Systematic Review and Meta-Analysis

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Efficacy and safety of puerarin injection in curing acute ischemic stroke

A meta-analysis of randomized controlled trials

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Abstract

Background: Previous studies indicated that the puerarin injection has been widely employed in China for the treatment of acute ischemic stroke. We aim to evaluate the efficacy and safety of the puerarin injection for the treatment of acute ischemic stroke.

Methods: A systematic literature search was performed in PUBMED, EMBASE, SPRINGER LINK, Scopus, Cochrane Library, China National Knowledge Infrastructure (CNKI), VIP Journals Database, Wanfang database and the China Biological Medicine database before November 2016, randomized controlled clinical trials (RCTs) of puerarin injection treating acute ischemic stroke were included. In addition, we searched reference lists of relevant retrieved articles. Two authors extracted data independently. The effective rate, the neurologic deficit score, the blood rheology indexes, and fibrinogen were assessed and analyzed by the Review Manager 5.3 software. The continuous variables were expressed as MD with 95% CI and dichotomous data used RR or ORs. Adverse reactions related to the puerarin injection were also examined.

Results: Thirty-five RCTs with a total of 3224 participants were identified in the meta-analysis. The combined results of 32 trials indicated that the puerarin injection was better than control drugs at the clinical effective rate (RR 1.22, 95% CI 1.17 to 1.28, $P < 0.001$) and 16 studies showed the neurological deficit was significantly improved (MD –3.69, 95% CI –4.67 to –2.71, $P < 0.001$); the hemorheology index and fibrinogen were much lower with the puerarin injection when compared with western conventional medicines (WCM) or other control drugs (the whole blood viscosity: MD –0.89, 95% CI –1.37 to –0.41, $P < 0.001$; the HCT: MD –0.04, 95% CI –0.06 to –0.02, $P < 0.001$; the fibrinogen: MD –0.64, 95% CI –0.96 to –0.31, $P < 0.001$). Eleven trials reported that the adverse reactions related to the puerarin injection included facial flushing, dizziness, vomiting, nausea, and other mild gastrointestinal discomfort and allergic reaction. No serious adverse drug reactions were reported.

Conclusions: Puerarin injection may be more effective and relatively safe in clinic for treating acute ischemic stroke. However, the current evidence is insufficient due to the poor methodological quality and lack of adequate safety data. Further RCTs are required to examine its efficacy.

Abbreviations: CI = confidence interval, HCT = hematocrit, MCAO = middle cerebral artery occlusion, MD = mean differences, ORs = odds ratios, RCTs = randomized controlled clinical trials, RR = relative risk, WCM = Western conventional medicines.

Keywords: acute cerebral infarction, acute ischemic stroke, meta-analysis, puerarin, randomized controlled trials

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Q-HZ and X-LL contributed equally to this study.

Authorship: Z-GM conceived and designed the study; Q-HZ, X-LL, Q-XM, and S-BY collected the data; Q-HZ, X-LL, and LX performed the analysis and prepared the manuscript; J-FW and L-JT made amendments to the manuscript; and Z-TF participated in designing the study and revised the manuscript. All authors read and approved the final version of the manuscript.

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1. Introduction

Stroke is the main cause of death and disability in the world. Although various surveillance systems are used to assess stroke and its sequela, stroke still remains one of the top causes of mortality, disability, and affects the disability-adjusted life years.[1] In China, there are 1.5 to 2 million new cases of stroke each year. Stroke has been ranked as the first leading cause of mortality and long-term disability, which caused a heavy economic burden to the family and even the whole society.[2] The incidence of stroke due to ischemia accounts for 68%.[3] The ischemic stroke is caused by blockages or narrowing of the arteries that provide blood to the brain, resulting in ischemia severely and decreased blood flow.[4] Acute ischemic stroke and metabolic syndrome patients triggered a more intense immune-inflammatory activation, which results in a higher degree of immuno-inflammation and arterial stiffness.[5] Regrettably, so far, no routine effective specific therapy for ischemic stroke is generally accepted, except for aspirin and thrombolytic treatment with recombinant tissue plasminogen activator for highly selected patients.[6] Therefore, various kinds of complementary and/or alternative medicine are being developed worldwide. Traditional Chinese medicine has been widely used in the treatment of ischemic stroke such as rhizoma gastrodiae, radix astragali, radix puerariae, and other Chinese herbal medicine or non-medication therapies for many years.[7]

