

Ginkgol Biloba extract as an adjunctive treatment for ischemic stroke

A systematic review and meta-analysis of randomized clinical trials

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Abstract

Objective: Ginkgo biloba extract (GBE) is widely used as an adjunctive treatment for ischemic stroke. This meta-analysis aimed to evaluate the effectiveness and safety of GBE specifically for long-term users at the convalescence stage of ischemic stroke.

Methods: MEDLINE, Cochrane Central Register of Controlled Trials, Embase Database, WHO Clinical Trials Registration Platform, Chinese National Knowledge Infrastructure, Wanfang Database, and Chinese Scientific Journal Database were searched from inception to 20 September 2018. Risk ratio (RR) and mean difference (MD) with a 95% confidence interval (CI) were used as effect estimates using RevMan software (5.3; Review Manager [RevMan], Nordic Cochrane Centre, Copenhagen, Denmark). A meta-analysis was performed where data were available. A trial sequential analysis was used to control random errors for recurrence rate and the GRADE (grading of recommendations, assessment, development, and evaluations) approach was used to assess the quality of the body of evidence. The meta-analysis design was registered on PROSPERO (CRD42018110211, <http://www.crd.york.ac.uk/PROSPERO>).

Results: We identified 15 randomized clinical trials involving 1829 participants. The majority of the included trials were of high risk of bias in methodological quality. For acute ischemic stroke, adding GBE to conventional therapy led to higher Barthel index scores (MD: 5.72; 95% CI: 3.11–8.33) and lower neurological function deficit scores (MD: –1.39; 95% CI: –2.15 to –0.62). For patients in their convalescence (or sequelae) stage of ischemic stroke, GBE was superior in improving dependence (MD: 7.17; 95% CI: 5.96–8.38) and neurological function deficit scores (MD: –1.15; 95% CI: –1.76 to –0.53) compared with placebo or conventional therapy, but there was no difference in vascular events (RR: 0.70; 95% CI: 0.44–1.14), recurrence rate (RR: 0.57; 95% CI: 0.26–1.25; trial sequential analysis: conclusive) and mortality (RR: 1.07; 95% CI: 0.41–2.81).

Conclusions: GBE appears to improve neurological function and dependence compared with conventional therapy for ischemic stroke at different stages and appears generally safe for clinical application. The lack of improvement in recurrence rate was confirmed by trial sequential analysis. Due to the generally weak evidence, further large, rigorous trials are warranted.

Abbreviations: ADR = adverse drug reaction, BI = Barthel index, CI = confidence interval, GBE = *Ginkgo biloba* extract, GRADE = grading of recommendations, assessment, development and evaluations, I^2 = inconsistency index, MD = mean difference, NFDS = Neurological Function Deficit Score, NIHSS = National Institute of Health Stroke Scale, PRISMA = Preferred Reporting Items for Systematic Reviews and Meta-Analysis, RCT = Randomized controlled trial, RR = risk ratio, TSA = Trial sequential analysis, WHO = World Health Organization.

Keywords: *Ginkgo biloba* extract, ischemic stroke, meta-analysis

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1. Introduction

A stroke is caused by poor blood flow to the brain.^[1] The number of people who die of stroke ranks as the second highest cause of death worldwide and is now a severe threat to human health. According to the World Health Organization (WHO), 15 million people suffer a stroke worldwide every year; 5 million people die and another 5 million are left permanently disabled, placing a heavy burden on family and community.^[2] Approximately 67% of all strokes are ischemic in Asian populations.^[3] In China, the stroke burden has increased over the past 30 years with the age-standardized prevalence rate at 1114.8/100,000 people for the past 10 years, 1.1 million stroke-related deaths per year, 11.1 million post-stroke survivors at any given time, and stroke being the leading cause of death at the national level in China in 2017.^[4] According to its natural course, ischemic stroke can be divided into 3 periods: the acute phase (less than 2 weeks from symptom onset), the stationary phase (2 weeks to 6 months from symptom onset), and the sequelae phase (6 months or longer from symptom onset).^[5] At present, available therapies for acute ischemic stroke are recanalization treatment strategies, including intravenous alteplase and endovascular intervention. Because of

limitations regarding time or indications, they are only available for few patients and have only a moderate effect.^[6,7] In addition, anti-platelet drugs are reported to have a high risk of intracranial bleeding and the anticoagulants do not improve the long-term outcomes.^[8] Furthermore, compared with other countries in the world, the recurrence rate of ischemic stroke in China is the highest.^[9]

We searched PubMed and identified 2 systematic reviews of *Ginkgo biloba* extract (GBE) use for ischemic stroke.^[10,11] Both of the reviews supported GBE as possibly being beneficial for the treatment of the acute phase of stroke based on an anti-oxidative, neuroprotective effect and reduced blood viscosity,^[12,13] but neither of the reports assessed the use of GBE long-term (>2 weeks) nor did they focus on GBE and a possible effect on the high recurrence of ischemic stroke. In China, GBE has been commonly used for cerebrovascular disease and prepared in various forms, such as tablet and injection. In addition, several formulations of GBE (trade names: Ginaton, Tanakan) imported from Germany or France are approved by the State Food and Drug Administration.^[14] GBE is now the most widely used adjunctive drug for ischemic stroke in China. This review aimed to systematically collect all relevant randomized trials and critical appraisals of the effectiveness and safety of GBE for different stages of ischemic stroke.

