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[Intervention Review]

Ginkgo biloba for acute ischaemic stroke

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ABSTRACT

Background

Ginkgo biloba extract is widely used in the treatment of acute ischaemic stroke in China. We aimed to assess the evidence from randomised controlled trials and quasi-randomised controlled trials on the use of Ginkgo biloba extract in acute ischaemic stroke.

Objectives

The primary objective was to determine whether Ginkgo biloba extract improves functional outcome without causing undue harm in patients with acute ischaemic stroke. Secondary objectives were to assess the effect of Ginkgo biloba extract on neurological impairment and quality of life.

Search methods

We searched the Cochrane Stroke Group Trials Register (last searched October 2004), the Trials Register of the Cochrane Complementary Medicine Field (last searched October 2004) and the Chinese Stroke Trials Register (last searched June 2004). In addition, we searched the Cochrane Central Register of Controlled Trials (CENTRAL) (*The Cochrane Library* Issue 3, 2004), MEDLINE (1966 to August 2004), EMBASE (1980 to June 2004), AMED (1985 to May 2002) and the China Biological Medicine Database (CBM-disc, 1979 to August 2004). We searched relevant clinical trials and research registers and contacted pharmaceutical companies and researchers in an effort to identify further published and unpublished studies.

Selection criteria

Randomised controlled trials or quasi-randomised controlled clinical trials comparing Ginkgo biloba extract with placebo or open control (no placebo) in patients with acute ischaemic stroke.

Data collection and analysis

Two reviewers independently selected trials for inclusion, assessed trial quality and extracted the data.

Main results

Fourteen trials were identified, of which 10 trials (792 patients) were included. Four trials are awaiting assessment. In the 10 included trials follow up was performed at 14 to 35 days after stroke. In all studies neurological outcome was assessed but none of them reported on disability (activities of daily living function) or quality of life. Only three trials reported adverse events. In nine trials, all of them assessed to be of inferior quality, significant improvement in neurological deficit at the end of the treatment was used as the outcome measure. When analysing these trials together, Ginkgo biloba extract was associated with a significant increase in the number of improved patients (Peto odds ratio (OR) 2.66; 95% confidence interval (CI) 1.79 to 3.94). One placebo-controlled trial, assessed to be of good quality, reported

neurological outcome as a continuous variable. It failed to show an improvement of neurological deficit at the end of treatment (weighted mean difference (fixed) 0.81; 95% CI -8.9 to 10.52). No deaths or major adverse events were reported during the follow-up period.

Authors' conclusions

There was no convincing evidence from trials of sufficient methodological quality to support the routine use of Ginkgo biloba extract to promote recovery after stroke. High-quality and large-scale randomised controlled trials are needed to test its efficacy.

PLAIN LANGUAGE SUMMARY

Ginkgo biloba for acute ischaemic stroke

Ginkgo biloba extract, a Chinese traditional medicine, is widely used in the treatment of acute ischaemic stroke in China and is also used occasionally in Europe but its efficacy is uncertain. There is limited experimental support for the use of Ginkgo biloba extract in ischaemic stroke. Hence, it has been shown that Ginkgo biloba extract leads to a significant increase in cerebral blood flow and glucose uptake into brain tissue. This review identified all randomised or quasi-randomised trials of Ginkgo biloba extract in patients with acute ischaemic stroke. There was no convincing evidence, from trials of sufficient methodological quality, to support the routine use of Ginkgo biloba extract to promote recovery after stroke. High-quality and large-scale randomised controlled trials are needed to test its efficacy.

BACKGROUND

Acute stroke is the leading medical cause of adult disability and loss of quality-adjusted life years and has a worse prognosis for survival than most forms of cancer (Lees 2000). Fifteen percent of survivors experience significant disability, and 10% require long-term institutional care (DPH 1994). This is a major burden for both families and society, and stroke consumes about 5% of most developed countries' health-service budgets. For patients with acute ischaemic stroke there is clear evidence of benefit from aspirin started within 48 hours of onset (Gubitz 2001). A systematic review of the randomised trials of thrombolytic therapy given within six hours of onset showed that selected patients were likely to benefit from this treatment, despite the risk of intracranial haemorrhage (Wardlaw 2002).