Gegen, the dried root of pueraria lobata, is one of the earliest and most important edible crude herbs used for various medical purposes in Chinese medicine. Puerarin (relative molecular weight 416.38, Fig. 1), the major bioactive component of the traditional Chinese medicine Radix puerariae (kudzu root), is a major isoflavonoid with polyhydroxy.[8] Puerariae radix has been reported to display anti-inflammatory effects,[9] antiplatelet aggregation,[10] antioxidant,[11] as well as decreasing plasma cholesterol.[12] Puerarin injection was a common dosage form of puerarin for curing microcirculation disturbance and cardio-cerebrovascular diseases as Chinese patent drug for more than 20 years.[13,14] Randomized controlled trials (RCTs) upon puerarin injection have exhibited to improve neurological deficit after cerebral ischemia in patients.[15] A previous review about puerarin treating ischemic stroke presented a positive conclusion;[16] however, the sample size was too small to draw a reliable conclusion. Therefore, in this paper, we included more trials and aimed to evaluate the clinical efficacy and safety of puerarin injection for treating acute ischemic stroke as well as to provide high-quality evidence for further clinical utilization.

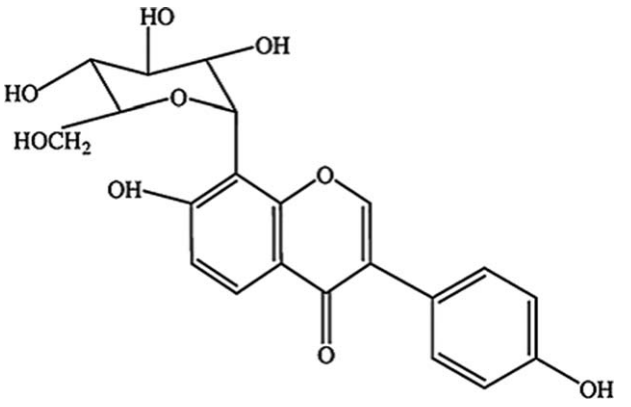

Figure 1. Chemical structure of puerarin.

2. Methods

2.1. Database searched

We used "puerarin," "ischemic stroke," or "cerebral infarction" as the search terms to search PUBMED, EMBASE, SPRINGER LINK, Scopus, Cochrane Library, China National Knowledge Infrastructure (CNKI), VIP Journals Database, Wanfang database, and the China Biological Medicine database before November 2016.

2.2. Inclusion criteria

Ischemic stroke was diagnosed clinically according to the World Health Organization definition or the diagnostic criteria issued at the Second and revised at the Fourth National Cerebrovascular Diseases Conference in China[17] and approved by CT scan or MRI. Patients with ischemic stroke within 7 days of onset and diagnosed without serious organic disease and complications were considered.[18] RCTs that evaluated efficacy and safety of puerarin for ischemic stroke patients were included.

2.3. Intervention measures

The experimental groups were given puerarin with sodium chloride or glucose injection, the intervention for treatment groups included only puerarin herbal without other Chinese medicine. The patients of the control group were given WCM such as aspirin or other medicine without puerarin. In some cases, 2 groups would be given basic treatment on the basis of the condition of the patient in the same time.

2.4. Outcomes

The total effective rate was the primary outcome. Secondary outcomes were the neurological deficit improvement after treatment. Third outcomes included hemorheology index with whole blood viscosity, hematocrit (HCT), and fibrinogen. The adverse events were recorded.

