Ginkgo biloba for cognitive impairment and dementia (Review)

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TABLE OF CONTENTS

[Intervention Review]

Ginkgo biloba for cognitive impairment and dementia

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ABSTRACT

Background

Products of the maidenhair tree, Ginkgo biloba, have long been used in China as a traditional medicine for various disorders of health. A standardized extract is widely used in the West for the treatment of a range of conditions including memory and concentration problems, confusion, depression, anxiety, dizziness, tinnitus and headache. The mechanisms of action are thought to reflect the action of several components of the extract and include increasing blood supply by dilating blood vessels, reducing blood viscosity, modification of neurotransmitter systems, and reducing the density of oxygen free radicals.

Objectives

To assess the efficacy and safety of Ginkgo biloba for dementia or cognitive decline.

Search methods

The Specialized Register of the Cochrane Dementia and Cognitive Improvement Group (CDCIG), *The Cochrane Library*, MEDLINE, EMBASE, PsycINFO, CINAHL and LILACS were searched on 20 September 2007 using the terms: ginkgo*, tanakan, EGB-761, EGB761, "EGB 761" and gingko*. The CDCIG Specialized Register contains records from all major health care databases (*The Cochrane Library*, MEDLINE, EMBASE, PsycINFO, CINAHL, LILACS) as well as from many trials databases and grey literature sources.

Selection criteria

Randomized, double-blind studies, in which extracts of Ginkgo biloba at any strength and over any period were compared with placebo for their effects on people with acquired cognitive impairment, including dementia, of any degree of severity.

Data collection and analysis

Data were extracted from the published reports of the included studies, pooled where appropriate and the treatment effects or the risks and benefits estimated.

Main results

36 trials were included but most were small and of duration less than three months. Nine trials were of six months duration (2016 patients). These longer trials were the more recent trials and generally were of adequate size, and conducted to a reasonable standard. Most trials tested the same standardised preparation of Ginkgo biloba, EGb 761, at different doses, which are classified as high or low. The results from the more recent trials showed inconsistent results for cognition, activities of daily living, mood, depression and carer burden. Of the four most recent trials to report results three found no difference between Ginkgo biloba and placebo, and one reported very large treatment effects in favour of Ginkgo biloba.

There are no significant differences between Ginkgo biloba and placebo in the proportion of participants experiencing adverse events.

A subgroup analysis including only patients diagnosed with Alzhiemer's disease (925 patients from nine trials) also showed no consistent pattern of any benefit associated with Ginkgo biloba.

Authors' conclusions

Ginkgo biloba appears to be safe in use with no excess side effects compared with placebo. Many of the early trials used unsatisfactory methods, were small, and publication bias cannot be excluded. The evidence that Ginkgo biloba has predictable and clinically significant benefit for people with dementia or cognitive impairment is inconsistent and unreliable.

PLAIN LANGUAGE SUMMARY

There is no convincing evidence that Ginkgo biloba is efficacious for dementia and cognitive impairment

Ginkgo biloba appears to be safe in use with no excess adverse effects compared with placebo. Many of the early trials used unsatisfactory methods, were small, and publication bias cannot be excluded. Overall, evidence that Ginkgo has predictable and clinically significant benefit for people with dementia or cognitive impairment is inconsistent and unreliable. Of the four most recent trials to report results, three found no difference between Ginkgo biloba and placebo, and one reported very large treatment effects in favour of Ginkgo biloba.

BACKGROUND

Medicinal products derived from the maidenhair tree, Ginkgo biloba, are some of the most widely used of any plant-based products. There is much literature devoted to Ginkgo biloba, and it has been investigated in many clinical trials. Many excellent reviews covering different aspects of Ginkgo biloba have been written (Chang 1997; De Feudis 1998; Curtis 1999; Massey 1999; van Dongen 2000a).

The tree, from the genus Ginkgo, probably originated in China and in evolutionary terms is one of the oldest living tree species. It grows to a height of about 30 m and can survive for 1000 years. The leaf shape, with two lobes (biloba) is distinctive and unusual. The trees are dioecious (separately male or female) . It is an extremely robust tree, resisting insect and fungus attack, and survives frosts. The tree is now cultivated in many parts of the world for use of its nuts for food and the exploitation of the supposed medicinal properties of its leaves. There are large commercial plantations in Western France, South Carolina, USA, Japan, Korea and China, and these provide enough leaves to satisfy demand.

The active components of Ginkgo biloba consist of flavonoids, terpenoids, and terpene lactones (ginkgolides and bilobalide). Except for the ginkgolides and bilobalide, which are unique to Ginkgo biloba, these are compounds found extensively in plants. A well-defined extract, EGb 761, is produced from the ground-up leaves which contains 24% w/w (weight of active compound/total weight of extract) flavone glycosides and 6% w/w terpene lactones. It is marketed as Tanakan, Tebonin, and Rökan. Kaveri (LI 1370) is similar but with 25% w/w glycosides. Ginkgo biloba is available without prescription in the UK, Europe, Canada and the USA, being marketed as a food supplement.

Ginkgo biloba has been used in China as a traditional medicine for a range of conditions, including asthma, bronchitis, heart dysfunction, for at least 5000 years. Dr Schwabe introduced Ginkgo biloba into Germany in 1965 where it is now prescribed extensively for cerebral insufficiency, a diagnosis that can cover a range of

conditions including memory and concentration problems, confusion, depression, anxiety, dizziness, tinnitus and headache. This use extends to France, but not to other European countries or the USA. Its properties may include protection of neuronal and myocardial cells against ischaemia and reperfusion injury. It is believed that the medicinal properties of Ginkgo biloba are due to a combination of effects and that it acts by increasing blood supply by dilating blood vessels, reducing blood viscosity, by modification of neurotransmitter systems, and by reducing the density of oxygen free radicals. Its effect on blood clotting is controversial; one of its components Ginkgolide B is an inhibitor of platelet-activating factor and there have been isolated case reports of subdural haematoma associated with high doses (Rowin 1996) and of hyphema (spontaneous bleeding into the anterior chamber of the eye) following combined therapy with Ginkgo extract and aspirin (Rosenblatt 1997).

The main use of Ginkgo biloba is in the treatment of cerebral dysfunction. The manufacturers of Ginkgo biloba products recommend it for age-related cognitive decline and for slowing the progress of neurodegenerative disorders such as Alzheimer's disease and for other forms of dementia. Many clinical trials have been conducted to assess these potential properties and several reviews of the results have been published (Warburton 1986; Kleijnen 1992; Hopfenmüller 1994; Knipschild 1994; Oken 1998; Søholm B 1998; Ernst 1999) but there is still no compelling evidence of the efficacy of Ginkgo biloba for cerebral function. New trials to assess the efficacy of Ginkgo biloba compared with placebo for dementia and cognitive decline are still being initiated.

OBJECTIVES

The aim of this review is to assess the efficacy and safety of Ginkgo biloba for the treatment of people with dementia or cognitive decline.

METHODS

Criteria for considering studies for this review

Types of studies

All relevant, unconfounded, randomized, double-blind placebo-controlled studies.

Types of participants

Included studies involve patients with dementia of any severity or cognitive impairment. The diagnosis of dementia may be based on accepted criteria such as ICD, DSM (American Psychiatric Association APA 1994) and NINCDS-ADRDA (National Institute of Neurological and Communicative Disorders and Stroke - Alzheimer's Disease and Related Disorders Association McKhann 1984), or, in the case of studies conducted before the widespread availability or use of the accepted criteria, it may be based on a comparable assessment using rating scales. The diagnosis of cognitive impairment is usually based on assessment using rating scales.

Types of interventions

The mode of administration of Ginkgo biloba may be oral or intravenous (infusion or injection). All doses and dosing schedules have been considered.

Types of outcome measures

The outcomes of interest are:
1. cognitive function
2. functional performance (activities of daily living)
3. behavioural disturbance
4. global impression
5. quality of life
6. dependency
7. acceptability of treatment
8. safety.

Search methods for identification of studies

The Specialized Register of the Cochrane Dementia and Cognitive Improvement Group (CDCIG) was searched on 20 September 2007 for all years up to December 2005. This register contains records from the following major healthcare databases *The Cochrane Library*, MEDLINE, EMBASE, PsycINFO, CINAHL and LILACS, and many ongoing trial databases and other grey literature sources. The following search terms were used: ginkgo* or gingko* or tanakan or EGB761 or "EGB 761" or EGB-761.
The Cochrane Library, MEDLINE, EMBASE, PsycINFO and CINAHL were searched separately on 3 January 2008 for records added to these databases after December 2005 to September 2007. The search terms used to identify relevant controlled trials on dementia, Alzheimer's disease and mild cognitive impairment for the Group's Specialized Register can be found in the Group's module on *The Cochrane Library*. These search terms were combined with the following search terms and adapted for each database, where appropriate: ginkgo* or gingko* or tanakan or EGB761 or "EGB 761" or EGB-761.
On 20 September 2007, the Specialized Register consisted of records from the following databases:

Healthcare databases

- *The Cochrane Library*: (2006, Issue 1);
- MEDLINE (1966 to 2006/07, week 5);
- EMBASE (1980 to 2006/07);
- PsycINFO (1887 to 2006/08, week 1);
- CINAHL (1982 to 2006/06);
- SIGLE (Grey Literature in Europe) (1980 to 2005/03);
- LILACS: Latin American and Caribbean Health Science Literature (http://bases.bireme.br/cgi-bin/wxislind.exe/iah/online/?IsisScript=iah/iah.xis&base=LILACS&lang=i&form=F) (last searched 29 August 2006).

Conference proceedings

- ISTP (http://portal.isiknowledge.com/portal.cgi) (Index to Scientific and Technical Proceedings) (to 29 August 2006);
- INSIDE (BL database of Conference Proceedings and Journals) (to June 2000);.

Theses

- Index to Theses (formerly ASLIB) (http://www.theses.com/) (UK and Ireland theses) (1716 to 11 August 2006);
- Australian Digital Theses Program (http://adt.caul.edu.au/): (last update 24 March 2006);
- Canadian Theses and Dissertations (http://www.collectionscanada.ca/thesescanada/index-e.html): 1989 to 28 August 2006);
- DATAD - Database of African Theses and Dissertations (http://www.aau.org/datad/backgrd.htm);
- Dissertation Abstract Online (USA) (http://wwwlib.umi.com/dissertations/gateway) (1861 to 28 August 2006).

Ongoing trials

UK

- National Research Register (http://www.update-software.com/projects/nrr/) (last searched issue 3/2006);
- ReFeR (http://www.refer.nhs.uk/ViewWebPage.asp?Page=Home) (last searched 30 August 2006);
- Current Controlled trials: Meta Register of Controlled trials (mRCT) (http://www.controlled-trials.com/) (last searched 30 August 2006) :
- ISRCTN Register - trials registered with a unique identifier
- Action medical research
- Kings College London
- Laxdale Ltd
- Medical Research Council (UK)
- NHS Trusts Clinical Trials Register
- National Health Service Research and Development Health Technology Assessment Programme (HTA)
- National Health Service Research and Development Programme 'Time-Limited' National Programmes
- National Health Service Research and Development Regional Programmes
- The Wellcome Trust
- Stroke Trials Registry (http://www.strokecenter.org/trials/index.aspx) (last searched 31 August 2006);

Netherlands

- Nederlands Trial Register (http://www.trialregister.nl/trialreg/index.asp) (last searched 31 August 2006);

USA/International

- ClinicalTrials.gov (http://www.ClinicalTrials.gov) (last searched 31 August 2006) (contains all records from http://clinicalstudies.info.nih.gov/);
- IPFMA Clinical trials Register: www.ifpma.org/clinicaltrials.html. The Ongoing Trials database within this Register searches http://www.controlled-trials.com/isrctn, http://www.ClinicalTrials.gov and http://www.centerwatch.com/. The ISRCTN register and Clinicaltrials.gov are searched separately. Centerwatch is very difficult to search for our purposes and no update searches have been done since 2003.
- The IFPMA Trial Results databases searches a wide variety of sources among which are:
- http://www.astrazenecaclinicaltrials.com (seroquel, statins)
- http://www.centerwatch.com
- http://www.clinicalstudyresults.org
- http://clinicaltrials.gov
- http://www.controlled-trials.com
- http://ctr.gsk.co.uk
- http://www.lillytrials.com (zyprexa)
- http://www.roche-trials.com (anti-abeta antibody)
- http://www.organon.com
- http://www.novartisclinicaltrials.com (rivastigmine)
- http://www.bayerhealthcare.com
- http://trials.boehringer-ingelheim.com
- http://www.cmrinteract.com
- http://www.esteve.es
- http://www.clinicaltrials.jp

This part of the IPFMA database is searched and was last updated on 4 September 2006;

- Lundbeck Clinical Trial Registry (http://www.lundbecktrials.com) (last searched 15 August 2006);
- Forest Clinical trial Registry (http://www.forestclinicaltrials.com/) (last searched 15 August 2006

The search strategies used to identify relevant records in MEDLINE, EMBASE, PsycINFO, CINAHL and LILACS can be found in the Group's module on the *Cochrane Library*.
In addition, the companies that manufacture Ginkgo biloba preparations were contacted.

Data collection and analysis

Selection of studies

Abstracts of the references retrieved by the search were read by two reviewers in order to discard those that are clearly not eligible for inclusion. The two reviewers studied the full text of the remaining references and they independently selected studies for inclusion. Any disparity in the final lists was resolved by discussion in order to arrive at the final list of included studies.

Quality assessment

The selection criteria ensured that the blinding and randomization of the included studies are adequate. Two reviewers assessed the quality of other aspects including design, assessment of outcomes and completion rate.

Data collection

Data for the meta-analyses are based on reported summary statistics for each study. For the intention-to-treat analyses we sought data for each outcome measure on every patient randomized, irrespective of compliance. For the analyses of completers we sought data on every patient who completed the study on treatment.
For continuous variables, or ordinal variables which can be approximated to continuous variables, the main outcomes of interest are the final assessment and the change from baseline at final assessment. For some ordinal and binary outcomes, the endpoint category relative to baseline category is the outcome of interest. For others, such as the global impression of change, the endpoint itself is of clinical relevance as all patients will have been, by definition, at the same baseline score. The baseline assessment is defined as the latest available assessment before randomization, but no longer than two months before.