A survey of treatments used in routine practice in China showed that 75% of doctors surveyed believed that Chinese herb products were effective treatments for acute ischaemic stroke, and 66% of doctors used them routinely for most patients (Chen 1997). Ginkgo biloba extract is a Chinese traditional medicine that has been used therapeutically in China for centuries but its efficacy in acute stroke is uncertain.

Ginkgo biloba extract is made from the dried leaves of the Ginkgo tree. The extract contains several biologically active substances. The important ingredients are ginkgo flavone glycosides (24% to 25%) and terpenoids (6%) (Braquet 1988; Braquet 1989). Experimental and human studies have demonstrated several vascular, haemorheological and metabolic actions that are supposed to exert a 'tissue irrigation effect', directed preferentially towards the ischaemic zone (Kleijnen 1992; Kriegelstein 1986) and support the use of Ginkgo biloba extract in ischaemic stroke. Thus, experimental studies have shown that Ginkgo biloba extract leads to a significant increase in cerebral blood flow (Kriegelstein 1986) and glucose uptake into brain tissue. It has also been demonstrated that it ameliorates the electrolyte imbalance associated with cerebral edema (Chatterjee 1989; Gabard 1980; Sancesario 1986). Other possible effects are oxygen free radical-scavenging activity, antagonism to platelet activating factor that induces platelet aggregation and arterial thrombosis, and a positive effect on haemorheology (Braquet 1991; Cahn 1985). In China, Ginkgo biloba extract is well accepted by doctors and it is used widely in the treatment of acute ischaemic stroke. Ginkgo biloba extract is also used occasionally in France and Germany to treat patients with acute stroke (Garg 1995). However, the scientific evidence has not been systematically reviewed. Some randomised controlled trials of Ginkgo biloba extract in acute ischaemic stroke have been reported. Whether the existing evidence is scientifically rigorous and whether Ginkgo biloba extract can be recommended for routine use based on the current evidence is still uncertain.

The aim of this review was to analyse systematically all randomised and quasi-randomised controlled trials of Ginkgo biloba extract for acute ischaemic stroke to provide the best available evidence for clinical practice and further research planning on acute stroke treatment.

OBJECTIVES

To determine whether Ginkgo biloba extract is effective on clinical outcomes when administered to patients with acute ischaemic stroke. We wished to test the following hypotheses.

- (1) Ginkgo biloba extract therapy reduces the risk of a poor outcome (that is, being dependent on others in activities of daily living or death) several months after stroke.
- (2) Ginkgo biloba extract therapy improves neurological function in patients with acute ischaemic stroke compared to placebo or no specific treatment.
- (3) Ginkgo biloba extract therapy is safe to use in patients with acute ischaemic stroke.

METHODS

Criteria for considering studies for this review

Types of studies

Randomised or quasi-randomised controlled clinical trials (published or unpublished) comparing Ginkgo biloba extract with placebo or open control (no placebo) in patients with acute ischaemic stroke were eligible for inclusion. Quasi-randomisation refers to allocation using alternation, the sequence of admission, case-record numbers, and dates of birth or day of the week. Confounded trials in which the treatment or control group received another active therapy (for example, Ginkgo biloba extract versus another drug) were excluded.

Types of participants

Trials that included patients of any age or sex within 30 days of acute ischaemic stroke and where computed tomography (CT) or magnetic resonance imaging (MRI) demonstrated an infarction or was normal were eligible.

Types of interventions

Trials evaluating both Ginkgo biloba extract intravenous injection and Ginkgo biloba extract in tablet form were included regardless of dosage of treatment. The control interventions were placebo or no treatment. When the addition of Ginkgo biloba extract to another treatment was compared to the other treatment alone, and the trial was therefore assessing Ginkgo biloba extract, the trial was included.

Types of outcome measures

According to the original review protocol, the primary outcome measure was:

- (1) death or dependency at the end of the scheduled follow-up period.
- Dependency is defined as severely dependent on others in activities of daily living for example, Barthel Index score 60 or less, or modified Rankin Scale grade 3 to 6 (Sulter 1999).

Secondary outcome measures were:

- (1) death or dependency at the end of the scheduled treatment period;
- (2) death from any cause by the end of the trial;
- (3) adverse events of bleeding, nausea, vomiting, abdominal pain, diarrhoea, allergic reaction, or other serious adverse event caused by Ginkgo biloba extract; where the number of patients developing at least one severe adverse event listed above was evaluated;
- (4) measures of neurological deficit before and after Ginkgo biloba extract (for instance, Mathew's scale (Mathew 1972), the NIH Stroke Scale or the Scandinavian Stroke Scale);
- (5) quality of life if assessed in the included trials.