2.5. Data extraction and statistical analysis

For all studies included in the systematic review, data extraction and study quality assessment were independently conducted by 2 authors (Q-HZ and X-LL), with disagreement resolved by consensus. The following data were extracted from each primary study, if available, including study types, patient characteristics, and treatment. The Review Manager 5.3 software was used for data-analysis. A fixed-effect model or random-effect model was used across the trials, and risk ratios with their 95% confidence intervals (CI) were calculated for dichotomous data. If continuous data were available, weighted mean difference or standardized mean difference was to be calculated. I^2 statistic showed the degree of heterogeneity. Groups were distributed to subgroups based on the different kinds of blood rheology indexes. The bias assessed through the Funnel plot or Egger tests in this study.

2.6. Quality assessment

We evaluated the risk of bias according to the Cochrane risk of bias tool, which included the following 7 domains, random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting, and other bias.

3. Results

3.1. Assessment of quality

On the basis of search strategy, 523 potentially relevant articles were identified after duplicates removed. Then, 378 articles were excluded by reviewing the types and designs of trials, and another 110 articles were excluded by reviewing the inclusion criteria. Thus, there were 35 primary studies, with 3224 participants in total, included in the systematic review. All of these studies were conducted in China and published before November 2016, described as randomized, and did not report the method of random sequences generation.[19–53] The study screening procedure was summarized in a flow diagram (Fig. 2). Detailed characteristics of the 35 studies and puerarin dose in each study were described in Table 1. Based on the GRADE system, the evidence of effective rate and neurological deficit score were weak recommendation (Figs. 3 and 4). There was no significant publication bias, and no small study effects were found in the funnel plot (Fig. 5) or revealed by the Egger ($P = 0.006$).

3.2. Outcomes

3.2.1. The clinical effective rate. In total, 32 trials adopted the effective rate to assess the clinical improvement and the

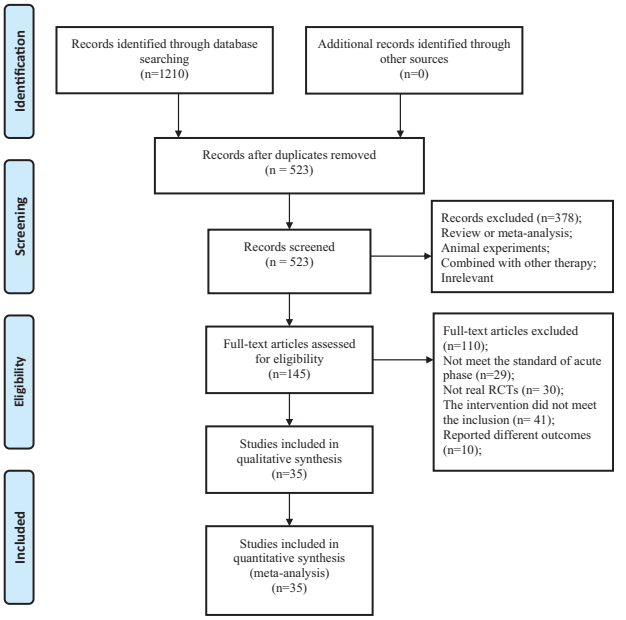

Figure 2. Flowchart summarizing the selection process of meta-analyses.

Table 1

Characteristics of 35 included studies on the effect of puerarin for acute ischemic stroke.

