



## REVIEW ARTICLE

# Comparative effectiveness of Ginkgo injections for treating vertebrobasilar insufficiency: A systematic review and network meta-analysis

Huijuan Cao MD, PhD<sup>1</sup>  | Di Tan MM<sup>2</sup> | Kaihuan Wang MM<sup>2</sup> | Xiaojiao Duan MM<sup>2</sup> | Jiarui Wu PhD<sup>2</sup>  | Xinkui Liu MM<sup>2</sup> | Mengwei Ni MM<sup>2</sup> | Jinhui Tian MD, PhD<sup>3</sup> | Shi Liu MM<sup>2</sup>

<sup>1</sup>Centre for Evidence-based Chinese Medicine, Beijing University of Chinese Medicine, Beijing, China

<sup>2</sup>Department of Clinical Chinese Pharmacy, School of Chinese Materia Medica, Beijing University of Chinese Medicine, Beijing, China

<sup>3</sup>Evidence-based Medicine Center of Lanzhou University, Lanzhou, China

## Correspondence

Jiarui Wu, Department of Clinical Chinese Pharmacology, School of Chinese Materia Medica, Beijing University of Chinese Medicine, Beijing 100102, China.  
Email: exogamy@163.com

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## Abstract

**What is known and objective:** This study sought to assess the clinical effectiveness of Ginkgo injections (GIs) combined with conventional drugs for vertebrobasilar insufficiency (VBI).

**Methods:** Randomized controlled trials (RCTs) that assessed the adjunctive effects of GIs for patients with VBI were retrieved from several English and Chinese databases from inception to December 2018. The Cochrane risk of bias method was used to evaluate the methodological quality of the eligible trials. The data were analysed by Stata 13.0 and WinBUGS 1.4.3 software.

**Results:** A total of 20 RCTs that included 1710 patients were included. All RCTs had an unclear risk of bias or a high risk of bias. The network meta-analysis (NMA) showed that the use of four kinds of GIs, especially Ginkgo leaf extract and dipyrindamole injections (GDs), as adjunctive therapies with drugs for VBI increased the total effectiveness rate. *Ginkgo biloba* leaf extract injections (EGbs) combined with conventional drugs were more effective than only conventional drugs for improving the results of transcranial Doppler ultrasonography (TCD). Shuxuening injections (SXNs) seemed superior for improving blood viscosity-related indicators. Adverse events were mentioned in nine trials, and there was no difference between the GI group and the control group for the incidence rate of adverse events.

**What is new and conclusions:** GIs showed significant benefits as an add-on therapy for VBI, as GIs increased the total effectiveness rate and improved the results of TCD examinations. Due to the limited sample size and quality of the included trials, the results of this review still need to be tested in larger, rigorous studies in the future.

## KEYWORDS

Ginkgo injections, network meta-analysis, systematic review, vertebrobasilar insufficiency

Cao and Tan are contributed equally to this paper.

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## 1 | WHAT IS KNOWN AND OBJECTIVE

Vertebrobasilar insufficiency (VBI) is a common clinical cerebrovascular disease. VBI is the ischaemia of the brainstem, cerebellum or occipital cortex, which is caused by vertebrobasilar artery stenosis or occlusion.<sup>1,2</sup> VBI mainly occurs in middle-aged and elderly people, but there is a trend towards an increased incidence in younger subjects, possibly because of longer working hours and the excessive intake of high-fat and high-protein foods. The main aetiologies of VBI are atherosclerosis, arterial stenosis and platelet aggregation, and its main clinical manifestations are vomiting, dizziness and blurred vision. *Ginkgo biloba* is the dried leaves of Ginkgo from the Ginkgo plant, and the active ingredients primarily include Ginkgo flavonoid glycosides and Ginkgolide lactones, which can effectively reduce the production of platelet-activating factors (PAFs), dilate blood vessels and increase blood flow to prevent blood clots and arterial occlusion. Therefore, *Ginkgo biloba* extract has good curative efficacy in patients with VBI.<sup>3-5</sup> There are four kinds of Ginkgo injections (GIs) that are frequently used in the clinical treatment of VBI, including Shuxuening injections (SXNs), Ginkgo leaf extract and dipyridamole injections (GDs), *Ginkgo biloba* leaf extract injections (EGbs), and folium Ginkgo extract and tertram ethypyrazine sodium chloride injections (FTs). This study aimed to compare the effectiveness of these four kinds of GIs in the treatment of VBI to provide a decision-making reference for the rational clinical selection of GIs for treating VBI.