2. Methods

2.1. Study design

This systematic review protocol has been registered at PROSPERO (CRD42018110211). Our team has investigated the protocol following the Preferred Reporting Items for Systematic Reviews and Meta-Analysis protocols (PRISMA) statement guidelines.^[15] Study selection was conducted in three consecutive stages. Firstly, the titles and/or abstracts of all electronic articles were screened to evaluate their eligibility. All articles that were presumed to meet the criteria were retrieved as full texts. Finally, all studies (both observational and randomized trials) that assessed the effectiveness of GBE administration as an adjuvant measure for ischemic stroke were selected. Case reports, conference abstracts, review articles, and animal studies were excluded from the present review. Any discrepancies concerning the retrieval of articles and statistical analyses were resolved by the consensus of all authors.

2.2. Literature search and data collection

We conducted a systematic search in 4 English databases and 3 Chinese databases: MEDLINE (1959–2018, available at <http://www.ncbi.nlm.nih.gov/pubmed/>), Cochrane Central Register of Controlled Trials (CENTRAL, 1996–2018, available at <http://www.cochrane.org/editorial-and-publishing-policy-resource/cochrane-central-registercontrolled-trials-central>), Embase Database (1980–2018, available at <http://www.elsevier.com/online-tools/embase>), WHO International Clinical Trials Registration Platform (WHO ICTRP, 2007–2018, available at <http://www.who.int/ictrp/en/>), the Chinese National Knowledge Infrastructure (CNKI, 1979–2018, available at <http://www.cnki.net/>), Wanfang Database (1985–2018, available at <http://www.wanfangdata.com.cn/>) and the Chinese Scientific Journal Database (VIP, 1989–2018, available at <http://www.cqvip.com/>). The search time frame ranged from the date of inception of each database until 20 September 2018. We also searched reference

lists for further publications. The search expression used in MEDLINE was ((stroke [MeSH Terms] OR stroke [All Fields]) OR (infarction [MeSH Terms] OR infarction [All Fields]) OR (ischemia [MeSH Terms] OR ischemia [All Fields])) AND ((“*Ginkgo biloba*” [MeSH Terms]) OR “*Ginkgo biloba* extract” [Text Word]) OR “ginkgo ketone ester dispersible tablet” [Text Word] OR “*Ginkgo biloba* leaf tablet” [Text Word] OR ginaton [Text Word] OR “shuxuening” [Text Word]) AND “Randomized Trial” AND Humans [MeSH]. Similar expressions were used in the other databases.

2.3. Investigated indices

All trials for evaluating the efficacy and safety of GBE were included in the literature regardless of language and the type of publication. People with ischemic stroke were included regardless of their sex, age, race, or disease stage. The treatment period was at least 2 weeks. The conventional medicine group comprised the blank control group or the conventional drug (angiotensin converting enzyme inhibitors, beta blockers, calcium antagonists, nitrate esters, statins, and so on) group. The use of traditional Chinese medicine or Chinese patent medicine as a control group was excluded. Oral GBE was included instead of GBE injection. Trials were excluded if there were other Chinese herbal medicines in the intervention group. The outcome measures met the primary or secondary outcomes. For the acute stage, the primary outcomes were all-cause mortality, Barthel index (BI) scores, and serious adverse events. The secondary outcomes were changes in neurological function deficit assessed by validated scales such as the National Institute of Health Stroke Scale (NIHSS) or the nationally approved Neurological Function Deficit Score (NFDS), recurrence rate, and non-serious adverse drug reactions (ADRs). For the convalescence (or sequelae) stage, the primary outcomes were dependence, recurrence rate, vascular events, and quality of life, and the secondary outcomes were all-cause mortality, neurological deficit, and non-serious ADRs.

2.4. Definitions

Patients should have been diagnosed by brain computed tomography or magnetic resonance imaging to confirm an infarction in the brain and exclude hemorrhage and transient ischemic attack. BI scores defined dependence.^[16] Vascular events included cerebrovascular events, cardiovascular events, death, and other serious life-threatening events.^[17] We regarded improvement (NFDS decreased $\geq 18\%$), no change (NFDS decreased $< 18\%$), deterioration (NFDS increased), and death as treatment failures for NFDS.^[18]

2.5. Quality assessment

The methodological quality of each included randomized controlled trial (RCT) was evaluated using the Cochrane risk of bias tool.^[19] Two researchers independently assessed all trials concerning the risk of selection bias (random sequence generation), detection bias (blinding of outcome assessment), performance bias (blinding of participants and personnel), attrition bias (incomplete outcome data) and reporting bias (selective reporting). Any potential disagreements were resolved through the consensus of all authors.

2.6. Statistical analysis

The statistical meta-analysis was carried out in RevMan software (version 5.3; Review Manager [RevMan], Nordic Cochrane

Centre, Copenhagen, Denmark). Confidence intervals (CIs) were set at 95%. Relative risk (RR) was calculated for dichotomous data or continuous data. The inter-study heterogeneity was evaluated with the inconsistency index (I^2).^[19] A fixed effects model was used if there was no significant heterogeneity of the data, $I^2 \leq 50\%$; an $I^2 > 50\%$ with a $P \leq .1$ indicated the possibility of statistical heterogeneity and a random-effects model was adopted. Funnel plots were used to assess the publication bias if more than 8 trials tested the same outcome in 1 meta-analysis. Subgroup analyses by disease stage or by different

neurological function deficit measurements were performed if data were available.

3. Results

3.1. Description of studies

The initial search yielded 17 potentially eligible reports by reviewing the study titles and abstracts.^[20–36] Ultimately, 1829 patients included in 15 trials (published between 2001 and 2018) were randomly assigned to the GBE treatment strategy (Table 1)

Table 1
The specific characteristics of the literatures.

