severe indigestion; (10) gastrointestinal tract obstruction or gastroduodenal ulcer; (11) use of cholinesterase inhibitors or memantine within 1 month; (12) history of hypersensitivity to the treatment drugs; (13) use of concomitant drugs with the potential to interfere with cognition, such as anticholinergics, anticonvulsants, antiparkinsonian agents, stimulants, cholinergic agents, antipsychotics, or antidepressants, or anxiolytics; (14) administration of other investigational drugs; (15) severe impairment of the liver or kidney function; and (16) vegetarians or contraindications for animal innards."

**Country:** China

**Setting:** outpatient

**Date recruitment began:** 2015

**Recruitment methods:** not described

**Diagnosis:** amnestic mild cognitive impairment (aMCI)

**Diagnostic criteria:** memory complaints and abnormal memory function on the Adult Memory and Information Processing Battery Logical Memory Delayed Story Recall (AMIPB-DSR) together with MMSE ≥ 24 and normal general cognitive function and ADL.

| | |
|---|---|
| Interventions | **Intervention characteristics**<br><br>Ginkgo |


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**Tian 2019** *(Continued)*

- EGb761 tablet (Ginaton; 80 mg per time, twice daily) and Qinggongshoutao (QGST) placebo (7 g per time, twice daily). EGb761 was supplied by Germany's Dr Weimar Shu Pei Pharmaceutical Factory (branch number: 5890913), and placebo for QGST (branch number: 150101) was supplied by Tianjin Zhongxin Pharmaceutical Group Co, Ltd. To preserve blinding, the placebo had an identical taste and appearance to the drug.

Qinggongshoutao

- 1 QGST pill (7 g per time, twice daily) and EGb761 placebo (2 tablets per time, twice daily). QGST was supplied by Tianjin Zhongxin Pharmaceutical Group Co, Ltd. Darentang Pharmaceutical Factory (branch number: 141001). Placebos for EGb761 (branch number: 5890915) were supplied by Tianjin Zhongxin Pharmaceutical GroupCo, Ltd. The active ingredients of QGST included Ginseng (Renshen in Chinese), Radix Asparagi (Tiandong in Chinese), Radix Ophiopogonis (Maidong in Chinese), Fructus Lyczz (Gouqizi in Chinese), Radux Rehmanniae (Dihuang in Chinese), Radix Angelicae Sinensis (Danggui in Chinese), Alpinia Oxyphylla Miq (Yizhiren in Chinese), Semen Ziziphi Spinosae (Suanzaoren in Chinese), and lignumdistraction (Fenxinmu in Chinese). The detailed quality control method for Chinese medicinal preparation of QGST was presented in a China Patent File (CN102048990B; see https://patents.google.com/patent/CN102048990B/en).

Placebo

- QGST placebo pill (7 g per time, twice daily) and EGb761 placebo (2 tablets per time, twice daily). Both placebos for EGb761 (branch number: 5890915) and QGST (branch number: 150101) were supplied by Tianjin Zhongxin Pharmaceutical Group Co, Ltd. To preserve blinding, the placebos of QGST and EGb761 had an identical taste and appearance to the matched drugs. Content of placebo NR.

Concomitant use of drugs such as anticholinergics, anticonvulsants, antiparkinsonian agents, stimulant, cholinergic agents, antipsychotics, antidepressants, or anxiolytics was not allowed.

Outcomes

**Outcomes collected**

- Rate of progression to possible or probable AD based on NIA-AA AD or CDR-GS score ≥ 1
- ADAS-cog
- MMSE
- AMIPD-DSR (Adult Memory and Information Processing Battery Logical Memory Delayed Story Recall, Chinese version)
- ADCS-ADL-MCI-24 (Alzheimer's Disease Cooperative Study – Activities of Daily Living Scale for patients with MCI)
- Clinical Global Impression of Change of Kidney Deficiency
- Change in the CDR – Sum of Boxes and the responder rate based on decrease of 4 or more points on ADAS-Cog

Notes

**Sponsorship source:** "The sponsor (Tianjin Zhongxin Pharmaceutical Group Co., Ltd. Darentang Pharmaceutical Factory) funded the trial and provided tested drugs and placebo." "The data collection was supported by a grant from the “111” project (No: B08006), National Natural Science Foundation of China, China [grant numbers 81473518 and 81573824], Capital Health Research and Development of Special, China [No: SF2016-4-4193], and Beijing Municipal Science and Technology Commission Foundation, China [No: Z151100003815021]."

**Trial registration number(s)**: NCT02982603

**Note:** the direction of changes in Table 2 was not consistent with the description in the text of improvement, and LSW emailed the contact author on 28 May 2021. He responded on 30 May 2021 that the changes were calculated by subtracting endpoint from baseline rather than by subtracting baseline from endpoint, and therefore the signs of the changes reflect this. The contact author also issued an erratum (DOI:10.1002/trc2.12266) correcting Table 2 data for the AMIPB-DSR.

***Risk of bias***

| Bias | Authors' judgement | Support for judgement |
|---|---|---|


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**Tian 2019** *(Continued)*

| | | |
|---|---|---|
| Random sequence generation (selection bias) | Low risk | The randomization was stratified by the center using SAS statistical software (version 9.13; SAS Institute Inc, Cary, NC, USA). Balanced randomization generated by SAS statistical software was carried out in 3 steps (in blocks of 10) by a statistician with no access to information on the participants or physicians. Participants were sequentially assigned to the lowest randomization number available at the time of each enrollment at each center. |
| Allocation concealment (selection bias) | Low risk | "Patients were sequentially assigned to the lowest randomization number available at the time of each enrollment at each center. The randomized code was generated in the randomization process and sealed in an envelope. Statisticians assigned the medication group according to the randomization code." |
| Blinding of participants and personnel (performance bias)<br>All outcomes | Low risk | Blinding was broken only if a participant's trial medication required specific emergency treatment. Once the blinding was broken, the participant was managed as off-trial. Participants, legal guardians, the study investigator, any other personnel involved in the study, and the investigating staff of the sponsor were blinded until all participants completed the study and analysis was completed. |
| Blinding of outcome assessment (detection bias)<br>All outcomes | Low risk | Participants, legal guardians, the study investigator, any other personnel involved in the study, and the investigating staff of the sponsor were blinded until all participants completed the study and analysis was completed. |
| Incomplete outcome data (attrition bias)<br>All outcomes | Low risk | 165 participants in the QGST group, 98 in the EGb761 group, and 69 in the placebo group completed the trial and were included in the PPS. Nine participants in the QGST group discontinued research (5 withdrew informed consent, 1 discontinued because of AEs, 2 were lost to follow-up, and 1 discontinued with unspecified reason); 6 participants in the EGb761 group discontinued the study (2 withdrew informed consent, 1 violated the protocol, and 3 were lost to follow-up); 1 participant in the placebo group discontinued the study after withdrawing informed consent. There was no statistically significant difference between groups in the number of dropouts (P = 0.362). Numbers discontinued were fairly low, and reasons were given which did not appear to differ greatly across groups. How many missing data there were and how they were handled was somewhat unclear. |
| Selective reporting (reporting bias) | Unclear risk | Trial registration available and outcomes are consistent, but the registration was not prior to completion of at least part of the study. Registration was first submitted on 30 November 2016, at which point the first participants enrolled would have been followed for over 1 year, although additional participants were still being enrolled. "A total of 459 patients were screened, and 350 were randomized between May 2015 and October 2017." |
| Other bias | Low risk | Table 2 data for AMIPB-DSR and ACDS-ADL-MCI-24 are identical, but an erratum reporting the correct data was published. |

**van Dongen 2000**

| ***Study characteristics*** | |
|---|---|
| Methods | **Study design:** RCT<br><br>**Study grouping:** parallel group<br><br>**Duration of intervention:** 24 weeks (at 12 weeks, the placebo group continued on placebo while the ginkgo groups were randomized to either continue on ginkgo or take placebo for the remaining 12 weeks) |


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**van Dongen 2000** *(Continued)*

**Duration of follow-up:** 24 weeks

**Washout or placebo run-in period:** "3-week placebo run-in period"

Participants

**Baseline characteristics**

*G biloba* 240 mg

- Number randomized: 82
- MMSE (mean, SD): 18.4, 4.2
- Age (mean, SD): 83.3, 5.3
- % female: 85%

*G biloba* 160 mg

- Number randomized: 84
- MMSE (mean, SD): 18.3, 4.8
- Age (mean, SD): 82.8, 4.9
- % female: 85%

Placebo

- Number randomized: 48
- MMSE (mean, SD): 18.5, 4.5
- Age (mean, SD): 82.6, 5.7
- % female: 81%

**Total number randomized:** 214

**Inclusion criteria**

- Mild to moderate dementia (defined as score 8–23 on the SKT) or age-associated memory impairment (defined as score 8–23 on the SKT) without dementia and with subjective memory complaints (score 12 or greater on the Memory Assessment Clinics Questionnaire)
- Age 50 years
- Score < 11 on the 15-item version of the Geriatric Depression Scale
- Premorbid IQ > 80

**Exclusion criteria**

- Serious comorbidity (especially non-treatable potential underlying causes of dementia)
- Conditions that would interfere with trial conduct (e.g. various neurologic disorders, brain traumata, tumors, severe infectious diseases, absorption disorders)
- Impermissible cointerventions (especially drugs with a debilitating influence on cognitive functioning or with a claimed nootropic action [e.g. antipsychotic drugs, antiparkinson medication, neuroleptics, cholinergic therapy, antidepressants, and vasoactive drugs])

**Country:** the Netherlands

**Setting:** nursing homes

**Date recruitment began:** 1994

**Recruitment methods:** "39 old peoples' homes participated in the trial. These homes housed 4459 residents, 781 (18%) of whom were preselected by the nursing staff for presumed cognitive problems."

**Diagnosis:** Alzheimer dementia, vascular dementia, or a mixed type of dementia; or age-associated memory impairment (AAMI)

**Diagnostic criteria:** uncomplicated dementia (according to the DSM-III-R and ICD-10 criteria) or AAMI (according to Crook et al criteria)


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**van Dongen 2000** *(Continued)*

| | |
|---|---|
| Interventions | **Intervention characteristics**<br><br>EGb 761 240 mg<br><br>• "The verum preparation in our trial consisted of round film-coated tablets, 10 mm in diameter, containing 120 mg of the dry extract EGb 761® from the leaves of the *G biloba* tree (35-67:1 ratio of raw plant material to extract), adjusted to 24% Ginkgo flavonol glycosides and 6% terpene trilactones (ginkgolide, bilobalide). Ginkgolic acids were kept below 5 ppm. The tablets were built up from a matrix consisting of lactose, silica, cellulose, maize starch, sodium carboxymethylcellulose, talc, and magnesium stearate, in which the brown extract was embedded. The yellow film coating consisted of hydroxypropyl methylcellulose, polyethylene glycol, titanium dioxide, iron (II) oxide, and camauba wax." "The Ginkgo and the placebo tablets were administered orally in a fixed dose. The tablets had to be swallowed with water or another beverage, not bitten or crushed. During the run-in period each potential participant received 2x 1 placebo tablet each day (morning and evening, during the meals)." "Subjects allocated to verum group 2 (240 mg of Ginkgo per day) swallowed 2 times 1 tablet EGb 761 (120 mg) each day (morning and evening, during the meals) during the first intervention phase, and 2 times 1 tablet EGb 761 (120mg) or 2 times 1 placebo tablet during the second intervention phase." "The study participants consumed their daily dose at fixed times (morning and evening, during the meal), mostly under direct supervision of a nursing staff member. Packaging and labelling of the study medication were per formed in accordance with the requirements of the Dutch Law of Medicine Supply and the guidelines for Good Clinical Practice (GCP)."<br><br>EGb 761 160 mg<br><br>• "The verum preparation in our trial consisted of round film-coated tablets, 10 mm in diameter, containing 80 mg of the dry extract EGb 761® from the leaves of the *G biloba* tree (35-67:1 ratio of raw plant material to extract), adjusted to 24% Ginkgo flavonol glycosides and 6% terpene trilactones (ginkgolide, bilobalide). Ginkgolic acids were kept below 5 ppm. The tablets were built up from a matrix consisting of lactose, silica, cellulose, maize starch, sodium carboxymethylcellulose, talc, and magnesium stearate, in which the brown extract was embedded. The yellow film coating consisted of hydroxypropyl methylcellulose, polyethylene glycol, titanium dioxide, iron (II) oxide, and camauba wax." "The Ginkgo and the placebo tablets were administered orally in a fixed dose. The tablets had to be swallowed with water or another beverage, not bitten or crushed. During the run-in period each potential participant received 2x 1 placebo tablet each day (morning and evening, during the meals). Subjects allocated to verum group 1 (160 mg of Ginkgo per day) swallowed 2 times 1 tablet EGb 761 (80 mg) each day (morning and evening, during the meals) during the first intervention phase, and 2 times 1 tablet EGb 761 (80 mg) or 2 times 1 placebo tablet during the second intervention phase." "The study participants consumed their daily dose at fixed times (morning and evening, during the meal), mostly under direct supervision of a nursing staff member. Packaging and labelling of the study medication were per formed in accordance with the requirements of the Dutch Law of Medicine Supply and the guidelines for Good Clinical Practice (GCP)<br><br>Placebo<br><br>• "The placebo treatment consisted of two film-coated tablets per day, but these contained no Ginkgo extract. We made special efforts to check the comparability of the verum and the placebotablets with respect to appearance, color, smell, taste, granularity, and solubility. To mimic the typical taste of ginkgo, 2 mg of quinine hydrochloride was added to the placebo tablets. The tablets were built up from a matrix consisting of lactose, silica, cellulose, maize starch, sodium carboxymethylcellulose, talc, and magnesium stearate. The yellow film coating consisted of hydroxypropyl methylcellulose, polyethylene glycol, titanium dioxide, iron (II) oxide, and camauba wax." "The placebo preparation consisted also of film-coated tablets, which contained no Gingko biloba extract at all (0 mg). Aiming at a pure intervention contrast, much effort was paid to develop a placebo formula that matched the verum formula perfectly with regard to all relevant aspects: shape, size, surface colour and texture, weight, taste on licking and chewing, internal colour and structure, smell, specific gravity, and also packaging and labelling. Comparability with regard to shape, size, surface colouration and texture, weight, taste on licking, and - to an acceptable approximation - smell and specific gravity, were ensured by pressing placebo tablets of the same shape and size from the same matrix, and by covering them with an identical film coating. To ensure that the internal colour and texture also matched, caramel and brown iron oxide were added to the tablet matrix. This resulted in a perfect match in colour and internal texture, so that any distinction between the placebo formulation and the EGb 761 |


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**van Dongen 2000** *(Continued)*

tablets could be ruled out, even after breaking or crushing. To mimic the pronounced bitter taste that is a characteristic of the Ginkgo extract, 2 mg of quinine hydrochloride were added to each tablet, after addition of a bitter principle derived from a gentian extract and of quinine sulfate to placebo test batches had failed to yield satisfying results. The bitter taste of these placebo tablets was found to be equally intense and unpleasant as that of the EGb 761 tablets, before the start of the trial and in a further test 3 1/2 years later, after the end of the study. Breaking, crushing and grinding did not reveal any differences in physical characteristics between the Ginkgo and placebo tablets. However, repeated tests showed that the initially placebo tablets swelled and completely disintegrated within one minute of being immersed in water, whereas the EGb 761 tablets, owing to the lipophilic components of the Ginkgo extract, swelled slowly and only began to disintegrate after about 11 minutes. After addition of hydrogenated castor oil, a common excipient in tablet manufacture, the disintegration time of the placebo tablets was sufficiently prolonged to prevent any distinction from the EGb 761 tablets. Caramel, brown iron oxide and hydrogenated castor oil were added only to the placebo tablets, not to the EGb 761 tablets. These substances can, however, be regarded as pharmacologically inactive. By contrast, quinine, which was added to the placebo tablets only, to avoid any risk of interactions with the active substance, is in no way pharmacologically inert. We believed, however, that the low dosage applied would preclude any pharmacological effect that is similar or counteracts to the Ginkgo effect. In the treatment of tropical malaria the recommended daily dose for adults is 1950 mg quinine sulfate, which is more than 450 times the daily dose in our trial (4 mg). Two placebo tablets contain even less quinine than half a glass of typical tonic water, a popular drink with a content of some 52 mg per litre. The Ginkgo and the placebo tablets were administered orally in a fixed dose. The tablets had to be swallowed with water or another beverage, not bitten or crushed. During the run-in period each potential participant received 2x 1 placebo tablet each day (morning and evening, during the meals)." "Those subjects allocated to the placebo group (0 mg of Ginkgo per day) received 2 times 1 placebo tablet each day (morning and evening, during the meals), during both the first and the second intervention phase." "The study participants consumed their daily dose at fixed times (morning and evening, during the meal), mostly under direct supervision of a nursing staff member. Packaging and labelling of the study medication were per formed in accordance with the requirements of the Dutch Law of Medicine Supply and the guidelines for Good Clinical Practice (GCP)."

Concomitant use of drugs with potential cognitive effects (e.g. cholinergics) was not allowed.

Outcomes

**Outcomes collected**

- From 2003 paper
  - SKT
  - Clinical Global Impression, item 2
  - *Nürnberger Alters Inventar* – Instrumental Activities of Daily Living of Elderly People (NAI-NAA; self-assessed)
- Additional secondary outcomes from 2000 paper
  - ZN-G version of the digit span test
  - Word list
  - *Zahlen-Verbindungs-Test* version of the Trail Making Test
  - SCAG
  - Geriatric Depression Scale (GDS)
  - Self-perceived health status
  - Self-perceived memory status

Notes

**Sponsorship source:** Dr Willmar Schwabe GmbH

**Trial registration number(s)**: none reported

The study population was mixed dementia and MCI (age-associated memory impairment without dementia), and subgroup analyses by diagnosis were not done. As 70% of participants were diagnosed with age-associated memory impairment without dementia, we classified the study as one conducted in MCI.

***Risk of bias***


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**van Dongen 2000** *(Continued)*

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Random sequence generation (selection bias) | Low risk | "For the concealed randomization procedure, we used a computer-generated random sampling set. Random allocation was done within four predefined strata according to diagnostic subcategory (dementia versus age-associated memory impairment [AAMI]) and perceived memory change during the 6-month pretreatment phase (improvement or no change versus impairment). The first random allocation procedure (week 0) was conducted in blocks of five patients and with a 2:2:1 ratio (Ginkgo 240 mg/Ginkgo 160 mg/placebo). By the end of the study, this ratio was changed to 1:1:1 to add statistical power for analyzing the primary research question. The second randomization procedure (week 12) used blocks of two patients and a 1:1 (Ginkgo/placebo) allocation ratio." |
| Allocation concealment (selection bias) | Unclear risk | Although randomization was done centrally by computer, there is no mention of allocation processes. |
| Blinding of participants and personnel (performance bias)<br>All outcomes | Low risk | Placebo controlled study. Study authors stated, "Study participants, caregivers, outcome assessors, and data analysts were all blinded." |
| Blinding of outcome assessment (detection bias)<br>All outcomes | Low risk | Blinding of outcome assessment ensured, and it is unlikely that the blinding could have been broken. The study outcomes were assessed under blind conditions. To verify blindness, the participants themselves, the nursing staff, and the interviewers involved in outcome measurements were all invited to report their perceived study medication (ginkgo 240 mg, ginkgo 160 mg, placebo). These checks did not disclose any association between actual and perceived type of treatment either at 4 or 18 weeks after the start of the intervention. Given these observations, we can hardly imagine that the trial results were seriously distorted as a result of differential misclassification. |
| Incomplete outcome data (attrition bias)<br>All outcomes | Low risk | Dropout numbers and reasons are clearly reported. Slightly higher dropouts in high-dose group (11%), but may not be important. "Thirteen of the study participants dropped out during the first 12 weeks, leaving 201 patients to be randomized for the second 12-week intervention period. Another five subjects withdrew during the second intervention phase. The dropouts were distributed as follows: Ginkgo 240 mg: 9/82(11%); Ginkgo 160 mg: 5/84 (6%); placebo: 4/48 (8%). Reasons for attrition were death (n 8), hospital admission or caregiver request (n 3), serious concurrent illness(n 4), and deliberative avoidance of further cognitive testing (n 3)." |
| Selective reporting (reporting bias) | Unclear risk | Trial protocol unavailable. Insufficient information available to permit a judgment. |
| Other bias | Low risk | The study appears to be free of other sources of bias. |

**Vesper 1994**

| ***Study characteristics*** | |
|---|---|
| Methods | **Study design:** RCT<br>**Study grouping:** parallel group<br>**Duration of intervention:** 12 weeks |


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**Vesper 1994** *(Continued)*

**Duration of follow-up:** 12 weeks

**Washout or placebo run-in period:** "During the valuation period of 3 weeks before the start of the trial, and during the entire treatment period, the use of nootropic agents, psychopharmaceuticals, vasoactive or psychotropic substances was prohibited."

| | |
|---|---|
| Participants | **Baseline characteristics**<br><br>*G biloba*<br><br>• Number randomized: 42<br>• MMSE (mean, SD): 28.8 (median), 1.7<br>• Age (mean, SD): 62.7 (median), 4.5<br>• % female: 52%<br><br>Placebo<br><br>• Number randomized: 44<br>• MMSE (mean, SD): 28.5 (median), 1.7<br>• Age (mean, SD): 61.9 (median), 4.7<br>• % female: 57%<br><br>**Total number randomized:** 90 (baseline data not provided for all randomized participants)<br><br>**Inclusion criteria**<br><br>• Premorbid IQ of at least 80 (MWT-B)<br>• Distinct subjective troubles (> 19 points on the cognitive impairment scale)<br>• No pseudodementia (DPD-value > 2).<br><br>**Exclusion criteria**<br><br>• Cerebral/myocardial infarction in the prior 6 months<br>• Serious cardiac or rental insufficiency<br>• Other serious internal diseases<br>• Cardiac arrhythmia<br>• Stenoses of the supra-aortic vessels<br>• Psychoses<br>• Epilepsy<br>• Cerebral tumors<br>• Abuse of alcohol, drugs, and medical remedies<br>• Other diseases generally accepted as exclusion criteria in clinical tests<br><br>**Country:** Germany<br><br>**Setting:** outpatient<br><br>**Date recruitment began:** 1992<br><br>**Recruitment methods:** recruited from 11 centers (6 neurologists and psychiatrists, 4 general practitioners, 1 internal specialist) where the study was conducted<br><br>**Diagnosis:** cerebral insufficiency<br><br>**Diagnostic criteria:** ICD-290.x |
| Interventions | **Intervention characteristics**<br><br>*G biloba* |


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**Vesper 1994** *(Continued)*

- The ginkgo extract LI 1370 was standardized to contain at least 25% flavonglycosides and 6% terpenes using HPLC methodology (German citation given). The preparation was administered in the form of film tablets of 50 mg each and was given to participants 3 times a day.

Placebo

- A placebo preparation of the same appearance and consistency as intervention was given.

| | |
|---|---|
| Outcomes | **Outcomes collected**<br>• Basis reaction time<br>• Time/tenacity training test<br>• Mental flexibility test<br>• Visual memory test<br>• Character discrimination test<br>• Short test of general basic parameters (KAI)<br>• "subjective changes of mental and physical impairments"<br>• "subjective troubles" |
| Notes | **Sponsorship source:** none reported<br>**Trial registration number(s)**: none reported<br>**Note:** none of the reported outcomes are familiar standardized scales or measures that could be classified with the outcomes for this review. No outcome data relevant to this review could be extracted from the study. |

***Risk of bias***

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Random sequence generation (selection bias) | Low risk | "Randomization of the trial was achieved, using a computer-controlled random number generator." |
| Allocation concealment (selection bias) | Unclear risk | Insufficient information available to permit a judgment. |
| Blinding of participants and personnel (performance bias)<br>All outcomes | Low risk | Placebo-controlled trial in which placebo had the same appearance as ginkgo. It is likely that both participants and all personnel were blinded. |
| Blinding of outcome assessment (detection bias)<br>All outcomes | Low risk | Computer-diagnostics exams were performed at the central diagnostic laboratory. All other exams were performed at the practices of the physicians in charge, who were most likely blinded. |
| Incomplete outcome data (attrition bias)<br>All outcomes | Low risk | Data were obtained from 86 participants. Three participants left the trial without giving any reasons (1 ginkgo, 2 placebo). One ginkgo participant was excluded from the trial because he didn't comply with instructions. There were no missing values. |
| Selective reporting (reporting bias) | Unclear risk | Study protocol not available. Insufficient information available to permit a judgment. |
| Other bias | Low risk | No other apparent sources of bias. |


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### Wang 2004

| *Study characteristics* | |
|---|---|
| Methods | **Study design:** RCT<br><br>**Study grouping:** parallel group<br><br>**Duration of intervention:** 3 months<br><br>**Duration of follow-up:** 3 months<br><br>**Washout or placebo run-in period:** none reported |
| Participants | **Baseline characteristics**<br><br>*G biloba*<br><br>• Number randomized: 22<br>• MMSE (mean, SD): NR<br>• Age (mean, SD): 65.23, 8.24<br>• % female: 63.64<br><br>Jiawei Wuzi Yanzong Particle<br><br>• Number randomized: 22<br>• MMSE (mean, SD): NR<br>• Age (mean, SD): 66.59, 8.57<br>• % female: 68.18<br><br>**Total number randomized:** 44<br><br>**Inclusion criteria**<br><br>• Chief complaint of memory loss provided by the participant or family member<br>• Clinical memory scale 1.5 seconds less than the normal value<br>• Blessed daily behavior scale is normal<br>• Hachinski Ischemia Index (His) < 4 points<br>• MMSE 24–27 points<br>• Clinical Dementia Rating Scale (CDR) score 0.5 points<br><br>**Exclusion criteria:** none reported<br><br>**Country:** China<br><br>**Setting:** community<br><br>**Date recruitment began:** 2001<br><br>**Recruitment methods:** family members of 10 national agencies in Beijing, 600 people aged 50 to 80 were screened for MCI.<br><br>**Diagnosis:** MCI<br><br>**Diagnostic criteria:** brain CT; MCI diagnosis developed by Peterson 1999 |
| Interventions | **Intervention characteristics**<br><br>*G biloba*<br><br>• *G biloba* capsules (3 times/day, 1 capsule each time, each capsule contained 9.6 g of total flavonols)<br><br>Jiawei Wuzi Yanzong Particle |


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**Wang 2004** *(Continued)*

| | |
|---|---|
| | • Jiawei Wuzi Yanzong Particle (JWYP; 3 times/day, 1 bag each time, 3 g per bag, containing 12 g crude drugs) |
| Outcomes | **Outcomes collected**<br>• MQ<br>• CT (hippocampus index and width of temporal horn) |
| Notes | **Sponsorship source:** Peking University 985 funded project.<br>**Trial registration number(s)**: none reported |

***Risk of bias***

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Random sequence generation (selection bias) | Unclear risk | "从随机数字表中查取数字,奇数的为治疗组"<br>Using numbers from the random number table, the odd number is the treatment group, and the even number is the control group. Possible that this was true randomization using the random number table but it may also be quasi-randomization. |
| Allocation concealment (selection bias) | Unclear risk | Allocation process not reported. |
| Blinding of participants and personnel (performance bias)<br>All outcomes | Low risk | 采用双盲、双模拟法。治疗组同时服用加味五子衍宗颗粒及“银杏叶胶囊”的安慰剂<br>安慰剂的形状、包装、颜色及剂量与加味五子衍宗颗粒完全相同<br>A double-blind, double-dummy method was used. The shape, packaging, color and dosage of the placebo, which were given both modified Wuzi Yanzong Granules and "Ginkgo Leaf Capsules" in the treatment group, were exactly the same as those of Jiawei Wuzi Yanzong Granules. |
| Blinding of outcome assessment (detection bias)<br>All outcomes | Unclear risk | Blinding of outcome assessment was not reported. |
| Incomplete outcome data (attrition bias)<br>All outcomes | Low risk | No apparent loss to follow-up other than one person who had an automobile accident. "试验过程中,对照组有1例因发生交通事故而终止试验." |
| Selective reporting (reporting bias) | Unclear risk | There was no available protocol or trial registration. |
| Other bias | Low risk | No other apparent sources of bias. |

**Wang 2014a**

***Study characteristics***

| | |
|---|---|
| Methods | **Study design:** RCT<br>**Study grouping:** parallel group<br>**Duration of intervention:** 24 weeks |


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**Wang 2014a** *(Continued)*

**Duration of follow-up:** 24 weeks

**Washout or placebo run-in period:** none reported

| | |
|---|---|
| Participants | **Baseline characteristics**<br><br>*G biloba* + Donepezil<br><br>• Number randomized: 27<br>• MMSE (mean, SD): 17.09, 4.49<br>• Age (mean, SD): NR<br>• % female: NR<br><br>Donepezil<br><br>• Number randomized: 26<br>• MMSE (mean, SD): 16.32, 4.17<br>• Age (mean, SD): NR<br>• % female: NR<br><br>**Total number randomized:** 53<br><br>**Inclusion criteria**<br><br>• Age ≥ 50 years<br>• Hachinski ischemia scale ≤ 4, without other types of dementia<br>• No cerebrovascular accident<br>• HAM-D ≤ 8 points<br><br>**Exclusion criteria:** NR<br><br>**Country:** China<br><br>**Setting:** inpatient<br><br>**Date recruitment began:** 2011<br><br>**Recruitment methods:** Alzheimer's inpatients who were hospitalized in the Suzhou Hospital of traditional Chinese Medicine from January 2011 to January 2013<br><br>**Diagnosis:** AD<br><br>**Diagnostic criteria:** none reported |
| Interventions | **Intervention Characteristics**<br><br>*G biloba* + Donepezil<br><br>• On the basis of the treatment plan of the control group, 87.5 mg Ginaton injection was added into 250 mL 0.9% sodium chloride solution for intravenous drip for 2 weeks, and then it was replaced with 1 tablet of *G biloba* 3 times a day. The total course of treatment was 24 weeks.<br><br>Donepezil<br><br>• Aricept 5 mg, oral, once a day, for 24 weeks.<br><br>"Other treatments of the two groups of patients are the same, including oral Nimotop and intravenous infusion of piracetam and so on." |
| Outcomes | **Outcomes collected**<br><br>• MMSE<br>• ADLs |


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**Wang 2014a** *(Continued)*

- ECG
- Laboratory tests

| | |
|---|---|
| Notes | **Sponsorship source:** none reported<br>**Trial registration number(s)**: none reported |

***Risk of bias***

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Random sequence generation (selection bias) | Low risk | SPSS statistical software was used to generate a random ranking table, and 1:1 random grouping was performed. |
| Allocation concealment (selection bias) | Unclear risk | Allocation process not reported. |
| Blinding of participants and personnel (performance bias)<br>All outcomes | Unclear risk | Blinding was not reported, but it was probably a participant-blinded study. |
| Blinding of outcome assessment (detection bias)<br>All outcomes | Unclear risk | Blinding of outcome assessment was not reported. |
| Incomplete outcome data (attrition bias)<br>All outcomes | Low risk | There was no apparent loss to follow-up in the study. |
| Selective reporting (reporting bias) | Unclear risk | There was no protocol. |
| Other bias | Low risk | No other apparent sources of bias. |

**Wang 2020a**

***Study characteristics***

| | |
|---|---|
| Methods | **Study design:** RCT<br>**Study grouping:** parallel group<br>**Duration of intervention:** 3 months<br>**Duration of follow-up:** 3 months<br>**Washout or placebo run-in period:** no |
| Participants | **Baseline characteristics**<br>*G biloba* + Piracetam<br>• Number randomized: 46<br>• MMSE (mean, SD): NR<br>• Age (mean, SD): 56.59, 5.76<br>• % female: 34.8% |


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**Wang 2020a** *(Continued)*

| | |
|---|---|
| | Piracetam<br>• Number randomized: 46<br>• MMSE (mean, SD): NR<br>• Age (mean, SD): 57.38, 5.68<br>• % female: 39.1%<br><br>**Total number randomized:** 92<br><br>**Inclusion criteria:**<br>• Diagnosis based on the *Guidelines for the Diagnosis and Treatment of Vascular Cognitive Impairment*<br>• No contraindications to the drugs in this study<br>• Varying degrees of memory loss and cognitive abnormalities<br>• Informed consent<br><br>**Exclusion criteria**<br>• History of traumatic brain injury or mental illness<br>• Recent use of choline preparations or nootropic drugs<br>• Severe liver or kidney dysfunction<br>• Severe digestive system diseases<br><br>**Country:** China<br><br>**Setting:** inpatient<br><br>**Date recruitment began:** 2017<br><br>**Recruitment methods:** NR<br><br>**Diagnosis:** VCIND<br><br>**Diagnostic criteria:** the diagnostic criteria referred to the *Guidelines for the Diagnosis and Treatment of Vascular Cognitive Impairment* |
| Interventions | **Intervention characteristics**<br><br>*G biloba* + Piracetam<br>• *G biloba* soft capsule (Luoyang Junshan Pharmaceutical Co, Ltd, Zhunzi Z20090920) combined with piracetam for treatment: *G biloba* soft capsule orally 1.0 g/time, 3 times/day. The dosage of piracetam was the same as that of the control group. Dose *G biloba* 3 g/day + piracetam 2.4 g/day.<br><br>Piracetam<br>• Piracetam (Hunan Dino Pharmaceutical Co, Ltd, Zhunzi H43020666): oral administration, 0. 8 g/time, 3 times/day. Dose 2.4 g/day. |
| Outcomes | **Outcomes collected**<br>• MoCA<br>• WMS<br>• ADLs (0–100)<br>• Curative effect<br>• Adverse events |
| Notes | **Sponsorship source:** none reported<br><br>**Trial registration number(s)**: none reported |


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**Wang 2020a** *(Continued)*

***Risk of bias***

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Random sequence generation (selection bias) | Low risk | Random number table. |
| Allocation concealment (selection bias) | Unclear risk | Not mentioned. |
| Blinding of participants and personnel (performance bias)<br>All outcomes | Unclear risk | Blinding not mentioned. |
| Blinding of outcome assessment (detection bias)<br>All outcomes | Unclear risk | Blinding not mentioned. |
| Incomplete outcome data (attrition bias)<br>All outcomes | Low risk | No attrition. |
| Selective reporting (reporting bias) | Unclear risk | No protocol. |
| Other bias | Low risk | No other apparent source of bias. |

**Wesnes 1987**

***Study characteristics***

| | |
|---|---|
| Methods | **Study design:** RCT<br><br>**Study grouping:** parallel group<br><br>**Duration of intervention:** 3 months<br><br>**Duration of follow-up:** 3 months<br><br>**Washout or placebo run-in period:** washout period of 1 to 3 weeks for psychotropic drugs, centrally acting hypertensives, drugs for Parkinson's disease, anticoagulants or antiplatelet aggregating agents, and central nervous system stimulants, which were not permitted during the trial. |
| Participants | **Baseline characteristics**<br><br>*G biloba*<br><br>• Number randomized: 27<br>• MMSE (mean, SD): NR<br>• Age (mean, SD): 70.7, 7.1<br>• % female: 30%<br><br>Placebo<br><br>• Number randomized: 27<br>• MMSE (mean, SD): NR |


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**Wesnes 1987** *(Continued)*

- Age (mean, SD): 71.3, 6.6
- % female: 44%

**Total number randomized:** 58 (baseline data not provided for all randomized participants)

**Inclusion criteria**

- Mild impairment of everyday functioning using the Crichton Geriatric Behavioural Scale, defined as a total score of 14 or more without a score of more than 3 on any individual item

**Exclusion criteria**

- Potential other cause for symptoms, including infection or psychiatric causes such as depression
- Renal, hepatic, or cardiac insufficiency
- Diabetes mellitus
- Malignant disease

**Country:** UK

**Setting:** outpatient

**Date recruitment began:** not reported (prior to 1987)

**Recruitment methods:** recruitment from a general practice population

**Diagnosis:** mild dementia

**Diagnostic criteria:** Crichton Behavioral Scale ≥ 14

| | |
|---|---|
| Interventions | **Intervention characteristics**<br><br>*G biloba*<br><br>• Tanakan is the trade name of a patented, defined extract of *G biloba* leaf. The active ingredients consist essentially of flavone heteroglycosides and terpene substances (ginkgolides and bilobalide). Participants received 40 mg Tanakan film-coated tablets to be taken three times daily.<br><br>Placebo<br><br>• Intervention-matched placebo, which was taken 3 times daily. Constitution of placebo not reported.<br><br>Psychotropic drugs, centrally-acting hypertensives, drugs for Parkinson's disease, anticoagulants or antiplatelet aggregating agents, and central nervous system stimulants were not permitted. |
| Outcomes | **Outcomes collected**<br><br>• Benton Visual Retention Test<br>• Wechsler Digit Span Test<br>• Immediate Word Recall<br>• Number Matching Task<br>• Rapid Visual Information Processing Test<br>• Choice Reaction Time Test<br>• Wechsler Digit Symbol Substitution Test<br>• Word Recognition Test<br>• Behavioral Rating Scale<br>• Visual analogue scales of mood and alertness |
| Notes | **Sponsorship source:** none reported<br><br>**Trial registration number(s)**: none reported |


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**Wesnes 1987** *(Continued)*

***Risk of bias***

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Random sequence generation (selection bias) | Unclear risk | "randomly allocated, balanced in groups of six." Although the method of sequence generation is not given, it appears that block randomization was done, and it is likely that true randomization was conducted. |
| Allocation concealment (selection bias) | Unclear risk | No mention of allocation processes. |
| Blinding of participants and personnel (performance bias)<br>All outcomes | Low risk | Placebo-controlled double-blind design. |
| Blinding of outcome assessment (detection bias)<br>All outcomes | Unclear risk | Placebo-controlled double-blind design, but the timing of unblinding and outcome assessment are unclear, particularly with regard to the behavioral questionnaire, which was administered "after the study". |
| Incomplete outcome data (attrition bias)<br>All outcomes | Low risk | Fifty-eight patients entered the study and 54 completed the trial (27 on Tanakan and 27 on placebo). Four participants of 58 withdrew and reasons were given. Although the numbers were unbalanced between groups, the small sample size and the reasons for placebo withdrawals (side effects) make this unlikely to lead to bias. |
| Selective reporting (reporting bias) | Unclear risk | Study protocol not available. Insufficient information available to permit a judgment. |
| Other bias | Low risk | No other apparent sources of bias. |

**Wu 2017**

***Study characteristics***

| | |
|---|---|
| Methods | **Study design:** RCT<br>**Study grouping:** parallel group<br>**Duration of intervention:** 3 months<br>**Duration of follow-up:** 3 months<br>**Washout or placebo run-in period:** not reported |
| Participants | **Baseline characteristics**<br>*G biloba*<br>• Number randomized: 32<br>• MMSE (mean, SD): 20.25, 2.77<br>• Age (mean, SD): 65.94, 5.35<br>• % female: 56.25<br>Shenma Yizhi Recipe<br>• Number randomized: 32 |


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**Wu 2017** *(Continued)*

- MMSE (mean, SD): 20.47, 3.13
- Age (mean, SD): 65.06, 5.65
- % female: 56.25

**Total number randomized:** 64

**Inclusion criteria**

- Diagnostic criteria of Western medicine for mild or moderate vascular dementia
- Course of dementia > 3 months
- TCM syndrome differentiation is qi deficiency, blood stasis, and liver-yang disturbance
- Age 45 to 80 years
- MMSE score 10–26
- Clinical Neurological Deficiency Scale (NIHSS): 5 to 15 points
- Hachinski Ischemia Scale ≥ 7 points
- HAM-D ≤ 17 points
- Informed consent

**Exclusion criteria**

- Severe gastrointestinal dysfunction, gastrointestinal obstruction, gastric or duodenal ulcers, and other gastrointestinal diseases that may affect drug absorption
- Severe heart, brain, liver, kidney, and hematopoietic disease
- Psychosis, epilepsy, mixed dementia, or traumatic brain injury
- Dementia before the onset of cerebrovascular disease
- Cerebral hemorrhage, subarachnoid hemorrhage, transient cerebral ischemia
- Severe neurological deficits, such as hand hemiplegia, visual and hearing impairment, aphasia
- Use of other nootropic drugs within 4 weeks before the study, or other drugs that affect the evaluation of the efficacy
- Participation in other clinical trials or use of drugs with the same multi-flavored ingredients as the trial drug within 4 weeks before the study
- Allergy to the ingredients of the study medication

**Country:** China

**Setting:** hospital and community

**Date recruitment began:** 2016

**Recruitment methods:** this study screened 108 post-stroke patients from Jingzhuang Health Center in Yanqing District, Beijing, Xiaoshizhuang Village, Sanhe City, Hebei Province, and Xiyuan Hospital.

**Diagnosis:** diagnostic criteria of Western medicine for mild or moderate vascular dementia

**Diagnostic criteria**

- Diagnostic criteria of Western medicine for mild or moderate vascular dementia
- TCM syndrome differentiation is qi deficiency, blood stasis, and liver-yang disturbance

| | |
|---|---|
| Interventions | **Intervention characteristics**<br><br>*G biloba*<br><br>• Ginkgo leaves 1 tablet/time, 3 times a day, taken orally for 3 months<br><br>Shenma Yizhi Recipe<br><br>• Shenma Yizhi Granules, 5 g/bag, 1 bag per time, twice a day |
| Outcomes | **Outcomes collected** |


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**Wu 2017** *(Continued)*

- MMSE
- MoCA
- ADL
- National Institute of Health Stroke Scale (NIHSS)
- Integrals of TCM syndromes
- ACh (μg/mL)
- Ace1tylcholine esterase (AchE; U/mL)
- MDA (nmol/mL)
- Superoxide dismutase (SOD; U/mL)
- Glutathione peroxidase (GSH-Px; U/mL)
- Interleukin-6 (IL-6; pg /mL)
- Tumor necrosis factor-alpha (TNF-α; pg /mL)

| | |
|---|---|
| Notes | **Sponsorship source:** National Natural Science Foundation of China (No. 81603616); Beijing Municipal Science and Technology Program Project "Ten Diseases and Ten Medicines" Research and Development Project (No. Z171100001717016)<br><br>**Trial registration number(s)**: none reported |

***Risk of bias***

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Random sequence generation (selection bias) | Unclear risk | "Generating 64 random numbers and sorting these random numbers in the form of "values". The first 32 numbers were the experimental group, and the last 32 numbers were the control group." The method is described, but it is unclear whether it was random sequence generation or quasi-randomization. |
| Allocation concealment (selection bias) | Unclear risk | Allocation process not reported. |
| Blinding of participants and personnel (performance bias)<br>All outcomes | Unclear risk | Blinding was not reported, but it was probably a participant-blinded study. |
| Blinding of outcome assessment (detection bias)<br>All outcomes | Low risk | Blinding of outcome assessment not reported. |
| Incomplete outcome data (attrition bias)<br>All outcomes | Low risk | There was no apparent loss to follow-up in the study. |
| Selective reporting (reporting bias) | Unclear risk | There was no protocol. |
| Other bias | Low risk | No other apparent source of bias. |

**Wu 2021a**

***Study characteristics***

| | |
|---|---|
| Methods | **Study design:** RCT |


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**Wu 2021a** *(Continued)*

**Study grouping:** parallel group

**Duration of intervention:** 6 months

**Duration of follow-up:** 6 months

**Washout or placebo run-in period:** no

Participants

**Baseline characteristics**

*G biloba* + Donepezil

- Number randomized: 49
- MMSE (mean, SD): 13.2, 2.9
- Age (mean, SD): 67.5, 6.2
- % female: 44.9%

Donepezil

- Number randomized: 49
- MMSE (mean, SD): 13.4, 2.9
- Age (mean, SD): 67.3, 6.4
- % female: 46.9%

**Total number randomized:** 98

**Inclusion criteria**

- Diagnostic criteria of probable AD in the NIA-AA diagnostic criteria released in 2011
- Declining in cognitive function and daily living ability for at least 6 months
- Moderate to severe AD (MMSE ≤ 19 points)
- Ability to cooperate, willingness to complete all parts of the study, and ability to do so alone or with the assistance of a guardian
- Informed consent

**Exclusion criteria**

- History of disturbance of consciousness
- Family genetic disease history
- Central nervous system infection, head injury, epilepsy, multiple sclerosis, toxic metabolic disease, Parkinson's disease, intracranial tumor, hypothyroidism, diabetes mellitus, and other physical diseases, and other systemic diseases that could cause brain function decline
- A history of mental illness such as schizophrenia and personality changes
- Depressive episodes or HAM-D score ≥ 8 points
- Serious heart, liver, kidney, brain, or hematopoietic system diseases

**Country:** China

**Setting:** inpatient

**Date recruitment began:** 2017

**Recruitment methods:** elderly inpatients with moderate to severe AD admitted to the author's hospital from June 2017 to June 2019

**Diagnosis:** moderate to severe AD

**Diagnostic criteria:** NIA-AA diagnostic criteria released in 2011

Interventions

**Intervention Characteristics**

Donepezil


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**Wu 2021a** *(Continued)*

| | |
|---|---|
| | • Donepezil hydrochloride (trade name: Aricept, manufacturer: Eisai Pharmaceutical Co, Ltd, lot number: H20050978, specification: 10 mg) 2 tablets/day, taken orally before going to bed. Dose 20 mg/day.<br><br>*G biloba* + donepezil<br><br>• In addition to donepezil, participants took *G biloba* leaves (trade name: Yikangning, manufacturer: Yangzijiang Pharmaceutical Group Co, Ltd, lot number: Z20027949, specification: 9.6 mg) 1 tablet/time, 3 times/day. Dose *G biloba* 28.8 mg/day + donepezil 20 mg/day. |
| Outcomes | **Outcomes collected**<br><br>• MMSE<br>• ADLs (Barthel index)<br>• NPI<br>• Adverse reactions |
| Notes | **Sponsorship source:** Lianyungang Youth Research Project (QN1802)<br><br>**Trial registration number:** none reported |

***Risk of bias***

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Random sequence generation (selection bias) | Low risk | Random number table. |
| Allocation concealment (selection bias) | Unclear risk | Not mentioned. |
| Blinding of participants and personnel (performance bias)<br>All outcomes | Unclear risk | Blinding not mentioned. |
| Blinding of outcome assessment (detection bias)<br>All outcomes | Unclear risk | Blinding not mentioned. |
| Incomplete outcome data (attrition bias)<br>All outcomes | Low risk | No attrition. |
| Selective reporting (reporting bias) | Unclear risk | No protocol. |
| Other bias | Low risk | No other apparent sources of bias. |

**Xia 2013**

***Study characteristics***

| | |
|---|---|
| Methods | **Study design:** RCT<br><br>**Study grouping:** parallel group<br><br>**Duration of intervention:** 1 year |


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**Xia 2013** *(Continued)*

**Duration of follow-up:** 1 year

**Washout or placebo run-in period:** none reported

| | |
|---|---|
| Participants | **Baseline characteristics**<br><br>*G biloba* + conventional medications<br><br>• Number randomized: 123<br>• MMSE (mean, SD): 25.75, 1.54<br>• Age (mean, SD): 64.1, 7.1<br>• % female: 50.41<br><br>Conventional medications<br><br>• Number randomized: 122<br>• MMSE (mean, SD): 25.84, 1.98<br>• Age (mean, SD): 63.7, 6.5<br>• % female: 49.18<br><br>**Total number randomized:** 245<br><br>**Inclusion criteria**<br><br>• MCI diagnosis based on the diagnostic criteria of the DSM-IV<br>• MMSE ≥ 24<br>• ADL score ≤ 26<br><br>**Exclusion criteria**<br><br>• Nervous system diseases and serious medical diseases that affect brain function or cognitive function<br>• History of head injury<br>• History of depression, anxiety, schizophrenia, etc.<br>• Severe hearing and vision impairment, etc.<br>• Use of medication that affects cognitive function<br><br>**Country:** China<br><br>**Setting:** inpatient and outpatient<br><br>**Date recruitment began:** 2007<br><br>**Recruitment methods:** from August 2007 to May 2012, the older outpatients and inpatients with MCI were diagnosed in the neurology department of Yuhang No.5 People's Hospital of Hangzhou.<br><br>**Diagnosis:** MCI<br><br>**Diagnostic criteria:** MCI diagnosis is based on the diagnostic criteria of the DSM-IV. |
| Interventions | **Intervention characteristics**<br><br>*G biloba* + conventional medications<br><br>• In addition to basic treatment, the interventional group was given *G biloba* extract (name: Tanakang, 40 mg per tablet), 40 mg each time, 3 times/day, for 1 year<br><br>Conventional medications<br><br>• Basic treatment included levodopa, nimodipine, general health education, moderate exercise, limb movement, nutritional support, blood pressure reduction (blood pressure control target < 140/90 mmHg, ideal level < 130/85 mmHg), reduced blood sugar (fasting blood glucose ≤ 7.0 mmol/L, the |


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**Xia 2013** *(Continued)*

| | |
|---|---|
| | blood glucose was less than 10 mmol/L 2 hours after meals), and antiplatelet therapy (aspirin or clopidogrel). |
| Outcomes | **Outcomes collected**<br>• MMSE<br>• CDT<br>• Activity of RBC-Ach and RBC-AchE (the basic hydroxylamine colorimetry and the iron trichloride colorimetry were used respectively) |
| Notes | **Sponsorship source:** none reported<br>**Trial registration number(s)**: none reported |

***Risk of bias***

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Random sequence generation (selection bias) | Low risk | Cases were assigned into treatment group or control group by using random number table method. |
| Allocation concealment (selection bias) | Unclear risk | Allocation process not reported. |
| Blinding of participants and personnel (performance bias)<br>All outcomes | Unclear risk | Blinding was not reported, but it was probably a non-blinded study. |
| Blinding of outcome assessment (detection bias)<br>All outcomes | Unclear risk | Blinding of outcome assessment not reported. |
| Incomplete outcome data (attrition bias)<br>All outcomes | Low risk | There was no apparent loss to follow-up in the study. |
| Selective reporting (reporting bias) | Unclear risk | There was no protocol. |
| Other bias | Low risk | There was no other apparent risk of bias. |

**Xu 2017**

***Study characteristics***

| | |
|---|---|
| Methods | **Study design:** RCT<br>**Study grouping:** parallel group<br>**Duration of intervention:** 6 months<br>**Duration of follow-up:** 6 months<br>**Washout or placebo run-in period:** none reported |
| Participants | **Baseline characteristics** |


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**Xu 2017** *(Continued)*

*G biloba* + Butylphthalide

- Number randomized: 36
- MMSE (mean, SD): 14.11, 1.05
- Age (mean, SD): 69.74, 6.49
- % female: 44.4

Butylphthalide

- Number randomized: 36
- MMSE (mean, SD): 14.05 (1.02)
- Age (mean, SD): 68.53 (6.29)
- % female: 47.2%

**Total number randomized:** 72

**Inclusion criteria**

- Age 50 to 80 years
- Mild to moderate disease
- Informed consent
- Support of family members for adhering to treatment
- Diagnosis of yin deficiency in liver and kidney, dampness of blood and phlegm block Qi and Blood Meridian by Chinese medicine practitioner

**Exclusion criteria**

- Secondary AD caused by other primary diseases
- Use of relevant therapeutic drugs in the past 6 months
- Serious diseases of heart, kidney and blood system
- Psychiatric disorder due to stimulations
- Brain trauma or brain surgery

**Country:** China

**Setting:** inpatient

**Date recruitment began:** 2015

**Recruitment methods:** people with AD treated in Dongyang people's hospital from January to April 2016

**Diagnosis:** AD

**Diagnostic criteria**

- Diagnostic criteria of Western medicine: refer to the relevant standards in *Chinese Guidelines for the Diagnosis and Treatment of Alzheimer's Disease and Other Dementias*
- Traditional Chinese medicine diagnostic criteria: refer to "yin deficiency in liver and kidney, dampness of blood and phlegm block Qi and Blood Meridian" in *Guidelines of clinical research on new drugs of traditional Chinese Medicine*

| Interventions | **Intervention characteristics**<br><br>*G biloba* + Butylphthalide<br><br>• On the basis of the treatment of the control group, the interventional group was additionally given *G biloba* extract tablets (Dr Willmar Schwabe GmbH & Co. KG, 40 mg × 10 tablets × 2 pieces, lot number 140613), oral, 80 mg/time, twice a day, for 6 months<br><br>Butylphthalide |
|---|---|


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**Xu 2017** *(Continued)*

| | |
|---|---|
| | • Butyphthalide (0. 1 g X 24 capsules, lot number:140806 provided by CSPC NBP Pharmaceutical Co, Ltd). Taken on an empty stomach and 0.2 g/time, 3 times/day for 6 months. |
| Outcomes | **Outcomes collected:**<br>• AD efficacy<br>  ○ Significant improvement: MMSE score increased ≥ 20%<br>  ○ Improvement: MMSE score improved 10% to 20%<br>  ○ No improvement: MMSE score improved < 10%<br>  ○ In addition, total effective rate = (significant improvement + improvement)/total cases × 100%<br>• MMSE score<br>• ADAS-cog score<br>• ADL score<br>• Plasma nitric oxide (NO): nitrate reductase assay<br>• Serum vascular endothelial growth factor (VEGF): detected by ELISA<br>• Malondialdehyde (MDA): TBA method<br>• Adverse drug reactions |
| Notes | **Sponsorship source:** none reported<br>**Trial registration number(s)**: none reported |

***Risk of bias***

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Random sequence generation (selection bias) | Unclear risk | Seventy-two AD patients were divided into 2 groups by a lottery method. |
| Allocation concealment (selection bias) | Unclear risk | Allocation process was not reported. |
| Blinding of participants and personnel (performance bias)<br>All outcomes | Unclear risk | Blinding was not reported, but it was probably a participant-blinded study. |
| Blinding of outcome assessment (detection bias)<br>All outcomes | Unclear risk | Blinding of outcome assessment was not reported. |
| Incomplete outcome data (attrition bias)<br>All outcomes | Low risk | There was no apparent loss to follow-up in the study. |
| Selective reporting (reporting bias) | Unclear risk | There was no protocol. |
| Other bias | Low risk | No other apparent risk of bias. |

**Xu 2019a**

***Study characteristics***

| | |
|---|---|
| Methods | **Study design:** RCT |


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**Xu 2019a** *(Continued)*

**Study grouping:** parallel group

**Duration of intervention:** 12 weeks

**Duration of follow-up:** 12 weeks

**Washout or placebo run-in period:** none reported

Participants

**Baseline characteristics**

*G biloba* + Donepezil

- Number randomized: 43
- MMSE (mean, SD): 17.87, 1.65
- Age (mean, SD): 63.86, 4.71
- % female: 34.9

Donepezil

- Number randomized: 43
- MMSE (mean, SD): 18.14, 1.69
- Age (mean, SD): 64.11, 4.52
- % female: 37.2%

**Total number randomized:** 86

**Inclusion criteria**

- Matched the VD diagnostic criteria in the *Draft Diagnostic Criteria for Vascular Dementia*
- Informed consent

**Exclusion criteria**

- Dementia due to other causes
- Mental illness
- Liver and kidney dysfunction
- Long-term use of anticonvulsive drugs
- Blood system diseases
- Allergy to the drugs used in the study

**Country:** China

**Setting:** inpatient

**Date recruitment began:** 2017

**Recruitment methods:** people with VD in institution from February 2017 to October 2018 were selected.

**Diagnosis:** VD

**Diagnostic criteria:** matched the VD diagnostic criteria in the *Draft Diagnostic Criteria for Vascular Dementia*

Interventions

**Intervention characteristics**

*G biloba* + Donepezil

- In addition to the treatment of the control group, the interventional group was given ginkgo tablet (manufacturer: Yangzijiang Pharmaceutical Group Co, Ltd, approval number: Z20027949), to be taken orally 19.2 mg/ time, 3 times/day (total dose 57.6 mg/day).

Donepezil


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**Xu 2019a** *(Continued)*

| | |
|---|---|
| | • Donepezil (manufacturer: Shaanxi Fangzhou Pharmaceutical Co, Ltd, approval number: H20030583), taken orally 5 mg/time, once a day<br><br>Both groups received treatment for primary disease. |
| Outcomes | **Outcomes collected**<br><br>• Clinical efficacy<br>• Incidence of adverse reactions<br>• MMSE score<br>• Barthel index score<br>• Hemorheological index (whole blood reduced viscosity high shear, whole blood reduced viscosity low shear, fibrinogen [Fib]) levels |
| Notes | **Sponsorship source:** none reported<br><br>**Trial registration number(s)**: none reported |

***Risk of bias***

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Random sequence generation (selection bias) | Low risk | Participants were divided into intervention group and control group according to the random number table method. |
| Allocation concealment (selection bias) | Unclear risk | Allocation process was not reported. |
| Blinding of participants and personnel (performance bias)<br>All outcomes | Unclear risk | Blinding was not reported, but it was probably a participant-blinded study. |
| Blinding of outcome assessment (detection bias)<br>All outcomes | Unclear risk | Blinding of outcome assessment was not reported. |
| Incomplete outcome data (attrition bias)<br>All outcomes | Low risk | There was no apparent loss to follow-up in the study. |
| Selective reporting (reporting bias) | Unclear risk | There was no protocol. |
| Other bias | Low risk | No other apparent risk of bias. |

**Xu 2021**

***Study characteristics***

| | |
|---|---|
| Methods | **Study design:** RCT<br><br>**Study grouping:** parallel group<br><br>**Duration of intervention:** 3 months<br><br>**Duration of follow-up:** 3 months |


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**Xu 2021** *(Continued)*

**Washout or placebo run-in period:** no

| | |
|---|---|
| Participants | **Baseline characteristics**<br><br>*G biloba* + Oxiracetam<br><br>• Number randomized: 51<br>• MMSE (mean, SD): 23.43, 2.01<br>• Age (mean, SD): 55.59, 4.11<br>• % female: 37.25%<br><br>Oxiracetam<br><br>• Number randomized: 51<br>• MMSE (mean, SD): 23.68, 1.89<br>• Age (mean, SD): 56.10, 3.91<br>• % female: 33.33%<br><br>**Total number randomized:** 102<br><br>**Inclusion criteria**<br><br>• VCIND diagnostic criteria<br>• Varying degrees of memory loss and cognitive abnormalities<br>• MMSE score < 26 points<br>• Informed consent<br><br>**Exclusion criteria**<br><br>• Cognitive dysfunction caused by non-vascular factors, such as traumatic brain injury, neurosyphilis, carbon monoxide toxic encephalopathy, alcoholic encephalopathy<br>• Peptic ulcer bleeding, cerebral hemorrhage, and other diseases within 3 months before inclusion in the study<br>• Use of cholinesterase inhibitors, antihistamines, benzodiazepines, antidepressants, and antiepileptics for a long time before inclusion in the study<br>• Severe renal and hepatic damage: transaminase increased by more than 5 times normal value, glomerular filtration rate less than 60 mL/min<br>• Neurodegenerative diseases such as AD and Parkinson's disease<br><br>**Date recruitment began:** 2016<br><br>**Recruitment methods:** cardiovascular and cerebrovascular patients diagnosed with VCIHD in the author's hospital from October 2016 to June 2018 were recruited.<br><br>**Diagnosis:** VCIND<br><br>**Diagnostic criteria:** not reported |
| Interventions | **Intervention characteristics**<br><br>*G biloba* + Oxiracetam<br><br>• Description of intervention from the report (both the product and administration): in addition to Oxiracetam, *G biloba* leaves (Hunan Huana Pharmaceutical Co, Ltd, Z20043061), 80 mg/time, taken orally 3 times/day. *G biloba* leaf treatment for 3 months. Dose *G biloba* 240 mg/day + oxiracetam 4 g/day.<br><br>Oxiracetam<br><br>• Oxiracetam (CSPC Ouyi Pharmaceutical Co, Ltd, Zhunzi H20100040), intravenous infusion of Oxiracetam 4 g + 250 mL normal saline, once/day, for 2 weeks. Dose 4 g/day. |


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**Xu 2021** *(Continued)*

| | |
|---|---|
| Outcomes | **Outcomes collected**<br>• MMSE<br>• MoCA<br>• ADLs (higher is better)<br>• WMS<br>• Curative effect<br>• Adverse events (vomiting & nausea, dizziness, and rash) |
| Notes | **Sponsorship source:** none reported<br>**Trial registration number(s)**: none reported |

***Risk of bias***

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Random sequence generation (selection bias) | Low risk | Random number table. |
| Allocation concealment (selection bias) | Unclear risk | Not mentioned. |
| Blinding of participants and personnel (performance bias)<br>All outcomes | Unclear risk | Blinding was not mentioned. |
| Blinding of outcome assessment (detection bias)<br>All outcomes | Unclear risk | Blinding was not mentioned. |
| Incomplete outcome data (attrition bias)<br>All outcomes | Low risk | No attrition. |
| Selective reporting (reporting bias) | Unclear risk | No protocol. |
| Other bias | Low risk | No other apparent source of bias. |

**Yancheva 2009**

***Study characteristics***

| | |
|---|---|
| Methods | **Study design:** RCT<br>**Study grouping:** parallel group<br>**Duration of intervention:** 22 weeks<br>**Duration of follow-up:** 22 weeks<br>**Washout or placebo run-in period:** use of anti-dementia drugs for 8 weeks before study treatment was not allowed. No other run-in period mentioned. |


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**Yancheva 2009** *(Continued)*

Participants

**Baseline characteristics**

*G biloba*

- Number randomized: 31
- MMSE (mean, SD): NR
- Age (mean, SD): 69, 8
- % female: 54.8%

*G biloba* + Donepezil

- Number randomized: 31
- MMSE (mean, SD): NR
- Age (mean, SD): 68, 9
- % female: 67.7%

Donepezil

- Number randomized: 32
- MMSE (mean, SD): NR
- Age (mean, SD): 66 (8)
- % female: 84%

**Number randomized:** 96 (baseline data not provided for all randomized participants)

**Inclusion criteria:** "Patients of both sexes, aged 50 years or above, were eligible if they met the diagnostic criteria proposed by the National Institute of Neurological and Communicative Disorders and Stroke (NINCDS) and the Alzheimer's Disease and Related Disorders Association (ADRDA) for probable AD (McKhann et al., 1984), scored below 36 on the cognitive part of the test for the early detection of dementia with differentiation from depression (TE4D) (Mahoney, Johnston, Katona, Maxmin, & Livingston, 2005), between 9 and 23 on the SKT test battery (Kim, Nibbelink, & Overall, 1993) (which indicates mild to moderate dementia) and below 6 on the Clock- Drawing Test (CDT) after Sunderland (Sunderland et al., 1989). … The presence of neuropsychiatric symptoms was required as indicated by a minimum score of three in at least one item (other than delusions or hallucinations) of the Neuropsychiatric Inventory (NPI) (Cummings, 1997), and a total composite score (frequency_ severity) of at least five. To exclude patients with severe depression, the total score of the 17-item Hamilton Rating Scale for Depression (HAM-D) (Hamilton, 1960) had to be below 20. A CT or MRI scan no more than one year old had to be consistent with the diagnosis of probable AD. A caregiver was required who had regular and frequent contact with the patient to serve as an informant with respect to neuropsychiatric symptoms and activities of daily living."

**Exclusion criteria:** "Patients were excluded if they had any other type of dementia, any psychiatric or neurological disorder or any history of a disorder that could account for cognitive impairment or neuropsychiatric symptoms. Any use of other anti-dementia drugs, cognition enhancers, drugs with cholinergic or strong anti-cholinergic effects, haemorrheologically active substances or anti-Parkinson drugs were prohibited during and within 8 weeks before randomised treatment. Patients were also excluded, if they had severe somatic diseases, gastrointestinal diseases with uncertain absorption of drug substances, severe sensory or motor disability that would have rendered cognitive testing unreliable, or any condition at which treatment with one of the drugs under study would have been unsafe."