## 2 | METHODS

### 2.1 | Eligibility criteria for the included trials

Randomized controlled trials (RCTs) that examined the adjuvant effectiveness of GIs for VBI were included. VBI was diagnosed by transcranial Doppler ultrasonography (TCD). The control therapy could be any kind of drug for VBI (eg aspirin, metoprolol and statins). The primary outcomes included the total effective rate for VBI (significant improvement of the patient's vertigo symptoms and normal TDP results) and the results of TCD examinations (such as the average velocity of the vertebral artery (VA), basilar artery (BA), left vertebral artery (LVA) and right vertebral artery (RVA)). The secondary outcomes included whole blood high-shear viscosity (WBHSV), whole blood low-shear viscosity (WBLSV), plasma viscosity (PV), fibrinogen (FIB) and adverse events.

### 2.2 | Search strategy

We searched the China National Knowledge Infrastructure Database (CNKI), the VIP Database for Chinese Technical Periodicals (VIP), the Wanfang Database, the Chinese Biomedical Literature Database (SINOMED), Web of Science, PubMed, EMBASE and the Cochrane Library from inception to December 2018 to retrieve potentially

eligible studies. We used the terms "Shuxuening Injection", "Ginatone Injection", "Extract of Ginkgo Biloba Leaves Injection", "Ginkgo Leaf Extract and Dipyridamole Injection", "Folium Ginkgo Extract and Tertram Ethypyrazine Sodium Chloride Injection" and "vertebrobasilar insufficiency" as theme words during the searches. Detailed search strategies are shown in Appendix S1.

### 2.3 | Data extraction and quality assessment

Two reviewers (D Tan and XJ Duan) independently screened and selected the eligible studies. Then, data were extracted from the included studies, such as the author information, the study design information, the characteristics of the participants, details on the intervention and control therapies, and the outcomes. The methodological quality of the included trials was evaluated by two reviewers according to the Cochrane risk of bias assessment tool.<sup>6</sup> Seven items were evaluated, including random sequence generation, allocation concealment, blinding to patients and personnel, blinding to outcome assessors, incomplete data, the selective reporting of results and other biases. Disagreements during the literature screening, data extraction and quality assessment were resolved by consultation with a third reviewer (JR Wu).