Data analysis

A vast number of rating scales and tests have been devised to assess outcomes in clinical trials testing treatments for dementia. There is much duplication, in so far as each scale purports to assess one of the five or six main characteristics of dementia, but with varying procedures. Meta-analyses are fairly straightforward in the situation where the included studies use the same outcome measures and the method of weighted mean difference is used. When different scales are used in the studies the method of standardized mean difference is used.
For continuous or ordinal variables, such as psychometric test scores, clinical global impression scales, and quality of life scales, there are two possible approaches. If ordinal scale data appear to be approximately normally distributed, or if the analyses reported by the investigators suggest that parametric methods and a normal approximation are appropriate, then the outcome measures will be treated as continuous variables. The second approach, which may not exclude the first, is to concatenate the data into two categories which best represent the contrasting states of interest, and to treat the outcome measure as binary. For binary outcomes, the endpoint itself is of interest and the Peto method of the typical odds ratio is used.
A test for heterogeneity of treatment effect between the trials is made using a I^2 statistic. If no heterogeneity is indicated then a fixed effect parametric approach is taken.

RESULTS

Description of studies

See: Characteristics of included studies; Characteristics of excluded studies; Characteristics of ongoing studies.
There are 36 included studies. The details are presented in Table 1 and Characteristics of included studies. The duration of the studies varies from three weeks to 52 weeks, with the majority being of 12 weeks duration. The participants of the studies were diagnosed either with dementia of any type or age-related cognitive impairment. The more recent studies used modern diagnostic criteria and computerized tomographic (CT) scans for dementia; the older studies, some of these studies were conducted more than 20 years ago, diagnosed conditions such as organic brain syndrome using signs and symptoms questionnaires. Some German studies refer to HOPS (Hirnorganisches Psychosyndrom). This is regarded as synonymous with cerebral vessel sclerosis, cerebrovascular insufficiency or cerebral sclerosis and the typical symptoms with which a patient presents are concentration and orientation disturbances, headache, and dizziness.
All studies except one, Brautigam 1998, use a Ginkgo preparation based on the standard extract, EGb 761. Thus the doses in mg/day are comparable across trials. The daily dose ranged from 80 to 600 mg/day, usually less than 200 mg/day. EGb 761 contains 24 mg of total flavone glycosides and 6 mg of ginkgolides per 100 mg.
Brautigam 1998 uses a new preparation called 'Geriaforce' which has a different ratio of active ingredients to EGb 761. Geriaforce is an ethanolic extract of Ginkgo biloba leaves (1:4) and contains 0.20 mg/ml total flavone glycosides and 0.34 mg/ml

total ginkgolides. The low dose used in the Brautigam 1998 study provided 0.57 mg total flavone glycosides /day and 0.969 mg ginkgolides/day, and the high dose provided double these amounts. The doses used in this study provided very low doses of the active components compared with the other 32 studies.

Le Bars 1997 enrolled 327 people with mildly to moderate dementia due to Alzheimer's disease or multiple cerebral infarcts. Treatment consisted of Ginkgo biloba 120 mg/day and primary outcome measures were ADAS-Cog, Geriatric Evaluation by Relative's Rating Instrument (GERRI) and CGIC.

For the meta-analyses results for doses below 200 mg/day and above were analysed separately, before combining all doses.

The meta-analyses attempted to pool all studies regardless of the diagnoses of the patients. The length of treatment was considered important and for the meta-analyses the data were divided into those relating to treatment of less than 12 weeks, of 12 weeks, 24 weeks and 52 weeks.

Many rating scales and tests were used in the included studies. A description of those that are used in the meta-analyses appears in Table 2.

Update 2006

Three new studies have been included, Kade 1993, Napryeyenko 2005, and Schneider 2005. Two studies that were included in the previous version have been excluded, Allain 1993 and Winther 1998. These two studies randomized people who were probably not cognitively impaired, their degree of cognitive impairment was slight. These trials will be included in a review of Ginkgo biloba for healthy elderly.

There is very little information available about Kade 1993, a cross-over trial for patients with mild or moderate signs of cerebral insufficiency, of two one-week phases without a wash-out between the phases. There are no results published that could be included in meta-analyses. The second trial, Napryeyenko 2005, is a large (N = 395) 22-week trial for patients with mild to moderate Alzheimer's disease or vascular dementia with one dose of Ginkgo biloba EGb 761, 240 mg/day, compared with placebo. Results have not yet been published in a peer-reviewed journal. The third new trial, Schneider 2005, enrolled 513 participants with moderate dementia due to Alzheimer's disease. In a search for a dose-response relationship Ginkgo biloba EGb 761 was given at doses of either 120 or 240 mg/day. Primary outcome measures were ADAS-Cog and CGIC. The results have been published and are included in the meta-analyses.

Update 2008

The results for Napryeyenko 2005 have now been published. There is one new trial, DIGGER 2008 (Dementia in General Practice Ginkgo Extract Research Trial), which randomized 176 patients with dementia, of any type. The intervention was 120 mg/day of EGb 761 compared with placebo. This intervention was crossed with another intervention, to compare standard follow up (visits at baseline, 2, 4 and 6 months) with minimal follow up (shorter baseline assessment and full 6 month assessment). Thus the trial has a randomized 2 by 2 factorial design. Primary outcome measures were the ADAS-Cog and quality of life measures. Secondary outcome measures assessed activities of daily living, carer's distress due to patient's neuropsychiatric symptoms and the carer's burden of care.

Many of the trials received funding from Dr Willmar Schwabe GmbH & Co, the company that manufactures the most widely used standardized extract of Ginkgo biloba. The later trials, Kanowski 1996, Le Bars 1997, and Schneider 2005, acknowledge this funding. The DIGGER 2008 study was one of the very few which was carried out independently of this company.

Risk of bias in included studies

Some studies included patients with any type of dementia, and patients with cognitive impairment. Other studies were more selective about the diagnoses and applied the appropriate inclusion and exclusion criteria. Generally after defining the diagnostic class, the studies excluded people with other serious illnesses, other mental illnesses and with other illness that could be causing the memory problems. Many studies excluded people with a history of abuse of alcohol, drugs or medication. Patients taking vasoactive drugs, antipsychotics, neuroleptics, cholinergics, antidepressants and anti-Parkinson's medication were often excluded, but some studies did not exclude the use of these drugs. Severity of cognitive impairment or dementia was commonly assessed by scores on the Mini-Mental State Examination (MMSE) of Folstein 1975.

There are a group of studies that diagnose and assess patients using a list of typical symptoms. These trials are Arrigo 1985, Arrigo 1986, Brüchert 1991, Eckmann 1982, Eckmann 1990, Halama 1988, Halama 1991, Hartmann 1991, Hofferberth 1989, Hofferberth 1991, Schmidt 1991, and Vorberg 1989. The patients are often described as having the vascular component of brain insufficiency (diffuse or localised) which manifests with transitory ischaemic attacks, tinnitus, dizziness, headache, anxiety, memory deficiency, forgetfulness, concentration problem, tiredness, decline in capacity, lack of motivation, depression. Patients are asked by a physician to grade the severity of each of these symptoms as, none, little, moderate or severe. Each patients is assessed at baseline, endpoint and sometimes at intermediate times. The baseline assessment usually determines whether the patient meets the criteria for the organic brain insufficiency and thus inclusion in the study. After treatment a patient is assessed as better or not better. The number of improved patients is enumerated for each treatment group for each symptom, to arrive at the treatment effect.

This procedure is unsatisfactory from several points of view. The method of questioning the patient is never described and therefore the situation is similar to that of using an unvalidated, unpublished

rating scale. It is often not clear what form the data take and how they were analysed. We shall summarise the findings as reported by the investigators but it is not possible in many cases to enter the data into the meta-analyses.

The initial report of the study Le Bars 1997 causes concern because participants could be removed from the trial if that they appeared to be declining. "Each subject was to complete 52 weeks, but if at any time a subject showed worsening of functioning or impairment, as assessed by an increase of 1 point on the CGIC, the subject could be dropped from the study and offered admission to an uncontrolled open-label humanitarian protocol. However, the investigator was encouraged to maintain the patient in the double-blind phase for at least 6 months". In response to our request for further information about this study, Dr Le Bars has confirmed that the humanitarian treatment protocol was open-label treatment with Ginkgo (120 mg/day). This is not a satisfactory procedure in a randomized trial. Le Bars 1997 had a greater percentage of drop-outs than other trials, and in addition to a 'per protocol' analysis, an ITT analysis based on last observation carried forward was carried out, in which data missing at 52 weeks were replaced by the last evaluable assessment after a minimum of 20 weeks of treatment. The investigators selected the ITT analyses as providing the primary criteria of efficacy, the reason given being that a relatively low proportion of patients completed the 52 weeks, and there was a difference in the proportion completing in each group. The results of the two analyses differ, especially at 52 weeks, but it is difficult to interpret these differences without knowing how any bias due to selective removal of non-responders from the treatment group was balanced against bias due to selective removal of participants who showed deterioration on placebo. However, the imbalance between treatment and control groups due to withdrawal on account of "intervention ineffective" emerged only after 26 weeks. The 26-week results of this trial have therefore been regarded as suitable for inclusion.

Schneider 2005 performed an unplanned subgroup analysis that has to be regarded as hypothesis-raising rather than hypothesis-testing and so not included in meta-analysis. After finding no statistically significant treatment effect in their planned analyses the investigators postulated that this might be because their placebo group had been unusual in showing less decline than expected. They therefore separated out and analysed a group of participants with neuropsychiatric features at presentation, a feature associated with more rapid deterioration. However the rate of deterioration in their placebo group of 0.9 points on the ADAS-Cog over six months was not strikingly different from the 1.03 shown in Figure 2 of Le Bars 1997 that did not raise similar concerns.

The earlier studies provide few details of the methods of randomization and blinding. The later studies provide more detail. DIGGER 2008 describes the placebo, the method of randomization and the procedures used to assess the success of blinding.

The percentage of patients leaving a study before end of treatment varied from zero to 30, but was mostly much lower. Loss of patients was not a serious problem, except for the Le Bars 1997 study.

Effects of interventions

Although there are 36 included studies (total participants = 4423), only 30 contribute data to the meta-analyses, and of these 15 studies contribute very little.

There was no consistent evidence of a higher incidence of adverse effects associated with Ginkgo biloba in comparison with placebo. In Napryeyenko 2005 the incidence of dizziness, headache, angina, and rise in blood pressure were significantly higher in the placebo group.

Overall, there are no significant differences between Ginkgo biloba and placebo in the proportions of participants dropping out before the scheduled end of treatment. The percentage of patients leaving a study before end of treatment varied from zero to 30, and was approximately related to duration of the treatment period, the longer studies lost a higher percentage of patients.

The smaller, shorter, and older studies lost few people, often none at all. Where there were losses, the completers analyses were reported. Therefore completers analyses are usually included in the meta-analyses where these studies contribute. Le Bars 1997, Schneider 2005 and Van Dongen 2000 report the analyses of the ITT-LOCF data which are included in the review. DIGGER 2008 used methods of multiple imputation for the missing values for the ITT analyses.

Global

The CGIC scale, measuring clinical global improvement as assessed by the physician (Schneider 1997), was dichotomized between participants who showed improvement or were unchanged and those who were worse. There is benefit associated with Ginkgo biloba (dose greater than 200 mg/day) at 24 weeks (207/276 compared with 178/273, OR 1.66, 95% CI 1.12 to 2.46, P = 0.01) (2 studies), but not for the lower dose.

Two studies used the SCAG (Shader 1974), an 18-item scale that assesses global function. There is benefit associated with Ginkgo biloba (dose less than 200 mg/day) compared with placebo at less than 12 weeks (MD -14.70, 95% CI -28.0 to -1.4, P = 0.03, one study), and at 12 weeks (MD -22.20, 95% CI -29.4 to -15.0, P < 0.00001, one study).

Le Bars 1997 found a significant difference between treatment and control groups in GERRI scores but not in CGIC.

Cognitive function

Several rating scales, or sub-tests from rating scales were used to assess cognition. Some trials assessed only one or two aspects of memory or cognition.

The meta-analysis of cognition included data from 4 trials of less than 12 weeks, using 4 different tests:
Brautigam 1998, Expanded Mental Control Test (EMCT)
Graessel 1992, speed of learning test
Hofferberth 1989, Vienna Reaction test
Mancini 1993, Toulouse-Pieron Cancellation Test.
There is significant heterogeneity between the trials (I^2= 92.1%).
There is no significant difference between Ginkgo biloba and placebo.
The removal of Hofferberth 1989 from the meta-analysis reduces the measure of heterogeneity (I^2 = 0%). Hofferberth 1989 has a significant treatment effect but the other three trials do not.
The meta-analysis of data at 12 weeks included 5 trials.
Graessel 1992, speed of learning test
Maurer 1997, the SKT
Vorberg 1989, Crichton memory impairment sub-test
Weitbrecht 1985, Wechslet digit symbol
Wesnes 1987, Benton digit span.
There is significant heterogeneity between the trials (I^2 = 76.6%).
There is a significant difference between Ginkgo biloba and placebo in favour of Ginkgo biloba (SMD -0.65, 95% CI-1.22 to -0.09, P = 0.02).
The treatment effect is very variable. The removal of the trial with the largest treatment effect (Vorberg 1989) reduces the measure of heterogeneity (I^2 = 46.5%)
The nine trials of duration of six months had some cognitive tests in common, and thus meta-analyses of ADAS-Cog and SKT were performed.

ADAS-Cog

Three trials used the ADAS-Cog DIGGER 2008, Schneider 2005 and Le Bars 1997. There was no significant difference between Ginkgo biloba and placebo for low or high dose. There was significant heterogeneity between the trials (I^2 = 65.5%).

SKT

Four trials used the SKT, Mazza 2006, Napryeyenko 2005, Kanowski 1996, and Van Dongen 2000. There was significant heterogeneity between the trials (I^2 = 97%).
There was significant difference in favour of Ginkgo biloba for the low and high dose, and all doses pooled.
(MD -3.07, 95% CI -3.96 to -2.17, P < 0.00001, 2 studies)
(MD -3.54, 95% CI -3.94 to -3.14, P < 0.00001, 3 studies)
(MD -3.57, 95% CI -3.94 to -3.20, P < 0.00001, 4 studies).
There are quite different treatment effects in Van Dongen 2000 and Kanowski 1996, compared with Mazza 2006 and Napryeyenko 2005.
A sensitivity analysis was carried out, analysing each pair of trials separately.
For all doses of Ginkgo biloba, there is no significant difference between placebo and Ginkgo biloba for a pooled analysis of Van Dongen 2000 and Kanowski 1996, but there is significant heterogeneity between these two trials (I^2 = 64%). The results of Mazza 2006 and Napryeyenko 2005 are very similar, and there is a significant effect of Ginkgo biloba (MD -4.47, 95% CI -4.89 to -4.04).