**Country:** Bulgaria

**Setting:** outpatient

**Date recruitment began:** 2003

**Recruitment methods:** the study states that participants were recruited from outpatient clinics of 4 hospital centers for psychiatry or neurology across Bulgaria. Methods not elaborated.

**Diagnosis:** probable AD


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**Yancheva 2009** *(Continued)*

| | |
|---|---|
| | **Diagnostic criteria:** National Institute of Neurological and Communicative Disorders and Stroke (NINCDS) and the Alzheimer's Disease and Related Disorders Association (ADRDA) criteria |
| Interventions | **Intervention characteristics**<br><br>*G biloba*<br><br>• "[A]ll patients took two film-coated tablets per day, one in the morning and one in the evening ... and one or two quickly dissolving, opaque capsules before sleeping...." Participants in the EGb761 group took EGb761 in the morning and placebo in the evening. "Drugs were administered in accordance with approved and recommended treatment regimens, i.e. EGb 761 at a daily dose of 240 mg (2 x 1 film-coated tablet with 120 mg)." "If a patient experienced an adverse event that was considered a side effect of donepezil, the daily dose could be reduced to 1 capsule without breaking the blind." "EGb 761 is a dry extract from *G biloba* leaves (35–67:1, extraction solvent was acetone 60% (w/w)). The extract is adjusted to 22.0–27.0% ginkgo flavonoids, calculated as Ginkgo flavone glycosides and 5.0–7.0% terpene lactones consisting of 2.8–3.4% ginkgolides A, B, C and 2.6–3.2% bilobalide and contains less than 5 ppm ginkgolic acids." EGb 761 was "indistinguishable from the matching placebo preparation."<br><br>*G biloba* + Donepezil<br><br>• "[A]ll patients took two film-coated tablets per day, one in the morning and one in the evening ... and one or two quickly dissolving, opaque capsules before sleeping...." Participants in the combined treatment group took EGb761 in the morning and EGb761 plus donepezil in the evening. "Drugs were administered in accordance with approved and recommended treatment regimens, i.e. EGb 761at a daily dose of 240 mg (2 x 1 film-coated tablet with 120 mg) and donepezil at a daily dose of 5 mg (1 capsule containing 1 tablet) during the first 4 weeks and 10 mg (2 capsules containing 1 tablet each) for the remaining 18 weeks. The combined treatment group received both drugs at recommended doses. If a patient experienced an adverse event that was considered a side effect of donepezil, the daily dose could be reduced to 1 capsule without breaking the blind. EGb 761 is a dry extract from *G biloba* leaves (35–67:1, extraction solvent:acetone 60% (w/w)). The extract is adjusted to 22.0–27.0% ginkgo flavonoids, calculated as Ginkgo flavone glycosides and 5.0–7.0% terpene lactones consisting of 2.8–3.4% ginkgolides A, B, C and 2.6–3.2% bilobalide and contains less than 5 ppm ginkgolic acids. Both drugs were indistinguishable from the matching placebo preparations."<br><br>Donepezil<br><br>• "[A]ll patients took two film-coated tablets per day, one in the morning and one in the evening ... and one or two quickly dissolving, opaque capsules before sleeping...." Participants in the donepezil group took placebo in the morning and placebo plus donepezil in the evening. "Drugs were administered in accordance with approved and recommended treatment regimens, i.e. ... donepezil at a daily dose of 5 mg (1 capsule containing 1 tablet) during the first 4 weeks and 10 mg (2 capsules containing 1 tablet each) for the remaining 18 weeks." "If a patient experienced an adverse event that was considered a side effect of donepezil, the daily dose could be reduced to 1 capsule without breaking the blind." Donepezil was "indistinguishable from the matching placebo preparation."<br><br>"other anti-dementia drugs, cognition enhancers, drugs with cholinergic or strong anti-cholinergic effects, haemorrheologically active substances or anti-Parkinson drugs were prohibited" |
| Outcomes | **Outcomes collected**<br><br>• SKT<br>• CDT<br>• Verbal Fluency Test<br>• NPI<br>• HAM-D<br>• GBS ADL<br>• GBS total without behavioral and psychological symptoms subscale |
| Notes | **Sponsorship source:** "The clinical trial was sponsored by Dr Willmar Schwabe Pharmaceuticals, Karlsruhe, Germany." |


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**Yancheva 2009** *(Continued)*

**Trial registration number(s)**: none reported

**Note:** study was also called the GINDON Study Group

**Note:** outcome data for GBS was obtained by email from Dr Robert Hörr to LSW on 21 October 2021

***Risk of bias***

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Random sequence generation (selection bias) | Low risk | "Randomisation in blocks of six patients was performed by the sponsor's biometrics unit using a validated computer program which matched treatments to drug numbers guaranteeing that a patient is assigned to one of the treatment groups with equal probability (1:1:1 randomisation). Randomisation was performed stratified by centres." |
| Allocation concealment (selection bias) | Low risk | "The person responsible for the randomisation was not involved in data management or data analysis of the study. Treatments were allocated by providing patients in the order of enrollment with drugs following an ascending sequence of drug numbers. All drug boxes looking identical, and the block length being kept secret, the sequence of treatments was effectively concealed." |
| Blinding of participants and personnel (performance bias)<br>All outcomes | Low risk | "Double-blind conditions were achieved by double-dummy technique, i.e. all patients took two film-coated tablets per day, one in the morning and one in the evening, either EGb 761 Õ or matching placebo, and one or two quickly dissolving, opaque capsules before sleeping, containing donepezil or matching placebo tablets." |
| Blinding of outcome assessment (detection bias)<br>All outcomes | Low risk | Double-blinded trial and no indication that blind was broken before outcome assessment. |
| Incomplete outcome data (attrition bias)<br>All outcomes | Unclear risk | Numbers and reasons for loss to follow up were given, and missing values were replaced by LOCF. The reasons (adverse event, lack of efficacy) may be related to the interventions, but the numbers of those lost to follow-up are low. Data for some outcomes were unclear and possible there was risk of bias from incomplete outcome data. |
| Selective reporting (reporting bias) | Unclear risk | No protocol or trial registration available, and authors described the trial as "explorative" and without defined primary outcomes. However, the outcomes in the methods section are consistent with outcomes in results. |
| Other bias | Low risk | No other apparent source of bias. |

**Yang 2015a**

***Study characteristics***

| | |
|---|---|
| Methods | **Study design:** RCT<br>**Study grouping:** parallel group<br>**Duration of intervention:** 12 weeks<br>**Duration of follow-up:** 12 weeks<br>**Washout or placebo run-in period:** none reported |


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**Yang 2015a** *(Continued)*

| | |
|---|---|
| Participants | **Baseline characteristics**<br><br>*G biloba*<br><br>• Number randomized: 33<br>• MMSE (mean, SD): 22.2, 4.4<br>• Age (mean, SD): 58.9, 6.6<br>• % female: 39.4<br><br>Yi Zhi Ling<br><br>• Number randomized: 33<br>• MMSE (mean, SD): 22.3, 4.6<br>• Age (mean, SD): 58.8, 6.4<br>• % female: 36.4<br><br>**Total number randomized:** 66<br><br>**Inclusion criteria**<br><br>• Stroke within 3 months<br>• No impairment in limb function or cognitive function before stroke<br>• The topic of the study was treatment of cognitive impairment after stroke. Therefore, cognitive impairment is implied as an inclusion criterion.<br><br>**Exclusion criteria**<br><br>• Vascular dementia<br>• AD<br>• Head injury and other conditions inducing limb function and cognitive impairment<br>• Depression<br>• Alcoholism<br>• Severe heart, liver and kidney insufficiency<br>• Gastrointestinal obstruction, ulcers<br><br>**Country:** China<br><br>**Setting:** hospital inpatient<br><br>**Date recruitment began:** 2013<br><br>**Recruitment source/methods:** not reported<br><br>**Diagnosis:** stroke (topic of study was cognitive impairment after stroke)<br><br>**Diagnostic criteria:** stroke |
| Interventions | **Intervention characteristics**<br><br>*G biloba*<br><br>• Oral ginkgo leaf 40 mg, 3 times a day<br><br>Yi Zhi Ling<br><br>• Oral Yi Zhi Ling 6 g, 3 times per day |
| Outcomes | **Outcomes collected**<br><br>• Blessed Behavior Schedule<br>• MMSE |


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**Yang 2015a** *(Continued)*

| | |
|---|---|
| Notes | **Sponsorship source:** none reported<br><br>**Trial registration number(s)**: none reported<br><br>**Note:** it was unclear whether the Blessed Behavior Schedule measured cognitive changes, ADLs, or another construct. Therefore, we did not use it. |

***Risk of bias***

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Random sequence generation (selection bias) | Low risk | Cases were assigned to the treatment group or the control group using a random number table method. |
| Allocation concealment (selection bias) | Unclear risk | Allocation process was not reported. |
| Blinding of participants and personnel (performance bias)<br>All outcomes | Unclear risk | Blinding was not reported. |
| Blinding of outcome assessment (detection bias)<br>All outcomes | Unclear risk | Blinding of outcome assessment was not reported. |
| Incomplete outcome data (attrition bias)<br>All outcomes | Low risk | There was no apparent loss to follow-up in the study. |
| Selective reporting (reporting bias) | Unclear risk | There was no protocol. |
| Other bias | Low risk | No other apparent risk of bias. |

**Yang 2020a**

***Study characteristics***

| | |
|---|---|
| Methods | **Study design:** RCT<br><br>**Study grouping:** parallel group<br><br>**Duration of intervention:** 12 weeks<br><br>**Duration of follow-up:** 12 weeks<br><br>**Washout or placebo run-in period:** none reported |
| Participants | **Baseline characteristics**<br><br>*G biloba* + Butylphthalide<br><br>• Number randomized: 51<br>• MMSE (mean, SD): 23.56, 1.02<br>• Age (mean, SD): 57.04, 6.81<br>• % female: 41.18 |


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**Yang 2020a** *(Continued)*

| | |
|---|---|
| | Butylphthalide<br>• Number randomized: 51<br>• MMSE (mean, SD): 23.78. 1.10<br>• Age (mean, SD): 57.18, 6.52<br>• % female: 35.3%<br><br>**Total number randomized:** 102<br><br>**Inclusion criteria**<br>• Matched with the curative effect standard of Chinese Guidelines for *Diagnosis and Treatment of Vascular Cognitive Impairment* (2016), there were cerebrovascular risk factors or cerebrovascular diseases<br>• No obvious abnormality in liver and kidney function<br>• Voluntary participation and informed consent<br>• MMSE score 21 to 26<br><br>**Exclusion criteria**<br>• Dementia<br>• Cognitive impairment caused by other factors<br>• Depression, anxiety, schizophrenia, and other mental diseases<br>• Severe heart, brain, hematopoiesis, kidney and liver diseases<br>• Brain injury or others that could interfere with cognitive function<br>• Use of relevant treatment within 30 days<br>• Allergic condition, allergy to the drugs used in the study<br><br>**Country:** China<br><br>**Setting:** outpatient<br><br>**Date recruitment began:** 2018<br><br>**Recruitment methods:** people with vascular mild cognitive impairment in Tianjin Academy of Traditional Chinese Medicine Affiliated Hospital from March 2018 to November 2019<br><br>**Diagnosis:** VaMCI<br><br>**Diagnostic criteria:** matched with the curative effect standard of Chinese Guidelines for *Diagnosis and Treatment of Vascular Cognitive Impairment* (2016), there were cerebrovascular risk factors or cerebrovascular diseases |
| Interventions | **Intervention characteristics**<br><br>*G biloba* + Butylphthalide<br>• In addition to the treatment of the control group, the participants in the interventional group were given Yinxing Tongzhi Tablets (0.25 g/tablet, lot number: 20180222, manufactured by SPH Xing Ling Sci. & Tech Pharmaceutical Co, Ltd), 0.15 g/time, 3 times/day. Butylphthalide soft capsules: 0.6 g/day; Yinxing Tongzhi Tablets: 0.45 g/day<br><br>Butylphthalide<br>• The control group was treated with Butylphthalide soft capsules (0.1 g, lot number 20180209, manufactured by CSPC NBP Pharmaceutical Co. Ltd), 0.2 g/time, 3 times/day |
| Outcomes | **Outcomes collected**<br>• Total effective rate: MMSE was used. Total effective rate = (clinical basic control + significant improvement + improvement)/total cases<br>• Serum inflammatory factors and serum neurological function indexes: serum IL-6, TNF-α, and homocysteine (Hcy) were measured by enzyme-linked immunosorbent assay; serum myelin basic protein |


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**Yang 2020a** *(Continued)*

| | |
|---|---|
| | (MBP), central nervous system specific protein (S100 β), and neuron specific enolase (NSE) were determined by radioimmunoassay.<br>• ADL (0–100)<br>• Adverse reactions |
| Notes | **Sponsorship source:** Tianjin Science and technology project (18 ZXDBSY00080)<br>**Trial registration number(s)**: none reported |

***Risk of bias***

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Random sequence generation (selection bias) | Low risk | Cases were assigned to the treatment group or the control group using the random number table method. |
| Allocation concealment (selection bias) | Unclear risk | Allocation process not reported. |
| Blinding of participants and personnel (performance bias)<br>All outcomes | Unclear risk | Blinding was not reported. |
| Blinding of outcome assessment (detection bias)<br>All outcomes | Unclear risk | Blinding of outcome assessment was not reported. |
| Incomplete outcome data (attrition bias)<br>All outcomes | Low risk | There was no apparent loss to follow-up in the study. |
| Selective reporting (reporting bias) | Unclear risk | There was no protocol. |
| Other bias | Low risk | No other apparent risk of bias. |

**Yu 2014**

***Study characteristics***

| | |
|---|---|
| Methods | **Study design:** RCT<br>**Study grouping:** parallel group<br>**Duration of intervention:** 3 months<br>**Duration of follow-up:** 3 months<br>**Washout or placebo run-in period:** none reported |
| Participants | **Baseline characteristics**<br>*G biloba* + Donepezil<br>• Number randomized: 35<br>• MMSE (mean, SD): 15.2, 2.75 |


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**Yu 2014** *(Continued)*

- Age (mean, SD): 63.1, 7.7
- % female: 51.4

Donepezil

- Number randomized: 35
- MMSE (mean, SD): 14.7, 2.81
- Age (mean, SD): 62.5, 7.3
- % female: 57.1

**Total number randomized:** 70

**Inclusion criteria**

- Vascular dementia
- Blood stasis obstruction syndrome (DSVD ≥ 7)
- Age ≥ 55 years
- Mild to moderate dementia
- Informed consent

**Exclusion criteria**

- Severe heart, liver, kidney, hematopoietic system and other primary diseases and malignant tumors
- Geriatric psychosis, schizophrenia
- Obvious comorbidities or complications
- Other diseases that interfere with cognitive function
- Epilepsy or Parkinson's disease
- Severe dementia or end-stage dementia

**Country:** China

**Setting:** hospital

**Date recruitment began:** 2011

**Recruitment methods:** none reported

**Diagnosis:** vascular dementia

**Diagnostic criteria:** DSM-IV, DSVD

| | |
|---|---|
| Interventions | **Intervention characteristics**<br><br>*G biloba* + Donepezil<br><br>• *G biloba* injection intravenous, 20 mL/time, 2 times/day + oral donepezil hydrochloride tablets, 10 mg/day, for 3 months<br><br>Donepezil<br><br>• Oral donepezil hydrochloride tablets, 10 mg/day, for 3 months |
| Outcomes | **Outcomes collected**<br><br>• ADLs, Vascular Dementia Scale, and MMSE before and after treatment<br>• Levels of serous endothelin (ET), NO, superoxide dismutase (SOD), and malonaldehyde (MDA)<br>• Average blood velocities of anterior cerebral artery and middle cerebral artery pulsatility index detected by transcranial Doppler |
| Notes | **Sponsorship source:** none reported |


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**Yu 2014** *(Continued)*

**Trial registration number(s)**: none reported

***Risk of bias***

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Random sequence generation (selection bias) | Low risk | Cases were assigned to the treatment group or the control group using the random number table method. |
| Allocation concealment (selection bias) | Unclear risk | Allocation process was not reported. |
| Blinding of participants and personnel (performance bias)<br>All outcomes | Unclear risk | Blinding was not reported. |
| Blinding of outcome assessment (detection bias)<br>All outcomes | Unclear risk | Blinding of outcome assessment was not reported. |
| Incomplete outcome data (attrition bias)<br>All outcomes | Low risk | There was no apparent loss to follow-up in the study. |
| Selective reporting (reporting bias) | Unclear risk | There was no protocol. |
| Other bias | Low risk | No other apparent risk of bias. |

**Yu 2021**

***Study characteristics***

| | |
|---|---|
| Methods | **Study design:** RCT<br>**Study grouping:** parallel group<br>**Duration of intervention:** 3 months<br>**Duration of follow-up:** 3 months<br>**Washout or placebo run-in period:** no |
| Participants | **Baseline characteristics**<br>*G biloba*<br>• Number randomized: 23<br>• MMSE (mean, SD): NR<br>• Age (mean, SD): 61.4, 3.5<br>• % female: 56.5%<br>Butylphthalide<br>• Number randomized: 23<br>• MMSE (mean, SD): NR<br>• Age (mean, SD): 60.2, 3.2 |


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**Yu 2021** *(Continued)*

- % female: 52.2%

**Total number randomized:** 46

**Inclusion criteria**

- Relevant diagnostic criteria for cerebral small vessel disease confirmed by CT and MRI

**Exclusion criteria**

- Cognitive impairment caused by serious underlying diseases, mental diseases, and other diseases

**Country:** China

**Setting:** inpatient

**Date recruitment began:** 2018

**Recruitment source/methods:** people with cerebral small vessel disease and cognitive impairment who were admitted to the author's hospital between December 2018 and December 2019 were recruited.

**Diagnosis:** cerebral small vessel disease

**Diagnostic criteria:** CT and MRI examinations

| | |
|---|---|
| Interventions | **Intervention characteristics**<br>Butylphthalide capsules<br>• Butylphthalide capsules (0.1 g/capsule, CSPC Enbipu Pharmaceutical Co, Ltd, National Pharmaceutical Approval H20050299) were taken orally on an empty stomach, 0.2 g/time, 3 times/day, for 3 consecutive months. Dose 0.6 g/day.<br>*G biloba*<br>• Description of intervention from the report (both the product and administration): *G biloba* extract tablets (40 mg/tablet, Dr Weimar Shupei Pharmaceutical Factory, Germany, registration number H20090296) taken orally, 40 mg/time, 3 times/day. Dose 120 mg/day. |
| Outcomes | **Outcomes collected**<br>• Curative effect<br>• MoCA<br>• IADL |
| Notes | **Sponsorship source:** none reported<br>**Trial registration number:** none reported |

***Risk of bias***

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Random sequence generation (selection bias) | Low risk | Random number table. |
| Allocation concealment (selection bias) | Unclear risk | Not mentioned. |
| Blinding of participants and personnel (performance bias) | Unclear risk | Not mentioned. |


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**Yu 2021** *(Continued)*

| | | |
|---|---|---|
| All outcomes | | |
| Blinding of outcome assessment (detection bias)<br>All outcomes | Unclear risk | Not mentioned. |
| Incomplete outcome data (attrition bias)<br>All outcomes | Low risk | No attrition. |
| Selective reporting (reporting bias) | Unclear risk | No protocol. |
| Other bias | Low risk | No other apparent risk of bias. |

**Zhang 2016a**

| ***Study characteristics*** | |
|---|---|
| Methods | **Study design:** RCT<br>**Study grouping:** parallel group<br>**Duration of intervention:** 12 weeks<br>**Duration of follow-up:** 12 weeks<br>**Washout or placebo run-in period:** none reported |
| Participants | **Baseline characteristics**<br>*G biloba*<br>• Number randomized: 60<br>• MMSE (mean, SD): 25.3, 3.00<br>• Age (mean, SD): 65.6, 3.1<br>• % female: 33.3<br>Tongxinluo capsule<br>• Number randomized: 60<br>• MMSE (mean, SD): 23.10, 2.12<br>• Age (mean, SD): 63.8, 3.2<br>• % female: 36.67<br>**Total number randomized:** 120<br>**Inclusion criteria**<br>• Age 50 to 80 years<br>• Slow progress, with mild or moderate dementia with:<br>  ◦ typical symptoms of dementia, such as memory, calculation, orientation impaired;<br>  ◦ significant changes in mood or personality;<br>  ◦ significant decline or defects within 6 months; and<br>  ◦ brain changes (diffuse lesions of the brain parenchyma) in annual CT examination.<br>**Exclusion criteria** |


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**Zhang 2016a** *(Continued)*

- Previous serious mental illnesses, such as schizophrenia
- Central nervous system infections, poisoning, or consciousness disorders

**Country:** China

**Setting:** hospital

**Date recruitment began:** 2012

**Recruitment source/methods:** none reported

**Diagnosis:** older people with cognitive impairment

**Diagnostic criteria:** Diagnostic Standards of Chinese Medicine for dementia based on *Guiding Principles for Clinical Research of New Chinese Medicines* published in 1993. Western medicine diagnostic standards are based on the *Standards for Diagnosis and Evaluation of Alzheimer's Disease* proposed by the First National Geriatrics Conference in Lanzhou in 1988.

| | |
|---|---|
| Interventions | **Intervention characteristics**<br>*G biloba*<br>• 2 tablets taken orally, 3 times a day, 12 weeks<br>Tongxinluo capsule<br>• 4 capsules taken orally, 3 times a day, 12 weeks |
| Outcomes | **Outcomes collected**<br>• MMSE<br>• Daily life self-care scale (ADLs)<br>• Laboratory tests |
| Notes | **Sponsorship source:** project funded by Hebei Provincial Administration of Traditional Chinese Medicine (20111095)<br>**Trial registration number(s)**: none reported |

***Risk of bias***

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Random sequence generation (selection bias) | Low risk | Cases were assigned to the treatment group or the control group using the random number table method. |
| Allocation concealment (selection bias) | Unclear risk | Allocation process not reported. |
| Blinding of participants and personnel (performance bias)<br>All outcomes | Unclear risk | Blinding not reported. |
| Blinding of outcome assessment (detection bias)<br>All outcomes | Unclear risk | Blinding of outcome assessment not reported. |
| Incomplete outcome data (attrition bias)<br>All outcomes | Low risk | There was no apparent loss to follow-up in the study. |


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**Zhang 2016a** *(Continued)*

| | | |
|---|---|---|
| Selective reporting (reporting bias) | Unclear risk | There was no protocol. |
| Other bias | Low risk | No other apparent risk of bias. |

**Zhang 2019a**

| ***Study characteristics*** | |
|---|---|
| Methods | **Study design:** RCT<br><br>**Study grouping:** parallel group<br><br>**Duration of intervention:** 12 weeks<br><br>**Duration of follow-up:** 12 weeks<br><br>**Washout or placebo run-in period:** none reported |
| Participants | **Baseline characteristics**<br><br>*G biloba* + Donepezil<br><br>• Number randomized: 36<br>• MMSE (mean, SD): 16.94, 1.91<br>• Age (mean, SD): 51.94, 1.73<br>• % female: 36.11<br><br>Donepezil<br><br>• Number randomized: 36<br>• MMSE (mean, SD): 17.15, 2.23<br>• Age (mean, SD): 52.31, 2.12<br>• % female: 41.67<br><br>**Total number randomized:** 72<br><br>**Inclusion criteria**<br><br>• CT or MRI diagnosis of cerebral infarction<br>• Diagnosis of cognitive impairment after cerebral infarction according to the 2011 "Guidelines for the Treatment of Cerebral Cognitive Impairment"<br>• No other serious complications or diseases that may affect the research outcomes<br>• Compliance with the whole protocol provided in this research<br>• Informed consent<br><br>**Exclusion criteria**<br><br>• Caregiver rejection of relevant testing and treatment process<br>• Severe diseases of the immune system, nervous system, or circulatory system, or diseases that may affect the outcomes of this study<br>• Caregiver refusal to sign the informed consent for this study<br>• Obvious symptoms of consciousness disorder, inability to co-operate to complete the treatment and research<br>• Severe allergies, or severe allergies to the drugs or equipment used in this study<br><br>**Country:** China |


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**Zhang 2019a** *(Continued)*

| | |
|---|---|
| | **Setting:** hospital<br><br>**Date recruitment began:** 2016<br><br>**Recruitment methods:** not reported<br><br>**Diagnosis:** cognitive impairment after cerebral infarction<br><br>**Diagnostic criteria**<br><br>• CT or MRI diagnosis of cerebral infarction<br>• Diagnosis of cognitive impairment after cerebral infarction according to the 2011 "Guidelines for the Treatment of Cerebral Cognitive Impairment" |
| Interventions | **Intervention characteristics**<br><br>*G biloba* + Donepezil<br><br>• *G biloba* (Zhejiang Conba Pharmaceutical Co, Ltd, number: 171120) on the basis of the control group, 1 tablet/time, 3 times/day, 30 minutes after each meal, 1 month for 1 treatment cycle, 3 consecutive cycles.<br><br>Donepezil<br><br>• Donepezil hydrochloride tablets alone, 1 tablet/day, once/day, every night before going to bed, 1 month as 1 cycle, and continuous treatment for 3 cycles. |
| Outcomes | **Outcomes collected**<br><br>• Kyohko Hasegawa Dementia Scale (HDS)<br>• MMSE<br>• EEG<br>• Curative effects (based on ADAS-cog)<br>• Adverse effects |
| Notes | **Sponsorship source:** Zhejiang Province Public Welfare Technology Research and Social Development Project (2016C33SAA01495)<br><br>**Trial registration number(s)**: none reported |

***Risk of bias***

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Random sequence generation (selection bias) | Low risk | Cases were assigned to the treatment group or the control group using a random number table method. |
| Allocation concealment (selection bias) | Unclear risk | Allocation process not reported. |
| Blinding of participants and personnel (performance bias)<br>All outcomes | Unclear risk | Blinding was not reported. |
| Blinding of outcome assessment (detection bias)<br>All outcomes | Unclear risk | Blinding of outcome assessment not reported. |
| Incomplete outcome data (attrition bias) | Low risk | There was no apparent loss to follow-up in the study. |


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**Zhang 2019a** *(Continued)*
All outcomes

| | | |
|---|---|---|
| Selective reporting (reporting bias) | Unclear risk | There was not a protocol. |
| Other bias | Low risk | No other apparent risk of bias. |

**Zhang 2022**

| | |
|---|---|
| ***Study characteristics*** | |
| Methods | **Study design:** RCT<br><br>**Study grouping:** parallel group<br><br>**Duration of intervention:** 24 weeks<br><br>**Duration of follow-up:** 24 weeks<br><br>**Washout or placebo run-in period:** no |
| Participants | **Baseline characteristics**<br><br>*G biloba*<br><br>• Number randomized: 45<br>• MMSE (mean, SD): median 24 (IQR 24 to 25)<br>• Age (mean, SD): 70.58, 7.22<br>• % female: 60%<br><br>Guilingji capsules<br><br>• Number randomized: 37<br>• MMSE (mean, SD): median 24 (IQR 24 to 25)<br>• Age (mean, SD): 69.54, 7.10<br>• % female: 46%<br><br>**Number randomized:** 96 at baseline, and follow-up data were only provided for the 82 who completed the study.<br><br>**Inclusion criteria:** "The inclusion criteria for this study were as follows: (1) age between 60 and 85 years; (2) fulfillment of the diagnostic criteria for VaMCI according to the fifth edition of the Diagnostic and Statistical Manual of Mental Disorders[49] and the guidelines of the American Heart Association/American Stroke Association [50]; (3) brain magnetic resonance imaging and computed tomography (CT) scans consistent with a diagnosis of MCI [3]; (4) Clinical Dementia Rating (CDR) score ≤ 0.5 [51]; (5) MMSE score > 24 and MoCA score > 22, indicating a diagnosis of MCI and not VaD; (6) case history that indicates a causal relationship between cognitive decline and cerebrovascular disease, for example, cognitive impairment that occurred within 3 months of cerebrovascular disease, Hachinski Ischemic Scale (HIS) score ≥ 7, or absence of cerebrovascular disease but presence of a decrease in information processing and/or execution function; and (7) Activity of Daily Living (ADL) score ≤ 26."<br><br>**Exclusion criteria:** "The exclusion criteria were as follows: (1) severe neurological deficits, such as Parkinson's disease, epilepsy, brain tumors, brain edema, traumatic brain injuries, hypothyroidism, encephalitis, Huntington's disease, severe anemia, infections, or other endocrine diseases; (2) depression(reference, Hamilton Depression Rating Scale) or other mental diseases; (3) recent use (within 3 months) of drugs that may affect cognitive function or an allergy to the drugs used in this study; and (4) an allergy to Ginkgo extract tablets and Chinese medicine ingredients."<br><br>**Country:** China |


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**Zhang 2022** *(Continued)*

**Setting:** inpatient and outpatient

**Date recruitment began:** 2019

**Recruitment methods:** NR other than "This study was performed at the outpatient and inpatient departments of the Xiyuan Hospital of China Academy of Chinese Medical Sciences and the Affiliated Hospital of Shandong University of Traditional Chinese Medicine from August 2019 to October 2020."

**Diagnosis:** vascular MCI (VaMCI)

**Diagnostic criteria:** DSM-V and the guidelines of the American Heart Association/American Stroke Association

| | |
|---|---|
| Interventions | **Intervention characteristics**<br><br>*G biloba*<br><br>• "Patients in the Ginkgo group took Ginkgo extract tablets (19.2 mg, orally, three times daily for a total of 57.6 mg per day; provided by Yangzijiang Pharmaceutical Group Co., Ltd., Nanjing, China; Batch No.: 10010321) combined with a placebo Guilingji capsule (0.6 g, orally, once daily). The placebo was consistent with the experimental drug in appearance, smell, and packaging. A 12-week intervention period constituted a course of treatment. Thus, the 24-week intervention period comprised two courses of treatment."<br><br>Guilingji capsules<br><br>• "Patients in the GLJC group took Guilingji capsules (0.6 g, orally, once daily; provided by GuangyuyuanCo., Ltd., Shanxi, China; Batch No.: 103180601) and placeboGinkgo extract tablets (19.2 mg, orally, three times daily)....The placebo was consistent with the experimental drug in appearance, smell, and packaging. A 12-week intervention period constituted a course of treatment. Thus, the 24-week intervention period comprised two courses of treatment." |
| Outcomes | **Outcomes collected**<br><br>• MoCA<br>• MMSE<br>• ADAS-Cog<br>• Chinese Medicine Symptom Scale (CM-SS)<br>• Serum ACh, AChE, Hcy, and hs-CRP |
| Notes | Sponsorship source: "This study was funded by the National Natural Science Foundation of China (No. 81873350), Innovation Team and Talents Cultivation Program of National Administration of Traditional Chinese Medicine (No. ZYYCXTD-C-202007), and the Beijing Natural Science Foundation (No. 7202174)."<br><br>Trial registration number: NCT03647384 |

***Risk of bias***

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Random sequence generation (selection bias) | Low risk | "SAS 9.2 software (SAS Institute Inc., Cary, NC, USA) was used to generate random numbers." SAS 9.2 software (SAS Institute Inc., Cary, NC, USA) was used to generate random numbers. "random numbers were assigned to the participants by an independent statistician at the GCP Center of Xiyuan Hospital. All participants were randomly and evenly divided either into the Ginkgo group (n = 48) or the GLJC group (n = 48) using blocked randomization (block = 16, length = 6)." |
| Allocation concealment (selection bias) | Low risk | "random numbers were assigned to the participants by an independent statistician at the GCP Center of Xiyuan Hospital. All participants were randomly and evenly divided either into the Ginkgo group (n = 48) or the GLJC group (n = 48) |


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**Zhang 2022** *(Continued)*

| | | |
|---|---|---|
| | | using blocked randomization (block = 16, length = 6). Drugs were numerically labeled and sequenced according to the random numbers, and the patients were assigned to either group in accordance with the sequence. Patients received either ginkgo extract tablets and a placebo or GLJC and a placebo, depending on their group. The clinicians, participants, statistician, and outcome assessors were blinded to the assignment until completion of the study. Allocation concealment was performed using sealed opaque envelopes." Allocation concealment was performed using sealed opaque envelopes. "database was locked after the input of all data, and group information were revealed when statistical analyses were conducted." |
| Blinding of participants and personnel (performance bias)<br>All outcomes | Low risk | "database was locked after the input of all data, and group information were revealed when statistical analyses were conducted. Unblinding was allowed only in the case of a patient emergency." The clinicians, participants, statistician, and outcome assessors were blinded to the assignment until completion of the study. |
| Blinding of outcome assessment (detection bias)<br>All outcomes | Low risk | The clinicians, participants, statistician, and outcome assessors were blinded to the assignment until completion of the study. |
| Incomplete outcome data (attrition bias)<br>All outcomes | High risk | "In total, 14 patients dropped out during the study and 82 completed the trial."<br><br>A high proportion of participants were missing data (15%), the proportion of participants missing data varied between groups (11 in GLJC group and 3 in ginkgo group), and there was no exploration of the participant characteristics and no sensitivity analyses or other approaches to exploring the possible impact on results. |
| Selective reporting (reporting bias) | High risk | "the trial was registered with the China Clinical Trials Registry (ID: https://clinicaltrials.gov/ct2/show/NCT03647384) on August 23, 2018."<br><br>Although the trial was preregistered, some outcomes were not reported. The CDR and ADL, which were 2 outcomes listed in the registration, were measured prior to the intervention but postintervention results were not reported or even mentioned. |
| Other bias | Low risk | No other apparent sources of bias. |

**Zhao 2020**

| | |
|---|---|
| ***Study characteristics*** | |
| Methods | **Study design:** RCT<br><br>**Study grouping:** parallel group<br><br>**Duration of intervention:** 12 months<br><br>**Duration of follow-up:** 12 months<br><br>**Washout or placebo run-in period:** no |
| Participants | **Baseline characteristics**<br><br>*G biloba*<br><br>• Number randomized: 50 |


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**Zhao 2020** *(Continued)*

- MMSE (mean, SD): 21.36, 2.69
- Age (mean, SD): NR
- % female: 52

Routine therapy

- Number randomized: 50
- MMSE (mean, SD): 20.98, 2.71
- Age (mean, SD): NR
- % female: 54

**Total number randomized:** 100

**Inclusion criteria**

- mVCI diagnostic criteria, set by the International Society for Vascular Behavioral and Cognitive Disorders in 2014
- Cerebrovascular disease duration ≤ 3 months
- NIHSS score ≤ 8
- Voluntary participation and informed consent

**Exclusion criteria**

- Hemorrhagic cerebrovascular disease
- Other diseases that cause cognitive impairment, (e.g. AD, Lewy body disease, frontal-temporal dementia, Parkinson's dementia, and traumatic dementia)
- Severe primary mental psychological disease
- Severe disease in heart, lung, liver, kidney or other severe systemic disease
- Communication difficulty due to aphasia and incapability to co-operate in questionnaire assessment
- Participation in other clinical trials 4 weeks before enrollment

**Country:** China

**Setting:** inpatient

**Date recruitment began:** 2017

**Recruitment source/methods:** inpatients in the neurology department in the third people's hospital in Bengbu city from May 2017 to November 2018

**Diagnosis:** mVCI

**Diagnostic criteria:** mVCI diagnostic criteria, set by the International Society for Vascular Behavioral and Cognitive Disorders in 2014

| | |
|---|---|
| Interventions | **Intervention characteristics**<br><br>*G biloba*<br><br>• Routine therapy + EGb761 (Dr Willmar Schwabe Pharmaceuticals, Germany): EGb761 injection (87.5 mg, once a day) for 14 days, and then EGb761 tablet (40 mg, 3 times/day) for 11.5 months<br><br>Routine therapy<br><br>• Standard therapy used for stroke |
| Outcomes | **Outcomes collected**<br><br>• MMSE<br>• MoCA<br>• HAM-D |


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**Zhao 2020** *(Continued)*

- HAMA
- TMT-A/B
- BNT-2
- AVLT-H
- CDT
- IADL
- NPI
- NIHSS
- MRS

| | |
|---|---|
| Notes | **Sponsorship source:** NR<br>**Trial registration number:** NR |

***Risk of bias***

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Random sequence generation (selection bias) | Low risk | Random number table. |
| Allocation concealment (selection bias) | Unclear risk | Not reported. |
| Blinding of participants and personnel (performance bias)<br>All outcomes | High risk | Not reported. However, since the dosage form in the treatment group is distinct from that in the control group, it is likely the outcomes were influenced by lack of blinding. |
| Blinding of outcome assessment (detection bias)<br>All outcomes | Unclear risk | Not reported. It is unclear the extent to which outcomes were influenced by lack of blinding. |
| Incomplete outcome data (attrition bias)<br>All outcomes | High risk | There is attrition, and new participants were enrolled after attrition. |
| Selective reporting (reporting bias) | Unclear risk | No protocol available. Insufficient information to permit judgment. |
| Other bias | Low risk | No other apparent sources of bias. |

**Zheng 2020**

***Study characteristics***

| | |
|---|---|
| Methods | **Study design:** RCT<br>**Study grouping:** parallel group<br>**Duration of intervention:** 3 months<br>**Duration of follow-up:** 3 months<br>**Washout or placebo run-in period:** none reported |


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**Zheng 2020** *(Continued)*

| | |
|---|---|
| Participants | **Baseline characteristics**<br><br>*G biloba* plus donepezil<br><br>• Number randomized: 50<br>• MMSE (mean, SD): 12.93, 1.43<br>• Age (mean, SD): 63.04, 6.83<br>• % female: 46<br><br>Donepezil<br><br>• Number randomized: 50<br>• MMSE (mean, SD): 12.80, 1.40<br>• Age (mean, SD): 63.13, 7.80<br>• % female: 48<br><br>**Total number randomized:** 100<br><br>**Inclusion criteria**<br><br>• "The diagnosis meets the diagnostic criteria by American Academy of Neurology "Diagnostic and Statistical Manual of Mental Disorders" [3] and the "Vascular Dementia Syndrome Differentiation Scale" [4], and CDR shows patients with mild to moderate dementia<br>• Memory impairment of different degrees diagnosed as cerebrovascular disease by MRI or CT and other imaging examinations<br>• Hachinski ischemia is less than 4 points<br>• The patient himself and his family members are willing to cooperate in completing all research projects and treatments, and obtain informed consent form voluntarily or by the family members."<br><br>**Exclusion criteria**<br><br>• Various neurological diseases or serious medical diseases<br>• History of severe brain injury that affects brain function and sensory function<br><br>**Country:** China<br><br>**Setting:** inpatients and outpatients<br><br>**Date recruitment began:** 2018<br><br>**Recruitment methods:** not reported<br><br>**Diagnosis:** mild and moderate vascular dementia<br><br>**Diagnostic criteria:** "the diagnosis meets the diagnostic criteria by American Academy of Neurology "Diagnostic and Statistical Manual of Mental Disorders" [3] and the "Vascular Dementia Syndrome Differentiation Scale" [4], and CDR shows patients with mild to moderate dementia" |
| Interventions | **Intervention characteristics**<br><br>*G biloba* + donepezil<br><br>• Ginkgo ketone ester dropping pills combined with donepezil orally, 4 pills each time, 3 times a day (120 mg/day ginkgo ketone ester and 5 mg/day donepezil hydrochloride)<br><br>Donepezil<br><br>• Donepezil hydrochloride tablets orally, 5 mg each time, once a day |
| Outcomes | **Outcomes collected**<br><br>• MMSE |


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**Zheng 2020** *(Continued)*

- ADLs
- Clinical Dementia Rating Scale (CDR)
- Carotid intimal thickness (mm)

| | |
|---|---|
| Notes | **Sponsorship source:** Scientific Research Project of Chaozhou Health and Family Planning Bureau<br>**Trial registration number(s)**: none reported |

***Risk of bias***

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Random sequence generation (selection bias) | Low risk | Cases were assigned into treatment group or control group by random number table method. |
| Allocation concealment (selection bias) | Unclear risk | Allocation process not reported. |
| Blinding of participants and personnel (performance bias)<br>All outcomes | Unclear risk | Blinding not reported. |
| Blinding of outcome assessment (detection bias)<br>All outcomes | Unclear risk | Blinding of outcome assessment not reported. |
| Incomplete outcome data (attrition bias)<br>All outcomes | Low risk | There was no apparent loss to follow-up in the study. |
| Selective reporting (reporting bias) | Unclear risk | There was no protocol. |
| Other bias | Low risk | No other apparent risk of bias. |

**Zheng 2021**

***Study characteristics***

| | |
|---|---|
| Methods | **Study design:** RCT<br>**Study grouping:** parallel group<br>**Duration of intervention:** 3 months<br>**Duration of follow-up:** 3 months<br>**Washout or placebo run-in period:** no |
| Participants | **Baseline characteristics**<br>*G biloba*<br>• Number randomized: 28<br>• MMSE (mean, SD): 24.03, 0.22<br>• Age (mean, SD): 61.75, 2.18 |


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**Zheng 2021** *(Continued)*

- % female: 46.4%

Fu Xiu Qi Zhi acupuncture

- Number randomized: 29
- MMSE (mean, SD): 24.57, 0.83
- Age (mean, SD): 63.21, 3.86
- % female: 51.7%

**Total number randomized:** 60

**Inclusion criteria**

- Diagnostic criteria of MCI
- Age 45 to 75 years
- Right-handed
- Junior high school education and above
- Voluntary participation and informed consent

**Exclusion criteria**

- Cognitive dysfunction caused by other diseases
- Clinically diagnosed dementia
- History of mental illness or cognitive function affected by antipsychotic drugs
- Severe heart, brain, liver, and kidney diseases
- Use of any drugs to improve cognitive function or other treatments related to improving cognitive function in the past 30 days

**Country:** China

**Setting:** outpatient

**Date recruitment began:** 2018

**Recruitment methods:** people with MCI who visited the Rehabilitation Hospital Affiliated to Fujian University of Traditional Chinese Medicine from July 2018 to June 2020 were recruited.

**Diagnosis:** MCI

**Diagnostic criteria:** standards formulated by the International MCI Working Group and the European Alzheimer's Disease MCI Working Group.

- Subjective perception of cognitive decline by the participant or informed person
- Objective examination of impaired cognitive function
- Ability of daily living is basically normal.

Interventions

**Intervention characteristics**

*G biloba*

- *G biloba* extract drops (Bayer Pharmaceutical and Healthcare Co, Ltd, lot number H20003010). 2 mL each time, 3 times a day (total of 6 mL/day), for 12 consecutive weeks.

Fu Xiu Qi Zhi acupuncture

- Acupoint selection: Shenting Toushangxing, Yintang, Yingxiang (both sides), Fengchi (both sides), Hegu (both sides), Zusanli (both sides). Once/day, treatment in the morning every day, continuous treatment for 5 days, rest for 2 days, 4 weeks as a course of treatment, a total of 3 courses of treatment.

Outcomes

**Outcomes collected**

- MMSE


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**Zheng 2021** *(Continued)*

| | |
|---|---|
| | • MoCA |
| Notes | **Sponsorship source:** Educational Research Project for Young and Middle-aged Teachers of Fujian Provincial Department of Education (JT180249)<br><br>**Trial registration number:** NR<br><br>We contacted the study author to obtain information regarding method of randomization and they reported use of a random number table. |

***Risk of bias***

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Random sequence generation (selection bias) | Low risk | Random number table. |
| Allocation concealment (selection bias) | Unclear risk | Not mentioned. |
| Blinding of participants and personnel (performance bias)<br>All outcomes | Unclear risk | Not mentioned. |
| Blinding of outcome assessment (detection bias)<br>All outcomes | Low risk | Not mentioned. |
| Incomplete outcome data (attrition bias)<br>All outcomes | Low risk | No attrition. |
| Selective reporting (reporting bias) | Unclear risk | No protocol. |
| Other bias | Low risk | No other apparent source of bias. |

**Abbreviations:** AAMI: age-associated memory impairment; ACA: anterior cerebral artery; ACh: acetylcholine; AChE: ace1tylcholine esterase; AD: Alzheimer's disease; ADAL-IS: Activities of Daily Living International Scale; ADAS-Cog: Alzheimer's Disease Assessment Scale – cognition; ADLs: activities of daily living; aMCI: amnestic mild cognitive impairment; AMIPB-DSR: Adult Memory and Information Processing Battery Logical Memory Delayed Story Recall; AVLT-H: Auditory Verbal Learning Test-Huashan version; BDI: Beck Depressive Inventory; BDI-II: Beck Depression Inventory-II; BDNF: brain-derived neurotrophic factor; BNT-2: Boston Naming Test Version 2; CAMCOG: Cambridge Cognitive Examination; CDR: Clinical Dementia Rating Scale; CDR-GS: Clinical Dementia Rating Global Score; CDT: Clock Drawing Task; CGI: Clinical Global Impression Scale; CGI Item 2: Clinical Global Impression Item 2; CI: confidence interval; CIBIC – PLUS: Clinician's Interview-Based Impression of Change (plus caregiver input); CIQ: Community Integration Questionnaire; CMS: clinical memory scale; CM-SS: Chinese Medicine Symptom Scale; COWAT: Controlled Oral Word Association Test; CSVCL: cognitive impairment caused by cerebral small vessel disease; CSVD: cerebral small vessel disease; CT: computed tomography; CVLT-II: California Verbal Learning Test II; DA: dopamine; DPD: Dementia-Pseudodementia-Differentiation Curve; DSM-3: *Diagnostic and Statistical Manual of Mental Disorders*, Third Edition; DSM-IV: *Diagnostic and Statistical Manual of Mental Disorders*, Fourth Edition; DSM-V: *Diagnostic and Statistical Manual of Mental Disorders*, Fifth Edition; DSMB: data and safety monitoring board; DSVD: Vascular Dementia Scale; D-S': Depression Scale; ECG: electrocardiogram; EEG: electroencephalogram; EMCT: Expanded Mental Control Test; ET: serous endothelin; FEAG: Questionnaire for Assessing Subjectively Experienced Memory Performance in Everyday Life (*Fragebogen zur Erfassung alltäglicher Gedächtniserfahrungen*); GBS: Gottfries, Brane and Steen scale; GERRI: Geriatric Evaluation by Relative's Rating Instrument; GSH-Px: glutathione peroxidase; HAM-D: Hamilton Rating Scale for Depression; HAMA: Hamilton Anxiety Scale; Hcy: homocysteine ; HDS: Hasegawa Dementia Scale; HIS: Hachinski ischemia score; HPLC: high-performance liquid chromatography; hs-CRP: high sensitivity C-reactive protein; IADL: Instrumental Activities of Daily Living; ICD-9: International Classification of Diseases, Ninth Revision; ICD-10: International Classification of Diseases, 10th Revision; ICD-290x: dementia and other organic psychotic conditions within the ICD-9-CM (International Classification of Diseases, Ninth Revision, Clinical Modification) system; IL-6: interleukin-6; IQ: intelligence quotient; ITT: intention-to-treat; LM: logical memory; LOCF: last observation


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carried forward; MBP: serum myelin basic protein; MCA: middle cerebral artery; MCI: mild cognitive impairment; MDA: malonaldehyde; MDBF: Multidimensional Wellbeing Questionnaire; MoCA: Montreal Cognitive Assessment; MDRS: Mattis Dementia Rating Scale; MFIS: Modified Fatigue Impact Scale; MMSE: Mini Mental State Examination; MQ: memorial quotient; MRI: magnetic resonance imaging; MRS: Modified Rankin Scale; MSQLI: Multiple Sclerosis Quality of Life Inventory; MSNSQ: Multiple Sclerosis Neuropsychological Screening Questionnaire; mVCI: mild vascular cognitive impairment; MWT-B: multiple-choice vocabulary test; NGF: neurotrophic factor; NIA-AA: National Institute on Aging–Alzheimer's Association; NIHSS: National Institute of Health Stroke Scale; NINCDS-ADRDA: National Institute of Neurological and Communicative Disorders and Stroke-Alzheimer's Disease and Related Disorders Association; NINDS/AIREN: National Institute of Neurological Disorders and Stroke-Association Internationale pour la Recherche et l'Enseignement en Neurosciences; NO: nitric oxide; NPI: Neuropsychiatric Inventory; NR: not reported; NSAIDs: nonsteroidal anti-inflammatory drugs; NSE: neuron-specific enolase; PASAT: Paced Auditory Serial Addition Test; PDQ: Perceived Deficits Questionnaire; QGST: Qinggongshoutao; RBC-Ach: red blood cell acetylcholine; RBC-AchE: red blood cell acetylcholinesterase; SCAG: Sandoz Clinical Assessment Geriatric Scale; SD: standard deviation; SDMT: Symbol Digit Modalities Test; SKT: *Syndrom-Kurztest* (short cognitive performance test); sLRP-1: soluble low-density lipoprotein receptor-related protein 1; SOD: superoxide dismutase; sRAGE: soluble receptor for advanced glycation end products; STAI-X1: State-Trait Anxiety Inventory-X1; Stroop: Stroop Color-Word Test Victoria version; S100 β: central nervous system specific protein; TBA: thiobarbituric acid; TCM: traditional Chinese medicine; TE4D:Test for Early Detection of Dementia with Discrimination from Depression; TMT: Trail Making Test; TNF-α: tumor necrosis factor-alpha; UFOV: Useful Field of View Test; VaMCI: vascular mild cognitive impairment; VCI: vascular cognitive impairment; VCIND: vascular cognitive impairment, no dementia; VD: vascular dementia; VFT: verbal fluency test; WMS: Wechsler Memory Scale; WMS-RC: Wechsler Memory Scale–Revised Chinese version; ZN-G: *Zahlen-Nachsprechen-Test G*; ZVT: *Zahlenverbindungstest*.

**Characteristics of excluded studies** *[ordered by study ID]*

| Study | Reason for exclusion |
|---|---|
| Allain 1993 | Duration < 12 weeks |
| Arrigo 1986 | Duration < 12 weeks |
| Attia 2012 | Ineligible patient population |
| Augustin 1976 | Ineligible patient population (unclear whether all participants had cognitive problems) |
| Baeurle 2009 | Duration < 12 weeks |
| Bai 2008 | Ineligible patient population |
| Barton 2013 | Ineligible patient population |
| Beck 2016 | Duration < 12 weeks |
| Bono 1975 | Duration < 12 weeks |
| Cai 2015 | Ineligible intervention |
| Cao 1999 | Duration < 12 weeks |
| Chang 2012 | Duration < 12 weeks |
| Chen 2008 | Duration < 12 weeks |
| Chen 2011 | Ineligible intervention |
| Chen 2014b | Ineligible patient population |
| Chen 2014c | Ineligible patient population |
| Chen 2015a | Duration < 12 weeks |
| Chen 2015b | Ineligible patient population |


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| Study | Reason for exclusion |
|---|---|
| Chen 2016a | Duration < 12 weeks |
| Chen 2016b | Ineligible patient population |
| Chen 2019a | Ineligible patient population |
| Chen 2019b | Duration < 12 weeks |
| Chen 2019c | Ineligible patient population |
| Chen 2020 | Ineligible intervention |
| Chen 2021 | Duration < 12 weeks |
| Cheng 2016 | Ineligible patient population |
| ChiCTR1900023665 2019 | Ineligible patient population |
| ChiCTR1900027301 2019 | Ineligible patient population |
| ChiCTR1900028391 2019 | Ineligible intervention |
| ChiCTR2200058031 2022 | Ineligible intervention |
| ChiCTR TRC 09000626 2005 | Ineligible intervention |
| ChiCTR TRC 12002688 2012 | Ineligible patient population |
| ChiCTR TRC 13003968 2013 | Ineligible patient population |
| ChiCTR TRC 14004380 2014 | Ineligible patient population |
| Cockle 2000 | Ineligible patient population |
| Cui 2017 | Ineligible patient population |
| Cui 2023 | Ineligible patient population |
| Dang 2009 | Duration < 12 weeks |
| Davydova 2011 | Duration < 12 weeks |
| Ding 2010 | Duration < 12 weeks |
| Dodge 2008 | Ineligible patient population |
| Drabaek 1996 | Ineligible patient population |
| Eckmann 1982 | Duration < 12 weeks |
| Eckmann 1990 | Duration < 12 weeks |
| EUCTR2007 005377 63 FR 2008 | Duration < 12 weeks |
| Fan 2014 | Ineligible patient population |


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| Study | Reason for exclusion |
|---|---|
| Fang 2010 | Duration < 12 weeks |
| Fang 2021 | Duration < 12 weeks |
| Feng 1999 | Ineligible patient population |
| Fu 2004 | Duration < 12 weeks |
| Fu 2011 | Ineligible intervention |
| Gao 2012 | Duration < 12 weeks |
| Gao 2020 | Ineligible intervention |
| Ge 2017 | Ineligible patient population |
| Gerhardt 1990 | Duration < 12 weeks |
| Gong 2020 | Ineligible patient population |
| Graessel 1992 | Ineligible patient population: unclear that all participants had cognitive problems |
| Guan 2015 | Ineligible comparator |
| Guo 2006 | Duration < 12 weeks |
| Guo 2015 | Ineligible intervention |
| Guo 2018 | Ineligible patient population |
| Haan 1982 | Duration < 12 weeks |
| Haase 1996 | Duration < 12 weeks |
| Hao 2011 | Ineligible patient population |
| Hao 2017 | Duration < 12 weeks |
| He 2015a | Ineligible patient population |
| He 2015b | Duration < 12 weeks |
| He 2021 | Duration < 12 weeks |
| He 2024 | Ineligible patient population |
| Hofferberth 1989 | Duration < 12 weeks |
| Hofferberth 1991 | Duration < 12 weeks |
| Hu 2009 | Duration < 12 weeks |
| Hu 2015 | Ineligible patient population |
| Hu 2018 | Duration < 12 weeks |


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| Study | Reason for exclusion |
|---|---|
| Hu 2019 | Ineligible patient population |
| Huang 2023 | Ineligible patient population |
| IRCT20191223045864N1 2020 | Ineligible patient population |
| IRCT20200218046537N1 2020 | Ineligible patient population |
| Itil 1998 | Duration < 12 weeks |
| Jeffrey 2008 | Ineligible patient population |
| Jia 2014 | Ineligible patient population |
| Jia 2015 | Ineligible patient population |
| Jian 2014 | Ineligible intervention |
| Jiang 2020 | Duration < 12 weeks |
| JPRN UMIN000020894 2016 | Ineligible intervention |
| Kade 1993 | Duration < 12 weeks |
| Karibinur 2013 | Duration < 12 weeks |
| Koltringer 1995 | Duration < 12 weeks |
| Lei 2017 | Ineligible patient population |
| Li 1999 | Duration < 12 weeks |
| Li 2007a | Ineligible patient population |
| Li 2012 | Ineligible patient population |
| Li 2013b | Duration < 12 weeks |
| Li 2014 | Duration < 12 weeks |
| Li 2015b | Ineligible patient population |
| Li 2016b | Ineligible patient population |
| Li 2017b | Ineligible patient population |
| Li 2017c | Ineligible patient population |
| Li 2017d | Ineligible patient population |
| Li 2017e | Follow-up range not reported |
| Li 2019b | Duration < 12 weeks |
| Li 2020a | Ineligible patient population |


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| Study | Reason for exclusion |
|---|---|
| Li 2020b | Duration < 12 weeks |
| Li 2021a | Ineligible patient population |
| Li 2021b | Ineligible comparator |
| Liao 2017b | Ineligible intervention |
| Liu 2006 | Ineligible patient population |
| Liu 2011 | Ineligible patient population |
| Liu 2015b | Duration < 12 weeks |
| Liu 2022 | Duration < 12 weeks |
| Lu 2015a | Duration < 12 weeks |
| Lu 2015b | Duration < 12 weeks |
| Luan 2021 | Duration < 12 weeks |
| Ma 2019 | Ineligible patient population |
| Maher 2002 | Ineligible patient population |
| Mancini 1993 | Duration < 12 weeks |
| Miao 2020 | Duration < 12 weeks |
| Miu 2013 | Ineligible patient population |
| NCT02386852 2015 | Ineligible patient population |
| NCT04492241 2020 | Ineligible intervention |
| Ouyang 2013 | Duration < 12 weeks |
| Pan 2009 | Duration < 12 weeks |
| Pang 2017 | Duration < 12 weeks |
| Qiao 2017 | Ineligible patient population |
| Qin 2012 | Ineligible intervention |
| Qin 2022 | Duration < 12 weeks |
| Roth 2014 | Duration < 12 weeks |
| Ruan 2017 | Duration < 12 weeks |
| Schenker 1983 | Duration < 12 weeks |
| Schmidt 1991 | Ineligible patient population: unclear that all participants had cognitive problems |


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| Study | Reason for exclusion |
|---|---|
| Shen 2017 | Ineligible patient population |
| Shi 2015 | Ineligible patient population |
| Shu 2019 | Ineligible patient population |
| Song 2013 | Duration < 12 weeks |
| Song 2021 | Ineligible comparator |
| Su 2015 | Duration < 12 weeks |
| Su 2017 | Ineligible patient population |
| Su 2019 | Ineligible patient population |
| Sun 2015 | Duration < 12 weeks |
| Sun 2019 | Ineligible patient population |
| Tang 2004 | Duration < 12 weeks |
| Tang 2011 | Duration < 12 weeks |
| Tang 2015 | Duration < 12 weeks |
| Tang 2021 | Ineligible patient population |
| Teigeler 1984 | Duration < 12 weeks |
| Tian 2020 | Ineligible patient population |
| Tian 2024 | Ineligible patient population |
| Vorberg 1989 | Ineligible patient population: unclear that all participants had cognitive problems |
| Wang 2008 | Ineligible patient population |
| Wang 2012 | Ineligible patient population |
| Wang 2013a | Ineligible patient population |
| Wang 2013b | Ineligible patient population |
| Wang 2013c | Duration < 12 weeks |
| Wang 2014b | Duration < 12 weeks |
| Wang 2017a | Follow-up range not reported |
| Wang 2017b | Ineligible patient population |
| Wang 2017c | Follow-up range not reported |
| Wang 2019a | Duration < 12 weeks |


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| Study | Reason for exclusion |
|---|---|
| Wang 2019b | Duration < 12 weeks |
| Wang 2020b | Ineligible intervention |
| Wang 2020c | Ineligible patient population |
| Wei 2019 | Duration < 12 weeks |
| Wen 2010 | Duration < 12 weeks |
| Weng 2019 | Duration < 12 weeks |
| Wu 2001a | Duration < 12 weeks |
| Wu 2003 | Duration < 12 weeks |
| Wu 2008 | Follow-up range not reported |
| Wu 2014 | Ineligible patient population |
| Wu 2020a | Ineligible patient population |
| Wu 2020b | Ineligible patient population |
| Wu 2021b | Duration < 12 weeks |
| Xiong 2009 | Duration < 12 weeks |
| Xu 2008 | Ineligible intervention |
| Xu 2009 | Duration < 12 weeks |
| Xu 2014 | Ineligible patient population |
| Xu 2019b | Ineligible patient population |
| Xu 2019c | Duration < 12 weeks |
| Xue 2016 | Follow-up range not reported |
| Yang 2006 | Ineligible patient population |
| Yang 2014 | Duration < 12 weeks |
| Yang 2015b | Duration < 12 weeks |
| Yang 2020b | Duration < 12 weeks |
| Yao 2017 | Duration < 12 weeks |
| Ye 2010 | Ineligible patient population |
| Ye 2015 | Duration < 12 weeks |
| Ye 2016 | Ineligible patient population |


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| Study | Reason for exclusion |
|---|---|
| Yin 2016 | Duration < 12 weeks |
| Yue 2010 | Ineligible intervention |
| Zhang 2005 | Duration < 12 weeks |
| Zhang 2006a | Duration < 12 weeks |
| Zhang 2006b | Duration < 12 weeks |
| Zhang 2007 | Duration < 12 weeks |
| Zhang 2008 | Ineligible patient population |
| Zhang 2009 | Duration < 12 weeks |
| Zhang 2013a | Duration < 12 weeks |
| Zhang 2013b | Ineligible patient population |
| Zhang 2013c | Duration < 12 weeks |
| Zhang 2013d | Duration < 12 weeks |
| Zhang 2014 | Ineligible patient population |
| Zhang 2015a | Duration < 12 weeks |
| Zhang 2015b | Duration < 12 weeks |
| Zhang 2015c | Ineligible patient population |
| Zhang 2016b | Ineligible patient population |
| Zhang 2017a | Ineligible patient population |
| Zhang 2017b | Ineligible patient population |
| Zhang 2017c | Duration < 12 weeks |
| Zhang 2018 | Ineligible intervention |
| Zhang 2019b | Ineligible patient population |
| Zhang 2019c | Ineligible patient population |
| Zhang 2019d | Ineligible patient population |
| Zhang 2019e | Ineligible intervention |
| Zhang 2019f | Duration < 12 weeks |
| Zhang 2020 | Ineligible patient population |
| Zhang 2024 | Ineligible patient population |


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| Study | Reason for exclusion |
|---|---|
| Zhao 2004 | Duration < 12 weeks |
| Zhao 2009 | Ineligible patient population |
| Zhao 2014 | Ineligible patient population |
| Zhao 2017 | Ineligible patient population |
| Zhao 2018 | Ineligible intervention |
| Zheng 2009 | Ineligible patient population |
| Zhong 2014 | Ineligible patient population |
| Zhong 2020 | Ineligible patient population |
| Zhou 2007a | Ineligible intervention |
| Zhou 2007b | Duration < 12 weeks |
| Zhou 2009 | Ineligible intervention |
| Zhou 2018 | Ineligible patient population |
| Zhou 2019 | Ineligible patient population |
| Zhu 1996 | Duration < 12 weeks |
| Zhu 2014 | Ineligible patient population |
| Zhu 2017 | Duration < 12 weeks |
| Zou 2017 | Ineligible patient population |
| Zuo 2005 | Duration < 12 weeks |
| Zuo 2006 | Duration < 12 weeks |

## Characteristics of studies awaiting classification *[ordered by study ID]*

### Cao 2010

| | |
|---|---|
| Methods | |
| Participants | |
| Interventions | |
| Outcomes | |
| Notes | Unable to obtain for full-text assessment |


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**Chen 1998**

| | |
|---|---|
| Methods | |
| Participants | |
| Interventions | |
| Outcomes | |
| Notes | Unable to obtain for full-text assessment |

**Chen 2009**

| | |
|---|---|
| Methods | |
| Participants | |
| Interventions | |
| Outcomes | |
| Notes | Unable to obtain for full-text assessment |

**Dieli 1981**

| | |
|---|---|
| Methods | |
| Participants | |
| Interventions | |
| Outcomes | |
| Notes | Unable to obtain for full-text assessment |

**Duan 2022**

| | |
|---|---|
| Methods | |
| Participants | |
| Interventions | |
| Outcomes | |
| Notes | Unable to obtain for full-text assessment |


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**Gomez 1997**

| | |
|---|---|
| Methods | |
| Participants | |
| Interventions | |
| Outcomes | |
| Notes | Unable to obtain for full-text assessment |

**GuidAge 2008**

| | |
|---|---|
| Methods | Randomized, double-blind, multicentre, parallel groups, placebo controlled |
| Participants | 70 years and older; spontaneous memory complaint; MMSE > 25; short anxiety battery test < 6; geriatric depression scale < 15 |
| Interventions | EGb 761 (Tanakan) |
| Outcomes | Efficacy on conversion rate of memory complaint to dementia of Alzheimer type by a survival analysis; efficacy on rate of cognitive abilities decline; effect on concomitant diseases; concomitant treatments' reports; global evaluation of memory complaint by the patient; clinical safety |
| Notes | The study collected data on the CDR, MMSE, and IADL during follow-up; however this data are not published. Review author LSW contacted Dr Nicola Coley by email in July 2021 to request the data, and Dr Coley planned to contact Ipsen, the study sponsor, for permission to share the data. Dr Coley was most recently contacted by email in November 2024. She responded that she no longer had contacts at Ipsen, but would attempt to obtain the data. |

**Halama 1991b**

| | |
|---|---|
| Methods | |
| Participants | |
| Interventions | |
| Outcomes | |
| Notes | Unable to obtain for full-text assessment |

**Jiang 2017**

| | |
|---|---|
| Methods | |
| Participants | |
| Interventions | |
| Outcomes | |


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**Jiang 2017** *(Continued)*

| | |
|---|---|
| Notes | Unable to obtain for full-text assessment |

**Jin 2006**

| | |
|---|---|
| Methods | |
| Participants | |
| Interventions | |
| Outcomes | |
| Notes | Unable to obtain for full-text assessment |

**Li 2007b**

| | |
|---|---|
| Methods | |
| Participants | |
| Interventions | |
| Outcomes | |
| Notes | Unable to obtain for full-text assessment |

**Li 2020**

| | |
|---|---|
| Methods | |
| Participants | |
| Interventions | |
| Outcomes | |
| Notes | Unable to obtain for full-text assessment |

**Li 2022**

| | |
|---|---|
| Methods | |
| Participants | |
| Interventions | |
| Outcomes | |


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**Li 2022** *(Continued)*

| | |
|---|---|
| Notes | Unable to obtain for full-text assessment |

**Lu 2023**

| | |
|---|---|
| Methods | RCT |
| Participants | Patients between 45 and 80 years of age who were diagnosed with VCI |
| Interventions | Naoxin'an capsule |
| Outcomes | Effects of the Naoxin'an capsule on brain function, gray matter density, white matter hyperintensity, and the relationship between altered brain function and cognitive performance |
| Notes | Contacted for further information about study, including randomization, on 03 August 2025 |

**Ming 2023**

| | |
|---|---|
| Methods | Secondary analysis of a large-scale multicenter randomized non-inferiority clinical trial |
| Participants | 120 AD patients with kidney-marrow deficiency pattern |
| Interventions | Guilingji capsule |
| Outcomes | MMSE, ADAS-Cog, ADL, and the Chinese Medicine Symptom Scale |
| Notes | Includes AD patients only; we will add available AD data to the next version/update of the review and in the meantime will seek the main study report and information on other diagnostic subgroups. |

**NCT00042172**

| | |
|---|---|
| Methods | RCT |
| Participants | Meet the following criteria for mild cognitive impairment (MCI): subjective complaint of memory problems; no impairment in activities of daily living; general cognitive function in the normal age-adjusted range; abnormal memory function for age; and lacking full DSM criteria for dementia |
| Interventions | Patients receive either donepezil or placebo for the first 6 months of the study. In the second 6 months of the study, patients are randomized to receive either donepezil plus GBE or donepezil alone. |
| Outcomes | Not described |
| Notes | Unable to determine trial status, results, and relevance |

**NCT00276341**

| | |
|---|---|
| Methods | RCT |


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**NCT00276341** *(Continued)*

| | |
|---|---|
| Participants | • Patients with multiple sclerosis relapsing-remitting form<br>• Patients with cognitive impairment (as spontaneous complaint by either patient or family) |
| Interventions | EGb 761® (Tanakan®) 120 mg twice a day versus placebo |
| Outcomes | PASAT (primary outcome) and the following secondary outcomes: Multiple Sclerosis Functional Composite Test, Selective Reminding Test, 10/36 Visual-Spatial Recall Test, SDMT, Trail Making Test A and B, Verbal Fluency Test, Empan Test, Cognitive Deficit Interview based screen, Anxiety Brief Scale, Beck Depression Inventory Scale, Modified Fatigue Impact Scale, Evolution of Quality of Life, Kurtzke Extended Disability Status Scale, and Clinician Interview Based Impression of Change |
| Notes | Unable to determine trial status or results |

**Ni 2002**

| | |
|---|---|
| Methods | |
| Participants | |
| Interventions | |
| Outcomes | |
| Notes | Unable to obtain for full-text assessment |

**Schreiter Gasser 2001**

| | |
|---|---|
| Methods | |
| Participants | |
| Interventions | |
| Outcomes | |
| Notes | Unable to obtain for full-text assessment |

**Song 2019**

| | |
|---|---|
| Methods | |
| Participants | |
| Interventions | |
| Outcomes | |
| Notes | Unable to obtain for full-text assessment |


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**Wang 1998**

| | |
|---|---|
| Methods | |
| Participants | |
| Interventions | |
| Outcomes | |
| Notes | Unable to obtain for full-text assessment |

**Wu 2001**

| | |
|---|---|
| Methods | |
| Participants | |
| Interventions | |
| Outcomes | |
| Notes | Unable to obtain for full-text assessment |

**Yuan 2021**

| | |
|---|---|
| Methods | |
| Participants | |
| Interventions | |
| Outcomes | |
| Notes | Unable to obtain for full-text assessment |

**Zhang 2000**

| | |
|---|---|
| Methods | |
| Participants | |
| Interventions | |
| Outcomes | |
| Notes | Unable to obtain for full-text assessment |


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**Zhiang 2019**

| | |
|---|---|
| Methods | |
| Participants | |
| Interventions | |
| Outcomes | |
| Notes | Unable to obtain for full-text assessment |

**Zhou 2012**

| | |
|---|---|
| Methods | |
| Participants | |
| Interventions | |
| Outcomes | |
| Notes | Unable to obtain for full-text assessment |

**Zhou 2014**

| | |
|---|---|
| Methods | |
| Participants | |
| Interventions | |
| Outcomes | |
| Notes | Unable to obtain for full-text assessment |

Abbreviations: AD: Alzheimer's disease; ADAS-Cog: Alzheimer's Disease Assessment Scale – cognition; ADL: activities of daily living; CDR: Clinical Dementia Rating; DSM: Diagnostic and Statistical Manual of Mental Disorders; GBE: Ginkgo biloba extract; IADL: Instrumental Activities of Daily Living; MCI: mild cognitive impairment; MMSE: Mini Mental State Examination; PASAT: Paced Auditory Serial Addition Test; RCT: randomized controlled trial; SDMT: Symbol Digit Modalities Test; VCI: vascular cognitive impairment.