Search methods for identification of studies

See: 'Specialized register' section in [Cochrane Stroke Group](#)

We searched the Cochrane Stroke Group Trials Register (last searched by the Review Group Co-ordinator in October 2004), the Trials Register of the Cochrane Complementary Medicine Field (last searched October 2004) and the Chinese Stroke Trials Register (last searched June 2004). In addition, we searched the Cochrane Central Register of Controlled Trials (CENTRAL) (*The Cochrane Library* Issue 3, 2004), MEDLINE (1966 to August 2004), EMBASE (1980 to June 2004), AMED (1985 to May 2002) and the China Biological Medicine Database (CBM-disc, 1979 to August 2004) ([Appendix 1](#)).

We also searched relevant clinical trials and research databases including the Stroke Trials Directory (<http://www.strokecenter.org/trials/>), the National Center for Complementary and Alternative Medicine (<http://www.nccam.nih.gov/clinicaltrials/>), the National Institute of Health Clinical Trials Database (<http://www.clinicaltrials.gov/>), and the Chinese Hospital Digital Library (<http://www.chkd.cnki.net/>).

In an effort to identify further published and unpublished studies we contacted some pharmaceutical companies (such as Dr. Willmar Schwabe Pharmaceuticals, Shenzhen Neptunus Pharmaceutical Co Ltd, Beaufour Ipsen Tianjin Pharmaceuticals, Yangtze River Pharmacy Group Co Ltd), and researchers and colleagues.

Data collection and analysis

Selection of studies

Two of the authors independently selected the trials for inclusion in the review. Additional information was sought from the principal investigators of each trial that potentially fulfilled the inclusion criteria. Disagreement was resolved by discussion with a third party, if necessary.

Quality assessment

The following internal validity criteria made the basis for quality assessment of each included trial:

- (1) method of randomisation (truly or quasi-randomised);
- (2) adequate allocation concealment;
- (3) blinding (both of participants and outcome assessors);
- (4) intention-to-treat analysis;
- (5) numbers lost to follow up.

Quality assessment was performed by two independent authors and agreement was resolved by discussion or by a third party.

Data extraction

Using a prespecified protocol, two authors independently extracted data on patients, methods, interventions, outcomes and results. Disagreement was resolved by discussion. Missing data were obtained from the trialists whenever possible.

Data synthesis

We analysed the effects of treatment in trials which compared:

- (1) Ginkgo biloba extract with placebo;
- (2) the addition of Ginkgo biloba extract to another treatment versus the other treatment alone.

We planned to do subgroup analyses to assess the interaction of the following with the main treatment effects:

- (1) time from stroke onset to randomisation (within 48 hours after stroke onset);
- (2) route of drug administration (intravenous or oral).

Heterogeneity between trial results was tested using a standard chi square test and the I^2 statistic. There was definite evidence of heterogeneity if P was less than 0.1 and I^2 was greater than 50%. The results were reported as odds ratios (OR) with corresponding 95% confidence interval (CI) for dichotomous data using the Peto fixed-effect method ([APT 1994](#)). For continuous data, weighted mean difference (WMD) were computed for outcomes measured on the same scale, and standardised mean difference (SMD) was calculated when the same outcome was measured on different scales (for example, neurological function).

RESULTS

Description of studies

Thirty-five trials were excluded, while 10 trials, including a total 792 patients, met our inclusion criteria. All 10 included trials had distinct inclusion criteria and two trials ([Li 1998](#); [Li 2001](#)) reported severity of stroke at entry into the trial. One trial ([Garg 1995](#)) described the exclusion criteria. All patients had a brain CT scan. For the excluded trials, 18 trials were confounded, seven trials were non-randomised, five trials were not clear with regard to the stroke stage or were in the rehabilitation stage, one trial included transient ischaemic attacks (TIA), and one trial was not clear with regard to the type of stroke.