Study	Subjects (trial/control)	Age		Intervention		Treatment/d	ADR
		Trial group	Control group	Trial group	Control group		
Zhang et al, 2006	30/30	58 ± 11.3	57.2 ± 10.8	Puerarin 500 mg, 20% Mannitol	20% Mannitol	10	2
Jiang, 2006	50/50	68.1	70.1	Puerarin 500 mg	Dextran, Troxerutin	14	4
Zhou and Liu, 2011	40/39	52.3 ± 9.6	54.6 ± 8.2	Puerarin 400 mg	Compound Danshen Injection	14	None
He, 2009	50/40	62.0 ± 18.0	61.0 ± 21.0	Puerarin 400 mg	Dextran, Compound Danshen Injection	20	None
Shan et al, 2006	82/78	51.2 ± 11.3	52.1 ± 10.2	Puerarin 500 mg, WCM	WCM	15	None
Wang and Dong, 2008	40/40	55–81	50–80	Puerarin 500mg	Compound Danshen Injection	14	Unclear
Wang, 2008	73/73	55.9 ± 14.2	55.9 ± 14.2	Puerarin 500mg	Compound Danshen Injection	14	None
Tong, 2007	28/18	63.0 ± 12.1	62.8 ± 10.5	Puerarin 400 mg, WCM	WCM	14	Unclear
Lu and Lu, 2011	58/58	72.8 ± 8.9	71.2 ± 10.0	Puerarin 500 mg, WCM	WCM	14	7
Wang, 2012	34/34	57.0 ± 3.6	57.4 ± 3.6	Puerarin, WCM	WCM	10	Unclear
Zhang, 2010	42/37			Puerarin 400 mg, WCM	WCM	15	Unclear
Xu and Zhou, 2011	30/30	43–79	42–80	Puerarin 500 mg,	Compound Danshen Injection	14	1
Deng et al, 2007	60/60	50–70	51–68	Puerarin 400mg	Danshen Injection	28	None
Li, 2008	60/60	42–86	42–86	Puerarin 500mg	Dextran	14	Unclear
Shi and He, 2006	32/32	45–76	43–72	Puerarin 400mg	Ligustrazine	20	None
Cui and Chen, 2007	43/43	43–78	45–76	Puerarin 500 mg, WCM	WCM	20	Unclear
Lin, 2006	55/55	63.0 ± 12.0	61.0 ± 10.5	Puerarin 400 mg, WCM	WCM	15	None
Han, 2009	56/54	40–82	38–80	Puerarin 400mg	Dextran, Troxerutin	15	None
Guo, 2007	45/30	43–85	45–88	Puerarin 200mg	Compound Danshen Injection, Dextran,	14	2
Sun, 2010	48/36	38–78	39–79	Puerarin 500 mg,	Ozagrel Injection	12	None
Bi et al, 2007	50/48	48–79	50–77	Puerarin 400 mg	Compound Danshen Injection	14	2
Guo, 2007	68/52	42–86	40–78	Puerarin 300 mg	Danshen Injection, Mailuoning	14	None
Su and Wang, 2007	46/45	60.6 ± 2.3	60.6 ± 2.3	Puerarin 400 mg	Danshen Injection	14	None
Li, 2013	60/50	54.4 ± 19	60.2 ± 21	Puerarin 450 mg	Dextran, Compound Danshen Injection	30	3
Liu et al, 2010	35/35	61.4 ± 10.2	60.9 ± 10.25	Puerarin 600 mg	Troxerutin	20	Unclear
Cai, 2011	45/45	42–83	45–82	Puerarin 400 mg	Compound Danshen Injection	28	None
Sun, 2009	69/69	55.9 ± 14.2	55.9 ± 14.2	Puerarin	Compound Danshen Injection	14	None
Cao, 2010	46/46	45–75	48–76	Puerarin 400 mg, WCM	WCM	14	3
Liu and Dong, 2008	30/30	46–72	48–76	Puerarin 400 mg	Compound Danshen Injection	14	None
Sun and Li, 2009	46/41	50–80	48–78	Puerarin 100–200 mg, WCM	WCM	15	None
Deng, 2010	51/40	45–80	46–79	Puerarin 200 mg	Xiangdan Injection	14	4
Zhang and Li, 2001	30/20	71.5 ± 5.3	71.5 ± 5.3	Puerarin 400 mg	Compound Danshen Injection	14	1
Wang, 2003	44/43	64.7 ± 9.6	65.6 ± 9.3	Puerarin 600 mg	Dextran, Troxerutin	28	None
Wu and Huang, 2001	60/48	60.4 ± 6.5	61.1 ± 7.1	Puerarin 400 mg	Compound Danshen Injection	14	None
Wei et al, 2003	42/37	64.4	69.6	Puerarin 400 mg	Compound Danshen Injection	21	2

ADR = adverse drug reactions, WCM = western conventional medicines.