## Characteristics of ongoing studies *[ordered by study ID]*

**ChiCTR1900027411**

| | |
|---|---|
| Study name | Effects of ginkgo diterpene lactone on cognitive function and brain magnetic resonance structure and functional connections in mild cognitive impairment |
| Methods | Parallel RCT |
| Participants | Diagnosed with MCI and aged ≥ 60 years old |
| Interventions | *G biloba* lactone and basic treatment |


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**ChiCTR1900027411** *(Continued)*

| | |
|---|---|
| Outcomes | Basic treatment |
| Starting date | 01 January 2020 |
| Contact information | Zhang Ying (497523433@qq.com) and Cai Zenglin (caizengling@163.com) |
| Notes | Estimated completion date 31 December 2022, but trial register record has not been updated since 24 November 2019 |

**ChiCTR2000030292**

| | |
|---|---|
| Study name | Exploratory study on the safety and effectiveness of Yizhi Qingxin decoction (capsules) in the treatment of hypertension in the elderly with mild cognitive impairment (deficiency of kidney essence syndrome) |
| Methods | RCT (parallel group design) |
| Participants | Aged 65 to 75 years with hypertension and MCI |
| Interventions | Yizhi Qingxin Decoction (capsules) |
| Outcomes | Conversion rate of dementia; 24-hour ambulatory pressure; Montreal cognitive assessment scale; MMSE; syndrome change of overall impression scale; ADCS-MCI-ADL-24 |
| Starting date | 01 March 2020 |
| Contact information | Wang Biqing, wangbq_95@126.com |
| Notes | Estimated completion date 1 April 2023, but trial registration record has not been updated since 26 February 2020. |

**ChiCTR2300067418**

| | |
|---|---|
| Study name | Study on the change of Alzheimer's disease syndrome brain function connectivity characteristics and prevention and treatment scheme based on cognitive classification |
| Methods | Prospective RCT |
| Participants | Patients aged 40 to 85 years with memory loss |
| Interventions | Dihuang Yizhi formula |
| Outcomes | MMSE, MoCA, ADAS-cog, functional brain connectivity characteristics, TCM clinical symptom score; ADL |
| Starting date | 01 October 2021 |
| Contact information | Zhang Mengxue, 2909406852@qq.com |
| Notes | |


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**Morató 2023**

| | |
|---|---|
| Study name | A randomized, open-label clinical trial in mild cognitive impairment with EGb 761 examining blood markers of inflammation and oxidative stress |
| Methods | Phase IV, single-center, randomized, open-label, parallel group clinical trial |
| Participants | Participants were between 50 and 85 years of age with a diagnosis of mild cognitive impairment |
| Interventions | EGb 761 |
| Outcomes | Compare changes in blood levels of inflammation and oxidative stress biomarkers; comparing neuropsychiatric and cognitive test scores; obtaining safety data over a 2-year treatment period |
| Starting date | |
| Contact information | |
| Notes | Estimated completion December 2023, but current status unknown. Only baseline results available so far. |

**NCT04121728**

| | |
|---|---|
| Study name | Modulation of attention in event related potential (ERPs) as a marker of early cognitive decline by Ginkgo biloba (AgilGinkgo) |
| Methods | RCT, crossover |
| Participants | Men and women aged 60 to 80 years with cognitive complaint questionnaire (CQC) score > 4 but no mild cognitive impairment or dementia. |
| Interventions | *G biloba*, placebo |
| Outcomes | • Change in cognitive performance as assessed using the Repeatable Battery for the Assessment of Neuropsychological Status (RBANS) test after 6 months of *G biloba* treatment<br>• Change in scores of categorical semantic verbal fluency after 6 months of *G biloba* treatment<br>• Change in scores of verbal fluency letter instruction after 6 months of *G biloba* treatment<br>• Change in anxiety and depression as assessed using the Hospital Anxiety and Depression Scale (HAD-A/D) after 6 months of *G biloba* treatment |
| Starting date | |
| Contact information | Principal Investigator: Prof Jean-François Démonet, Lausanne University Hospital |
| Notes | "The study will be carried out in a randomized cross-over design, with "Ginkgo" vs. Placebo", or inversely, for 170 days each (approximately 6 months), separated by an 8-weeks wash-out period." |

**NCT04525144**

| | |
|---|---|
| Study name | Evaluating the role of EGb 761 in the syndrome of mild cognitive impairment with concomitant cerebrovascular disease (MCI plus CVD) |
| Methods | Randomized parallel single blind trial |


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**NCT04525144** *(Continued)*

| | |
|---|---|
| Participants | 45 to 85 years old diagnosed with MCI |
| Interventions | Tebonin Forte |
| Outcomes | ADAS-Cog 13, CDR-SOB, VCAT, MBI-C |
| Starting date | 26 October 2020 |
| Contact information | Joanna Wang, joanna.wang.s@singhealth.com.sg |
| Notes | |

**NCT05855863**

| | |
|---|---|
| Study name | Clinical study of *Ginkgo biloba* ketone ester tablets in diabetes related dementia |
| Methods | Randomized, parallel group |
| Participants | 60 to 90 years of age with type 2 diabetes with MCI |
| Interventions | Ginkgo ketone ester tablets versus placebo |
| Outcomes | ADAS-Cog, AVLT-H, FAQ, STT-A&B, SDMT |
| Starting date | 01 December 2023 |
| Contact information | Guoxiang Fu, Shanghai 10th People's Hospital |
| Notes | |

**NCT06495476**

| | |
|---|---|
| Study name | Study on *Ginkgo biloba* extract fifty in the treatment of mild cognitive impairment associated with cerebral small vessel disease |
| Methods | Randomized, multicenter, double-blind, placebo-controlled parallel trial |
| Participants | Aged 50 to 75 years old with SVD lesions and mild vascular cognitive impairment |
| Interventions | *G biloba* extract 50 dropping pills |
| Outcomes | Montreal Cognitive Assessment Scale, MMSE, ADL, FAQ |
| Starting date | 01 September 2024 |
| Contact information | Yilong Wang, Beijing Tiantan Hospital |
| Notes | |

**Abbreviations**: ADAS-Cog: Alzheimer's Disease Assessment Scale – cognition; ADAS-Cog 13: Alzheimer's Disease Assessment Scale – cognition – 13-item version; ADCS-MCI-ADL-24: Alzheimer's Disease Cooperative Study – Activities of Daily Living scale for Mild Cognitive Impairment – 24-item version; ADLs: activities of daily living; AVLT-H: Auditory Verbal Learning Test-Huashan version; CDR-


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SOB: Clinical Dementia Rating – Sum of Boxes; CQC: cognitive complaint questionnaire; CVD: cardiovascular disease; FAQ: Functional Activity Questionnaire; HAD-A/D: Hospital Anxiety and Depression Scale; MBI-C: Mild Behavioral Impairment Checklist; MCI: mild cognitive impairment; MMSE: Mini Mental State Examination; MoCA: Montreal Cognitive Assessment; RBANS: Repeatable Battery for the Assessment of Neuropsychological Status; RCT: randomized controlled trial; SDMT: Symbol Digit Modalities Test; STT-A&B: Shape Trails Test Parts A and B; TCM clinical symptom score: Traditional Chinese Medicine clinical symptom score; VCAT: Visual Cognitive Assessment Test.

## DATA AND ANALYSES

**Comparison 1. Subjective cognitive impairment: *Ginkgo biloba* versus placebo**

| Outcome or subgroup title | No. of studies | No. of participants | Statistical method | Effect size |
|---|---|---|---|---|
| 1.1 Global clinical status: 3 months - Geriaforce | 1 | | Mean Difference (IV, Random, 95% CI) | Subtotals only |
| 1.2 Global clinical status: 6 months - Geriaforce | 1 | | Mean Difference (IV, Random, 95% CI) | Subtotals only |
| 1.3 Adverse events (all) | 1 | | Risk Ratio (M-H, Random, 95% CI) | Subtotals only |
| 1.4 Adverse events: serious | 1 | | Risk Ratio (M-H, Random, 95% CI) | Subtotals only |
| 1.5 Memory: 3 months - Geriaforce | 1 | | Std. Mean Difference (IV, Random, 95% CI) | Subtotals only |
| 1.6 Memory: 6 months - Geriaforce | 1 | | Std. Mean Difference (IV, Random, 95% CI) | Subtotals only |
| 1.7 Memory: 3 months - EGb 761 | 1 | | Mean Difference (IV, Random, 95% CI) | Subtotals only |
| 1.8 Executive function: 3 months - Geriaforce | 1 | | Mean Difference (IV, Random, 95% CI) | Subtotals only |
| 1.9 Executive function: 6 months - Geriaforce | 1 | | Mean Difference (IV, Random, 95% CI) | Subtotals only |
| 1.10 Executive function: 3 months - EGb 761 | 1 | | Mean Difference (IV, Random, 95% CI) | Subtotals only |
| 1.11 Neuropsychiatric outcomes: anxiety - 3 months - EGb 761 | 1 | | Mean Difference (IV, Random, 95% CI) | Subtotals only |
| 1.12 Neuropsychiatric outcomes: depression - 3 months - EGb 761 | 1 | | Mean Difference (IV, Random, 95% CI) | Subtotals only |


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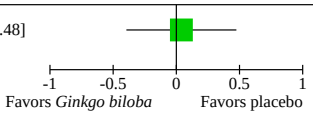
## Analysis 1.1. Comparison 1: Subjective cognitive impairment: *Ginkgo biloba* versus placebo, Outcome 1: Global clinical status: 3 months - Geriaforce

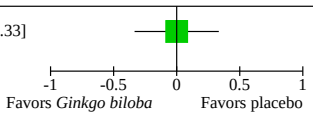
| Study or Subgroup | *Ginkgo biloba* Mean | SD | Total | Placebo Mean | SD | Total | Mean Difference IV, Random, 95% CI | Mean Difference IV, Random, 95% CI | Risk of Bias A B C D E F G |
|---|---|---|---|---|---|---|---|---|---|
| Brautigam 1998 | 2.18 | 2.0523 | 130 | 2.14 | 1.0641 | 67 | 0.04 [-0.40 , 0.48] | | + ? + + ? ? + |




**Risk of bias legend**
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

## Analysis 1.2. Comparison 1: Subjective cognitive impairment: *Ginkgo biloba* versus placebo, Outcome 2: Global clinical status: 6 months - Geriaforce

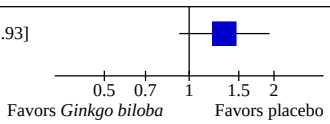
| Study or Subgroup | Ginkgo biloba Mean | SD | Total | Placebo Mean | SD | Total | Mean Difference IV, Random, 95% CI | Mean Difference IV, Random, 95% CI | Risk of Bias A B C D E F G |
|---|---|---|---|---|---|---|---|---|---|
| Brautigam 1998 | 2.34 | 1.9383 | 130 | 2.34 | 0.09004 | 67 | 0.00 [-0.33 , 0.33] | | + ? + + ? ? + |




**Risk of bias legend**
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

## Analysis 1.3. Comparison 1: Subjective cognitive impairment: *Ginkgo biloba* versus placebo, Outcome 3: Adverse events (all)

| Study or Subgroup | Ginkgo biloba Events | Total | Placebo Events | Total | Risk Ratio M-H, Random, 95% CI | Risk Ratio M-H, Random, 95% CI | Risk of Bias A B C D E F G |
|---|---|---|---|---|---|---|---|
| EUCTR2005-005765-11-EE | 48 | 152 | 36 | 152 | 1.33 [0.92 , 1.93] | | + + + + + + + |




**Risk of bias legend**
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias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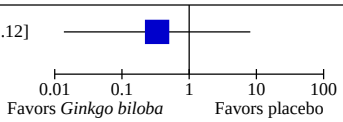
## Analysis 1.4. Comparison 1: Subjective cognitive impairment: *Ginkgo biloba* versus placebo, Outcome 4: Adverse events: serious

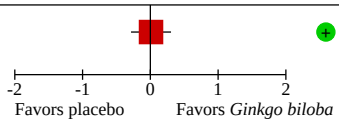
| Study or Subgroup | Ginkgo biloba Events | Ginkgo biloba Total | Placebo Events | Placebo Total | Risk Ratio M-H, Random, 95% CI | Risk Ratio M-H, Random, 95% CI | Risk of Bias A B C D E F G |
|---|---|---|---|---|---|---|---|
| EUCTR2005-005765-11-EE | 0 | 152 | 1 | 152 | 0.33 [0.01 , 8.12] | | + + + + + + + |




**Risk of bias legend**
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

## Analysis 1.5. Comparison 1: Subjective cognitive impairment: *Ginkgo biloba* versus placebo, Outcome 5: Memory: 3 months - Geriaforce

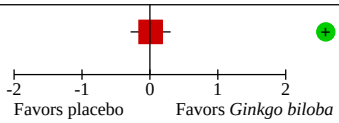
| Study or Subgroup | SMD | SE | Gingko biloba Total | Placebo Total | Std. Mean Difference IV, Random, 95% CI | Std. Mean Difference IV, Random, 95% CI | Risk of Bias A B C D E F G |
|---|---|---|---|---|---|---|---|
| Brautigam 1998 | 0.01 | 0.15051 | 130 | 67 | 0.01 [-0.28 , 0.30] | | + ? + + ? ? + |




**Risk of bias legend**
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

## Analysis 1.6. Comparison 1: Subjective cognitive impairment: *Ginkgo biloba* versus placebo, Outcome 6: Memory: 6 months - Geriaforce

| Study or Subgroup | SMD | SE | Gingko biloba Total | Placebo Total | Std. Mean Difference IV, Random, 95% CI | Std. Mean Difference IV, Random, 95% CI | Risk of Bias A B C D E F G |
|---|---|---|---|---|---|---|---|
| Brautigam 1998 | 0.0101 | 0.1504 | 130 | 67 | 0.01 [-0.28 , 0.30] | | + ? + + ? ? + |




**Risk of bias legend**
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias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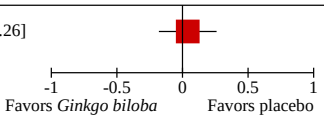
## Analysis 1.7. Comparison 1: Subjective cognitive impairment: *Ginkgo biloba* versus placebo, Outcome 7: Memory: 3 months - EGb 761

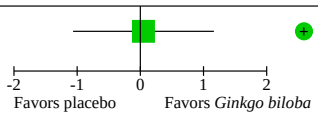
| Study or Subgroup | MD | SE | Gingko biloba Total | Placebo Total | Mean Difference IV, Random, 95% CI | Mean Difference IV, Random, 95% CI | Risk of Bias A B C D E F G |
|---|---|---|---|---|---|---|---|
| EUCTR2005-005765-11-EE | 0.04 | 0.1122 | 149 | 147 | 0.04 [-0.18 , 0.26] | | + + + + + + + |




**Risk of bias legend**
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

## Analysis 1.8. Comparison 1: Subjective cognitive impairment: *Ginkgo biloba* versus placebo, Outcome 8: Executive function: 3 months - Geriaforce

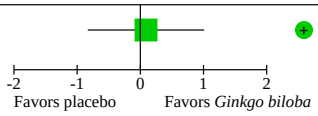
| Study or Subgroup | Ginkgo biloba Mean | SD | Total | Placebo Mean | SD | Total | Mean Difference IV, Random, 95% CI | Mean Difference IV, Random, 95% CI | Risk of Bias A B C D E F G |
|---|---|---|---|---|---|---|---|---|---|
| Brautigam 1998 | 21.69 | 5.0168 | 130 | 21.64 | 2.9467 | 67 | 0.05 [-1.06 , 1.16] | | + ? + + ? ? + |




**Risk of bias legend**
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

## Analysis 1.9. Comparison 1: Subjective cognitive impairment: *Ginkgo biloba* versus placebo, Outcome 9: Executive function: 6 months - Geriaforce

| Study or Subgroup | Ginkgo biloba Mean | SD | Total | Placebo Mean | SD | Total | Mean Difference IV, Random, 95% CI | Mean Difference IV, Random, 95% CI | Risk of Bias A B C D E F G |
|---|---|---|---|---|---|---|---|---|---|
| Brautigam 1998 | 22.15 | 4.2186 | 130 | 22.06 | 2.3738 | 67 | 0.09 [-0.83 , 1.01] | | + ? + + ? ? + |




**Risk of bias legend**
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias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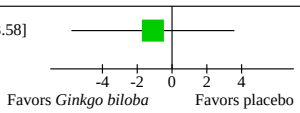
### Analysis 1.10. Comparison 1: Subjective cognitive impairment: *Ginkgo biloba* versus placebo, Outcome 10: Executive function: 3 months - EGb 761

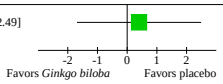
| Study or Subgroup | Ginkgo biloba Mean | SD | Total | Placebo Mean | SD | Total | Mean Difference IV, Random, 95% CI | Mean Difference IV, Random, 95% CI | Risk of Bias A B C D E F G |
|---|---|---|---|---|---|---|---|---|---|
| EUCTR2005-005765-11-EE | -17.7 | 18 | 149 | -16.6 | 22.8 | 147 | -1.10 [-5.78 , 3.58] | | |




**Risk of bias legend**
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

### Analysis 1.11. Comparison 1: Subjective cognitive impairment: *Ginkgo biloba* versus placebo, Outcome 11: Neuropsychiatric outcomes: anxiety - 3 months - EGb 761

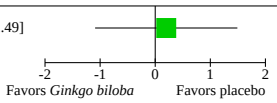
| Study or Subgroup | Ginkgo biloba Mean [STAI-XI state] | SD [STAI-XI state] | Total | Placebo Mean [STAI-XI state] | SD [STAI-XI state] | Total | Mean Difference IV, Random, 95% CI [STAI-XI state] | Mean Difference IV, Random, 95% CI [STAI-XI state] | Risk of Bias A B C D E F G |
|---|---|---|---|---|---|---|---|---|---|
| EUCTR2005-005765-11-EE | -2.5 | 10.3 | 149 | -2.9 | 7.9 | 147 | 0.40 [-1.69 , 2.49] | | |




**Risk of bias legend**
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

### Analysis 1.12. Comparison 1: Subjective cognitive impairment: *Ginkgo biloba* versus placebo, Outcome 12: Neuropsychiatric outcomes: depression - 3 months - EGb 761

| Study or Subgroup | Ginkgo biloba Mean [D-S'] | SD [D-S'] | Total | Placebo Mean [D-S'] | SD [D-S'] | Total | Mean Difference IV, Random, 95% CI [D-S'] | Mean Difference IV, Random, 95% CI [D-S'] | Risk of Bias A B C D E F G |
|---|---|---|---|---|---|---|---|---|---|
| EUCTR2005-005765-11-EE | -3.6 | 6.1 | 149 | -3.8 | 5.2 | 147 | 0.20 [-1.09 , 1.49] | | |




**Risk of bias legend**
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

## Comparison 2. Multiple sclerosis: *Gingko biloba* versus placebo

| Outcome or subgroup title | No. of studies | No. of participants | Statistical method | Effect size |
|---|---|---|---|---|
| 2.1 Global cognitive function: 3 months | 2 | 152 | Mean Difference (IV, Random, 95% CI) | -0.09 [-0.41, 0.22] |
| 2.2 Memory: 3 months - adjusted means | 1 | | Mean Difference (IV, Random, 95% CI) | Subtotals only |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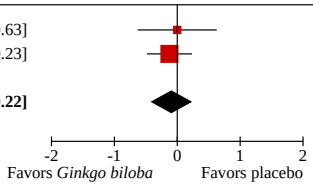
| Outcome or subgroup title | No. of studies | No. of participants | Statistical method | Effect size |
|---|---|---|---|---|
| 2.3 Memory: 3 months - adjusted z-scores | 1 | | Mean Difference (IV, Random, 95% CI) | Subtotals only |
| 2.4 Executive function: 3 months - combined adjusted means | 1 | | Std. Mean Difference (IV, Random, 95% CI) | Subtotals only |
| 2.5 Executive function: 3 months - combined adjusted z-scores | 1 | | Std. Mean Difference (IV, Random, 95% CI) | Subtotals only |
| 2.6 Neuropsychiatric: depression - 3 months | 1 | | Mean Difference (IV, Random, 95% CI) | Subtotals only |

## Analysis 2.1. Comparison 2: Multiple sclerosis: *Gingko biloba* versus placebo, Outcome 1: Global cognitive function: 3 months

| Study or Subgroup | MD | SE | Ginkgo biloba Total | Placebo Total | Weight | Mean Difference IV, Random, 95% CI |
|---|---|---|---|---|---|---|
| Lovera 2007 | 0 | 0.3204 | 16 | 16 | 24.6% | 0.00 [-0.63 , 0.63] |
| Lovera 2012 | -0.124593 | 0.182783 | 61 | 59 | 75.4% | -0.12 [-0.48 , 0.23] |
| **Total (Wald[a])** | | | **77** | **75** | **100.0%** | **-0.09 [-0.41 , 0.22]** |



Test for overall effect: Z = 0.59 (P = 0.55)

Heterogeneity: Tau² (DL[b]) = 0.00; Chi² = 0.11, df = 1 (P = 0.74); I² = 0%

**Footnotes**

[a]CI calculated by Wald-type method.

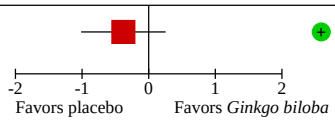
[b]Tau² calculated by DerSimonian and Laird method.

**Risk of bias legend**

(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

## Analysis 2.2. Comparison 2: Multiple sclerosis: *Gingko biloba* versus placebo, Outcome 2: Memory: 3 months - adjusted means

| Study or Subgroup | MD | SE | Ginkgo biloba Total | Placebo Total | Mean Difference IV, Random, 95% CI |
|---|---|---|---|---|---|
| Lovera 2007 | -0.380155 | 0.323562 | 20 | 19 | -0.38 [-1.01 , 0.25] |



**Risk of bias legend**

(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias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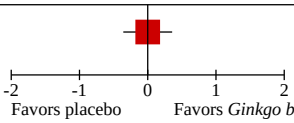
## Analysis 2.3. Comparison 2: Multiple sclerosis: *Gingko biloba* versus placebo, Outcome 3: Memory: 3 months - adjusted z-scores

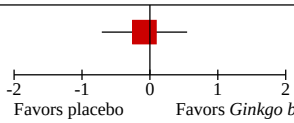
| Study or Subgroup | MD | SE | Ginkgo biloba Total | Placebo Total | Mean Difference IV, Random, 95% CI | Mean Difference IV, Random, 95% CI | Risk of Bias A B C D E F G |
|---|---|---|---|---|---|---|---|
| Lovera 2012 | 0 | 0.1826 | 61 | 59 | 0.00 [-0.36 , 0.36] | | + + + + + + + |




**Risk of bias legend**
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

## Analysis 2.4. Comparison 2: Multiple sclerosis: *Gingko biloba* versus placebo, Outcome 4: Executive function: 3 months - combined adjusted means

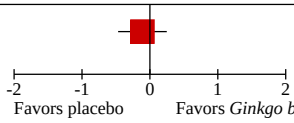
| Study or Subgroup | SMD | SE | Ginkgo biloba Total | Placebo Total | Std. Mean Difference IV, Random, 95% CI | Std. Mean Difference IV, Random, 95% CI | Risk of Bias A B C D E F G |
|---|---|---|---|---|---|---|---|
| Lovera 2007 | -0.0801 | 0.3205 | 20 | 19 | -0.08 [-0.71 , 0.55] | | + + + + ? ? + |




**Risk of bias legend**
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

## Analysis 2.5. Comparison 2: Multiple sclerosis: *Gingko biloba* versus placebo, Outcome 5: Executive function: 3 months - combined adjusted z-scores

| Study or Subgroup | SMD | SE | Ginkgo biloba Total | Placebo Total | Std. Mean Difference IV, Random, 95% CI | Std. Mean Difference IV, Random, 95% CI | Risk of Bias A B C D E F G |
|---|---|---|---|---|---|---|---|
| Lovera 2012 | -0.1098 | 0.1827 | 61 | 59 | -0.11 [-0.47 , 0.25] | | + + + + + + + |




**Risk of bias legend**
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias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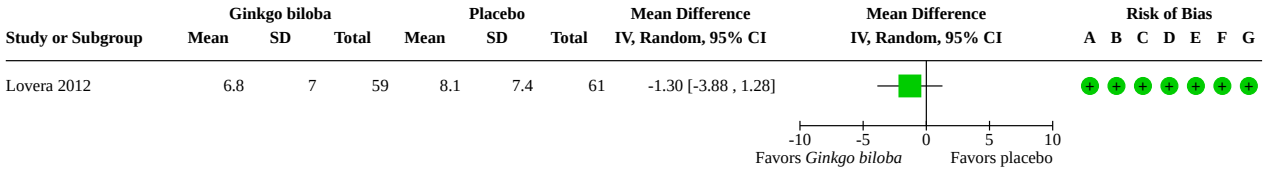
### Analysis 2.6. Comparison 2: Multiple sclerosis: *Gingko biloba* versus placebo, Outcome 6: Neuropsychiatric: depression - 3 months




**Risk of bias legend**
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

## Comparison 3. Mild cognitive impairment: *Ginkgo biloba* versus placebo

| Outcome or subgroup title | No. of studies | No. of participants | Statistical method | Effect size |
|---|---|---|---|---|
| 3.1 Global clinical status: 3 months | 1 | | Mean Difference (IV, Random, 95% CI) | Subtotals only |
| 3.2 Global clinical status: 6 months | 3 | 631 | Std. Mean Difference (IV, Random, 95% CI) | -0.12 [-0.28, 0.04] |
| 3.3 Global clinical status: 6 months: sensitivity analysis by risk of bias | 1 | | Mean Difference (IV, Random, 95% CI) | Subtotals only |
| 3.4 Global clinical status: 12 months | 2 | 604 | Std. Mean Difference (IV, Random, 95% CI) | -0.17 [-0.33, -0.01] |
| 3.5 Global clinical status: 12 months: sensitivity analysis by risk of bias | 1 | | Mean Difference (IV, Random, 95% CI) | Subtotals only |
| 3.6 Global cognitive function: 3 months | 1 | | Mean Difference (IV, Random, 95% CI) | Subtotals only |
| 3.7 Global cognitive function: 6 months - endpoint | 2 | 508 | Std. Mean Difference (IV, Random, 95% CI) | -0.02 [-0.20, 0.15] |
| 3.8 Global cognitive function: 6 months - endpoint: sensitivity analysis by risk of bias | 1 | | Mean Difference (IV, Random, 95% CI) | Subtotals only |
| 3.9 Global cognitive function: 6 months - change | 1 | | Mean Difference (IV, Random, 95% CI) | Subtotals only |
| 3.10 Global cognitive function: 12 months | 2 | 604 | Mean Difference (IV, Random, 95% CI) | -1.95 [-5.29, 1.39] |
| 3.11 Global cognitive function: 12 months: sensitivity analysis by risk of bias | 1 | | Mean Difference (IV, Random, 95% CI) | Subtotals only |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| Outcome or subgroup title | No. of studies | No. of participants | Statistical method | Effect size |
|---|---|---|---|---|
| 3.12 ADL: 3 months | 1 | | Mean Difference (IV, Random, 95% CI) | Subtotals only |
| 3.13 ADL: 6 months - endpoint | 1 | | Mean Difference (IV, Random, 95% CI) | Subtotals only |
| 3.14 ADL: 6 months - change | 1 | | Mean Difference (IV, Random, 95% CI) | Subtotals only |
| 3.15 ADL: 12 months - endpoint | 1 | | Mean Difference (IV, Random, 95% CI) | Subtotals only |
| 3.16 ADL: 12 months - change | 1 | | Mean Difference (IV, Random, 95% CI) | Subtotals only |
| 3.17 Adverse events: all | 7 | 991 | Risk Ratio (IV, Random, 95% CI) | 0.98 [0.77, 1.24] |
| 3.17.1 3 months | 3 | 550 | Risk Ratio (IV, Random, 95% CI) | 1.17 [0.87, 1.56] |
| 3.17.2 6 months | 3 | 267 | Risk Ratio (IV, Random, 95% CI) | 0.88 [0.55, 1.40] |
| 3.17.3 12 months | 1 | 174 | Risk Ratio (IV, Random, 95% CI) | 0.96 [0.68, 1.38] |
| 3.18 Adverse events: serious - 6 months | 3 | 714 | Risk Ratio (IV, Random, 95% CI) | 0.95 [0.82, 1.09] |
| 3.19 Adverse events: serious - 6 to 12 months | 1 | | Risk Ratio (IV, Random, 95% CI) | Subtotals only |
| 3.20 Memory: 3 months | 2 | 510 | Std. Mean Difference (IV, Random, 95% CI) | 0.06 [-0.12, 0.25] |
| 3.21 Memory: 6 months | 1 | | Std. Mean Difference (IV, Random, 95% CI) | Totals not selected |
| 3.22 Memory: 12 months | 1 | | Mean Difference (IV, Random, 95% CI) | Subtotals only |
| 3.23 Executive function: 3 months | 1 | | Std. Mean Difference (IV, Random, 95% CI) | Subtotals only |
| 3.24 Executive function: 6 months | 1 | | Mean Difference (IV, Random, 95% CI) | Subtotals only |
| 3.25 Quality of life: mental - 3 months | 1 | | Mean Difference (IV, Random, 95% CI) | Subtotals only |
| 3.26 Quality of life: physical - 3 months | 1 | | Mean Difference (IV, Random, 95% CI) | Subtotals only |
| 3.27 Neuropsychiatric outcomes: anxiety - 6 months | 1 | | Mean Difference (IV, Random, 95% CI) | Subtotals only |
| 3.28 Neuropsychiatric outcomes: depression - 3 months | 1 | | Mean Difference (IV, Random, 95% CI) | Subtotals only |


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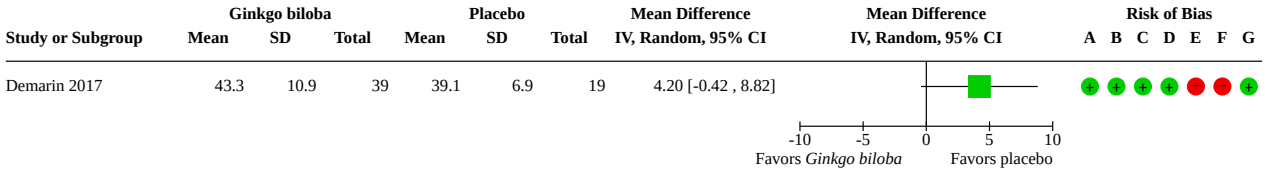
| Outcome or subgroup title | No. of studies | No. of participants | Statistical method | Effect size |
|---|---|---|---|---|
| 3.29 Neuropsychiatric outcomes: depression - 6 months - change | 2 | 282 | Std. Mean Difference (IV, Random, 95% CI) | -0.04 [-0.46, 0.38] |
| 3.30 Neuropsychiatric outcomes: depression - 6 months - endpoint | 1 | | Mean Difference (IV, Random, 95% CI) | Subtotals only |
| 3.31 Neuropsychiatric outcomes: depression - 12 months | 1 | | Mean Difference (IV, Random, 95% CI) | Subtotals only |
| 3.32 Neuropsychiatric outcomes: mental well-being - 3 months | 1 | | Mean Difference (IV, Random, 95% CI) | Subtotals only |
| 3.33 Neuropsychiatric outcomes: NPI - 6 months | 1 | | Mean Difference (IV, Random, 95% CI) | Subtotals only |

**Analysis 3.1. Comparison 3: Mild cognitive impairment: *Ginkgo biloba* versus placebo, Outcome 1: Global clinical status: 3 months**




**Risk of bias legend**
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias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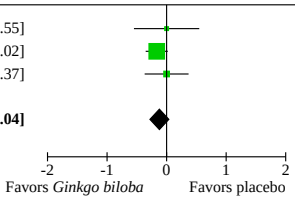
## Analysis 3.2. Comparison 3: Mild cognitive impairment: *Ginkgo biloba* versus placebo, Outcome 2: Global clinical status: 6 months

| Study or Subgroup | Ginkgo biloba Mean | SD | Total | Placebo Mean | SD | Total | Weight | Std. Mean Difference IV, Random, 95% CI |
|---|---|---|---|---|---|---|---|---|
| Demarin 2017 | 2.8 | 0.8 | 39 | 2.8 | 0.7 | 19 | 8.4% | 0.00 [-0.55 , 0.55] |
| GEM 2010 | 0.33 | 0.25 | 239 | 0.37 | 0.23 | 211 | 73.1% | -0.17 [-0.35 , 0.02] |
| van Dongen 2000 | 4.3 | 1.2 | 79 | 4.3 | 1.1 | 44 | 18.5% | 0.00 [-0.37 , 0.37] |
| **Total (Wald[a])** | | | **357** | | | **274** | **100.0%** | **-0.12 [-0.28 , 0.04]** |



Test for overall effect: Z = 1.50 (P = 0.13)

Heterogeneity: Tau² (DL[b]) = 0.00; Chi² = 0.83, df = 2 (P = 0.66); I² = 0%

**Footnotes**

[a]CI calculated by Wald-type method.

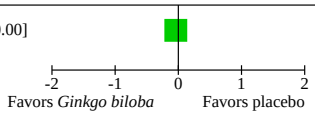
[b]Tau² calculated by DerSimonian and Laird method.

**Risk of bias legend**

(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

## Analysis 3.3. Comparison 3: Mild cognitive impairment: *Ginkgo biloba* versus placebo, Outcome 3: Global clinical status: 6 months: sensitivity analysis by risk of bias

| Study or Subgroup | Ginkgo biloba Mean | SD | Total | Placebo Mean | SD | Total | Mean Difference IV, Random, 95% CI |
|---|---|---|---|---|---|---|---|
| GEM 2010 | 0.33 | 0.25 | 239 | 0.37 | 0.23 | 211 | -0.04 [-0.08 , 0.00] |



**Risk of bias legend**

(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias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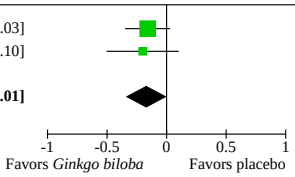
## Analysis 3.4. Comparison 3: Mild cognitive impairment: *Ginkgo biloba* versus placebo, Outcome 4: Global clinical status: 12 months

| Study or Subgroup | Ginkgo biloba Mean | SD | Total | Placebo Mean | SD | Total | Weight | Std. Mean Difference IV, Random, 95% CI | Std. Mean Difference IV, Random, 95% CI | Risk of Bias A B C D E F G |
|---|---|---|---|---|---|---|---|---|---|---|
| GEM 2010 | 0.32 | 0.25 | 230 | 0.36 | 0.25 | 200 | 71.9% | -0.16 [-0.35 , 0.03] | | + + + + + + + |
| Tian 2019 | -0.25 | 1.33 | 104 | 0.02 | 1.34 | 70 | 28.1% | -0.20 [-0.51 , 0.10] | | + + + + + ? + |
| **Total (Wald[a])** | | | **334** | | | **270** | **100.0%** | **-0.17 [-0.33 , -0.01]** | | |




Test for overall effect: Z = 2.09 (P = 0.04)

Heterogeneity: Tau² (DL[b]) = 0.00; Chi² = 0.05, df = 1 (P = 0.82); I² = 0%

**Footnotes**

[a]CI calculated by Wald-type method.

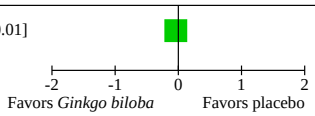
[b]Tau² calculated by DerSimonian and Laird method.

**Risk of bias legend**

(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

## Analysis 3.5. Comparison 3: Mild cognitive impairment: *Ginkgo biloba* versus placebo, Outcome 5: Global clinical status: 12 months: sensitivity analysis by risk of bias

| Study or Subgroup | Ginkgo biloba Mean | SD | Total | Placebo Mean | SD | Total | Mean Difference IV, Random, 95% CI | Mean Difference IV, Random, 95% CI | Risk of Bias A B C D E F G |
|---|---|---|---|---|---|---|---|---|---|
| GEM 2010 | 0.32 | 0.25 | 230 | 0.36 | 0.25 | 200 | -0.04 [-0.09 , 0.01] | | + + + + + + + |

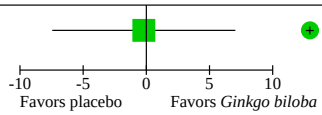



**Risk of bias legend**

(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

## Analysis 3.6. Comparison 3: Mild cognitive impairment: *Ginkgo biloba* versus placebo, Outcome 6: Global cognitive function: 3 months

| Study or Subgroup | Ginkgo biloba Mean | SD | Total | Placebo Mean | SD | Total | Mean Difference IV, Random, 95% CI | Mean Difference IV, Random, 95% CI | Risk of Bias A B C D E F G |
|---|---|---|---|---|---|---|---|---|---|
| Demarin 2017 | 125.7 | 14.2 | 39 | 125.9 | 12.7 | 19 | -0.20 [-7.44 , 7.04] | | + + + + − − + |




**Risk of bias legend**

(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias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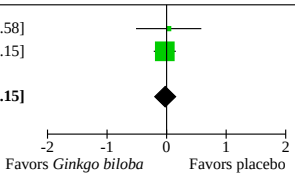
## Analysis 3.7. Comparison 3: Mild cognitive impairment: *Ginkgo biloba* versus placebo, Outcome 7: Global cognitive function: 6 months - endpoint

| Study or Subgroup | Ginkgo biloba Mean | SD | Total | Placebo Mean | SD | Total | Weight | Std. Mean Difference IV, Random, 95% CI | Risk of Bias A B C D E F G |
|---|---|---|---|---|---|---|---|---|---|
| Demarin 2017 | -126.7 | 15.03 | 39 | -127.2 | 12.4 | 19 | 10.2% | 0.03 [-0.51 , 0.58] | + + + + − − + |
| GEM 2010 | 8.32 | 3.2 | 239 | 8.42 | 3.37 | 211 | 89.8% | -0.03 [-0.22 , 0.15] | + + + + + + + |
| **Total (Wald[a])** | | | **278** | | | **230** | **100.0%** | **-0.02 [-0.20 , 0.15]** | |




Test for overall effect: Z = 0.27 (P = 0.79)

Heterogeneity: Tau² (DL[b]) = 0.00; Chi² = 0.05, df = 1 (P = 0.83); I² = 0%

**Footnotes**

[a]CI calculated by Wald-type method.

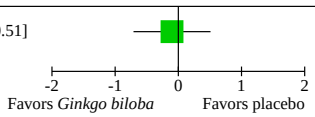
[b]Tau² calculated by DerSimonian and Laird method.

**Risk of bias legend**

(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

## Analysis 3.8. Comparison 3: Mild cognitive impairment: *Ginkgo biloba* versus placebo, Outcome 8: Global cognitive function: 6 months - endpoint: sensitivity analysis by risk of bias

| Study or Subgroup | Ginkgo biloba Mean | SD | Total | Placebo Mean | SD | Total | Mean Difference IV, Random, 95% CI | Risk of Bias A B C D E F G |
|---|---|---|---|---|---|---|---|---|
| GEM 2010 | 8.32 | 3.2 | 239 | 8.42 | 3.37 | 211 | -0.10 [-0.71 , 0.51] | + + + + + + + |

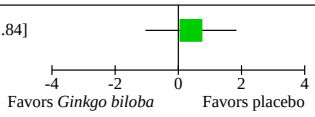



**Risk of bias legend**

(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

## Analysis 3.9. Comparison 3: Mild cognitive impairment: *Ginkgo biloba* versus placebo, Outcome 9: Global cognitive function: 6 months - change

| Study or Subgroup | Ginkgo biloba Mean | SD | Total | Placebo Mean | SD | Total | Mean Difference IV, Random, 95% CI | Risk of Bias A B C D E F G |
|---|---|---|---|---|---|---|---|---|
| van Dongen 2000 | -0.8 | 4.1 | 79 | -1.2 | 3.8 | 44 | 0.40 [-1.04 , 1.84] | + ? + + + ? + |




**Risk of bias legend**

(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias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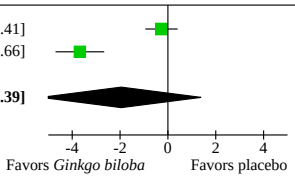
## Analysis 3.10. Comparison 3: Mild cognitive impairment: *Ginkgo biloba* versus placebo, Outcome 10: Global cognitive function: 12 months

| Study or Subgroup | Ginkgo biloba Mean | SD | Total | Placebo Mean | SD | Total | Weight | Mean Difference IV, Random, 95% CI | Risk of Bias A B C D E F G |
|---|---|---|---|---|---|---|---|---|---|
| GEM 2010 | 8.14 | 3.24 | 230 | 8.41 | 3.83 | 200 | 50.6% | -0.27 [-0.95 , 0.41] | + + + + + + + |
| Tian 2019 | -2.43 | 3.37 | 104 | 1.25 | 3.35 | 70 | 49.4% | -3.68 [-4.70 , -2.66] | + + + + + ? + |
| **Total (Wald[a])** | | | **334** | | | **270** | **100.0%** | **-1.95 [-5.29 , 1.39]** | |




Test for overall effect: Z = 1.15 (P = 0.25)

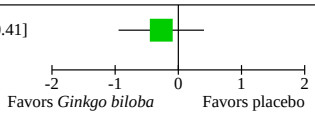
Heterogeneity: Tau² (DL[b]) = 5.62; Chi² = 29.93, df = 1 (P < 0.00001); I² = 97%

**Footnotes**
[a]CI calculated by Wald-type method.
[b]Tau² calculated by DerSimonian and Laird method.

**Risk of bias legend**
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

## Analysis 3.11. Comparison 3: Mild cognitive impairment: *Ginkgo biloba* versus placebo, Outcome 11: Global cognitive function: 12 months: sensitivity analysis by risk of bias

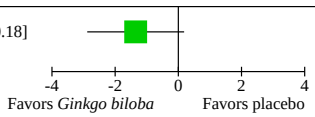
| Study or Subgroup | Ginkgo biloba Mean | SD | Total | Placebo Mean | SD | Total | Mean Difference IV, Random, 95% CI | Risk of Bias A B C D E F G |
|---|---|---|---|---|---|---|---|---|
| GEM 2010 | 8.14 | 3.24 | 230 | 8.41 | 3.83 | 200 | -0.27 [-0.95 , 0.41] | + + + + + + + |




**Risk of bias legend**
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

## Analysis 3.12. Comparison 3: Mild cognitive impairment: *Ginkgo biloba* versus placebo, Outcome 12: ADL: 3 months

| Study or Subgroup | Ginkgo biloba Mean | SD | Total | Placebo Mean | SD | Total | Mean Difference IV, Random, 95% CI | Risk of Bias A B C D E F G |
|---|---|---|---|---|---|---|---|---|
| van Dongen 2000 | 0.42 | 3.8 | 166 | 1.77 | 5.02 | 48 | -1.35 [-2.88 , 0.18] | + ? + + + ? + |




**Risk of bias legend**
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias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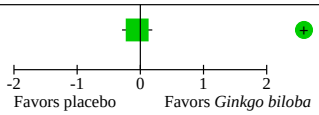
## Analysis 3.13. Comparison 3: Mild cognitive impairment: *Ginkgo biloba* versus placebo, Outcome 13: ADL: 6 months - endpoint

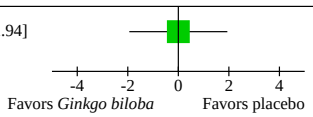
| Study or Subgroup | Ginkgo biloba Mean | SD | Total | Placebo Mean | SD | Total | Mean Difference IV, Random, 95% CI | Mean Difference IV, Random, 95% CI | Risk of Bias A B C D E F G |
|---|---|---|---|---|---|---|---|---|---|
| GEM 2010 | 0.68 | 1.11 | 181 | 0.73 | 1.17 | 169 | -0.05 [-0.29 , 0.19] | | + + + + + + + |




**Risk of bias legend**
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

## Analysis 3.14. Comparison 3: Mild cognitive impairment: *Ginkgo biloba* versus placebo, Outcome 14: ADL: 6 months - change

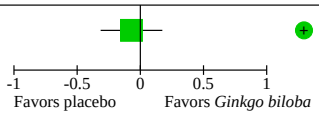
| Study or Subgroup | Ginkgo biloba Mean | SD | Total | Placebo Mean | SD | Total | Mean Difference IV, Random, 95% CI | Mean Difference IV, Random, 95% CI | Risk of Bias A B C D E F G |
|---|---|---|---|---|---|---|---|---|---|
| van Dongen 2000 | 1.4 | 4.8 | 79 | 1.4 | 5.5 | 44 | 0.00 [-1.94 , 1.94] | | + ? + + + ? + |




**Risk of bias legend**
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

## Analysis 3.15. Comparison 3: Mild cognitive impairment: *Ginkgo biloba* versus placebo, Outcome 15: ADL: 12 months - endpoint

| Study or Subgroup | Ginkgo biloba Mean | SD | Total | Placebo Mean | SD | Total | Mean Difference IV, Random, 95% CI | Mean Difference IV, Random, 95% CI | Risk of Bias A B C D E F G |
|---|---|---|---|---|---|---|---|---|---|
| GEM 2010 | 0.66 | 1.09 | 177 | 0.73 | 1.19 | 161 | -0.07 [-0.31 , 0.17] | | + + + + + + + |




**Risk of bias legend**
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias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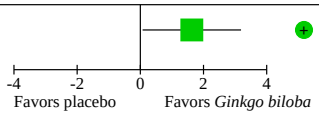
## Analysis 3.16. Comparison 3: Mild cognitive impairment: *Ginkgo biloba* versus placebo, Outcome 16: ADL: 12 months - change

| Study or Subgroup | Ginkgo biloba Mean | SD | Total | Placebo Mean | SD | Total | Mean Difference IV, Random, 95% CI | Risk of Bias A | B | C | D | E | F | G |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Tian 2019 | 2.98 | 5.2 | 104 | 1.35 | 5.1 | 70 | 1.63 [0.07 , 3.19] | + | + | + | + | + | ? | + |




**Risk of bias legend**

(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias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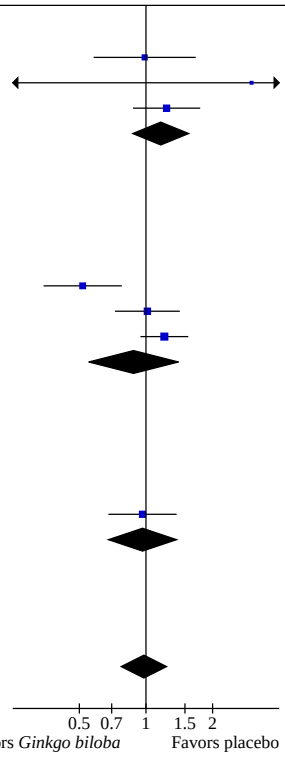
## Analysis 3.17. Comparison 3: Mild cognitive impairment: *Ginkgo biloba* versus placebo, Outcome 17: Adverse events: all




| Study or Subgroup | Ginkgo biloba Events | Total | Placebo Events | Total | Weight | Risk Ratio IV, Random, 95% CI | Risk of Bias A B C D E F G |
|---|---|---|---|---|---|---|---|
| **3.17.1 3 months** | | | | | | | |
| Grass-Kapanke 2011 | 23 | 149 | 23 | 147 | 11.5% | 0.99 [0.58 , 1.68] | + + + + + + + |
| Halama 1988 | 1 | 20 | 0 | 20 | 0.6% | 3.00 [0.13 , 69.52] | + + + + ? ? + |
| van Dongen 2000 | 90 | 166 | 21 | 48 | 17.1% | 1.24 [0.87 , 1.76] | + ? + + + ? + |
| **Subtotal (Wald[a])** | | **335** | | **215** | **29.2%** | **1.17 [0.87 , 1.56]** | |
| Total events: | 114 | | 44 | | | | |
| Test for overall effect: Z = 1.04 (P = 0.30) | | | | | | | |
| Heterogeneity: Tau² (DL[b]) = 0.00; Chi² = 0.84, df = 2 (P = 0.66); I² = 0% | | | | | | | |
| **3.17.2 6 months** | | | | | | | |
| Demarin 2017 | 17 | 39 | 16 | 19 | 15.1% | 0.52 [0.34 , 0.78] | + + + + − − + |
| Gavrilova 2014 | 37 | 80 | 36 | 79 | 17.6% | 1.01 [0.72 , 1.42] | + + + + + ? + |
| Gschwind 2017 | 23 | 25 | 19 | 25 | 21.1% | 1.21 [0.94 , 1.55] | + + + + − + + |
| **Subtotal (Wald[a])** | | **144** | | **123** | **53.8%** | **0.88 [0.55 , 1.40]** | |
| Total events: | 77 | | 71 | | | | |
| Test for overall effect: Z = 0.54 (P = 0.59) | | | | | | | |
| Heterogeneity: Tau² (DL[b]) = 0.14; Chi² = 12.27, df = 2 (P = 0.002); I² = 84% | | | | | | | |
| **3.17.3 12 months** | | | | | | | |
| Tian 2019 | 43 | 104 | 30 | 70 | 17.0% | 0.96 [0.68 , 1.38] | + + + + + ? + |
| **Subtotal** | | **104** | | **70** | **17.0%** | **0.96 [0.68 , 1.38]** | |
| Total events: | 43 | | 30 | | | | |
| Test for overall effect: Z = 0.20 (P = 0.84) | | | | | | | |
| Heterogeneity: Not applicable | | | | | | | |
| **Total (Wald[a])** | | **583** | | **408** | **100.0%** | **0.98 [0.77 , 1.24]** | |
| Total events: | 234 | | 145 | | | | |
| Test for overall effect: Z = 0.18 (P = 0.86) | | | | | | | |
| Test for subgroup differences: Chi² = 1.26, df = 2 (P = 0.53), I² = 0% | | | | | | | |
| Heterogeneity: Tau² (DL[b]) = 0.05; Chi² = 14.26, df = 6 (P = 0.03); I² = 58% | | | | | | | |

**Footnotes**

[a]CI calculated by Wald-type method.

[b]Tau² calculated by DerSimonian and Laird method.

**Risk of bias legend**

(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias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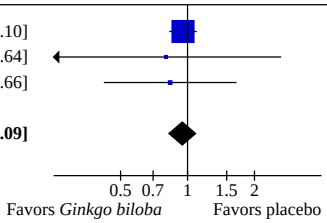
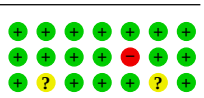
## Analysis 3.18. Comparison 3: Mild cognitive impairment: *Ginkgo biloba* versus placebo, Outcome 18: Adverse events: serious - 6 months

| Study or Subgroup | Ginkgo biloba Events | Ginkgo biloba Total | Placebo Events | Placebo Total | Weight | Risk Ratio IV, Random, 95% CI |
|---|---|---|---|---|---|---|
| GEM 2010 | 147 | 239 | 136 | 211 | 94.6% | 0.95 [0.83 , 1.10] |
| Gschwind 2017 | 4 | 25 | 5 | 25 | 1.3% | 0.80 [0.24 , 2.64] |
| van Dongen 2000 | 26 | 166 | 9 | 48 | 4.0% | 0.84 [0.42 , 1.66] |
| **Total (Wald[a])** | | **430** | | **284** | **100.0%** | **0.95 [0.82 , 1.09]** |
| Total events: | 177 | | 150 | | | |

Test for overall effect: Z = 0.78 (P = 0.44)




Heterogeneity: Tau² (DL[b]) = 0.00; Chi² = 0.22, df = 2 (P = 0.90); I² = 0%

**Footnotes**

[a]CI calculated by Wald-type method.

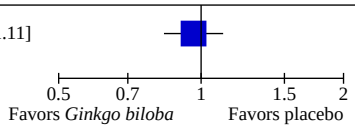
[b]Tau² calculated by DerSimonian and Laird method.

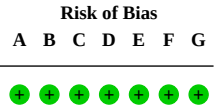
**Risk of bias legend**

(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

## Analysis 3.19. Comparison 3: Mild cognitive impairment: *Ginkgo biloba* versus placebo, Outcome 19: Adverse events: serious - 6 to 12 months

| Study or Subgroup | Ginkgo biloba Events | Ginkgo biloba Total | Placebo Events | Placebo Total | Risk Ratio IV, Random, 95% CI |
|---|---|---|---|---|---|
| GEM 2010 | 143 | 230 | 129 | 200 | 0.96 [0.83 , 1.11] |




**Risk of bias legend**

(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias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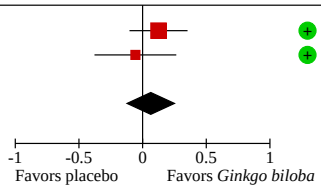
## Analysis 3.20. Comparison 3: Mild cognitive impairment: *Ginkgo biloba* versus placebo, Outcome 20: Memory: 3 months

| Study or Subgroup | SMD | SE | Gingko biloba Total | Placebo Total | Weight | Std. Mean Difference IV, Random, 95% CI | Std. Mean Difference IV, Random, 95% CI | Risk of Bias A B C D E F G |
|---|---|---|---|---|---|---|---|---|
| Grass-Kapanke 2011 | 0.125 | 0.1163 | 149 | 147 | 66.5% | 0.13 [-0.10 , 0.35] | | + + + + + + + |
| van Dongen 2000 | -0.0567 | 0.1639 | 166 | 48 | 33.5% | -0.06 [-0.38 , 0.26] | | + ? + + + ? + |
| **Total (Wald[a])** | | | **315** | **195** | **100.0%** | **0.06 [-0.12 , 0.25]** | | |




Test for overall effect: Z = 0.68 (P = 0.50)

Heterogeneity: Tau² (DL[b]) = 0.00; Chi² = 0.82, df = 1 (P = 0.37); I² = 0%

**Footnotes**

[a]CI calculated by Wald-type method.

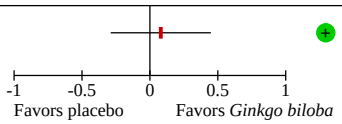
[b]Tau² calculated by DerSimonian and Laird method.