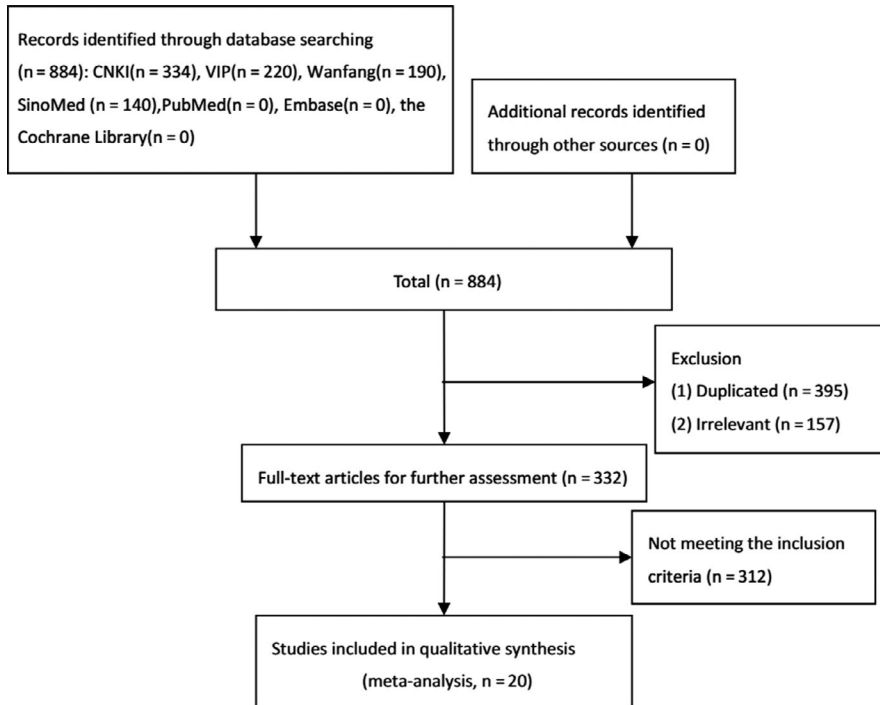
### 2.4 | Statistical analysis

We used WinBUGS 1.4.3 software (MRC Biostatistics Unit, Cambridge, UK) to analyse the data and used Stata V.13.0 software (Stata Corporation) to generate graphics. The estimated effect of dichotomous outcomes is presented as an odds ratio (OR) with a 95% confidence interval (95% CI), and the continuous outcomes are presented as the standardized mean difference (SMD) with a 95% CI. For network meta-analysis (NMA), two Markov chains were set in WinBUGS. We performed 70 000 iterations of the data, of which the first 10 000 were for the annealing algorithm, and the next 60 000 were for sampling. Furthermore, the surface under the cumulative ranking area (SUCRA) was calculated to determine the probability values of the reports. The SUCRA value was 100% for the best treatment, whereas the SUCRA value was 0% for the worst treatment.<sup>7</sup> Funnel plots were drawn to evaluate the publication bias by the Harbord test or the Egger test.

## 3 | RESULTS

### 3.1 | Literature selection

Eight hundred and eighty-four reports were retrieved from the seven previously mentioned databases. After screening the titles and abstracts, the full text of 332 articles was reviewed. Finally, 20 trials<sup>8-27</sup> were included in this review (Figure 1). The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) checklist is shown in Appendix S2.



### 3.2 | Characteristics of the included studies

The 20 included trials involved 1710 patients, of which 880 were in the GI group, and 830 were in the control group. All the trials compared the combination of GIs and drugs (including oral aspirin, metoprolol and statins) to drugs alone. The GIs were administered by an intravenous drip at a dosage of 10–100 mL/d. The duration of the treatment ranged from 7 to 15 days. More details are shown in Table 1.

### 3.3 | Quality of the included studies

Only one trial, which used a random number table, used a method of random sequence generation.<sup>16</sup> Two<sup>20,22</sup> trials were judged as 'quasi-randomized controlled trials' since they alternately allocated the participants according to odd and even numbers. Blinding to patients was rarely used due to the absence of placebo controls, but insufficient information was provided to determine whether blinding to outcome assessors was used. The incomplete data assessments of all RCTs were defined as 'low'. In addition, insufficient information was provided to determine the other biases of the included trials (Figure 2).

### 3.4 | NMA

#### 3.4.1 | Total effective rate of VBI

Twenty RCTs<sup>8-27</sup> involving 4 kinds of GIs (Gbe, GD, SXN and FT) were included (Figure 3). NMA showed that combination therapies increased the total effective rate more than conventional drugs. However, there were no differences among the 4 kinds of GIs regarding this outcome (Table 2).

The SUCRA results showed that the total effective rate of GD combined with drug treatment was the highest (74.90%), followed by SXN (63.64%), EGb (56.03%) and FT (54.93%) (Table 3).

#### 3.4.2 | VA

There were four trials<sup>15,17,18,26</sup> with data on the VA that included 3 kinds of GIs (Gbe, GD and SXN). The results of NMA showed that SXN and EGb may have had better adjunctive effects in regard to this outcome, and EGb was superior to GD as an adjunctive therapy (Table 4). The SUCRA results also showed that the maximum probability for the VA was from EGb combined with drugs (92.30%), followed by SXN (72.96%) and GD (31.18%) (Table 3).