Ginkgo biloba extract oral tablets were studied in six trials ([Feng 2002](#); [Garg 1995](#); [Hu 1999](#); [Li 1998](#); [Li 2001](#); [Tu 2000](#)), the dosage ranging from 120 mg to 240 mg per day for 20 to 28 days. The other four trials ([Li 2003](#); [Song 2001](#); [Yuan 2002](#); [Zhu 2001](#)) studied Ginkgo biloba extract intravenous injections, the dosage being from 15 ml to 20 ml (Ginkgo biloba extract 17.5 mg per 5 ml) per day for 14 to 30 days.

Six trials ([Feng 2002](#); [Garg 1995](#); [Hu 1999](#); [Li 1998](#); [Tu 2000](#); [Zhu 2001](#)) reported the timing of the start of treatment after stroke onset. In two trials, all patients were included within the first 48 hours of stroke onset; in four trials, patients were also included later after onset; and in four trials the time of start of treatment was not specified in relation to stroke onset.

The outcome measure used in nine trials was the proportion of patients with improvement of neurological deficit using the Modified Edinburgh-Scandinavian Stroke Scale (MESSS). One trial ([Garg 1995](#)) measured neurological deficit as a continuous variable by Mathew's scale and only this trial used blinded assessment.

The patients were not followed up after drug discontinuation in all trials. No deaths were reported in these trials. Three trials ([Garg 1995](#); [Hu 1999](#); [Li 1998](#)) reported adverse events. Assessment of disability (functional outcome) or quality of life was not undertaken in any of the trials.

Risk of bias in included studies

One trial ([Garg 1995](#)) was randomised, placebo controlled and double blind. The drug code was provided in an envelope which was kept secret until the final analysis of the trial was completed.

Thus, this trial had adequate concealment of randomisation. Four patients in the treatment group and three in the control group were lost to follow up. In the final analysis, these patients were not included and this trial did not use intention-to-treat analysis.

One trial (Li 1998) had inadequate concealment of randomisation and was graded as level C because patients were allocated according to their sequence of admission. The other eight trials did not report the method of allocation and were graded as level B, unclear allocation concealment. The baseline characteristics of the patients did not differ between treatment and control groups in these trials. Nine trials did not mention whether they used a blinded method of outcome assessment and intention-to-treat analysis. No patients were reported to be lost to follow up in the nine trials, but the follow-up period was short (14 to 35 days).

Effects of interventions

There were few disagreements between the authors in selecting primary studies, assessing quality or extracting data, and these were easily resolved by consensus. Meta-analysis of the nine trials that used a dichotomous outcome variable (improvement of neurological deficit) showed a significantly higher proportion of patients treated with Ginkgo biloba extract improving compared with control patients (Peto OR 2.66; 95% CI 1.79 to 3.94).

The only trial that was assessed to be of good methodological quality, and also the only one reporting neurological improvement on a continuous scale (Garg 1995), failed to show an improvement of neurological deficit between the two groups at the end of treatment (WMD (fixed) 0.81; 95% CI -8.9 to 10.52).

Deaths during follow up

No deaths were reported during the period of treatment in the 10 trials. This may mean that only mild strokes were included in the trials or that deaths occurred but were not reported by the trialists. The patients were not followed up after drug treatment was discontinued in any of the trials.

Functional outcome and quality of life

Assessment of activities of daily living function or any other measure of disability or quality of life was not undertaken in any of these trials.

Subgroup analysis

With separation into the route of administration (intravenous and oral), there was no evidence of heterogeneity of effect between the two routes (P value 0.61). Only two trials clearly declared that patients were randomised within 48 hours after stroke onset; the time to randomisation was not clear in the other trials because we failed to get the primary data from the trialists.

Sensitivity analysis

Meaningful sensitivity analyses could not be performed because of the small number of patients in the trials.

DISCUSSION

This systematic review was initiated because Ginkgo biloba extract is widely used in clinical practice in China yet there is uncertainty about its effectiveness and safety in acute ischaemic stroke. In our original protocol, we also planned to include confounded trials of

Ginkgo biloba extract in acute ischaemic stroke. However, those trials were many and they included a wide variety of concomitant medicines, making it difficult to isolate the effects of Ginkgo biloba extract alone.

Originally, we also planned to include non-randomised trials in the safety analysis, but no major side effects were reported in any of these trials. We, therefore, agreed to change the protocol to focus on randomised and quasi-randomised controlled trials.