**Risk of bias legend**

(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

## Analysis 3.21. Comparison 3: Mild cognitive impairment: *Ginkgo biloba* versus placebo, Outcome 21: Memory: 6 months

| Study or Subgroup | SMD | SE | Gingko biloba Total | Placebo Total | Std. Mean Difference IV, Random, 95% CI | Std. Mean Difference IV, Random, 95% CI | Risk of Bias A B C D E F G |
|---|---|---|---|---|---|---|---|
| van Dongen 2000 | 0.0801 | 0.1882 | 79 | 44 | 0.08 [-0.29 , 0.45] | | + ? + + + ? + |

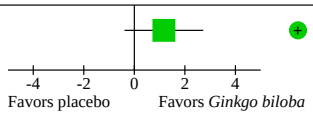



**Risk of bias legend**

(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

## Analysis 3.22. Comparison 3: Mild cognitive impairment: *Ginkgo biloba* versus placebo, Outcome 22: Memory: 12 months

| Study or Subgroup | Ginkgo biloba Mean | SD | Total | Placebo Mean | SD | Total | Mean Difference IV, Random, 95% CI | Mean Difference IV, Random, 95% CI | Risk of Bias A B C D E F G |
|---|---|---|---|---|---|---|---|---|---|
| Tian 2019 | 6.13 | 5.2 | 104 | 4.96 | 5.1 | 70 | 1.17 [-0.39 , 2.73] | | + + + + + ? + |




**Risk of bias legend**

(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias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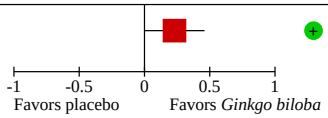
## Analysis 3.23. Comparison 3: Mild cognitive impairment: *Ginkgo biloba* versus placebo, Outcome 23: Executive function: 3 months

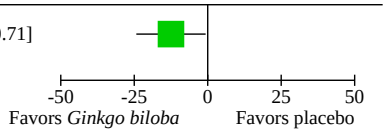
| Study or Subgroup | SMD | SE | Gingko biloba Total | Placebo Total | Std. Mean Difference IV, Random, 95% CI | Std. Mean Difference IV, Random, 95% CI | Risk of Bias A B C D E F G |
|---|---|---|---|---|---|---|---|
| Grass-Kapanke 2011 | 0.23 | 0.117346939 | 149 | 147 | 0.23 [0.00 , 0.46] | | + + + + + + + |




**Risk of bias legend**
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

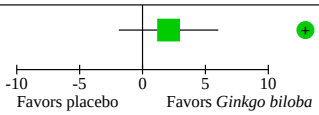
## Analysis 3.24. Comparison 3: Mild cognitive impairment: *Ginkgo biloba* versus placebo, Outcome 24: Executive function: 6 months

| Study or Subgroup | Ginkgo biloba Mean | SD | Total | Placebo Mean | SD | Total | Mean Difference IV, Random, 95% CI | Mean Difference IV, Random, 95% CI |
|---|---|---|---|---|---|---|---|---|
| Gavrilova 2014 | -44.7 | 36.8 | 80 | -32.2 | 39 | 79 | -12.50 [-24.29 , -0.71] | |




## Analysis 3.25. Comparison 3: Mild cognitive impairment: *Ginkgo biloba* versus placebo, Outcome 25: Quality of life: mental - 3 months

| Study or Subgroup | Ginkgo biloba Mean | SD | Total | Placebo Mean | SD | Total | Mean Difference IV, Random, 95% CI | Mean Difference IV, Random, 95% CI | Risk of Bias A B C D E F G |
|---|---|---|---|---|---|---|---|---|---|
| Grass-Kapanke 2011 | 11.07 | 17.84 | 149 | 9 | 16.86 | 147 | 2.07 [-1.88 , 6.02] | | + + + + + + + |




**Risk of bias legend**
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias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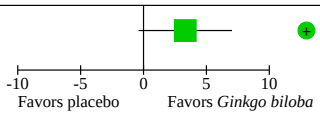
## Analysis 3.26. Comparison 3: Mild cognitive impairment: *Ginkgo biloba* versus placebo, Outcome 26: Quality of life: physical - 3 months

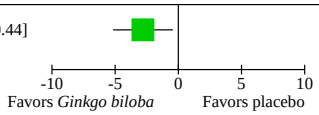
| Study or Subgroup | Ginkgo biloba Mean | SD | Total | Placebo Mean | SD | Total | Mean Difference IV, Random, 95% CI | Mean Difference IV, Random, 95% CI | Risk of Bias A B C D E F G |
|---|---|---|---|---|---|---|---|---|---|
| Grass-Kapanke 2011 | 9.02 | 16.04 | 149 | 5.7 | 16.55 | 147 | 3.32 [-0.39 , 7.03] | | + + + + + + + |




**Risk of bias legend**
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

## Analysis 3.27. Comparison 3: Mild cognitive impairment: *Ginkgo biloba* versus placebo, Outcome 27: Neuropsychiatric outcomes: anxiety - 6 months

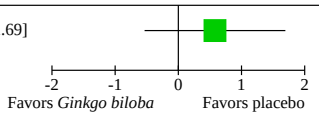
| Study or Subgroup | Ginkgo biloba Mean | SD | Total | Placebo Mean | SD | Total | Mean Difference IV, Random, 95% CI | Mean Difference IV, Random, 95% CI | Risk of Bias A B C D E F G |
|---|---|---|---|---|---|---|---|---|---|
| Gavrilova 2014 | -6.6 | 7.9 | 80 | -3.8 | 7.3 | 79 | -2.80 [-5.16 , -0.44] | | + + + + + ? + |




**Risk of bias legend**
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

## Analysis 3.28. Comparison 3: Mild cognitive impairment: *Ginkgo biloba* versus placebo, Outcome 28: Neuropsychiatric outcomes: depression - 3 months

| Study or Subgroup | Ginkgo biloba Mean | SD | Total | Placebo Mean | SD | Total | Mean Difference IV, Random, 95% CI | Mean Difference IV, Random, 95% CI | Risk of Bias A B C D E F G |
|---|---|---|---|---|---|---|---|---|---|
| van Dongen 2000 | -0.62 | 2.84 | 166 | -1.2 | 3.63 | 48 | 0.58 [-0.53 , 1.69] | | + ? + + + ? + |




**Risk of bias legend**
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias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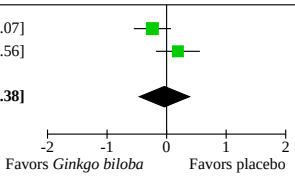
## Analysis 3.29. Comparison 3: Mild cognitive impairment: *Ginkgo biloba* versus placebo, Outcome 29: Neuropsychiatric outcomes: depression - 6 months - change

| Study or Subgroup | Ginkgo biloba Mean | SD | Total | Placebo Mean | SD | Total | Weight | Std. Mean Difference IV, Random, 95% CI | Risk of Bias A B C D E F G |
|---|---|---|---|---|---|---|---|---|---|
| Gavrilova 2014 | -3 | 2.6 | 80 | -2.3 | 3.2 | 79 | 52.8% | -0.24 [-0.55 , 0.07] | + + + + + ? + |
| van Dongen 2000 | -0.58 | 2.82 | 79 | -1.14 | 3.14 | 44 | 47.2% | 0.19 [-0.18 , 0.56] | + ? + + + ? + |
| **Total (Wald[a])** | | | **159** | | | **123** | **100.0%** | **-0.04 [-0.46 , 0.38]** | |




Test for overall effect: Z = 0.17 (P = 0.86)

Heterogeneity: Tau² (DL[b]) = 0.06; Chi² = 3.02, df = 1 (P = 0.08); I² = 67%

**Footnotes**

[a]CI calculated by Wald-type method.

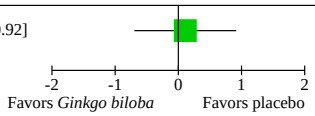
[b]Tau² calculated by DerSimonian and Laird method.

**Risk of bias legend**

(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

## Analysis 3.30. Comparison 3: Mild cognitive impairment: *Ginkgo biloba* versus placebo, Outcome 30: Neuropsychiatric outcomes: depression - 6 months - endpoint

| Study or Subgroup | Ginkgo biloba Mean | SD | Total | Placebo Mean | SD | Total | Mean Difference IV, Random, 95% CI | Risk of Bias A B C D E F G |
|---|---|---|---|---|---|---|---|---|
| GEM 2010 | 5.15 | 4.34 | 239 | 5.04 | 4.37 | 211 | 0.11 [-0.70 , 0.92] | + + + + + + + |

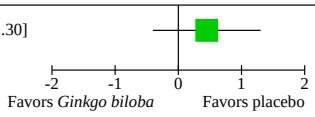



**Risk of bias legend**

(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

## Analysis 3.31. Comparison 3: Mild cognitive impairment: *Ginkgo biloba* versus placebo, Outcome 31: Neuropsychiatric outcomes: depression - 12 months

| Study or Subgroup | Ginkgo biloba Mean | SD | Total | Placebo Mean | SD | Total | Mean Difference IV, Random, 95% CI | Risk of Bias A B C D E F G |
|---|---|---|---|---|---|---|---|---|
| GEM 2010 | 5.11 | 4.87 | 230 | 4.66 | 4.16 | 200 | 0.45 [-0.40 , 1.30] | + + + + + + + |




**Risk of bias legend**

(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias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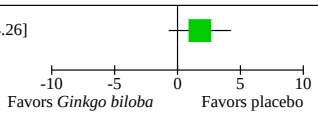
### Analysis 3.32. Comparison 3: Mild cognitive impairment: *Ginkgo biloba* versus placebo, Outcome 32: Neuropsychiatric outcomes: mental well-being - 3 months

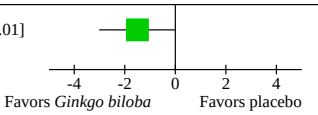
| Study or Subgroup | Ginkgo biloba Mean | SD | Total | Placebo Mean | SD | Total | Mean Difference IV, Random, 95% CI | Mean Difference IV, Random, 95% CI | Risk of Bias A B C D E F G |
|---|---|---|---|---|---|---|---|---|---|
| Grass-Kapanke 2011 | -2.32 | 10.84 | 149 | -4.1 | 10.95 | 147 | 1.78 [-0.70 , 4.26] | | + + + + + + + |




**Risk of bias legend**
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

### Analysis 3.33. Comparison 3: Mild cognitive impairment: *Ginkgo biloba* versus placebo, Outcome 33: Neuropsychiatric outcomes: NPI - 6 months

| Study or Subgroup | Ginkgo biloba Mean | SD | Total | Placebo Mean | SD | Total | Mean Difference IV, Random, 95% CI | Mean Difference IV, Random, 95% CI | Risk of Bias A B C D E F G |
|---|---|---|---|---|---|---|---|---|---|
| Gavrilova 2014 | -7 | 4.5 | 80 | -5.5 | 5.2 | 79 | -1.50 [-3.01 , 0.01] | | + + + + + ? + |




**Risk of bias legend**
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

## Comparison 4. Mild cognitive impairment: *Ginkgo biloba* versus conventional medication

| Outcome or subgroup title | No. of studies | No. of participants | Statistical method | Effect size |
|---|---|---|---|---|
| 4.1 Global cognitive function: butylphthalide - 3 months | 1 | | Mean Difference (IV, Random, 95% CI) | Subtotals only |
| 4.2 Global cognitive function: donepezil - 3 months | 1 | | Mean Difference (IV, Random, 95% CI) | Subtotals only |
| 4.3 Global cognitive function: Nimodipine - 6 months | 1 | | Mean Difference (IV, Random, 95% CI) | Subtotals only |
| 4.4 ADL: butylphthalide - 3 months | 1 | | Mean Difference (IV, Random, 95% CI) | Subtotals only |
| 4.5 ADL: donepezil - 3 months | 1 | | Mean Difference (IV, Random, 95% CI) | Subtotals only |
| 4.6 ADL: Nimodipine - 6 months | 1 | | Mean Difference (IV, Random, 95% CI) | Subtotals only |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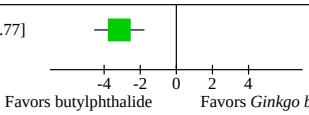
| Outcome or subgroup title | No. of studies | No. of participants | Statistical method | Effect size |
|---|---|---|---|---|
| 4.7 Memory: donepezil - 3 months | 1 | | Mean Difference (IV, Random, 95% CI) | Subtotals only |

### Analysis 4.1. Comparison 4: Mild cognitive impairment: *Ginkgo biloba* versus conventional medication, Outcome 1: Global cognitive function: butylphthalide - 3 months

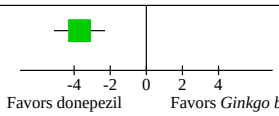
| Study or Subgroup | Ginkgo biloba Mean | SD | Total | Butylphthalide Mean | SD | Total | Mean Difference IV, Random, 95% CI | Mean Difference IV, Random, 95% CI | Risk of Bias A B C D E F G |
|---|---|---|---|---|---|---|---|---|---|
| Yu 2021 | 23.17 | 2.21 | 23 | 26.33 | 2.59 | 23 | -3.16 [-4.55 , -1.77] | | + ? ? ? + ? + |




**Risk of bias legend**
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

### Analysis 4.2. Comparison 4: Mild cognitive impairment: *Ginkgo biloba* versus conventional medication, Outcome 2: Global cognitive function: donepezil - 3 months

| Study or Subgroup | Ginkgo biloba Mean | SD | Total | Donepezil Mean | SD | Total | Mean Difference IV, Random, 95% CI | Mean Difference IV, Random, 95% CI | Risk of Bias A B C D E F G |
|---|---|---|---|---|---|---|---|---|---|
| He 2016 | 17.2 | 3.8 | 50 | 20.9 | 3.4 | 50 | -3.70 [-5.11 , -2.29] | | + ? − ? ? ? − |




**Risk of bias legend**
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias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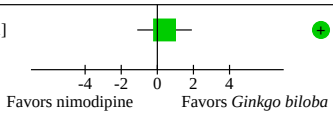
## Analysis 4.3. Comparison 4: Mild cognitive impairment: *Ginkgo biloba* versus conventional medication, Outcome 3: Global cognitive function: Nimodipine - 6 months

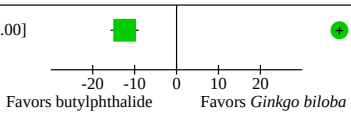
| Study or Subgroup | Ginkgo biloba Mean | SD | Total | Nimodipine Mean | SD | Total | Mean Difference IV, Random, 95% CI | Mean Difference IV, Random, 95% CI | Risk of Bias A B C D E F G |
|---|---|---|---|---|---|---|---|---|---|
| Tan 2016 | 18.6 | 3.5 | 40 | 18.2 | 3.4 | 40 | 0.40 [-1.11 , 1.91] | | + ? ? ? + ? + |




**Risk of bias legend**
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

## Analysis 4.4. Comparison 4: Mild cognitive impairment: *Ginkgo biloba* versus conventional medication, Outcome 4: ADL: butylphthalide - 3 months

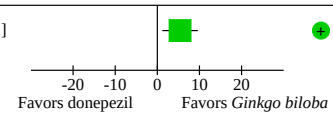
| Study or Subgroup | Ginkgo biloba Mean | SD | Total | Butylphthalide Mean | SD | Total | Mean Difference IV, Random, 95% CI | Mean Difference IV, Random, 95% CI | Risk of Bias A B C D E F G |
|---|---|---|---|---|---|---|---|---|---|
| Yu 2021 | 64.54 | 6.06 | 23 | 76.92 | 5.62 | 23 | -12.38 [-15.76 , -9.00] | | + ? ? ? + ? + |




**Risk of bias legend**
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

## Analysis 4.5. Comparison 4: Mild cognitive impairment: *Ginkgo biloba* versus conventional medication, Outcome 5: ADL: donepezil - 3 months

| Study or Subgroup | Ginkgo biloba Mean | SD | Total | Donepezil Mean | SD | Total | Mean Difference IV, Random, 95% CI | Mean Difference IV, Random, 95% CI | Risk of Bias A B C D E F G |
|---|---|---|---|---|---|---|---|---|---|
| He 2016 | 42.5 | 11.6 | 50 | 37.1 | 9.8 | 50 | 5.40 [1.19 , 9.61] | | + ? − ? ? ? − |




**Risk of bias legend**
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias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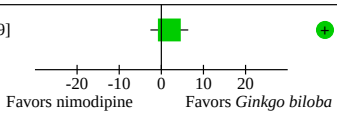
### Analysis 4.6. Comparison 4: Mild cognitive impairment: *Ginkgo biloba* versus conventional medication, Outcome 6: ADL: Nimodipine - 6 months

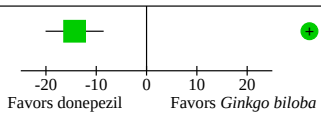
| Study or Subgroup | Ginkgo biloba Mean | SD | Total | Nimodipine Mean | SD | Total | Mean Difference IV, Random, 95% CI | Risk of Bias A B C D E F G |
|---|---|---|---|---|---|---|---|---|
| Tan 2016 | 68.4 | 10.4 | 40 | 66.5 | 10.1 | 40 | 1.90 [-2.59 , 6.39] | + ? ? ? + ? + |




**Risk of bias legend**
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

### Analysis 4.7. Comparison 4: Mild cognitive impairment: *Ginkgo biloba* versus conventional medication, Outcome 7: Memory: donepezil - 3 months

| Study or Subgroup | Ginkgo biloba Mean | SD | Total | Donepezil Mean | SD | Total | Mean Difference IV, Random, 95% CI | Risk of Bias A B C D E F G |
|---|---|---|---|---|---|---|---|---|
| He 2016 | 54.1 | 13.8 | 50 | 68.4 | 15.6 | 50 | -14.30 [-20.07 , -8.53] | + ? − ? ? ? − |




**Risk of bias legend**
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

## Comparison 5. Mild cognitive impairment: *Ginkgo biloba* versus Chinese herbal medicine or acupuncture

| Outcome or subgroup title | No. of studies | No. of participants | Statistical method | Effect size |
|---|---|---|---|---|
| 5.1 Global cognitive function: acupuncture - 3 months | 1 | | Mean Difference (IV, Random, 95% CI) | Subtotals only |
| 5.2 Global cognitive function: Guilingji capsule - 3 months | 1 | | Mean Difference (IV, Random, 95% CI) | Subtotals only |
| 5.3 Global cognitive function: Yi Zhi Ling - 3 months | 1 | | Mean Difference (IV, Random, 95% CI) | Subtotals only |
| 5.4 Global cognitive function: Compound Xueshuantong - 6 months | 1 | | Mean Difference (IV, Random, 95% CI) | Subtotals only |
| 5.5 Global cognitive function: Guilingji capsule - 6 months | 1 | | Mean Difference (IV, Random, 95% CI) | Subtotals only |
| 5.6 Global cognitive function: Qinggongshoutao - 12 months | 1 | | Mean Difference (IV, Random, 95% CI) | Subtotals only |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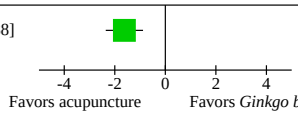
| Outcome or subgroup title | No. of studies | No. of participants | Statistical method | Effect size |
|---|---|---|---|---|
| 5.7 ADL: Compound Xueshuantong - 6 months | 1 | | Mean Difference (IV, Random, 95% CI) | Subtotals only |
| 5.8 Adverse events: Qinggongshoutao - all | 1 | | Risk Ratio (IV, Random, 95% CI) | Subtotals only |
| 5.9 Adverse events: Qinggongshoutao - serious | 1 | | Risk Ratio (IV, Random, 95% CI) | Subtotals only |
| 5.10 Memory: Jiawei Wuzi Yanzong - 3 months | 1 | | Mean Difference (IV, Random, 95% CI) | Subtotals only |

### Analysis 5.1. Comparison 5: Mild cognitive impairment: *Ginkgo biloba* versus Chinese herbal medicine or acupuncture, Outcome 1: Global cognitive function: acupuncture - 3 months

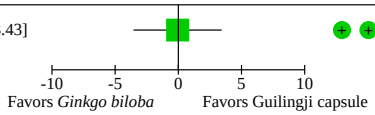
| | Ginkgo biloba | | | Acupuncture | | | Mean Difference | Mean Difference | Risk of Bias |
|---|---|---|---|---|---|---|---|---|---|
| Study or Subgroup | Mean | SD | Total | Mean | SD | Total | IV, Random, 95% CI | IV, Random, 95% CI | A B C D E F G |
| Zheng 2021 | 24.56 | 1.17 | 28 | 26.18 | 1.64 | 29 | -1.62 [-2.36 , -0.88] | | + ? ? + + ? + |




**Risk of bias legend**
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

### Analysis 5.2. Comparison 5: Mild cognitive impairment: *Ginkgo biloba* versus Chinese herbal medicine or acupuncture, Outcome 2: Global cognitive function: Guilingji capsule - 3 months

| | Ginkgo biloba | | | Guilingji capsule | | | Mean Difference | Mean Difference | Risk of Bias |
|---|---|---|---|---|---|---|---|---|---|
| Study or Subgroup | Mean | SD | Total | Mean | SD | Total | IV, Random, 95% CI | IV, Random, 95% CI | A B C D E F G |
| Zhang 2022 | 15.76 | 8.28 | 45 | 15.82 | 7.81 | 37 | -0.06 [-3.55 , 3.43] | | + + + + − − + |




**Risk of bias legend**
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias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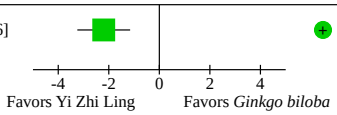
## Analysis 5.3. Comparison 5: Mild cognitive impairment: *Ginkgo biloba* versus Chinese herbal medicine or acupuncture, Outcome 3: Global cognitive function: Yi Zhi Ling - 3 months

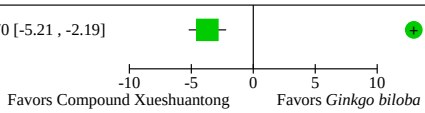
| Study or Subgroup | Ginkgo biloba Mean | SD | Total | Yi Zhi Ling Mean | SD | Total | Mean Difference IV, Random, 95% CI | Mean Difference IV, Random, 95% CI | Risk of Bias A B C D E F G |
|---|---|---|---|---|---|---|---|---|---|
| Yang 2015a | 23.1 | 1.9 | 33 | 25.3 | 2.4 | 33 | -2.20 [-3.24 , -1.16] | | + ? ? ? + ? + |




**Risk of bias legend**
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

## Analysis 5.4. Comparison 5: Mild cognitive impairment: *Ginkgo biloba* versus Chinese herbal medicine or acupuncture, Outcome 4: Global cognitive function: Compound Xueshuantong - 6 months

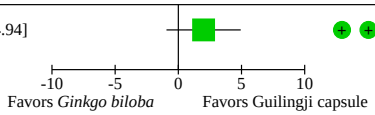
| Study or Subgroup | Ginkgo biloba Mean | SD | Total | Compound Xueshuantong Mean | SD | Total | Mean Difference IV, Random, 95% CI | Mean Difference IV, Random, 95% CI | Risk of Bias A B C D E F G |
|---|---|---|---|---|---|---|---|---|---|
| Tan 2016 | 18.6 | 3.5 | 40 | 22.3 | 3.4 | 40 | -3.70 [-5.21 , -2.19] | | + ? ? ? + ? + |




**Risk of bias legend**
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

## Analysis 5.5. Comparison 5: Mild cognitive impairment: *Ginkgo biloba* versus Chinese herbal medicine or acupuncture, Outcome 5: Global cognitive function: Guilingji capsule - 6 months

| Study or Subgroup | Ginkgo biloba Mean | SD | Total | Guilingji capsule Mean | SD | Total | Mean Difference IV, Random, 95% CI | Mean Difference IV, Random, 95% CI | Risk of Bias A B C D E F G |
|---|---|---|---|---|---|---|---|---|---|
| Zhang 2022 | 14.02 | 7.59 | 45 | 12.02 | 5.98 | 37 | 2.00 [-0.94 , 4.94] | | + + + + − − + |




**Risk of bias legend**
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias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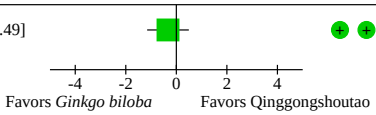
## Analysis 5.6. Comparison 5: Mild cognitive impairment: *Ginkgo biloba* versus Chinese herbal medicine or acupuncture, Outcome 6: Global cognitive function: Qinggongshoutao - 12 months

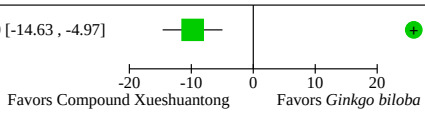
| Study or Subgroup | Ginkgo biloba Mean | SD | Total | Qinggongshoutao Mean | SD | Total | Mean Difference IV, Random, 95% CI | Mean Difference IV, Random, 95% CI | Risk of Bias A B C D E F G |
|---|---|---|---|---|---|---|---|---|---|
| Tian 2019 | 2.43 | 3.37 | 104 | 2.76 | 3.43 | 174 | -0.33 [-1.15 , 0.49] | | + + + + + ? + |




**Risk of bias legend**
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

## Analysis 5.7. Comparison 5: Mild cognitive impairment: *Ginkgo biloba* versus Chinese herbal medicine or acupuncture, Outcome 7: ADL: Compound Xueshuantong - 6 months

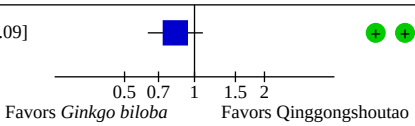
| Study or Subgroup | Ginkgo biloba Mean | SD | Total | Compound Xueshuantong Mean | SD | Total | Mean Difference IV, Random, 95% CI | Mean Difference IV, Random, 95% CI | Risk of Bias A B C D E F G |
|---|---|---|---|---|---|---|---|---|---|
| Tan 2016 | 68.4 | 10.4 | 40 | 78.2 | 11.6 | 40 | -9.80 [-14.63 , -4.97] | | + ? ? ? + ? + |




**Risk of bias legend**
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

## Analysis 5.8. Comparison 5: Mild cognitive impairment: *Ginkgo biloba* versus Chinese herbal medicine or acupuncture, Outcome 8: Adverse events: Qinggongshoutao - all

| Study or Subgroup | Ginkgo biloba Events | Total | Qinggongshoutao Events | Total | Risk Ratio IV, Random, 95% CI | Risk Ratio IV, Random, 95% CI | Risk of Bias A B C D E F G |
|---|---|---|---|---|---|---|---|
| Tian 2019 | 43 | 104 | 87 | 174 | 0.83 [0.63 , 1.09] | | + + + + + ? + |




**Risk of bias legend**
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias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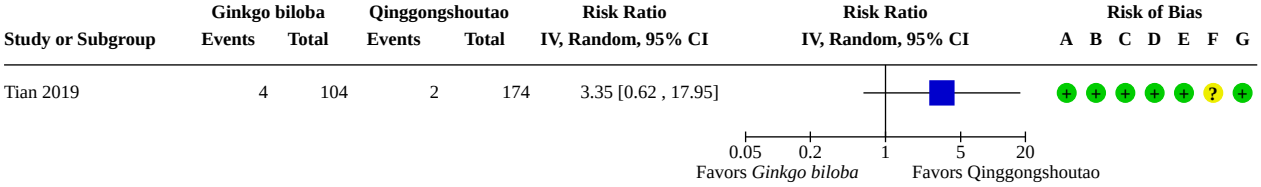
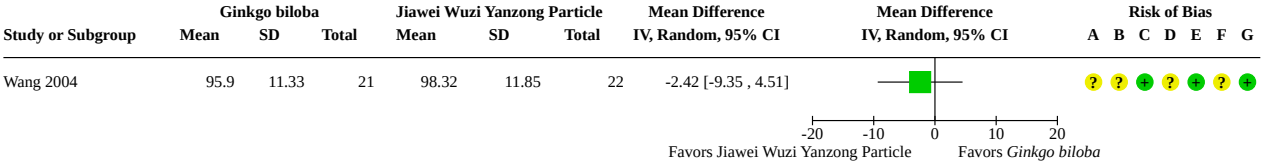
### Analysis 5.9. Comparison 5: Mild cognitive impairment: *Ginkgo biloba* versus Chinese herbal medicine or acupuncture, Outcome 9: Adverse events: Qinggongshoutao - serious




**Risk of bias legend**
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

### Analysis 5.10. Comparison 5: Mild cognitive impairment: *Ginkgo biloba* versus Chinese herbal medicine or acupuncture, Outcome 10: Memory: Jiawei Wuzi Yanzong - 3 months




**Risk of bias legend**
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

## Comparison 6. Mild cognitive impairment: *Ginkgo biloba* added to conventional treatment

| Outcome or subgroup title | No. of studies | No. of participants | Statistical method | Effect size |
|---|---|---|---|---|
| 6.1 Global clinical status: 3 months | 1 | | Mean Difference (IV, Random, 95% CI) | Subtotals only |
| 6.2 Global clinical status: 6 months | 1 | | Mean Difference (IV, Random, 95% CI) | Subtotals only |
| 6.3 Global cognitive function: 3 months | 15 | 1339 | Std. Mean Difference (IV, Random, 95% CI) | 0.98 [0.73, 1.24] |
| 6.4 Global cognitive function: 6 months | 11 | 1160 | Std. Mean Difference (IV, Random, 95% CI) | 0.90 [0.74, 1.06] |
| 6.5 Global cognitive function: 12 months | 4 | 578 | Std. Mean Difference (IV, Random, 95% CI) | 0.97 [0.70, 1.24] |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| Outcome or subgroup title | No. of studies | No. of participants | Statistical method | Effect size |
|---|---|---|---|---|
| 6.6 Cognition: MMSE analysis - 3 to 12 months: to check for publication bias | 15 | 1533 | Mean Difference (IV, Random, 95% CI) | 2.81 [2.15, 3.48] |
| 6.7 Cognition: 3 months: subgroup analysis by diagnosis | 15 | | Std. Mean Difference (IV, Random, 95% CI) | Subtotals only |
| 6.7.1 Vascular diagnosis | 13 | 1170 | Std. Mean Difference (IV, Random, 95% CI) | 1.03 [0.74, 1.31] |
| 6.7.2 Not Vascular diagnosis | 2 | 169 | Std. Mean Difference (IV, Random, 95% CI) | 0.70 [0.19, 1.20] |
| 6.8 Cognition: 6 months: subgroup analysis by diagnosis | 11 | | Std. Mean Difference (IV, Random, 95% CI) | Subtotals only |
| 6.8.1 Vascular diagnosis | 5 | 378 | Std. Mean Difference (IV, Random, 95% CI) | 0.81 [0.54, 1.09] |
| 6.8.2 Not vascular diagnosis | 6 | 782 | Std. Mean Difference (IV, Random, 95% CI) | 0.96 [0.77, 1.15] |
| 6.9 Cognition: 3 months: subgroup analysis by EGb 761 versus other | 15 | | Std. Mean Difference (IV, Random, 95% CI) | Subtotals only |
| 6.9.1 EGb 761 | 13 | 1181 | Std. Mean Difference (IV, Random, 95% CI) | 0.91 [0.65, 1.17] |
| 6.9.2 Not EGb 761 or unclear | 2 | 158 | Std. Mean Difference (IV, Random, 95% CI) | 1.52 [0.32, 2.71] |
| 6.10 ADL: 3 months | 7 | 636 | Std. Mean Difference (IV, Random, 95% CI) | 0.94 [0.31, 1.56] |
| 6.11 ADL: 6 months | 2 | 180 | Std. Mean Difference (IV, Random, 95% CI) | 1.07 [0.43, 1.71] |
| 6.12 ADL: 12 months | 1 | | Std. Mean Difference (IV, Random, 95% CI) | Subtotals only |
| 6.13 Adverse events: all | 5 | 430 | Risk Ratio (IV, Random, 95% CI) | 1.08 [0.62, 1.87] |
| 6.13.1 3 months | 4 | 350 | Risk Ratio (IV, Random, 95% CI) | 1.16 [0.63, 2.14] |
| 6.13.2 6 months | 1 | 80 | Risk Ratio (IV, Random, 95% CI) | 0.80 [0.23, 2.76] |
| 6.14 Memory: 3 months | 3 | 294 | Mean Difference (IV, Random, 95% CI) | 6.62 [3.06, 10.19] |
| 6.15 Memory: 6 months | 3 | 293 | Std. Mean Difference (IV, Random, 95% CI) | 0.41 [0.18, 0.65] |
| 6.16 Memory: 12 months | 2 | 233 | Std. Mean Difference (IV, Random, 95% CI) | 0.64 [0.38, 0.90] |


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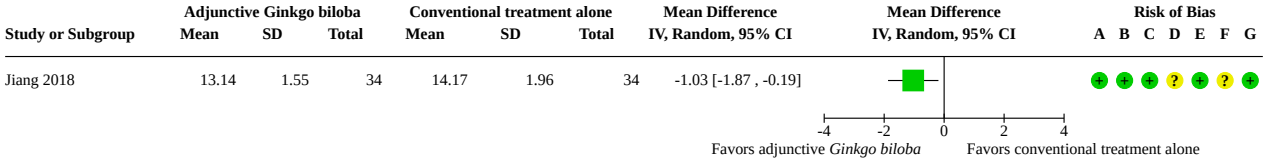
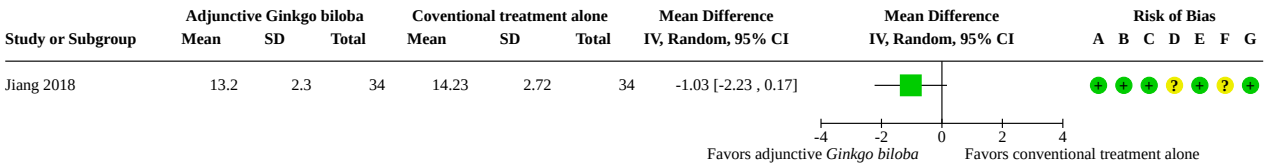
| Outcome or subgroup title | No. of studies | No. of participants | Statistical method | Effect size |
|---|---|---|---|---|
| 6.17 Executive function: 3 months | 1 | | Mean Difference (IV, Random, 95% CI) | Subtotals only |
| 6.18 Executive function: 6 months | 3 | 418 | Std. Mean Difference (IV, Random, 95% CI) | 0.57 [0.37, 0.77] |
| 6.19 Executive function: 12 months | 2 | 358 | Mean Difference (IV, Random, 95% CI) | 0.57 [0.39, 0.75] |

### Analysis 6.1. Comparison 6: Mild cognitive impairment: *Ginkgo biloba* added to conventional treatment, Outcome 1: Global clinical status: 3 months




**Risk of bias legend**
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

### Analysis 6.2. Comparison 6: Mild cognitive impairment: *Ginkgo biloba* added to conventional treatment, Outcome 2: Global clinical status: 6 months




**Risk of bias legend**
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias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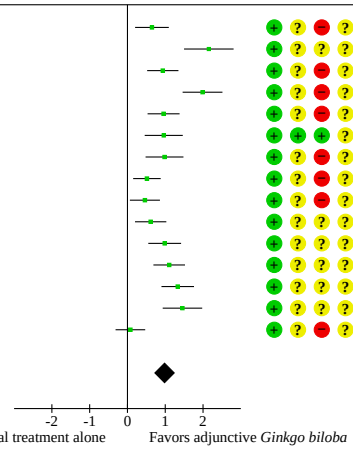
## Analysis 6.3. Comparison 6: Mild cognitive impairment: *Ginkgo biloba* added to conventional treatment, Outcome 3: Global cognitive function: 3 months

| Study or Subgroup | Adjunctive Ginkgo biloba Mean | SD | Total | Conventional treatment alone Mean | SD | Total | Weight | Std. Mean Difference IV, Random, 95% CI |
|---|---|---|---|---|---|---|---|---|
| Bu 2016 | 24.37 | 3.31 | 44 | 22.21 | 3.29 | 38 | 6.7% | 0.65 [0.20 , 1.09] |
| Deng 2021 | 22.35 | 1.36 | 29 | 19.36 | 1.38 | 29 | 5.4% | 2.15 [1.50 , 2.81] |
| He 2016 | 24.2 | 3.6 | 50 | 20.9 | 3.4 | 50 | 6.9% | 0.94 [0.52 , 1.35] |
| He 2018a | 23.84 | 1.64 | 42 | 20.46 | 1.73 | 42 | 6.2% | 1.99 [1.46 , 2.51] |
| He 2018b | 28.95 | 3.35 | 48 | 25.77 | 3.25 | 48 | 6.9% | 0.96 [0.53 , 1.38] |
| Jiang 2018 | -13.18 | 1.59 | 34 | -14.94 | 2.01 | 34 | 6.4% | 0.96 [0.46 , 1.46] |
| Li 2013a | 28.17 | 2.46 | 35 | 25.34 | 3.21 | 34 | 6.4% | 0.98 [0.48 , 1.48] |
| Li 2015a | 25.91 | 6.28 | 60 | 22.4 | 7.23 | 60 | 7.2% | 0.52 [0.15 , 0.88] |
| Liu 2015a | 21.71 | 4.52 | 50 | 19.65 | 4.33 | 50 | 7.0% | 0.46 [0.06 , 0.86] |
| Qu 2020 | 26.28 | 3.34 | 47 | 24.26 | 3.18 | 47 | 6.9% | 0.61 [0.20 , 1.03] |
| Wang 2020a | 24.53 | 4.16 | 46 | 20.71 | 3.5 | 46 | 6.8% | 0.99 [0.55 , 1.42] |
| Xu 2021 | 24.18 | 3.35 | 51 | 20.63 | 3.02 | 51 | 6.9% | 1.10 [0.69 , 1.52] |
| Yang 2020a | 26.91 | 1.49 | 51 | 25.06 | 1.26 | 51 | 6.8% | 1.33 [0.90 , 1.76] |
| Zhang 2019a | 23.27 | 2.81 | 36 | 19.35 | 2.51 | 36 | 6.3% | 1.46 [0.93 , 1.98] |
| Zhao 2020 | 25.79 | 2.96 | 50 | 25.58 | 2.37 | 50 | 7.1% | 0.08 [-0.31 , 0.47] |
| **Total (Wald[a])** | | | **673** | | | **666** | **100.0%** | **0.98 [0.73 , 1.24]** |

Test for overall effect: Z = 7.53 (P < 0.00001)

Heterogeneity: Tau² (DL[b]) = 0.20; Chi² = 68.80, df = 14 (P < 0.00001); I² = 80%



**Footnotes**

[a]CI calculated by Wald-type method.

[b]Tau² calculated by DerSimonian and Laird method.

**Risk of bias legend**

(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias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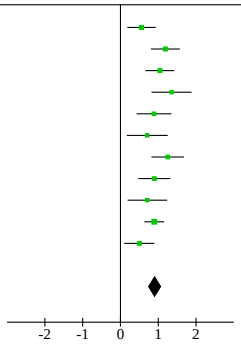
## Analysis 6.4. Comparison 6: Mild cognitive impairment: *Ginkgo biloba* added to conventional treatment, Outcome 4: Global cognitive function: 6 months

| Study or Subgroup | Adjunctive Ginkgo biloba Mean | SD | Total | Conventional treatment alone Mean | SD | Total | Weight | Std. Mean Difference IV, Random, 95% CI |
|---|---|---|---|---|---|---|---|---|
| Dong 2011 | 27.08 | 2.27 | 58 | 25.44 | 3.49 | 55 | 10.3% | 0.56 [0.18 , 0.93] |
| Gu 2017 | 27.84 | 1.36 | 62 | 26.19 | 1.4 | 62 | 10.1% | 1.19 [0.81 , 1.57] |
| Han 2016 | 25.11 | 3.08 | 60 | 22.17 | 2.49 | 60 | 10.1% | 1.04 [0.66 , 1.43] |
| Jiang 2018 | -13.03 | 1.95 | 34 | -15.88 | 2.21 | 34 | 6.6% | 1.35 [0.82 , 1.88] |
| Li 2016a | 26.85 | 2.03 | 40 | 24.6 | 2.91 | 40 | 8.0% | 0.89 [0.43 , 1.35] |
| Li 2019a | 23.61 | 2.71 | 28 | 21.48 | 3.19 | 28 | 6.3% | 0.71 [0.17 , 1.25] |
| Liu 2015a | 25.63 | 3.68 | 50 | 20.78 | 4.01 | 50 | 8.7% | 1.25 [0.82 , 1.68] |
| Qu 2020 | 26.74 | 3.21 | 47 | 24.19 | 2.37 | 47 | 8.9% | 0.90 [0.47 , 1.32] |
| Shi 2017 | 23.6 | 2.67 | 30 | 21.46 | 3.23 | 30 | 6.7% | 0.71 [0.19 , 1.24] |
| Xia 2013 | 27.31 | 2.14 | 123 | 25.34 | 2.25 | 122 | 14.7% | 0.89 [0.63 , 1.16] |
| Zhao 2020 | 27.01 | 2.85 | 50 | 25.62 | 2.67 | 50 | 9.6% | 0.50 [0.10 , 0.90] |
| **Total (Wald[a])** | | | **582** | | | **578** | **100.0%** | **0.90 [0.74 , 1.06]** |

Std. Mean Difference IV, Random, 95% CI

Risk of Bias: A B C D E F G




Test for overall effect: Z = 11.18 (P < 0.00001)

Heterogeneity: Tau² (DL[b]) = 0.03; Chi² = 16.12, df = 10 (P = 0.10); I² = 38%

**Footnotes**

[a]CI calculated by Wald-type method.

[b]Tau² calculated by DerSimonian and Laird method.

**Risk of bias legend**

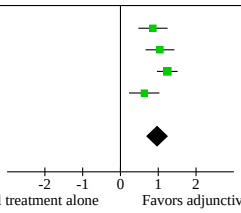
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

## Analysis 6.5. Comparison 6: Mild cognitive impairment: *Ginkgo biloba* added to conventional treatment, Outcome 5: Global cognitive function: 12 months

| Study or Subgroup | Adjunctive Ginkgo biloba Mean | SD | Total | Conventional treatment alone Mean | SD | Total | Weight | Std. Mean Difference IV, Random, 95% CI |
|---|---|---|---|---|---|---|---|---|
| Dong 2011 | 27.62 | 2.18 | 58 | 25.27 | 3.18 | 55 | 23.3% | 0.86 [0.47 , 1.25] |
| Han 2016 | 26.41 | 3.79 | 60 | 22.55 | 3.54 | 60 | 23.5% | 1.05 [0.66 , 1.43] |
| Xia 2013 | 27.81 | 2.08 | 123 | 25.42 | 1.75 | 122 | 30.7% | 1.24 [0.97 , 1.51] |
| Zhao 2020 | 27.78 | 2.96 | 50 | 25.96 | 2.78 | 50 | 22.4% | 0.63 [0.23 , 1.03] |
| **Total (Wald[a])** | | | **291** | | | **287** | **100.0%** | **0.97 [0.70 , 1.24]** |

Std. Mean Difference IV, Random, 95% CI

Risk of Bias: A B C D E F G




Test for overall effect: Z = 7.10 (P < 0.00001)

Heterogeneity: Tau² (DL[b]) = 0.04; Chi² = 6.75, df = 3 (P = 0.08); I² = 56%

**Footnotes**

[a]CI calculated by Wald-type method.

[b]Tau² calculated by DerSimonian and Laird method.

**Risk of bias legend**

(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias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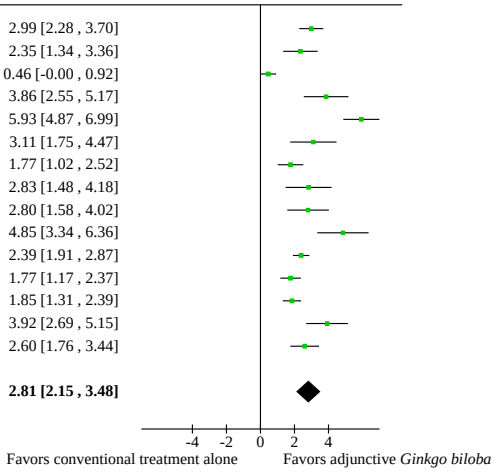
## Analysis 6.6. Comparison 6: Mild cognitive impairment: *Ginkgo biloba* added to conventional treatment, Outcome 6: Cognition: MMSE analysis - 3 to 12 months: to check for publication bias

| Study or Subgroup | Adjunctive Ginkgo biloba Mean | SD | Total | Conventional treatment alone Mean | SD | Total | Weight | Mean Difference IV, Random, 95% CI |
|---|---|---|---|---|---|---|---|---|
| Deng 2021 | 22.35 | 1.36 | 29 | 19.36 | 1.38 | 29 | 7.2% | 2.99 [2.28 , 3.70] |
| Dong 2011 | 27.62 | 2.18 | 58 | 25.27 | 3.18 | 55 | 6.6% | 2.35 [1.34 , 3.36] |
| Gu 2017 | 27.98 | 1.36 | 62 | 27.52 | 1.27 | 62 | 7.5% | 0.46 [-0.00 , 0.92] |
| Han 2016 | 26.41 | 3.79 | 60 | 22.55 | 3.54 | 60 | 6.0% | 3.86 [2.55 , 5.17] |
| He 2018a | 25.1 | 2.31 | 42 | 19.17 | 2.63 | 42 | 6.5% | 5.93 [4.87 , 6.99] |
| He 2018b | 27.8 | 3.49 | 48 | 24.69 | 3.31 | 48 | 5.9% | 3.11 [1.75 , 4.47] |
| Jiang 2018 | 23.59 | 1.23 | 34 | 21.82 | 1.87 | 34 | 7.1% | 1.77 [1.02 , 2.52] |
| Li 2013a | 28.17 | 2.46 | 35 | 25.34 | 3.21 | 34 | 5.9% | 2.83 [1.48 , 4.18] |
| Li 2016a | 28.33 | 1.46 | 40 | 25.53 | 3.66 | 40 | 6.2% | 2.80 [1.58 , 4.02] |
| Liu 2015a | 25.63 | 3.68 | 50 | 20.78 | 4.01 | 50 | 5.6% | 4.85 [3.34 , 6.36] |
| Xia 2013 | 27.81 | 2.08 | 123 | 25.42 | 1.75 | 122 | 7.5% | 2.39 [1.91 , 2.87] |
| Xu 2021 | 26.81 | 1.69 | 51 | 25.04 | 1.41 | 51 | 7.4% | 1.77 [1.17 , 2.37] |
| Yang 2020a | 26.91 | 1.49 | 51 | 25.06 | 1.26 | 51 | 7.5% | 1.85 [1.31 , 2.39] |
| Zhang 2019a | 23.27 | 2.81 | 36 | 19.35 | 2.51 | 36 | 6.2% | 3.92 [2.69 , 5.15] |
| Zhao 2020 | 24.96 | 2.18 | 50 | 22.36 | 2.13 | 50 | 6.9% | 2.60 [1.76 , 3.44] |
| **Total (Wald[a])** | | | **769** | | | **764** | **100.0%** | **2.81 [2.15 , 3.48]** |




Test for overall effect: Z = 8.32 (P < 0.00001)

Heterogeneity: Tau² (DL[b]) = 1.46; Chi² = 142.08, df = 14 (P < 0.00001); I² = 90%

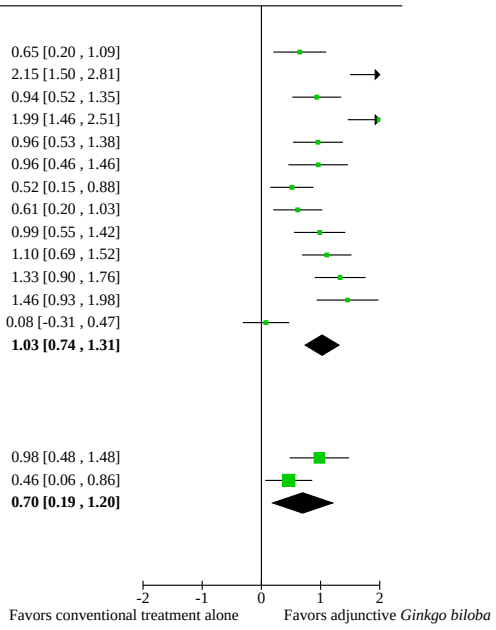
**Footnotes**

[a]CI calculated by Wald-type method.

[b]Tau² calculated by DerSimonian and Laird method.

## Analysis 6.7. Comparison 6: Mild cognitive impairment: *Ginkgo biloba* added to conventional treatment, Outcome 7: Cognition: 3 months: subgroup analysis by diagnosis

| Study or Subgroup | Adjunctive Ginkgo biloba Mean | SD | Total | Conventional treatment alone Mean | SD | Total | Weight | Std. Mean Difference IV, Random, 95% CI |
|---|---|---|---|---|---|---|---|---|
| **6.7.1 Vascular diagnosis** | | | | | | | | |
| Bu 2016 | 24.37 | 3.31 | 44 | 22.21 | 3.29 | 38 | 7.8% | 0.65 [0.20 , 1.09] |
| Deng 2021 | 22.35 | 1.36 | 29 | 19.36 | 1.38 | 29 | 6.4% | 2.15 [1.50 , 2.81] |
| He 2016 | 24.2 | 3.6 | 50 | 20.9 | 3.4 | 50 | 8.0% | 0.94 [0.52 , 1.35] |
| He 2018a | 23.84 | 1.64 | 42 | 20.46 | 1.73 | 42 | 7.2% | 1.99 [1.46 , 2.51] |
| He 2018b | 28.95 | 3.35 | 48 | 25.77 | 3.25 | 48 | 7.9% | 0.96 [0.53 , 1.38] |
| Jiang 2018 | -13.18 | 1.59 | 34 | -14.94 | 2.01 | 34 | 7.4% | 0.96 [0.46 , 1.46] |
| Li 2015a | 25.91 | 6.28 | 60 | 22.4 | 7.23 | 60 | 8.3% | 0.52 [0.15 , 0.88] |
| Qu 2020 | 26.28 | 3.34 | 47 | 24.26 | 3.18 | 47 | 8.0% | 0.61 [0.20 , 1.03] |
| Wang 2020a | 24.53 | 4.16 | 46 | 20.71 | 3.5 | 46 | 7.9% | 0.99 [0.55 , 1.42] |
| Xu 2021 | 24.18 | 3.35 | 51 | 20.63 | 3.02 | 51 | 8.0% | 1.10 [0.69 , 1.52] |
| Yang 2020a | 26.91 | 1.49 | 51 | 25.06 | 1.26 | 51 | 7.9% | 1.33 [0.90 , 1.76] |
| Zhang 2019a | 23.27 | 2.81 | 36 | 19.35 | 2.51 | 36 | 7.3% | 1.46 [0.93 , 1.98] |
| Zhao 2020 | 25.79 | 2.96 | 50 | 25.58 | 2.37 | 50 | 8.1% | 0.08 [-0.31 , 0.47] |
| **Subtotal (Wald[a])** | | | **588** | | | **582** | **100.0%** | **1.03 [0.74 , 1.31]** |
| Test for overall effect: Z = 7.05 (P < 0.00001) | | | | | | | | |
| Heterogeneity: Tau² (DL[b]) = 0.22; Chi² = 63.70, df = 12 (P < 0.00001); I² = 81% | | | | | | | | |
| **6.7.2 Not Vascular diagnosis** | | | | | | | | |
| Li 2013a | 28.17 | 2.46 | 35 | 25.34 | 3.21 | 34 | 45.5% | 0.98 [0.48 , 1.48] |
| Liu 2015a | 21.71 | 4.52 | 50 | 19.65 | 4.33 | 50 | 54.5% | 0.46 [0.06 , 0.86] |
| **Subtotal (Wald[a])** | | | **85** | | | **84** | **100.0%** | **0.70 [0.19 , 1.20]** |
| Test for overall effect: Z = 2.70 (P = 0.007) | | | | | | | | |
| Heterogeneity: Tau² (DL[b]) = 0.08; Chi² = 2.53, df = 1 (P = 0.11); I² = 60% | | | | | | | | |




Test for subgroup differences: Chi² = 1.23, df = 1 (P = 0.27), I² = 18.5%

**Footnotes**

[a]CI calculated by Wald-type method.

[b]Tau² calculated by DerSimonian and Laird method.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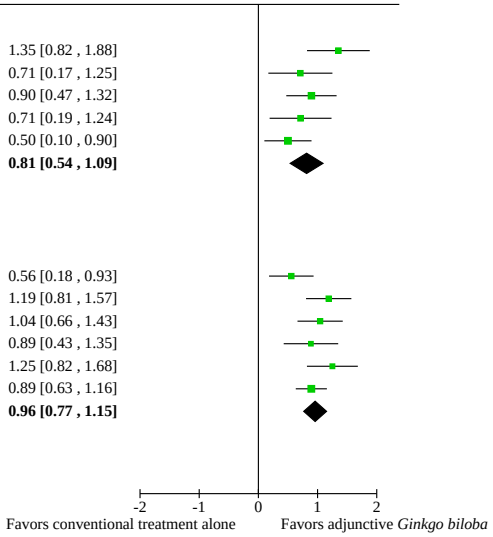
## Analysis 6.8. Comparison 6: Mild cognitive impairment: *Ginkgo biloba* added to conventional treatment, Outcome 8: Cognition: 6 months: subgroup analysis by diagnosis

| Study or Subgroup | Adjunctive Ginkgo biloba Mean | SD | Total | Conventional treatment alone Mean | SD | Total | Weight | Std. Mean Difference IV, Random, 95% CI |
|---|---|---|---|---|---|---|---|---|
| **6.8.1 Vascular diagnosis** | | | | | | | | |
| Jiang 2018 | -13.03 | 1.95 | 34 | -15.88 | 2.21 | 34 | 17.6% | 1.35 [0.82 , 1.88] |
| Li 2019a | 23.61 | 2.71 | 28 | 21.48 | 3.19 | 28 | 17.1% | 0.71 [0.17 , 1.25] |
| Qu 2020 | 26.74 | 3.21 | 47 | 24.19 | 2.37 | 47 | 22.9% | 0.90 [0.47 , 1.32] |
| Shi 2017 | 23.6 | 2.67 | 30 | 21.46 | 3.23 | 30 | 17.9% | 0.71 [0.19 , 1.24] |
| Zhao 2020 | 27.01 | 2.85 | 50 | 25.62 | 2.67 | 50 | 24.5% | 0.50 [0.10 , 0.90] |
| **Subtotal (Wald[a])** | | | **189** | | | **189** | **100.0%** | **0.81 [0.54 , 1.09]** |
| Test for overall effect: Z = 5.75 (P < 0.00001) | | | | | | | | |
| Heterogeneity: Tau² (DL[b]) = 0.04; Chi² = 6.77, df = 4 (P = 0.15); I² = 41% | | | | | | | | |
| **6.8.2 Not vascular diagnosis** | | | | | | | | |
| Dong 2011 | 27.08 | 2.27 | 58 | 25.44 | 3.49 | 55 | 16.6% | 0.56 [0.18 , 0.93] |
| Gu 2017 | 27.84 | 1.36 | 62 | 26.19 | 1.4 | 62 | 16.2% | 1.19 [0.81 , 1.57] |
| Han 2016 | 25.11 | 3.08 | 60 | 22.17 | 2.49 | 60 | 16.2% | 1.04 [0.66 , 1.43] |
| Li 2016a | 26.85 | 2.03 | 40 | 24.6 | 2.91 | 40 | 12.6% | 0.89 [0.43 , 1.35] |
| Liu 2015a | 25.63 | 3.68 | 50 | 20.78 | 4.01 | 50 | 13.9% | 1.25 [0.82 , 1.68] |
| Xia 2013 | 27.31 | 2.14 | 123 | 25.34 | 2.25 | 122 | 24.4% | 0.89 [0.63 , 1.16] |
| **Subtotal (Wald[a])** | | | **393** | | | **389** | **100.0%** | **0.96 [0.77 , 1.15]** |
| Test for overall effect: Z = 9.73 (P < 0.00001) | | | | | | | | |
| Heterogeneity: Tau² (DL[b]) = 0.02; Chi² = 8.04, df = 5 (P = 0.15); I² = 38% | | | | | | | | |
| Test for subgroup differences: Chi² = 0.70, df = 1 (P = 0.40), I² = 0% | | | | | | | | |



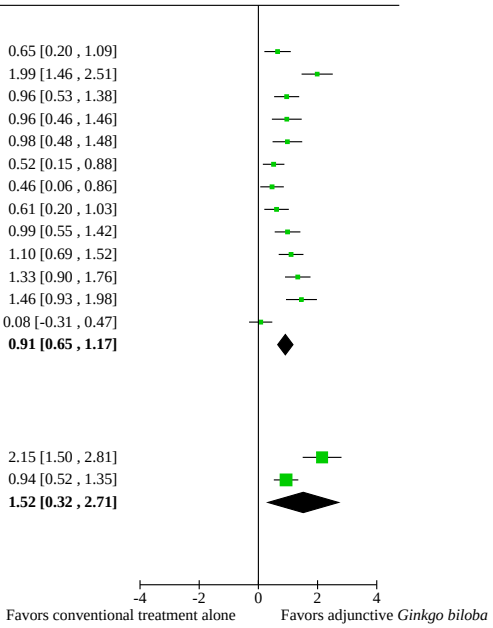

**Footnotes**

[a]CI calculated by Wald-type method.

[b]Tau² calculated by DerSimonian and Laird method.

## Analysis 6.9. Comparison 6: Mild cognitive impairment: *Ginkgo biloba* added to conventional treatment, Outcome 9: Cognition: 3 months: subgroup analysis by EGb 761 versus other

| Study or Subgroup | Adjunctive Ginkgo biloba Mean | SD | Total | Conventional treatment alone Mean | SD | Total | Weight | Std. Mean Difference IV, Random, 95% CI |
|---|---|---|---|---|---|---|---|---|
| **6.9.1 EGb 761** | | | | | | | | |
| Bu 2016 | 24.37 | 3.31 | 44 | 22.21 | 3.29 | 38 | 7.7% | 0.65 [0.20 , 1.09] |
| He 2018a | 23.84 | 1.64 | 42 | 20.46 | 1.73 | 42 | 7.0% | 1.99 [1.46 , 2.51] |
| He 2018b | 28.95 | 3.35 | 48 | 25.77 | 3.25 | 48 | 7.9% | 0.96 [0.53 , 1.38] |
| Jiang 2018 | -13.18 | 1.59 | 34 | -14.94 | 2.01 | 34 | 7.2% | 0.96 [0.46 , 1.46] |
| Li 2013a | 28.17 | 2.46 | 35 | 25.34 | 3.21 | 34 | 7.2% | 0.98 [0.48 , 1.48] |
| Li 2015a | 25.91 | 6.28 | 60 | 22.4 | 7.23 | 60 | 8.3% | 0.52 [0.15 , 0.88] |
| Liu 2015a | 21.71 | 4.52 | 50 | 19.65 | 4.33 | 50 | 8.1% | 0.46 [0.06 , 0.86] |
| Qu 2020 | 26.28 | 3.34 | 47 | 24.26 | 3.18 | 47 | 7.9% | 0.61 [0.20 , 1.03] |
| Wang 2020a | 24.53 | 4.16 | 46 | 20.71 | 3.5 | 46 | 7.8% | 0.99 [0.55 , 1.42] |
| Xu 2021 | 24.18 | 3.35 | 51 | 20.63 | 3.02 | 51 | 7.9% | 1.10 [0.69 , 1.52] |
| Yang 2020a | 26.91 | 1.49 | 51 | 25.06 | 1.26 | 51 | 7.8% | 1.33 [0.90 , 1.76] |
| Zhang 2019a | 23.27 | 2.81 | 36 | 19.35 | 2.51 | 36 | 7.1% | 1.46 [0.93 , 1.98] |
| Zhao 2020 | 25.79 | 2.96 | 50 | 25.58 | 2.37 | 50 | 8.1% | 0.08 [-0.31 , 0.47] |
| **Subtotal (Wald[a])** | | | **594** | | | **587** | **100.0%** | **0.91 [0.65 , 1.17]** |
| Test for overall effect: Z = 6.91 (P < 0.00001) | | | | | | | | |
| Heterogeneity: Tau² (DL[b]) = 0.17; Chi² = 54.16, df = 12 (P < 0.00001); I² = 78% | | | | | | | | |
| **6.9.2 Not EGb 761 or unclear** | | | | | | | | |
| Deng 2021 | 22.35 | 1.36 | 29 | 19.36 | 1.38 | 29 | 47.7% | 2.15 [1.50 , 2.81] |
| He 2016 | 24.2 | 3.6 | 50 | 20.9 | 3.4 | 50 | 52.3% | 0.94 [0.52 , 1.35] |
| **Subtotal (Wald[a])** | | | **79** | | | **79** | **100.0%** | **1.52 [0.32 , 2.71]** |
| Test for overall effect: Z = 2.49 (P = 0.01) | | | | | | | | |
| Heterogeneity: Tau² (DL[b]) = 0.66; Chi² = 9.48, df = 1 (P = 0.002); I² = 89% | | | | | | | | |
| Test for subgroup differences: Chi² = 0.95, df = 1 (P = 0.33), I² = 0% | | | | | | | | |




**Footnotes**

[a]CI calculated by Wald-type method.

[b]Tau² calculated by DerSimonian and Laird method.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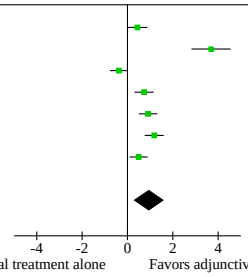
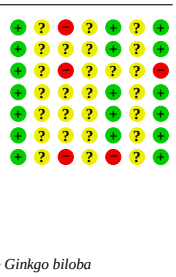
## Analysis 6.10. Comparison 6: Mild cognitive impairment: *Ginkgo biloba* added to conventional treatment, Outcome 10: ADL: 3 months

| Study or Subgroup | Adjunctive Ginkgo biloba Mean | SD | Total | Conventional treatment alone Mean | SD | Total | Weight | Std. Mean Difference IV, Random, 95% CI |
|---|---|---|---|---|---|---|---|---|
| Bu 2016 | 83.83 | 9.44 | 44 | 80.33 | 5.58 | 38 | 14.5% | 0.44 [-0.00 , 0.88] |
| Deng 2021 | 86.35 | 4.24 | 29 | 72.18 | 3.28 | 29 | 12.1% | 3.69 [2.82 , 4.55] |
| He 2016 | 33.4 | 9.7 | 50 | 37.1 | 9.8 | 50 | 14.7% | -0.38 [-0.77 , 0.02] |
| Wang 2020a | 72.09 | 7.64 | 46 | 66.53 | 7.41 | 46 | 14.6% | 0.73 [0.31 , 1.16] |
| Xu 2021 | 71.68 | 8.12 | 51 | 64.59 | 7.28 | 51 | 14.7% | 0.91 [0.50 , 1.32] |
| Yang 2020a | 87.24 | 1.85 | 51 | 85.18 | 1.6 | 51 | 14.6% | 1.18 [0.76 , 1.60] |
| Zhao 2020 | 21.12 | 2.19 | 50 | 20.04 | 2.16 | 50 | 14.7% | 0.49 [0.09 , 0.89] |
| **Total (Wald[a])** | | | **321** | | | **315** | **100.0%** | **0.94 [0.31 , 1.56]** |

Test for overall effect: Z = 2.95 (P = 0.003)

Heterogeneity: Tau² (DL[b]) = 0.65; Chi² = 82.56, df = 6 (P < 0.00001); I² = 93%




**Footnotes**

[a]CI calculated by Wald-type method.

[b]Tau² calculated by DerSimonian and Laird method.

**Risk of bias legend**

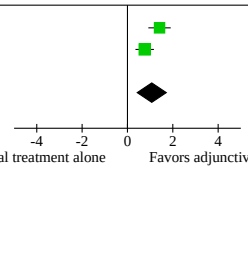
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

## Analysis 6.11. Comparison 6: Mild cognitive impairment: *Ginkgo biloba* added to conventional treatment, Outcome 11: ADL: 6 months

| Study or Subgroup | Adjunctive Ginkgo biloba Mean | SD | Total | Conventional treatment alone Mean | SD | Total | Weight | Std. Mean Difference IV, Random, 95% CI |
|---|---|---|---|---|---|---|---|---|
| Li 2016a | -20.84 | 0.61 | 40 | -21.93 | 0.89 | 40 | 47.7% | 1.41 [0.92 , 1.91] |
| Zhao 2020 | 22.06 | 2.14 | 50 | 20.41 | 2.17 | 50 | 52.3% | 0.76 [0.35 , 1.17] |
| **Total (Wald[a])** | | | **90** | | | **90** | **100.0%** | **1.07 [0.43 , 1.71]** |

Test for overall effect: Z = 3.28 (P = 0.001)

Heterogeneity: Tau² (DL[b]) = 0.16; Chi² = 4.04, df = 1 (P = 0.04); I² = 75%



**Footnotes**

[a]CI calculated by Wald-type method.

[b]Tau² calculated by DerSimonian and Laird method.