Serial number	Study ID	Sample	Sex (M/F)	Age (years)	Diagnose standard	Interventions	Duration (week)	Outcomes	Follow up
20	Gui 2018	T:53	T:30/23	T:67.93±7.35	1995“diagnostic criteria for cerebrovascular disease”in china	T:GBE (A,qd)+CM	2	NFDS*, ADRs	NR
21	Fang 2018	C:53 T:42	C:32/21 T:28/14	C:68.14±7.39 T:71.23±5.12	2010 “diagnosis and treatment for cerebral ischemic stroke”in china	T:GBE (B,tid)+CM	2	Clinical effect (NIHSS)*, BI	NR
22	Shi 2017	C:41 T:41	C:27/14 T:13/18	C:72.09±6.81 T:69.42±7.24	1995“diagnostic criteria for cerebrovascular disease”in china	T:GBE (B,tid)+CM	2	Clinical effect*	NR
23	Li 2017	C:41 T:179	C:26/15 T:59/120	C:68.72±8.14 T:64.5±0.7	TOAST	T:GBE (B,tid) + CM	24	NIHSS, BI, Death, Recurrence rate, VEs	2 year
24	Liang 2016	C:169 T:54	C:73/96 T:30/24	C:63.3±0.8 T:61.8±10.7	Cerebral ischemic stroke diagnostic criteria (NR)	T:GBE (A,qd) + CM	2	Clinical effect*	NR
25	Du 2016	C:53 T:49	C:29/24 T:31/18	C:62.2±11.5 T:61.2±3.7	Cerebral ischemic stroke diagnostic criteria (NR)	T:GBE (A,qd) + CM	2	NFDS	NR
26	Yu 2016	C:49 T:33	C:29/20 T:20/13	C:63.1±4.0 T:74.3±4.3	1995“diagnostic criteria for cerebrovascular disease”in china	T:GBE (A,qd) + CM	3	Clinical effect (NIHSS)*,BI, ADRs (no)	NR
27	Wang 2014	C:32 T:40	C:18/14 T:22/18	C:75.2±4.2 T:58.9±7.3	1995“diagnostic criteria for cerebrovascular disease”in china	T:GBE (A,qd) + CM	2	NIHSS	NR
28	Qin 2014	C:40 T:30	C:25/15 T:20//10	C:60.1±7.5 not mentioned	1995“diagnostic criteria for cerebrovascular disease”in china	T:GBE (A,qd) + CM	2	NFDS	NR
29	Ma 2014	C:30 T:150	C:18//12 NR	NR NR	2010 “diagnosis and treatment for cerebral ischemic stroke”in china	T:GBE (A,qd) + CM	4	Clinical effect (NFDS)*	NR
30	Ge 2014	C:150 T:44	NR NR	NR NR	Cerebral ischemic stroke diagnostic criteria (NR)	T:GBE (A,qd) + CM	2	Clinical effect (NFDS)*,ADRs	NR
31	Oskouei 2013	C:44 T:52	T:26/26	T:70.0±11.3	Cerebral ischemic stroke diagnostic criteria (NR)	T:GBE (C,tid) + CM	16	VEs, Death, Recurrence rate	4 mo
32	hou 2005	C:50 T:90	C:20/30 T:45/45	C:69.3±12.3 T:59.4	1995“diagnostic criteria for cerebrovascular disease”in china	T:GBE (A,qd) + CM	2	Clinical effect*, ADRs	4 wk
33	Yuan 2002	C:90 T:38	C:50/40 T:23/15	C:57.7 T:59.32	1995“diagnostic criteria for cerebrovascular disease”in china	T:GBE (A,qd) + CM	4	Clinical effect (NFDS)*	NR
34	Zhu 2001	C:30 T:31	C:16/14 T:22/9	C:57.38 T:65	1986“diagnostic criteria for cerebrovascular disease”in china	T:GBE (A,qd) + CM	2	Clinical effect*	NR
		C:31	C:25/6	C:67		C:CM			

A: 17.5 mg per injection, 70 mg/d B: 150 mg per dispersible tablet, 450 mg/d C: 40 mg per tablet, 120 mg/d.

ADRs= adverse drug reactions, BI= Barthel Index, C= control group, CT= conventional therapy, F= females, GBE= Ginkgol Biloba Extract, M= males, NFDS= neurological function deficit score, NIHSS= National Institutes of Health Stroke Scale, NR= not reported, T= treatment group, VEs= vascular events.

* Clinical effect defined according to the nationally approved criteria, which divided clinical effect into ‘almost healed’, ‘markedly effective’, ‘effective’, ‘ineffective’, ‘exacerbation’ and ‘dead’.

or blank based on conventional treatment. Two trials were excluded because of different criteria for stroke^[35] and considered as a partial duplicate of another study already included in the present review.^[36] The sample size of each individual trial ranged between 62 and 348 participants (mean of 88). The specific characteristics of the literature are shown in Table 1. According to the disease stages of ischemic stroke, ten trials^[20–22,24,25,27,28,30,32,34] enrolled participants to estimate the therapeutic effects in the acute stage (n=946), four trials^[26,29,31,33] enrolled participants to estimate the long-term effects in the convalescence stage (n=535), and only one trial enrolled participants to estimate the effects in different stages including the acute stage and the convalescence stage.^[23] There were two comparisons: GBE plus conventional therapy versus conventional therapy^[22,24–30,32–34] and GBE plus conventional therapy versus placebo plus conventional therapy.^[23,31] The conventional therapy included antiplatelet therapy, anticoagulant therapy, neuroprotective agents, nutritional support, controlling serum glucose, and blood pressure.