EMCT

One trial, Brautigam 1998, used the EMCT. There was no significant difference between Ginkgo biloba (low dose) and placebo.
A meta-analysis of all trials of 6 months duration with a measure of cognition was carried out using a standardized mean difference. For this analysis the standard deviation for ADAS-cog for the DIGGER 2008 trial had to be estimated as it is not reported explicitly. There is considerable heterogeneity between the trials for both lower dose and higher dose of Ginkgo biloba, which is much reduced when Mazza 2006 and Napryeyenko 2005 are omitted. There is no benefit of Ginkgo biloba at the lower dose with and without Mazza 2006, and at the higher dose a significant benefit of Ginkgo biloba (SMD -0.64, 95% CI -0.77 to -0.51, P < 0.0001, I^2 = 98%) is reduced (SMD -0.07, 95% CI -0.23 to 0.09, P = 0.40, I^2 = 65%) and there is no significant difference between Ginkgo biloba and placebo.

Activities of daily living

We report results from seven studies for activities of daily living (ADLs). Some of the tests assessed additional areas of function. The NAI-NAA (Oswald 1995) (Haase 1996 and Van Dongen 2000) measures ADLs and cognitive performance as assessed by a carer, the Crichton Geriatric Scale (CRS) (Weitbrecht 1985) is more comprehensive than just ADLs, the Progressive Deterioration Scale (PDS, DeJong 1989) (Schneider 2005) assesses 29 items of ADL using information from the carer, the Geriatric Evaluation by Relative's Rating Instrument (GERRI Schwartz 1983) (Le Bars 1997 and Schneider 2005) includes cognitive , social and mood items assessed by a carer, and the NAI-NAB (Oswald 1995; Kanowski 1996) assesses the degree of independence by means of the patient's ability to cope with everyday tasks.
The GBS-ADL subscore (Bråne 2001) (used in Napryeyenko 2005) is based on information from the carer of 6 items of activities of daily living.
The result from one study using the Crichton Rating Scale (CRS Robinson 1964) shows benefit for Ginkgo biloba (dose less than 200 mg/day) compared with placebo at 12 weeks (MD -5.0, 95% CI -7.88, -2.12, P = 0.0007, one study), but not at 22-26 weeks using the GERRI and NAI-NAA, at 24 weeks, and for the higher dose at 24 weeks (SMD -0.43, 95% CI -0.55 to -0.30, P < 0.00001, 4 studies) and for all doses pooled (SMD -0.36, 95% CI -0.46 to -0.25, P < 0.00001, 5 studies). There is significant heterogeneity within the higher dose studies (I^2 > 90%) which was reduced to 0% by removing Napryeyenko 2005 from the analysis and then

the results show no significant difference between Ginkgo biloba and placebo for the high dose and for all doses pooled.

Mood and emotional function

One study used the ADAS-Noncog (Rosen 1984), which assesses function over several domains not including cognitive function. There was no difference between Ginkgo biloba, high dose, at 12 weeks and placebo. Napryeyenko 2005 and DIGGER 2008 used the NPI-12 and there was a significant difference in favour of Ginkgo biloba (MD -7.10, 95% CI -7.95 to -6.25, P < 0.00001) for the higher dose but not for the lower dose. Napryeyenko 2005 assessed depression using the Hamilton Depression Scale and found a significant difference in favour of Ginkgo biloba higher dose (MD -5.30, 95% CI -6.07 to -4.53, P < 0.00001).

Quality of life

Quality of life, patient and carer rated was assessed in the DIGGER 2008 study, using three different measures. There were no significant differences between Ginkgo biloba and placebo.

Adverse events

There are no significant differences between Ginkgo biloba and placebo in the proportion of participants experiencing any adverse events. There were significant differences, in favour of high dose Ginkgo biloba compared with placebo for three causes of adverse events, dizziness, tinnitus, headache, angina pectoris and increased blood pressure. The two studies were Napryeyenko 2005 and Schneider 2005, the single study Napryeyenko 2005.
dizziness (23/370 compared with 48/374) (OR 0.45 95% CI 0.27 to 0.75, P = 0.002) (2 studies)
tinnitus (16/370 compared with 30/374) (OR 0.52 95% CI 0.28 to 0.97, P = 0.04) (2 studies)
headache (56/370 compared with 94/374) (OR 0.48 95% CI 0.32 to 0.71, P = 0.0002) (2 studies)
angina pectoris (20/200 compared with 35/200) (OR 0.52 95% CI 0.29 to 0.94, P = 0.03) (1 study)
increased blood pressure (4/200 compared with 13/200) (OR 0.29 95% CI 0.09 to 0.92, P = 0.03) (1 study).

Subgroup analyses

A secondary objective, as stated in the protocol for the review, was that diagnostic subgroups would be examined if possible. When the first version of the review was written very few of the included trials identified the cause of the dementia or memory loss of the patients. The more recent trials include the diagnoses, and the trials usually include patients with Alzheimer's disease and patients with vascular dementia but not all present results for Alzheimer's disease or vascular causes separately. At the time of the 2008 update a subgroup analysis for those with Alzheimer's disease was carried out.
Two studies included only patients with Alzheimer's disease, Mazza 2006 and Schneider 2005, and two studies reported some results for separate subgroup (Kanowski 1996 and Le Bars 1997), results for 958 patients in total. Results were reported for only a limited number of outcomes.

Global

The CGIC scale, measuring clinical global improvement as assessed by the physician (Schneider 1997), was dichotomized between participants who showed improvement or were unchanged and those who were worse. There are benefits associated with Ginkgo biloba (dose greater than 200 mg/day) at 24 weeks (181/249 compared with 154/253, OR 1.79, 95% CI 1.21 to 2.65, P = 0.003) (2 studies), but not for the lower dose.

ADAS-Cog

Two trials used the ADAS-Cog, Le Bars 1997 and Schneider 2005. There was no significant difference between Ginkgo biloba and placebo for low or high dose.

SKT

Two trials used the SKT, Mazza 2006 and Kanowski 1996.
There was significant difference in favour of Ginkgo biloba for the low dose (MD -4.30, 95% CI -5.34 to -3.26, P < 0.00001) (1 study) and high dose (MD -1.30, 95% CI -2.29 to -0.31, P = 0.01) (1 study).

Activities of daily living

Schneider 2005 and Le Bars 1997 used the Geriatric Evaluation by Relative's Rating Instrument (GERRI) which includes cognitive, social and mood items assessed by a carer, and Kanowski 1996 used the NAI-NAB which assesses the degree of independence by means of the patient's ability to cope with everyday tasks. There was no significant difference between Ginkgo biloba and placebo for low or high dose.

Adverse events

There are no significant differences between Ginkgo biloba and placebo in the proportion of participants experiencing any adverse events.

DISCUSSION

Several of the earlier smaller studies found positive effects of Ginkgo biloba that have not been confirmed in more recent trials. We are unable to exclude the possibility of publication bias affecting earlier studies. There is no consistent pattern in the results from the more recent, better quality trials. In meta-analysis the CGIC shows benefit at 24 weeks, but not at 12, the tests for cognitive function and activities of daily living show benefit at 12 but not 24 weeks. The results from the meta-analyses reveal no effect of dose, there appears to be no difference between high and low dose. Schneider 2005 has two treatment arms, 120 and 240 mg/day and there are no significant differences between the two doses for all outcomes. Some of the results showing benefit are based on only one trial, for example the treatment effect for the low dose (Mazza 2006) and high dose (Napryeyenko 2005) for the SKT measure of cognition, but the meta-analyses for another measure of cognition (ADAS-Cog) show no treatment benefit. In recent trials, the results of Le Bars 1997 were not confirmed by DIGGER 2008, Van Dongen 2000 or Schneider 2005. Le Bars 1997 found a significant difference between treatment and control groups in GERRI scores but not in CGIC. Similar inconsistent results emerged from a subgroup analysis which included only patients diagnosed with Alzheimer's disease.

The results of the recent study by Napryeyenko 2005 are anomalous. It is the only study to have restricted participants to people with neuropsychiatric features of dementia. This design was presumably stimulated by the subgroup analysis of Schneider 2005 that led to the hypothesis that patients with neuropsychiatric features decline more rapidly than average and would benefit more from Ginkgo biloba. The authors recruited 400 such patients from sixteen Ukraine clinics into a six-month trial that began in June 2003 and was completed in August 2004. The results from this study were strongly in favour of Ginkgo biloba and so different statistically from the findings of the non-selective studies, the treatment effects were much larger and the standard deviations of the outcomes measures were much smaller. The much smaller study, Mazza 2006, also showed much greater treatment effects and smaller standard deviations than the other studies. When these two studies were removed from the meta-analyses of cognitive function and activities of daily living the very high degree of heterogeneity was much reduced, and any significant treatment effect previously demonstarted for Ginkgo biloba was no longer present. The most recent study to report results, DIGGER 2008, found no significant treatment effects for any outcome.

Unfortunately, as pointed out by Schneider 2005, further trials of Ginkgo biloba in Europe and North America are likely to prove difficult to the point of impracticability now that the cholinesterase inhibitors are established treatment. In view of the inconsistency of results so far obtained, data from further trials designed along conventional lines are unlikely to prove conclusive. Unless some radically new findings emerge from trials of Ginkgo biloba still in progress, researchers in dementia and cognitive impairment will probably give priority to more consistently promising forms of treatment.

AUTHORS' CONCLUSIONS

Implications for practice

Ginkgo biloba appears to be safe in use with no excess adverse effects compared with placebo. The evidence that Ginkgo biloba has predictable and clinically significant benefit for people with dementia or cognitive impairment is inconsistent and unreliable.

Implications for research

Further conventionally designed clinical trials of Ginkgo biloba in the treatment of acquired cognitive impairment would be unlikely to prove useful. Further studies restricted to people with neuropsychiatric features of dementia are needed.

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* *Indicates the major publication for the study*

CHARACTERISTICS OF STUDIES

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

Arrigo 1985

Methods	24 week, randomized double-blind, placebo-controlled crossover study, (11 weeks + 2 week washout + 11 weeks)
Participants	Country: Italy 80 patients, age range 40-80 years with chronic cerebrovascular insufficiency Exclusion criteria: serious neurological or mental deficit, psychiatric disease, chronic illness liable to impair drug absorption, metabolism or catabolism, or by high risk acute disease. Other drugs were forbidden
Interventions	1. placebo 2. Ginkgo biloba extract (Tebonin), 50 drops (100 mg) x 3 times a day, 300 mg/day
Outcomes	State Trait Anxiety Inventory (STAI) Wechsler scale Self assessment of symptoms Rey shape form B
Notes	Very little detail on the outcomes and the results

Arrigo 1986

Methods	14 week, randomized, double-blind, cross-over, placebo-controlled study (6.5 weeks + 1 week washout + 6.5 weeks)
Participants	Country: Germany 90 patients, mean age 66.5 years
Interventions	1. placebo 2. Ginkgo biloba extract (Tebonin forte), 20 drops (40 mg) , 3 times a day, 120 mg/day
Outcomes	Wechsler WAIS Rey Figure Test -B memory and Word Recognition Anxiety questionnaire Dice test adverse effects
Notes	

Augustin 1976

Methods	26 week, randomized, double-blind, placebo-controlled parallel-group study
Participants	Country : France 189 inpatients, (all female), mean age 76 years, with atherosclerosis, and signs of vascular disease (cardiac , cerebral, ocular, renal etc), diagnosed by symptoms and signs
Interventions	1. placebo 2. Ginkgo biloba (Tanakan) 120 mg/day
Outcomes	global activities psychometric test battery Rey Test Benton visual retention test
Notes	groups stratified by age before randomization

Brautigam 1998

Methods	24 week, randomized, double-blind, parallel-group, placebo controlled study
Participants	Country: Netherlands 241 outpatients , mean age 68.9 years, with self reported memory or concentration complaint, MMSE >= 20
Interventions	1. placebo 2. low dose Ginkgo biloba 2.85 ml/day Geriaforce 3. high dose Ginkgo biloba 5.7 ml/day Geriaforce
Outcomes	Beck Depressive Inventory MMSE Expanded Mental Control Test (EMCT) Benton Visual Retention Test Rey Test part 1 + 2 Subjective assessment by clinician and patient
Notes	4 week wash out period before randomization

Brüchert 1991

Methods	12 week, randomized, double-blind, parallel-group, placebo-controlled study
Participants	Country: Germany 33 centres 303 patients, 45 to 80 years old, with cerebral insufficiency with typical symptoms
Interventions	1. placebo 2. Ginkgo biloba special extract, LI 1370 (Kaveri), 3 X 50 mg tablet daily, 150 mg/day

Brüchert 1991 (*Continued*)

Outcomes	Symptom score dizziness, headache, tinnitus, memory deficiency, concentration, anxiety, forgetfulness, tiredness, motivation, depression, function, confusion, counting association test global assessment (patient) global assessment (physician)
Notes	

Chartres 1987

Methods	26 week, randomized, double-blind, parallel-group, placebo-controlled study
Participants	Country: France 44 nursing home patients,(33 women, 11 men) mean age 81.8 years with slight age-related memory impairment, MMSE 20-26, GDS 1-4
Interventions	1. placebo 2. Ginkgo biloba extract EGb 761 (Tanakan) dose not mentioned
Outcomes	MMSE GDS Geriatric Rating Scale (Plutchik)
Notes	

DIGGER 2008

Methods	double-blind, parallel-group, placebo-controlled study
Participants	Country: UK 1 centre (n = 176) mean age = 79.5 (7.6), 107 : 68 (female :male), with a clinical diagnosis of dementia made by the referring clinician. Median MMSE=22 Inclusion criteria: age >55, presence of a carer, MMSE between 12 and 26 inclusive, living in the community. Exclusion criteria: use of Ginkgo in 2 weeks prior to baseline, commencement of a cholinesterase inhibitor within 2 months of baseline, concomitant warfarin therapy, known bleeding abnormalities,
Interventions	1. placebo 2. Ginkgo biloba extract (EGb 761) 120 mg/d (2 x 60 mg)
Outcomes	MMSE QOL-AD NPI-D GERRI ZBI EQ-VAS ACT GLOBAL MEASURE OF BENEFIT (CARER ASSESSED)

DIGGER 2008 (*Continued*)

Notes	The Ginkgo intervention was crossed with an intervention with 2 levels of follow up treatment, standard or minimal