**Risk of bias legend**

(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias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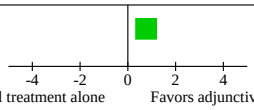
## Analysis 6.12. Comparison 6: Mild cognitive impairment: *Ginkgo biloba* added to conventional treatment, Outcome 12: ADL: 12 months

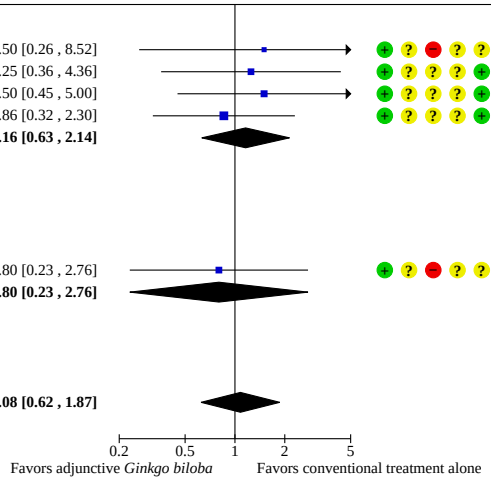
| Study or Subgroup | Adjunctive Ginkgo biloba Mean | SD | Total | Conventional treatment alone Mean | SD | Total | Std. Mean Difference IV, Random, 95% CI | Std. Mean Difference IV, Random, 95% CI | Risk of Bias A B C D E F G |
|---|---|---|---|---|---|---|---|---|---|
| Zhao 2020 | 22.31 | 2.15 | 50 | 20.68 | 2.1 | 50 | 0.76 [0.35 , 1.17] | | |




**Risk of bias legend**
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

## Analysis 6.13. Comparison 6: Mild cognitive impairment: *Ginkgo biloba* added to conventional treatment, Outcome 13: Adverse events: all

| Study or Subgroup | Adjunctive Ginkgo biloba Events | Total | Conventional treatment alone Events | Total | Weight | Risk Ratio IV, Random, 95% CI | Risk Ratio IV, Random, 95% CI | Risk of Bias A B C D E F G |
|---|---|---|---|---|---|---|---|---|
| **6.13.1 3 months** | | | | | | | | |
| He 2018a | 3 | 42 | 2 | 42 | 9.9% | 1.50 [0.26 , 8.52] | | |
| Wang 2020a | 5 | 46 | 4 | 46 | 19.2% | 1.25 [0.36 , 4.36] | | |
| Xu 2021 | 6 | 51 | 4 | 51 | 20.7% | 1.50 [0.45 , 5.00] | | |
| Zhang 2019a | 6 | 36 | 7 | 36 | 30.7% | 0.86 [0.32 , 2.30] | | |
| **Subtotal (Wald[a])** | | **175** | | **175** | **80.5%** | **1.16 [0.63 , 2.14]** | | |
| Total events: | 20 | | 17 | | | | | |
| Test for overall effect: Z = 0.48 (P = 0.63) | | | | | | | | |
| Heterogeneity: Tau² (DL[b]) = 0.00; Chi² = 0.63, df = 3 (P = 0.89); I² = 0% | | | | | | | | |
| **6.13.2 6 months** | | | | | | | | |
| Li 2016a | 4 | 40 | 5 | 40 | 19.5% | 0.80 [0.23 , 2.76] | | |
| **Subtotal** | | **40** | | **40** | **19.5%** | **0.80 [0.23 , 2.76]** | | |
| Total events: | 4 | | 5 | | | | | |
| Test for overall effect: Z = 0.35 (P = 0.72) | | | | | | | | |
| Heterogeneity: Not applicable | | | | | | | | |
| **Total (Wald[a])** | | **215** | | **215** | **100.0%** | **1.08 [0.62 , 1.87]** | | |
| Total events: | 24 | | 22 | | | | | |
| Test for overall effect: Z = 0.27 (P = 0.79) | | | | | | | | |
| Test for subgroup differences: Chi² = 0.28, df = 1 (P = 0.60), I² = 0% | | | | | | | | |
| Heterogeneity: Tau² (DL[b]) = 0.00; Chi² = 0.91, df = 4 (P = 0.92); I² = 0% | | | | | | | | |




**Footnotes**
[a]CI calculated by Wald-type method.
[b]Tau² calculated by DerSimonian and Laird method.

**Risk of bias legend**
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias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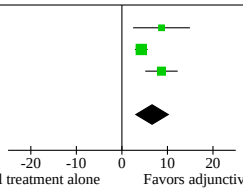
## Analysis 6.14. Comparison 6: Mild cognitive impairment: *Ginkgo biloba* added to conventional treatment, Outcome 14: Memory: 3 months

| Study or Subgroup | Adjunctive Ginkgo biloba Mean | SD | Total | Conventional treatment alone Mean | SD | Total | Weight | Mean Difference IV, Random, 95% CI |
|---|---|---|---|---|---|---|---|---|
| He 2016 | 77.1 | 16.2 | 50 | 68.4 | 15.6 | 50 | 19.8% | 8.70 [2.47 , 14.93] |
| Wang 2020a | 25.64 | 3.17 | 46 | 21.38 | 3.63 | 46 | 46.7% | 4.26 [2.87 , 5.65] |
| Xu 2021 | 76.91 | 9.67 | 51 | 68.22 | 8.65 | 51 | 33.5% | 8.69 [5.13 , 12.25] |
| **Total (Wald[a])** | | | **147** | | | **147** | **100.0%** | **6.62 [3.06 , 10.19]** |



Test for overall effect: Z = 3.64 (P = 0.0003)

Heterogeneity: Tau² (DL[b]) = 6.58; Chi² = 6.56, df = 2 (P = 0.04); I² = 70%

**Footnotes**

[a]CI calculated by Wald-type method.

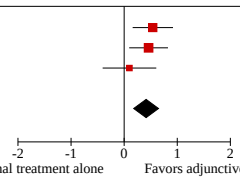
[b]Tau² calculated by DerSimonian and Laird method.

**Risk of bias legend**

(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

## Analysis 6.15. Comparison 6: Mild cognitive impairment: *Ginkgo biloba* added to conventional treatment, Outcome 15: Memory: 6 months

| Study or Subgroup | SMD | SE | Adjunctive Ginkgo biloba Total | Conventional treatment alone Total | Weight | Std. Mean Difference IV, Random, 95% CI |
|---|---|---|---|---|---|---|
| Dong 2011 | 0.54 | 0.1938 | 58 | 55 | 37.8% | 0.54 [0.16 , 0.92] |
| Han 2016 | 0.46 | 0.1862 | 60 | 60 | 40.9% | 0.46 [0.10 , 0.82] |
| Shi 2017 | 0.1 | 0.2577 | 30 | 30 | 21.4% | 0.10 [-0.41 , 0.61] |
| **Total (Wald[a])** | | | **148** | **145** | **100.0%** | **0.41 [0.18 , 0.65]** |



Test for overall effect: Z = 3.47 (P = 0.0005)

Heterogeneity: Tau² (DL[b]) = 0.00; Chi² = 1.97, df = 2 (P = 0.37); I² = 0%

**Footnotes**

[a]CI calculated by Wald-type method.

[b]Tau² calculated by DerSimonian and Laird method.

**Risk of bias legend**

(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias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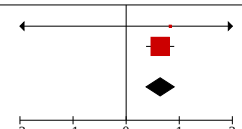
## Analysis 6.16. Comparison 6: Mild cognitive impairment: *Ginkgo biloba* added to conventional treatment, Outcome 16: Memory: 12 months

| Study or Subgroup | SMD | SE | Adjunctive Ginkgo biloba Total | Conventional treatment alone Total | Weight | Std. Mean Difference IV, Random, 95% CI | Std. Mean Difference IV, Random, 95% CI | Risk of Bias A B C D E F G |
|---|---|---|---|---|---|---|---|---|
| Dong 2011 | 0.83 | 30 | 58 | 55 | 0.0% | 0.83 [-57.97 , 59.63] | | + ? − ? ? ? + |
| Han 2016 | 0.64 | 0.1352 | 60 | 60 | 100.0% | 0.64 [0.38 , 0.90] | | + ? − ? ? ? + |
| **Total (Wald[a])** | | | **118** | **115** | **100.0%** | **0.64 [0.38 , 0.90]** | | |




Test for overall effect: Z = 4.73 (P < 0.00001)

Heterogeneity: Tau² (DL[b]) = 0.00; Chi² = 0.00, df = 1 (P = 0.99); I² = 0%

**Footnotes**

[a]CI calculated by Wald-type method.

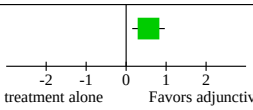
[b]Tau² calculated by DerSimonian and Laird method.

**Risk of bias legend**

(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

## Analysis 6.17. Comparison 6: Mild cognitive impairment: *Ginkgo biloba* added to conventional treatment, Outcome 17: Executive function: 3 months

| Study or Subgroup | Adjunctive Ginkgo biloba Mean | SD | Total | Conventional treatment alone Mean | SD | Total | Mean Difference IV, Random, 95% CI | Mean Difference IV, Random, 95% CI | Risk of Bias A B C D E F G |
|---|---|---|---|---|---|---|---|---|---|
| Li 2013a | 3.44 | 0.49 | 35 | 2.88 | 1.11 | 34 | 0.56 [0.15 , 0.97] | | + ? − ? ? ? + |




**Risk of bias legend**

(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias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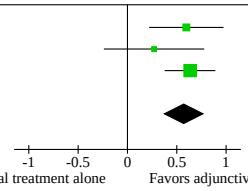
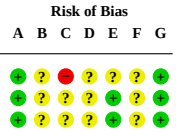
## Analysis 6.18. Comparison 6: Mild cognitive impairment: *Ginkgo biloba* added to conventional treatment, Outcome 18: Executive function: 6 months

| Study or Subgroup | Adjunctive Ginkgo biloba Mean | SD | Total | Conventional treatment alone Mean | SD | Total | Weight | Std. Mean Difference IV, Random, 95% CI |
|---|---|---|---|---|---|---|---|---|
| Dong 2011 | 3.45 | 0.38 | 58 | 3 | 1 | 55 | 27.0% | 0.60 [0.22 , 0.97] |
| Shi 2017 | 1.73 | 0.45 | 30 | 1.6 | 0.5 | 30 | 14.8% | 0.27 [-0.24 , 0.78] |
| Xia 2013 | 3.47 | 0.71 | 123 | 3.04 | 0.64 | 122 | 58.2% | 0.63 [0.38 , 0.89] |
| **Total (Wald[a])** | | | **211** | | | **207** | **100.0%** | **0.57 [0.37 , 0.77]** |




Test for overall effect: Z = 5.70 (P < 0.00001)

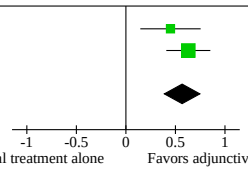
Heterogeneity: Tau² (DL[b]) = 0.00; Chi² = 1.60, df = 2 (P = 0.45); I² = 0%

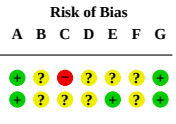
**Footnotes**
[a]CI calculated by Wald-type method.
[b]Tau² calculated by DerSimonian and Laird method.

**Risk of bias legend**
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

## Analysis 6.19. Comparison 6: Mild cognitive impairment: *Ginkgo biloba* added to conventional treatment, Outcome 19: Executive function: 12 months

| Study or Subgroup | Adjunctive Ginkgo biloba Mean | SD | Total | Conventional treatment alone Mean | SD | Total | Weight | Mean Difference IV, Random, 95% CI |
|---|---|---|---|---|---|---|---|---|
| Dong 2011 | 3.35 | 0.55 | 58 | 2.9 | 1.02 | 55 | 34.7% | 0.45 [0.15 , 0.75] |
| Xia 2013 | 3.54 | 0.83 | 123 | 2.91 | 0.94 | 122 | 65.3% | 0.63 [0.41 , 0.85] |
| **Total (Wald[a])** | | | **181** | | | **177** | **100.0%** | **0.57 [0.39 , 0.75]** |




Test for overall effect: Z = 6.20 (P < 0.00001)

Heterogeneity: Tau² (DL[b]) = 0.00; Chi² = 0.88, df = 1 (P = 0.35); I² = 0%

**Footnotes**
[a]CI calculated by Wald-type method.
[b]Tau² calculated by DerSimonian and Laird method.

**Risk of bias legend**
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

## Comparison 7. Dementia: *Ginkgo biloba* versus placebo

| Outcome or subgroup title | No. of studies | No. of participants | Statistical method | Effect size |
|---|---|---|---|---|
| 7.1 Global clinical status: 3 months | 1 | | Std. Mean Difference (IV, Random, 95% CI) | Subtotals only |
| 7.2 Global clinical status: 6 months | 5 | 1359 | Std. Mean Difference (IV, Random, 95% CI) | -0.55 [-0.89, -0.21] |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| Outcome or subgroup title | No. of studies | No. of participants | Statistical method | Effect size |
|---|---|---|---|---|
| 7.3 Global clinical status: 12 months | 1 | | Std. Mean Difference (IV, Random, 95% CI) | Subtotals only |
| 7.4 Global clinical status: 6 months: sensitivity analysis by inclusion criteria, intervention, and outcome measure | 2 | 806 | Mean Difference (IV, Random, 95% CI) | -0.70 [-0.85, -0.55] |
| 7.5 Global cognitive function: 3 months | 1 | | Mean Difference (IV, Random, 95% CI) | Subtotals only |
| 7.6 Global cognitive function: 6 months | 9 | 2801 | Std. Mean Difference (IV, Random, 95% CI) | -0.47 [-0.88, -0.06] |
| 7.7 Global cognitive function: 12 months | 1 | | Mean Difference (IV, Random, 95% CI) | Subtotals only |
| 7.8 Global cognitive function: 6 months - sensitivity analysis by inclusion criteria, intervention, and outcome measure | 4 | 1598 | Mean Difference (IV, Random, 95% CI) | -2.09 [-3.98, -0.19] |
| 7.9 ADL: 6 months | 8 | 2571 | Std. Mean Difference (IV, Random, 95% CI) | -0.32 [-0.59, -0.05] |
| 7.10 ADL: 12 months | 1 | | Mean Difference (IV, Random, 95% CI) | Subtotals only |
| 7.11 ADL: 6 months: sensitivity analysis by inclusion criteria, intervention, and outcome measure | 4 | | Mean Difference (IV, Random, 95% CI) | Subtotals only |
| 7.11.1 ADLs measured on GBS | 2 | 792 | Mean Difference (IV, Random, 95% CI) | -1.60 [-3.95, 0.76] |
| 7.11.2 ADLs measured on ADL--IS | 2 | 806 | Mean Difference (IV, Random, 95% CI) | -0.17 [-0.22, -0.12] |
| 7.12 Adverse events: all | 9 | 2746 | Risk Ratio (IV, Random, 95% CI) | 0.95 [0.90, 1.00] |
| 7.13 Adverse events: serious | 6 | | Risk Ratio (IV, Random, 95% CI) | Subtotals only |
| 7.13.1 6 months | 6 | 2463 | Risk Ratio (IV, Random, 95% CI) | 0.88 [0.58, 1.33] |
| 7.14 Memory: 3 months | 1 | | Mean Difference (IV, Random, 95% CI) | Subtotals only |
| 7.15 Executive function: 6 months | 4 | 1598 | Std. Mean Difference (IV, Random, 95% CI) | 0.64 [0.02, 1.26] |
| 7.16 Quality of life: 6 months | 4 | 1392 | Std. Mean Difference (IV, Random, 95% CI) | 0.11 [-0.06, 0.28] |


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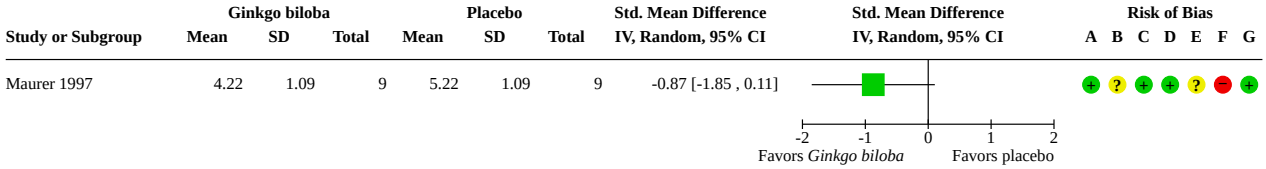
| Outcome or subgroup title | No. of studies | No. of participants | Statistical method | Effect size |
|---|---|---|---|---|
| 7.17 Quality of life: 6 months: sensitivity analysis by inclusion criteria, intervention, and outcome measure | 2 | 806 | Mean Difference (IV, Random, 95% CI) | 2.00 [0.84, 3.16] |
| 7.18 Neuropsychological outcomes: depression - 6 months - change | 2 | 792 | Mean Difference (IV, Random, 95% CI) | -2.31 [-6.03, 1.42] |
| 7.19 Neuropsychological outcomes: depression - 6 months - endpoint | 1 | | Mean Difference (IV, Random, 95% CI) | Subtotals only |
| 7.20 Neuropsychological outcomes: NPI - 6 months | 5 | 1686 | Mean Difference (IV, Random, 95% CI) | -3.95 [-7.34, -0.57] |
| 7.21 Sensitivity analysis by inclusion criteria and intervention: NPI at 6 months | 4 | 1598 | Mean Difference (IV, Random, 95% CI) | -3.85 [-7.60, -0.09] |

### Analysis 7.1. Comparison 7: Dementia: *Ginkgo biloba* versus placebo, Outcome 1: Global clinical status: 3 months




**Risk of bias legend**
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias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## Analysis 7.2. Comparison 7: Dementia: *Ginkgo biloba* versus placebo, Outcome 2: Global clinical status: 6 months

| Study or Subgroup | Ginkgo biloba Mean | Ginkgo biloba SD | Ginkgo biloba Total | Placebo Mean | Placebo SD | Placebo Total | Weight | Std. Mean Difference IV, Random, 95% CI | Std. Mean Difference IV, Random, 95% CI | Risk of Bias A B C D E F G |
|---|---|---|---|---|---|---|---|---|---|---|
| GOT IT 2012 | 3.1 | 1.0823062977345115 | 200 | 3.8 | 1.4502724901583566 | 202 | 22.6% | -0.55 [-0.74 , -0.35] | | + + + + + ? + |
| GOTADAY 2011 | 3.4 | 0.7251362450791783 | 202 | 4.1 | 1.0877043676187674 | 202 | 22.6% | -0.76 [-0.96 , -0.55] | | + + + + + ? + |
| Kanowski 1996 | 4.1 | 1.038486 | 106 | 4.5 | 1.002775 | 99 | 21.1% | -0.39 [-0.67 , -0.11] | | + + + + + ? + |
| Le Bars 1997 | 4.2 | 0.6351989590810578 | 155 | 4.2 | 0.6331466145913702 | 154 | 22.2% | 0.00 [-0.22 , 0.22] | | + + + + − ? + |
| Mazza 2006 | 3.75 | 0.96 | 20 | 5.2 | 0.95 | 19 | 11.6% | -1.49 [-2.21 , -0.77] | | + ? + + − ? + |
| **Total (Wald[a])** | | | **683** | | | **676** | **100.0%** | **-0.55 [-0.89 , -0.21]** | | |

Test for overall effect: Z = 3.19 (P = 0.001)

Heterogeneity: Tau² (DL[b]) = 0.12; Chi² = 33.34, df = 4 (P < 0.00001); I² = 88%

-2 -1 0 1 2
Favors *Ginkgo biloba* Favors placebo

**Footnotes**
[a]CI calculated by Wald-type method.
[b]Tau² calculated by DerSimonian and Laird method.

**Risk of bias legend**
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

## Analysis 7.3. Comparison 7: Dementia: *Ginkgo biloba* versus placebo, Outcome 3: Global clinical status: 12 months

| Study or Subgroup | Ginkgo biloba Mean | Ginkgo biloba SD | Ginkgo biloba Total | Placebo Mean | Placebo SD | Placebo Total | Std. Mean Difference IV, Random, 95% CI | Std. Mean Difference IV, Random, 95% CI | Risk of Bias A B C D E F G |
|---|---|---|---|---|---|---|---|---|---|
| Le Bars 1997 | 4.2 | 0.9527984386215868 | 155 | 4.2 | 0.6331466145913702 | 154 | 0.00 [-0.22 , 0.22] | | + + + + − ? + |

-2 -1 0 1 2
Favors *Ginkgo biloba* Favors placebo

**Risk of bias legend**
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

## Analysis 7.4. Comparison 7: Dementia: *Ginkgo biloba* versus placebo, Outcome 4: Global clinical status: 6 months: sensitivity analysis by inclusion criteria, intervention, and outcome measure

| Study or Subgroup | Ginkgo biloba Mean | Ginkgo biloba SD | Ginkgo biloba Total | Placebo Mean | Placebo SD | Placebo Total | Weight | Mean Difference IV, Random, 95% CI | Mean Difference IV, Random, 95% CI |
|---|---|---|---|---|---|---|---|---|---|
| GOT IT 2012 | 3.1 | 1.0823062977345115 | 200 | 3.8 | 1.4502724901583566 | 202 | 34.2% | -0.70 [-0.95 , -0.45] | |
| GOTADAY 2011 | 3.4 | 0.7251362450791783 | 202 | 4.1 | 1.0877043676187674 | 202 | 65.8% | -0.70 [-0.88 , -0.52] | |
| **Total (Wald[a])** | | | **402** | | | **404** | **100.0%** | **-0.70 [-0.85 , -0.55]** | |

Test for overall effect: Z = 9.38 (P < 0.00001)

Heterogeneity: Tau² (DL[b]) = 0.00; Chi² = 0.00, df = 1 (P = 1.00); I² = 0%

-2 -1 0 1 2
Favors *Ginkgo biloba* Favors placebo

**Footnotes**
[a]CI calculated by Wald-type method.
[b]Tau² calculated by DerSimonian and Laird method.


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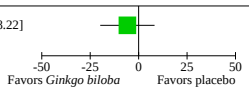
## Analysis 7.5. Comparison 7: Dementia: *Ginkgo biloba* versus placebo, Outcome 5: Global cognitive function: 3 months

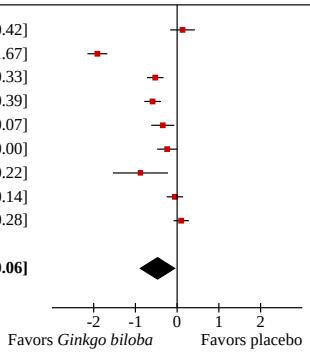
| Study or Subgroup | Ginkgo biloba Mean [ADAS-Cog] | Ginkgo biloba SD [ADAS-Cog] | Ginkgo biloba Total | Placebo Mean [ADAS-Cog] | Placebo SD [ADAS-Cog] | Placebo Total | Mean Difference IV, Random, 95% CI [ADAS-Cog] | Risk of Bias A B C D E F G |
|---|---|---|---|---|---|---|---|---|
| Maurer 1997 | 30.33 | 14.77 | 9 | 36.13 | 15.56 | 9 | -5.80 [-19.82 , 8.22] | + ? + + ? − + |




**Risk of bias legend**
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

## Analysis 7.6. Comparison 7: Dementia: *Ginkgo biloba* versus placebo, Outcome 6: Global cognitive function: 6 months

| Study or Subgroup | SMD | SE | Ginkgo biloba Total | Placebo Total | Weight | Std. Mean Difference IV, Random, 95% CI | Risk of Bias A B C D E F G |
|---|---|---|---|---|---|---|---|
| DIGGER 2008 | 0.1289 | 0.1509 | 88 | 88 | 11.1% | 0.13 [-0.17 , 0.42] | + + + + ? ? + |
| GINDEM-NP 2005 | -1.910908 | 0.121637 | 198 | 197 | 11.3% | -1.91 [-2.15 , -1.67] | + + + + + ? + |
| GOT IT 2012 | -0.524393 | 0.101469 | 200 | 202 | 11.5% | -0.52 [-0.72 , -0.33] | + + + + + ? + |
| GOTADAY 2011 | -0.588535 | 0.101656 | 202 | 202 | 11.5% | -0.59 [-0.79 , -0.39] | + + + + + ? + |
| Kanowski 1996 | -0.34403 | 0.140817 | 106 | 99 | 11.2% | -0.34 [-0.62 , -0.07] | + + + + + ? + |
| Le Bars 1997 | -0.238567 | 0.122158 | 136 | 134 | 11.3% | -0.24 [-0.48 , 0.00] | + + + + − ? + |
| Mazza 2006 | -0.8804 | 0.3372 | 20 | 19 | 9.0% | -0.88 [-1.54 , -0.22] | + ? + + − ? + |
| PLAGIN 2013 | -0.052424 | 0.100402 | 196 | 201 | 11.5% | -0.05 [-0.25 , 0.14] | + + + + ? ? + |
| Schneider 2005 | 0.097493 | 0.093308 | 339 | 174 | 11.5% | 0.10 [-0.09 , 0.28] | + + + + ? ? + |
| **Total (Wald[a])** | | | **1485** | **1316** | **100.0%** | **-0.47 [-0.88 , -0.06]** | |




Test for overall effect: Z = 2.25 (P = 0.02)

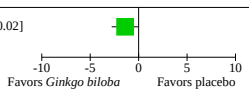
Heterogeneity: Tau² (DL[b]) = 0.37; Chi² = 215.76, df = 8 (P < 0.00001); I² = 96%

**Footnotes**
[a]CI calculated by Wald-type method.
[b]Tau² calculated by DerSimonian and Laird method.

**Risk of bias legend**
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

## Analysis 7.7. Comparison 7: Dementia: *Ginkgo biloba* versus placebo, Outcome 7: Global cognitive function: 12 months

| Study or Subgroup | Ginkgo biloba Mean [ADAS-Cog] | Ginkgo biloba SD [ADAS-Cog] | Ginkgo biloba Total | Placebo Mean [ADAS-Cog] | Placebo SD [ADAS-Cog] | Placebo Total | Mean Difference IV, Random, 95% CI [ADAS-Cog] | Risk of Bias A B C D E F G |
|---|---|---|---|---|---|---|---|---|
| Le Bars 1997 | 0.1 | 5.35 | 136 | 1.5 | 6.29 | 138 | -1.40 [-2.78 , -0.02] | + + + + − ? + |




**Risk of bias legend**
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias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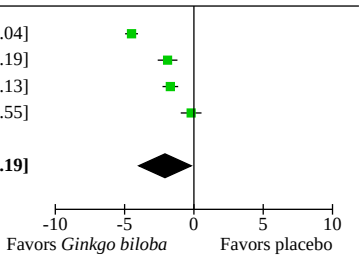
## Analysis 7.8. Comparison 7: Dementia: *Ginkgo biloba* versus placebo, Outcome 8: Global cognitive function: 6 months - sensitivity analysis by inclusion criteria, intervention, and outcome measure

| Study or Subgroup | Ginkgo biloba Mean | SD | Total | Placebo Mean | SD | Total | Weight | Mean Difference IV, Random, 95% CI |
|---|---|---|---|---|---|---|---|---|
| GINDEM-NP 2005 | -3.2 | 2.3 | 198 | 1.3 | 2.4 | 197 | 25.3% | -4.50 [-4.96 , -4.04] |
| GOT IT 2012 | -2.2 | 3.25 | 200 | -0.3 | 3.99 | 202 | 24.8% | -1.90 [-2.61 , -1.19] |
| GOTADAY 2011 | -1.4 | 2.9 | 202 | 0.3 | 2.9 | 202 | 25.1% | -1.70 [-2.27 , -1.13] |
| PLAGIN 2013 | -2.2 | 3.6 | 196 | -2 | 4 | 201 | 24.7% | -0.20 [-0.95 , 0.55] |
| **Total (Wald[a])** | | | **796** | | | **802** | **100.0%** | **-2.09 [-3.98 , -0.19]** |




Test for overall effect: Z = 2.16 (P = 0.03)

Heterogeneity: Tau² (DL[b]) = 3.63; Chi² = 117.45, df = 3 (P < 0.00001); I² = 97%

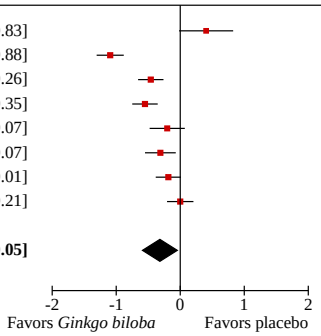
**Footnotes**

[a]CI calculated by Wald-type method.

[b]Tau² calculated by DerSimonian and Laird method.

## Analysis 7.9. Comparison 7: Dementia: *Ginkgo biloba* versus placebo, Outcome 9: ADL: 6 months

| Study or Subgroup | SMD | SE | Ginkgo biloba Total | Placebo Total | Weight | Std. Mean Difference IV, Random, 95% CI | Risk of Bias A | B | C | D | E | F | G |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| DIGGER 2008 | 0.4043 | 0.2155 | 44 | 44 | 10.4% | 0.40 [-0.02 , 0.83] | + | + | + | + | ? | ? | + |
| GINDEM-NP 2005 | -1.0939 | 0.108 | 198 | 197 | 12.9% | -1.09 [-1.31 , -0.88] | + | + | + | + | + | ? | + |
| GOT IT 2012 | -0.46 | 0.1011 | 200 | 202 | 13.0% | -0.46 [-0.66 , -0.26] | + | + | + | + | + | ? | + |
| GOTADAY 2011 | -0.5508 | 0.1014 | 202 | 202 | 13.0% | -0.55 [-0.75 , -0.35] | + | + | + | + | + | ? | + |
| Kanowski 1996 | -0.2034 | 0.1401 | 106 | 99 | 12.2% | -0.20 [-0.48 , 0.07] | + | + | + | + | + | ? | + |
| Le Bars 1997 | -0.3101 | 0.1225 | 138 | 132 | 12.6% | -0.31 [-0.55 , -0.07] | + | + | + | + | − | ? | + |
| PLAGIN 2013 | -0.1856 | 0.1006 | 196 | 201 | 13.0% | -0.19 [-0.38 , 0.01] | + | + | + | + | ? | ? | + |
| Schneider 2005 | 0 | 0.1051 | 275 | 135 | 12.9% | 0.00 [-0.21 , 0.21] | + | + | + | + | ? | ? | + |
| **Total (Wald[a])** | | | **1359** | **1212** | **100.0%** | **-0.32 [-0.59 , -0.05]** | | | | | | | |




Test for overall effect: Z = 2.29 (P = 0.02)

Heterogeneity: Tau² (DL[b]) = 0.14; Chi² = 79.12, df = 7 (P < 0.00001); I² = 91%

**Footnotes**

[a]CI calculated by Wald-type method.

[b]Tau² calculated by DerSimonian and Laird method.

**Risk of bias legend**

(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias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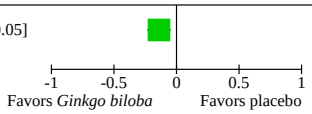
## Analysis 7.10. Comparison 7: Dementia: *Ginkgo biloba* versus placebo, Outcome 10: ADL: 12 months

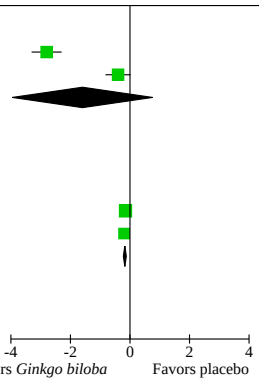
| Study or Subgroup | Ginkgo biloba Mean | SD | Total | Placebo Mean | SD | Total | Mean Difference IV, Random, 95% CI | Risk of Bias A B C D E F G |
|---|---|---|---|---|---|---|---|---|
| Le Bars 1997 | -0.06 | 0.41585 | 138 | 0.08 | 0.377504 | 132 | -0.14 [-0.23 , -0.05] | + + + + − ? + |




**Risk of bias legend**
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

## Analysis 7.11. Comparison 7: Dementia: *Ginkgo biloba* versus placebo, Outcome 11: ADL: 6 months: sensitivity analysis by inclusion criteria, intervention, and outcome measure

| Study or Subgroup | Ginkgo biloba Mean | SD | Total | Placebo Mean | SD | Total | Weight | Mean Difference IV, Random, 95% CI | Risk of Bias A B C D E F G |
|---|---|---|---|---|---|---|---|---|---|
| **7.11.1 ADLs measured on GBS** | | | | | | | | | |
| GINDEM-NP 2005 | -1.9 | 2.7 | 198 | 0.9 | 2.4 | 197 | 49.8% | -2.80 [-3.30 , -2.30] | + + + + + ? + |
| PLAGIN 2013 | -0.1 | 2.1 | 196 | 0.3 | 2.2 | 201 | 50.2% | -0.40 [-0.82 , 0.02] | + + + + ? ? + |
| **Subtotal (Wald[a])** | | | **394** | | | **398** | **100.0%** | **-1.60 [-3.95 , 0.76]** | |
| Test for overall effect: Z = 1.33 (P = 0.18) | | | | | | | | | |
| Heterogeneity: Tau² (DL[b]) = 2.82; Chi² = 51.14, df = 1 (P < 0.00001); I² = 98% | | | | | | | | | |
| **7.11.2 ADLs measured on ADL--IS** | | | | | | | | | |
| GOT IT 2012 | -0.11 | 0.36079 | 200 | 0.04 | 0.29005 | 202 | 54.7% | -0.15 [-0.21 , -0.09] | + + + + + ? + |
| GOTADAY 2011 | -0.2 | 0.36256 | 202 | 0 | 0.36257 | 202 | 45.3% | -0.20 [-0.27 , -0.13] | + + + + + ? + |
| **Subtotal (Wald[a])** | | | **402** | | | **404** | **100.0%** | **-0.17 [-0.22 , -0.12]** | |
| Test for overall effect: Z = 6.94 (P < 0.00001) | | | | | | | | | |
| Heterogeneity: Tau² (DL[b]) = 0.00; Chi² = 1.06, df = 1 (P = 0.30); I² = 5% | | | | | | | | | |




**Footnotes**
[a]CI calculated by Wald-type method.
[b]Tau² calculated by DerSimonian and Laird method.

**Risk of bias legend**
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias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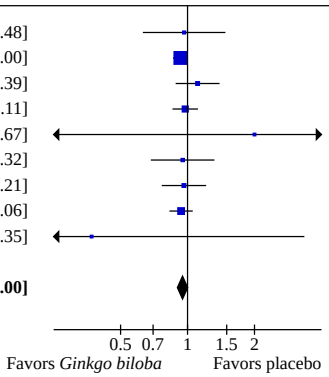
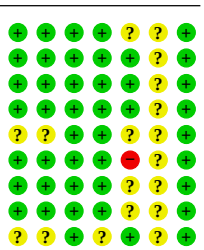
## Analysis 7.12. Comparison 7: Dementia: *Ginkgo biloba* versus placebo, Outcome 12: Adverse events: all

| Study or Subgroup | Ginkgo biloba Events | Ginkgo biloba Total | Placebo Events | Placebo Total | Weight | Risk Ratio IV, Random, 95% CI |
|---|---|---|---|---|---|---|
| DIGGER 2008 | 28 | 88 | 29 | 88 | 1.6% | 0.97 [0.63 , 1.48] |
| GINDEM-NP 2005 | 166 | 198 | 178 | 197 | 48.9% | 0.93 [0.86 , 1.00] |
| GOT IT 2012 | 91 | 205 | 82 | 205 | 5.5% | 1.11 [0.88 , 1.39] |
| GOTADAY 2011 | 139 | 206 | 141 | 204 | 16.4% | 0.98 [0.86 , 1.11] |
| Halama 1991a | 2 | 25 | 1 | 25 | 0.1% | 2.00 [0.19 , 20.67] |
| Le Bars 1997 | 49 | 166 | 50 | 161 | 2.6% | 0.95 [0.68 , 1.32] |
| PLAGIN 2013 | 83 | 203 | 87 | 205 | 5.4% | 0.96 [0.77 , 1.21] |
| Schneider 2005 | 226 | 339 | 124 | 174 | 19.5% | 0.94 [0.83 , 1.06] |
| Wesnes 1987 | 1 | 27 | 3 | 30 | 0.1% | 0.37 [0.04 , 3.35] |
| **Total (Wald[a])** | | **1457** | | **1289** | **100.0%** | **0.95 [0.90 , 1.00]** |
| Total events: | 785 | | 695 | | | |

Test for overall effect: Z = 1.91 (P = 0.06)




Heterogeneity: Tau² (DL[b]) = 0.00; Chi² = 3.50, df = 8 (P = 0.90); I² = 0%

**Footnotes**

[a]CI calculated by Wald-type method.

[b]Tau² calculated by DerSimonian and Laird method.

**Risk of bias legend**

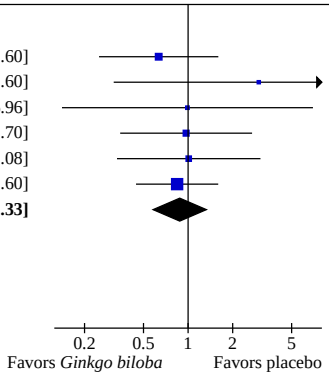
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

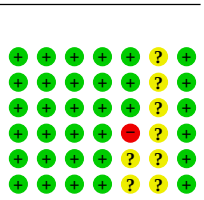
## Analysis 7.13. Comparison 7: Dementia: *Ginkgo biloba* versus placebo, Outcome 13: Adverse events: serious

| Study or Subgroup | Ginkgo biloba Events | Ginkgo biloba Total | Placebo Events | Placebo Total | Weight | Risk Ratio IV, Random, 95% CI |
|---|---|---|---|---|---|---|
| **7.13.1 6 months** | | | | | | |
| GINDEM-NP 2005 | 7 | 198 | 11 | 197 | 20.0% | 0.63 [0.25 , 1.60] |
| GOT IT 2012 | 3 | 205 | 1 | 205 | 3.4% | 3.00 [0.31 , 28.60] |
| GOTADAY 2011 | 2 | 206 | 2 | 204 | 4.5% | 0.99 [0.14 , 6.96] |
| Le Bars 1997 | 7 | 166 | 7 | 161 | 16.3% | 0.97 [0.35 , 2.70] |
| PLAGIN 2013 | 6 | 203 | 6 | 205 | 13.8% | 1.01 [0.33 , 3.08] |
| Schneider 2005 | 23 | 339 | 14 | 174 | 42.0% | 0.84 [0.45 , 1.60] |
| **Subtotal (Wald[a])** | | **1317** | | **1146** | **100.0%** | **0.88 [0.58 , 1.33]** |
| Total events: | 48 | | 41 | | | |

Test for overall effect: Z = 0.61 (P = 0.54)

Heterogeneity: Tau² (DL[b]) = 0.00; Chi² = 1.75, df = 5 (P = 0.88); I² = 0%




**Footnotes**

[a]CI calculated by Wald-type method.

[b]Tau² calculated by DerSimonian and Laird method.

**Risk of bias legend**

(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias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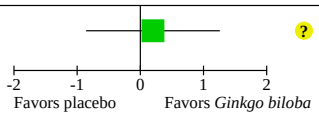
## Analysis 7.14. Comparison 7: Dementia: *Ginkgo biloba* versus placebo, Outcome 14: Memory: 3 months

| Study or Subgroup | Ginkgo biloba Mean | SD | Total | Placebo Mean | SD | Total | Mean Difference IV, Random, 95% CI | Mean Difference IV, Random, 95% CI | Risk of Bias A B C D E F G |
|---|---|---|---|---|---|---|---|---|---|
| Wesnes 1987 | 6.6 | 1.9 | 25 | 6.4 | 1.8 | 22 | 0.20 [-0.86 , 1.26] | | ? ? + ? + ? + |

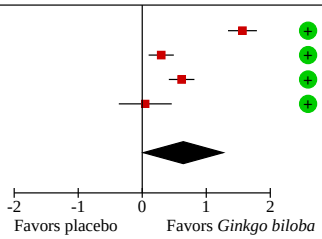



**Risk of bias legend**
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

## Analysis 7.15. Comparison 7: Dementia: *Ginkgo biloba* versus placebo, Outcome 15: Executive function: 6 months

| Study or Subgroup | SMD | SE | Ginkgo biloba Total | Placebo Total | Weight | Std. Mean Difference IV, Random, 95% CI | Std. Mean Difference IV, Random, 95% CI | Risk of Bias A B C D E F G |
|---|---|---|---|---|---|---|---|---|
| GINDEM-NP 2005 | 1.5652 | 0.1151 | 198 | 197 | 25.4% | 1.57 [1.34 , 1.79] | | + + + + + ? + |
| GOT IT 2012 | 0.2965 | 0.1003 | 200 | 202 | 25.6% | 0.30 [0.10 , 0.49] | | + + + + + ? + |
| GOTADAY 2011 | 0.6152 | 0.1019 | 202 | 202 | 25.5% | 0.62 [0.42 , 0.81] | | + + + + + ? + |
| PLAGIN 2013 | 0.0475 | 0.2109 | 196 | 201 | 23.5% | 0.05 [-0.37 , 0.46] | | + + + + ? ? + |
| **Total (Wald[a])** | | | **796** | **802** | **100.0%** | **0.64 [0.02 , 1.26]** | | |

Test for overall effect: Z = 2.02 (P = 0.04)




Heterogeneity: Tau² (DL[b]) = 0.39; Chi² = 82.93, df = 3 (P < 0.00001); I² = 96%

**Footnotes**
[a]CI calculated by Wald-type method.
[b]Tau² calculated by DerSimonian and Laird method.

**Risk of bias legend**
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias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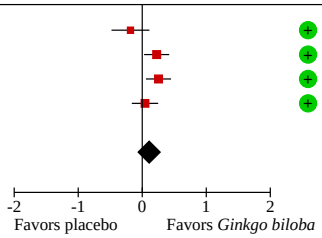
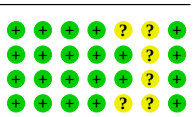
## Analysis 7.16. Comparison 7: Dementia: *Ginkgo biloba* versus placebo, Outcome 16: Quality of life: 6 months

| Study or Subgroup | SMD | SE | Ginkgo biloba Total | Placebo Total | Weight | Std. Mean Difference IV, Random, 95% CI |
|---|---|---|---|---|---|---|
| DIGGER 2008 | -0.1838 | 0.1511 | 88 | 88 | 18.8% | -0.18 [-0.48 , 0.11] |
| GOT IT 2012 | 0.2253 | 0.1001 | 200 | 202 | 27.4% | 0.23 [0.03 , 0.42] |
| GOTADAY 2011 | 0.2544 | 0.0999 | 202 | 202 | 27.4% | 0.25 [0.06 , 0.45] |
| Schneider 2005 | 0.0432 | 0.1051 | 275 | 135 | 26.4% | 0.04 [-0.16 , 0.25] |
| **Total (Wald[a])** | | | **765** | **627** | **100.0%** | **0.11 [-0.06 , 0.28]** |




Test for overall effect: Z = 1.23 (P = 0.22)

Heterogeneity: Tau² (DL[b]) = 0.02; Chi² = 7.45, df = 3 (P = 0.06); I² = 60%

**Footnotes**

[a]CI calculated by Wald-type method.

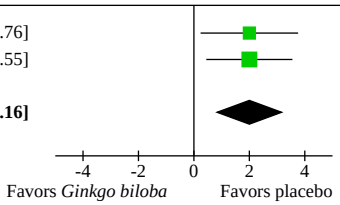
[b]Tau² calculated by DerSimonian and Laird method.

**Risk of bias legend**

(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

## Analysis 7.17. Comparison 7: Dementia: *Ginkgo biloba* versus placebo, Outcome 17: Quality of life: 6 months: sensitivity analysis by inclusion criteria, intervention, and outcome measure

| Study or Subgroup | Ginkgo biloba Mean | SD | Total | Placebo Mean | SD | Total | Weight | Mean Difference IV, Random, 95% CI |
|---|---|---|---|---|---|---|---|---|
| GOT IT 2012 | 3.5 | 9.3231 | 200 | 1.5 | 8.6494 | 202 | 43.8% | 2.00 [0.24 , 3.76] |
| GOTADAY 2011 | 3.4 | 8.6494 | 202 | 1.4 | 7.2078 | 202 | 56.2% | 2.00 [0.45 , 3.55] |
| **Total (Wald[a])** | | | **402** | | | **404** | **100.0%** | **2.00 [0.84 , 3.16]** |




Test for overall effect: Z = 3.37 (P = 0.0008)

Heterogeneity: Tau² (DL[b]) = 0.00; Chi² = 0.00, df = 1 (P = 1.00); I² = 0%

**Footnotes**

[a]CI calculated by Wald-type method.

[b]Tau² calculated by DerSimonian and Laird method.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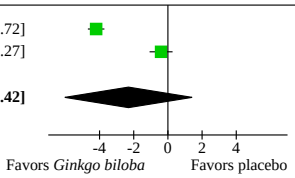
## Analysis 7.18. Comparison 7: Dementia: *Ginkgo biloba* versus placebo, Outcome 18: Neuropsychological outcomes: depression - 6 months - change

| Study or Subgroup | Ginkgo biloba Mean | SD | Total | Placebo Mean | SD | Total | Weight | Mean Difference IV, Random, 95% CI |
|---|---|---|---|---|---|---|---|---|
| GINDEM-NP 2005 | -3.3 | 2.4 | 198 | 0.9 | 2.5 | 197 | 50.2% | -4.20 [-4.68 , -3.72] |
| PLAGIN 2013 | -2.1 | 3.7 | 196 | -1.7 | 3.1 | 201 | 49.8% | -0.40 [-1.07 , 0.27] |
| **Total (Wald[a])** | | | **394** | | | **398** | **100.0%** | **-2.31 [-6.03 , 1.42]** |




Risk of Bias: A B C D E F G

GINDEM-NP 2005: + + + + + ? +
PLAGIN 2013: + + + + ? ? +

Test for overall effect: Z = 1.21 (P = 0.22)

Heterogeneity: Tau² (DL[b]) = 7.13; Chi² = 80.91, df = 1 (P < 0.00001); I² = 99%

**Footnotes**

[a]CI calculated by Wald-type method.

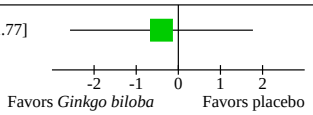
[b]Tau² calculated by DerSimonian and Laird method.

**Risk of bias legend**

(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

## Analysis 7.19. Comparison 7: Dementia: *Ginkgo biloba* versus placebo, Outcome 19: Neuropsychological outcomes: depression - 6 months - endpoint

| Study or Subgroup | Ginkgo biloba Mean | SD | Total | Placebo Mean | SD | Total | Mean Difference IV, Random, 95% CI |
|---|---|---|---|---|---|---|---|
| Kanowski 1996 | 13.2 | 6.5 | 79 | 13.6 | 7.3 | 77 | -0.40 [-2.57 , 1.77] |




Risk of Bias: A B C D E F G

Kanowski 1996: + + + + + ? +

**Risk of bias legend**

(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias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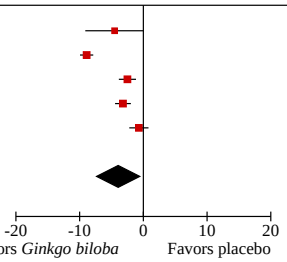
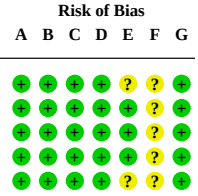
## Analysis 7.20. Comparison 7: Dementia: *Ginkgo biloba* versus placebo, Outcome 20: Neuropsychological outcomes: NPI - 6 months

| Study or Subgroup | MD | SE | Ginkgo biloba Total | Placebo Total | Weight | Mean Difference IV, Random, 95% CI |
|---|---|---|---|---|---|---|
| DIGGER 2008 | -4.512 | 2.346154 | 44 | 44 | 15.5% | -4.51 [-9.11 , 0.09] |
| GINDEM-NP 2005 | -8.9 | 0.528976 | 198 | 197 | 21.3% | -8.90 [-9.94 , -7.86] |
| GOT IT 2012 | -2.5 | 0.686409 | 200 | 202 | 21.1% | -2.50 [-3.85 , -1.15] |
| GOTADAY 2011 | -3.2 | 0.631603 | 202 | 202 | 21.2% | -3.20 [-4.44 , -1.96] |
| PLAGIN 2013 | -0.7 | 0.768307 | 196 | 201 | 20.9% | -0.70 [-2.21 , 0.81] |
| **Total (Wald[a])** | | | **840** | **846** | **100.0%** | **-3.95 [-7.34 , -0.57]** |




Test for overall effect: Z = 2.29 (P = 0.02)

Heterogeneity: Tau² (DL[b]) = 13.69; Chi² = 106.06, df = 4 (P < 0.00001); I² = 96%

**Footnotes**

[a]CI calculated by Wald-type method.

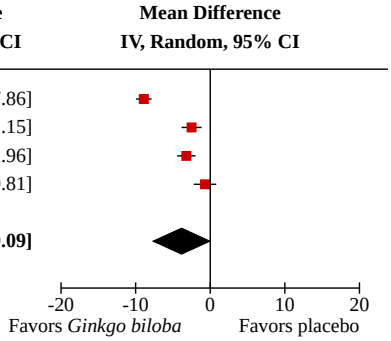
[b]Tau² calculated by DerSimonian and Laird method.

**Risk of bias legend**

(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

## Analysis 7.21. Comparison 7: Dementia: *Ginkgo biloba* versus placebo, Outcome 21: Sensitivity analysis by inclusion criteria and intervention: NPI at 6 months

| Study or Subgroup | MD | SE | Ginkgo biloba Total | Placebo Total | Weight | Mean Difference IV, Random, 95% CI |
|---|---|---|---|---|---|---|
| GINDEM-NP 2005 | -8.9 | 0.528976 | 198 | 197 | 25.3% | -8.90 [-9.94 , -7.86] |
| GOT IT 2012 | -2.5 | 0.686409 | 200 | 202 | 24.9% | -2.50 [-3.85 , -1.15] |
| GOTADAY 2011 | -3.2 | 0.631603 | 202 | 202 | 25.1% | -3.20 [-4.44 , -1.96] |
| PLAGIN 2013 | -0.7 | 0.768307 | 196 | 201 | 24.7% | -0.70 [-2.21 , 0.81] |
| **Total (Wald[a])** | | | **796** | **802** | **100.0%** | **-3.85 [-7.60 , -0.09]** |




Test for overall effect: Z = 2.01 (P = 0.04)

Heterogeneity: Tau² (DL[b]) = 14.26; Chi² = 106.06, df = 3 (P < 0.00001); I² = 97%

**Footnotes**

[a]CI calculated by Wald-type method.

[b]Tau² calculated by DerSimonian and Laird method.

## Comparison 8. Dementia: *Ginkgo biloba* versus conventional medication

| Outcome or subgroup title | No. of studies | No. of participants | Statistical method | Effect size |
|---|---|---|---|---|
| 8.1 Global clinical status: 6 months | 1 | | Mean Difference (IV, Random, 95% CI) | Subtotals only |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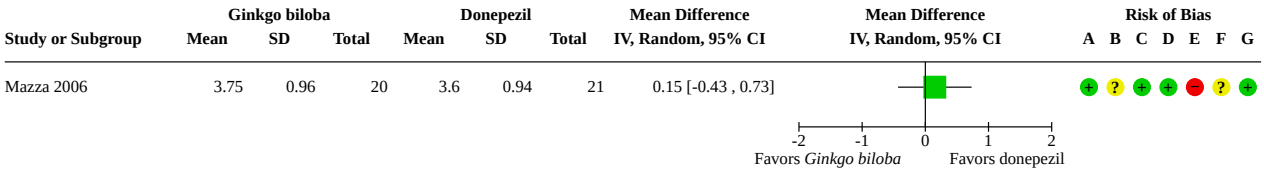
| Outcome or subgroup title | No. of studies | No. of participants | Statistical method | Effect size |
|---|---|---|---|---|
| 8.2 Global cognitive function: 6 months | 2 | 103 | Mean Difference (IV, Random, 95% CI) | 1.03 [-0.29, 2.36] |
| 8.3 ADL: 6 months | 1 | | Mean Difference (IV, Random, 95% CI) | Subtotals only |
| 8.4 Adverse events: all | 2 | 112 | Risk Ratio (IV, Random, 95% CI) | 0.42 [0.25, 0.72] |
| 8.5 Adverse events: serious | 1 | | Risk Ratio (IV, Fixed, 95% CI) | Subtotals only |
| 8.6 Executive function: 6 months | 1 | | Std. Mean Difference (IV, Random, 95% CI) | Subtotals only |
| 8.7 Neuropsychiatric outcomes: depression - 6 months | 1 | | Mean Difference (IV, Random, 95% CI) | Subtotals only |
| 8.8 Neuropsychiatric outcomes: NPI - 6 months | 1 | | Mean Difference (IV, Random, 95% CI) | Subtotals only |

**Analysis 8.1. Comparison 8: Dementia: *Ginkgo biloba* versus conventional medication, Outcome 1: Global clinical status: 6 months**




**Risk of bias legend**
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias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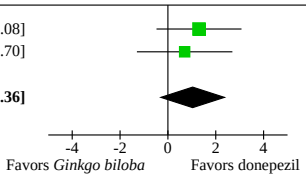
## Analysis 8.2. Comparison 8: Dementia: *Ginkgo biloba* versus conventional medication, Outcome 2: Global cognitive function: 6 months

| Study or Subgroup | Ginkgo biloba Mean | SD | Total | Donepezil Mean | SD | Total | Weight | Mean Difference IV, Random, 95% CI |
|---|---|---|---|---|---|---|---|---|
| Mazza 2006 | 13.15 | 2.9 | 20 | 11.85 | 2.9 | 21 | 55.8% | 1.30 [-0.48 , 3.08] |
| Yancheva 2009 | -1.8 | 4.5 | 30 | -2.5 | 3.4 | 32 | 44.2% | 0.70 [-1.30 , 2.70] |
| **Total (Wald[a])** | | | **50** | | | **53** | **100.0%** | **1.03 [-0.29 , 2.36]** |



Test for overall effect: Z = 1.53 (P = 0.13)

Heterogeneity: Tau² (DL[b]) = 0.00; Chi² = 0.19, df = 1 (P = 0.66); I² = 0%

**Footnotes**

[a]CI calculated by Wald-type method.

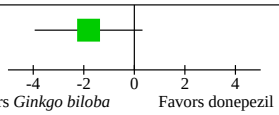
[b]Tau² calculated by DerSimonian and Laird method.

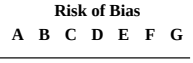
**Risk of bias legend**

(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

## Analysis 8.3. Comparison 8: Dementia: *Ginkgo biloba* versus conventional medication, Outcome 3: ADL: 6 months

| Study or Subgroup | Ginkgo biloba Mean | SD | Total | Donepezil Mean | SD | Total | Mean Difference IV, Random, 95% CI |
|---|---|---|---|---|---|---|---|
| Yancheva 2009 | 2 | 2.6 | 30 | 3.81 | 5.54 | 32 | -1.81 [-3.94 , 0.32] |




**Risk of bias legend**

(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias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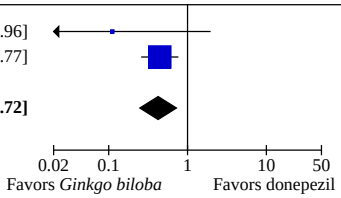
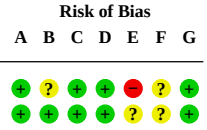
## Analysis 8.4. Comparison 8: Dementia: *Ginkgo biloba* versus conventional medication, Outcome 4: Adverse events: all

| Study or Subgroup | Ginkgo biloba Events | Ginkgo biloba Total | Donepezil Events | Donepezil Total | Weight | Risk Ratio IV, Random, 95% CI |
|---|---|---|---|---|---|---|
| Mazza 2006 | 0 | 25 | 4 | 25 | 3.5% | 0.11 [0.01 , 1.96] |
| Yancheva 2009 | 10 | 30 | 24 | 32 | 96.5% | 0.44 [0.26 , 0.77] |
| **Total (Wald[a])** | | **55** | | **57** | **100.0%** | **0.42 [0.25 , 0.72]** |
| Total events: | 10 | | 28 | | | |

Test for overall effect: Z = 3.15 (P = 0.002)




Heterogeneity: Tau² (DL[b]) = 0.00; Chi² = 0.86, df = 1 (P = 0.35); I² = 0%

**Footnotes**

[a]CI calculated by Wald-type method.

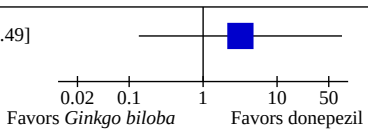
[b]Tau² calculated by DerSimonian and Laird method.

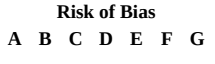
**Risk of bias legend**

(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

## Analysis 8.5. Comparison 8: Dementia: *Ginkgo biloba* versus conventional medication, Outcome 5: Adverse events: serious

| Study or Subgroup | Ginkgo biloba Events | Ginkgo biloba Total | Donepezil Events | Donepezil Total | Risk Ratio IV, Fixed, 95% CI |
|---|---|---|---|---|---|
| Yancheva 2009 | 1 | 30 | 0 | 32 | 3.19 [0.14 , 75.49] |




**Risk of bias legend**

(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias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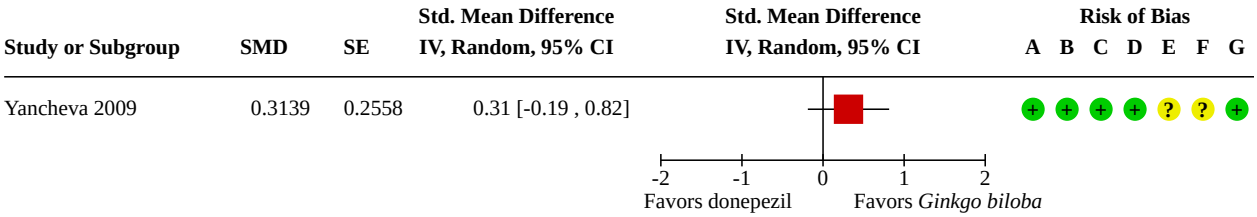
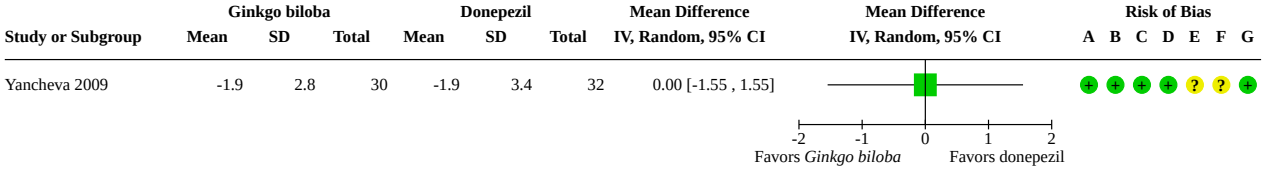
### Analysis 8.6. Comparison 8: Dementia: *Ginkgo biloba* versus conventional medication, Outcome 6: Executive function: 6 months




**Risk of bias legend**

(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

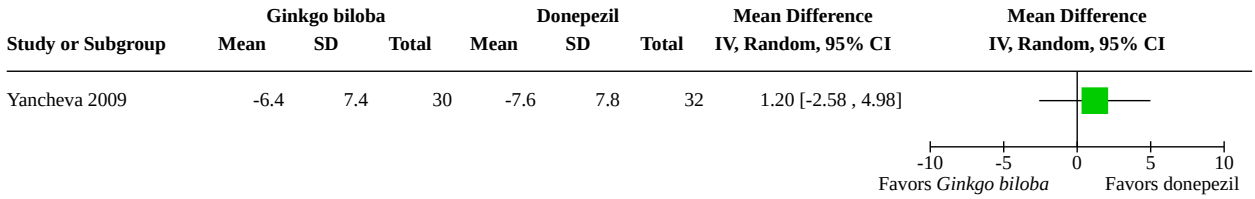
### Analysis 8.7. Comparison 8: Dementia: *Ginkgo biloba* versus conventional medication, Outcome 7: Neuropsychiatric outcomes: depression - 6 months




**Risk of bias legend**

(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

### Analysis 8.8. Comparison 8: Dementia: *Ginkgo biloba* versus conventional medication, Outcome 8: Neuropsychiatric outcomes: NPI - 6 months




## Comparison 9. Dementia: *Ginkgo biloba* versus Chinese herbal medicine or acupuncture

| Outcome or subgroup title | No. of studies | No. of participants | Statistical method | Effect size |
|---|---|---|---|---|
| 9.1 Global cognitive function: acupuncture - 3 months | 1 | | Mean Difference (IV, Random, 95% CI) | Subtotals only |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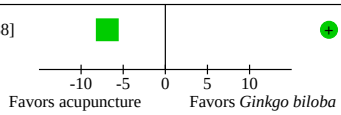
| Outcome or subgroup title | No. of studies | No. of participants | Statistical method | Effect size |
|---|---|---|---|---|
| 9.2 Global cognitive function: Chinese herbal decoction - 3 months | 1 | | Mean Difference (IV, Random, 95% CI) | Subtotals only |
| 9.3 Global cognitive function: Shenma Yizhi Recipe - 3 months | 1 | | Mean Difference (IV, Random, 95% CI) | Subtotals only |
| 9.4 Global cognitive function: Tongxinluo capsule - 3 months | 1 | | Mean Difference (IV, Random, 95% CI) | Subtotals only |
| 9.5 ADL: acupuncture - 3 months | 1 | | Mean Difference (IV, Random, 95% CI) | Subtotals only |
| 9.6 ADL: Chinese herbal decoction - 3 months | 1 | | Std. Mean Difference (IV, Random, 95% CI) | Subtotals only |
| 9.7 ADL: Shenma Yizhi recipe - 3 months | 1 | | Std. Mean Difference (IV, Random, 95% CI) | Subtotals only |
| 9.8 ADL: Tongxinluo capsule - 3 months | 1 | | Std. Mean Difference (IV, Random, 95% CI) | Subtotals only |

**Analysis 9.1. Comparison 9: Dementia: *Ginkgo biloba* versus Chinese herbal medicine or acupuncture, Outcome 1: Global cognitive function: acupuncture - 3 months**

| Study or Subgroup | Ginkgo biloba Mean | SD | Total | Control Mean | SD | Total | Mean Difference IV, Random, 95% CI | Mean Difference IV, Random, 95% CI | Risk of Bias A B C D E F G |
|---|---|---|---|---|---|---|---|---|---|
| Liao 2017a | 23.23 | 2.25 | 50 | 30.12 | 2.85 | 50 | -6.89 [-7.90 , -5.88] | | + ? − ? ? ? + |




**Risk of bias legend**
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias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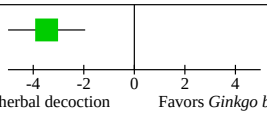
## Analysis 9.2. Comparison 9: Dementia: *Ginkgo biloba* versus Chinese herbal medicine or acupuncture, Outcome 2: Global cognitive function: Chinese herbal decoction - 3 months

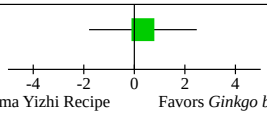
| Study or Subgroup | Ginkgo biloba Mean | SD | Total | Control Mean | SD | Total | Mean Difference IV, Random, 95% CI | Mean Difference IV, Random, 95% CI | Risk of Bias A B C D E F G |
|---|---|---|---|---|---|---|---|---|---|
| Chen 2014a | 20.27 | 3.284 | 48 | 23.74 | 4.276 | 48 | -3.47 [-5.00 , -1.94] | | + ? − ? ? ? + |




**Risk of bias legend**
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

## Analysis 9.3. Comparison 9: Dementia: *Ginkgo biloba* versus Chinese herbal medicine or acupuncture, Outcome 3: Global cognitive function: Shenma Yizhi Recipe - 3 months

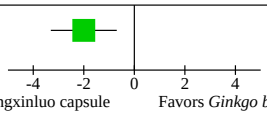
| Study or Subgroup | Ginkgo biloba Mean | SD | Total | Control Mean | SD | Total | Mean Difference IV, Random, 95% CI | Mean Difference IV, Random, 95% CI | Risk of Bias A B C D E F G |
|---|---|---|---|---|---|---|---|---|---|
| Wu 2017 | 17.09 | 4.52 | 32 | 16.75 | 4.17 | 32 | 0.34 [-1.79 , 2.47] | | ? ? ? + + ? + |




**Risk of bias legend**
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

## Analysis 9.4. Comparison 9: Dementia: *Ginkgo biloba* versus Chinese herbal medicine or acupuncture, Outcome 4: Global cognitive function: Tongxinluo capsule - 3 months

| Study or Subgroup | Ginkgo biloba Mean | SD | Total | Control Mean | SD | Total | Mean Difference IV, Random, 95% CI | Mean Difference IV, Random, 95% CI | Risk of Bias A B C D E F G |
|---|---|---|---|---|---|---|---|---|---|
| Zhang 2016a | 28.23 | 3.1 | 60 | 30.23 | 4.12 | 60 | -2.00 [-3.30 , -0.70] | | + ? ? ? + ? + |




**Risk of bias legend**
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias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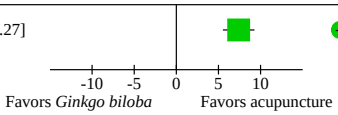
## Analysis 9.5. Comparison 9: Dementia: *Ginkgo biloba* versus Chinese herbal medicine or acupuncture, Outcome 5: ADL: acupuncture - 3 months

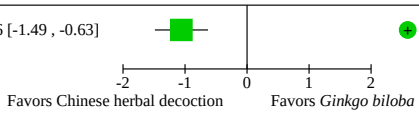
| Study or Subgroup | Ginkgo biloba Mean | SD | Total | Acupuncture Mean | SD | Total | Mean Difference IV, Random, 95% CI | Mean Difference IV, Random, 95% CI | Risk of Bias A B C D E F G |
|---|---|---|---|---|---|---|---|---|---|
| Liao 2017a | 18.12 | 4.75 | 50 | 10.72 | 4.81 | 50 | 7.40 [5.53 , 9.27] | | + ? − ? ? ? + |