3.2. Risk of bias in included studies

The quality of each of the 15 RCTs was evaluated from seven aspects using the risk of bias scale in the Cochrane Handbook for Systematic Reviews of Interventions of the Cochrane Collaboration.^[15] Although all the included trials reported “randomly allocating” participants, only 5 trials reported generating random numbers by using a random number table or centralized randomization.^[21,23,26,27,31] One trial reported using central randomization to conceal the allocation,^[31] and the remaining trials reported no information about concealment. One trial was a double-blind trial,^[31] another single trial was single-blind trial^[23] and the remaining 13 trials appeared impossible to blind the participant and personnel as GBE was used only in the experimental groups.^[21,22,24–30,32–34] Two trials reported the dropout,^[23,31] but the remaining trials were unclear about dropout.^[20–22,24–30,32–34] Two trials provided information about trial registry^[23,31]; we assessed reporting bias by judging consistency between outcomes in the method section of the publication and in the protocol. Because all of the remaining trials provided no information about trial registry, we assessed trials which reported all outcomes mentioned in the “Methods” section as low risk of reporting bias, otherwise high risk of reporting bias would be rated. For other bias, 12 trials were assessed as having low risk^[22–31] and three trials were assessed as having high risk for baseline comparability (Figs. 1 and 2).^[32–34]

3.3. Effects of interventions

3.3.1. Acute stage of ischemic stroke

3.3.1.1. Primary outcomes. No trial reported primary outcomes including all-cause mortality or serious adverse events.

3.3.1.1.1. Dependence. Two trials assessed dependence by BI score in 425 participants which significantly improved in GBE plus conventional therapy compared with placebo therapy (MD: 5.72; 95% CI: 3.11–8.33; $I^2=29\%$; $P<.001$) (Fig. 3).^[21,23]

3.3.1.2. Secondary outcomes

3.3.1.2.1. Changes of neurological function deficit or clinical effect. Seven trials measured neurological function deficit or clinical effect outcomes by NFDS,^[20,21,24,25,28,30,34] and the

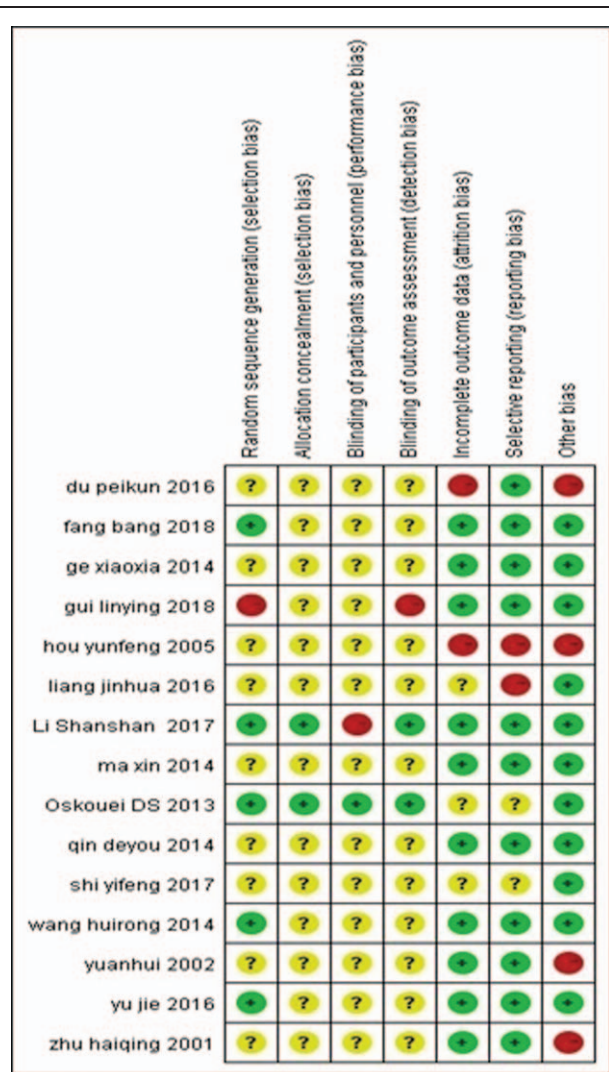


Figure 1. Risk of bias summary.

results showed that the GBE use was more effective at 14 days after treatment (RR: 1.2; 95% CI 1.12–1.29; $I^2=0$; $P<.001$; 607 participants) compared to conventional therapy (Fig. 4). Three trials measured the outcomes by NIHSS,^[22,23,27] and the results showed that adding GBE can significantly decrease the NFDS compared with conventional or placebo therapy (MD: -1.39; 95% CI: -2.15 to -0.62; $I^2=0$; $P<.001$; 504 participants) (Fig. 5).

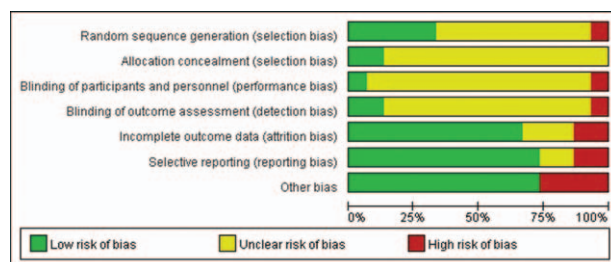


Figure 2. Risk of bias graph.