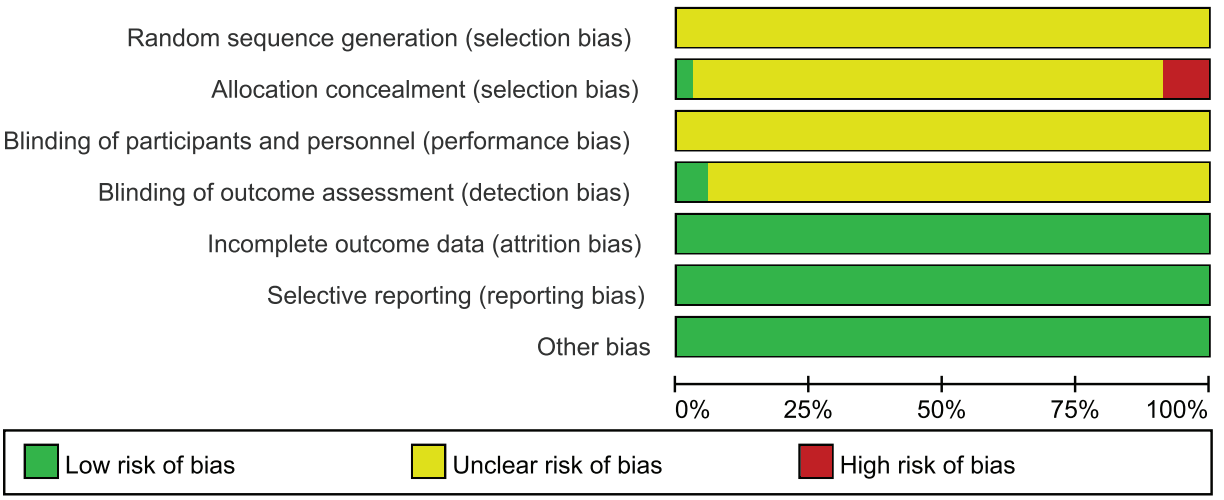

Figure 3. Risk of bias graph: review authors' judgments about each risk of bias item presented as percentages across all included studies.

random-effective model was used for statistical analysis. The analysis showed favor of puerarin (n = 2967, RR 1.22, 95% CI 1.17 to 1.28, $P < 0.001$), heterogeneity $\chi^2 = 58.69$, $P = 0.002$, $I^2 = 47\%$, Fig. 6).

3.2.2. The scores of neurological deficits. However, 16 studies which used the neurologic deficit score were qualified to perform a meta-analysis, and the random effective model was used for statistical analysis because of the heterogeneity (n = 1358, MD –3.69, 95% CI –4.67 to –2.71, $P < 0.001$, heterogeneity $\chi^2 = 49.43$, $P < 0.0001$, $I^2 = 70\%$), and favored the puerarin group (Fig. 7).

3.2.3. Blood rheology indexes and fibrinogen. Twelve studies involved whole blood viscosity, and the random effective model was used for statistical analysis because of the heterogeneity (n = 1036, MD –0.89, 95% CI –1.37 to –0.41, $P < 0.001$, heterogeneity $\chi^2 = 359.22$, $P < 0.0001$, $I^2 = 97\%$) and favored the puerarin group (Fig. 8).

Twelve studies adopted HCT to evaluate the clinical significance of puerarin for the ischemic stroke in hemocyte, due to the heterogeneity (n = 1070, MD –0.04, 95% CI –0.06 to –0.02, $P < 0.001$, heterogeneity $\chi^2 = 245.98$, $P < 0.0001$, $I^2 = 96\%$), the random effective model was used. The consequence showed the favor of experimental group (Fig. 9).

Eleven of the studies adopted the fibrinogen to assess the clinical improvement and the random-effective model was used for statistical analysis (heterogeneity $\chi^2 = 233.64$, $P < 0.0001$, $I^2 = 96\%$). The puerarin group was significantly lower than the fibrinogen control group (n = 1011, MD –0.64, 95% CI –0.96 to –0.31, $P < 0.001$) (Fig. 10).