**Risk of bias legend**
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

## Analysis 9.6. Comparison 9: Dementia: *Ginkgo biloba* versus Chinese herbal medicine or acupuncture, Outcome 6: ADL: Chinese herbal decoction - 3 months

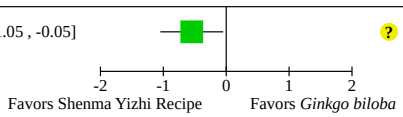
| Study or Subgroup | Ginkgo biloba Mean | SD | Total | Chinese herbal decoction Mean | SD | Total | Std. Mean Difference IV, Random, 95% CI | Std. Mean Difference IV, Random, 95% CI | Risk of Bias A B C D E F G |
|---|---|---|---|---|---|---|---|---|---|
| Chen 2014a | 37.8 | 7.2 | 48 | 46.2 | 8.5 | 48 | -1.06 [-1.49 , -0.63] | | + ? − ? ? ? + |




**Risk of bias legend**
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

## Analysis 9.7. Comparison 9: Dementia: *Ginkgo biloba* versus Chinese herbal medicine or acupuncture, Outcome 7: ADL: Shenma Yizhi recipe - 3 months

| Study or Subgroup | Ginkgo Biloba Mean | SD | Total | Shenma Yizhi Recipe Mean | SD | Total | Std. Mean Difference IV, Random, 95% CI | Std. Mean Difference IV, Random, 95% CI | Risk of Bias A B C D E F G |
|---|---|---|---|---|---|---|---|---|---|
| Wu 2017 | -31.28 | 4.04 | 32 | -29.16 | 3.59 | 32 | -0.55 [-1.05 , -0.05] | | ? ? ? + + ? + |




**Risk of bias legend**
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias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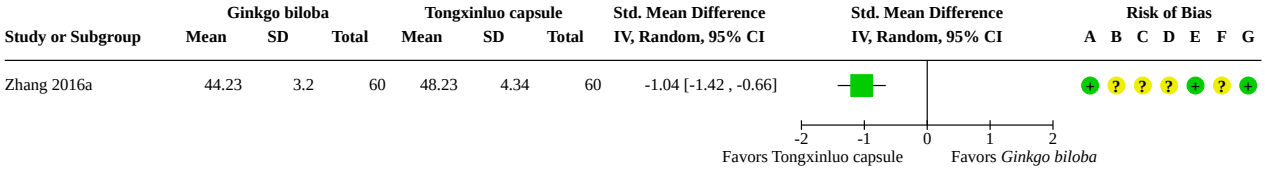
### Analysis 9.8. Comparison 9: Dementia: *Ginkgo biloba* versus Chinese herbal medicine or acupuncture, Outcome 8: ADL: Tongxinluo capsule - 3 months




**Risk of bias legend**
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

## Comparison 10. Dementia: *Ginkgo biloba* added to conventional treatment

| Outcome or subgroup title | No. of studies | No. of participants | Statistical method | Effect size |
|---|---|---|---|---|
| 10.1 Global clinical status: 3 months | 1 | | Mean Difference (IV, Random, 95% CI) | Subtotals only |
| 10.2 Global cognitive function: 3 months | 9 | 728 | Std. Mean Difference (IV, Random, 95% CI) | 1.25 [0.81, 1.69] |
| 10.3 Global cognitive function: 6 to 9 months | 7 | 585 | Std. Mean Difference (IV, Random, 95% CI) | 1.63 [0.92, 2.34] |
| 10.4 Global cognitive function: 6 months - change | 1 | | Mean Difference (IV, Random, 95% CI) | Subtotals only |
| 10.5 Cognition: 3 to 9 months: subgroup analysis by diagnosis | 14 | | Std. Mean Difference (IV, Random, 95% CI) | Subtotals only |
| 10.5.1 AD | 7 | 588 | Std. Mean Difference (IV, Random, 95% CI) | 1.91 [1.14, 2.68] |
| 10.5.2 VD | 7 | 574 | Std. Mean Difference (IV, Random, 95% CI) | 1.16 [0.78, 1.53] |
| 10.6 Cognition: 3 to 9 months: subgroup analysis by medication | 12 | | Std. Mean Difference (IV, Random, 95% CI) | Subtotals only |
| 10.6.1 Butylphthalide | 3 | 244 | Std. Mean Difference (IV, Random, 95% CI) | 2.57 [0.79, 4.34] |
| 10.6.2 Donepezil | 7 | 615 | Std. Mean Difference (IV, Random, 95% CI) | 1.21 [0.81, 1.61] |
| 10.6.3 Memantine hydrochloride | 2 | 169 | Std. Mean Difference (IV, Random, 95% CI) | 1.91 [0.32, 3.50] |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| Outcome or subgroup title | No. of studies | No. of participants | Statistical method | Effect size |
|---|---|---|---|---|
| 10.7 Cognition: MMSE analysis - 3 to 9 months: to check for publication bias | 14 | 1162 | Mean Difference (IV, Random, 95% CI) | 3.32 [2.61, 4.03] |
| 10.8 ADL: 3 months | 9 | 728 | Std. Mean Difference (IV, Random, 95% CI) | 1.38 [0.76, 2.00] |
| 10.9 ADL: 6 to 9 months | 8 | 678 | Std. Mean Difference (IV, Random, 95% CI) | 1.46 [0.77, 2.16] |
| 10.10 ADL: 3 to 6 months: subgroup analysis by diagnosis | 15 | | Std. Mean Difference (IV, Random, 95% CI) | Subtotals only |
| 10.10.3 AD | 8 | 651 | Std. Mean Difference (IV, Random, 95% CI) | 1.79 [0.91, 2.67] |
| 10.10.4 VD | 7 | 604 | Std. Mean Difference (IV, Random, 95% CI) | 1.30 [0.85, 1.74] |
| 10.11 ADL: 3 to 9 months: subgroup analysis by medication | 13 | | Std. Mean Difference (IV, Random, 95% CI) | Subtotals only |
| 10.11.1 Butylphthalide | 3 | 244 | Std. Mean Difference (IV, Random, 95% CI) | 2.32 [0.33, 4.31] |
| 10.11.2 Donepezil | 8 | 678 | Std. Mean Difference (IV, Random, 95% CI) | 1.26 [0.75, 1.77] |
| 10.11.3 Memantine hydrochloride | 2 | 167 | Std. Mean Difference (IV, Random, 95% CI) | 2.28 [-0.93, 5.50] |
| 10.12 Adverse events: all | 8 | 640 | Risk Ratio (M-H, Random, 95% CI) | 0.88 [0.67, 1.16] |
| 10.12.1 3 months | 4 | 315 | Risk Ratio (M-H, Random, 95% CI) | 1.23 [0.68, 2.23] |
| 10.12.2 6 months | 4 | 325 | Risk Ratio (M-H, Random, 95% CI) | 0.81 [0.59, 1.10] |
| 10.13 Adverse events: serious | 1 | | Risk Ratio (M-H, Random, 95% CI) | Subtotals only |
| 10.14 Memory - 6 months | 1 | | Mean Difference (IV, Random, 95% CI) | Subtotals only |
| 10.15 Executive function - 6 months | 1 | | Std. Mean Difference (IV, Random, 95% CI) | Subtotals only |
| 10.16 Neuropsychiatric outcomes: depression - 6 months | 1 | | Mean Difference (IV, Random, 95% CI) | Subtotals only |
| 10.17 Neuropsychiatric outcomes: NPI - 3 months | 1 | | Mean Difference (IV, Random, 95% CI) | Subtotals only |
| 10.18 Neuropsychiatric outcomes: NPI - 6 months | 2 | 161 | Mean Difference (IV, Random, 95% CI) | -3.13 [-7.27, 1.02] |


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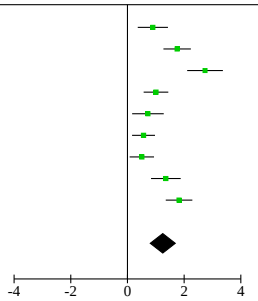
## Analysis 10.1. Comparison 10: Dementia: *Ginkgo biloba* added to conventional treatment, Outcome 1: Global clinical status: 3 months

| Study or Subgroup | Adjunctive Ginkgo biloba Mean | SD | Total | Conventional treatment alone Mean | SD | Total | Mean Difference IV, Random, 95% CI | Mean Difference IV, Random, 95% CI | Risk of Bias A B C D E F G |
|---|---|---|---|---|---|---|---|---|---|
| Zheng 2020 | 0.8 | 0.1 | 50 | 1.2 | 0.3 | 50 | -0.40 [-0.49 , -0.31] | | + ? ? ? + ? + |

**Risk of bias legend**
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

## Analysis 10.2. Comparison 10: Dementia: *Ginkgo biloba* added to conventional treatment, Outcome 2: Global cognitive function: 3 months

| Study or Subgroup | Adjunctive Ginkgo biloba Mean | SD | Total | Conventional treatment alone Mean | SD | Total | Weight | Std. Mean Difference IV, Random, 95% CI | Std. Mean Difference IV, Random, 95% CI | Risk of Bias A B C D E F G |
|---|---|---|---|---|---|---|---|---|---|---|
| Fang 2020 | 22.3 | 4.9 | 30 | 18.2 | 4.1 | 30 | 10.9% | 0.90 [0.36 , 1.43] | | + ? ? ? + ? + |
| Guan 2019 | 20.09 | 2.01 | 46 | 16.58 | 1.96 | 46 | 11.2% | 1.75 [1.27 , 2.24] | | + ? - ? ? ? + |
| Li 2017a | 27.66 | 2.34 | 39 | 20.37 | 2.91 | 38 | 10.2% | 2.74 [2.11 , 3.37] | | + ? - ? ? ? + |
| Liu 2021 | 24.64 | 4.65 | 46 | 20.23 | 4.02 | 46 | 11.5% | 1.01 [0.57 , 1.44] | | + ? ? ? + ? + |
| Wang 2014a | 23.43 | 5.41 | 27 | 19.75 | 4.57 | 26 | 10.7% | 0.72 [0.17 , 1.28] | | + ? ? ? + ? + |
| Wu 2021a | 17.6 | 2 | 49 | 15.9 | 3.7 | 49 | 11.7% | 0.57 [0.16 , 0.97] | | + ? ? ? + ? + |
| Xu 2019a | 21.43 | 2.92 | 43 | 20.1 | 2.23 | 43 | 11.5% | 0.51 [0.08 , 0.94] | | + ? ? ? + ? + |
| Yu 2014 | 23.5 | 2.66 | 35 | 19.8 | 2.74 | 35 | 11.0% | 1.36 [0.83 , 1.88] | | + ? ? ? + ? + |
| Zheng 2020 | 20.39 | 2.35 | 50 | 16.55 | 1.8 | 50 | 11.3% | 1.82 [1.35 , 2.29] | | + ? ? ? + ? + |
| **Total (Wald[a])** | | | **365** | | | **363** | **100.0%** | **1.25 [0.81 , 1.69]** | | |




Test for overall effect: Z = 5.54 (P < 0.00001)

Heterogeneity: Tau² (DL[b]) = 0.39; Chi² = 58.94, df = 8 (P < 0.00001); I² = 86%

**Footnotes**
[a]CI calculated by Wald-type method.
[b]Tau² calculated by DerSimonian and Laird method.

**Risk of bias legend**
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias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## Analysis 10.3. Comparison 10: Dementia: *Ginkgo biloba* added to conventional treatment, Outcome 3: Global cognitive function: 6 to 9 months

| Study or Subgroup | Adjunctive Ginkgo biloba Mean | SD | Total | Conventional treatment alone Mean | SD | Total | Weight | Std. Mean Difference IV, Random, 95% CI |
|---|---|---|---|---|---|---|---|---|
| Dong 2021 | 23.25 | 3.55 | 37 | 20.49 | 3.45 | 37 | 14.6% | 0.78 [0.31 , 1.25] |
| Gao 2019 | -29.13 | 3.1 | 58 | -33.98 | 3.14 | 58 | 14.8% | 1.54 [1.13 , 1.96] |
| Huang 2017 | -31.19 | 0.97 | 40 | -35.16 | 1.02 | 40 | 13.2% | 3.95 [3.18 , 4.72] |
| Kang 2020 | 24.69 | 3.49 | 43 | 21.05 | 3.01 | 49 | 14.7% | 1.11 [0.67 , 1.55] |
| Wang 2014a | 24.35 | 5.79 | 27 | 20.12 | 6.73 | 26 | 14.2% | 0.66 [0.11 , 1.22] |
| Wu 2021a | 18.5 | 1.6 | 49 | 17.1 | 1.8 | 49 | 14.8% | 0.82 [0.40 , 1.23] |
| Xu 2017 | -31.59 | 1.13 | 36 | -34.82 | 1.15 | 36 | 13.7% | 2.80 [2.14 , 3.46] |
| **Total (Wald[a])** | | | **290** | | | **295** | **100.0%** | **1.63 [0.92 , 2.34]** |

Std. Mean Difference IV, Random, 95% CI

Risk of Bias: A B C D E F G

-4 -2 0 2 4

Favors conventional treatment alone | Favors adjunctive *Ginkgo biloba*

Test for overall effect: Z = 4.50 (P < 0.00001)

Heterogeneity: Tau² (DL[b]) = 0.84; Chi² = 82.75, df = 6 (P < 0.00001); I² = 93%

**Footnotes**

[a]CI calculated by Wald-type method.

[b]Tau² calculated by DerSimonian and Laird method.

**Risk of bias legend**

(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

## Analysis 10.4. Comparison 10: Dementia: *Ginkgo biloba* added to conventional treatment, Outcome 4: Global cognitive function: 6 months - change

| Study or Subgroup | Adjunctive Ginkgo biloba Mean | SD | Total | Conventional treatment alone Mean | SD | Total | Mean Difference IV, Random, 95% CI |
|---|---|---|---|---|---|---|---|
| Yancheva 2009 | -3.5 | 3.4 | 31 | -2.5 | 3.4 | 32 | -1.00 [-2.68 , 0.68] |

Mean Difference IV, Random, 95% CI

Risk of Bias: A B C D E F G

-4 -2 0 2 4

Favors adjunctive *Ginkgo biloba* | Favors conventional treatment alone

**Risk of bias legend**

(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias


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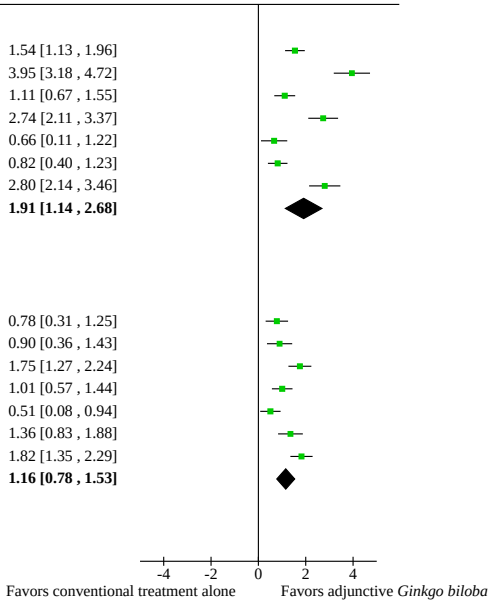
## Analysis 10.5. Comparison 10: Dementia: *Ginkgo biloba* added to conventional treatment, Outcome 5: Cognition: 3 to 9 months: subgroup analysis by diagnosis

| Study or Subgroup | Adjunctive Ginkgo biloba Mean | SD | Total | Conventional treatment alone Mean | SD | Total | Weight | Std. Mean Difference IV, Random, 95% CI |
|---|---|---|---|---|---|---|---|---|
| **10.5.1 AD** | | | | | | | | |
| Gao 2019 | -29.13 | 3.1 | 58 | -33.98 | 3.14 | 58 | 14.8% | 1.54 [1.13 , 1.96] |
| Huang 2017 | -31.19 | 0.97 | 40 | -35.16 | 1.02 | 40 | 13.4% | 3.95 [3.18 , 4.72] |
| Kang 2020 | 24.69 | 3.49 | 43 | 21.05 | 3.01 | 49 | 14.7% | 1.11 [0.67 , 1.55] |
| Li 2017a | 27.66 | 2.34 | 39 | 20.37 | 2.91 | 38 | 14.0% | 2.74 [2.11 , 3.37] |
| Wang 2014a | 24.35 | 5.79 | 27 | 20.12 | 6.73 | 26 | 14.3% | 0.66 [0.11 , 1.22] |
| Wu 2021a | 18.5 | 1.6 | 49 | 17.1 | 1.8 | 49 | 14.8% | 0.82 [0.40 , 1.23] |
| Xu 2017 | -31.59 | 1.13 | 36 | -34.82 | 1.15 | 36 | 13.9% | 2.80 [2.14 , 3.46] |
| **Subtotal (Wald[a])** | | | **292** | | | **296** | **100.0%** | **1.91 [1.14 , 2.68]** |
| Test for overall effect: Z = 4.86 (P < 0.00001) | | | | | | | | |
| Heterogeneity: Tau² (DL[b]) = 1.00; Chi² = 90.95, df = 6 (P < 0.00001); I² = 93% | | | | | | | | |
| **10.5.2 VD** | | | | | | | | |
| Dong 2021 | 23.25 | 3.55 | 37 | 20.49 | 3.45 | 37 | 14.3% | 0.78 [0.31 , 1.25] |
| Fang 2020 | 22.3 | 4.9 | 30 | 18.2 | 4.1 | 30 | 13.5% | 0.90 [0.36 , 1.43] |
| Guan 2019 | 20.09 | 2.01 | 46 | 16.58 | 1.96 | 46 | 14.2% | 1.75 [1.27 , 2.24] |
| Liu 2021 | 24.64 | 4.65 | 46 | 20.23 | 4.02 | 46 | 14.9% | 1.01 [0.57 , 1.44] |
| Xu 2019a | 21.43 | 2.92 | 43 | 20.1 | 2.23 | 43 | 14.9% | 0.51 [0.08 , 0.94] |
| Yu 2014 | 23.5 | 2.66 | 35 | 19.8 | 2.74 | 35 | 13.7% | 1.36 [0.83 , 1.88] |
| Zheng 2020 | 20.39 | 2.35 | 50 | 16.55 | 1.8 | 50 | 14.4% | 1.82 [1.35 , 2.29] |
| **Subtotal (Wald[a])** | | | **287** | | | **287** | **100.0%** | **1.16 [0.78 , 1.53]** |
| Test for overall effect: Z = 5.98 (P < 0.00001) | | | | | | | | |
| Heterogeneity: Tau² (DL[b]) = 0.20; Chi² = 26.62, df = 6 (P = 0.0002); I² = 77% | | | | | | | | |
| Test for subgroup differences: Chi² = 2.98, df = 1 (P = 0.08), I² = 66.4% | | | | | | | | |




**Footnotes**

[a]CI calculated by Wald-type method.

[b]Tau² calculated by DerSimonian and Laird method.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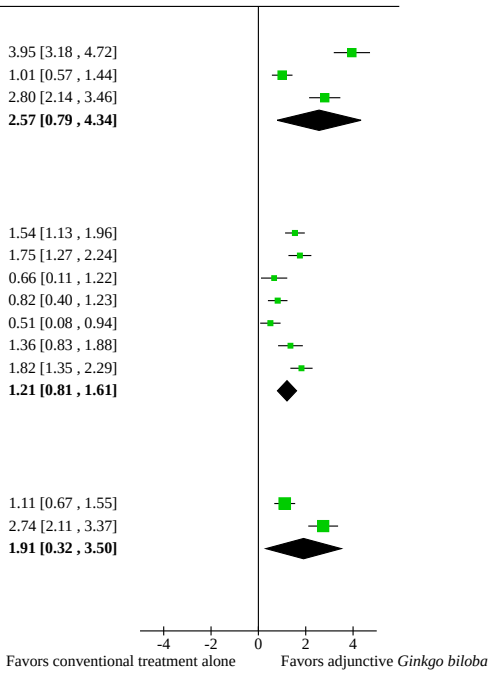
## Analysis 10.6. Comparison 10: Dementia: *Ginkgo biloba* added to conventional treatment, Outcome 6: Cognition: 3 to 9 months: subgroup analysis by medication

| Study or Subgroup | Adjunctive Ginkgo biloba Mean | SD | Total | Conventional treatment alone Mean | SD | Total | Weight | Std. Mean Difference IV, Random, 95% CI |
|---|---|---|---|---|---|---|---|---|
| **10.6.1 Butylphthalide** | | | | | | | | |
| Huang 2017 | -31.19 | 0.97 | 40 | -35.16 | 1.02 | 40 | 32.7% | 3.95 [3.18 , 4.72] |
| Liu 2021 | 24.64 | 4.65 | 46 | 20.23 | 4.02 | 46 | 34.1% | 1.01 [0.57 , 1.44] |
| Xu 2017 | -31.59 | 1.13 | 36 | -34.82 | 1.15 | 36 | 33.2% | 2.80 [2.14 , 3.46] |
| **Subtotal (Wald[a])** | | | **122** | | | **122** | **100.0%** | **2.57 [0.79 , 4.34]** |
| Test for overall effect: Z = 2.84 (P = 0.005) | | | | | | | | |
| Heterogeneity: Tau² (DL[b]) = 2.35; Chi² = 50.68, df = 2 (P < 0.00001); I² = 96% | | | | | | | | |
| **10.6.2 Donepezil** | | | | | | | | |
| Gao 2019 | -29.13 | 3.1 | 58 | -33.98 | 3.14 | 58 | 14.9% | 1.54 [1.13 , 1.96] |
| Guan 2019 | 20.09 | 2.01 | 46 | 16.58 | 1.96 | 46 | 14.1% | 1.75 [1.27 , 2.24] |
| Wang 2014a | 24.35 | 5.79 | 27 | 20.12 | 6.73 | 26 | 13.3% | 0.66 [0.11 , 1.22] |
| Wu 2021a | 18.5 | 1.6 | 49 | 17.1 | 1.8 | 49 | 15.0% | 0.82 [0.40 , 1.23] |
| Xu 2019a | 21.43 | 2.92 | 43 | 20.1 | 2.23 | 43 | 14.8% | 0.51 [0.08 , 0.94] |
| Yu 2014 | 23.5 | 2.66 | 35 | 19.8 | 2.74 | 35 | 13.7% | 1.36 [0.83 , 1.88] |
| Zheng 2020 | 20.39 | 2.35 | 50 | 16.55 | 1.8 | 50 | 14.3% | 1.82 [1.35 , 2.29] |
| **Subtotal (Wald[a])** | | | **308** | | | **307** | **100.0%** | **1.21 [0.81 , 1.61]** |
| Test for overall effect: Z = 5.87 (P < 0.00001) | | | | | | | | |
| Heterogeneity: Tau² (DL[b]) = 0.24; Chi² = 31.60, df = 6 (P < 0.0001); I² = 81% | | | | | | | | |
| **10.6.3 Memantine hydrochloride** | | | | | | | | |
| Kang 2020 | 24.69 | 3.49 | 43 | 21.05 | 3.01 | 49 | 51.0% | 1.11 [0.67 , 1.55] |
| Li 2017a | 27.66 | 2.34 | 39 | 20.37 | 2.91 | 38 | 49.0% | 2.74 [2.11 , 3.37] |
| **Subtotal (Wald[a])** | | | **82** | | | **87** | **100.0%** | **1.91 [0.32 , 3.50]** |
| Test for overall effect: Z = 2.35 (P = 0.02) | | | | | | | | |
| Heterogeneity: Tau² (DL[b]) = 1.24; Chi² = 17.13, df = 1 (P < 0.0001); I² = 94% | | | | | | | | |
| Test for subgroup differences: Chi² = 2.72, df = 2 (P = 0.26), I² = 26.4% | | | | | | | | |



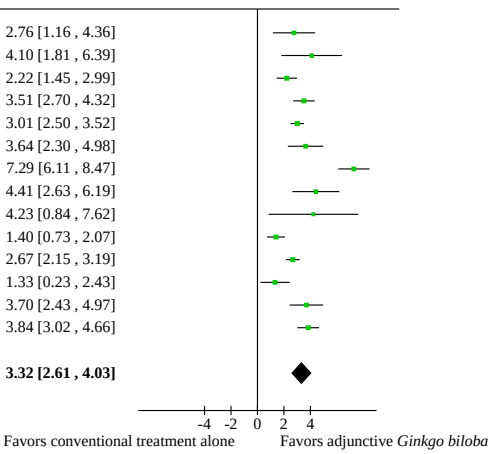

**Footnotes**

[a]CI calculated by Wald-type method.

[b]Tau² calculated by DerSimonian and Laird method.

## Analysis 10.7. Comparison 10: Dementia: *Ginkgo biloba* added to conventional treatment, Outcome 7: Cognition: MMSE analysis - 3 to 9 months: to check for publication bias

| Study or Subgroup | Adjunctive Ginkgo biloba Mean | SD | Total | Conventional treatment alone Mean | SD | Total | Weight | Mean Difference IV, Random, 95% CI |
|---|---|---|---|---|---|---|---|---|
| Dong 2021 | 23.25 | 3.55 | 37 | 20.49 | 3.45 | 37 | 6.3% | 2.76 [1.16 , 4.36] |
| Fang 2020 | 22.3 | 4.9 | 30 | 18.2 | 4.1 | 30 | 4.7% | 4.10 [1.81 , 6.39] |
| Gao 2019 | 21.08 | 2.15 | 58 | 18.86 | 2.09 | 58 | 8.4% | 2.22 [1.45 , 2.99] |
| Guan 2019 | 20.09 | 2.01 | 46 | 16.58 | 1.96 | 46 | 8.3% | 3.51 [2.70 , 4.32] |
| Huang 2017 | 20.38 | 1.17 | 40 | 17.37 | 1.14 | 40 | 8.9% | 3.01 [2.50 , 3.52] |
| Kang 2020 | 24.69 | 3.49 | 43 | 21.05 | 3.01 | 49 | 7.0% | 3.64 [2.30 , 4.98] |
| Li 2017a | 27.66 | 2.34 | 39 | 20.37 | 2.91 | 38 | 7.4% | 7.29 [6.11 , 8.47] |
| Liu 2021 | 24.64 | 4.65 | 46 | 20.23 | 4.02 | 46 | 5.8% | 4.41 [2.63 , 6.19] |
| Wang 2014a | 24.35 | 5.79 | 27 | 20.12 | 6.73 | 26 | 3.0% | 4.23 [0.84 , 7.62] |
| Wu 2021a | 18.5 | 1.6 | 49 | 17.1 | 1.8 | 49 | 8.6% | 1.40 [0.73 , 2.07] |
| Xu 2017 | 20.16 | 1.14 | 36 | 17.49 | 1.11 | 36 | 8.8% | 2.67 [2.15 , 3.19] |
| Xu 2019a | 21.43 | 2.92 | 43 | 20.1 | 2.23 | 43 | 7.6% | 1.33 [0.23 , 2.43] |
| Yu 2014 | 23.5 | 2.66 | 35 | 19.8 | 2.74 | 35 | 7.2% | 3.70 [2.43 , 4.97] |
| Zheng 2020 | 20.39 | 2.35 | 50 | 16.55 | 1.8 | 50 | 8.2% | 3.84 [3.02 , 4.66] |
| **Total (Wald[a])** | | | **579** | | | **583** | **100.0%** | **3.32 [2.61 , 4.03]** |
| Test for overall effect: Z = 9.22 (P < 0.00001) | | | | | | | | |
| Heterogeneity: Tau² (DL[b]) = 1.40; Chi² = 98.00, df = 13 (P < 0.00001); I² = 87% | | | | | | | | |




**Footnotes**

[a]CI calculated by Wald-type method.

[b]Tau² calculated by DerSimonian and Laird method.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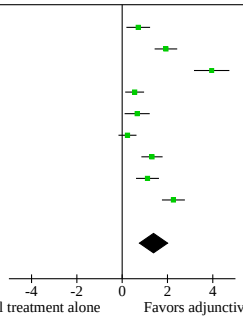
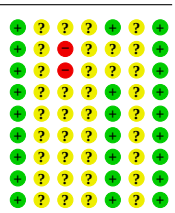
## Analysis 10.8. Comparison 10: Dementia: *Ginkgo biloba* added to conventional treatment, Outcome 8: ADL: 3 months

| Study or Subgroup | Adjunctive Ginkgo Biloba Mean | SD | Total | Conventional treatment alone Mean | SD | Total | Weight | Std. Mean Difference IV, Random, 95% CI |
|---|---|---|---|---|---|---|---|---|
| Fang 2020 | 54.7 | 13.9 | 30 | 45.2 | 12.5 | 30 | 11.1% | 0.71 [0.19 , 1.23] |
| Guan 2019 | 67.16 | 4.7 | 46 | 58.21 | 4.49 | 46 | 11.2% | 1.93 [1.43 , 2.43] |
| Li 2017a | 82.87 | 4.02 | 39 | 67.85 | 3.48 | 38 | 10.1% | 3.95 [3.17 , 4.73] |
| Liu 2021 | 62.33 | 12.02 | 46 | 56.13 | 10.24 | 46 | 11.4% | 0.55 [0.13 , 0.97] |
| Wang 2014a | -12.43 | 5.57 | 27 | -16.32 | 6.01 | 26 | 11.0% | 0.66 [0.11 , 1.22] |
| Wu 2021a | 54.2 | 10.7 | 49 | 51.8 | 9.6 | 49 | 11.5% | 0.23 [-0.16 , 0.63] |
| Xu 2019a | 83.98 | 5.71 | 43 | 76.03 | 6.25 | 43 | 11.3% | 1.32 [0.85 , 1.78] |
| Yu 2014 | 61.3 | 6.72 | 35 | 53.8 | 6.55 | 35 | 11.2% | 1.12 [0.61 , 1.62] |
| Zheng 2020 | 64.2 | 6.88 | 50 | 50.21 | 5.29 | 50 | 11.2% | 2.26 [1.76 , 2.77] |
| **Total (Wald[a])** | | | **365** | | | **363** | **100.0%** | **1.38 [0.76 , 2.00]** |




Test for overall effect: Z = 4.37 (P < 0.0001)

Heterogeneity: Tau² (DL[b]) = 0.83; Chi² = 111.96, df = 8 (P < 0.00001); I² = 93%

**Footnotes**

[a]CI calculated by Wald-type method.

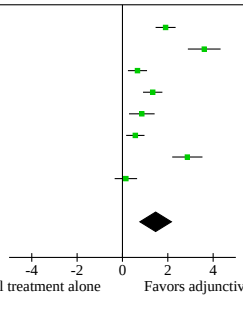
[b]Tau² calculated by DerSimonian and Laird method.

**Risk of bias legend**

(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

## Analysis 10.9. Comparison 10: Dementia: *Ginkgo biloba* added to conventional treatment, Outcome 9: ADL: 6 to 9 months

| Study or Subgroup | Adjunctive Ginkgo biloba Mean | SD | Total | Conventional treatment alone Mean | SD | Total | Weight | Std. Mean Difference IV, Random, 95% CI |
|---|---|---|---|---|---|---|---|---|
| Gao 2019 | -30.01 | 2.15 | 58 | -34.09 | 2.11 | 58 | 12.8% | 1.90 [1.46 , 2.34] |
| Huang 2017 | -27.94 | 1.15 | 40 | -32.02 | 1.09 | 40 | 11.8% | 3.61 [2.88 , 4.33] |
| Kang 2020 | 67.02 | 9.27 | 43 | 61.25 | 8.04 | 49 | 12.8% | 0.66 [0.24 , 1.08] |
| Meng 2012 | 61.24 | 9.25 | 52 | 49.79 | 7.72 | 52 | 12.8% | 1.33 [0.91 , 1.76] |
| Wang 2014a | -10.1 | 5.45 | 27 | -14.94 | 5.72 | 26 | 12.4% | 0.85 [0.29 , 1.42] |
| Wu 2021a | 60.8 | 8.7 | 49 | 56.1 | 7.7 | 49 | 12.9% | 0.57 [0.16 , 0.97] |
| Xu 2017 | -28.91 | 1.06 | 36 | -32.02 | 1.09 | 36 | 12.0% | 2.86 [2.19 , 3.53] |
| Yancheva 2009 | -3.03 | 4.61 | 31 | -3.81 | 5.54 | 32 | 12.6% | 0.15 [-0.34 , 0.65] |
| **Total (Wald[a])** | | | **336** | | | **342** | **100.0%** | **1.46 [0.77 , 2.16]** |



Test for overall effect: Z = 4.13 (P < 0.0001)

Heterogeneity: Tau² (DL[b]) = 0.93; Chi² = 111.09, df = 7 (P < 0.00001); I² = 94%

**Footnotes**

[a]CI calculated by Wald-type method.

[b]Tau² calculated by DerSimonian and Laird method.

**Risk of bias legend**

(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias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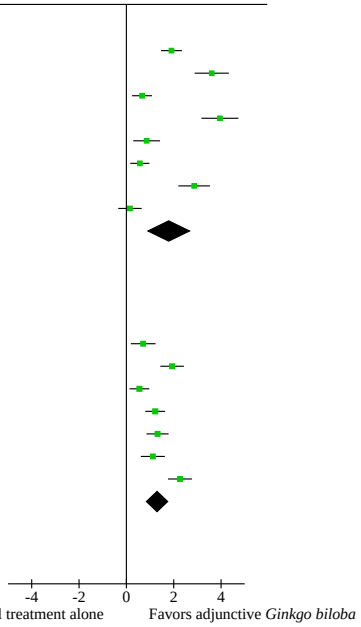
## Analysis 10.10. Comparison 10: Dementia: *Ginkgo biloba* added to conventional treatment, Outcome 10: ADL: 3 to 6 months: subgroup analysis by diagnosis

| Study or Subgroup | Adjunctive Ginkgo biloba Mean | SD | Total | Conventional treatment alone Mean | SD | Total | Weight | Std. Mean Difference IV, Random, 95% CI |
|---|---|---|---|---|---|---|---|---|
| **10.10.3 AD** | | | | | | | | |
| Gao 2019 | -30.01 | 2.15 | 58 | -34.09 | 2.11 | 58 | 12.8% | 1.90 [1.46 , 2.34] |
| Huang 2017 | -27.94 | 1.15 | 40 | -32.02 | 1.09 | 40 | 12.1% | 3.61 [2.88 , 4.33] |
| Kang 2020 | 67.02 | 9.27 | 43 | 61.25 | 8.04 | 49 | 12.8% | 0.66 [0.24 , 1.08] |
| Li 2017a | 82.87 | 4.02 | 39 | 67.85 | 3.48 | 38 | 12.0% | 3.95 [3.17 , 4.73] |
| Wang 2014a | -10.1 | 5.45 | 27 | -14.94 | 5.72 | 26 | 12.5% | 0.85 [0.29 , 1.42] |
| Wu 2021a | 60.8 | 8.7 | 49 | 56.1 | 7.7 | 49 | 12.8% | 0.57 [0.16 , 0.97] |
| Xu 2017 | -28.91 | 1.06 | 36 | -32.02 | 1.09 | 36 | 12.3% | 2.86 [2.19 , 3.53] |
| Yancheva 2009 | -3.03 | 4.61 | 31 | -3.81 | 5.54 | 32 | 12.7% | 0.15 [-0.34 , 0.65] |
| **Subtotal (Wald[a])** | | | **323** | | | **328** | **100.0%** | **1.79 [0.91 , 2.67]** |
| Test for overall effect: Z = 3.99 (P < 0.0001) | | | | | | | | |
| Heterogeneity: Tau² (DL[b]) = 1.52; Chi² = 156.12, df = 7 (P < 0.00001); I² = 96% | | | | | | | | |
| **10.10.4 VD** | | | | | | | | |
| Fang 2020 | 54.7 | 13.9 | 30 | 45.2 | 12.5 | 30 | 13.8% | 0.71 [0.19 , 1.23] |
| Guan 2019 | 67.16 | 4.7 | 46 | 58.21 | 4.49 | 46 | 14.1% | 1.93 [1.43 , 2.43] |
| Liu 2021 | 62.33 | 12.02 | 46 | 56.13 | 10.24 | 46 | 14.9% | 0.55 [0.13 , 0.97] |
| Meng 2012 | 60.24 | 9.25 | 52 | 49.79 | 7.72 | 52 | 14.8% | 1.22 [0.80 , 1.64] |
| Xu 2019a | 83.98 | 5.71 | 43 | 76.03 | 6.25 | 43 | 14.4% | 1.32 [0.85 , 1.78] |
| Yu 2014 | 61.3 | 6.72 | 35 | 53.8 | 6.55 | 35 | 14.0% | 1.12 [0.61 , 1.62] |
| Zheng 2020 | 64.2 | 6.88 | 50 | 50.21 | 5.29 | 50 | 14.0% | 2.26 [1.76 , 2.77] |
| **Subtotal (Wald[a])** | | | **302** | | | **302** | **100.0%** | **1.30 [0.85 , 1.74]** |
| Test for overall effect: Z = 5.65 (P < 0.00001) | | | | | | | | |
| Heterogeneity: Tau² (DL[b]) = 0.31; Chi² = 37.83, df = 6 (P < 0.00001); I² = 84% | | | | | | | | |
| Test for subgroup differences: Chi² = 0.96, df = 1 (P = 0.33), I² = 0% | | | | | | | | |




**Footnotes**

[a]CI calculated by Wald-type method.

[b]Tau² calculated by DerSimonian and Laird method.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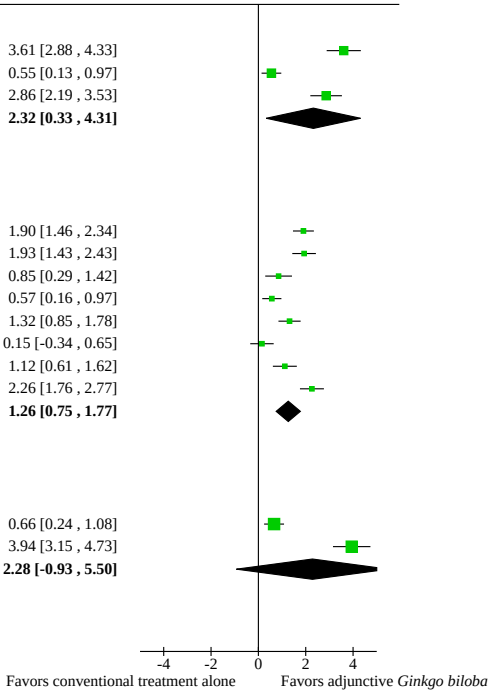
## Analysis 10.11. Comparison 10: Dementia: *Ginkgo biloba* added to conventional treatment, Outcome 11: ADL: 3 to 9 months: subgroup analysis by medication

| Study or Subgroup | Adjunctive Ginkgo biloba Mean | SD | Total | Conventional treatment alone Mean | SD | Total | Weight | Std. Mean Difference IV, Random, 95% CI |
|---|---|---|---|---|---|---|---|---|
| **10.11.1 Butylphthalide** | | | | | | | | |
| Huang 2017 | -27.94 | 1.15 | 40 | -32.02 | 1.09 | 40 | 32.9% | 3.61 [2.88 , 4.33] |
| Liu 2021 | 62.33 | 12.02 | 46 | 56.13 | 10.24 | 46 | 33.9% | 0.55 [0.13 , 0.97] |
| Xu 2017 | -28.91 | 1.06 | 36 | -32.02 | 1.09 | 36 | 33.1% | 2.86 [2.19 , 3.53] |
| **Subtotal (Wald[a])** | | | **122** | | | **122** | **100.0%** | **2.32 [0.33 , 4.31]** |
| Test for overall effect: Z = 2.29 (P = 0.02) | | | | | | | | |
| Heterogeneity: Tau² (DL[b]) = 2.99; Chi² = 67.66, df = 2 (P < 0.00001); I² = 97% | | | | | | | | |
| **10.11.2 Donepezil** | | | | | | | | |
| Gao 2019 | -30.01 | 2.15 | 58 | -34.09 | 2.11 | 58 | 12.8% | 1.90 [1.46 , 2.34] |
| Guan 2019 | 67.16 | 4.7 | 46 | 58.21 | 4.49 | 46 | 12.4% | 1.93 [1.43 , 2.43] |
| Wang 2014a | -10.1 | 5.45 | 27 | -14.94 | 5.72 | 26 | 12.0% | 0.85 [0.29 , 1.42] |
| Wu 2021a | 60.8 | 8.7 | 49 | 56.1 | 7.7 | 49 | 13.0% | 0.57 [0.16 , 0.97] |
| Xu 2019a | 83.98 | 5.71 | 43 | 76.03 | 6.25 | 43 | 12.6% | 1.32 [0.85 , 1.78] |
| Yancheva 2009 | -3.03 | 4.61 | 31 | -3.81 | 5.54 | 32 | 12.5% | 0.15 [-0.34 , 0.65] |
| Yu 2014 | 61.3 | 6.72 | 35 | 53.8 | 6.55 | 35 | 12.4% | 1.12 [0.61 , 1.62] |
| Zheng 2020 | 64.2 | 6.88 | 50 | 50.21 | 5.29 | 50 | 12.4% | 2.26 [1.76 , 2.77] |
| **Subtotal (Wald[a])** | | | **339** | | | **339** | **100.0%** | **1.26 [0.75 , 1.77]** |
| Test for overall effect: Z = 4.85 (P < 0.00001) | | | | | | | | |
| Heterogeneity: Tau² (DL[b]) = 0.48; Chi² = 63.11, df = 7 (P < 0.00001); I² = 89% | | | | | | | | |
| **10.11.3 Memantine hydrochloride** | | | | | | | | |
| Kang 2020 | 67.02 | 9.27 | 43 | 61.25 | 8.04 | 49 | 50.5% | 0.66 [0.24 , 1.08] |
| Li 2017a | 82.87 | 4.02 | 39 | 67.85 | 3.48 | 36 | 49.5% | 3.94 [3.15 , 4.73] |
| **Subtotal (Wald[a])** | | | **82** | | | **85** | **100.0%** | **2.28 [-0.93 , 5.50]** |
| Test for overall effect: Z = 1.39 (P = 0.16) | | | | | | | | |
| Heterogeneity: Tau² (DL[b]) = 5.27; Chi² = 51.48, df = 1 (P < 0.00001); I² = 98% | | | | | | | | |
| Test for subgroup differences: Chi² = 1.36, df = 2 (P = 0.51), I² = 0% | | | | | | | | |




**Footnotes**

[a]CI calculated by Wald-type method.

[b]Tau² calculated by DerSimonian and Laird method.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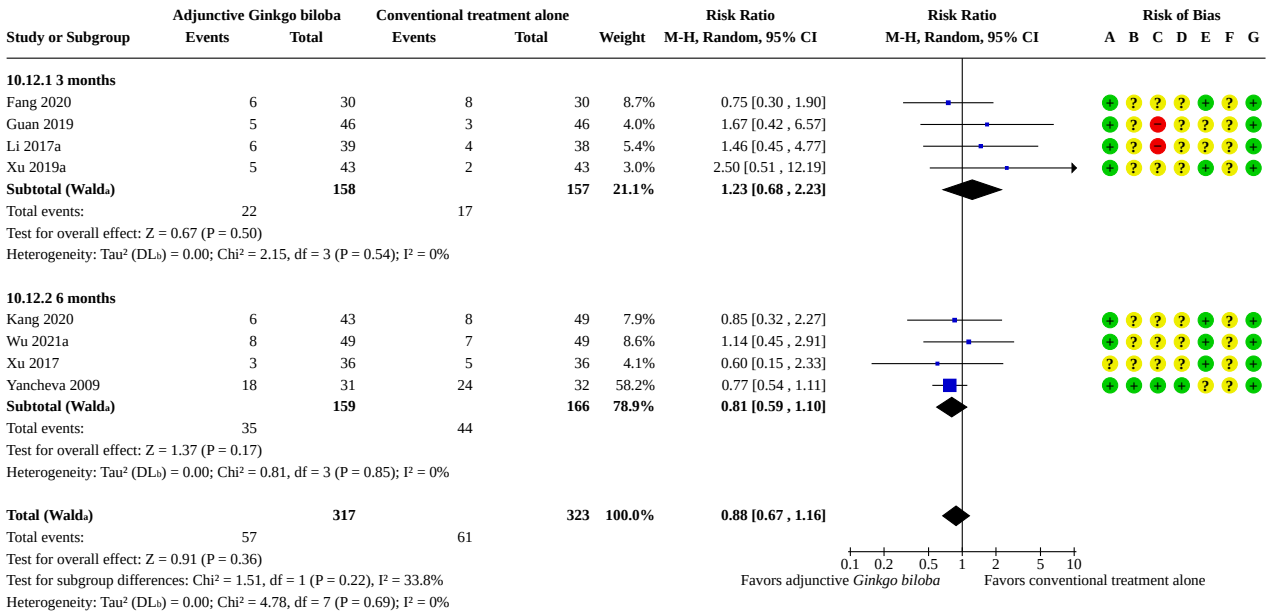
## Analysis 10.12. Comparison 10: Dementia: *Ginkgo biloba* added to conventional treatment, Outcome 12: Adverse events: all




**Footnotes**

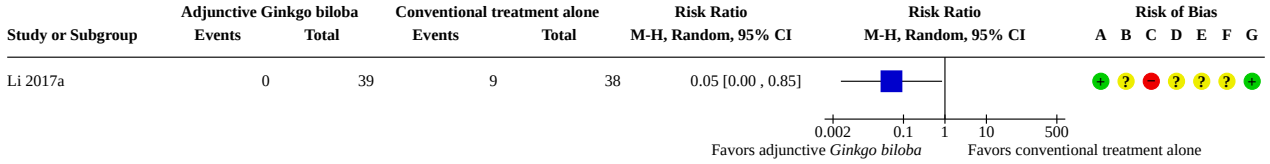
[a]CI calculated by Wald-type method.

[b]Tau² calculated by DerSimonian and Laird method.

**Risk of bias legend**

(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

## Analysis 10.13. Comparison 10: Dementia: *Ginkgo biloba* added to conventional treatment, Outcome 13: Adverse events: serious




**Risk of bias legend**

(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias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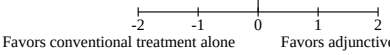
## Analysis 10.14. Comparison 10: Dementia: *Ginkgo biloba* added to conventional treatment, Outcome 14: Memory - 6 months

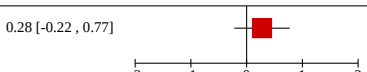
| Study or Subgroup | Adjunctive Ginkgo biloba Mean | SD | Total | Conventional treatment alone Mean | SD | Total | Mean Difference IV, Random, 95% CI | Mean Difference IV, Random, 95% CI | Risk of Bias A B C D E F G |
|---|---|---|---|---|---|---|---|---|---|
| Meng 2012 | 4.69 | 0.97 | 52 | 3.97 | 0.88 | 52 | 0.72 [0.36 , 1.08] | | + ? ? ? + ? + |




**Risk of bias legend**
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

## Analysis 10.15. Comparison 10: Dementia: *Ginkgo biloba* added to conventional treatment, Outcome 15: Executive function - 6 months

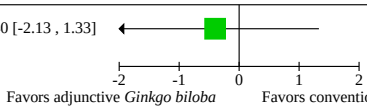
| Study or Subgroup | SMD | SE | Adjunctive Ginkgo biloba Total | Conventional treatment alone Total | Std. Mean Difference IV, Random, 95% CI | Std. Mean Difference IV, Random, 95% CI | Risk of Bias A B C D E F G |
|---|---|---|---|---|---|---|---|
| Yancheva 2009 | 0.2762 | 0.2533 | 31 | 32 | 0.28 [-0.22 , 0.77] | | + + + + ? ? + |




**Risk of bias legend**
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

## Analysis 10.16. Comparison 10: Dementia: *Ginkgo biloba* added to conventional treatment, Outcome 16: Neuropsychiatric outcomes: depression - 6 months

| Study or Subgroup | Adjunctive Ginkgo biloba Mean | SD | Total | Conventional treatment alone Mean | SD | Total | Mean Difference IV, Random, 95% CI | Mean Difference IV, Random, 95% CI | Risk of Bias A B C D E F G |
|---|---|---|---|---|---|---|---|---|---|
| Yancheva 2009 | -2.3 | 3.6 | 31 | -1.9 | 3.4 | 32 | -0.40 [-2.13 , 1.33] | | + + + + ? ? + |




**Risk of bias legend**
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias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## Analysis 10.17. Comparison 10: Dementia: *Ginkgo biloba* added to conventional treatment, Outcome 17: Neuropsychiatric outcomes: NPI - 3 months

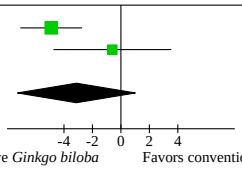
| Study or Subgroup | Adjunctive Ginkgo biloba Mean | SD | Total | Conventional treatment alone Mean | SD | Total | Mean Difference IV, Random, 95% CI | Mean Difference IV, Random, 95% CI | Risk of Bias A B C D E F G |
|---|---|---|---|---|---|---|---|---|---|
| Liu 2021 | 9.22 | 1.52 | 46 | 11.15 | 2.07 | 46 | -1.93 [-2.67 , -1.19] | | + ? ? ? + ? + |

Favors adjunctive *Ginkgo biloba* Favors conventional treatment alone

**Risk of bias legend**
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

## Analysis 10.18. Comparison 10: Dementia: *Ginkgo biloba* added to conventional treatment, Outcome 18: Neuropsychiatric outcomes: NPI - 6 months

| Study or Subgroup | Adjunctive Ginkgo biloba Mean | SD | Total | Conventional treatment alone Mean | SD | Total | Weight | Mean Difference IV, Random, 95% CI | Mean Difference IV, Random, 95% CI | Risk of Bias A B C D E F G |
|---|---|---|---|---|---|---|---|---|---|---|
| Wu 2021a | 25.3 | 6 | 49 | 30.2 | 4.9 | 49 | 58.7% | -4.90 [-7.07 , -2.73] | | + ? ? ? + ? + |
| Yancheva 2009 | -8.2 | 8.9 | 31 | -7.6 | 7.8 | 32 | 41.3% | -0.60 [-4.74 , 3.54] | | + + + + ? ? + |
| **Total (Wald[a])** | | | **80** | | | **81** | **100.0%** | **-3.13 [-7.27 , 1.02]** | | |




Favors adjunctive *Ginkgo biloba* Favors conventional treatment alone

Test for overall effect: Z = 1.48 (P = 0.14)

Heterogeneity: Tau² (DL[b]) = 6.40; Chi² = 3.25, df = 1 (P = 0.07); I² = 69%

**Footnotes**
[a]CI calculated by Wald-type method.
[b]Tau² calculated by DerSimonian and Laird method.

**Risk of bias legend**
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias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## ADDITIONAL TABLES

**Table 1. Summary characteristics of studies in people with subjective cognitive impairment**

| Study | Number of participants<br>Mean age<br>% female | Study duration | Participant diagnosis | Diagnostic criteria | *Ginkgo biloba* intervention | *G biloba* dose/day | Comparator(s) | Country<br>Setting<br>Additional interventions | Notes |
|---|---|---|---|---|---|---|---|---|---|
| Brautigam 1998 | n = 241<br>69 years<br>60.4% female | 6 months | Memory impairment with MMSE ≥ 20 | Self-reported memory or concentration complaint | Geriaforce | 5.7 mL and 2.85 mL doses | Placebo | The Netherlands<br>Outpatient<br>Participants stopped (wherever possible) any medication that might affect memory or concentration | — |
| EUC-TR2005-005765-11-EE | n = 296<br>54.5 years<br>76.4% female | 3 months | Subjectively perceived mental impairment present for at least 3 months | Ascertained by subjective complaints together with MMSE > 23 and no indication of dementia | EGb 761 | 240 mg | Placebo | Estonia<br>Outpatient<br>No indication of additional medications | — |
| Gessner 1985 | n = 60<br>NR<br>NR | 3 months | Symptoms of cerebral deterioration (not specified) | Self-reported | Tanakan (EGb 761) | 120 mg | 1. Placebo<br>2. Nicergoline | Germany<br>Community<br>Concomitant psychoactive medications not allowed during the study | No relevant data could be extracted |

**Abbreviations:** MMSE: Mini-Mental State Examination; n: number of participants; NR: not reported.

**Table 2. Summary characteristics of studies in people with multiple sclerosis and cognitive impairment**

| Study | Number of participants<br>Mean age<br>% female | Study duration | Diagnosis | Diagnostic criteria | *Ginkgo biloba* intervention | *G biloba* dose/day | Comparator(s) | Country<br>Setting<br>Additional interventions | Notes |
|---|---|---|---|---|---|---|---|---|---|



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**Table 2. Summary characteristics of studies in people with multiple sclerosis and cognitive impairment** *(Continued)*

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| Lovera 2007 | n = 43<br>49 years<br>69% | 3 months | MS with cognitive impairment | 0.5–2.5 SDs below mean on one or more of the CVLT-II or PASAT | Described as similar to EGb 761 | 240 mg | Placebo | USA<br>Outpatient/ community<br>Concomitant use of anticoagulants not allowed | — |
| Lovera 2012 | n = 121<br>52.1 years<br>55.5% | 3 months | MS with cognitive impairment | ≥ 1 SD below mean on one or more of the Stroop, CVLT-II COWAT, or PASAT | EGb 761 | 240 mg | Placebo | USA<br>Outpatient/ community<br>Participants were on drug treatments for MS (e.g. interferon) | — |

**Abbreviations:** CVLT-II: California Learning Verbal Test, 2nd edition; COWAT: Controlled Oral Word Association Test; MS: multiple sclerosis; n: number of participants; PASAT: Paced Auditory Serial Addition Test; SD: standard deviation.

**Table 3. Summary characteristics of studies in people with mild cognitive impairment**

| Study | Number of participants<br>Mean age<br>% female | Study duration | Diagnosis | Diagnostic criteria | *Ginkgo biloba* intervention(s) | *G biloba* dose/day | Comparator(s) | Setting; background interventions | Notes |
|---|---|---|---|---|---|---|---|---|---|
| Bu 2016 | n = 87<br>NR<br>NR | 3 months | VCIND | DSM-V | EGb 761 + basic treatment | 2.7 g | Basic treatment (aspirin, oral atorvastatin calcium, donepezil hydrochloride) | China<br>Inpatient<br>Basic drug treatments were standard and received by all participants | — |
| Demarin 2017 | n = 58<br>66.7 years<br>63.8% | 6 months | VCI | "VCI criteria based on cerebrovascular insufficiency and Folstein Mini-Mental State Examination (MMSE) score of >20 and <=28" | EGb 761 (2 dose arms) | 60 mg and 120 mg | Placebo | Croatia<br>Outpatient<br>Several drugs were in the exclusion criteria, but others were allowed, including "medications for cardiovascular conditions, | — |


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**Table 3. Summary characteristics of studies in people with mild cognitive impairment** *(Continued)*

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | | neurological conditions, and nonsteroidal anti-inflammatory drugs (except acetylsalicylic acid)". | |
| Deng 2021 | n = 58<br>65.1 years<br>39.7% | 3 months | Cognitive impairment after infarction | NR | *G biloba* leaves + donepezil | 57.6 mg | Donepezil | China<br>NR<br>NR | — |
| Dong 2011 | n = 113<br>73.1 years<br>64.4% | 12 months | MCI | MMSE, Global Deterioration Scale, maintains general function, ADL | EGb tablet (Si Tai Long [EGb 761]) + basic treatment | 240 mg | Basic treatment (general health education [adjust and treat old diseases], moderate exercise, body exercise, nutrition support) | China<br>Outpatient<br>It is possible that other diseases are treated with drugs, but not explicitly stated one way or the other. | — |
| Feng 2008 | n = 50<br>70.9 years<br>24% | 3 months | MCI | Guiding Principles for Clinical Research of New Drugs of Traditional Chinese Medicine and Diagnostic and Statistical Manual of Mental Disorders (version 3) | *G biloba* (Jiang Yin Tian Jiang Pharmaceuticals) [EGb 761] + Bu Shen Yi Nao placebo | 28.8 g [sic] | Bu Shen Yi Nao + placebo *G biloba* | China<br>NR<br>Other drug treatments not explicitly stated. | — |
| Gavrilova 2014 | n = 160<br>64 years<br>78.5% | 6 months | MCI | International consensus criteria (Winblad 2004) | EGb 761 | 240 mg | Placebo | Russia<br>Outpatient "psychotropic drugs" not allowed and any others not described. | Eligibility included a score of at least 6 on the 12-item NPI. |
| GEM 2010 | n = 482<br>79.7 years<br>49% | 60 months | MCI | The Modified Mini Mental State Examination (3MSE) administered to the partic- | EGb 761 | 240 mg | Placebo | USA<br>Outpatients | Unpublished data obtained |



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**Table 3. Summary characteristics of studies in people with mild cognitive impairment** *(Continued)*

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | | | ipant and Dementia Questionnaire (DQ) completed by proxy | | | | Warfarin (Coumadin), use of antipsychotic agents or treatment with tricyclic antidepressants not allowed. | from study authors. |
| Grass-Kapanke 2011 | n = 300<br>55 years<br>82.4% | 3 months | Very mild cognitive impairment | Subjective complaints and low functioning in at least one screening test but MMSE above 23 and no indication of dementia. | EGb 761 | 240 mg | Placebo | Latvia<br>Outpatient<br>"Patients were not allowed to take any psychoactive drugs, cognition-enhancing drugs or drugs acting on haemorrheology." | — |
| Gschwind 2017 | n = 50<br>68.5 years<br>50% | 12 months | MCI | International consensus criteria (Winblad 2004) and impaired executive function defined as a reduction in gait velocity of ≥ 10% during dual-task compared to single-task walking | LI 1370 (Symfona Forte) | 240 mg | Placebo | Switzerland<br>Outpatient<br>Treatment with antipsychotics or warfarin-like drugs not allowed | — |
| Gu 2017 | n = 124<br>59.9 years<br>40.3% | 6 months | MCI | Diagnostic criteria of the National Institute of Neurology, Speech Communication Disorders and Stroke/Alzheimer's Disease and Related Disorders | *G biloba* Tablets (Manufacturer: Beijing Wanhui Double Crane Pharmaceutical Co, Ltd) [EGb 761] + nimodipine | NR | Nimodipine | China<br>Outpatient<br>Taking cholinergic or anticholinergic drugs or other drugs with adverse effects on cognitive function was not allowed. | — |
| Halama 1988 | n = 40<br>65.9 years<br>42.5% | 3 months | Cerebral insufficiency of vascular origin | Basis of the clinical findings and the results of the psychometric tests carried out and scale assessments (Hachinski:> 7, Crichton: levels 1 to 3) | EGb 761 (Tebonin forte) | 120 mg | Placebo | Germany<br>Outpatient<br>Treatment with psychotropic drugs or nootropics was not allowed. | — |

**Table 3. Summary characteristics of studies in people with mild cognitive impairment** *(Continued)*

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| He 2005 | n = 43<br>71.8 years<br>30.3% | 3 months | MCI | Chief complaint of memory loss and evidence of MCI on basis of clinical examination including MMSE score ≥ 24 but insufficient damage to diagnose dementia | *G biloba* capsules (produced by Beijing Shuguang Pharmaceutical Co, Ltd) + placebo Jianpi Tianjing | 2400 mg | Jianpi Tianjing + placebo *G biloba* | China<br>Inpatient<br>No mention of included or excluded co-interventions | No relevant data could be extracted. Study affirmatively stated that there were no adverse events. |
| Han 2016 | n = 120<br>72 years<br>65.9% | 12 months | MCI | MCI International Working Group 2004 Diagnostic Criteria | EGb Tablet (trade name: Si Tai Long, manufacturer: Shanghai Xingling Technology Pharmaceutical Co, Ltd) [EGb 761] + basic treatment | 240 mg | Basic treatment (health publicity and education, walking, handball and other sports, nutrition support) | China<br>Outpatient<br>It is possible that other diseases are treated with drugs, but not explicitly stated one way or the other. | — |
| He 2016 | n = 150<br>67.7 years<br>39.3% | 3 months | VCI | Clinical diagnostic criteria for VCI established by Rockwood | 1. *G biloba* extract tablets<br>2. *G biloba* extract tablets + donepezil | 6 tablets (mg NR) | Donepezil | China<br>Inpatient<br>No mention of excluded interventions | — |
| He 2018a | n = 84<br>65.6 years<br>39.3% | 3 months | Cognitive dysfunction after cerebral infarction | NR | EGb Tablet (Jiangsu Chenpai Pharmaceutical Group Co, Ltd) [EGb 761] + donepezil | NR | Donepezil | China<br>Inpatient<br>Mention that cholinesterase inhibitors must not have been used recently | — |
| He 2018b | n = 96<br>65.5 years<br>41.7% | 3 months | Cognitive impairment due to CSVD (cerebral | MRI, ultrasound, MMSE, MoCA | Ginkgo Leaf capsules (Hangzhou KangEnBei Pharmaceutical Co, Ltd) | NR | Nimodipine | China<br>Inpatient<br>No mention of included or excluded co-interventions | — |


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**Table 3. Summary characteristics of studies in people with mild cognitive impairment** *(Continued)*

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | | small vessel disease) | | [EGb 761] + nimodipine | | | | |
| Israel 1987 | n = 80<br>NR<br>NR | 3 months | Age-related memory impairment | MMSE score 20–26 | EGb 761 (Tanaken®) | 160 mg | Placebo | France<br>Outpatient<br>No mention of included or excluded co-interventions | No relevant data could be extracted |
| Jiang 2018 | n = 68<br>NR<br>NR | 6 months | VCIND | Referred to the diagnostic criteria of VCIND developed by Ingles and colleagues, and combined with the suggestions of domestic expert Jia Jianping, the following criteria were formulated: cerebrovascular disease or risk factors of cerebrovascular disease; fluctuating course of cognitive impairment; no damage or less damage to memory. | Ginkgo ketone ester tablet (Shanghai Shangyao Xingling Technology Pharmaceutical Co, Ltd) [EGb 761] + basic treatment | NR | Placebo + basic treatment (The basic treatment measures for vascular risk factor: 1. people with cerebral infarction to receive antiplatelet aggregation drugs; 2. people with hypertension were treated with calcium antagonists, beta receptor inhibitors, angiotensin converting enzyme inhibitors, angiotensin Ⅱ receptor blockers and other drugs; 3. people with diabetes | China<br>Inpatient and outpatient<br>Participants received concomitant treatments according to their diagnoses (cerebral infarction, hypertension, diabetes, hyperlipidemia). No specification of excluded therapies. | — |


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**Table 3. Summary characteristics of studies in people with mild cognitive impairment** *(Continued)*

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | were treated with insulin secretants, biguanides, α-glucosidase inhibitors, insulin sensitizers, insulin and other drugs); 4. people with hyperlipidemia should be treated with statins or beta blockers. | | |
| Li 2013a | n = 69<br>72 years<br>56.5% | 3 months | MCI | MMSE score 24–27 points, General Decline Scale was 2–3, general functions are still maintained. Difficulty in daily living may increase. ADL score < 26. | *G biloba* leaves (Ekangning) [EGb 761] + basic treatment | NR | Basic treatment (allopurinol and moderate exercise) | China<br>Inpatient<br>Participants received allopurinol as part of basic treatment. | — |
| Li 2015a | n = 120<br>71.9 years<br>44.4% | 6 months | VCIND | The 4th National Conference on Cerebrovascular Diseases | Ginkgo leaves (Guizhou Xinbang Pharmaceutical) [EGb 761] + nimodipine | 58 mg | Nimodipine | China<br>Inpatient<br>No mention of included or excluded co-interventions | — |
| Li 2016a | n = 80<br>66.4 years<br>52.5% | 6 months | Cognitive dysfunction | NR | *G biloba* leaf extract (Dr Willmar Schwabe GmbH & Co) [EGb 761] + donepezil | 80 mg | Donepezil | China<br>Inpatient and outpatient<br>No mention of included or excluded co-interventions | — |