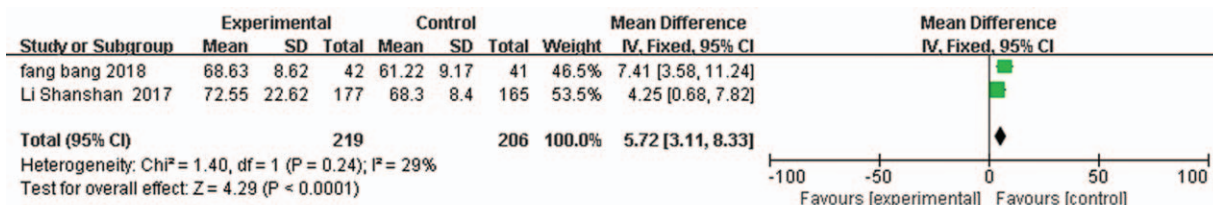


Figure 3. Meta-analysis of the Barthel index score in ginkgo biloba extract and conventional medicine groups at acute stage of ischemic stroke.

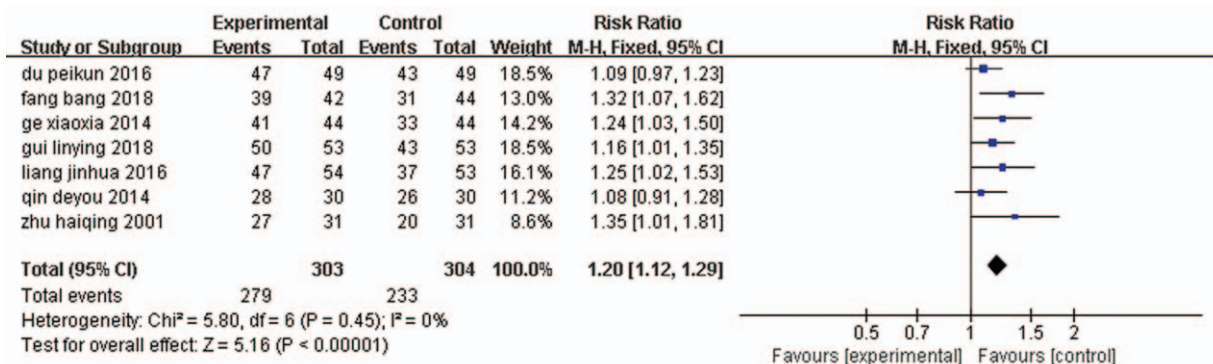


Figure 4. Meta-analysis of Neurological Function Deficit Score in ginkgo biloba extract and conventional medicine groups at acute stage of ischemic stroke.

3.3.1.2.2. *Recurrence rate.* No trial reported recurrence rate outcome.

3.3.1.2.3. *Non-serious adverse events.* One trial that observed 64 participants did not report any ADRs.^[26] One trial observed 106 participants and reported adverse events that included dizziness (n=1) and nausea (n=1) in GBE group as well as dizziness (n=1) in the control group.^[20] Another trial observed 88 participants and only reported facial flushing (n=2) from the GBE group.^[30] These adverse events disappeared after symptomatic treatment though one patient dropped out because of an adverse event.

3.3.2. *Convalescence stage of ischemic stroke*

3.3.2.1. *Primary outcomes*

3.3.2.1.1. *Vascular events.* Two included RCTs reported vascular events. There was low between-trial heterogeneity (RR: 0.70; 95% CI: 0.44 to 1.14; I²=0; P=.15; 406 participants). A meta-analysis was performed using a fixed effect model. The vascular events of the GBE group were not significantly different from the conventional medicine group (Fig. 6).^[23,31]

3.3.2.1.2. *Dependence.* Two trials assessed dependence by BI scores in 407 participants,^[23,26] and significant differences were found when GBE plus conventional therapy was compared with conventional therapy or placebo (MD: 7.17; 95% CI: 5.96 to 8.38, I²=0; P<.001) (Fig. 7).

3.3.2.1.3. *Recurrence rate.* Two trials compared GBE as an add-on treatment to conventional therapy for recurrence rate.^[23,31] One trial reported 29 patients who received GBE and 28 patients who were in the placebo group, and only 1 patient reported recurrent stroke in the placebo group for the 4-month follow-up period.^[31] Another multi-center trial with 348 participants compared GBE with placebo based on conventional therapy and the recurrence of stroke was evaluated for nearly 2 years. In this trial, nine cases in the treatment group and fourteen cases in the control group reported recurrent stroke and the results showed no significant difference between the two groups (RR: 0.57, 95% CI: 0.26 to 1.25, I²=0; P=.16) (Fig. 8).

3.3.2.1.4. *Quality of life.* No trial reported on quality of life by the SF-36 Short Form Health Survey or the SS-QOL Stroke-Specific Quality of Life scores.

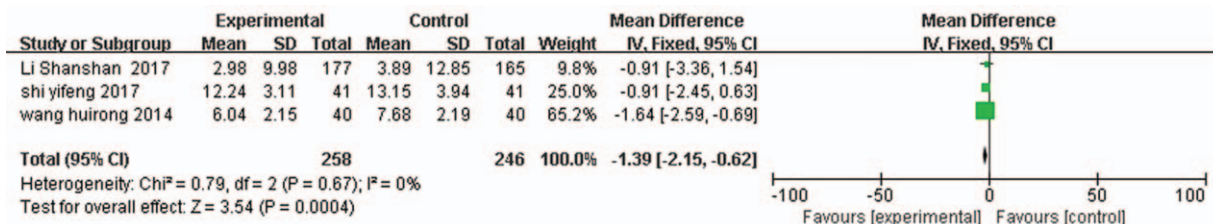


Figure 5. Meta-analysis of National Institute of Health Stroke Scale in ginkgo biloba extract and conventional medicine groups at acute stage of ischemic stroke.