We identified 14 completed randomised or quasi-randomised controlled trials of Ginkgo biloba extract for acute ischaemic stroke. Outcome data were available in 10 trials which included a total 792 patients. Four trials are awaiting assessment because of insufficient data (we have written to the trialists twice to request supplementary data; they have not replied). One trial (Garg 1995), which was regarded as the only high quality study, failed to show that Ginkgo biloba extract was superior to placebo in the treatment of acute ischaemic stroke. On the other hand, meta-analysis of the other nine included trials showed that the proportion of patients with improvement in neurological score at the end of the treatment period was significantly higher among those treated with Ginkgo biloba extract than in control patients. These results should be interpreted cautiously because of the inferior methodological quality of these nine trials. Subgroup analysis showed no evidence of a difference in efficacy between Ginkgo biloba extract tablets and intravenous injections.

A strength of the trials included in this systematic review was that a diagnosis of ischaemic stroke was confirmed by CT scan in all patients. Yet, all the included trials except one (Garg 1995) were assessed to be of inferior methodological quality. The limitations of the nine trials assessed to be of inferior methodological quality were as follows.

- (1) There was uncertainty whether or not the trials were truly randomised with adequate concealment of allocation, which allows the possibility of a selection bias; eight trials did not mention how the randomisation procedure was performed (methods of allocation and concealment). One trial (Li 1998) was a quasi-randomised controlled trial in which concealment was not adequate.
- (2) Outcome assessment should preferably be blinded. Whether the nine trials used a blinded method to assess outcome is unclear, leaving the possibility of measurement bias (exaggerating or minimising the effect of the intervention).
- (3) Sample sizes were too small.

The experience of the present authors is that negative trial results are not easy to get published in China. Therefore, publication bias is probably high in the Chinese medical literature. Among the 10 included trials, nine were from China. Although considerable efforts were made to obtain all results from pharmaceutical companies, there were no negative results available.

Three trials in this review reported adverse events. No major side effects were reported in the 10 trials or in those confounded trials and non-randomised trials that we did not include in the formal analysis. This is consistent with observations in other Cochrane reviews. No serious adverse events were reported among more than 1500 patients treated with Ginkgo biloba extracts for cognitive impairment and dementia (Birks 2004) and more than 500 patients with tinnitus (Hilton 2004). In both reviews, minor adverse events

in actively-treated patients were reported to occur at the same frequency as in control patients.

For the following reasons, the usefulness of the trials was limited.

(1) In the 10 trials, follow up ranged from 14 days to 35 days after the start of treatment. The follow-up time was insufficient to assess the long-term effects of Ginkgo biloba extract.

(2) Primary outcome measures were at the level of impairment (neurological deficits). It has been increasingly recognised that high-quality trials in acute stroke should measure outcome at the level of disability (functional outcome) and ideally also quality of life, that is, outcomes that are of primary importance for the patients. All included trials focused on the level of neurological deficit.

(3) It was remarkable that no deaths were reported in any of the included trials. One obvious reason would be that many of the trials included patients several days, or even weeks, after stroke onset. It is also possible that the trials did not include patients with severe strokes, although this was not clearly stated in the inclusion criteria. This notwithstanding, the absence of deaths, stroke-related or from other causes, strongly suggests that the results of the trials were not reported with sufficient rigour.

A definite conclusion on efficacy associated with Ginkgo biloba extract cannot be drawn from this review due to the poor-quality trials. High-quality, large-scale trials are needed to confirm the efficacy of Ginkgo biloba extract.

AUTHORS' CONCLUSIONS

Implications for practice

There is no scientific support from high-quality studies for the routine use of Ginkgo biloba extract in the treatment of patients with acute ischaemic stroke.

Implications for research

Our meta-analysis suggests that Ginkgo biloba extract intravenous injections and Ginkgo biloba extract tablets both improve neurological impairment after acute ischaemic stroke. A caveat is, however, that with one exception, the trials included were assessed to be of inferior methodological quality. High-quality, large-scale randomised trials are needed to confirm or refute the results. Future trials should overcome the methodological limitations of the trials presented in this review. In particular, they should assure adequate concealment of allocation, blinding of outcome assessors, use functional outcome as the primary outcome measured at long-term follow up, and they should be large enough to provide adequate statistical power.