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**Table 3. Summary characteristics of studies in people with mild cognitive impairment** *(Continued)*

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| Li 2019a | n = 56<br>74.4 years<br>37.5% | 6 months | MCI | Diagnostic criteria of vascular cognitive impairment | EGb tablet (Yangzijiang Pharmaceutical Group Co, Ltd) [EGb 761] + basic treatment | NR | Basic treatment (lipid-lowering, antiplatelet and neurotrophic processes) | China<br>Inpatient<br>Participants received additional drug treatments that are not specified and appear to be individualized. | — |
| Liu 2015a | n = 100<br>71.7 years<br>44% | 9 months | MCI | Guidelines for the Diagnosis and Treatment of Dementia and Cognitive Disorders in China | Ginkgo leaves tablet [EGb 761] + donepezil | NR | Donepezil | China<br>Outpatient<br>Use of drugs affecting brain function not allowed | — |
| Moreau 1975 | n = 60<br>84 years<br>92% | 3 months | NR | NR | Ipsen 225 (Tanaken®)[EGb 761] | 120 mg | Placebo | France<br>NR<br>No mention of included or excluded co-interventions | No relevant data could be extracted. |
| Qu 2020 | n = 94<br>63.1 years<br>41.5% | 4 months (follow-up to 6 months) | Cognitive impairment caused by cerebral small vessel disease | Clinical criteria (not specified) | Ginkgo Leaf Capsules (Shanghai Xinyi Paluda Pharmaceutical Co, Ltd, Z20010169) [EGb 761] | 28.8 mg | Mecobalamin | China<br>Inpatient<br>No mention of included or excluded co-interventions | — |
| Rai 1991 | n = 31<br>76.1 years<br>73.5% | 6 months | Mild to moderate memory impairment of organic origin | NINCDS-ADRDA | EGb 761 (Tanakan®) | 120 mg | Placebo | UK<br>Outpatient<br>Participants not allowed to take drugs acting on cerebral metabolism or cerebral blood flow | No relevant data could be extracted. |
| Shi 2017 | n = 60<br>74.5 years<br>41.7% | 6 months | VCIND | CT/ MRI, Guidelines for diagnosis and treatment of vascular cognitive impairment (Chi- | *G biloba* leaves (Tanakang) [EGb 761] + basic treatment | 120 mg | Basic treatment (individualized antiplatelet, lipid-low- | China<br>Inpatient<br>Use of sedatives, antianxiety drugs, hypnotics, | — |



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**Table 3. Summary characteristics of studies in people with mild cognitive impairment** *(Continued)*

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | | | nese Medical Association published in 2011) | | | ering and nerve nutrition treatments) | nootropics and choline mimics was not allowed | |
| Tan 2016 | n = 120<br>62.7 years<br>32.5% | 6 months | VCIND | CT, MRI | Ginkgo leaf dripping pills (Zhejiang Wanbang Pharmaceutical) [EGb 761] | 900 mg | 1. Nimodipine<br>2. Compound xueshuantong capsule | China<br>Inpatient<br>No mention of included or excluded co-interventions | — |
| Tian 2019 | n = 350<br>63.7 years<br>53.5% | 12 months | Amnestic MCI | Memory complaints and abnormal memory function on the Adult Memory and Information Processing Battery Logical Memory Delayed Story Recall together with MMSE of 24 or greater and normal general cognitive function and activities of daily living | EGb 761 (Ginaton) | 160 mg | 1. Placebo<br>2. Qinggongshoutao | China<br>Outpatient<br>Concomitant use of drugs that might interfere with cognition (e.g. cholinergic agents) was not allowed. | — |
| van Dongen 2000 | n = 214<br>83 years<br>85% | 6 months | 1. AD, VD, or a mixed type of dementia; or 2. AAMI | Uncomplicated dementia (according to the DSM-III-R and ICD-10 criteria) or AAMI (according to Crook et al criteria) | EGb 761 (2different doses) | 160 mg and 240 mg | Placebo | The Netherlands<br>Nursing homes<br>Concomitant use of drugs with potential cognitive effects (e.g. cholinergics) was not allowed. | — |
| Vesper 1994 | n = 90<br>62.3 years<br>54.5% | 3 months | Cerebral insufficiency | ICD-290 | LI 1370 | 150 mg | Placebo | Germany<br>Outpatient<br>No mention of included or excluded co-interventions | No relevant data could be extracted. |
| Wang 2020a | n = 92<br>57 years | 3 months | VCIND | Diagnostic criteria referred to the "Guidelines for the Diagnosis | *G biloba* soft capsule (Luoyang Junshan | 3 g | Piracetam | China<br>Inpatient | — |


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**Table 3. Summary characteristics of studies in people with mild cognitive impairment** *(Continued)*

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | 37% | | | and Treatment of Vascular Cognitive Impairment". | Pharmaceutical Co, Ltd) [EGb 761] + piracetam | | | No mention of included or excluded co-interventions | |
| Wang 2004 | n = 44<br>65.9 years<br>65.9% | 3 months | MCI | Brain CT, MCI diagnosis developed by Peterson 1999 | *G biloba* capsules [EGb 761] | 28.8 g [sic] | Jiawei Wuzi Yanzong Particle | China<br>Community<br>No mention of included or excluded co-interventions | — |
| Xia 2013 | n = 245<br>63.9 years<br>49.8% | 12 months | MCI | DSM-IV | *G biloba* extract (Tanakang) [EGb 761] + basic treatment | 120 mg | Basic treatment (levodopa, nimodipine, general health education, moderate exercise, limb movement, nutritional support, etc. blood pressure reduction, reduced blood sugar, and antiplatelet therapy (aspirin or clopidogrel)) | China<br>Inpatient<br>Participants received individualized antiplatelet, lipid-lowering and nerve nutrition treatments, but use of sedatives, anti-anxiety drugs, hypnotics, nootropics, and choline mimics was not allowed. | — |
| Xu 2021 | n = 102<br>55.8 years<br>35.3% | 3 months | VCIND | NR | *G biloba* leaves (Hunan Huana Pharmaceutical Co, Ltd, Z20043061) [EGb 761] + oxiracetam | 240 mg | Oxiracetam | China<br>Inpatient<br>No mention of included or excluded co-interventions | — |
| Yang 2020a | n = 102 | 3 months | Vascular MCI | Matched with the curative effect standard | Yinxing Tongzhi tablets (SPH | 0.45 g | Butylphthalide | China | — |



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**Table 3. Summary characteristics of studies in people with mild cognitive impairment** *(Continued)*

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | 57.1 years<br>37.3% | | | of Chinese Guidelines for "Diagnosis and Treatment of Vascular Cognitive Impairment (2016)", there were cerebrovascular risky factors or cerebrovascular diseases. | Xing Ling Sci. & Tech Pharmaceutical Co, Ltd) [EGb 761] + butylphthalide | | | Outpatient<br>No mention of included or excluded co-interventions | |
| Yang 2015a | n = 66<br>58.9 years<br>37.9% | 3 months | Cognitive impairment with stroke | Diagnostic criteria NR | Oral Ginkgo leaf not described in detail | 120 mg | Yi Zhi Ling | China<br>Inpatient<br>No mention of included or excluded co-interventions | — |
| Yu 2021 | n = 46<br>60.8 years<br>54.3% | 3 months | Cerebral small vessel disease and cognitive impairment | Cerebral small vessel disease diagnosed by brain CT and MRI, diagnostic criteria for cognitive impairment NR | *G biloba* extract tablets (Dr Weimar Shupei Pharmaceutical Factory, Germany) [EGb 761] | 120 mg | Butylphthalide | China<br>Inpatient<br>No mention of included or excluded co-interventions | — |
| Zhang 2022 | n = 96<br>70 years<br>54% | 6 months | Vascular MCI | DSM-V and the guidelines of the American Heart Association/American Stroke Association | Ginkgo extract tablets (Yangzijiang Pharmaceutical Group Co, Ltd) + Guilingji capsule | 57.6 mg | Guilingji capsules | China<br>Inpatient and outpatient<br>People excluded for recent use (within 3 months) of drugs that may affect cognitive function | — |
| Zhang 2019a | n = 72<br>52.1 years<br>38.9% | 3 months | Cognitive impairment after cerebral infarction | Diagnosed as cerebral infarction using brain CT or MRI. According to the standard of "Guidelines for the Treatment of Cerebral Cognitive Impairment" in 2011, participants were diagnosed with cognitive impairment after cerebral infarction. | *G biloba* (Zhejiang Conba Pharmaceutical Co, Ltd) [EGb 761] + donepezil | NR | Donepezil | China<br>Inpatient<br>No mention of included or excluded co-interventions | — |


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**Table 3. Summary characteristics of studies in people with mild cognitive impairment** *(Continued)*

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| Zhao 2020 | n = 100<br>NR<br>53% | 12 months | mVCI | mVCI diagnostic criteria set by the International Society for Vascular Behavioral and Cognitive Disorders in 2014 | EGb 761 injection for 14 days, and then EGb 761 tablet + routine therapy | 87.5 mg for 14 days and then 120 mg for 11.5 months | Routine therapy | China<br>Inpatient<br>No mention of excluded co-interventions | — |
| Zheng 2021 | n = 60<br>62.5 years<br>49% | 3 months | MCI | Standards formulated by the International MCI Working Group and the European Alzheimer's Disease MCI Working Group | *G biloba* extract drops [EGb 761] | 6 mL | Fu Xiu Qi Zhi Acupuncture | China<br>Outpatient<br>Use of antipsychotic drugs or any drugs used to improve cognitive function were excluded. | — |

**Abbreviations:** AAMI: age-associated memory impairment; ADL: activities of daily living; CT: computed tomography; DSM-III: *Diagnostic and Statistical Manual of Mental Disorders*, Third Edition; DSM-IV: *Diagnostic and Statistical Manual of Mental Disorders*, Fourth Edition; DSM-V: *Diagnostic and Statistical Manual of Mental Disorders*, Fifth Edition; ICD-10: International Classification of Diseases, 10th Revision; ICD-290: International Classification of Diseases code 290: Dementias; MCI: Mild cognitive impairment; MMSE: Mini Mental State Examination; MoCA: Montreal Cognitive Assessment; MRI: magnetic resonance imaging; mVCI: mild vascular cognitive impairment; n: number of participants; NINCDS-ADRDA: National Institute of Neurological and Communicative Diseases and Stroke/Alzheimer's Disease and Related Disorders Association; NPI: neuropsychiatric inventory; NR: not reported; VCI: vascular cognitive impairment; VCIND: vascular cognitive impairment, no dementia.

**Table 4. Summary characteristics of studies in people with dementia**

| Study | Number of participants<br>Mean age<br>% female | Study duration | Diagnosis | Diagnostic criteria | *Ginkgo biloba* intervention(s) | *G biloba* dose/day | Comparator(s) | Setting, background, interventions | Notes |
|---|---|---|---|---|---|---|---|---|---|
| Chen 2014a | n = 96<br>Range 49–94 years<br>45.8% | 3 months | VD | DSM-IV, the diagnostic criteria of dementia and the diagnostic criteria of dementia in the Internal Medicine of Traditional Chinese Medicine | Ginkgo Dispersible Tablets (Shenyang Gelin Pharmaceutical Co, Ltd) [EGb 761] | 1500 mg | Chinese herbal decoction (Yinyanghuo [Epimedii Folium], Nuzhenzi [Ligustri Lucidi Fructus], Gouqizi | China<br>Outpatient<br>No mention of included or excluded other treatments | — |



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**Table 4. Summary characteristics of studies in people with dementia** *(Continued)*

| | | | | | | | | | |
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| | | | | | | | [Lycii Fructus], Zhiheshouwu [Polygoni Multiflori Radix Praeparata], Tusizi [Cuscutae Semen], Huangjing [Polygonati Rhizoma], Huangqi [Astragali Radix], Danggui [Angelicae Sinensis Radix], Danshen [Sal Viae Miltiorrhizae Radix et Rhizoma], Shanzha [Crataegi Fructus]) | | |
| DIGGER 2008 | n = 176<br>79.5 years<br>60.8% | 6 months | Dementia | Clinical diagnosis of referring physician | EGb 761 | 120 mg | Placebo | UK<br>Outpatient<br>Participants were not allowed to begin treatment with AChI but were allowed to remain on treatment and 33% of participants were on AChI. | — |
| Dong 2021 | n = 74<br>65.8 years<br>28% | 6 months | VD | Clinical symptoms | *G biloba* capsules (Guilin Honghui Pharmaceutical Co.) [EGb 761] | 1.5 g | Idebenone | China<br>Inpatient | — |


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**Table 4. Summary characteristics of studies in people with dementia** *(Continued)*

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| | | | | | | | | No mention of included or excluded co-interventions | |
| Fang 2020 | n = 60<br>63.56 years<br>41.7% | 3 months | VD | DSM. TCM syndrome differentiation criteria was also used. | *G biloba* leaves (Nanjing Yiheng Pharmaceutical Co, Ltd, Z20063958) [EGb 761] + citicoline sodium tablets | NR | Citicoline sodium tablets | China<br>Inpatient<br>Other treatment was not allowed and, if present, it was washed out prior to starting the trial | — |
| Gao 2019 | n = 116<br>70.8 years<br>49.1% | 9 months | AD | *Guidelines for the diagnosis and treatment of dementia in China* | *G biloba* extract tablets (Dr. Willmar Schwabe GmbH & Co.) [EGb 761] + Donepezil | 160 mg | Donepezil | China<br>Inpatient<br>No mention of included or excluded co-interventions | — |
| GIN-DEM-NP 2005 | n = 400<br>64 years<br>72% | 5.5 months | Probable AD, possible AD with CVD, or probable VD | Probable AD criteria were NINCDS/ADRDA, possible AD with CVD were NINCDS/ADRDA and NINDS/AIREN, probable VD was NINDS/AIREN | EGb 761 | 240 mg | Placebo | Ukraine<br>Outpatient<br>"Treatment with other anti-dementia drugs, cognitive enhancers, cholinergic, anti-cholinergic or haemorheologically active drugs [...] was prohibited." | Inclusion criteria included score of at least 5 on the 12-item NPI. |
| GOTADAY 2011 | n = 410<br>65 years<br>67.5% | 6 months | Possible or probable AD or probable VD | NINCDS-ADRDA criteria for probable AD, NINDS-AIREN criteria for possible AD with CVD, and NINDS-AIREN criteria for probable VD | EGb 761 | 240 mg | Placebo | Ukraine<br>Outpatient<br>"Treatment with other anti-dementia drugs, cognitive enhancers, cholinergic, anti-cholinergic or haemorheologically active drugs [...] was prohibited." | Inclusion criteria included score of at least 5 on the 12-item NPI. |
| GOT IT 2012 | n = 410<br>65 years<br>69.4% | 6 months | Mild to moderate AD/VD | NINCDS-ADRDA criteria for probable AD, NINDS-AIREN criteria for possible AD with CVD, and | EGb 761 | 240 mg | Placebo | Russian Federation, Republic of Belarus, Republic of Moldova<br>Outpatient | Inclusion criteria included score of at least 6 |

**Table 4. Summary characteristics of studies in people with dementia** *(Continued)*

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| | | | | NINDS-AIREN criteria for VD | | | | "Treatment with other anti-dementia drugs, cognitive enhancers, cholinergic, anti-cholinergic or haemorheologically active drugs [...] was prohibited." | on the 12-item NPI. |
| Guan 2019 | n = 92<br>63.8 years<br>34.8% | 3 months | VD | NR | *G biloba* leaf extract injection (Yuekang Pharmaceutical Group Co, Ltd) [EGb 761] + donepezil | 40 mL | Donepezil | China<br>Inpatient<br>"[...] two groups were given interventions such as anti-platelet accumulation and lowering blood lipid, etc." | — |
| Halama 1991a | n = 42<br>61 years<br>65% | 3 months | Presenile, simple senile or arteriosclerotic dementia | NR | LI 1370 | 150 mg | Placebo | Germany<br>Outpatient<br>Treatment with psychotropic drugs or nootropics was not allowed. | — |
| Huang 2017 | n = 80<br>70 years<br>46.3% | 6 months | AD | DSM | EGb extract tablets (German Dr Willmar Schwabe GmbH & Co) [EGb 761] + butylphthalide | 160 mg | Butylphthalide | China<br>Inpatient<br>Relevant therapeutic drugs not allowed | — |
| Ji 2020 | n = 60<br>NR<br>41% | 3 months | AD | Chinese Medical Association diagnostic criteria from 1989 | *G biloba* leaf tablet (Nanjing Yiheng Pharmaceutical Co, Ltd) [EGb 761] | Unclear | Donepezil | China<br>Inpatient<br>Anticoagulant therapy not allowed | No relevant data could be extracted. |
| Kang 2020 | n = 92<br>69.5 years<br>59.8% | 6 months | AD | Alzheimer's disease criteria from Shaw LM, Arias J, Blennow K, et al (2018) | *G biloba* tablets (Dr. Willmar Schwabe GmbH & Co.)[EGb 761] + memantine hydrochloride | 2.4 mg | Memantine hydrochloride | China<br>Inpatient | — |


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**Table 4. Summary characteristics of studies in people with dementia** *(Continued)*

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| | | | | | | | | Nootropic drug treatment during the trial or the previous 2 weeks was not allowed. | |
| Kanowski 1996 | n = 222<br>72 years<br>69.5% | 6 months | AD or MID (multi-infarct dementia) of mild–moderate severity | DSM-III-R criteria | EGb 761 | 240 mg | Placebo | Germany<br>Outpatient<br>"[...] drugs which might have interfered with the assessment of efficacy, such as psychostimulants, nootropics, centrally acting vasoactive substances, psychotropic substances, and reserpine" were not allowed. | — |
| Le Bars 1997 | n = 327<br>69 years<br>53.5% | 12 months | Uncomplicated AD or MID | DSM-III-R and ICD-10 criteria | EGb 761 (Tebonin forte) | 120 mg | Placebo | USA<br>Outpatient<br>"[...] change in regimen or prescription of new concomitant medications known to affect cognitive function was not permitted during the study." No description of concomitant medications actually received. | — |
| Li 2017a | n = 77<br>74.1 years<br>46.1% | 3 months | AD | DSM-IV | Shuxuening injection (Beijing China Resources High-tech Natural Medicine Co, Ltd) [EGb 761] + memantine hydrochloride | 20 mL | Memantine hydrochloride | China<br>Inpatient<br>No mention of included or excluded co-interventions | — |
| Liao 2017a | n = 100<br>68.8 years<br>59% | 3 months | AD | ICD-10 | *G biloba* extract tablets [EGb 761] | NR | Acupuncture + cognitive rehabilitation | China<br>Inpatient<br>No mention of included or excluded co-interventions | — |



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**Table 4. Summary characteristics of studies in people with dementia** *(Continued)*

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| Liu 2021 | n = 92<br>72.5 years<br>41% | 3 months | VD | DSM-IV | *G biloba* extract injection (Taiwan ZhongHao International Co, Ltd) [EGb 761] + butylphthalide | 20 mL/time + 0.9% sodium chloride solution 500 mL/time intravenous drip treatment, 2 times/day, 10 days as a treatment cycle, stop the drug for 5 days after 1 cycle of treatment and then start the next cycle of treatment for 3 months | Butylphthalide | China<br>Inpatient<br>No mention of included or excluded co-interventions | — |
| Ma 2015 | n = 132<br>60.1 years<br>47% | 3 months | VD | NR | *G biloba* tablet + basic treatment | NR | Basic treatment (routine therapy to control against blood glucose, blood pressure, coronary heart disease, and anemia; participants also took 3 | China<br>Outpatient<br>In addition to Piracetam, participants appeared to receive concomitant drug treatments according to their diagnoses. | No relevant data could be extracted. |

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**Table 4. Summary characteristics of studies in people with dementia** *(Continued)*

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| | | | | | | | piracetam tablets per time, 3 times per day) | | |
| Maurer 1997 | n = 20<br>64.6 years<br>50% | 3 months | Mild to moderate AD | DSM-III-R and NINCDS/ADRDA criteria | EGb 761 (Tebonin forte) | 240 mg | Placebo | Germany<br>Outpatient<br>Treatment with vasoactive drugs or nootropics not allowed | — |
| Mazza 2006 | n = 76<br>66.9 years<br>53.7% | 6 months | Primary degenerative dementia of the Alzheimer type | DSM-IV | EGb 761 | 160 mg | 1. Placebo<br>2. Donepezil | Italy<br>Outpatient<br>"Vasoactive drugs, nootropics and long-term treatment with other drugs were proscribed during the study, with the exception of low doses of benzodiazepines and neuroleptics in the treatment of behavioral disturbances." | — |
| Meng 2012 | n = 104<br>68.2 years<br>41.3% | 6 months | VD | Diagnostic criteria of DSM-3, MMSE score was 12–24. | EGb tablet [EGb 761] + piracetam | NR | Piracetam | China<br>Outpatient<br>No mention of included or excluded co-interventions | — |
| PLAGIN 2013 | n = 408<br>NR<br>NR | 5.5 months | Probable AD, possible AD with CVD, or probable VD | NINCDS/ADRDA and NINDS/AIREN | EGb 761 | 240 mg | Placebo | Bulgaria<br>Outpatient<br>"[...] treatment with other anti-dementia drugs, cognitive enhancers, cholinergic, anti-cholinergic or haemorheologically active drugs [...] was prohibited." | Inclusion criteria included score of at least 5 on the 12-item NPI. Trial was described as "[i]dentical to the GIN- |

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**Table 4. Summary characteristics of studies in people with dementia** *(Continued)*

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| | | | | | | | | | DEM-NP Study<br><br>with respect to patient selection, study design and treatment." |
| Oswald 1997 | n = 226<br><br>71 years<br><br>64% | 3 months | Mild to moderate organic brain syndrome | DSM-III, ICD-9 | EGb 761 | 120 mg | Placebo | Germany<br><br>Outpatient<br><br>Participants not allowed to take antidepressants, neuroleptics, blood-circulating enhancing medications or other nootropics | No relevant data could be extracted. |
| Schneider 2005 | n = 513<br><br>78.1 years<br><br>53% | 6.5 months | AD | DSM-IV, NINCDS-ADRDA | EGb 761 (2 different doses) | 120 mg and 240 mg | Placebo | USA<br><br>Outpatient<br><br>Antidementia or psychoactive drugs not allowed | — |
| Wang 2014a | n = 53<br><br>NR<br><br>NR | 6 months | AD | NR | Ginaton injection for 2 weeks, then *G biloba* tablet [EGb 761] + donepezil | 87.5 mg Ginaton; Ginkgo tablet dose NR | Donepezil | China<br><br>Inpatient<br><br>"Other treatments of the two groups of patients are the same, including oral Nimotop and intravenous infusion of piracetam and so on." | — |
| Wesnes 1987 | n = 58<br><br>71 years<br><br>37% | 3 months | Mild dementia | Crichton Behavioural Scale ≥ 14 | Tanakan (EGb 761) | 120 mg | Placebo | UK<br><br>Outpatient<br><br>Psychotropic drugs, centrally-acting hypertensives, drugs for Parkinson's disease, anticoagulants or antiplatelet aggre- | — |



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**Table 4. Summary characteristics of studies in people with dementia** *(Continued)*

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| | | | | | | | | gating agents, and central nervous system stimulants were not permitted during the trial. | |
| Wu 2021a | n = 98<br>67.4 years<br>45.9% | 6 months | AD | NIA-AA diagnostic criteria released in 2011 | *G biloba* leaves (Yangzijiang Pharmaceutical Group Co, Ltd.) [EGb 761] + donepezil | 28.8 mg | Donepezil | China<br>Inpatient<br>No mention of included or excluded co-interventions | — |
| Wu 2017 | n = 64<br>65.5 years<br>56.3% | 3 months | Mild or moderate VD | TCM syndrome differentiation is qi deficiency, blood stasis, and liver-yang disturbance. | Ginkgo leaves [EGb 761] | NR | Shenma Yizhi Recipe | China<br>Inpatient and community<br>Other nootropic drugs not allowed | — |
| Xu 2017 | n = 72<br>69.1 years<br>45.8% | 6 months | AD | *Chinese Guidelines for the Diagnosis and Treatment of Alzheimer's Disease and Other Dementias*, traditional Chinese medicine diagnostic criteria "yin deficiency in liver and kidney, dampness of blood and phlegm block Qi and Blood Meridian" in *Guidelines of clinical research on new drugs of traditional Chinese medicine*. | *G biloba* Extract Tablets (Dr. Willmar Schwabe GmbH & Co) [EGb 761] + butylphthalide | 160 mg | Butylphthalide | China<br>Inpatient<br>Use of relevant therapeutic drugs not allowed | — |
| Xu 2019a | n = 86<br>64 years<br>36.4% | 3 months | VD | Draft Diagnostic Criteria for Vascular Dementia | Ginkgo tablet (Yangzijiang Pharmaceutical Group Co, Ltd) [EGb 761] + donepezil | 57.6 mg | Donepezil | China<br>Inpatient<br>"[...] both groups gave treatment for primary disease" | — |



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**Table 4. Summary characteristics of studies in people with dementia** *(Continued)*

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| Yancheva 2009 | n = 96<br>67.6 years<br>68.8% | 5.5 months | Probable AD | NINCDS-ADRDA criteria | 1. EGb761<br>2. EGb 761 + donepezil | 240 mg | Donepezil | Bulgaria<br>Outpatient<br>"[...] other anti-dementia drugs, cognition enhancers, drugs with cholinergic or strong anti-cholinergic effects, haemorrheologically active substances or anti-Parkinson drugs were prohibited." | Inclusion criteria included score of at least 5 on the 12-item NPI |
| Yu 2014 | n = 70<br>62.7 years<br>54.3% | 3 months | VD | DSM-IV, DSVD | *G biloba* intravenous injection [EGb 761] + donepezil | 40 mL | Donepezil | China<br>Inpatient<br>No mention of included or excluded co-interventions | — |
| Zhang 2016a | n = 120<br>64.7 years<br>35% | 3 months | Cognitive impairment meeting dementia diagnostic standards | Diagnostic Standards of Chinese Medicine for dementia based on *Guiding Principles for Clinical Research of New Chinese Medicines* published in 1993. Western medicine diagnostic standards are based on the *Standards for Diagnosis and Evaluation of Alzheimer's Disease* proposed by the First National Geriatrics Conference in Lanzhou in 1988. | *G biloba* tablets (Shijiazhuang Yiling Pharmaceutical Co, Ltd) [EGb 761] | NR | Tongxinluo capsule | China<br>Inpatient<br>No mention of included or excluded co-interventions | — |
| Zheng 2020 | n = 100<br>63.1 years<br>47% | 3 months | Mild or moderate VD | American Academy of Neurology *Diagnostic and Statistical Manual of Mental Disorders*, *Vascular Dementia* | Ginkgo ketone ester dropping pills + donepezil | Ginkgo ketone ester 120 mg | Donepezil | China<br>Inpatient and outpatient<br>No mention of included or excluded co-interventions | — |



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**Table 4. Summary characteristics of studies in people with dementia** *(Continued)*

| | | |
|---|---|---|
| | | *Syndrome Differentiation Scale*, CDR shows people with mild to moderate dementia. |

**Abbreviations:** ACHI: acetylcholinesterase inhibitors; AD: Alzheimer's disease; CDR: Clinical Dementia Rating; CVD: cardiovascular disease; DSM: *Diagnostic and Statistical Manual of Mental Disorders*; DSM-3: *Diagnostic and Statistical Manual of Mental Disorders*, Third Edition; DSM-III-R: *Diagnostic and Statistical Manual of Mental Disorders*, Third Edition, revised; DSM-IV: *Diagnostic and Statistical Manual of Mental Disorders*, Fourth Edition; DSVD: Vascular Dementia Scale; ICD-9: International Classification of Diseases, Ninth Revision; ICD-10: International Statistical Classification of Diseases, 10th Revision; MMSE: Mini Mental State Examination; NIA-AA: National Institute on Aging – Alzheimer's Association; NINCDS/ADRDA: National Institute of Neurological and Communicative Diseases and Stroke/Alzheimer's Disease and Related Disorders Association; NINDS/AIREN: National Institute of Neurological Disorders and Stroke/Association Internationale pour la Recherche et l'Enseignement en Neurosciences; NPI: Neuropsychiatric Inventory; TCM: traditional Chinese medicine; VD: vascular dementia.




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**Table 5. Description of rating scales used in the studies**

| Scale | Abbreviation | Description | Reference |
|---|---|---|---|
| Alzheimer's Disease Assessment Scale – cognition | ADAS-Cog | Scale designed to measure cognition in Alzheimer's Disease. Scores range from 0 to 70 (higher is more impairment). | Rosen 1984 |
| Alzheimer's Disease Cooperative Study – Activities of Daily Living – Mild Cognitive Impairment 24-items version | ADCS-ADL-MCI-24 | Assessment of ability to perform ADLs in people with MCI. Scores range from 0 to 69 (lower is more impairment). | Galasko 1997 |
| Alzheimer's Disease Cooperative Study adaptation of the Clinical Global Impression of Change | ADCS-CGIC | Likert scale from 1 to 7; higher is more impairment. | Schneider 1997 |
| Activities of Daily Living – International Scale | ADL-IS | 40-item scale measuring ADLs across 13 categories in people with dementia. Higher scores reflect more deficits in ADL. | Reisberg 2001 |
| Adult Memory and Information Processing Battery – Delayed Story Recall | AMIPB-DSR | Test of verbal episodic memory used in MCI and AD. Examinees are read a short story and asked to recall ideas presented. Scores range from 0 to 56 (lower is worse memory performance). | Coughlan 1985; Shi 2014 |
| Barthel Index | Barthel | Measure of functional ability designed to measure improvement in clients participating in rehabilitation. Scores range from 0 to 100 (lower is more deficits in ADLs). | Mahoney 1965 |
| Beck Depressive Inventory | BDI (also BDI-II) | Measures the presence and severity of depressive symptoms. Scores range from 0 to 63 (higher is worse symptoms of depression). | Beck 1974 |
| *Befindlichkeitsskala*<br><br>(mental balance scale) | BfS' | Self-rating scale of general well-being. Higher scores represent worse well-being. | von Zerssen 1986 |
| Benton test of Visual Retention –<br><br>Revised | Benton | Assessment of visual memory. The examinee is asked to reproduce drawings from memory. Scores range from 0 to 10 (lower is worse memory performance). | Benton 1945 |
| California Verbal Learning Test | CVLT (also CVLT-II) | Measure of linguistic-episodic memory and memory strategies using a list of 16 words to be reproduced. The test was revised in 2000 and 2017. Lower scores reflect worse performance. | Delis 1987 |
| Clinical Dementia Rating Scale; Clinical Dementia Rating Scale – Sum of Boxes | CDR; CDR-SB | Interview instrument to determine the global severity of dementia. Scores range from 0 to 4 (higher scores reflect worse dementia). The sum of boxes is the sum of each of the 6 domains of the CDR and ranges from 0 to 18 (higher scores reflect worse dementia). | Hughes 1982; Lynch 2006 |


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**Table 5. Description of rating scales used in the studies** *(Continued)*

| | | | |
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| Center for Epidemiologic Studies Depression Scale | CESD | Scale measuring depression symptoms. Scores range from 0 to 60 (higher is more depression symptomatology). | Radloff 1977 |
| Clinical Global Impression;<br><br>Clinical Global Impression of Change | CGI; CGIC; CGI-1; CGI-2 | The CGI is a clinician evaluation of global improvement, designed to provide a brief, standalone assessment of the clinician's view of the person's global functioning prior to and after initiating a study medication. The CGI consists of 2 measures. The CGI-S (sometimes called CGI-1) rates the severity of pathology on a scale from 1 to 7 and the CGIC (sometimes called the CGI or CGI-2) rates the change from baseline on a similar scale. | Guy 1976 |
| Clinician's Interview-Based Impression of Change; Clinician's Interview-Based Impression of Change (plus caregiver input) | CIBIC; CIBIC-Plus | An assessment comprising Likert scales for disease severity and change, and written accounts summarizing semi-structured interviews evaluating behavior, cognition, and function. Higher scores indicate worse severity. | Schneider 1997; Stanley 2021 |
| Clinical Memory Scale | CMS | An assessment of visual and auditory memory. Scores can be converted to the MQ (see Wechsler Memory Scale – Memory Quotient). Lower scores reflect worse memory function. | Xu 1996 |
| Clock Drawing Test | CDT | Test of executive function assessing the accuracy with which a clock is drawn. Lower scores indicate worse executive function. | Shulman 1986; Shulman 2000 |
| Controlled Oral Word Association Test | COWAT | A verbal fluency test consisting of 3 word naming trials. Lower scores indicate worse executive function. | Benton 1983 |
| Crichton Geriatric Behavioral Scale | Crichton | A neuropsychiatric rating scale that assesses behavioral concerns in dementia. Scores range from 0 to 39 (higher scores indicate greater concerns). | Cole 1989 |
| *Depressions-Skala* (depression scale) | D-S and D-S' | A German depression scale used in Estonian translation for the EudraCT No. 2005-005765-11 trial. Higher is worse symptoms of depression. | von Zerssen 1986 |
| Dementia Quality of Life | DEMQOL<br><br>DEMQOL-Proxy | An interviewer-administered questionnaire to evaluate QoL in dementia. If the carer is interviewed, the instrument is the DEMQOL-Proxy. Lower scores reflect a worse QoL. | Smith 2005 |
| European Quality of Life Visual<br><br>Analogue Scale | EQ-VAS | QoL assessment that is part of the European Quality of Life Scale, together with the EQ-5D. The EQ-VAS is a visual scale from 0 to 100 (lower ratings reflect a worse QoL). | EuroQol 1990 |
| Expanded Memory Control Test | EMCT | Test of attention and concentration in which word lists and arithmetic progression are used in 12 tasks. Lower scores reflect poorer executive functioning. | Lindeboom 1993 |
| *Fragebogen zur Erfassung alltäglicher Gedächtnisleistungen* (questionnaire for assessing subjectively experienced mem- | FEAG | Test assessing subjective memory performance in daily life. Higher scores reflect worse memory performance. | Hupfeld 2009 |


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**Table 5. Description of rating scales used in the studies** *(Continued)*

| | | | |
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| ory performance in everyday life) | | | |
| Gottfries, Brane and Steen ADL scale | GBS-ADL | ADL subscale of a global assessment tool for evaluating dementia symptoms. The assessment is based on a semi-structured interview and observation. Higher scores indicate more impairment. | Bråne 2001; Gottfries 1982 |
| Geriatric Depression Scale | GDS | Self-report 30-item depression scale for older people. Scores range from 0 to 30 (higher scores indicate greater depression). | Sheikh 1986 |
| Geriatric Evaluation by Relative's Rating Instrument | GERRI | A 49-item questionnaire for carers to assess the functioning of older outpatients with cognitive decline. Summary scores range from 1 to 5 (higher scores indicate worse functioning). | Schwartz 1983 |
| Hamilton Rating Scale for Depression | HAM-D | A 17-item scale designed to measure the frequency and intensity of depressive symptoms. Higher scores indicate more severe depression. | Hamilton 1967 |
| Hasegawa Dementia Scale | HDS | Cognitive assessment scale for dementia. Scores range from 0 to 30 (lower suggests worse cognitive functioning). | Hasegawa 1983 |
| Instrumental Activities of Daily Living | IADL | Assessment of instrumental activities of daily living. Scores range from 0 to 8 (lower scores indicate worse functioning). | Lawton 1969 |
| Mattis Dementia Rating Scale | MDRS | A dementia screening and staging instrument testing 5 different cognitive domains (attention, initiation/perseveration, construction, conceptualization, and memory). Scores range from 0 to 144 (lower scores suggest worse cognition). | Mattis 1976 |
| Mini Mental State Examination | MMSE | Cognitive assessment scale for dementia. Scores range from 0 to 30 (lower scores suggest worse cognitive functioning). | Folstein 1975 |
| Revised Mini Mental State Examination | 3MSE | Cognitive assessment scale for dementia based on the MMSE. Scores range from 0 to 100 (lower scores suggest worse cognitive functioning). | Teng 1987 |
| Montreal Cognitive Assessment | MoCA | Cognitive assessment scale for dementia. Scores range from 0 to 30 (lower scores suggest worse cognitive functioning). | Nasreddine 2005 |
| Montgomery Asberg Depression Rating Scale | MADRS | Depression rating scale. Higher scores reflect higher depression symptoms. | Montgomery 1979 |
| *Nürnberger Alters Inventar* (Nuremberg gerontopsychological inventory) | NAI | Collection of 19 subtests measuring various aspects of functioning in older people. Scores are reported for individual subtests. | Oswald 1986; Oswald 1995 |
| *Nürnberger Alters Inventar – Beobachtungs-Skala* / Nuremberg gerontopsychological observation scale for activities of daily living | NAB | An NAI subtest assessing ADL. The test is completed by a relative or carer. Higher scores reflect greater impairment in ADLs. | Oswald 1986; Oswald 1995 |
| *Nürnberger Alters Alltagsaktivitäten* | NAI-NAA | An NAI subtest comprised of a 20-item assessment of ADL including instrumental activities and social activities. The test | Oswald 1986; Oswald 1995 |


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**Table 5. Description of rating scales used in the studies** *(Continued)*

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| *Skala* / Nuremberg gerontopsychological rating scale for activities of daily living | | was originally designed to be self-rated but may also be rated by others (e.g. carers). Scores range from 20 to 60 (higher reflects greater impairment in ADL). | |
| *Nürnberger Alters Inventar – Wortliste* / verbal learning test | Verbal learning test | An NAI subtest assessing verbal memory. Lower scores reflect worse memory functioning. | Oswald 1986; Oswald 1995 |
| *Zahlen-Nachsprechen-Test* / Digit Span Memory Test | Digit span | Test of working memory in which the examinee is asked to repeat a sequence of numbers. The span of numbers varies, as may the order of recall (forward or backward). Lower scores reflect poorer memory function. | Wechsler 2008 |
| *Nürnberger Alters Inventar – Zahlen-Verbindungs-Test* / Number connection test | NAI-ZVT-G | Test of processing speed | Oswald 1986; Oswald 1995 |
| Neuropsychiatric Inventory | NPI; NPI-12; NPI-D | The NPI is an informant-based questionnaire assessing neuropsychiatric symptoms in 10 domains over the previous month. Two additional domains were later added (NPI-12), as was a caregiver distress scale (NPI-D). Higher scores reflect more neuropsychiatric symptoms. | Cummings 1994 |
| Paced Auditory Serial Addition Test | PASAT | Test evaluating auditory information processing, calculation ability, and sustained and divided attention. The PASAT was originally developed to assess cognitive functioning in people with traumatic brain injury, and is also used for people with multiple sclerosis. Lower scores reflect worse cognitive function. | Rao 1989 |
| Perceived Deficits Questionnaire | PDQ | Self-report measure of cognitive dysfunction often used for people with multiple sclerosis. There are versions with 5 and 20 items. Higher scores reflect greater cognitive dysfunction. | Sullivan 1990 |
| Progressive Deterioration Scale | PDS | Instrument to measure QoL in people with dementia through interviews with caregivers. The PDS has also been used to measure ADLs. Higher scores indicate worse QoL/ADLs. | DeJong 1989 |
| Quality of Life – Alzheimer's Disease | QoL-AD | Brief 13-item measure designed to obtain a rating of QoL in dementia, from the person and caregiver perspective. Lower scores reflect worse QoL. | Logsdon 1999;Logsdon 2002 |
| Rey Test 1 and 2 | Rey 1, Rey 2 | Tests of memory function. Lower scores reflect worse functioning. | Schmidt 1996 |
| Sandoz Clinical Assessment Geriatric Scale | SCAG | 18-item multidomain scale designed to test global changes in dementia after pharmacotherapy. An additional item is used for overall severity. Higher scores reflect greater impairment. | Shader 1974; Venn 1983 |
| Symbol Digit Modalities Test | SDMT | Test in which the examinee is asked to pair specific numbers with geometric figures. The test is used to assess divided attention, visual scanning, tracking, and motor speed. The maximum number of correct responses is 110. | Smith 1968; Smith 1982 |


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**Table 5. Description of rating scales used in the studies** *(Continued)*

| | | | |
|---|---|---|---|
| Short Form (36-item) Health Survey | SF-36 | Self-reported 36-item questionnaire of mental and physical health and QoL. Mental and physical summary scores are reported separately. Scores range from 0 to 100, with lower scores reflecting lower QoL. | Ware 1992 |
| *Syndrom-Kurztest* (short cognitive performance test) | SKT | Short cognitive test with 9 subtests measuring deficits in memory and attention and speed of information processing. Scores range from 0 to 27, with higher scores reflecting more impairment. | Erzigkeit 1986; Kim 1993; Overall 1992 |
| State-Trait Anxiety Inventory | STAI-X1 (state); STAI-X2 (trait) | Test of anxiety that has subscales for state anxiety and trait anxiety. All items are rated on a 4-point scale, and higher scores reflect higher anxiety. | Spielberger 1983 |
| Stroop Test | Stroop | The Stroop Test is a test of concentration effectiveness requiring the examinee to selectively process only 1 visual feature whilst continuously blocking out the processing of others. There are many formats of this test, but in general, higher scores are considered to reflect worse functioning. | Stroop 1935 |
| Test for Early Detection of Dementia with Discrimination from Depression | TE4D | Screening instrument for AD which differentiates between early dementia and depression. Lower scores reflect worse cognition. | Ihl 2000; Mahoney 2005 |
| *Termine Test* (appointments test) Immediate Recall; *Termine Test* (appointments test) Delayed Recall | TT-immediate; TT-delated | Test for memory in which 8 appointments including specifics of time, location, and purpose are presented, and the examinee is asked to recall the appointments first immediately (immediate recall) and then after 45 minutes (delayed recall). Lower scores reflect worse memory functioning. | Kaschel 1994 |
| Trail-Making Test part B | TMT B | Timed tests of visual attention and switching. Part B may be considered a test of executive function. Higher scores are worse. | Llinàs-Reglà 2017 |
| Verbal fluency test | Verbal fluency | A class of timed tests during which the examinee is asked to produce words from a given category. Lower scores are worse. | Rosen 1980 |
| Wechsler Memory Scale | WMS | Test of memory in adults, first published in 1945 and amended and updated several times since then. WMS-IV is the most recent version, issued in 2009. Lower scores are worse. | Wechsler 2009 |
| Wechsler Memory Scale III Faces I and Wechsler Memory Scale III Faces II | WMS III Faces I<br>WMS III Faces II | Nonverbal tests of immediate and delayed recall that are subtests of the WMS. Twenty-four photos of human faces are presented, and the examinee is asked to recognize them from a set of 48 photographs immediately after (Faces I) and 30 minutes after (Faces II) the initial presentation. Lower scores are worse. | Wechsler 1997 |
| Wechsler Memory Scale III – Logical Memory | WMS III – LM I<br>WMS III – LM II | Tests of narrative episodic memory that are subtests of the WMS. A story is told to the person being examined, who is asked to repeat it immediately (immediate recall) and then again 20 to 30 minutes later (delayed recall). Lower scores are worse. | Wechsler 1987 |


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**Table 5. Description of rating scales used in the studies** *(Continued)*

| | | | |
|---|---|---|---|
| Wechsler Memory Scale – Memory Quotient | MQ | Memory evaluation that is obtained from the WMS. Lower scores reflect worse memory function. | Xu 1996 |
| *Wien Test System*—Work Performance Series (Arbeitsleistungsserie) | WTS-ALS | Computerized test of executive function (concentration and fatigability). More answered stimuli are reflected in higher scores and lower scores are worse. | Neuwirth 2004 |
| Wien Test System—Determination Test | WTS-DT | Computerized test of executive function (attention, reaction time, speed of processing, motor co-ordination, endurance, and overall performance/efficiency). More correct reactions are reflected in higher scores, and lower scores are worse. | Neuwirth 2005 |
| Unknown scales | — | Several studies measured ADLs on unspecified continuous scales where it appeared higher scores indicated better outcomes (Bu 2016; Deng 2021; Gao 2019; Guan 2019; He 2016; Huang 2017; Li 2017a; Li 2016a; Liu 2021; Meng 2012; Wang 2020a; Wang 2014a; Xu 2017; Xu 2021; Yang 2020a; Yu 2014; Zhao 2020; Zheng 2020). | -- |

Abbreviations: AD: Alzheimer's disease; ADL: activities of daily living; MCI: mild cognitive impairment; QoL: quality of life.

## APPENDICES

### Appendix 1. Sources searched and search strategies

| Source | Search strategy | Hits retrieved |
|---|---|---|
| CDCIG Register (https://crswe-b.cochrane.org/login.html)<br><br>[Date of most recent search: 8 December 2022] | ginkgo OR gingko OR EGb761 OR EGb OR tanakan OR tebonin OR rokan OR ginkoba OR yinxingye | June 2020: 232<br><br>Dec 2021: 13<br><br>Dec 2022: 10 |
| MEDLINE In-process and other non-indexed citations and MEDLINE 1950-present (Ovid SP)<br><br>[Date of most recent search: 18 November 2024] | 1. exp Dementia/<br><br>2. exp *Cognition Disorders/<br><br>3. Neurocognitive Disorders/<br><br>4. alzheimer*.ti,ab.<br><br>5. dement*.ti,ab.<br><br>6. ((lewy* adj2 bod*) or (DLB or LBD or FTLD or FTD or frontotemporal or PDD)).ti,ab.<br><br>7. "major neurocognitive disorder*".ti,ab.<br><br>8. "mild neurocognitive disorder*".ti,ab. | June 2020: 503<br><br>Dec 2021: 33<br><br>Dec 2022: 41<br><br>November 2024: 52 |


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(Continued)

9. ((cognit* or memory or cerebr* or mental*) adj3 (declin* or impair* or los* or deteriorat* or degenerat* or complain* or disturb* or disorder* or insufficient* or chronic)).ti,ab.

10. MCI.ti,ab.

11. (aMCI or MCIa or nMCI or mMCI).ti,ab.

12. (ACMI or ARCD or SMC or CIND or BSF or AAMI or AACD or MNCD).ti,ab.

13. "Benign senescent forgetfulness".ti,ab.

14. ((CDR adj2 "0.5") or ("clinical dementia rating" adj3 "0.5")).ab.

15. ("organic brain disease" or "organic brain syndrome").ti,ab.

16. "preclinical AD".ti,ab.

17. "pre-clinical AD".ti,ab.

18. "preclinical alzheimer*".ti,ab.

19. "pre-clinical alzheimer*".ti,ab.

20. or/1-19

21. exp Ginkgo biloba/

22. ginkgo.ti,ab.

23. "maidenhair extract*".ti,ab.

24. "maidenhair tree*".ti,ab.

25. GbE.ti,ab.

26. EGb.ti,ab.

27. EGb761.ti,ab.

28. Tanakan.ti,ab.

29. Tebonin.ti,ab.

30. Rokan.ti,ab.

31. Ginkoba.ti,ab.

32. "Pterophyllus salisburiensis leaf".ti,ab.

33. "Salisburia adiantifolia leaf".ti,ab.

34. "Salisburia biloba leaf".ti,ab.

35. "Salisburia macrophylla leaf".ti,ab.

36. Yinxingye.ti,ab.

37. gingko.ti,ab.

38. or/21-37

39. randomized controlled trial.pt.

40. controlled clinical trial.pt.

41. randomized.ab.


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(Continued)

| | | |
|---|---|---|
| | 42. placebo.ab.<br>43. drug therapy.fs.<br>44. randomly.ab.<br>45. trial.ab.<br>46. groups.ab.<br>47. or/39-46<br>48. exp animals/ not humans.sh.<br>49. 47 not 48<br>50. 49 and 38 and 20 | |
| EMBASE<br>1974-15 June 2020 (Ovid SP)<br>[Date of most recent search: 18 November 2024] | 1. exp Dementia/<br>2. exp cognitive defect/<br>3. "disorders of higher cerebral function"/<br>4. alzheimer*.ti,ab.<br>5. dement*.ti,ab.<br>6. ((lewy* adj2 bod*) or (DLB or LBD or FTLD or FTD or frontotemporal or PDD)).ti,ab.<br>7. "major neurocognitive disorder".ti,ab.<br>8. "mild neurocognitive disorder*".ti,ab.<br>9. ((cognit* or memory or cerebr* or mental*) adj3 (declin* or impair* or los* or deteriorat* or degenerat* or complain* or disturb* or disorder* or insufficient* or chronic)).ti,ab.<br>10. MCI.ti,ab.<br>11. (aMCI or MCIa or nMCI or mMCI).ti,ab.<br>12. (ACMI or ARCD or SMC or CIND or BSF or AAMI or AACD or MNCD).ti,ab.<br>13. "Benign senescent forgetfulness".ti,ab.<br>14. ((CDR adj2 "0.5") or ("clinical dementia rating" adj3 "0.5")).ab.<br>15. ("organic brain disease" or "organic brain syndrome").ti,ab.<br>16. "preclinical AD".ti,ab.<br>17. "pre-clinical AD".ti,ab.<br>18. "preclinical alzheimer*".ti,ab.<br>19. "pre-clinical alzheimer*".ti,ab.<br>20. or/1-19<br>21. exp Ginkgo biloba/<br>22. ginkgo.ti,ab.<br>23. "maidenhair extract*".ti,ab. | June 2020: 524<br>Dec 2021: 41<br>Dec 2022: 46<br>November 2024: 75 |


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| | | |
|---|---|---|
| | 24. "maidenhair tree*".ti,ab.<br>25. GbE.ti,ab.<br>26. EGb.ti,ab.<br>27. EGb761.ti,ab.<br>28. Tanakan.ti,ab.<br>29. Tebonin.ti,ab.<br>30. Rokan.ti,ab.<br>31. Ginkoba.ti,ab.<br>32. "Pterophyllus salisburiensis leaf".ti,ab.<br>33. "Salisburia adiantifolia leaf".ti,ab.<br>34. "Salisburia biloba leaf".ti,ab.<br>35. "Salisburia macrophylla leaf".ti,ab.<br>36. Yinxingye.ti,ab.<br>37. gingko.ti,ab.<br>38. or/21-37<br>39. randomized controlled trial/<br>40. controlled clinical trial/<br>41. randomi?ed.ab.<br>42. placebo.ab.<br>43. randomly.ab.<br>44. trial.ab.<br>45. groups.ab.<br>46. randomi?ed.ti.<br>47. or/39-46<br>48. 20 and 38 and 47<br>49. 20 and 38 and 47 | |
| PsycINFO<br>1806-June 15 2020 (Ovid SP)<br>[Date of most recent search: 8 December 2022] | 1. exp Dementia/<br>2. exp Cognitive Impairment/<br>3. exp Neurocognitive Disorders/<br>4. alzheimer*.ti,ab.<br>5. dement*.ti,ab.<br>6. ((lewy* adj2 bod*) or (DLB or LBD or FTLD or FTD or frontotemporal or PDD)).ti,ab.<br>7. "major neurocognitive disorder".ti,ab. | June 2020: 154<br>Dec 2021: 5<br>Dec 2022: 7 |


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*(Continued)*

8. "mild neurocognitive disorder*".ti,ab.

9. ((cognit* or memory or cerebr* or mental*) adj3 (declin* or impair* or los* or deteriorat* or degenerat* or complain* or disturb* or disorder* or insufficient* or chronic)).ti,ab.

10. MCI.ti,ab.

11. (aMCI or MCIa or nMCI or mMCI).ti,ab.

12. (ACMI or ARCD or SMC or CIND or BSF or AAMI or AACD or MNCD).ti,ab.

13. "Benign senescent forgetfulness".ti,ab.

14. ((CDR adj2 "0.5") or ("clinical dementia rating" adj3 "0.5")).ab.

15. ("organic brain disease" or "organic brain syndrome").ti,ab.

16. "preclinical AD".ti,ab.

17. "pre-clinical AD".ti,ab.

18. "preclinical alzheimer*".ti,ab.

19. "pre-clinical alzheimer*".ti,ab.

20. or/1-19

21. ginkgo.ti,ab.

22. "maidenhair extract*".ti,ab.

23. "maidenhair tree*".ti,ab.

24. GbE.ti,ab.

25. EGb.ti,ab.

26. EGb761.ti,ab.

27. Tanakan.ti,ab.

28. Tebonin.ti,ab.

29. Rokan.ti,ab.

30. Ginkoba.ti,ab.

31. "Pterophyllus salisburiensis leaf".ti,ab.

32. "Salisburia adiantifolia leaf".ti,ab.

33. "Salisburia biloba leaf".ti,ab.

34. "Salisburia macrophylla leaf".ti,ab.

35. Yinxingye.ti,ab.

36. gingko.ti,ab.

37. or/21-36

38. randomized controlled trial/

39. exp Clinical Trials/

40. randomi?ed.ti,ab.


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(Continued)

| | | |
|---|---|---|
| | 41. placebo.ab. | |
| | 42. randomly.ab. | |
| | 43. trial.ab. | |
| | 44. groups.ab. | |
| | 45. ("double blind*" or "single blind*").ti,ab. | |
| | 46. or/38-45 | |
| | 47. 20 and 37 and 46 | |
| CINAHL (EBSCOhost)<br><br>[Date of most recent search: 8 December 2022] | S1 (MH "Dementia+") | June 2020: 188<br><br>Dec 2021: 17<br><br>Dec 2022: 14 |
| | S2 (MH "Cognition Disorders+") | |
| | S3 "Neurocognitive Disorders" | |
| | S4 TX "neurocognitive disorder*" | |
| | S5 TX alzheimer* | |
| | S6 TX dement* | |
| | S7 TX "lewy* bod*" OR DLB OR LDB OR FTLD OR FTD | |
| | S8 TX frontotemporal | |
| | S9 TX PDD | |
| | S10 TX "cognit* impair*" | |
| | S11 TX "cognit* declin*" | |
| | S12 TX "cognit* disorder*" | |
| | S13 TX memory | |
| | S14 TX "cerebral insufficien*" | |
| | S15 TX MCI | |
| | S16 TX aMCI OR MCIa OR nMCI OR mMCI | |
| | S17 TX ACMI or ARCD or SMC or CIND or BSF or AAMI or AACD or MNCD | |
| | S18 TX "Benign senescent forgetfulness" | |
| | S19 TX "clinical dementia rating" | |
| | S20 TX "organic brain disease" OR "organic brain syndrome" | |
| | S21 TX "preclinical AD" | |
| | S22 TX "pre-clinical AD" | |
| | S23 TX "preclinical alzheimer*" | |
| | S24 TX "pre-clinical alzheimer*" | |
| | S25 S1 OR S2 OR S3 OR S4 OR S5 OR S6 OR S7 OR S8 OR S9 OR S10 OR S11 OR S12 OR S13 OR S14 OR S15 OR S16 OR S17 OR S18 OR S19 OR S20 OR S21 OR S22 OR S23 OR S24 | |
| | S26 (MH "Ginkgo Biloba") | |


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| | | |
|---|---|---|
| | S27 TX ginkgo<br>S28 TX "maidenhair extract*"<br>S29 TX "maidenhair tree*"<br>S30 TX GbE<br>S31 TX EGb<br>S32 TX EGb761<br>S33 TX Tanakan<br>S34 TX Tebonin<br>S35 TX Rokan<br>S36 TX Ginkoba<br>S37 TX Yinxingye<br>S38 TX gingko<br>S39 S27 OR S28 OR S29 OR S30 OR S31 OR S32 OR S33 OR S34 OR S35 OR S36 OR S37 OR S38<br>S40 S39 and S25<br>S41 (MH "Randomized Controlled Trials")<br>S42 TX randomised<br>S43 TX randomized<br>S44 AB randomly<br>S45 AB trial<br>S46 TI trial<br>S47 AB groups<br>S48 AB placebo<br>S49 S41 OR S42 OR S43 OR S44 OR S45 OR S46 OR S47 OR S48<br>S40 AND S49 | |
| Web of Science Core Collection (Clarivate)<br>[Date of most recent search: 8 December 2022] | (dement* OR alzheimer* OR "lewy bod*" OR DLB OR "vascular cognitive impairment*" OR FTD OF FTLD OR "cerebrovascular insufficienc*" OR "mild cognitive impairment" OR MCI) AND TOPIC: (ginkgo OR gingko OR maidenhair OR GbE OR EGb761 OR tanakan OR tebonin OR roman OR ginkoba OR yinxingye) AND TOPIC: (randomly OR randomised OR randomized OR placebo OR "double-blind*" OR trial OR RCT OR CCT)<br>Timespan: All years. Indexes: SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, BKCI-S, BKCI-SSH, ESCI, CCR-EXPANDED, IC. | June 2020: 636<br>Dec 2021: 74<br>Dec 2022: 88 |
| LILACS (BIREME)<br>[Date of most recent search: 8 December 2022] | dementia OR demencia OR demência OR alzheimer OR alzheimers OR alzheimer's OR cognition OR "mild cognitive impairment" [Words] and ginkgo OR gingko OR maidenhair OR GbE OR EGb761 OR tanakan OR tebonin OR roman OR ginkoba OR yinxingye [Words] and randomly OR randomised OR randomized OR RCT OR "controlled trial" [Words] | June 2020: 0<br>Dec 2021: 0<br>Dec 2022: 0 |


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*(Continued)*

| | | |
|---|---|---|
| CENTRAL (the Cochrane Library)<br><br>[Date of most recent search: 18 November 2024] | #1 MeSH descriptor: [Dementia] explode all trees<br><br>#2 MeSH descriptor: [Cognitive Dysfunction] explode all trees<br><br>#3 MeSH descriptor: [Neurocognitive Disorders] this term only<br><br>#4 dement*<br><br>#5 ((lewy* adj2 bod*) or (DLB or LBD or FTLD or FTD or frontotemporal or PDD))<br><br>#6 "major neurocognitive disorder"<br><br>#7 "mild neurocognitive disorder*"<br><br>#8 ((cognit* or memory or cerebr* or mental*) adj3 (declin* or impair* or los* or deteriorat* or degenerat* or complain* or disturb* or disorder* or insufficient* or chronic))<br><br>#9 MCI<br><br>#10 (aMCI or MCIa or nMCI or mMCI)<br><br>#11 (ACMI or ARCD or SMC or CIND or BSF or AAMI or AACD or MNCD)<br><br>#12 "Benign senescent forgetfulness"<br><br>#13 ((CDR adj2 "0.5") or ("clinical dementia rating" adj3 "0.5"))<br><br>#14 "organic brain disease" or "organic brain syndrome"<br><br>#15 "preclinical AD"<br><br>#16 "pre-clinical AD"<br><br>#17 "preclinical alzheimer*"<br><br>#18 "pre-clinical alzheimer*"<br><br>#19 #1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9 or #10 or #11 or #12 or #13 or #14 or #15 or #16 or #17 or #18<br><br>#20 MeSH descriptor: [Ginkgo biloba] explode all trees<br><br>#21 ginkgo<br><br>#22 "maidenhair extract*"<br><br>#23 "maidenhair tree*"<br><br>#24 GbE<br><br>#25 EGb<br><br>#26 EGb761<br><br>#27 Tanakan<br><br>#28 Tebonin<br><br>#29 Rokan<br><br>#30 Ginkoba<br><br>#31 "Pterophyllus salisburiensis leaf"<br><br>#32 "Salisburia adiantifolia leaf" | June 2020: 321<br><br>Dec 2021: 21<br><br>Dec 2022: 9<br><br>November 2024: 33 |


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(Continued)

| | | |
|---|---|---|
| | #33 "Salisburia biloba leaf"<br><br>#34 "Salisburia macrophylla leaf"<br><br>#35 Yinxingye<br><br>#36 gingko<br><br>#37 #20 or #21 or #22 or #23 or #24 or #25 or #26 or #27 or #28 or #29 or #30 or #31 or #32 or #33 or #34 or #35 or #36<br><br>#38 #37 and #19 | |
| Clinicaltrials.gov (www.clinicaltrials.gov)<br><br>[Date of most recent search: 18 November 2024] | dementia OR alzheimer OR alzheimers OR lewy OR PDD OR FTLD OR MCI OR "cognitive impairment" \| ginkgo OR gingko OR EGb761 OR EGb OR tanakan OR tebonin OR rokan OR ginkoba OR yinxingye | June 2020: 21<br><br>Dec 2021: 2<br><br>Dec 2022: 2<br><br>November 2024: 32 |
| ICTRP Search Portal (http://apps.who.int/trialsearch) [includes: Australian New Zealand Clinical Trials Registry; ClinicalTrilas.gov; ISRCTN; Chinese Clinical Trial Registry; Clinical Trials Registry – India; Clinical Research Information Service – Republic of Korea; German Clinical Trials Register; Iranian Registry of Clinical Trials; Japan Primary Registries Network; Pan African Clinical Trial Registry; Sri Lanka Clinical Trials Registry; The Netherlands National Trial Register]<br><br>[Date of most recent search: 18 November 2024] | ginkgo OR gingko OR EGb761 OR EGb OR tanakan OR tebonin OR rokan OR ginkoba OR yinxingye | June 2020: 167<br><br>Dec 2021: 2<br><br>Dec 2022: 0<br><br>November 2024: 5 |
| Relevant Chinese databases: CNKI, VIP, WanFang Database, SinoMed<br><br>[Date of most recent search 08 December 2021] | **CNKI:**<br><br>((SU = 银杏+白果+银杏树+白果树+银杏叶+银杏内酯+白果内酯+银杏提取物+银杏叶提取物+EGb+舒血宁+银杏总黄酮+银杏黄酮+黄酮醇+银杏叶片+银杏达莫+杏丁+金纳多+达纳康+塔纳康+达那康) or<br>(TKA = 银杏+白果+银杏树+白果树+银杏叶+银杏内酯+白果内酯+银杏提取物+银杏叶提取物+EGb+舒血宁+银杏总黄酮+银杏黄酮+黄酮醇+银杏叶片+银杏达莫+杏丁+金纳多+达纳康+塔纳康+达那康) or<br>(SU % 银杏) or<br>(SU % 白果)) and<br>((SU = 阿尔茨海默+阿尔茨海默病+老年痴呆+老年性痴呆+痴呆+痴呆症+认知+认知功能+认知障碍+认知损害+认知损伤+认知减退+认知功能障碍+认知功能损害+认知功能损伤+认知功能减退+ | Jun 2020: 2991<br><br>Dec 2021: 2061 |


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记忆+记忆功能+记忆障碍+记忆损害+记忆损伤+记忆减退+记忆功能障碍+记忆功能损害+记忆功能损伤+记忆功能减退+
健忘+健忘症+良性健忘+失智症+
器质性脑疾患+器质性脑综合征+器质性脑症候群+
脑功能不全+脑血管机能不全+脑血管功能不全+脑供血不足+脑血管缺血+路易小体+路易体) or
(SU % 脑供血不足)) and
((TI = 随机+对照+对比+比较+试验+双盲+安慰剂+临床+临床观察+临床研究+临床疗效+临床效果+疗效+效果) or
KY = 随机+对照+对比+比较+试验+双盲+安慰剂+临床+临床观察+临床研究+临床疗效+临床效果+疗效+效果)

**VIP:**

任意字段= 银杏+白果+银杏树+白果树+银杏叶+银杏内酯+白果内酯+银杏提取物+银杏叶提取物+EGb+舒血宁+银杏总黄酮+银杏黄酮+黄酮醇+银杏叶片+银杏达莫+杏丁+金纳多+达纳康+塔纳康+达那康AND
任意字段= 阿尔茨海默+阿尔茨海默病+老年痴呆+老年性痴呆+痴呆+痴呆症+认知+认知功能+认知障碍+认知损害+认知损伤+认知减退+认知功能障碍+认知功能损害+认知功能损伤+认知功能减退+
记忆+记忆功能+记忆障碍+记忆损害+记忆损伤+记忆减退+记忆功能障碍+记忆功能损害+记忆功能损伤+记忆功能减退+
健忘+健忘症+良性健忘+失智症+
器质性脑疾患+器质性脑综合征+器质性脑症候群+
脑功能不全+脑血管机能不全+脑血管功能不全+脑供血不足+脑血管缺血+路易小体+路易体AND
题名或关键词=随机+对照+对比+比较+试验+双盲+安慰剂+临床+临床观察+临床研究+临床疗效+临床效果+疗效+效果