#### 3.4.3 | BAs

Four trials<sup>9,15,23,26</sup> had information about the BA, and there was a significant difference between EGb and SXN for this outcome (Table 4). Ranking probability analysis showed that EGb plus drugs had the maximum probability for the BA (SUCRA = 99.09%), followed by SXN plus drugs (SUCRA = 50.40%) (Table 3).

#### 3.4.4 | LVA

Four trials<sup>9,17,18,23</sup> described the LVA and included three kinds of GIs (EGb, GD and SXN). The results of NMA showed that there was a statistically significant difference between GD/EGb plus drugs and drugs alone for this outcome (Table 4).

The SUCRA results showed that EGb plus drugs had the maximum probability for the LVA (94.69%), followed by SXN (52.17%) and GD (51.60%) (Table 3).

**TABLE 1** Characteristics of the 20 included studies

Research ID	Gender (male/female)	Average age (y)	Sample size (GI/control)	GI	Control	Treatment duration (d)	Result outcomes
Zhang 2013 <sup>8</sup>	72/48	62.20 ± 4.95	60/60	SXN20 mL	Anisodamine	14	①
Du 2011 <sup>9</sup>	NR	NR	30/30	SXN20 mL	Usual care	7	①③④⑥⑦⑧⑨
Li 2011 <sup>10</sup>	65/55	37.5 ± 4.5	60/60	SXN20 mL	Usual care	NR	①
Yan 2011 <sup>11</sup>	14/31	56.7	23/22	SXN20 mL	Betahistine hydrochloride 20 mg	14	①
Xiao 2011 <sup>12</sup>	40/40	63	42/38	SXN20 mL	Betahistine hydrochloride 20 mg	7	①⑩
Liu 2011 <sup>13</sup>	47/47	57.76	48/46	sxn20 mL	Flunarizine hydrochloride capsules 10mg	14	①
Zhang 2010 <sup>14</sup>	40/22	64.75	32/30	SXN20 mL	Buflomedil hydrochloride injection	15	①
Luo 2009 <sup>15</sup>	67/41	NR	64/44	SXN15 mL	Usual care	14	①②③⑩
Kong 2015 <sup>16</sup>	49/33	46.8 ± 1.7	41/41	GD20 mL	Betahistine hydrochloride 20 mg	10	①
Zhang 2014 <sup>17</sup>	55/31	61.2 ± 3.4	43/43	GD20 mL	Betahistine hydrochloride 20mg	10	①②④⑤⑩
Yue 2013 <sup>18</sup>	51/35	55.87 ± 9.12	45/41	GD20 mL	Betahistine hydrochloride 20 mg	10	①②④⑤⑩
Zhang 2012 <sup>19</sup>	68/52	NR	60/60	GD20 mL	Betahistine hydrochloride 20mg	7	①⑩
Zheng 2010 <sup>20</sup>	34/46	56.5	40/40	GD20 mL	Betahistine hydrochloride 20 mg	10	①⑩
Zhao 2009 <sup>21</sup>	51/35	62.4	43/43	GD20 mL	Betahistine hydrochloride 250 mL + venoruton 0.42g	NR	①⑩
Zou 2008 <sup>22</sup>	26/23	58.7	26/23	GD20 mL	Betahistine hydrochloride 20 mg	10	①
Qi 2015 <sup>23</sup>	32/34	70 ± 6	33/33	EGb20 mL	Usual care	NR	①③④⑤⑥⑦⑧⑨
Lin 2011 <sup>24</sup>	54/65	47.35 ± 9.77	61/60	EGb20ml	Usual care	14	①
Wang 2009 <sup>25</sup>	36/46	NR	40/42	EGb15 mL	Sodium ozagrel injection	7	①⑩
Lin 2008 <sup>26</sup>	72/30	61	58/44	EGb10 mL	Nimodipine tablet	10	①②③⑥⑦⑧⑨⑩
Yang 2006 <sup>27</sup>	24/37	54.94 ± 6.34	31/30	FT100 mL	Buflomedil hydrochloride injection	7	①

Note: Outcomes: ①the total effective rate of VBI; ②the average velocity of vertebral artery; ③the average velocity of basilar artery; ④the average velocity of left vertebral artery; ⑤the average velocity of right vertebral artery; ⑥whole blood high-shear viscosity; ⑦whole blood low-shear viscosity; ⑧plasma viscosity; ⑨fibrinogen; ⑩adverse events.