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CHARACTERISTICS OF STUDIES

Characteristics of included studies [ordered by study ID]

Feng 2002

Methods	RCT Randomisation: method not specified Blinding: not stated Number of losses to follow up: none
Participants	Country: China 67 acute ischaemic stroke patients within 6 h to 48 h after stroke onset, all had CT scan excluded brain haemorrhage T: 35 cases, male 29, female 6; average age 63.1 y C: 32 cases, male 25, female 7; average age 60.6 y
Interventions	T: Tanakan 40 mg tid for 28 days + RT (hydroxyethyl starch + venoruton + diphosphate choline) C: RT
Outcomes	NPNI at 35 days
Notes	FU: 35 days

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	B - Unclear

Garg 1995

Methods	RCT, double blind placebo controlled Randomised by random number table
Participants	Country: India 62 acute ischaemic stroke patients more than 2 days not within few hours, all had brain CT scan Patients with ischaemia in posterior cerebral territory, overt systemic diseases and deeply comatose were excluded T: group A, 33 cases C: group B, 29 cases
Interventions	T: GBET 40 mg qid for 28 days C: placebo
Outcomes	Mathew's scale for neurological function at 28 days No death occurred in any group under the drug trial
Notes	FU: 28 days Loss to FU: T - 4 cases; C - 3 cases No major side effects, 4 cases in T had gastrointestinal upsets

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Low risk	A - Adequate

Ginkgo biloba for acute ischaemic stroke (Review)

Hu 1999

Methods	RCT Randomisation: method not specified Blinding: not stated Number of losses to follow up: none Allocation concealment: not explicit
Participants	Country: China Patients with acute ischaemic stroke within 1 day to 3 weeks, mean 10 days, all had brain CT scan T: 64 cases, male 48, female 16, age 44 to 85 y, mean age 64.2 y C: 50 cases, male 38, female 12, age 42 to 86 y, mean age 65.1 y
Interventions	T: GBET 80 mg tid for 20 days + cerebralysin C: cerebralysin
Outcomes	NPNI at 20 days
Notes	FU: 20 days 2 cases in T had stomach discomfort

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	B - Unclear

Li 1998

Methods	Quasi-RCT (according to the sequence of admission), alternate allocation Blinding: no Losses to FU: none
Participants	Country: China 128 acute ischaemic stroke patients within 8 days, all had brain CT scan T: 65 cases, male 44, female 21; age 41 to 73 y; L 38, M 25, S 2 C: 63 cases, male 43, female 20; age 40 to 75 y; L 37, M 24, S 2
Interventions	T: GBET 80 mg tid for 21 days + RT (dextran 40 + venoruton + CXQ) C: RT
Outcomes	NPNI at 21 days
Notes	FU: 21 days In T, one case had abdominal pain and diarrhoea, one had skin scratch

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	High risk	C - Inadequate

Li 2001

Methods	RCT Randomisation: method not specified Blinding: not stated Number of losses to follow up: none Allocation concealment: not explicitly stated
Participants	Country: China Acute ischaemic stroke patients, male 35, female 26; Age 49 to 80 y; mean age 59 y All patients had first-ever stroke events All had brain CT scan T: 32 cases, L 10, M 16, S 6 C: 29 cases, L 9, M 15, S 5
Interventions	T: Tanakan 40 mg tid for 20 days + RT (citicoline + dextran 40 + danshen) C: RT
Outcomes	NPNI at 20 days
Notes	FU: 20 days
Risk of bias	
Bias	Authors' judgement Support for judgement
Allocation concealment?	Unclear risk B - Unclear

Li 2003

Methods	RCT Method of randomisation and concealment not stated Blinding: not stated Losses to FU: none
Participants	Country: China 93 acute ischaemic stroke patients, all had brain CT scan T: 47 cases, Male 39, female 8; age 61.2 ± 19.3 y C: 46 cases, male 33, female 13; age 56.4 ± 18.7 y
Interventions	T: GBEI 52.5 mg (15 ml) iv once a day for 15 days + RT (venoruton + aspirin) C: RT
Outcomes	NPNI at 28 days
Notes	FU: 28 days
Risk of bias	
Bias	Authors' judgement Support for judgement
Allocation concealment?	Unclear risk B - Unclear