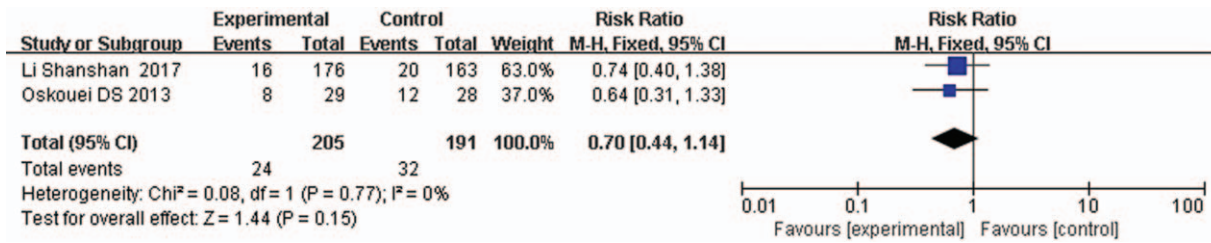


Figure 6. Meta-analysis of the vascular events of ginkgo biloba extract group and the conventional medicine group at convalescence stage of ischemic stroke.

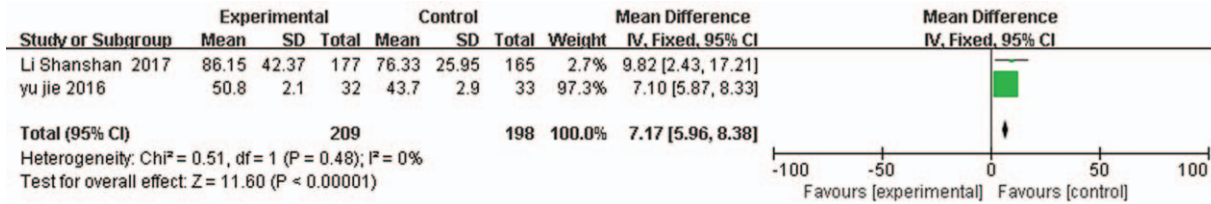


Figure 7. Meta-analysis of Barthel index scores in ginkgo biloba extract and conventional medicine groups at sequelae stage of ischemic stroke.

3.3.2.2. Secondary outcomes

3.3.2.2.1. All-cause mortality. One trial assessed mortality during 2 years of follow-up and during treatment and the follow-up period, four patients in the GBE group and 1 patient in the placebo group died.^[23] In another trial, 7 patients died during the course of the study in the GBE group and nine patients died in the placebo group^[31] with the results showing no significant difference between the 2 groups (RR: 1.07; 95% CI: 0.41 to 2.81; I² = 46%; P = .90) (Fig. 9).

3.3.2.2.2. Changes of neurological function deficit. Four trials with 613 participants compared GBE as an add-on treatment on conventional therapy and measured changes of neurological function deficit by NFDS. They found that the GBE groups did significantly differ in improving NFDS (RR: 1.17; 95% CI: 1.09–1.27; I² = 0; P < .001; 613 participants) (Fig. 10). Two trials measured changes of neurological function deficit by NIHSS and showed significant differences between the 2 groups (MD: -1.15; 95% CI: -1.76 to -0.53; I² = 0; P < .001; 424 participants) (Fig. 11).

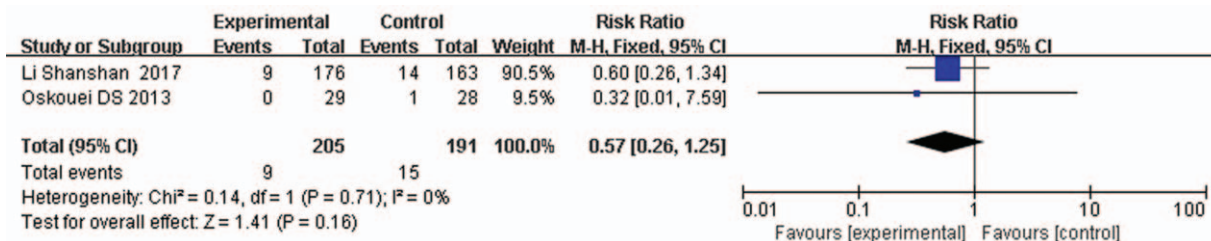


Figure 8. Meta-analysis of the recurrence rate of ginkgo biloba extract group and the conventional medicine group at convalescence stage of ischemic stroke.

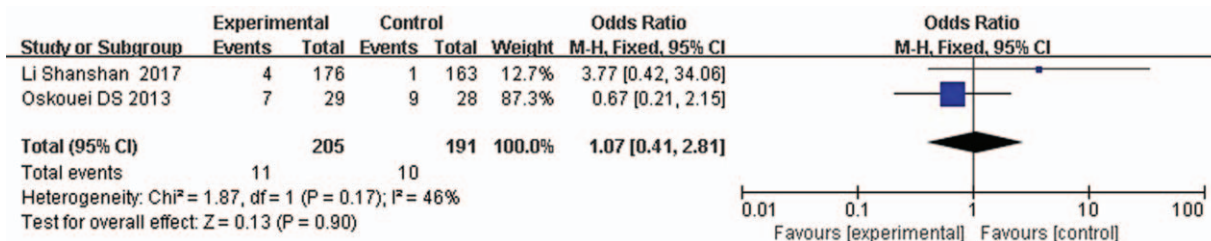


Figure 9. Meta-analysis of the mortality of ginkgo biloba extract group and the conventional medicine group at convalescence stage of ischemic stroke.