Eckmann 1982

Methods	4 week, randomized, double-blind, parallel group, placebo controlled study
Participants	Country: Germany 40 outpatients, mean age 65.9 years, with a diagnosis of mild to moderate cerebrovascular insufficiency inclusion: Hachinski 7 or more Exclusion: primary degenerative dementia
Interventions	1. placebo 2. Ginkgo biloba extract (Tebonin forte Filmtabletten) 120 mg/day (3 x 40 mg)
Outcomes	SCAG Crichton Scale SKT syndrome rating
Notes	

Eckmann 1990

Methods	6 week, randomized, double-blind, parallel-group, placebo-controlled study
Participants	Country: Germany 60 patients (29 women, 31 men), mean age 55 years, with a diagnosis of cerebrovascular insufficiency and leading symptom depressive mood
Interventions	1. placebo 2. Ginkgo biloba extract (Ginkgo-Flavonglykosiden, Kaveri) 160 mg /day
Outcomes	Symptom score 1-4 dizziness headache tinnitus memory deficiency concentration anxiety forgetfulness tiredness motivation depression function confusion
Notes	

Graessel 1992

Methods	24 week, randomized, double-blind, parallel-group, placebo-controlled study
Participants	Country: Germany 3 centres 72 outpatients (37 women, 35 men), mean age 63.8 years, with a diagnosis of cerebral insufficiency
Interventions	1. placebo 2. Ginkgo biloba extract 160 mg/d (2 x 80 mg)(Rökan Filmtabletten 9.6 mg Ginkgo-Flavonglykosiden, and 2.4 mg terpenlactone)
Outcomes	IQ Memory quotient
Notes	

Haase 1996

Methods	4 week, randomized, double-blind, parallel group, placebo controlled study
Participants	Country: Germany 40 out patients (24 women, 16 men), mean age 68 years, with a diagnosis of AD, VD or mixed DSM-III-R inclusion criteria: GDS = 4 or 5, Hachinski
Interventions	1. placebo 2. Ginkgo biloba EGb 761 infusion of 200 mg/day (4 days per week)
Outcomes	NAI-NAB CGI KAI NAI-NAA self rating depression scale
Notes	

Halama 1988

Methods	12 week, randomized, double-blind, parallel-group, placebo-controlled study
Participants	Country: Germany 40 outpatients, mean age 65.9 years, with a diagnosis of mild to moderate cerebrovascular insufficiency inclusion: Hachinski >= 7, Crichton GS 1-3 Exclusion: primary degenerative dementia
Interventions	1. placebo 2. Ginkgo biloba extract (Tebonin forte Filmtabletten) 120mg /day (3x40mg)

Halama 1988 (*Continued*)

Outcomes	SCAG Crichton Scale SKT syndrome rating
Notes	

Halama 1991

Methods	12 week, randomized, double-blind, parallel-group, placebo-controlled study
Participants	Country: Germany 50 outpatients, mean age 61 years, with degenerative and vascular dementia Inclusion criteria: ICD 290.0, 290.1 290.4
Interventions	1. placebo 2. Ginkgo biloba special extract (Kaveri) 3 tablets of 50mg daily, 150mg/day
Outcomes	SKT ZVT Number connection test (NAI-ZVT) Intelligence Test Symptom score 1-4 dizziness headache tinnitus memory deficiency concentration anxiety forgetfulness tiredness motivation depression function confusion Zahlenverbindungstest Syndrom-Kurztest Multiple choice Vocabulary Intelligenztest
Notes	

Hartmann 1991

Methods	12 week, randomized, double-blind, parallel-group, placebo-controlled study
Participants	Country: Germany 52 patients, (34 men, 18 women) mean age 62.5 years, with vascular dementia, diagnosed with typical symptoms (HOPS), CT scan
Interventions	1. placebo 2. Ginkgo biloba special extract (LI 1370) 3 x 20 ml per day (150 mg/day)
Outcomes	global assessment physician global assessment patient memory, forgetfulness, concentration, fatigue, performance, motivation, depression, anxiety, dizziness, headache, tinnitus, confusion Grunberger Verbale Gedachtnis Test trail making test
Notes	

Hofferberth 1989

Methods	8 week, randomized, double-blind, parallel-group, placebo-controlled study
Participants	Country: Germany 36 outpatients, (13 women, 23 men) mean age 63.3 years, with a diagnosis of organic syndrome (HOPS)
Interventions	1. placebo 2. Ginkgo biloba extract (EGb 761 Rökan) 120mg/d (3x40mg)
Outcomes	Sakkaden Test Wiener Determination test Number Connection Test overall effect (patient) overall effect (physician)
Notes	

Hofferberth 1991

Methods	6 week, randomized, double-blind, parallel-group, placebo-controlled study
Participants	Country: Germany 50 inpatients (21 women and 29 men) mean age 65(5) years with cerebro-organic syndrome (HOPS)
Interventions	1. placebo 2. Ginkgo biloba extract LI 1370 (Kaveri) 150mg/day

Hofferberth 1991 (*Continued*)

Outcomes	Sakkaden Test Wiener Determination Test Number Connection Test Symptom score 1-4 dizziness headache tinnitus memory deficiency concentration anxiety forgetfulness tiredness motivation depression function confusion Zahlenverbindungstest(ZVT)
Notes	

Hofferberth 1994

Methods	12 week, randomized, double-blind, parallel-group, placebo-controlled study
Participants	Country: Germany 40 inpatients (67% male) mean age 63.5 years, with a diagnosis of incipient senile dementia of the Alzheimer type. Inclusion criteria: Hachinski < 4
Interventions	1. placebo 2. Ginkgo biloba extract (EGb 761 Tebonin forte Filmtabletten) 3x80mg /day (240mg/day)
Outcomes	SKT Saccade test Wiener determination test SCAG Global assessment (physician)
Notes	

Israel 1987

Methods	13 week, randomized, double-blind, factorial design , placebo-controlled study
Participants	Country: France 80 patients, (26 men, 54 women), aged between 56 and 83 years, living in the community, who had complained of memory problems, serious enough to interfere with everyday life. Exclusion criteria: serious illness

Israel 1987 (*Continued*)

	Inclusion criteria: MMSE 20-26 depression score < 18 on L'Échelle de Dépression Gériatrique de J-A Yesavage
Interventions	1. placebo 2. Ginkgo biloba extract EGb 761 (Tanakan) 160 mg/d (2 x 80mg) 3. memory exercises 4. Ginkgo biloba extract EGb 761 (Tanakan) 160 mg/d (2 x 80mg) + memory exercises
Outcomes	La batterie de mémoire pour personnes âgées ambulatoires de L Israël L'Échelle de dynamisme intellectuel de L Israël
Notes	

Kade 1993

Methods	1 week+1 week, randomized, cross-over, placebo controlled study
Participants	97 patients with minor, or moderate signs of cerebral insufficiency, mean age 69.4 years
Interventions	1. placebo 2. 250mg/day whole plant extract 3. 500mg/day whole plant extract
Outcomes	mood well being physical activity
Notes	

Kanowski 1996

Methods	24 week, randomized, double-blind, parallel-group, placebo-controlled study
Participants	Country: Germany 41 centres 216 outpatients with a diagnosis of AD or MID of mild or moderate severity DSM-III-R, and CT scan inclusion criteria;MMSE 13-25, SKT 6-18, Hachinski
Interventions	1. placebo 2. Ginkgo biloba extract EGb 761(Tebonin) 240 mg/d (2 x 120 mg)
Outcomes	CGI SKT NAB
Notes	

Le Bars 1997

Methods	52 week, randomized, double-blind, parallel-group, placebo-controlled study
Participants	Country: USA 6 centres 327 outpatients with a diagnosis of AD (70%) or MID (30%) DSM-III-R, ICD-10 Inclusion criteria: MMSE 9-26 GDS 3-6
Interventions	1. placebo 2. Ginkgo biloba extract EGb 761 (Tebonin)120 mg/d (3 x 40 mg)
Outcomes	ADAS-Cog CGIC GERRI
Notes	

Mancini 1993

Methods	6 week, randomized, double-blind, parallel-group, placebo-controlled study
Participants	Country: Italy 80 patients (30 male, 50 female) mean age 74.5 (4.4), with a diagnosis of senile psychorganic dementia on a arteriosclerotic basis (Hachinski >7)
Interventions	1. placebo 2. Ginkgo biloba (Egb 4% solution) 80 mg x 2 /day 160 mg/day
Outcomes	SCAG Toulouse-Pieron
Notes	

Maurer 1997

Methods	12 week, randomized, double-blind, parallel-group, placebo-controlled study
Participants	Country: Germany 20 outpatients (50% male), mean age 64.5 years, with a diagnosis of mild to moderate dementia of the Alzheimer type. DSM-III-R, NINCDS-ADRDA Inclusion criteria: BCRS 3-5, Hachinski <= 4, CT scan
Interventions	1. placebo 2. Ginkgo biloba extract EGb 761 (Tebonin forte Filmtabletten) 240 mg/d (80 mg x 3)

Maurer 1997 (*Continued*)

Outcomes	SKT-test trail making test ADAS CGI BCRS Number Connection Test (ZVT)
Notes	

Mazza 2006

Methods	24 week, randomized, double-blind, parallel-group, placebo-controlled study
Participants	Country: Italy Country: Germany 76 outpatients (46% male), mean age 68.5 years, with a diagnosis of primary degenerative dementia of the Alzheimer type. DSM-IV Inclusion criteria: BCRS 3-5, Hachinski < 4, and an adequate level of premorbid IQ >80 degree of dementia mild to moderate (SKT 8-23), MMSE 13-25 Exclusion criteria: dementia of other etiology, severe organic disease, history of schizophrenia or affective psychoses
Interventions	1. placebo 2. Ginkgo biloba 160 mg/day 3. donepezil 5 mg/day
Outcomes	SKT CGI MMSE
Notes	

Napryeyenko 2005

Methods	22 week, randomized, double-blind, parallel-group, placebo-controlled study
Participants	Country: Ukraine 16 hospitals 395 patients (72% female) with a diagnosis of probable AD (NINCDS-ADRDA), possible AD according to NINCDS-ADRDA together withCVD (NINDS) and AIREN or probable VaD according to NINDS-AIREN. Inclusion criteria: age > 50, TE4D <34, clock-drawing test <6, SKt 9-23, total NPI >=5, with at least one item other than delusions or hallucinations >=3. Exclusion criteria: any other type of dementia, or neurological disorder, current or recent major depression or other psychiatric disorder, severe or insufficiently controlled cardiovascular, renal or hepatic disorder, diabetes, anaemia or thyroid dysfunction. active malignant disease, HIV, or lues infection. treatment with other anti-dementia drugs, cognitive enhancers, cholinergic, anti-cholinergic or haemorheologically active drugs

Napryeyenko 2005 (*Continued*)

Interventions	1. placebo 2. Ginkgo biloba extract EGb 761 240 mg/d (2 x 120 mg)
Outcomes	SKT
Notes	

Oswald 1997

Methods	12 week, randomized, double-blind, parallel-group, placebo-controlled study
Participants	Country: Germany 226 outpatients mean age 70.9 years, (145 women, 81 men) with a diagnosis of mild to moderate organic brain syndrome, DSM-III, ICD9
Interventions	1. placebo 2. Ginkgo biloba extract (EGb 761 Filmtabletten) 120 mg/d (3 x 40 mg)
Outcomes	Nuremburg Gerontopsychological Inventory (NAI) number test trail making
Notes	

Pidoux 1983

Methods	12 week, randomized, double-blind, parallel-group, placebo-controlled study
Participants	Country: France 14 patients (all women), mean age 85 years,with senile deterioration Exclusion criteria:disorders which could interfere with EEG determination Inclusion criteria: these related to EEG characteristics
Interventions	1. placebo 2. Ginkgo biloba extract 160 mg/day
Outcomes	SCAG SGRS
Notes	

Rai 1991

Methods	24 week, randomized, double-blind, parallel-group, placebo-controlled study
Participants	Country: UK 31 outpatients, mean age 76.1 years with mild to moderate memory impairment NINCDS-ADRDA
Interventions	1. placebo 2. Ginkgo biloba extract (Tanakan) 3 x 40 mg/day
Outcomes	Kendrick Digit Copying Task Kendrick Object Learning Task Classification task Digit Recall Task
Notes	

Schmidt 1991

Methods	12 week, randomized, double-blind, parallel-group, placebo-controlled study
Participants	Country: Germany 99 outpatients (54 women, 45 men), mean age 59(5) years with cerebral insufficiency Inclusion criteria: Typical symptoms (HOPS)
Interventions	1. placebo 2. Ginkgo biloba special extract LI 1370 (Kaveri)150 mg/day
Outcomes	Global assessment (patient) Global assessment (physician) Symptom score dizziness headache tinnitus memory deficiency concentration anxiety forgetfulness tiredness motivation depression function confusion
Notes	

Schneider 2005

Methods	26 week, randomized, double-blind, parallel-group, placebo-controlled study
Participants	Country: USA, 44 centres 513 people, mean age 78.1 years with dementia of the Alzheimer's type(DSM-IV), probable AD (NINCDS-ADRDA) , CT or MRI scan within 1 year of study entry consistent with diagnosis. Inclusion criteria: MMSE >=20, duration of dementia symptoms > 6 months, mod Hackinski <4, carer present at assessments. Exclusion criteria: dementia other than AD, other CNS disorder, recent history of or current major depression, other current psychiatric disorder, severe, uncontrolled cardiovascular disease,severe renal or hepatic dysfunction, insufficiently controlled diabetes, B12 or folic acid deficiency, active malignant disease, peptic ulcer. Prohibitition of concomitant antidepressant, antipsychotic, anxiolytic and other medication
Interventions	1. placebo 2. Ginkgo biloba extract (EGb 761) 120 mg/day (2 x 60 mg) 3. Ginkgo biloba extract (EGb 761) 240 mg/day (2 x 120 mg)
Outcomes	ADAS-Cog CIBIC+ PDS GERRI ADAS-Noncog HAMD presence and rating of dizziness and tinnitus
Notes	To avoid an over-representation of people with mild impairment, recruitment restricted to only 33% with MMSE >= 20

Taillandier 1986

Methods	52 week, randomized, double-blind, parallel group, placebo controlled study
Participants	Country: France 4 centres 166 inpatients (140 women, 26 men), mean age 82.1 years with a diagnosis of cerebral disorder due to ageing from mild to severe. E.A.C.G Hachinski score over full range.
Interventions	1. placebo 2. Ginkgo biloba extract (Tanakan) 160 mg /day (2 x 80 mg)
Outcomes	global assessment geriatric clinical evaluation scale (EACG - French version of SCAG)
Notes	