Song 2001

Methods	RCT Randomisation: method not specified Blinding: not stated Number of losses to follow up: none Allocation concealment: not explicit
Participants	Country: China Acute ischaemic stroke patients, all had brain CT scan T: 42 cases, male 24, female 18; age 36 to 82 y, mean age 59.2 y C: 42 cases, male 23, female 19; age 35 to 79 y, mean age 58.2 y
Interventions	T: GBEI 70.0 mg (20 ml) iv for 20 to 30 days + RT (CDSI + venoruton + dextran 40) C: RT
Outcomes	NPNI at 30 days
Notes	FU: 30 days

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	B - Unclear

Tu 2000

Methods	RCT Randomisation: method not specified Blinding: not stated Number of losses to follow up: none Allocation concealment: not explicit
Participants	Country: China Patients with acute ischaemic stroke within 24 to 72 hours, all had brain CT scan T: 40 cases, male 17, female 23; age 47 to 81 y, mean age 62 ± 15 y C: 20 cases, male 8, female 12; age 44 to 78 y, mean age 61 ± 15 y
Interventions	T: Tanakan 40 mg tid for 28 days + RT C: RT
Outcomes	NPNI at 28 days
Notes	FU: 28 days

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	B - Unclear

Yuan 2002

Methods	RCT
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Ginkgo biloba for acute ischaemic stroke (Review)

Yuan 2002 (Continued)

Randomisation: method not specified
Blinding: not stated
Number of losses to follow up: none
Allocation concealment: not explicit

Participants	Country: China Acute cerebral infarction patients, all had brain CT or MRI scan T: 38 cases, male 23, female 15; mean age 59.3 y C: 30 cases, male 16, female 14; mean age 57.4 y
Interventions	T: GBEI 70.0 mg (20 ml) iv for 20 days + RT (aspirin 100 mg + diphosphate choline) C: RT
Outcomes	NPNI at 20 days
Notes	FU: 20 days

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	B - Unclear

Zhu 2001

Methods	RCT, method of randomisation and concealment not stated Blinding: not stated Losses to FU: none
Participants	Country: China 62 acute ischaemic stroke within 48 h, all had brain CT scan T: 31 cases, male 22, female 9, average age 65 y C: 31 cases, male 25, female 6, average age 67 y
Interventions	T: GBEI 70.0 mg (20ml) iv qd for 14 days + RT (aspirin 100 mg qd and dextran 40 500 ml iv qd) C: RT
Outcomes	NPNI at 14 days
Notes	FU: 14 days

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	B - Unclear

C: control group
CT: computed tomography
CXQ: chuan xiong qin (herb)
FU: follow up
GBET: Ginkgo biloba extract tablet
GBEI: Ginkgo biloba extract injection
iv: intravenous injection
L: mild

M: moderate

MESSS: Modified Edinburgh-Scandinavian Stroke Scale

MSS: Mathew's scale score

NPNI: number of patients with neurological improvement (MESSS score > 18%)

qid: four times a day

RCT: randomised controlled trial

RT: routine treatment

S: severe

T: treatment group

tid: three times a day

y: years

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

Study	Reason for exclusion
Anadere 1985	Laboratory variable used as outcome
Cai 2002	Confounded trial (GBE and CDSI)
Chen 1999	Outcome measurement not qualified
Chen 2000	Laboratory variable used as outcome
Chen 2001	Confounded trial (GBE and venoruton) Laboratory variable used as outcome
Du 2000	Confounded trial (GBE and CXQ)
Dzyak 1996	Patients were in the rehabilitation stage
Feng 1999	Confounded trial (GBE and CDSI), not clear about the stage of stroke
Gu 2000	Confounded trial (GBE and venoruton)
Guo 2001	Confounded trial
Li 2000	Confounded trial (GBE and CXQ plus dextran 40)
Li 2002	Confounded trial (GBE and CXQ)
Lian 1997	The stage of stroke was not stated
Liu 2000	Confounded trial (GBE and dextran 40)
Qin 1999	Confounded trial (GBE and venoruton)
Qu 2003	Confounded trial (GBE and xiangdan)
Shen 2002	Confounded trial
Song 2004	Confounded trial (GBE and CDSI and dextran 40)
Sun 1997	Confounded trial (GBE and venoruton)
Tan 2003	Confounded trial (GBE and venoruton)