3.3. Safety

Due to the variety of symptoms and the low number of adverse reactions reported, it was difficult to conduct a meta-analysis, so the adverse reactions were described. Eleven studies reported that patients might be temporary bloating, nausea and other gastrointestinal reactions, dizziness and facial flushing, but the symptoms were relieved after continued treatment,[19,20,27,30,37,39,42,46,49,50,53] rashes was reported in 2 trials,[37,49] whereas the left trials reported no adverse effects. No serious adverse drug reactions occurred.

4. Discussion

In our study, the efficacy and safety of puerarin injection in curing acute ischemic stroke were investigated. Thirty-five RCTs involving a total of 3224 participants with acute ischemic stroke were included. The results demonstrated that puerarin could improve the neurological deficit of acute ischemic stroke, lower blood viscosity, and reduce fibrinogen production. The outcomes were partially similar to the results of a previous review,[13] which just assessed the efficiency of puerarin for ischemic stroke and showed that puerarin improved neurological deficit significantly more than the control. However, the review neither evaluated the effect on blood rheology indexes nor fibrinogen, and its possible mechanism was not discussed. Actually, plasma fibrinogen played a major determinant in platelet aggregation and blood viscosity, whereas high blood viscosity led to blood stagnation and then promoted thrombosis, resulting in the development of ischemic stroke.[54,55] So evaluating the effect of puerarin injection on blood rheology indexes and fibrinogen was important. Moreover, our enrolled sample size was much larger and we focused on acute ischemic stroke treatment, whereas they included acute and chronic ischemic stroke. In summary, our study tried to offer a high-quality evidence-based approach upon puerarin injection for treating ischemic stroke.

As we all know, the ischemic stroke is a common cardiovascular disease involves death of brain tissue (cerebral infarction) resulting from an inadequate supply of blood and oxygen to the brain due to blockage of an artery.[56] Ischemic stroke causes a lot of damage to body and seriously affects the quality of life. Because the high morbidity and mortality of acute ischemic stroke patients increased with increasing age, which threatens the health of human beings.[57] Hypoxic ischemic brain injury often causes irreversible brain damage and the cascade of events leading to neuronal injury and death in ischemia includes the release of cytokines and free radicals, and induction of inflammation, apoptosis, and excitotoxicity.[58]

Many pharmacological interventions such as thrombolytic, antioxidant, cerebral vasodilator, Ca^{2+} channel blocker, and free

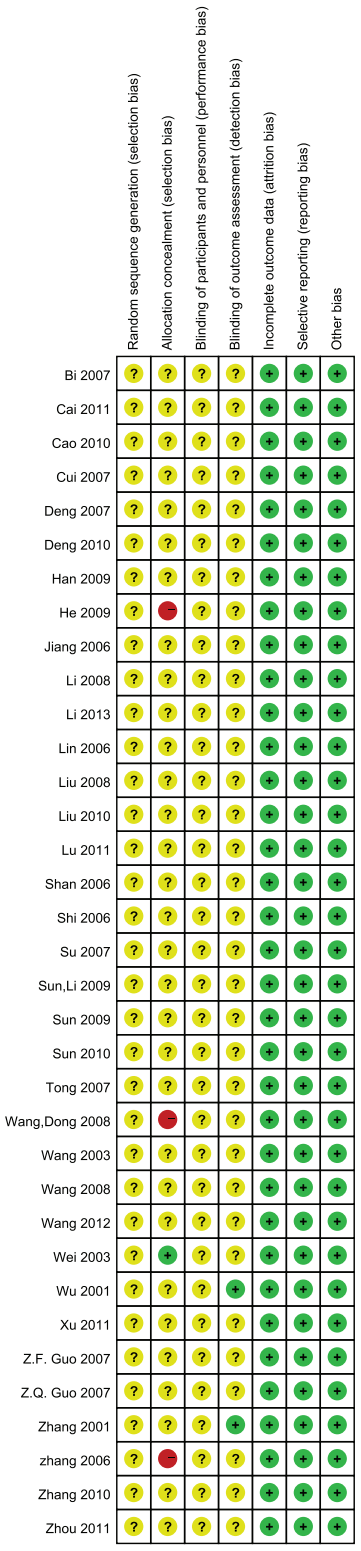

Figure 4. Risk of bias summary: review authors' judgments about each risk of bias item for each included study.