Abbreviations: EGb, extract of Ginkgo biloba leaf injection; FT, folium Ginkgo extract and tertram ethyprazine sodium chloride injection; GD, Ginkgo leaf extract and diprydamole injection; NR, not report; SXN, Shuxuening injection.

### 3.4.5 | RVA

Three trials<sup>17,18,23</sup> described the RVA and included two kinds of GIs. EGb seemed to have a good adjunctive effective with drugs for this outcome (Table 4), and it had the maximum probability for the RVA (98.29%; Table 3).

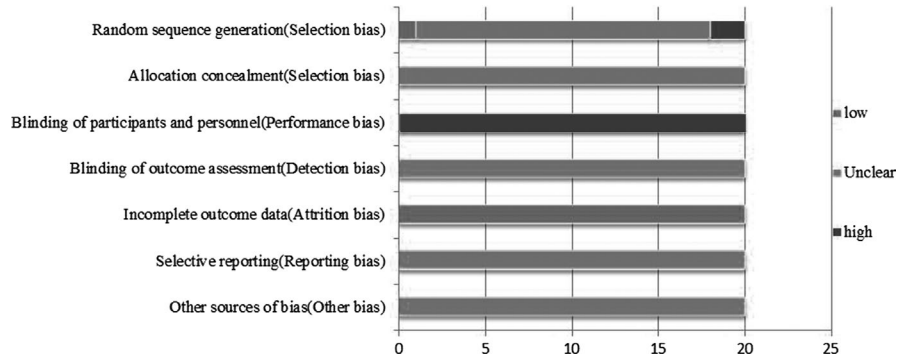
### 3.4.6 | Secondary outcomes

The results from three trials<sup>9,23,26</sup> showed that EGb or SXN combined with drugs had a larger effect than drugs alone on WBHSV

(mPa-s) (Table 5). The results of SUCRA showed that SXN plus drugs had the maximum probability for WBHSV (99.74%), followed by EGb (49.55%, Table 3).

These three trials<sup>9,23,26</sup> also showed that EGb plus drugs had a greater effect than drugs alone for WBHSV (Table 5), with the maximum probability (SUCRA = 93.60%; Table 3).

Similar results were found for PV (mPa-s) and FIB (g/L), where EGb and SXN may have had good adjunctive effects with the drugs for these two outcomes (Table 5), and SXN plus drugs had the maximum probability for both PV (SUCRA = 91.14%) and FIB (88.99%; Table 3).



**FIGURE 2** Summary of the risk of bias of the included trials

### 3.4.7 | Publication bias

Both the funnel plot conducted by the Harbord test ( $P = .013 < 0.05$ , Figure 4) and the Egger test (Figure 5) with the data on the total effective rate showed a potential publication bias, which may have also been caused by the small study effect.