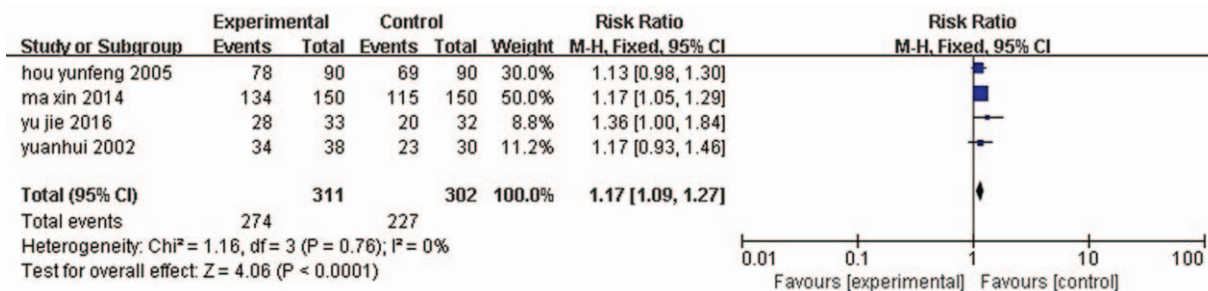


Figure 10. Meta-analysis of changes of Neurological Function Deficit Score in ginkgo biloba extract and conventional medicine groups at sequelae stage of ischemic stroke.

3.3.2.2.3. *Non-serious adverse events.* One trial tested 64 participants and reported no non-serious adverse events in the two groups.^[26] One trial observed 346 participants for 6 months of treatment and reported non-serious adverse events including vomiting (n=3), blood sugar change (n=2), myocardial infarction (n=1), nephritis (n=1), sick sinus syndrome (n=1) and pneumonia event (n=2). Except for vomiting, the rest of the events were considered to be not related to the study.^[23]

3.4. Additional analysis

3.4.1. *Trial sequential analysis (TSA) for recurrence rate.* TSA was used to examine the reliability and conclusiveness of recurrence rate. In the current meta-analysis, the TSA was performed by maintaining 95% CIs with a control event rate of 20%, from 2 studies included in this meta-analysis,^[23,31] a 1-sided $\alpha=5\%$ to minimize the possibility of type I error, and a statistical test power of 80%. TSA software version 0.9.5.10 Beta (Copenhagen Trial Unit; <http://www.ctu.dk/tsa>) was used in this study. If the cumulative Z-curve neither crossed the trial sequential monitoring boundary nor exceeded the required information size, a no difference result had been reached and no further studies were needed.

In the TSA, our calculations indicated that the required size needed to detect a difference in recurrence rate was 580 patients and the cumulative Z-curve did not cross the trial sequential monitoring boundary before exceeding the information size, which indicated that the cumulative evidence was not conclusive regarding the efficacy of GBE in preventing recurrence during the convalescence stage (Fig. 12).

3.5. Quality of evidence by GRADE

We assessed the quality of the available evidence using the GRADE approach. The quality of the evidence for vascular

events and the quality of the evidence for recurrence rate were moderate because of the risk of imprecision (the small number of total events or small sample size). The quality of evidence for mortality was low because of the risk of imprecision (the small number of total events or small sample size) and inconsistency (heterogeneity with high I²) (Table 2).

4. Discussion

4.1. Summary of findings

In this systematic review, for the acute stage of ischemic stroke, we found that GBE may have an effect on decreasing the NFDS by NFDS or NIHSS scores and improving dependence by BI scores in comparison to placebo or conventional therapy. In the convalescence stage, the addition of GBE may have an effect of decreasing treatment failure by NIHSS or NFDS by NFDS and improving dependence.

According to a report in the literature, GBE could cause serious adverse drug events.^[37] Both vascular events and all-cause mortality were included in the meta-analysis, and the results indicated that there was no significant difference in vascular events and all-cause mortality between the 2 groups. Five of the 15 trials described the non-serious adverse events, with two reporting non-serious adverse events with GBE use. The symptoms disappeared after symptomatic treatment or improved without treatment, which suggested that GBE is safe for ischemic stroke.

Compared with placebo, GBE may have no effect for preventing cerebral infarction for long-term users (>2 weeks) based on traditional meta-analysis and TSA. Although this is a negative result, it is important for long-term users especially ischemic stroke survivors and for clinical pharmacists focusing on rational drug use. Furthermore, in order to better guide clinical practice, we assessed the evidence using the GRADE approach.

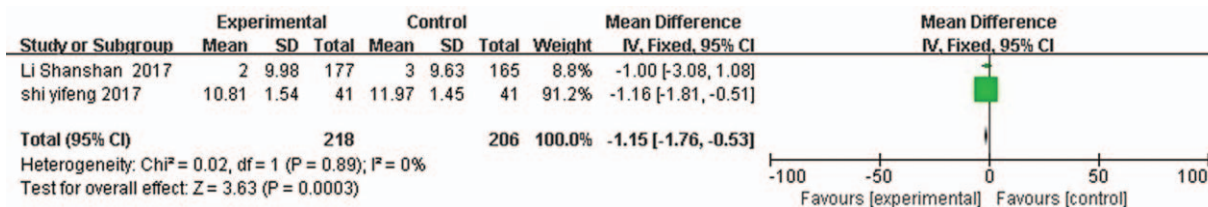


Figure 11. Meta-analysis of changes of National Institute of Health Stroke Scale in ginkgo biloba extract and conventional medicine groups at sequelae stage of ischemic stroke.