Van Dongen 2000

Methods	24 week, randomized, double-blind, parallel-group, placebo-controlled study
Participants	Country: Netherlands 214 institutionalised people, mean age 69.3 years with slight age-related memory impairment, MMSE 25-28, or mild to moderate dementia according to DSM-III-R
Interventions	1. placebo 2. Ginkgo biloba extract (EGb 761) 160 mg/day 3. Ginkgo biloba extract (EGb 761) 240 mg/day
Outcomes	SKT CGI NAI-NAA NAI-ZVT-G NAI-ZN-G NAI-WL SCAG GDS Self assessment of health status Self assessment of memory
Notes	The study design is more complex than usual, with a re-randomization at 12 weeks for those in the Ginkgo groups to placebo or to continue with existing dose of Ginkgo

Vesper 1994

Methods	12 week, randomized, double-blind, parallel-group, placebo-controlled study
Participants	Country: Germany 11 centres 86 patients (39 male, 47 female) mean age 62.3 (4.6) years with cerebral insufficiency, diagnosed according to ICD-290.x Exclusion criteria: pseudo dementias cerebral or myocardial infarction in the previous 6 months serious cardiac or renal insufficiency other serious internal diseases psychoses epilepsy cerebral tumours alcohol abuse nootropic agents psycho pharmaceuticals vasoactive substances psychotropic substances
Interventions	1. placebo 2. Ginkgo biloba special extract LI 1370 (Kaveri) 150 mg/d (3 x 50 mg)

Vesper 1994 (*Continued*)

Outcomes	long and short term memory test concentration KAI MWT-B information processing
Notes	Some unverified scales, administered by computer were used to assess outcome

Vorberg 1989

Methods	12 week, randomized, double-blind, parallel-group, placebo-controlled study
Participants	Country: Germany 100 patients (60 male, 40 female) mean age 70 years with cerebral insufficiency presence of typical symptoms
Interventions	1. placebo 2. Ginkgo biloba solution (Kaveri solution) 3 x 15 ml (112 mg Ginkgo biloba extract per day)
Outcomes	modified Crichton Scale for severity of memory, headache, dizziness, noise, thought disturbance, concentration and anxiety
Notes	

Weitbrecht 1985

Methods	12 week, randomized, double-blind, parallel-group, placebo-controlled study
Participants	Country: Germany 60 patients (43 women, 17 men), mean age 72.4 years, with a diagnosis of mild to moderate primary degenerative dementia. Inclusion criteria: Hachinski<= 7
Interventions	1. placebo 2. Ginkgo biloba extract (Tebonin forte Filmtabletten) 120 mg/d (3 x 40 mg) 3. 1.98 mg ergotalkaloid
Outcomes	SCAG Crichton Self-assessment Wechsler number symbol Wechsler number recall
Notes	

Wesnes 1987

Methods	12 week, randomized, double-blind, parallel-group, placebo-controlled study
Participants	Country: UK 54 patients (20 women and 34 men) mean age 71 years with mild impairment of everyday functioning as assessed by the Crichton Geriatric Behavioural Scale for diagnosis of dementia
Interventions	1. placebo 2. Ginkgo biloba extract 120mg/d (3 x 40mg)(Tanakan film coated tablets)
Outcomes	Benton Visual Retention Test Wechsler digit span Psychometric test battery QoL Behavioural rating scale
Notes	washout of 1-3 weeks

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Allain 1993	Participants had MMSE scores of 25 to 28. This study is to be transferred to the review of trials with healthy individuals
Ercoli 2003	A very small study (n=10) of people with mild cognitive impairment but no diagnostic criteria given
Erdincler 1996	There is no placebo group
Franco 1991	Ginkgo biloba compared with nicergoline. No placebo group
Gerhardt 1990	Ginkgo biloba compared with dihydroergotoxine. No placebo group
Gessner 1985	Outcomes limited to quantitative pharmaco-EEG and psychometric measurements
Gomez 1997	Open study with no control group
Haan 1982	Ginkgo biloba compared with Vincamin. No placebo group
Heinen 2005	Not randomized
Israel 1977	Tanakan was compared with placebo, but the groups were matched; randomization was not mentioned
Itil 1995	Bioequivalence study, comparing 3 Ginkgo biloba formulations, on healthy volunteers
Itil 1998	Open label study comparing tacrine with Ginkgo biloba

(*Continued*)

Koltringer 1995	Patients were suffering from vascular dementia, and outcome was microperfusion only
Moreau 1975	Double-blind study, of Ginkgo biloba (Tanakan) compared with placebo in 60 patients. No mention of randomization
Rigney 1999	Investigation of memory enhancement with healthy volunteers
Schultz 2002	Participants to be in normal general cognitive range for age. Study aims to find if Ginkgo has effect in addition to donepezil already taken for six months. Main outcome PET changes
Schulz 1991	16 patients with cerebral insufficiency randomized to Ginkgo biloba or placebo. The only outcomes were EEG measurements
Semlitsck 1995	Outcomes were ERP measurements only
Teigeler 1984	Double-blind, placebo controlled trial of 40 patients with cerebral insufficiency. No mention of randomization
Vorberg 1985	Open label
Wesnes 1997	Patients were suffering from neurasthenia and not memory impairment primarily
Winther 1998	Participants had MMSE scores of 22 to 28. This study is to be transferred to the review of trials with healthy individuals

Characteristics of ongoing studies *[ordered by study ID]*

Vellas 2006

Trial name or title	The GuidAge study
Methods	A five-year double-blind, placebo-controlled, randomized trial
Participants	N = 2854 enrolled. Patients with a memory complaint. The age of the study population was 76.8 ± 4.4 with mean MMSE at entry of 27.8 ± 1.7
Interventions	240 mg EGb 761®
Outcomes	Primary: Incidence of AD during the five-year follow-up period. The mean time to development of dementia will be determined. Conversion of memory complaint with normal performance to mild cognitive impairment (MCI) and conversion of MCI to dementia will be recorded. Evolution of cognitive function using standard rating scales will be regularly assessed (Grober and Buschke, MMSE, verbal fluency, TMT)
Starting date	Enrollment: March 2002 and September 2004. Final results should be available in 2010
Contact information	Prof. B. Vellas (Toulouse)

Vellas 2006 (*Continued*)

Notes	

DATA AND ANALYSES

Comparison 1. Ginkgo biloba vs placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Dropouts during treatment of less than 12 weeks	8		Odds Ratio (M-H, Fixed, 95% CI)	Subtotals only
1.1 Ginkgo biloba dose less than 200mg/day special extract	8	683	Odds Ratio (M-H, Fixed, 95% CI)	1.52 [0.71, 3.25]
2 Dropouts during treatment of 12 weeks	17		Odds Ratio (M-H, Fixed, 95% CI)	Subtotals only
2.1 Ginkgo biloba dose less than 200mg/day special extract	14	1556	Odds Ratio (M-H, Fixed, 95% CI)	1.16 [0.86, 1.58]
2.2 Ginkgo biloba dose greater than 200mg/day special extract	4	592	Odds Ratio (M-H, Fixed, 95% CI)	0.72 [0.26, 1.98]
2.3 Ginkgo biloba any dose	17	2100	Odds Ratio (M-H, Fixed, 95% CI)	1.14 [0.85, 1.54]
3 Dropouts during treatment of 22-26 weeks	9		Odds Ratio (M-H, Fixed, 95% CI)	Subtotals only
3.1 Ginkgo biloba dose less than 200mg/day special extract	7	1241	Odds Ratio (M-H, Fixed, 95% CI)	1.01 [0.77, 1.32]
3.2 Ginkgo biloba dose greater than 200mg/day special extract	3	949	Odds Ratio (M-H, Fixed, 95% CI)	0.93 [0.63, 1.37]
3.3 Ginkgo biloba any dose	9	2016	Odds Ratio (M-H, Fixed, 95% CI)	1.01 [0.80, 1.28]
4 Dropouts during treatment of 52 weeks	1		Odds Ratio (M-H, Fixed, 95% CI)	Subtotals only
4.1 Ginkgo biloba dose less than 200mg/day special extract	1	166	Odds Ratio (M-H, Fixed, 95% CI)	0.97 [0.49, 1.94]
5 Global (CGIC) (numbers improved or unchanged compared with baseline) by physician after treatment of less than	3		Odds Ratio (M-H, Fixed, 95% CI)	Subtotals only
5.1 Ginkgo biloba dose less than 200mg/day special extract	3	126	Odds Ratio (M-H, Fixed, 95% CI)	4.34 [0.46, 40.59]
6 Global (CGIC) (numbers improved or unchanged compared with baseline) by physician after treatment of 12 weeks	1		Odds Ratio (M-H, Fixed, 95% CI)	Subtotals only
6.1 Ginkgo biloba dose greater than 200mg/day special extract	1	18	Odds Ratio (M-H, Fixed, 95% CI)	4.0 [0.33, 48.66]
7 Global (CGIC) (numbers improved or unchanged compared with baseline) after treatment of 24-26 weeks	3		Peto Odds Ratio (Peto, Fixed, 95% CI)	Subtotals only
7.1 Ginkgo biloba dose less than 200mg/day special extract	2	652	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.25 [0.91, 1.70]

7.2 Ginkgo biloba dose greater than 200mg/day special extract	2	549	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.80 [1.22, 2.65]
8 Global (SCAG) (change from baseline after treatment of less than 12 weeks)	1		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
8.1 Ginkgo biloba dose less than 200mg/day special extract	1	70	Mean Difference (IV, Fixed, 95% CI)	-14.7 [-28.01, -1.39]
9 Global (SCAG) (change from baseline after treatment of 12 weeks)	1		Mean Difference (IV, Random, 95% CI)	Subtotals only
9.1 Ginkgo biloba dose less than 200mg/day special extract	1	38	Mean Difference (IV, Random, 95% CI)	-22.2 [-29.36, -15.04]
10 Cognition (change from baseline after treatment of less than 12 weeks)	4		Std. Mean Difference (IV, Random, 95% CI)	Subtotals only
10.1 Ginkgo biloba dose less than 200mg/day special extract	4	351	Std. Mean Difference (IV, Random, 95% CI)	-0.81 [-1.73, 0.11]
10.2 Ginkgo biloba dose less than 200mg/day special extract (Hofferberth omitted)	3	315	Std. Mean Difference (IV, Random, 95% CI)	-0.08 [-0.31, 0.15]
11 Cognition (change from baseline after treatment of 12 weeks)	5		Std. Mean Difference (IV, Random, 95% CI)	Subtotals only
11.1 Ginkgo biloba dose less than 200mg/day special extract	4	232	Std. Mean Difference (IV, Random, 95% CI)	-0.57 [-1.22, 0.08]
11.2 Ginkgo biloba dose greater than 200mg/day special extract	1	18	Std. Mean Difference (IV, Random, 95% CI)	-1.09 [-2.10, -0.08]
11.3 Ginkgo biloba any dose	5	250	Std. Mean Difference (IV, Random, 95% CI)	-0.65 [-1.22, -0.09]
11.4 Ginkgo biloba any dose (Vorberg 1989 omitted)	4	154	Std. Mean Difference (IV, Random, 95% CI)	-0.41 [-0.87, 0.05]
12 Cognition, ADAS-Cog (change from baseline after treatment of 22-26 weeks)	3		treatment effect (Fixed, 95% CI)	Subtotals only
12.1 Ginkgo biloba dose less than 200mg/day special extract	3		treatment effect (Fixed, 95% CI)	-0.06 [-0.86, 0.74]
12.2 Ginkgo biloba dose greater than 200mg/day special extract	1		treatment effect (Fixed, 95% CI)	0.4 [-0.78, 1.58]
12.3 Ginkgo biloba any dose	3		treatment effect (Fixed, 95% CI)	-0.03 [-0.77, 0.71]
13 Cognition, SKT (change from baseline after treatment of 22-26 weeks)	4		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
13.1 Ginkgo biloba dose less than 200mg/day special extract	2	135	Mean Difference (IV, Fixed, 95% CI)	-3.07 [-3.96, -2.17]
13.2 Ginkgo biloba dose greater than 200mg/day special extract	3	683	Mean Difference (IV, Fixed, 95% CI)	-3.54 [-3.94, -3.14]
13.3 Ginkgo biloba any dose	4	775	Mean Difference (IV, Fixed, 95% CI)	-3.57 [-3.94, -3.20]

14 Cognition , EMCT (change from baseline after treatment of 22-26 weeks)	1		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
14.1 Ginkgo biloba dose less than 200mg/day special extract	1	197	Mean Difference (IV, Fixed, 95% CI)	-0.05 [-0.88, 0.78]
15 Cognition (change from baseline after treatment of 22-26 weeks)	8		Std. Mean Difference (Fixed, 95% CI)	Subtotals only
15.1 Ginkgo biloba dose less than 200mg/day special extract	6	1121	Std. Mean Difference (Fixed, 95% CI)	-0.06 [-0.18, 0.06]
15.2 Ginkgo biloba dose less than 200mg/day special extract (Mazza 2006 omitted)	5	1070	Std. Mean Difference (Fixed, 95% CI)	0.00 [-0.12, 0.12]
15.3 Ginkgo biloba dose greater than 200mg/day special extract	4	1027	Std. Mean Difference (Fixed, 95% CI)	-0.64 [-0.77, -0.51]
15.4 Ginkgo biloba dose greater than 200mg/day special extract (Napryeyenko 2005 omitted)	3	632	Std. Mean Difference (Fixed, 95% CI)	-0.07 [-0.23, 0.09]
15.5 Ginkgo biloba any dose	8	1930	Std. Mean Difference (Fixed, 95% CI)	-0.38 [-0.47, -0.28]
15.6 Ginkgo biloba any dose (Mazza 2006 and Napryeyenko 2005 omitted)	6	959	Std. Mean Difference (Fixed, 95% CI)	-0.04 [-0.14, 0.06]
16 Activities of daily living (NAI-NAA) (change from baseline after treatment of less than 12 weeks)	1		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
16.1 Ginkgo biloba dose less than 200mg/day special extract	1	40	Mean Difference (IV, Fixed, 95% CI)	-7.5 [-17.36, 2.36]
17 Activities of Daily Living (Crichton Geriatric Scale) (change from baseline after treatment of 12 weeks)	1		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
17.1 Ginkgo biloba dose less than 200mg/day special extract	1	38	Mean Difference (IV, Fixed, 95% CI)	-5.0 [-7.88, -2.12]
18 Activities of Daily Living (change from baseline after treatment of 22-24 weeks)	5		Std. Mean Difference (IV, Fixed, 95% CI)	Subtotals only
18.1 Ginkgo biloba dose less than 200mg/day special extract	3	697	Std. Mean Difference (IV, Fixed, 95% CI)	-0.11 [-0.26, 0.03]
18.2 Ginkgo biloba dose greater than 200mg/day special extract	4	1027	Std. Mean Difference (IV, Fixed, 95% CI)	-0.43 [-0.56, -0.30]
18.3 Ginkgo biloba dose greater than 200mg/day special extract (Napryeyenko 2005 omitted)	3	632	Std. Mean Difference (IV, Fixed, 95% CI)	-0.07 [-0.22, 0.09]
18.4 Ginkgo biloba any dose	5	1506	Std. Mean Difference (IV, Fixed, 95% CI)	-0.36 [-0.46, -0.25]
18.5 Ginkgo biloba any dose (Napryeyenko 2005 omitted)	4	1111	Std. Mean Difference (IV, Fixed, 95% CI)	-0.12 [-0.24, 0.00]