**WanFang:**

(主题: (银杏+白果+银杏树+白果树+银杏叶+银杏内酯+白果内酯+银杏提取物+银杏叶提取物+EGb+舒血宁+银杏总黄酮+银杏黄酮+黄酮醇+银杏叶片+银杏达莫+'杏丁'+'金纳多'+'达纳康'+'塔纳康'+'达那康') +
题名或关键词: (银杏+白果+银杏树+白果树+银杏叶+银杏内酯+白果内酯+银杏提取物+银杏叶提取物+EGb+舒血宁+银杏总黄酮+银杏黄酮+黄酮醇+银杏叶片+银杏达莫+'杏丁'+'金纳多'+'达纳康'+'塔纳康'+'达那康'))*
主题: (阿尔茨海默+阿尔茨海默病+老年痴呆+老年性痴呆+痴呆+痴呆症+认知+'认知功能'+'认知障碍'+'认知损害'+'认知损伤'+'认知减退'+'认知功能障碍'+'认知功能损害'+'认知功能损伤'+'认知功能减退'+
记忆+'记忆功能'+'记忆障碍'+'记忆损害'+'记忆损伤'+'记忆减退'+'记忆功能障碍'+'记忆功能损害'+'记忆功能损伤'+'记忆功能减退'+
健忘+健忘症+良性健忘+失智症+
器质性脑疾患+器质性脑综合征+器质性脑症候群+
'脑功能不全'+'脑血管机能不全'+'脑血管功能不全'+'脑供血不足'+'脑血管缺血'+
'路易小体'+'路易体')*
题名或关键词: (随机+对照+对比+比较+试验+双盲+安慰剂+临床+临床观察+临床研究+临床疗效+临床效果+疗效+效果)

**SinoMed:**

(( "银杏"[常用字段:智能] OR "白果"[常用字段:智能] OR "银杏树"[常用字段:智能] OR "白果树"[常用字段:智能] OR "银杏叶"[常用字段:智能] OR "银杏内酯"[常用字段:智能] OR "白果内酯"[常用字段:智能] OR "银杏提取物"[常用字段:智能] OR "银杏叶提取物"[常用字段:智能] OR "EGb"[常用字段:智能] OR "舒血宁"[常用字段:智能] OR "银杏总黄酮"[常用字段:智能] OR "银杏黄酮"[常用字段:智能] OR "黄酮醇"[常用字段:智能] OR "银杏叶片"[常用字段:智能] OR "银杏达莫"[常用字段:智能] OR "杏丁"[常用字段:智能] OR "金纳多"[常用字段:智能] OR "达纳康"[常用字段:智能] OR "塔纳康"[常用字段:智能] OR "达那康"[常用字段:智能]))
AND


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| | (( "阿尔茨海默"[常用字段:智能] OR "阿尔茨海默病"[常用字段:智能] OR "老年痴呆"[常用字段:智能] OR "老年性痴呆"[常用字段:智能] OR "痴呆"[常用字段:智能] OR "痴呆症"[常用字段:智能] OR " 认知"[常用字段:智能] OR "认知功能"[常用字段:智能] OR "认知障碍"[常用字段:智能] OR "认知损害"[常用字段:智能] OR "认知损伤"[常用字段:智能] OR "认知减退"[常用字段:智能] OR "认知功能障碍"[常用字段:智能] OR "认知功能损害"[常用字段:智能] OR "认知功能损伤"[常用字段:智能] OR "认知功能减退"[常用字段:智能] OR " 记忆"[常用字段:智能] OR "记忆功能"[常用字段:智能] OR "记忆障碍"[常用字段:智能] OR "记忆损害"[常用字段:智能] OR "记忆损伤"[常用字段:智能] OR "记忆减退"[常用字段:智能] OR "记忆功能障碍"[常用字段:智能] OR "记忆功能损害"[常用字段:智能] OR "记忆功能损伤"[常用字段:智能] OR "记忆功能减退"[常用字段:智能] OR " 健忘"[常用字段:智能] OR "健忘症"[常用字段:智能] OR "良性健忘"[常用字段:智能] OR "失智症"[常用字段:智能] OR " 器质性脑疾患"[常用字段:智能] OR "器质性脑综合征"[常用字段:智能] OR "器质性脑症候群"[常用字段:智能] OR " 脑功能不全"[常用字段:智能] OR "脑血管机能不全"[常用字段:智能] OR "脑血管功能不全"[常用字段:智能] OR "脑供血不足"[常用字段:智能] OR "脑血管缺血"[常用字段:智能] OR " 路易小体"[常用字段:智能] OR "路易体"[常用字段:智能])) AND (( "随机"[标题:智能] OR "对照"[标题:智能] OR "对比"[标题:智能] OR "比较"[标题:智能] OR "试验"[标题:智能] OR "双盲"[标题:智能] OR "安慰剂"[标题:智能] OR "临床"[标题:智能] OR "临床观察"[标题:智能] OR "临床研究"[标题:智能] OR "临床疗效"[标题:智能] OR "临床效果"[标题:智能] OR "疗效"[标题:智能] OR "效果"[标题:智能])) |
| TOTAL before de-duplication | **June 2020: 5737**<br>**Dec 2021: 2269**<br>**Dec 2022:**<br>**TOTAL: 8006** |
| TOTAL after de-duplication prior to import into Covidence | **6395** |


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## Appendix 2. GRADE assessment for subjective cognitive impairment: *Ginkgo biloba* versus placebo

| Outcome (scale)/ time | Ginkgo preparation | Analysis | Results | Reasons for downgrading certainty of evidence | | | | | GRADE rating |
|---|---|---|---|---|---|---|---|---|---|
| | | | | Risk of bias | Inconsistency ($I^2 \geq 50\%$; NA if only 1 study) | Indirectness (review and study PICO do not match) | Imprecision (events < 300 [twice for events < 25], n < 400 [twice for n < 50], CI includes no effect and important effect (SMD ± 0.5, RR ± 1.25) | Other reasons (e.g. publication bias) | |
| Global clinical status (5-point Likert scale)/3 months | Geriaforce | Analysis 1.1 | MD 0.04, 95% CI −0.40 to 0.48; 1 study, n = 197 | 1 level: RoB unclear in multiple areas | NA | 1 level: Brautigam 1998 eligibility criteria may not exclude people with MCI or mild dementia. | 1 level: n < 400 | No | Very low |
| Global clinical status (5-point Likert scale)/6 months | Geriaforce | Analysis 1.2 | MD 0.00, 95% CI −0.33 to 0.33; 1 study, n = 197 | 1 level: RoB unclear in multiple areas | NA | 1 level: Brautigam 1998 eligibility criteria may not exclude people with MCI or mild dementia. | 1 level: n < 400 | No | Very low |
| AEs/3 months | EGb 761 | Analysis 1.3 | RR 1.33 95% CI 0.92 to 1.93; 1 study, n = 304, events = 84 | No | NA | No: although participants may have had undiagnosed MCI, this should not impact adverse effects. | 2 levels: events < 300, and CI includes both no difference and an important difference. | No | Low |
| SAEs/3 months | EGb 761 | Analysis 1.4; | RR 0.33 95% CI 0.01 to 8.12; 1 study, n = 304 | No | NA | No: although participants may have had undiagnosed MCI, this should not impact adverse effects. | 3 levels: < 25 events, and CI includes both no difference and an important difference. | No | Very low |
| Memory (combined | Geriaforce | Analysis 1.5 | SMD 0.01, 95% CI −0.28 to 0.30; 1 study, n = 197 | 1 level: RoB unclear in | NA | 1 level: Brautigam 1998 eligibility criteria may not exclude people with MCI or mild dementia. | 1 level: n < 400 | No | Very low |



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| outcome)/3 months | | | | multiple areas | | | | | |
| Memory (combined outcome)/6 months | Geriaforce | Analysis 1.6 | SMD 0.01, 95% CI −0.28 to 0.30; 1 study, n = 197 | 1 level: RoB unclear in multiple areas | NA | 1 level: Brautigam 1998 eligibility criteria may not exclude people with MCI or mild dementia. | 1 level: n < 400 | No | Very low |
| Memory (FEAG)/3 months | EGb 761 | Analysis 1.7 | MD 0.04, 95% CI −0.18 to 0.26; 1 study, n = 296 | No | NA | 1 level: participants may have had undiagnosed MCI. | 1 level: n < 400 | No | Low |
| Executive function (EMCT)/3 months | Geriaforce | Analysis 1.8 | MD 0.05, 95% CI −1.06 to 1.16; 1 study, n = 197 | 1 level: RoB unclear in multiple areas | NA | 1 level: Brautigam 1998 eligibility criteria may not exclude people with MCI or mild dementia. | 1 level: n < 400 | No | Very low |
| Executive function (EMCT)/6 months | Geriaforce | Analysis 1.9 | MD 0.09, 95% CI −0.83 to 1.01; 1 study, n = 197 | 1 level: RoB unclear in multiple areas | NA | 1 level: Brautigam 1998 eligibility criteria may not exclude people with MCI or mild dementia. | 1 level: n < 400 | No | Very low |
| Executive function (TMT)/3 months | EGb 761 | Analysis 1.10 | MD −1.10, 95% CI −5.78 to 3.58; 1 study, n = 296 | No | NA | 1 level: participants may have had undiagnosed MCI. | 1 level: n < 400 | No | Low |
| Anxiety – (STAI-X1)/3 months | EGb 761 | Analysis 1.11 | MD 0.40, 95% CI −1.69 to 2.49; 1 study, n = 296 | No | NA | 1 level: participants may have had undiagnosed MCI. | 1 level: n < 400 | No | Low |
| Depression (D-S')/3 months | EGb 761 | Analysis 1.12 | MD 0.20, 95% CI −1.09 to 1.49; 1 study, n = 296 | No | NA | 1 level: participants may have had undiagnosed MCI. | 1 level: n < 400 | No | Low |


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AEs: adverse events; CI: confidence interval; D-S': Depressions-Skala; EMCT: Expanded Memory Control Test; FEAG: *Fragebogen zur Erfassung alltäglicher Gedachtniserfahrungen* (questionnaire for assessing subjectively experienced memory performance in everyday life); MCI: mild cognitive impairment; MD: mean difference; n: number of participants; NA: not applicable; RoB: risk of bias; RR: risk ratio; SAEs: serious adverse events; SMD: standardized mean difference; STAI-X1: state subscale of State-Trait Anxiety Inventory; TMT: Trail Making Test.


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## Appendix 3. GRADE assessment for multiple sclerosis and cognitive impairment: *Ginkgo biloba* versus placebo

| Outcome (scale)/time | Analysis | Results | Reasons for downgrading certainty of evidence | | | | | GRADE rating |
|---|---|---|---|---|---|---|---|---|
| | | | Risk of bias | Inconsistency ($I^2$ ≥ 50%; NA if only 1 study) | Indirectness (review and study PICO do not match) | Imprecision (events < 300 [twice for events < 25], n < 400 [twice for n < 50], CI includes no effect and important effect (SMD ± 0.5, RR ± 1.25) | Other reasons (e.g. publication bias) | |
| Cognition (PDQ)/3 months | Analysis 2.1 | MD −0.09, 95% CI −0.41 to 0.22; P = 0.74; $I^2$ = 0%; 2 studies, n = 152 | No: the low RoB study was weighted > 75% | No | No | 1 level: n < 400 | No | Moderate |
| | | Lovera 2012 only:<br>MD −0.12, 95% CI −0.48 to 0.23; P = 0.50, 1 study, n = 120 | No | No | No | 1 level: n < 400 | No | Moderate |
| Memory (CVLT-II)/3 months – adjusted means | Analysis 2.2 | MD −0.38, 95% CI −1.01 to 0.25; 1 study, n = 39 (corresponds to SMD −0.37, 95% CI −1.00 to 0.26) | 1 level | NA | No | 3 levels: n < 50, and CI possibly covers important value and the null based on the SMD. | No | Very low |
| Memory (CVLT-II)/3 months – adjusted Z-scores | Analysis 2.3 | MD 0.00, 95% CI 0.36 to 0.36; 1 study, n = 120 | No | NA | No | 1 level: n < 400 | No | Moderate |
| Executive function (combined PASAT, COWAT, Stroop and SDMT)/3 months – adjusted means | Analysis 2.4 | SMD −0.08, 95% CI −0.71 to 0.55; 1 study, n = 39 | 1 level | NA | No | 3 levels: n < 50, and CI possibly includes both important effect and the null based on SMD. | No | Very low |
| Executive function (combined PASAT, COWAT, Stroop)/3 months | Analysis 2.5 | SMD −0.11, 95% CI −0.47 to 0.25; 1 study, n = 120 | No | NA | No | 1 level: n < 400 | No | Moderate |

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| – adjusted Z-scores | | | | | | | | |
| Depression (BDI)/3 months – adjusted means | Analysis 2.6 | MD −1.30, 95% CI −3.88 to 1.28; 1 study, n = 120 | No | NA | No | 2 levels: n < 400, and CI possibly includes clinically important effect as well as the null value (it is unclear what is an important difference, but previous research indicates that it may be as small as 2 or 3 points; https://pmc.ncbi.nlm.nih.gov/articles/PMC4611356/). | No | Low |


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CI: confidence interval; COWAT: Controlled Oral Word Association Test; CVLT-II: California Verbal Learning Test; MD: mean difference; n: number of participants; NA: not applicable; PASAT: Paced Auditory Serial Addition Test; PDQ: Perceived Deficits Questionnaire; RoB: risk of bias; RR: risk ratio; SDMT: Symbol Digit Modalities Test; SMD: standardized mean difference.


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## Appendix 4. GRADE assessment for mild cognitive impairment: *Ginkgo biloba* versus placebo

| Outcome (scale)/time | Analysis | Results | Reasons for downgrading certainty of evidence | | | | | GRADE rating |
|---|---|---|---|---|---|---|---|---|
| | | | Risk of bias | Inconsistency ($I^2 \geq 50\%$; NA if only 1 study) | Indirectness (review and study PICO do not match) | Imprecision (events < 300 [twice for events < 25], n < 400 [twice for n < 50], CI includes no effect and important effect (SMD ± 0.5, RR ± 1.25) | Other reasons (e.g. publication bias) | |
| Global status (SCAG) /3 months | Analysis 3.1 | MD 4.20, 95% CI −0.42 to 8.82; 1 study, n = 58<br>(corresponds to SMD 0.42, 95% CI −0.13 to 0.98) | 2 levels: 2 domains with high RoB | NA | No | 2 levels: n < 400, and CI includes null and possibly important effect based on SMD. | No | Very low |
| Global status (endpoint across multiple scales)/6 months | Analysis 3.2. | SMD −0.12, 95% CI −0.28 to 0.04; 3 studies, n = 631 | 1 level: high RoB in 2 domains (study weighted < 10%) and unclear in 2 domains (study weighted < 20% | No | No: some concern with indirectness (30% dementia in study weighted < 20%), but insufficient for downgrading certainty another level | No | No | Moderate |
| Global status (endpoint across multiple scales)/6 months<br>Sensitivity analysis by risk of bias | Analysis 3.3 | MD −0.04, 95% CI −0.08 to 0; 1 study, n = 450 | No | NA | No | No | No | High |
| Global status (CDR)/12 months | Analysis 3.4 | SMD −0.17, 95% CI −0.33 to −0.01; $I^2$ = 0%; 2 studies, n = 604 | ½ level: unclear RoB in 1 domain in | No | No | No | No | Moderate |



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| | | | study weighted 28% | | | | | |
| Global status (CDR) /12 months<br><br>Sensitivity analysis by risk of bias | Analysis 3.5 | MD −0.04, 95% CI −0.09 to 0.01; 1 study, n = 430 | No | NA | No | No | No | High |
| Cognition (MDRS) /3 months | Analysis 3.6 | MD −0.20, 95% CI −7.44 to 7.04; 1 study, n = 58<br><br>(corresponds to SMD −0.01, 95% CI −0.56 to 0.53) | 2 levels: 2 domains with high RoB | NA | No | 2 levels: n < 400, and CI includes null and possibly important effect based on SMD (important change for MDRS unknown). | No | Very low |
| Cognition (MDRS) /6 months | Analysis 3.7 | SMD −0.02, 95% CI −0.20 to 0.15; $I^2$ = 0%; 2 studies, n = 508 | 1 level: high RoB in study that is weighted 10% | No | No | No | No | Moderate |
| Cognition (MDRS)/6 months<br><br>Sensitivity analysis by risk of bias | Analysis 3.8 | MD −0.10, 95% CI −0.71 to 0.51; 1 study, n = 450 | No | NA | No | No | No | High |
| Cognition (SKT change) /6 months | Analysis 3.9 | MD 0.40, 95% CI −1.04 to 1.84; 1 study, n = 123 | ½ level: 2 domains with unclear RoB | NA | ½ level: some indirectness | 1 level: n<400 | No | Low |
| Cognition (endpoint and change on ADAS-Cog)/12 months | Analysis 3.10 | MD 1.95, 95% CI −5.29 to 1.39; $I^2$= 96%; 2 studies, n = 604<br><br>(corresponds to SMD −0.57, 95% CI −1.57 to 0.42) | No, though there is 1 area with unclear RoB in 49% weight study | 1 level: $I^2$= 96% | No | 1 level: CI includes null and important effect based on SMD (important ADAS-Cog change for people with mild impairment may be 2 or 3 points; PMID: 38561021). | No | Low |
| Cognition (endpoint and change on ADAS-Cog)/12 months | Analysis 3.11 | MD −0.27, 95% CI −0.95 to 0.41; P = 0.43; 1 study, n = 430 | No | No | No | No | No | High |


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| ADLs (NAI-NAA self-assessed)/3 months | Analysis 3.12 | MD −1.35, 95% CI −2.88 to 0.18; 1 study, n = 214 | ½ level: 2 domains with unclear RoB | NA | ½ level: some indirectness | 1 level: n < 400. Trialist states that clinical relevance was predetermined as 4 points so no downgrade for null and important effect. | No | Low |
| ADLs (endpoint-IADL)/6 months | Analysis 3.13 | MD −0.05, 95% CI −0.29 to 0.19; 1 study, n = 350 | No | NA | No | 1 level: n < 400 | No | Moderate |
| ADLs (NAI-NAA staff-assessed change)/6 months | Analysis 3.14 | MD 0.00, 95% CI −1.94 to 1.94; 1 study, n = 123 | ½ level: 2 domains with unclear RoB | NA | ½ level: some indirectness | 1 level: n < 400 | No | Low |
| ADLs (endpoint-IADL)/12 months | Analysis 3.15 | MD −0.07, 95% CI −0.31 to 0.17; 1 study, n = 338 | No | NA | No | 1 level: n < 400 | No | Moderate |
| ADLs (AD-CS-ADL-MCI-24-change)/12 months | Analysis 3.16 | MD 1.63, 95% CI 0.07 to 3.19; 1 study, n = 174 | 1 level: unclear RoB in 1 domain, downgraded 1 full level to be conservative | NA | No | 1 level: n < 400 | No | Low |
| AEs/up to 12 months | Analysis 3.17 | RR 0.98, 95% CI 0.77 to 1.24; $I^2$= 58%; 7 studies, n = 991; 379 events; | 1 level: studies with high RoB contributing substantially to effect estimate | 1 level: $I^2$= 58% | No | No | No | Low |
| AEs/up to 12 months Sensitivity analysis by risk of bias | Analysis 3.17; | RR 0.99, 95% CI 0.58 to 1.68; 1 study, n = 296, 46 events | No | NA | No | 1 level: < 300 events | No | Moderate |


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| SAEs/6 months | Analysis 3.18 | RR 0.95, 95% CI 0.82 to 1.09; $I^2$ = 0%; 3 studies, n = 714, 327 events | No: 95% of evidence is from study with low RoB | No | No | No | No | High |
| SAEs/6–12 months | Analysis 3.19 | RR 0.96, 95% CI 0.83 to 1.11; 1 study, n = 430, 272 events | No | NA | No | No (although number of events slightly below 300) | No | High |
| Memory (combined outcome)/3 months | Analysis 3.20 | SMD 0.06, 95% CI −0.12 to 0.25; $I^2$=0%; 2 studies, n = 510 | ½ level: 2 domains with unclear RoB in study weighted 33% | No | ½ level: some indirectness in study weighted 33% | No | No | Moderate |
| Memory (combined outcome)/3 months Sensitivity analysis by risk of bias | Analysis 3.20; Grass-Kapanke 2011 only | SMD 0.13, 95% CI −0.10 to 0.35; n = 296 | No | NA | No | 1 level: n < 400 | No | Moderate |
| Memory (combined outcome)/6 months | Analysis 3.21 | SMD 0.08, 95% CI −0.29 to 0.45; 1 study, n = 123 | ½ level: 2 domains with unclear RoB | NA | ½ level: some indirectness | 1 level: n < 400 | No | Low |
| Memory (AMIPB-DSR)/12 months | Analysis 3.22 | MD 1.17, 95% CI −0.39 to 2.73; 1 study, n = 174<br>(corresponds to SMD 0.23, 95% CI −0.08 to 0.53) | ½ level: unclear RoB in 1 domain | NA | No | 1½–2 levels: 1 level for n < 400 and ½–1 level for CI including null and important effect based on SMD. | No | Low |
| Executive function (combined outcome)/3 months | Analysis 3.23 | SMD 0.23, 95% CI 0.00 to −0.46; 1 study, n = 296 | No | NA | | 2 levels: n < 400, and CI includes null and important effect (based on SMD touching zero and close to −0.5; downgraded 1 full level to be conservative). | No | Low |
| Executive function (TMT B)/6 months | Analysis 3.24 | MD −12.50, 95% CI −24.29 to −0.71; 1 study, n = 159 | ½ level: unclear RoB in 1 domain | NA | No | 1 level: n < 400 | No | Low |


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| Mental QoL (SF-36)/3 months | Analysis 3.25 | MD 2.07, 95% CI −1.88 to 6.02; 1 study, n = 296 | No | NA | No | 2 levels: n < 400, and CI includes null and important effect (estimate as low as 5 for mental health; PMID: 38734041). | No | Low |
| Physical QoL (SF-36)/3 months | Analysis 3.26 | MD 3.32, 95% CI −0.39 to 7.03; 1 study, n = 296 | No | NA | No | 2 levels: n < 400, and CI includes null and important effect (estimate as low as 3 for physical health; PMID: 38734041). | No | Low |
| Anxiety (STAI-X1)/6 months | Analysis 3.27 | MD −2.80, 95% CI −5.16 to −0.44; 1 study, n = 159 | 1 level: unclear RoB in 1 domain, downgraded 1 full level to be conservative | NA | No | 1 level: n < 400 | No | Low |
| Depression (GDS changes)/3 months | Analysis 3.28 | MD 0.58, 95% CI −0.53 to 1.69; 1 study, n = 214 (corresponds to SMD 0.19, 95% CI −0.13 to 0.51) | ½ level: unclear RoB in 2 domains | NA | ½ level: some indirectness | 1 level: n < 400. While SMD indicates CI may cover both null and important effect, other literature suggests important change may be at least 2 points, so we did not downgrade further (PMID: 38942179). | No | Low |
| Depression (GDS changes)/6 months | Analysis 3.29 | MD −0.04, 95% CI −0.46 to 1.38; $I^2$ = 67%; 2 studies, n = 282 (corresponds to SMD −0.04, 95% CI −0.46 to 0.38) | 1 level | 1 level: $I^2$ = 66% | ½ level: some indirectness in study weighted 46.5% | 1 level: n < 400 | No | Very low |
| Depression (CESD endpoint)/6 months | Analysis 3.30 | MD 0.11, 95% CI −0.70 to 0.92; 1 study, n = 450 | No | NA | No | No | No | High |


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| Depression (CESD endpoint)/12 months | Analysis 3.31 | MD 0.45, 95% CI −0.40 to 1.30; 1 study, n = 430 | No | NA | No | No | No | High |
| Mental well-being (BfS')/3 months | Analysis 3.32 | MD 1.78, 95% CI −0.70 to 4.26; 1 study, n = 296 (corresponds to SMD 0.16, 95% CI −0.07 to 0.39) | No | NA | No | 1 level: n < 400 | No | Moderate |
| NPI/6 months | Analysis 3.33 | MD −1.50, 95% CI −3.01 to 0.01; 1 study, n = 159 (corresponds to SMD −0.31, 95% CI −0.62 to 0.01) | ½ level: unclear RoB in 1 domain | NA | No | 2 levels: n < 400, and CI includes null and important effect (based on SMD – an estimate of NPI important change may be as low as 2.77; PMID: 26046666). | No | Low |


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ADAS-Cog: Alzheimer Disease Assessment Scale – cognition; ADCS-ADL-MCI: Alzheimer's Disease Cooperative Study – Activities of Daily Living for Mild Cognitive Impairment; ADLs: activities of daily living; AEs: adverse events; AMIPB-DSR: Adult Memory and Information Processing Battery – Delayed Story Recall; BfS': *Befindlichkeitsskala* (mental balance scale); CI: confidence interval; CDR: Clinical Dementia Rating; CESD: Center for Epidemiologic Studies Depression Scale; GDS: Geriatric Depression Scale; IADL: Instrumental Activities of Daily Living; MCI: mild cognitive impairment; MD: mean difference; MDRS: Mattis Rating Dementia Scale; n: number of participants; NA: not applicable; NAI-NAA: *Nürnberger Alters Alltagsaktivitäten Skala* (Nuremberg gerontopsychological rating scale for activities of daily living); NPI: Neuropsychiatric Inventory; QoL: quality of life; RoB: risk of bias; RR: risk ratio; SAEs: serious adverse events; SCAG: Sandoz Clinical Assessment Geriatric Scale; SF-36: 36-item Short Form Health Survey; SKT: *Syndrom-Kurztest* (short cognitive performance test); SMD: standardized mean difference; STAI-X1: State subscale of State-Trait Anxiety Inventory; TMT: Trail Making Test.


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## Appendix 5. GRADE assessment for mild cognitive impairment: *Ginkgo biloba* versus conventional medications

| Outcome (scale)/ time | Conventional medication | Analysis | Results | Reasons for downgrading certainty of evidence | | | | | GRADE rating |
|---|---|---|---|---|---|---|---|---|---|
| | | | | Risk of bias | Inconsistency ($I^2 \geq 50\%$; NA if only 1 study) | Indirectness (review and study PICO do not match) | Imprecision (events < 300 [twice for events < 25], n < 400 [twice for n < 50], CI includes no effect and important effect (SMD ± 0.5, RR ± 1.25) | Other reasons (e.g. publication bias) | |
| Cognition (MoCA)/3 months | Butylphthalide | Analysis 4.1 | MD −3.16, 95% CI −4.55 to −1.77; 1 study, n = 46 | 1 level | NA | No | 2 levels: n < 50 | No | Very low |
| Cognition (MoCA)/3 months | Donepezil | Analysis 4.2 | MD −3.70, 95% CI −5.11 to −2.29; 1 study, n = 100 | 2 levels: very serious RoB | NA | No | l level: n < 400 | No | Very low |
| Cognition (MoCA)/6 months | Nimodipine | Analysis 4.3 | MD 0.40, 95% CI −1.11 to 1.91; 1 study, n = 80 (corresponds to SMD 0.11, 95% CI −0.32 to 0.55) | 1 level | NA | No | 2 levels: n < 400, and CI includes both null and possibly meaningful effect based on SMD (important change for MoCA in MCI unknown). | No | Very low |
| ADLs (Lamton IADL scale)/3 months | Butylphthalide | Analysis 4.4 | MD −12.38, 95% CI −15.76 to −9.00; 1 study, n = 46 | 1 level | NA | No | 2 levels: n < 50 | No | Very low |
| ADLs (100-point scale)/3 months | Donepezil | Analysis 4.5 | MD 5.40, 95% 1.19 to 9.61; 1 study, n = 100 | 2 levels: very serious RoB | NA | No | l level: n < 400 | No | Very low |
| ADLs (100-point scale)/6 months | Nimodipine | Analysis 4.6 | MD 1.90, 95% CI −2.59 to 6.39; 1 study, n = 80 (corresponds to SMD 0.18, 95% CI −0.26 to 0.62) | 1 level | NA | No | 2 levels: n < 400, and CI includes both null and possibly meaningful effect based on SMD (important change on 100-point scale unknown). | No | Very low |
| Memory (WMS)/3 months | Donepezil | Analysis 4.7 | MD −14.30, 95% CI −20.07 to −8.53; 1 study, n = 100 | 2 levels: very serious RoB | NA | No | 1 level: n < 400 | No | Very low |



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ADLs: activities of daily living; CI: confidence interval; IADL: Instrumental Activities of Daily Living; MD: mean difference; MCI: mild cognitive impairment; MoCA: Montreal Cognitive Assessment; n: number of participants; NA: not applicable; RoB: risk of bias; RR: risk ratio; SMD: standardized mean difference; WMS: Wechsler Memory Scale.


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**Appendix 6. GRADE assessment for mild cognitive impairment: *Ginkgo biloba* versus Chinese herbal medicine or acupuncture**

| Outcome (scale)/time | Chinese herbal medicine/acupuncture | Analysis | Results | Reasons for downgrading certainty of evidence | | | | | GRADE rating |
|---|---|---|---|---|---|---|---|---|---|
| | | | | Risk of bias | Inconsistency ($I^2 \geq 50\%$; NA if only 1 study) | Indirectness (review and study PICO do not match) | Imprecision (events < 300 [twice for events < 25], n < 400 [twice for n < 50], CI includes no effect and important effect (SMD ± 0.5, RR ± 1.25) | Other reasons (e.g. publication bias) | |
| Cognition (MoCA)/3 months | Acupuncture | Analysis 5.1 | MD −1.62, 95% CI −2.36 to −0.88; P < 0.01; 1 study, n = 57 | 1-2 levels | NA | No | 1 level: n < 400 | No | Very low |
| Cognition (ADAS-Cog)/3 months | Guilingji capsule | Analysis 5.2 | MD −0.06, 95% CI −3.55 to 3.43; P = 0.97; 1 study, n = 82 | 2 levels | NA | No | 1 level: n < 400 | No | Very low |
| Cognition (MMSE)/3 months | Yi Zhi Ling | Analysis 5.3 | MD −2.20, 95% CI −3.24 to −1.16; P < 0.01; 1 study, n = 66 | 2 levels | NA | No | 1 level: n < 400 | No | Very low |
| Cognition (MoCA)/3 months | Compound xueshuantong capsule | Analysis 5.4 | MD −3.70, 95% CI −5.21 to −2.19; P < 0.01; 1 study, n = 80 | 2 levels | NA | No | 1 level: n < 400 | No | Very low |
| Cognition (ADAS-Cog)/6 months | Guilingji capsule | Analysis 5.5 | MD 2.00, 95% CI −0.94 to 4.94; P = 0.18; 1 study, n = 82 | 2 levels | NA | No | 1 level: n < 400 | No | Very low |
| Cognition (ADAS-Cog)/12 months | Qinggongshoutao | Analysis 5.6 | MD −0.33, 95% CI −1.15 to 0.49; P = 0.43; 1 study, n = 278 | 1 level | NA | No | 1 level: n < 400 | No | Low |
| ADLs (100-point scale)/6 months | Compound xueshuantong | Analysis 5.7 | MD −9.80, 95% CI −14.63 to −4.97; P < 0.01; 1 study, n = 80 | 2 levels | NA | No | 1 level: n < 400 | 1 level: scale unknown | Very low |



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| AEs/up to 12 months | Qinggong-shoutao | Analysis 5.8 | RR 0.83, 95% CI 0.63 to 1.09; 130 events; 1 study, n = 278 | 1 level | NA | No | 1 level: events < 300 | No | Low |
| SAEs/up to 12 months | Qinggong-shoutao | Analysis 5.9 | RR 3.35, 95% CI 0.62 to 17.95; 1 study, n = 278, 6 events | No: possible selective reporting but seems unlikely that it would affect reporting of SAEs | NA | No | 3 levels: events < 25, and CI includes no effect/benefit and harm. | No | Very low |
| Memory (MQ)/3 months | Jiawei Wuzi Yanzong | Analysis 5.10 | MD −2.42, 95% CI −9.35 to 4.51; P = 0.49; 1 study, n = 43 | 2 levels | NA | No | 3 levels: n < 50, and CI includes no effect and benefit/harm. | No | Very low |


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ADAS-Cog: Alzheimer Disease Assessment Scale – cognition; ADLs: activities of daily living; AEs: adverse effects; CI: confidence interval; MD: mean difference; n: number of participants; MQ: Wechsler Memory Scale – Memory Quotient; NA: not applicable; RoB: risk of bias; RR: risk ratio; SAEs: serious adverse effects; SMD: standardized mean difference.


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## Appendix 7. GRADE assessment for mild cognitive impairment: *Ginkgo biloba* added to conventional treatment

| Outcome (scale)/time | Analysis | Results | Reasons for downgrading certainty of evidence | | | | | GRADE rating |
|---|---|---|---|---|---|---|---|---|
| | | | Risk of bias | Inconsistency ($I^2 \geq 50\%$; NA if only 1 study) | Indirectness (review and study PICO do not match) | Imprecision (events < 300 [twice for events < 25], n < 400 [twice for n < 50], CI includes no effect and important effect (SMD ± 0.5, RR ± 1.25) | Other reasons (e.g. publication bias) | |
| Global status (CIBIC)/3 months | Analysis 6.1 | MD −1.03, 95% CI −1.87 to −0.19; P = 0.02; 1 study, n = 68 | 1 level | NA | No | 1 level: n < 400 | No | Low |
| Global status (CIBIC)/6 months | Analysis 6.2 | MD −1.03, 95% CI −2.23 to 0.17; P = 0.09; 1 study, n = 68 (corresponds to SMD −0.40, 95% CI −0.88 to 0.08) | 1 level | NA | No | 2 levels: n < 400, and CI includes no effect and important effect based on SMD (important change on CIBIC+ unknown). | No | Very low |
| Cognition (compound scale)/3 months | Analysis 6.3 | SMD 0.98, 95% CI 0.73 to 1.24; $I^2$= 80%; 15 studies, n = 1339 | 2 levels: high RoB in multiple studies | 1 level: $I^2$= 80% | No | No | 1 level: strong suspicion of publication bias based on Fig 4 | Very low |
| Cognition (compound scale)/6 months | Analysis 6.4 | SMD 0.90, 95% CI 0.74 to 1.06; $I^2$=38%; 11 studies, n = 1160 | 2 levels: high RoB in multiple studies | No | No | No | 1 level: strong suspicion of publication bias based on Fig 4 | Very low |



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| Cognition (compound scale)/12 months | Analysis 6.5 | SMD 0.97, 95% CI 0.70 to 1.24; $I^2$= 56%; 4 studies, n = 578 | 2 levels: high RoB in multiple studies | 1 level: $I^2$= 56% | No | No | 1 level: strong suspicion of publication bias based on Fig 4 | Very low |
| ADLs (unspecified scale)/3 months | Analysis 6.10 | SMD 0.94, 95% CI 0.31 to 1.56; $I^2$= 93%; 7 studies, n = 636 | 2 levels: high RoB in multiple studies | 1 level: $I^2$= 93% | No | No | Suspicion of publication bias for cognitive outcome but GRADE rating already very low | Very low |
| ADLs (unspecified scale)/6 months | Analysis 6.11 | SMD 1.07, 95% CI 0.43 to 1.71; $I^2$= 75%; 2 studies, n = 180 | 2 levels: high RoB in multiple studies | 1 level: $I^2$= 75% | No | 1 level: n < 400 | Suspicion of publication bias for cognitive outcome but GRADE rating already very low | Very low |
| ADLs (unspecified scale)/12 months | Analysis 6.12 | SMD 0.76, 95% CI 0.35 to 1.17; 1 study, n = 100 | 2 levels: high RoB in multiple studies | NA | No | 1 level: n < 400 | Suspicion of publication bias for cognitive outcome but GRADE rating already very low | Very low |
| AEs/up to 6 months | Analysis 6.13 | RR 1.08, 95% CI 0.62 to 1.87; $I^2$=0%; 5 studies, n = 430, 46 events | 1 or 2 levels: high RoB in multiple studies. | No | No | 2 levels: < 300 events, and CI includes both meaningful increase (> 1.25) and protective effect (< 1). | Unclear whether possible publication bias would affect AE outcomes (and GRADE rating already very low) | Very low |
| Memory (WMS)/3 months | Analysis 6.14 | MD 6.62, 95% CI 3.06 to 10.19; $I^2$= 70%; 3 studies, n = 294 | 2 levels: high RoB in multiple studies | 1 level: $I^2$= 70%; | No | 1 level: n < 400 | Suspicion of publication bias but GRADE rating already very low | Very low |
| Memory (compound scale)/6 months | Analysis 6.15 | SMD 0.41, 95% CI 0.18 to 0.65; $I^2$=0%; 3 studies, n = 293 | 2 levels: high RoB in multiple studies | No | No | 1 level: n < 400 | Suspicion of publication bias but GRADE rating already very low | Very low |
| Memory (compound scale)/12 months | Analysis 6.16 | SMD 0.64, 95% CI 0.38 to 0.90; $I^2$= 0%; 2 studies, n = 233 | 2 levels: high RoB in multiple studies | No | No | 1 level: n < 400 | Suspicion of publication bias but GRADE rating already very low | Very low |


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| Executive function (CDT)/3 months | Analysis 6.17 | MD 0.56, 95% CI 0.15 to 0.97; 1 study, n = 69 | 2 levels: high RoB in multiple studies | NA | No | 1 level: n < 400 | Suspicion of publication bias but GRADE rating already very low | Very low |
| Executive function/6 months | Analysis 6.18 | SMD 0.57, 95% CI 0.37 to 0.77; $I^2$=0%; 3 studies, n = 418 | 2 levels: high RoB in multiple studies | No | No | No | No: some suspicion of publication bias but no direct evidence | Low |
| Executive function (CDT)/12 months | Analysis 6.19 | MD 0.57, 95% CI 0.39 to 0.75; $I^2$= 0%; 2 studies, n = 358 | 2 levels: high RoB in 1 study and unclear RoB in several domains in all studies | No | No | 1 level: n < 400 | Suspicion of publication bias but GRADE rating already very low | Very low |


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ADLs: activities of daily living; AEs: adverse events; CDT: Clock Drawing Test; CI: confidence interval; CIBIC: Clinician's Interview-Based Impression of Change; MD: mean difference; n: number of participants; NA: not applicable; RoB: risk of bias; RR: risk ratio; SMD: standardized mean difference; WMS: Wechsler Memory Scale.


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## Appendix 8. GRADE assessment for dementia: *Ginkgo biloba* versus placebo

| Outcome (scale)/time | Analysis | Results | Reasons for downgrading certainty of evidence | | | | | GRADE rating |
|---|---|---|---|---|---|---|---|---|
| | | | Risk of bias | Inconsistency ($I^2$≥ 50%; NA if only 1 study) | Indirectness (review and study PICO do not match) | Imprecision (events < 300 [twice for events < 25], n < 400 [twice for n < 50], CI includes no effect and important effect (SMD ± 0.5, RR ± 1.25) | Other reasons (e.g. publication bias) | |
| Global status (Likert scale)/3 months | Analysis 7.1; | SMD −0.87, 95% CI −1.85 to 0.11; 1 study, n = 18 | 1 level | NA | No | 3 levels: n < 50, and CI covers important effect and the null based on SMD (important difference on Likert scale is unknown). | No | Very Low |
| Global status (Likert scale)/6 months | Analysis 7.2 | SMD −0.55, 95% CI −0.89 to −0.21; $I^2$= 88%; 5 studies, n = 1359 | 1 level | 1 level: $I^2$= 88% | No | No | No | Low |
| Global status (Likert scale)/12 months | Analysis 7.3 | SMD 0.00, 95% CI −0.22 to 0.22; 1 study, n = 309 | 1 level | NA | No | 1 level: n < 400 | No | Low |
| Cognition (ADAS-Cog)/3 months | Analysis 7.5 | MD −5.80, 95% CI −19.82 to 8.22; 1 study, n = 18 | 1 level | NA | No | 2 levels: n < 50, and CI covers important effect and the null (important ADAS-Cog change may be as low as 3 points; PMID 3856021). | No | Very Low |
| Cognition (combined scale)/6 months | Analysis 7.6 | SMD −0.47, 95% CI −0.88 to −0.06; $I^2$= 96%; 9 studies, n = 2801 | 1 level | 1 level: $I^2$= 96%. Considered downgrading twice but the negative studies were not statistically significant | No | No | No | Low |


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| | | | | (not clearly negative). | | | | |
| Cognition (ADAS-Cog)/12 months | Analysis 7.7 | MD −1.40, 95% CI −2.78 to −0.02; 1 study, n = 274 | 1 level | NA | No | 1 level: n < 400 | No | Low |
| ADLs (combined scale)/6 months | Analysis 7.9 | SMD −0.32, 95% CI −0.59 to −0.05; $I^2$= 91%; 8 studies, n = 2571 | 1 level | 1 level: $I^2$= 91%. Considered downgrading twice but the negative study was not statistically significant (not clearly negative). | No | No | No | Low |
| ADLs (GERRI)/12 months | Analysis 7.10 | MD −0.14, 95% CI −0.2 to −0.05; P < 0.01; 1 study, n = 270 | 1 level | NA | No | 1 level: n < 400 | No | Low |
| AEs/up to 12 months | Analysis 7.12 | RR 0.95, 95% CI 0.90 to 1.00; $I^2$= 0%; 9 studies, n = 2746, 1480 events | 1 level | No | No | No | No | Moderate |
| SAEs/up to 6 months | Analysis 7.13 | RR 0.88, 95% CI 0.58 to 1.33; $I^2$= 0%; 6 studies, n = 2463, 89 events | No: some RoB but unlikely to affect detection and reporting of SAEs | No | No | 2 levels: < 300 events, and CI ranges from increased risk (> 1.25) to protective effect (< 1.00). | No | Low |
| Memory (Benton)/3 months | Analysis 7.14 | MD 0.20, 95% CI −0.86 to 1.26; 1 study, n = 47 (corresponds to SMD 0.42, 95% CI −0.47 to 0.68) | 1 level | NA | No | 3 levels: n < 50, and CI covers important effect and the null based on SMD (important difference on Benton is unknown). | No | Very Low |
| Executive function (combined | Analysis 7.15 | SMD 0.64, 95% CI 0.02 to 1.26; $I^2$= 96%; 4 studies, n = 1698 | 1 level | 1 level: $I^2$= 96%. Considered downgrading twice but there | No | No | No | Low |


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| scale)/6 months | | | | were not clearly negative and positive studies. | | | | |
| QoL (combined scale)/6 months | Analysis 7.16 | SMD 0.11, 95% CI −0.06 to 0.28; $I^2$= 60%; 4 studies, n = 1392 | 1 level | 1 level: $I^2$= 60% | No | No | No | Low |
| Depression (HAM-D)/6 months (change) | Analysis 7.18 | MD −2.31, 95% CI −6.03 to 1.42; $I^2$= 99%; 2 studies, n = 792 (corresponds to SMD −0.91, 95% CI −2.47 to 0.65) | No | 1 level: $I^2$= 99%. Considered downgrading twice but there were not clearly negative and positive studies. | No | 1 level: CI covers important effect and the null based on SMD (important difference on HAM-D in dementia is unknown). | No | Low |
| Depression (MADRS)/6 months (endpoint measure) | Analysis 7.19 | MD −0.40, 95% CI −2.57 to 1.77; P = 0.72; 1 study, n = 156<br><br>(corresponds to SMD −0.06, 95% CI −0.37 to 0.26) | No | No | No | 1 level: n < 400. No further downgrade as important change on MADRS in dementia is unknown and the CI for the SMD does not reach −0.50. | No | Moderate |
| NPI/6 months | Analysis 7.20 | MD −3.95, 95% CI −7.34 to −0.57; $I^2$= 96%; 5 studies, n = 1686 | 1 level | 1 level: $I^2$= 96%. Considered downgrading twice but there were not clearly negative and positive studies. | No | No | No | Low |


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ADAS-Cog: Alzheimer Disease Assessment Scale – cognition; AEs: adverse events; CI: confidence interval; GERRI: Geriatric Evaluation of Relative's Rating Instrument; HAM-D: Hamilton Rating Scale for Depression; MADRS: Montgomery Åsberg Depression Rating Scale; MD: mean difference; n: number of participants; NA: not applicable; NPI: Neuropsychiatric Inventory; QoL: quality of life; RoB: risk of bias; RR: risk ratio; SAEs: serious adverse events; SMD: standardized mean difference.


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## Appendix 9. GRADE assessment for dementia: *Ginkgo biloba* versus conventional medications (donepezil)

| Population/comparison/outcome/time | Analysis | Results | Reasons for downgrading certainty of evidence | | | | | GRADE rating |
|---|---|---|---|---|---|---|---|---|
| | | | Risk of bias | Inconsistency ($I^2$≥ 50%; NA if only 1 study) | Indirectness (review and study PICO do not match) | Imprecision (events < 300 [twice for events < 25], n < 400 [twice for n < 50], CI includes no effect and important effect (SMD ± 0.5, RR ± 1.25) | Other reasons (e.g. publication bias) | |
| Global status (CGIC)/6 months | Analysis 8.1 | MD 0.15, 95% CI −0.43 to 0.73; P = 0.61; 1 study, n = 41 (corresponds to SMD 0.15, 95% CI −0.46 to 0.77) | 1 level | NA | No | 3 levels: n < 50, and CI includes important effect and the null based on the SMD (important difference on CGIC is unknown). | No | Very low |
| Cognition (SKT)/6 months | Analysis 8.2 | MD 1.03, 95% CI −0.29 to 2.36; P = 0.13; $I^2$= 0%; 2 studies, n = 103 (corresponds to SMD 0.28, 95% CI −0.11 to 0.67) | 1 level | No | No | 2 levels: n < 400, and CI includes important effect and the null based on the SMD (important difference on SKT is unknown). | No | Very low |
| ADLs (GBS-ADL)/6 months | Analysis 8.3 | MD −1.81, 95% CI −3.94 to 0.32; P = 0.10; 1 study, n = 62 (corresponds to SMD −0.41, 95% CI −0.91 to 0.09) | 1 level | NA | No | 2 levels: n < 400, and CI includes important effect and the null based on the SMD (important difference on GBS-ADL is unknown). | No | Very low |
| AEs/up to 6 months | Analysis 8.4 | RR 0.42, 95% CI 0.25 to 0.72; P < 0.01; $I^2$= 0%; 2 studies, n = 112, 38 events | 1 level | No | No | 1 level: < 300 events | No | Low |
| SAEs/up to 6 months | Analysis 8.5 | RR 3.19, 95% CI 0.14 to 75.49; 1 study, n = 62, 1 event | No, although there is some RoB it is unlikely that it would affect detection and reporting of SAEs. | NA | No | 3 levels: < 25 events, and CI includes important effect and the null. | No | Very low |


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| Executive function (combined scale)/6 months | Analysis 8.6 | SMD 0.31, 95% CI −0.19 to 0.82; 1 study, n = 62 | 1 level | NA | No | 2 levels: n < 400, and CI includes important effect and the null based on the SMD. | No | Very low |
| Depression (HAM-D)/6 months | Analysis 8.7 | MD 0.00, 95% CI −1.55 to 1.55; P = 1.00; 1 study, n = 62 (corresponds to SMD −0.50, 95% CI −0.50 to 0.50) | 1 level | NA | No | 2 levels: n < 400, and CI includes important effect and the null based on the SMD (important difference on HAM-D in dementia, is unknown and small change is possibly important in dementia). | No | Very low |
| NPI/6 months | Analysis 8.8 | MD 1.20, 95% CI −2.58 to 4.98; P = 0.53; 1 study, n = 62 | 1 level | NA | No | 2 levels: n < 400, and CI includes important effect and the null based on the SMD and an estimate of NPI importan.t change as low as 2.77 (PMID: 26046666). | No | Very low |


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ADLs: activities of daily living; AEs: adverse events; CGIC: Clinical Global Impression of Change; CI: confidence interval; GBS-ADL: Gottfries, Bråne and Steen ADL scale; HAM-D: Hamilton Rating Scale for Depression; MD: mean difference; n: number of participants; NA: not applicable; NPI: Neuropsychiatric Inventory; RoB: risk of bias; RR: risk ratio; SAEs: serious adverse events; SKT: *Syndrom-Kurztest* (short cognitive performance test); SMD: standardized mean difference.


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## Appendix 10. GRADE assessment for dementia: *Ginkgo biloba* versus Chinese herbal medicine or acupuncture

| Outcome/time | Chinese herbal medicine/acupuncture | Analysis | Results | Reasons for downgrading certainty of evidence | | | | | GRADE rating |
|---|---|---|---|---|---|---|---|---|---|
| | | | | Risk of bias | Inconsistency ($I^2 \geq 50\%$; NA if only 1 study) | Indirectness (review and study PICO do not match) | Imprecision (events < 300 [twice for events < 25], n < 400 [twice for n < 50], CI includes no effect and important effect (SMD ± 0.5, RR ± 1.25) | Other reasons (e.g. publication bias) | |
| Cognition (FIM)/3 months | Acupuncture | Analysis 9.1 | MD −6.89, 95% CI −7.90 to −5.88; P < 0.01; 1 study, n = 100 | 2 levels | NA | No | 1 level: n < 400 | *Ginkgo biloba* is the control condition in each of these studies. There is some concern that publication bias could be operating and that studies showing the benefit of the active intervention versus *Ginkgo biloba* are more likely to be published. However, there was no explicit downgrading. | Very low |
| Cognition (MMSE)/3 months | Chinese herbal decoction | Analysis 9.2 | MD −3.47, 95% CI −5.00 to −1.94; P < 0.01; 1 study, n = 96 | 2 levels | NA | No | 1 level: n < 400 | | Very low |
| Cognition (MoCA)/3 months | Shenma Yizhi Recipe | Analysis 9.3 | MD 0.34, 95% CI −1.79 to 2.47; P = 0.75; 1 study, n = 64 (corresponds to SMD 0.08, 95% CI −0.41 to 0.57) | 2 levels | NA | No | 2 level: n < 400, and CI covers important effect and the null based on the SMD (important difference in MoCA is unknown). | | Very low |
| Cognition (MMSE)/3 months | Tongxinluo capsule | Analysis 9.4 | MD −2.00, 95% CI −3.30 to −0.70; P < 0.01; 1 study, n = 120 | 2 levels | NA | No | 1 level: n < 400 | | Very low |
| ADLs (IADL)/3 months | Acupuncture | Analysis 9.5 | MD 7.40, 95% CI 5.53 to 9.27; P < 0.01; 1 study, n = 100 | 2 levels | NA | No | 1 level: n < 400 | | Very low |
| ADLs (combined scale)/3 months | Chinese herbal decoction | Analysis 9.6 | SMD −1.06, 95% CI −1.49 to −0.63; P < 0.01; 1 study, n = 96 | 2 levels | No | No | 1 level: n < 400 | | Very low |



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| ADLs (combined scale)/3 months | Shenma Yizhi Recipe | Analysis 9.7 | SMD −0.55, 95% CI −1.05 to −0.05; P = 0.03; 1 study, n = 64 | 2 levels | NA | No | 1 level: n < 400 | Very low |
| ADLs (combined scale)/3 months | Tongxinluo capsule | Analysis 9.8 | SMD −1.04, 95% CI −1.42 to −0.66; P < 0.01; 1 study, n = 120 | 2 levels | NA | No | 1 level: n < 400 | Very low |


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ADLs: activities of daily living; CI: confidence interval; FIM: Function Independence Measure; IADL: Instrumental Activities of Daily Living functional activities questionnaire; MD: mean difference; MMSE: Mini Mental State Examination; MoCA: Montreal Cognitive Assessment; n: number of participants; NA: not applicable; RoB: risk of bias; RR: risk ratio; SMD: standardized mean difference.


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## Appendix 11. GRADE assessment for dementia: *Ginkgo biloba* added to conventional treatment

| Outcome (scale)/time | Analysis | Results | Reasons for downgrading certainty of evidence | | | | | GRADE rating |
|---|---|---|---|---|---|---|---|---|
| | | | Risk of bias | Inconsistency ($I^2 \geq 50\%$; NA if only 1 study) | Indirectness (review and study PICO do not match) | Imprecision (events < 300 [twice for events < 25], n < 400 [twice for n < 50], CI includes no effect and important effect (SMD ± 0.5, RR ± 1.25) | Other reasons (e.g. publication bias) | |
| Global status (CDR)/3 months | Analysis 10.1 | MD −0.40, 95% CI −0.49 to −0.31; P < 0.01; 1 study, n = 100 | 1 level | NA | No | 1 level: n < 400 | No | Low |
| Cognition (combined scale)/3 months | Analysis 10.2 | SMD 1.25, 95% CI 0.81 to 1.69; P < 0.01; $I^2$= 86%; 9 studies, n = 728 | 2 levels | 1 level: $I^2$= 86% | No | No | 1 level: strong suspicion of publication bias based on Figure 5 | Very low |
| Cognition (combined scale) /6–9 months | Analysis 10.3 | SMD 1.63, 95% CI 0.92 to 2.34; P < 0.01; $I^2$= 93%; 7 studies, n = 585 | 2 levels | 1 level: $I^2$= 93% | No | No | 1 level: strong suspicion of publication bias based on Figure 5 | Very low |
| Cognition (change value on SKT)/6 months | Analysis 10.4 | MD −1.00, 95% CI −2.68 to 0.68; P = 0.24; 1 study, n = 63<br><br>(corresponds to SMD −0.29, 95% CI −0.79 to 0.21) | 1 level | NA | No | 2 levels: n < 400, and CI includes both important effect and the null based on the SMD (important difference on SKT is unknown). | No: study did not report MMSE at any time point and was not included in Figure 5. | Very low |
| ADLs (combined scale)/3 months | Analysis 10.8 | SMD 1.38, 95% CI 0.76 to 2.00; P < 0.01; $I^2$= 93%; 9 studies, n = 728 | 2 levels | 1 level: $I^2$= 93%. Considered downgrading twice, but there | No | No | No | Very low |


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| | | | | were no clearly negative and positive studies. | | | | |
| ADLs (combined scale)/6–9 months | Analysis 10.9 | SMD 1.46, 95% CI 0.77 to 2.16; P < 0.01; $I^2$= 94%; 8 studies, n = 678 | 2 levels | 1 level: $I^2$= 94%. Considered downgrading twice, but there were no clearly negative and positive studies. | No | No | No | Very low |
| AEs/overall events up to 6 months | Analysis 10.12 | RR 0.88, 95% CI 0.67 to 1.16; $I^2$= 0%, P = 0.36; 8 studies, n = 640, 118 events | 1 level | No | No | 1 level: < 300 events | No | Low |
| SAEs/overall events up to 6 months | Analysis 10.13 | RR 0.05, 95% CI 0.00 to 0.85; 1 study, n = 77, 9 events | 1 level: while RoB may not be very important for detection SAEs, this study has major problems and may be considered unreliable. | NA | No | 2 levels: < 25 events | No | Very low |
| Memory (MMSE)/6 months | Analysis 10.14 | MD 0.72, 95% CI 0.36 to 1.08; P < 0.01; 1 study, n = 104 | 1 level | NA | No | 1 level: n < 400 | No | Low |
| Executive function (combined | Analysis 10.15 | SMD 0.28, 95% CI −0.22 to 0.77; 1 study, n = 63 | 1 level | NA | No | 2 levels: n < 400, and CI includes both important effect and the null based on the SMD. | No | Very low |


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| | | | | | | | | |
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| scale)/6 months | | | | | | | | |
| Depression (HAM-D)/6 months | Analysis 10.16 | MD −0.40, 95% CI −2.13 to 1.33; 1 study, n = 63 (corresponds to SMD −0.11, 95% CI −0.61 to 0.38) | 1 level | NA | No | 2 levels: n < 400, and CI includes both important effect and the null based on the SMD (important difference on HAM-D in dementia is unknown; small change may be important in dementia). | No | Very low |
| NPI/3 months | Analysis 10.17 | MD −1.93, 95% CI −2.67 to −1.19; P < 0.01; 1 study, n = 92 | 1 level | NA | No | 1 level: n < 400 | No | Low |
| NPI/6 months | Analysis 10.18 | MD −3.13, 95% CI −7.27 to 1.02; P = 0.14; $I^2$= 69%; 2 studies, n = 161 (corresponds to SMD −0.49, 95% CI −1.29 to 0.31) | 1 level | 1 level: $I^2$= 69% | No | 2 levels: n < 400, and CI includes both important effect and the null based on the SMD and an estimate of NPI important change as low as 2.77 (PMID: 26046666). | No | Very low |

ADLs: activities of daily living; AEs: adverse events; CDR: Clinical Dementia Rating; CI: confidence interval; HAM-D: Hamilton Rating Scale for Depression; MD: mean difference; MMSE: Mini Mental State Examination; n: number of participants; NA: not applicable; NPI: Neuropsychiatric Inventory; RoB: risk of bias; RR: risk ratio; SAEs: serious adverse events; SKT: *Syndrom-Kurztest* (short cognitive performance test); SMD: standardized mean difference.


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## HISTORY

Protocol first published: Issue 7, 2020

## CONTRIBUTIONS OF AUTHORS

LSW: screening of studies, correspondence with study authors, correspondence with translators, data extraction, data entry, risk of bias assessment, data analysis and interpretation, GRADE assessment, drafting and revising of review.
EL: screening of studies, correspondence with translators, correspondence with study authors, data extraction, data entry, risk of bias assessment, GRADE assessment, drafting of review.
TMF: data extraction, analysis of raw data from the GEM trial, advising on types of intervention, comments on draft review.
YC: searching for trials, screening of studies, correspondence with study authors, data extraction, data entry, risk of bias assessment, comments on draft review.
IHC: screening of studies, correspondence with study authors, data extraction, data entry, risk of bias assessment, comments on draft review.
KHC: searching for trials, screening of studies, correspondence with study authors, data extraction, data entry, risk of bias assessment, comments on draft review.
YZ: screening of studies, correspondence with study authors, data extraction, data entry, risk of bias assessment, comments on draft review.
EW: advising on types of cognitive impairment or dementia, advising on outcome measures, comments on draft review.
HA: comments on protocol, comments on draft review.

## DECLARATIONS OF INTEREST

LSW: is the Director of Cochrane Complementary Medicine. She was not involved in the editorial process for this review.
EL: none known.
YC: was a member of the Cochrane Governing Board until 2025. She was not involved in the editorial process for this review.
IHC: none known.
KHC: is the Deputy Director and Chief Executive Officer of Cochrane Taiwan. She was not involved in the editorial process for this review.
YZ: none known.
EW: none known.
TMF: serves as a long-term epidemiology contractor for the National Institutes of Health's National Center for Complementary and Integrative Health.
HA: none known.

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## DIFFERENCES BETWEEN PROTOCOL AND REVIEW

In the protocol, we did not explicitly state whether we would include or exclude studies in which participants were at extremely high risk of cognitive problems and were treated on this basis rather than on the basis of any existing cognitive problems or complaints. A key example is studies of people who have had strokes. People who have had strokes have a high risk of cognitive deficits post-stroke and may


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receive treatments to prevent or limit cognitive problems. Since these participants are at extremely high risk of cognitive problems and are not 'healthy', we considered including such studies even when the participants were not characterized as having cognitive problems at baseline. However, we decided that to be consistent with our inclusion criteria of 'existing cognitive impairment or dementia' and with the other studies in the review, we would only include such studies when the participants were included on the basis of some existing subjective or objective cognitive impairment, or were all characterized as suffering from existing subjective or objective cognitive problems, and not when they were included solely on the basis of having had a stroke or other health problem that put them at high risk of manifesting cognitive issues.

We added neuropsychiatric outcomes (including depression or anxiety and the Neuropsychiatric Inventory [NPI]) to our review outcomes because there have recently been suggestions that ginkgo could be helpful for neuropsychiatric outcomes.

In the protocol, we gave examples of scales to measure global clinical status, but we did not specify whether we would use only continuous data from scales or also calculate effects from dichotomous judgments reported by trialists. We decided that both the variability between how cut-off points are used for scales and the possibility of bias from unblinded trials that tended to use dichotomous statements about benefit rendered dichotomous outcomes less desirable than continuous estimates, and we restricted our analysis to continuous effects.

In the protocol, we did not prespecify our preferred outcomes for global cognitive function. When we observed that many studies used more than one measure of global cognitive function, we sought advice from the Cochrane Review Group Co-ordinating Editor, who advised us to choose the more comprehensive measure when one measure covered more information about cognitive functioning. When a study used more than one measure, and we could not say that one was more comprehensive than the other, we chose the measure used by most other studies in the analysis.

In the protocol, we did not prespecify our preferred outcomes for memory and executive function, or how we would handle multiple outcome measures. We decided that we could not choose a preferred measure, and so we combined different measures using the methods outlined by Borenstein 2009.

In the protocol, we planned to analyze ginkgo plus another active intervention versus placebo plus the same active intervention separately from ginkgo plus another active intervention versus the same active intervention alone. We had only one study testing ginkgo plus other active intervention versus placebo plus the same active intervention, and we combined it with all other studies testing ginkgo plus another active intervention versus the same active intervention alone, because the two comparisons differ primarily in the blinding of the intervention. We reflected this in the risk of bias assessment for this study.

In the protocol, we planned to carry out subgroup analyses by stage of cognitive impairment or dementia. When we looked at the populations of our included studies, we noticed that most studies investigated only mild cognitive impairment (MCI) or only dementia. The diagnoses are distinct (in dementia, more than one cognitive area is impaired, and daily functioning is compromised), and MCI is a risk factor for dementia but does not necessarily progress to dementia. We therefore chose to carry out separate primary analyses by cognitive impairment or dementia, and we constructed separate summary of findings tables for the ginkgo versus placebo comparison within each group (subjective problems without diagnosis of impairment or dementia, cognitive problems in the presence of multiple sclerosis, MCI, and dementia).

We did not originally plan to carry out subgroup analyses by vascular versus non-vascular types of cognitive impairment or dementia, but given that previous reviews have sometimes focused on one or the other, we added subgroup analyses to explore whether effects might differ by type of impairment.

In the protocol, we stated that we would test for differences between subgroups when there were at least two studies in each subgroup, and when testing was not appropriate, we would describe subgroup findings narratively. We did not specify how many studies were needed to justify creating a subgroup analysis. Updated Cochrane guidance suggests there should be at least 10 studies in an analysis for a subgroup analysis to be considered. We therefore restricted our subgroup analyses to cases in which there were at least 10 studies overall and at least two studies in each subgroup.

In the protocol, we did not specify the effect measure we would use in constructing funnel plots. We used the standardized mean difference to combine effect estimates based on different scales; however, we discovered some controversy about whether the standardized mean difference is methodologically appropriate for funnel plots. We therefore constructed funnel plots only when we had sufficient data that could be used to calculate mean differences (i.e. 10 or more studies using the same outcome scale), and limited the funnel plot to those studies. We explained our rationale in the Methods.

We initially searched multiple Chinese and non-Chinese databases for this review. To update our search prior to resubmission after peer review in 2025, we chose to search only the main non-Chinese databases and registers. We had previously found multiple studies from Chinese-language databases testing the addition of ginkgo to other treatments for MCI or dementia, but these studies were mostly small and at high risk of bias and required extensive time and effort for selection, risk of bias assessment, and data extraction. Therefore, we decided to focus on the main non-Chinese databases.

One author left the review team after the protocol was published (NK Prasad), and five authors joined the review team (YC, IHC, YZ, KHC, EW).


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