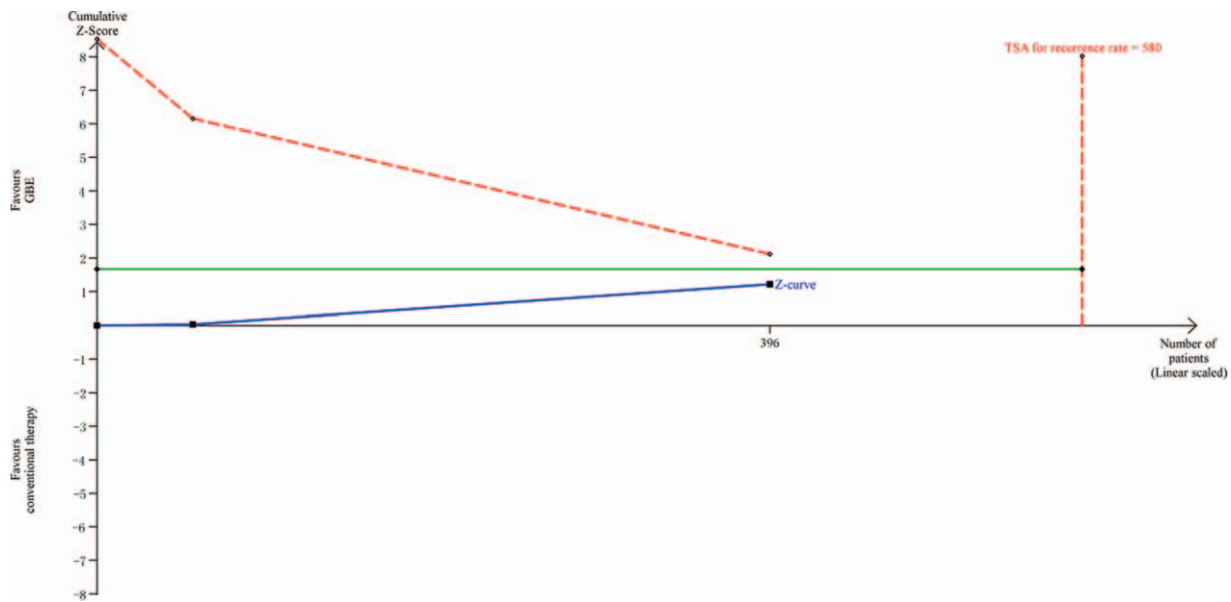


Figure 12. Trial sequential analysis for recurrence rate in ginkgo biloba extract and conventional medicine groups at sequelae stage of ischemic stroke.

Due to the moderate quality of included trials and the above outcomes from a few trials, we could not draw firm conclusions from the current evidence.

4.2. Comparisons to previous studies

We could identify systematic reviews or meta-analyses about GBE use for acute ischemic stroke stage with findings similar to ours,^[10,11] which are different from that of Zeng et al, who reported that GBE did not lead to improvement of neurological deficit at the acute stage of treatment.^[38] Our primary findings for the convalescent stage were first reported, and this review presents a detailed analysis of GBE use. Regardless of whether it has an effect on recurrence rate, the results are interesting and confirmed by TSA, which differs from previously published literature.^[10]

4.3. Strengths and limitations of the study

In our review, we performed a comprehensive search of major databases to try to identify all available randomized trials on GBE for ischemic stroke. We limited the control intervention to placebo or conventional therapy and evaluated all clinically relevant outcomes.

However, the promising findings are not conclusive due to the limited number and low quality of the included studies. A major limitation of this review is the low quality of the original trials and

insufficient information reported from these included trials, which may weaken the implication of the findings.

Poor quality trials may have a high risk of performance bias and detection bias. In addition, we believe that dropout or withdrawal was inevitable during the period of treatment and follow-up, yet only 2 trials reported dropout or withdrawal. Second, for acute stage of ischemic stroke, none of trials reported on all-cause mortality and serious ADRs; furthermore, none of trials reported on quality of life at the sequelae stage.

4.4. Implications for current clinical practice and future research

Future research by adopting a multi-center, large sample size and double-blind placebo controlled design is required, which should include reporting the trial according to the CONSORT (Consolidated Standards of Reporting Trials) Statement.

5. Conclusion

GBE appears to improve neurological function and dependence compared with conventional therapy for different ischemic stroke stages based on an overall analysis of 15 randomized trials. GBE seems generally safe for clinical application. However, beneficial findings have not been found with regard to recurrence rate; further, due to the generally weak evidence, further large, rigorous trials are still warranted.

Table 2
Summary of main finding.

Outcomes	Assumed effects		No. of participants (trials)	Quality of the evidence (GRADE)
	Risk with GBE	Risk with placebo, no intervention		
Vascular events	117 per 1000	168 per 1000	396 (2 trials) ^[23,31]	⊕ ⊕ ⊕ moderate*
Recurrence rate	44 per 1000	79per 1000	396 (2 trials) ^[23,31]	⊕ ⊕ ⊕ moderate*
Mortality	53 per 1000	52per 1000	396 (2 trials) ^[23,31]	⊕ ⊕ low ^{*,†}

* Total sample size is less than 400.

† The heterogeneity with a large *I*² value.

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