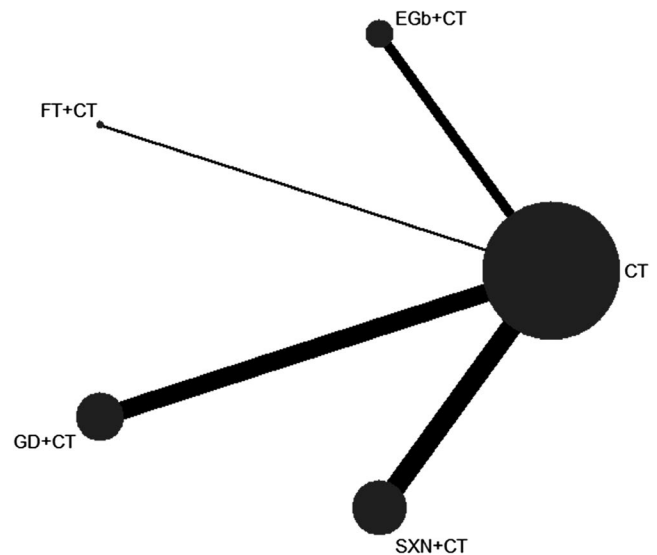
### 3.5 | Safety

In total, 9 trials mentioned safety issues. Three<sup>20,21,25</sup> of these studies found no adverse events during the treatment, and the other six trials<sup>12,15,17-19,26</sup> described the adverse events in detail. The GI groups included 15 cases of adverse events, which included two cases of headache, one case of distension, one case of gastrointestinal discomfort, seven cases of flushing and headache, three cases of skin itching and one case of facial flushing. The control groups reported 22 cases of adverse events, including three cases of headache, one case of distension and fatigue, three cases of flushing and headache, seven cases of skin itching and eight cases of flushing. No severe adverse events were reported, and no difference was found between the groups regarding the incidence rate of mild adverse events (OR 0.57, 95% CI 0.29 to 1.12, 6 trials, 582 participants).

## 4 | DISCUSSION

This study included 20 trials, all of which had an unclear risk of bias or a high risk of bias. The results of NMA showed that GIs improved the total effective rate of VBI in the clinic as an adjunctive therapy with drugs (the average OR ranged from 4.00 to 4.99), and GD may have had the optimal effectiveness (OR 4.99, 95% CI 2.73 to 8.53). In the four outcomes of head TCD examinations, the best adjunctive intervention was probably EGb. In the four outcomes of hemorheology, SXN combined drugs may have had the optimal effectiveness. Only nine studies mentioned adverse events during treatment, and 6 of these studies reported mild adverse events in both groups. There was no significant difference between the groups in the incidence rate of adverse events (4.81% vs 8.15%).

The aetiology of VBI is atheromatous plaque formation in the VA and BAs by lipid metabolism disorders and vascular intimal injury, which results in decreased blood flow and blood circulation and increased



**FIGURE 3** Network graph of the total effective rate. Note: Each node indicates a treatment included in the analysis. The lines represent the direct (head-to-head) comparisons identified in the research. The size of each node is proportional to the number of randomized participants (sample size). CT, conventional treatment; EGb, *Ginkgo biloba* leaf extract injection; FT, folium of *Ginkgo* extract and tertram ethyprazine sodium chloride injection; GD, *Ginkgo* leaf extract and dipyrindamole injection; SXN, Shuxuening injection

blood viscosity. At the same time, decreased blood flow and elevated blood lipids lead to thrombosis. Ultimately, VA and BA ischaemia syndrome develops, with increasing hemorheological indicators.<sup>28</sup> The main active components of GIs are *Ginkgo* flavone glycosides and terpenolactones. Related pharmacological studies showed that *Ginkgo* flavone glycosides can remove free radicals, dilate blood vessels, inhibit thrombosis and improve cerebral vascular peripheral microcirculation. *Ginkgolides* are PAF antagonists that can effectively inhibit PAF, reduce thrombus formation and allergic reactions, and play an important role in cerebrovascular disease.<sup>29,30</sup> The findings from this review may support the results from previous pharmacological studies.

Regarding the safety of GIs, our study did not find a difference between the groups regarding the incidence rate of adverse events. A previous literature analysis based on case reports showed that the main adverse reaction to *Ginkgo biloba* leaf injection was an allergy,

**TABLE 2** Odds ratio and the 95% confidence interval of network meta-analysis compared Ginkgo injection plus drugs to drugs alone concerning the total effective rate of vertebrobasilar insufficiency

SXN + drugs				
1.24 [0.51, 2.57]	GD + drugs			
1.00 [0.38, 2.26]	0.86 [0.32, 1.87]	EGb + drugs		
1.14 [0.22, 3.82]	0.99 [0.18, 3.35]	1.31 [0.22, 4.68]	FT + drugs	
<b>4.33 [2.45, 7.2]</b>	<b>4.99 [2.73, 8.53]</b>	<b>4.00 [1.97, 7.58]</b>	<b>4.61 [1.05, 14.93]</b>	Drugs

Abbreviations: EGb, extract of Ginkgo biloba leaf injection; FT, folium Ginkgo extract and tertram ethypyrazine sodium chloride injection; GD, Ginkgo leaf extract and dipyrindamole injection; SXN, Shuxuening injection.