19 Mood and emotional function (ADAS-Noncog) (change from baseline after treatment of 12 weeks)	1		Mean Difference (IV, Random, 95% CI)	Subtotals only
19.1 Ginkgo biloba dose greater than 200mg/day special extract	1	18	Mean Difference (IV, Random, 95% CI)	-0.33 [-6.99, 6.33]
20 Mood and emotional function (NPI-12) (change from baseline after treatment of 22 weeks)	2		Treatment effect (Fixed, 95% CI)	Subtotals only
20.1 Ginkgo biloba dose less than 200mg/day special extract	1		Treatment effect (Fixed, 95% CI)	4.51 [-0.15, 9.18]
20.2 Ginkgo biloba dose greater than 200 mg/day special extract	1		Treatment effect (Fixed, 95% CI)	-7.1 [-7.94, -6.26]
21 Hamilton Depression Scale (change from baseline after 22-24 weeks of treatment)	2		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
21.1 Ginkgo biloba dose less than 200 mg/day special extract	1	343	Mean Difference (IV, Fixed, 95% CI)	-0.60 [-1.25, 0.05]
21.2 Ginkgo biloba dose greater than 200mg/day special extract	2	739	Mean Difference (IV, Fixed, 95% CI)	-2.82 [-3.21, -2.43]
22 Quality of Life (change from baseline after treatment of 22-26 weeks)	1		Treatment effect (Fixed, 95% CI)	Subtotals only
22.1 QOL-AD patient rated (ginkgo biloba dose less than 200 mg/day)	1		Treatment effect (Fixed, 95% CI)	-0.19 [-1.54, 1.17]
22.2 QOL-AD carer rated (Ginkgo biloba dose less than 200mg/day)	1		Treatment effect (Fixed, 95% CI)	-0.98 [-2.55, 0.59]
22.3 EQ-VAS (Ginkgo biloba dose less than 200 mg/day)	1		Treatment effect (Fixed, 95% CI)	-1.67 [-5.92, 2.58]
23 NPI-D carer distress caused by patient's neuropsychiatric symptoms	2		Treatment effect (Fixed, 95% CI)	Subtotals only
23.1 Ginkgo biloba dose less than 200 mg/day special extract	1		Treatment effect (Fixed, 95% CI)	2.36 [-0.60, 5.32]
23.2 Ginkgo biloba dose greater than 200 mg/day special extract	1		Treatment effect (Fixed, 95% CI)	-5.30 [-6.06, -4.54]
24 ZARIT Burden Interview - Carer reported burden of caring	1		treatment effect (Fixed, 95% CI)	Subtotals only
24.1 Ginkgo biloba dose less than 200mg/day special extract	1		treatment effect (Fixed, 95% CI)	0.02 [-2.43, 2.46]
25 Number of patients experiencing an adverse event during treatment of less than 12 weeks	2		Odds Ratio (M-H, Fixed, 95% CI)	Subtotals only

25.1 Ginkgo biloba dose less than 200mg/day special extract	2	76	Odds Ratio (M-H, Fixed, 95% CI)	1.0 [0.17, 5.77]
26 Number of patients experiencing an adverse event during treatment of 12 weeks	11		Odds Ratio (M-H, Fixed, 95% CI)	Subtotals only
26.1 Ginkgo biloba dose less than 200mg/day special extract	9	920	Odds Ratio (M-H, Fixed, 95% CI)	0.89 [0.59, 1.35]
26.2 Ginkgo biloba dose greater than 200mg/day special extract	3	190	Odds Ratio (M-H, Fixed, 95% CI)	1.64 [0.80, 3.37]
26.3 Ginkgo biloba any dose	11	1062	Odds Ratio (M-H, Fixed, 95% CI)	0.93 [0.63, 1.38]
27 Number of patients experiencing an adverse event during treatment of 24-26 weeks	6		Odds Ratio (M-H, Fixed, 95% CI)	Subtotals only
27.1 Ginkgo biloba dose less than 200mg/day special extract	5	969	Odds Ratio (M-H, Fixed, 95% CI)	0.88 [0.66, 1.17]
27.2 Ginkgo biloba dose greater than 200mg/day special extract	2	744	Odds Ratio (M-H, Fixed, 95% CI)	0.71 [0.49, 1.01]
28 Number of patients experiencing a serious adverse event during treatment of 24 weeks	2		Odds Ratio (M-H, Fixed, 95% CI)	Subtotals only
28.1 Ginkgo biloba dose less than 200mg/day special extract	1	343	Odds Ratio (M-H, Fixed, 95% CI)	0.95 [0.43, 2.09]
28.2 Ginkgo biloba dose greater than 200mg/day special extract	2	744	Odds Ratio (M-H, Fixed, 95% CI)	0.67 [0.36, 1.27]
29 Number of patients experiencing an adverse event of upper respiratory tract infection during treatment of 24 w	2		Odds Ratio (M-H, Fixed, 95% CI)	Subtotals only
29.1 Ginkgo biloba dose less than 200mg/day special extract	1	343	Odds Ratio (M-H, Fixed, 95% CI)	1.10 [0.55, 2.17]
29.2 Ginkgo biloba dose greater than 200mg/day special extract	2	744	Odds Ratio (M-H, Fixed, 95% CI)	0.75 [0.41, 1.34]
30 Number of patients experiencing an adverse event of dizziness during treatment of 24 weeks	2		Odds Ratio (M-H, Fixed, 95% CI)	Subtotals only
30.1 Ginkgo biloba dose less than 200mg/day special extract	1	343	Odds Ratio (M-H, Fixed, 95% CI)	1.51 [0.70, 3.27]
30.2 Ginkgo biloba dose greater than 200mg/day special extract	2	744	Odds Ratio (M-H, Fixed, 95% CI)	0.45 [0.27, 0.75]

31 Number of patients experiencing an adverse event of tinnitus/aggravated tinnitus during treatment of 24 weeks	2		Odds Ratio (M-H, Fixed, 95% CI)	Subtotals only
31.1 Ginkgo biloba dose less than 200mg/day special extract	1	343	Odds Ratio (M-H, Fixed, 95% CI)	0.41 [0.14, 1.19]
31.2 Ginkgo biloba dose greater than 200mg/day special extract	2	744	Odds Ratio (M-H, Fixed, 95% CI)	0.52 [0.28, 0.97]
32 Number of patients experiencing an adverse event of weight loss during treatment of 24 weeks	1		Odds Ratio (M-H, Fixed, 95% CI)	Subtotals only
32.1 Ginkgo biloba dose less than 200mg/day special extract	1	343	Odds Ratio (M-H, Fixed, 95% CI)	0.40 [0.12, 1.29]
32.2 Ginkgo biloba dose greater than 200mg/day special extract	1	344	Odds Ratio (M-H, Fixed, 95% CI)	0.81 [0.31, 2.10]
33 Number of patients experiencing an adverse event of nausea/vomiting during treatment of 24 weeks	1		Odds Ratio (M-H, Fixed, 95% CI)	Subtotals only
33.1 Ginkgo biloba dose less than 200mg/day special extract	1	343	Odds Ratio (M-H, Fixed, 95% CI)	0.63 [0.20, 1.97]
33.2 Ginkgo biloba dose greater than 200mg/day special extract	1	344	Odds Ratio (M-H, Fixed, 95% CI)	1.44 [0.56, 3.66]
34 Number of patients experiencing an adverse event of agitation/aggravated agitation during treatment of 24 week	1		Odds Ratio (M-H, Fixed, 95% CI)	Subtotals only
34.1 Ginkgo biloba dose less than 200mg/day special extract	1	343	Odds Ratio (M-H, Fixed, 95% CI)	1.31 [0.50, 3.39]
34.2 Ginkgo biloba dose greater than 200mg/day special extract	1	344	Odds Ratio (M-H, Fixed, 95% CI)	0.63 [0.20, 1.96]
35 Number of patients experiencing an adverse event of headache during treatment of 24 weeks	2		Odds Ratio (M-H, Fixed, 95% CI)	Subtotals only
35.1 Ginkgo biloba dose less than 200mg/day special extract	1	343	Odds Ratio (M-H, Fixed, 95% CI)	0.44 [0.13, 1.47]
35.2 Ginkgo biloba dose greater than 200mg/day special extract	2	744	Odds Ratio (M-H, Fixed, 95% CI)	0.48 [0.32, 0.71]
36 Number of patients experiencing an adverse event of angina pectoris during treatment of 24 weeks	1		Odds Ratio (M-H, Fixed, 95% CI)	Subtotals only

36.1 Ginkgo biloba dose greater than 200mg/day special extract	1	400	Odds Ratio (M-H, Fixed, 95% CI)	0.52 [0.29, 0.94]
37 Number of patients experiencing an adverse event of back pain during treatment of 24 weeks	1		Odds Ratio (M-H, Fixed, 95% CI)	Subtotals only
37.1 Ginkgo biloba dose greater than 200mg/day special extract	1	400	Odds Ratio (M-H, Fixed, 95% CI)	0.52 [0.25, 1.07]
38 Number of patients experiencing an adverse event of diarrhoea during treatment of 24 weeks	1		Odds Ratio (M-H, Fixed, 95% CI)	Subtotals only
38.1 Ginkgo biloba dose greater than 200mg/day special extract	1	400	Odds Ratio (M-H, Fixed, 95% CI)	1.14 [0.56, 2.30]
39 Number of patients experiencing an adverse event of cough during treatment of 24 weeks	1		Odds Ratio (M-H, Fixed, 95% CI)	Subtotals only
39.1 Ginkgo biloba dose greater than 200mg/day special extract	1	400	Odds Ratio (M-H, Fixed, 95% CI)	1.29 [0.57, 2.92]
40 Number of patients experiencing an adverse event of hypertensive crisis during treatment of 24 weeks	1		Odds Ratio (M-H, Fixed, 95% CI)	Subtotals only
40.1 Ginkgo biloba dose greater than 200mg/day special extract	1	400	Odds Ratio (M-H, Fixed, 95% CI)	0.82 [0.35, 1.95]
41 Number of patients experiencing an adverse event of increased blood pressure during treatment of 24 weeks	1		Odds Ratio (M-H, Fixed, 95% CI)	Subtotals only
41.1 Ginkgo biloba dose greater than 200mg/day special extract	1	400	Odds Ratio (M-H, Fixed, 95% CI)	0.29 [0.09, 0.92]

Comparison 2. Ginkgo biloba vs placebo (Alzheimer's disease subgroup)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Dropouts during treatment of 22-26 weeks	2		Odds Ratio (M-H, Fixed, 95% CI)	Subtotals only
1.1 Ginkgo biloba dose less than 200mg/day special extract	2	394	Odds Ratio (M-H, Fixed, 95% CI)	0.87 [0.53, 1.41]

1.2 Ginkgo biloba dose greater than 200mg/day special extract	1	344	Odds Ratio (M-H, Fixed, 95% CI)	0.74 [0.44, 1.26]
1.3 Ginkgo biloba any dose	2	564	Odds Ratio (M-H, Fixed, 95% CI)	0.81 [0.53, 1.24]
2 Global (CGIC) (numbers improved or unchanged compared with baseline) after treatment of 24-26 weeks	2		Peto Odds Ratio (Peto, Fixed, 95% CI)	Subtotals only
2.1 Ginkgo biloba dose less than 200mg/day special extract	1	343	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.35 [0.88, 2.07]
2.2 Ginkgo biloba dose greater than 200mg/day special extract	2	502	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.79 [1.21, 2.65]
3 Cognition, ADAS-Cog (change from baseline after treatment of 22-26 weeks)	2		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
3.1 Ginkgo biloba dose less than 200mg/day special extract	2	546	Mean Difference (IV, Fixed, 95% CI)	-0.29 [-1.21, 0.64]
3.2 Ginkgo biloba dose greater than 200mg/day special extract	1	344	Mean Difference (IV, Fixed, 95% CI)	0.4 [-0.77, 1.57]
3.3 Ginkgo biloba any dose	2	716	Mean Difference (IV, Fixed, 95% CI)	-0.21 [-1.05, 0.63]
4 Cognition, SKT (change from baseline after treatment of 22-26 weeks)	2		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
4.1 Ginkgo biloba dose less than 200mg/day special extract	1	51	Mean Difference (IV, Fixed, 95% CI)	-4.3 [-5.34, -3.26]
4.2 Ginkgo biloba dose greater than 200mg/day special extract	1	158	Mean Difference (IV, Fixed, 95% CI)	-1.30 [-2.29, -0.31]
4.3 Ginkgo biloba any dose	2	210	Mean Difference (IV, Fixed, 95% CI)	-2.74 [-3.46, -2.03]
5 Activities of Daily Living (change from baseline after treatment of 22-24 weeks)	3		Std. Mean Difference (IV, Fixed, 95% CI)	Subtotals only
5.1 Ginkgo biloba dose less than 200mg/day special extract	2	548	Std. Mean Difference (IV, Fixed, 95% CI)	-0.15 [-0.32, 0.02]
5.2 Ginkgo biloba dose greater than 200mg/day special extract	2	502	Std. Mean Difference (IV, Fixed, 95% CI)	-0.09 [-0.26, 0.09]
5.3 Ginkgo biloba any dose	3	876	Std. Mean Difference (IV, Fixed, 95% CI)	-0.15 [-0.29, -0.02]
6 Number of patients experiencing an adverse event during treatment of 24-26 weeks	2		Odds Ratio (M-H, Fixed, 95% CI)	Subtotals only
6.1 Ginkgo biloba dose less than 200mg/day special extract	2	394	Odds Ratio (M-H, Fixed, 95% CI)	0.84 [0.53, 1.32]
6.2 Ginkgo biloba dose greater than 200mg/day special extract	1	344	Odds Ratio (M-H, Fixed, 95% CI)	0.78 [0.49, 1.23]