Study	Reason for exclusion
Wang 1996	Confounded trial (GBE and venoruton)
Wang 2000	Confounded trial (GBE and CXQ)
Wang 2001a	Non-randomised trial
Wang 2001b	Confounded trial (GBE and dextran 40)
Wei 2001	Non-randomised trial, confounded (GBE and urokinase)
Witte 1986	Type of stroke patients in trial unknown (no CT scan) Laboratory variable used as outcome
Wu 2000a	Non-randomised trial
Wu 2000b	The stage of stroke not stated
Xin 1998	Non-randomised
Zhang 2001	The stage of stroke not clear
Zhang 2002	Non-randomised
Zhang 2002a	Included TIA patients
Zhang 2002b	Non-randomised
Zhen 2000	Non-randomised
Zhu 1998	The stage of stroke not clear

CDSI: compound dan shen injection (herbs)

CXQ: chuan xiong qin (herb)

GBE: ginkgo biloba extract

TIA: transient ischaemic attack

Pharmacological studies indicated that CDSI, DS and CXQ have the effects of dilating the cardiocerebral vessels, suppressing the aggregation of platelets, improving circulation, removing blood stasis, protecting against ischaemic reperfusion injury, and enhancing the tolerance of ischaemic tissue to hypoxia.

DATA AND ANALYSES

Comparison 1. Ginkgo biloba versus control

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Proportion of patients with improvement of neurological deficit at the end of follow up	9	737	Peto Odds Ratio (Peto, Fixed, 95% CI)	2.66 [1.79, 3.94]
1.1 MESSS	9	737	Peto Odds Ratio (Peto, Fixed, 95% CI)	2.66 [1.79, 3.94]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
2 Outcome reported as continuous variable (neurological deficit) at follow up	1	55	Mean Difference (IV, Fixed, 95% CI)	0.81 [-8.90, 10.52]
2.1 MSS	1	55	Mean Difference (IV, Fixed, 95% CI)	0.81 [-8.90, 10.52]

Analysis 1.1. Comparison 1 Ginkgo biloba versus control, Outcome 1 Proportion of patients with improvement of neurological deficit at the end of follow up.

Analysis 1.2. Comparison 1 Ginkgo biloba versus control, Outcome 2 Outcome reported as continuous variable (neurological deficit) at follow up.

Comparison 2. Subgroup analysis

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 By treatment type	9	737	Peto Odds Ratio (Peto, Fixed, 95% CI)	2.66 [1.79, 3.94]
1.1 Ginkgo biloba extract injections	4	307	Peto Odds Ratio (Peto, Fixed, 95% CI)	3.00 [1.63, 5.55]
1.2 Ginkgo biloba tablets	5	430	Peto Odds Ratio (Peto, Fixed, 95% CI)	2.44 [1.46, 4.07]

Analysis 2.1. Comparison 2 Subgroup analysis, Outcome 1 By treatment type.

APPENDICES

Appendix 1. MEDLINE search strategy

The following search strategy was used for MEDLINE and was modified for the other databases.

Database MEDLINE (Ovid) 1966 to August 2004

1. exp cerebrovascular disorders/
2. (stroke\$ or cva\$ or cerebrovascular or cerebral vascular).tw.
3. (cerebral or cerebellar or brain\$ or vertebrobasilar).tw.
4. (infarcts\$ or isch? emi\$ or thrombo\$ or emboli\$ or apoplexy).tw.
5. 3 and 4
6. 1 or 2 or 5
7. Ginkgo biloba/
8. (Ginkgo\$ or tanakan or rokan or EGB\$ or LI 1370).tw.
9. 7 or 8
10. 6 and 9
11. limit 10 to human

WHAT'S NEW

Date	Event	Description
21 August 2008	Amended	Converted to new review format.

CONTRIBUTIONS OF AUTHORS

Xianrong Zeng: wrote the first draft of the protocol, redrafted it in response to comments, did the searches and identified trials, extracted data and performed the analyses, and wrote the review.

Yang Li: did the searches and identified trials, extracted data, entered data into RevMan.

Yousong Yang: data management for the review.

Ming Liu: commented on the protocol and the draft review.

Kjell Asplund: commented on the protocol and the draft review.

DECLARATIONS OF INTEREST

None known

INDEX TERMS

Medical Subject Headings (MeSH)

*Ginkgo biloba; *Phytotherapy; Plant Preparations [*therapeutic use]; Randomized Controlled Trials as Topic; Stroke [*drug therapy]

MeSH check words

Humans