The bold values showed those with significant statistical meaning's results.

**TABLE 3** Surface under the cumulative ranking probabilities (SUCRA) results of 9 outcomes

	Drugs (%)	EGb + drugs (%)	FT + drugs (%)	GD + drugs (%)	SXN + drugs (%)
Total effective rate	0.51	56.03	54.93	74.90	63.64
Vertebral artery	3.56	92.30	-	31.18	72.96
Basilar artery	0.51	99.09	-	-	50.40
Left vertebral artery	1.54	94.69	-	51.60	52.17
Right vertebral artery	1.93	98.29	-	49.78	/
Whole blood high-shear viscosity	0.70	49.55	-	-	99.74
Whole blood low-shear viscosity	4.01	93.60	-	-	52.39
Plasma viscosity	4.86	53.99	-	-	91.14
Fibrinogen	1.09	59.93	-	-	88.99

Abbreviations: EGb, extract of Ginkgo biloba leaf injection; FT, folium Ginkgo extract and tertram ethypyrazine sodium chloride injection; GD, Ginkgo leaf extract and dipyrindamole injection; SXN, Shuxuening injection.

**TABLE 4** The Results of Network Meta-analysis of transcranial Doppler ultrasonography

Comparison	Estimate effect (standard mean difference [95% confidence interval])			
	VA	BA	LVA	RVA
SXN + drugs vs drugs	<b>1.59 [0.59, 2.60]</b>	<b>0.92 [0.21, 1.6]</b>	0.95 [-0.08, 1.99]	-
GD + drugs vs drugs	0.37 [-0.33, 1.08]	-	<b>0.93 [0.22, 1.67]</b>	0.60 [-0.09, 1.30]
EGb + drugs vs drugs	<b>1.98 [0.97, 2.97]</b>	<b>1.99 [1.31, 2.69]</b>	<b>1.77 [0.75, 2.81]</b>	<b>1.75 [0.73, 2.75]</b>
SXN + drugs vs GD + drugs	1.22 [-0.007, 2.44]	-	0.01 [-1.27, 1.29]	-
SXN + drugs vs EGb + drugs	-0.38 [-1.79, 1.04]	<b>-1.07 [-2.07, -0.10]</b>	-0.82 [-2.31, 0.62]	-
GD + drugs vs EGb + drugs	<b>-1.61 [-2.84, -0.37]</b>	-	-0.83 [-2.10, 0.41]	-1.14 [-2.37, 0.09]

Abbreviations: EGb, extract of Ginkgo biloba leaf injection; GD, Ginkgo leaf extract and dipyrindamole injection; SXN, Shuxuening injection. The bold values showed those with significant statistical meaning's results.

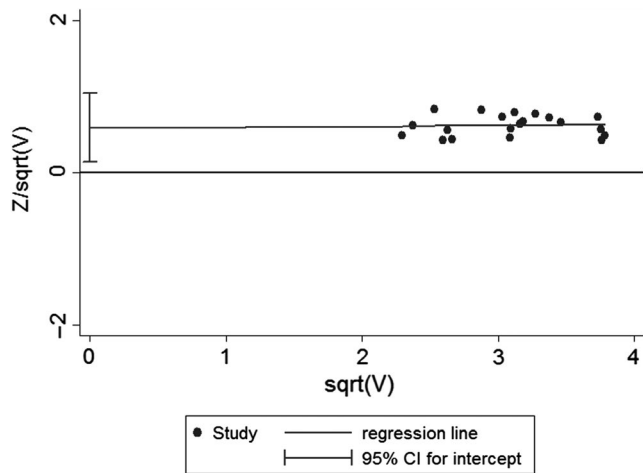
**TABLE 5** The Results of network meta-analysis of hemorheology