ADDITIONAL TABLES

Table 1. Description of the included studies

Study	number of patients	duration weeks	diagnosis	diagnostic criteria	mean age	intervention	dose mg/d	% females	study design
Arrigo 1985	80	11 +2 washout +11	chronic cerebrovascular insufficiency	signs of vertigo, headache, tinnitus, loss of memory and of learning ability	40-80	Tebonin	300	36	crossover
Arrigo 1986	90 in and outpatients	6½+1 washout +6½	chronic cerebrovascular insufficiency	Transitory ischaemic attacks and symptoms (headache, tinnitus, dizziness and anxiety)	66.5	Tebonin	120	34	crossover
Augustin 1976	189 inpatients	26	vascular dementia	signs	76	Tanakan	120	100	parallel group stratified by age
Brautigam 1998	241 outpatients	24	memory impairment MMSE >= 20	self reported memory and/or concentration complaint	68.9 (7.8)	Geriaforce	2.85 ml, 5.7 ml	59	parallel group
Brüchert 1991	303 outpatients	12	cerebral insufficiency	typical symptoms	69	Kaveri	150		parallel group
Chartres 1987	44 inpatients	26	mild cognitive impairment	MMSE 20-26, GDS 3 or 4	81.8	Tanakan	not given	75	parallel group
DIGGER 2008	176 outpatients	26	dementia	as diagnosed by referring	79.5 (7.6)	EGb 761	120	61	parallel group

Table 1. Description of the included studies (*Continued*)

				clinician					
Dongen 2000	214 (in institutions)	24	all dementias + aged related cognitive impairment	DSM-III-R, ICD-10	69.3	EGB761	120, 240		parallel group
Eckmann 1982	50 inpatients	4	cerebral insufficiency	signs and symptoms	45-74	Tebonin	120	40	parallel group
Eckmann 1990	60	6	cerebrovascular insufficiency	6 /12 of typical symptoms assessed as moderate or severe	55	Kaveri	160	48	parallel group
Graessel 1992	72	24	cerebrovascular insufficiency (demented)	IQ-Wert, MWT-IQ	63.8 (8.4)	Rökan	160	51	parallel group
Haase 1996	40 outpatients	4	AD, VD or mixed	DSM-III-R, GDS 4 or 5	68 (12.5)	EGB761infu	200/ 4days per week	60	parallel group
Halama 1988	40	12	mild to moderate cerebrovascular insufficiency	exclude primary degenerative dementia, Hachinski >7, Crichton 1-3	65.9	Tebonin	120		parallel group
Halama 1991	50 outpatients	12	Primary degenerative dementia , vascular dementia	none given	61	Kaveri	150	64	parallel group
Hartmann 1991	52 outpatients	12	vascular dementia	CT scan, HOPS	62.5	Kaveri	150	35	parallel group

Table 1. Description of the included studies (*Continued*)

				symptoms					
Hofferberth 1989	36 inpatients	8	organic syndrome (HOPS)	Hachinski, 2 out of 4 other tests	63.3	Rökan	120	36	parallel group
Hofferberth 1991	36 inpatients	6	cerebro-organic syndrome (HOPS)	Hachinski + EEG, Sakkaden test +Wiener test +number test	65	Kaveri	150	42	parallel group
Hofferberth 1994	40 inpatients	12	AD	Hachinski <4, CT scan , Blessed DS	63.5	Tebonin	240	33	parallel group
Israel 1987	80 outpatients	12	age related memory impairment	MMSE 20-26	68.4	Tanakan	160	68	parallel group
Kade 1993	97	1+1	mild or moderate signs of cerebral insufficiency		69.4 (9.3)	GK extract	250, 500	-	crossover
Kanowski 1996	216 outpatients	24	mild or moderate AD or MID	DSM-III-R, CT scan, MMSE 13-25, SKT 6-18	70.1	Tebonin	240	67	parallel group
Le Bars 1997	327 outpatients	52	AD or MID	DSM-III-R, ICD-10, MMSE 9-26, GDS 3-6	69 (10)	Tebonin	120	54	parallel group
Mancini 1993	80	6	psycho-organic senile dementia of arteroschlero origin	Hachinski >7	74.5 (4.4)		160	63	parallel group

Table 1. Description of the included studies (*Continued*)

Mazza 2006	76	24	Primary degenerative dementia of the Alzheimer type	DSM-IV, Hachinski >4, MMSE 13-25	68.5 (5)	EGb 761	160	54	parallel group
Maurer 1997	20	12	mild or moderate AD	DSM-III-R, NINCDS-ADRDA, Hachinski <=4, Ct-scan	64.5	Tebonin	240	50	parallel group
Napryeyenk 2005	395	22	mild to moderate probable AD, possible Ad with CVD, probable VaD	NINCDS-ADRDA, NINCDS-ADRDA with NINDS-AIREN or NINDS-AIREN	64	EGb 761	240	72	parallel group
Oswald 1997	226 outpatients	12	mild or moderate organic brain syndrome	DSM-III-R, ICD-9	70.9	EGB761	120	64	parallel group
Pidoux 1983	14	12	clinical chronic brain ischaemic syndrome	none given	85.3		160	100	parallel group
Rai 1991	31 outpatients	24	mild to moderate memory impairment of organic origin	NINCDS-ADRDA	76.1 (6.5)	Tanakan	120	74	parallel group
Schmidt 1991	99 outpatients	12	cerebral insufficiency	typical symptoms	59 (5)	Kaveri	150	54	parallel group

Table 1. Description of the included studies (*Continued*)

Schneider 2005	513 outpatients	26	AD	DSM-IV, NINCDS-ADRDA	78.1	EGb 761	120, 240	52	parallel group
Taillandier 1986	166	52	cerebral disorder due to ageing	EACG	82.1(6.4)	Tanakan	160	84	parallel group
Vesper 1994	90 outpatients	12	cerebral insufficiency	ICD 290.x	62	Kaveri	150	52	parallel group
Vorberg 1989	100 outpatients	12	cerebral insufficiency	at least 4 of 6 essential symptoms	70	Kaveri	112	40	parallel group
Weitbrecht 1985	40	12	mild to moderate primary degenerative dementia	Hachinski 7 or less	71.7 (4.6)	Tebonin	120	65	parallel group
Wesnes 1987	58 outpatients	12	mild dementia , probably PDD	Crichton Behavioural Scale >= 14	71 (6.8)	Tanakan	120	37	parallel group

Table 2. Description of rating scales used in the trials

Scale	Abbreviation	Description	Reference
Alzheimer's Disease Assessment Scale -cognition	ADAS-Cog	ADAS-Cog comprises 11 individual tests, spoken language ability (0-5), comprehension of spoken language (0-5), recall of test instructions (0-5), word finding difficulty (0-5), following commands (0-5), naming object (0-5), construction drawing (0-5), ideational praxis (0-5), orientation (0-8), word recall (0-10) and word recognition (0-12). The total score ranges from 0-70, the high score indicating greater impairment	Rosen 1984

Table 2. Description of rating scales used in the trials (*Continued*)

Alzheimer's Disease Assessment Scale -noncog	ADAS-Noncog	There are 23 items evaluating mood, depression, anxiety, vegetative symptoms, and in addition behavioural disorder - socialization skills, cooperation, initiation of ADLs, psychotic symptoms, motor activity, agitation, concentration, nocturnal confusion. The maximum score is 99, the high score indicating greater impairment	Rosen 1984
Beck Depressive Inventory	BDI	Assesses the presence and seriousness of depression. Questionnaire of 21 multiple-choice questions about the symptoms and complaints of depression	Beck 1974
Benton test of Visual Retention-Revised		Assesses short term visual memory (maximum score 10), when presented with geometric images	Benton 1974, Cohen 1988
Clinical Global Impression of Change	CGIC	Without following a structured interview, the clinician judges the amount of change in overall impairment compared with study baseline, on a 7-point scale. 1 indicates extreme improvement, 4 unchanged and 7 extreme worsening	Guy 1976
Clinician's Interview-Based Impression of Change scale	ADCS-CGIC	This scale provides a global rating of patient function in four areas, general, cognitive, behaviour and activities of daily living. All patients are scored on global severity at baseline and subsequent assessments on a scale of 1-7 are relative to baseline, with 1 showing marked improvement, 7 marked worsening with 4 representing no change. Information is obtained from the caregiver and patient and the clinician is blind to all other measures	Schneider 1997
Crichton Geriatric Behavioural Scale Scale	CGBS	A measure of the severity of disease.	Robinson 1964
European Quality of Life Visual Analogue Scale	EQ-VAS	Reporting carer health scoring 0-100, with higher score indication better health	EuroQol 1990

Table 2. Description of rating scales used in the trials (*Continued*)

Expanded Memory Control Test	EMCT	Based on the Wechsler memory scale, this test is used for a rapid examination of attention and concentration in the elderly. It is composed of 12 mental control tasks, divided into 3 types (maximum score 24), reproduction of 4 items, backward reciting of the same 4 items, 4 items of serial calculation	Lindeboom 1993
Gottfries, Brane and Steen scale	GBS	The global assessment. The GBS is a comprehensive scale for rating dementia syndromes, based on a semi-structured interview with the caregiver. A seven-point scoring system, from 0 (normal function) to 6 (maximum disturbance or presence of symptoms) measures orientation, memory and concentration (12 items), activities of daily living (6 items), emotional function (3 items) and pathological aspects of behaviour (6 items)	Gottfries 1982, Bråne 2001
Geriatric Depression Scale	GDS	30 item (0-30) or short form score 0-15 (severe depression)	Yesavage 1982, Burke 1991
Geriatric Evaluation by Relative's Rating Scale	GERRI	A 49 item inventory (each scaled 1-5, with higher score indicating poorer functioning) completed by the carer. The total score is the grand mean of the 3 subscale means, cognitive (21 items), social (18 items) and mood (18 items)	Schwartz 1983
Global Deterioration Scale	GDS	The GDS was developed for the assessment of primary degenerative dementia and the delineation of the stages of disease. the stages are scored from 1 (no cognitive decline) to 7 (severe cognitive decline)	Reisberg 1982
Modified Hachinski Ischemic Scale	Mod Hach		Rosen 1980
Hamilton Rating Scale for Depression	HAMD		Hamilton 1960
Mini Mental State Examination	MMSE	The MMSE was developed as a short test suitable for the elderly with dementia. It concentrates on the cognitive aspects of mental function, the five sec-	Folstein 1975

Table 2. Description of rating scales used in the trials (*Continued*)

		tions cover orientation, immediate recall, attention and calculation, delayed recall and language. A maximum score of 30 indicates no impairment	
Neuropsychiatric Instrument	NPI-12	12 item, carer rated instrument to evaluate behavioural and neuropsychiatric symptoms, including delusions, hallucinations, agitation/aggression, depression/dysphoria, anxiety, elation/euphoria, apathy, disinhibition, irritability, aberrant motor behaviour, night-time behaviour, and appetite/eating disorder. Frequency is rated from 1(occasional, less than once a week) to 4 (very frequent) and severity from 1(mild) to 3 (severe). The product of frequency and severity ranges from 1 to 12, with a total score ranging from 12 to 120 for the 10 domains summed. A lower score indicates improvement	Cummings 1994
Neuropsychiatric Inventory Distress scale	NPI-D	The NPI-D assesses the degree of distress caused to the carer by the 10 individual items (each scores 0-5) of the NPI	Cummings 1994
Nürnberger Alters Alltagsaktivitäten Skala	NAI-NAA	Cognition related behaviour as assessed by carer. (20-60) low score is better. 20-items cover instrumental activities of daily living, social activities, cognitive performance with a total score 20 (very good) - 60(very poor)	Oswald 1995
Nürnberger Alters Inventar	NAI	ZVT-G, ZN-G, WL and NAA are components of NAI, a German battery of psychometric tests, questionnaires and observational rating scales that measures cognitive function, activities of daily living, well-being and care needs, adapted to the needs of older population	Oswald 1995
Nürnberger Alters Inventar-Beobachtungsskala	NAB	Assesses the degree of independence by means of the patient's ability to cope with everyday tasks	Oswald 1986

Table 2. Description of rating scales used in the trials (*Continued*)

Nürnberger Alters Inventar-word list total	NAI-WL	0-16 (higher score is better) Verbal learning test, in which 8 carefully selected words have to be recalled and recognised. The scores for free, immediate and delayed recall are combined giving a total score (0-16)	Oswald 1995
Nürnberger Alters Inventar-Zahlennachsprechen Test	NAI-ZN-G	0-17 higher is better. Digit memory span test. A short term memory test aimed at immediate reproduction of digit combinations of increasing lengths, in forward and backward format. Total score (0-17) is obtained by summing scaled scores for both formats	Oswald 1995
Nürnberger Alters Inventar-Zahlen-Verbindungs Test G	NAI-ZVT-G	0-300 (higher is worse) This is an adaptation of the trail making test, in which 30 numbers have to be connected in the right sequence as quickly as possible .It assesses cognitive speed , planning and organization	Oswald 1995
Progressive Deterioration Scale	PDS	This is a disease specific measure of changes in 29 items of the activities of daily living. The interview is conducted with the caregiver. DeJong describes this scale as a measure of quality of life for AD, on account of the correlation between ability to perform ADLs and quality of life	DeJong 1989
Quality of life - AD	QOL-AD	Rated by the patient and the carer, two 13-item scales scoring 13-52 points with a higher score indicating better quality of life	Logsdon 1999
Rey	Rey	Rey 1 assesses short term verbal memory and learning, the same series of 15 words is presented 5 times. Rey 2 assesses long term memory by recognition. A short story including the previous 15 words is read out and the patient must indicate recognition of the words	Cohen 1988
Sandoz Clinical Assessment - Geriatric Scale	SCAG	An 18-item symptom rating scale (each rated from 1=not present to 7=severe), aimed at domains of possible impaired function: Cognitive dysfunction, dis-	Shader 1974

Table 2. Description of rating scales used in the trials (*Continued*)

		turbed interpersonal relationship, affective disorders, inability to cope with ordinary activities of daily living, and somatic dysfunction. Total score is 18-126 (H	
Syndrom Kurz Test	SKT	0-27 (severe impairment) Brief psychometric test battery for the assessment of memory and attention. 9 subtests, 6 speed orientated (language fluency, number fluency, attention planning and praxis, short-term memory, attention and concentration. 3 span orientated- short term visual memory, long term memory span,recognition memory span	Overall 1992
Wiener Determinationsgerät	WDT	A reaction test. The patient must recognise the correct answer under different options by corresponding reaction (hand and foot pedal). The speed can be varied, and false and correct reactions are summed	
Wortliste	WL	Verbal learning test, in which 8 carefully selected words have to be recalled and recognised. The scores for free, immediate and delayed recall are combined giving a total score (0-16)	Oswald 1995
Zahlennachsprechen Test	ZN-G	Digit memory span test. A short term memory test aimed at immediate reproduction of digit combinations of increasing lengths, in forward and backward format. Total score (0-17) is obtained by summing scaled scores for both formats	Oswald 1995
Zahlen-Verbindungs Test G	ZVT-G	This is an adaptation of the trail making test, in which 30 numbers have to be connected in the right sequence as quickly as possible .It assesses cognitive speed , planning and organization	Oswald 1995
Burden of caring reported by carer	ZBI	12-item Zarit Burden Interview scoring 0-48 with a higher score indicating greater burden	Bedard 2001

Table 2. Description of rating scales used in the trials (*Continued*)

Wechsler Memory Scale	WMS	The memory quotient is derived from 7 sub tests: personal and current information, orientation, mental control, logical memory, digit span, delayed recall, visual reproduction	Wechsler 1945

FEEDBACK

Robert Hoerr 6 June 2007

Summary

Feedback

The review covers the relevant literature on Ginkgo biloba in cognitive impairment and dementia and provides an overview of the results of the largest, the most important and the most recent trials. Meta-analyses show benefits of the Ginkgo biloba extract EGb 761 in global assessments, cognitive tests and activities of daily living (ADL) scales, yet the conclusion is reserved. Since the conclusion inherently depends on the methods, the presentation and evaluation of the results, some comments appear to be warranted. Giving careful consideration to the distinctive features of the studies could lead to more specific results.

Methodological issues

Studies in patients with merely subjective complaints about memory or concentration, studies in patients with cognitive impairment proven by neuropsychological testing and studies in patients with dementia are included in the same meta-analyses. From a clinical point of view, this is both surprising and inappropriate because these three groups of patients differ from each other with respect to the cognitive and non-cognitive domains affected, the severity of impairment, the type of progression of impairment and the natural rate of deterioration. Different instruments are required to adequately measure the efficacy of treatments, and the domains of interest vary with the type of disease.

The review includes studies on Ginkgo products of essentially different qualities. The proportions of flavone glycosides and terpene lactones of the product Geriaforce used by Brautigam 1998 differ markedly from those of the extract EGb 761, and the daily intake of flavone glycosides and terpene lactones even in the low-dose studies of EGb 761 was manifold higher than under Geriaforce treatment in the study by Brautigam 1998. It is therefore unfeasible to jointly analyse studies with Geriaforce and low-dose EGb 761 under the heading “less than 200 mg/day” in one and the same meta-analysis. The extract is the active substance in a phytomedical product and it is not possible to make any claim of efficacy or inefficacy for a group of products whose bioequivalence has not been proven.

In the third paragraph of the “Discussion” it is pointed out that the results from the study by Napryeyenko 2007 are so different from those of other studies that they cannot be merged in a meta-analysis. Do not patient characteristics and treatments, even more than results, determine whether studies can be merged in a meta-analysis? This raises the question why the results from Le Bars 1997 and Schneider 2005 can be merged, although the patients of the latter were selected from a restricted basic population and according to much more rigorous criteria. Even more astonishing is why the results from studies in subjects with merely subjective complaints (Brautigam 1998) or AAMI (van Dongen 2003) can be merged in a meta-analysis with those from studies in patients with dementia (Hofferberth 1994, Mancini 1993, Kanowski 1996, Le Bars 1997, Mazza 2006, Napryeyenko 2007).

Evidence-based medicine is defined as “the conscientious, explicit, and judicious use of current best evidence in making decisions about the care of individual patients” (Sackett 1996, Brit Med J 312:71-2). An individual patient may have dementia or aging-related cognitive impairment or subjective memory complaints, and treatment decisions are to be taken accordingly. So, how useful are standardised or weighted mean differences obtained by meta-analysis of effects of different drug products tested in a variety of diseases and ailments to make a decision about the appropriate treatment for an individual patient?

The studies by Allain 1993 and Winther 1998 are no longer included in the
updated review because the people enrolled were probably not demented and
their degree of cognitive impairment was slight. Considering that the subjects enrolled by Allain were required to have subjective cognitive complaints and low performance in a cognitive test and that the subjects enrolled by Winther had to have MMSE scores

between 22 and 28, which roughly corresponds to mild cognitive impairment, the question arises why the study by Brautigam 1998 still was included. The subjects enrolled by Brautigam were required to have no more than subjective complaints about memory and/or concentration.

Errors and misleading wording

The last sentence of the "Results" section states that there were no data available on measures of depression and in the abstract it is said that no
study assessed mood and function separately. Yet there are data on standard
measures of depression from three trials. In the studies by Kanowski 1996
and Schneider 2005, the Montgomery Asberg Depression Rating Scale (MADRS) and the Hamilton Rating Scale for Depression (HAM-D), respectively, were administered to ensure that no patients with clinically significant
depression were included and that improvements in the cognitive domain are
not due to improvements in depression. That was in line with former
recommendations of the FDA and the German drug agency. In the study by
Napryeyenko 2007 patients with mild to moderate depression were admitted
since more recent studies (Powlishta 2004, Arch Neurol 61:1265-68) had
demonstrated that even in mild dementia depression has no impact on
cognitive performance. Hence, depression was a secondary outcome in this
study.

As a matter of fact, the findings are not as inconsistent and contradictory
as presented in the "Results" section and in the abstract. There is no contradiction when there are significant differences in the CGIC after 22-26 weeks, but not after 12 weeks. The CGIC is not the most sensitive measure to demonstrate benefits of anti-dementia treatments, and it appears that it just requires more than 12 weeks of differential development of treatment groups for benefits to become clearly discernible. That there is significant superiority of EGb 761 in the cognitive domain after 12 weeks, but not after 24 weeks is only true if the ADAS-cog results of two studies (Le Bars 1997, Schneider 2005) are picked out selectively, which would have to be justified. Looking at the SKT, which was used in the studies by Kanowski 1996, van Dongen 2003, Mazza 2006 and Napryeyenko 2007, there clearly is a significant difference in favour of Ginkgo at 22-26 weeks. Similarly, the statement in the discussion that in ADL scales there was a benefit after 12 weeks, but not after 24 weeks is only true for one single meta-analysis, i.e. for doses above 200 mg/day under exclusion of the data from Napryeyenko 2007. For doses below 200 mg/day, for doses above 200 mg/day including data from Napryeyenko 2007 and for the overall analysis
there are significant differences in favour of Ginkgo.

Comments

Under "Methodological Quality" the opinion is expressed that the rate of deterioration in the placebo group of the study by Schneider 2005 as measured by the ADAS-cog was not strikingly different from that found in the study by Le Bars 1997. This is true for the bare numbers. Yet, the AD patients enrolled by Le Bars 1997 had a mean baseline ADAS-cog score of 20.0 and 52% scored above 23 on the MMSE, i.e. they had very mild dementia. It is well known that patients in the early stage of AD deteriorate slowly under naturalistic conditions, whereas those with moderate AD usually deteriorate much faster (Stern 1994, Am J Psychiatry 151:390-6; Schmeidler 1998, Alzheimer Dis Assoc Disord 12:146-51). In the study by Schneider 2005 the mean ADAS-cog at baseline was 24.8 and two thirds of the patients scored below 20 on the MMSE, i.e. most of the patients were already in the stage of moderate dementia or at least in the transition from mild to moderate dementia. Hence, it was justified to expect that those patients deteriorate more quickly than they actually did.

The statement in the "Discussion" saying that "the results of Le Bars 1997
were not confirmed by van Dongen 2000 or Schneider 2005" is surprising. How
can a study in which most of the patients had AAMI confirm or contradict the results of a study in patients with dementia? The study by Schneider 2005 does not confirm the findings from Le Bars 1997, but the patient sample and the circumstances of recruitment were clearly different. The positive findings of Le Bars 1997 are in line with those of Kanowski 1996 and were later confirmed by Napryeyenko 2007. Hence, one dementia study with inconclusive results is counterbalanced by three modern dementia studies with positive outcomes.

Submitter has modified conflict of interest statement:

I am an employee of Dr. Willmar Schwabe Pharmaceuticals, the manufacturer
of EGb 761.

Reply

We would like to thank Robert Hoerr for his comments on the review. We have considered his points carefully.
The objective of this review is to assess the efficacy and safety of Ginkgo biloba for the treatment of people with dementia or cognitive decline. Most people with memory problems or dementia who take Ginkgo biloba are self-prescribing. There are many Ginkgo biloba products available. It is hoped that this review answers some of the questions this population may have. The protocol written for the review of Ginkgo biloba for cognitive impairment and dementia makes clear that the intention was to include trials whose participants had a wide range of diagnoses, and were treated with Ginkgo biloba in some form. A secondary objective was to look at subgroups, those with different diagnoses. When the review was first written it would not have been possible to conduct meta-analyses for diagnostic groups, there were too few participants in trials with identifiable types of dementia.
Since the first review was carried out several new trials of Ginkgo biloba have been completed. These are larger than the older studies and the diagnoses of the included patients have been more precisely defined, often using accepted criteria. It may be possible now to carry out these subgroup analyses. We intend to address this issue in the next update of the review.
To address Robert Hoerr's specific comments.
1.'That it is incorrect to state that there are no data on depression' -
There are three trials named by Robert Hoerr as having data on depression, Kanowski 1996, Schneider 2005, and Napryeyenko 2005. Kanowski 1996 does not assess depression as an outcome measure. Schneider 2005 does assess depression as an outcome measure and although it is reported that there are no significant differences between the treatment groups and placebo the standard deviations of the treatment effects are missing, and therefore this outcome cannot be reported in an analysis. Napryeyenko assesses depression as an outcome measure but the data were not available at the time the review was updated. The only published report of this trial reports the results for the SKT. Therefore it is correct to say that there are no data available on measures of depression, but we shall make efforts to obtain the unpublished data on depression.
2.'That the findings are not as inconsistent and contradictory as presents in the "Results" section and in the abstract'.
The results do not add up to a consistent conclusion, either across outcomes or within outcomes. The meta-analysis for SKT and activities of daily living (higher dose after 22-24 weeks of treatment) have I2 values of 95% and 96% respectively. This indicates serious heterogeneity between the studies which appears to be due to the inclusion of the Napryeyenko study. The results from this study are inconsistent with those of the other studies.
3.'Under "Methodological Quality" the opinion is expressed that the rate of deterioration in the placebo group of the study by Schneider 2005 as measured by the ADAS-cog was not strikingly different from that found in the study by Le Bars 1997'.
The mean baseline MMSE and ADAS-Cog scores of the Schneider study were 18 and 23 respectively, of the Le Bars study 21 and 20. The differences are not great. The change in ADAS-Cog over approximately 6 months was 0.9 in the Schneider study and 1.0 in the Le Bars. The result from the Schneider study does not seem to be exceptional.
Perhaps another point should be made, and that is if the placebo group decline less than expected the treatment group will also. This is a randomized trial. If the decline were less rapid than expected it would not affect the estimate of the treatment effect which in this study was not significantly different from zero.
4.'The statement in the "Discussion" saying that "the results of Le Bars 1997 were not confirmed by van Dongen 2000 or Schneider 2005" is surprising.'
I refer again to my more general comment that this review was intended to cover dementia of all types, and cognitive impairment. There has been no attempt to conduct meta-analyses of diagnostic subtypes.

Contributors

Feedback: Robert Hoerr, submitted 6 June 2007.
Reply from review authors: Jacqueline Birks, 22 January 2008

WHAT'S NEW

Last assessed as up-to-date: 25 March 2008.

Date	Event	Description
5 December 2008	Amended	Corrections made to text

HISTORY

Protocol first published: Issue 2, 2000

Review first published: Issue 4, 2002

Date	Event	Description
28 March 2008	New search has been performed	Update search done in September 2007 retrieved new studies for consideration by the authors
28 March 2008	New citation required and conclusions have changed	Results are available from a new trial, DIGGER, which are included in the review. A report of the trial by Napryeyenko has been published Subgroup analysis in Alzheimer's patients according to dosage has been done
23 January 2008	Feedback has been incorporated	Updated reply by the authors to feedback added
14 November 2007	Feedback has been incorporated	Reply from authors to feedback added
2 August 2007	Feedback has been incorporated	Feedback added to review
1 February 2007	New citation required and conclusions have changed	Three new studies have been included, Kade 1993, Napryeyenko 2005, and Schneider 2005. Two studies that were included in the previous version have been excluded, Allain 1993 and Winther 1998. Allain 1993 and Winther 1998 randomized people who were probably not demented, their degree of cognitive impairment was slight There is very little information available about Kade 1993, a cross-over trial for patients with mild or moderate signs of cerebral insufficiency. There are no results published that could be included in meta-analyses. The second trial, Napryeyenko 2005, is a large (N= 395) 22-week trial for patients with mild to moderate Alzheimer's disease with one dose of Ginkgo biloba, 240 mg/day, compared with placebo. Although the results have not yet been published in a peer-reviewed

(*Continued*)

		journal, the results are included in meta-analyses. The third new trial, Schneider 2005, enrolled 513 participants with moderate dementia due to Alzheimer's disease. The results have been published and are included in the meta-analyses

CONTRIBUTIONS OF AUTHORS

-Jacqueline Birks: all correspondence; drafting review versions, in-and excluding of studies, extraction of data, data-analyses and interpretation of data analyses

-John Grimley Evans: drafting review versions, in -and excluding of studies, interpretation of data analyses

-Martien van Dongen helped with drafting of an early version of the protocol

-Dymphna Hermans and Vittoria Lutje: searches

-Consumer editor: U Hl Htay

-Contact editor: Leon Flicker

-A substantive update of this review has been peer reviewed (February 2007)

Update 2008: JB updated the review in 2008, which was peer reviewed.

DECLARATIONS OF INTEREST

None known.

SOURCES OF SUPPORT

Internal sources

- The University of Oxford, UK.

External sources

- Alzheimer Society, UK.

NOTES

To make the complex information from the trials available in a more easily accessible form, we have created two additional tables: one which describes the included studies in more detail and a second describing the rating scales used in the trials. It is important that these tables should be read with the review.

INDEX TERMS

Medical Subject Headings (MeSH)

*Ginkgo biloba; *Phytotherapy; Cognition Disorders [*drug therapy]; Dementia [*drug therapy]; Plant Extracts [*therapeutic use]; Randomized Controlled Trials as Topic

MeSH check words

Humans