Comparison	Estimate effect (standard mean difference [95% confidence interval])			
	WBHSV	WBLSV	PV	FIB
SXN + drugs vs drugs	<b>-2.84 [-3.87, -1.81]</b>	-0.69 [-1.82, 0.41]	-1.03 [0.003, -1.04]	<b>-2.12 [-3.78, -0.45]</b>
EGb + drugs vs drugs	<b>-0.85 [-1.57, -0.14]</b>	<b>-1.33 [-2.09, -0.54]</b>	-0.49 [0.002, -0.50]	<b>-1.33 [-2.47, -0.16]</b>
SXN + drugs vs EGb + drugs	<b>-1.98 [-3.23, -0.73]</b>	0.63 [-0.77, 1.98]	<b>-0.54 [-0.004, -0.54]</b>	-0.79 [-2.82, 1.24]

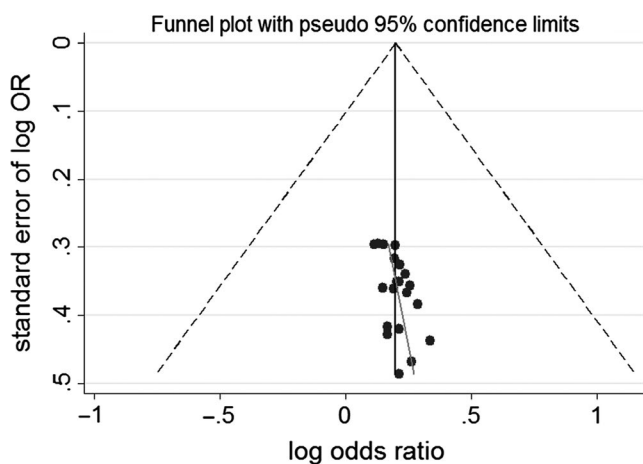
Abbreviations: EGb, extract of Ginkgo biloba leaf injection; SXN, Shuxuening injection. The bold values showed those with significant statistical meaning's results.

which may be caused by using GIs either alone or in combination.<sup>31</sup> The main symptoms of adverse events included gastrointestinal discomfort, stress ulcers and headache. However, only 11% (13 cases)

of the included patients in that study were diagnosed with an insufficient blood supply, and this result may not represent the overall population using GIs for VBI.



**FIGURE 4** The funnel plot of the Harbord test



**FIGURE 5** The funnel plot of the Egger test

In this study, an evidence-based medicine approach was used to critically appraise the existing evidence. NMA was conducted to directly and indirectly compare the effectiveness of various types of GIs, which provided relatively complete and up-to-date evidence on the use of GIs as adjunctive therapies for VBI. However, there are limitations to this study. We searched only English and Chinese databases to identify relevant studies, and eligible trials that were published in other languages may have been missed, leading to a selection bias. Due to the small sample size of the included trials, the statistical power of our findings may not have been high enough. Meanwhile, the poor quality of the included trials also affected the quality of the evidence. We suggest that future studies register their protocols before conducting the study and use appropriate methods to randomly allocate patients, blind the outcome assessors and report the results.

## 5 | WHAT IS NEW AND CONCLUSION

In conclusion, GI adjuvant drugs for VBI may be superior to drugs alone for increasing the total effectiveness rate and improving the

results of TCD examinations. Due to the limited sample size and quality of the included trials, the results of this review still need to be tested in larger and rigorous studies in the future.

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## CONFLICT OF INTEREST

The authors declare no competing interests.

## AUTHOR CONTRIBUTIONS

D Tan, XJ Duan and JR Wu conceived and designed the network meta-analysis. D Tan and XJ Duan carried out the performance of the network meta-analysis. D Tan, XJ Duan and JR Wu performed quality assessment of the network meta-analysis. D Tan, HJ Cao, XJ Duan, KH Wang, XK Liu and MW Ni analysed the study data. HJ Cao, D Tan and XJ Duan wrote the manuscript. HJ Cao, JH Tian and S Liu reviewed the manuscript. All authors read and approved the final version of the manuscript.

## ORCID

Huijuan Cao  <https://orcid.org/0000-0003-3244-6288>

Jiarui Wu  <https://orcid.org/0000-0002-1617-6110>

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## SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

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