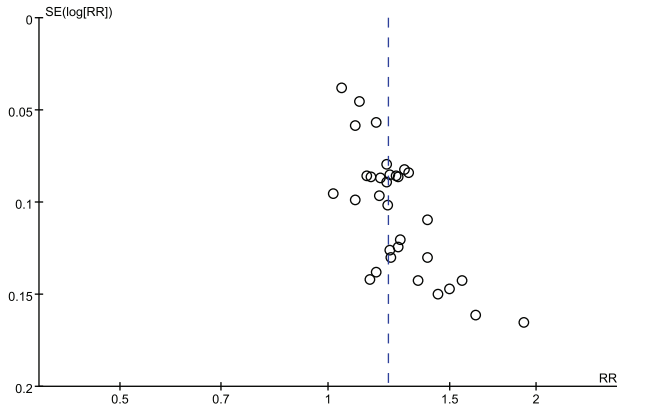

Figure 5. Funnel plot of the total effective rate.

radical scavenger have been observed to produce acute ischemia and cerebral ischemia-reperfusion protection.[7] Insufficiently, the usage criteria and administration time window are limited in thrombolytic,[59] and cerebral hemorrhagic complications occur more easily.[60] Therefore, it is necessary to seek some new alternative medicine with the characteristics of high safety, high efficiency, and synthetic therapeutic effects. In China, multiple kinds of Chinese medicinal herbs or effective constituents, such as Buyang Huanwu decoction[6], compound salvia injection[61], Xuesetong injection[62] and puerarin injection we discussed here, have been widely used to treat ischemic stroke for a long history. Puerarin is a major isoflavonoid derived from the Chinese medical herb radix puerariae (Gegen), which is the root of the familiar kudzu vine. In traditional Chinese medicine, radix puerariae has been widely used in the treatment of cerebrovascular disorders, cardiovascular diseases, cancer, Alzheimer's disease (AD), and diabetes and diabetic complications.[63] Puerarin is an isoflavone compound separated from the drying of kudzu root and its injection was purified and developed from the 1990s of the 20th century.[13]

By reviewing the recent pharmacological researches, we found that puerarin was a potent neuroprotective drug on MCAO-induced focal cerebral ischemia in vivo, by inhibiting both HIF-1α and TNF-α activation, followed by the inhibition of inflammatory responses (i.e., iNOS expression), apoptosis formation (active caspase-3), and neutrophil activation, resulting in a reduction of infarct volume in ischemia reperfusion brain injury.[64] Also, Liu et al[65] reported that puerarin reduced the ischemic infarct volume and improved neurological deficit after cerebra ischemia/reperfusion by activating the cholinergic anti-inflammatory pathway. In our meta-analysis, the neurologic deficit score of puerarin injection group did improve when compared with the control group (MD –3.69, 95% CI –4.67 to –2.71, $P<0.001$). Yan et al[66] indicated that puerarin was relevant to triggering extracellular Ca^{2+} influx into endothelial cytosol, which involved the endothelial Ca^{2+}–NO–cGMP pathway, prostacyclin, and opening of the 3 K^+ channels and then effected the endothelium-dependent antivasoconstrictive; Pan et al[10] suggested that the puerarin injection could ameliorate the hemorheology and the abnormal augmentation of platelet aggregation, which these pharmacological researches met with the results of our meta-analysis that puerarin injection could reduce blood viscosity.

There are still some limitations in our study. For example, the period of most observation lasted for only 14 days and none of studies reported the record of results and dropout data, long-term observation, and flowing-up are required in further study. And there are several methodological limitations in the primary studies; all trials were RCTs but none of them reported

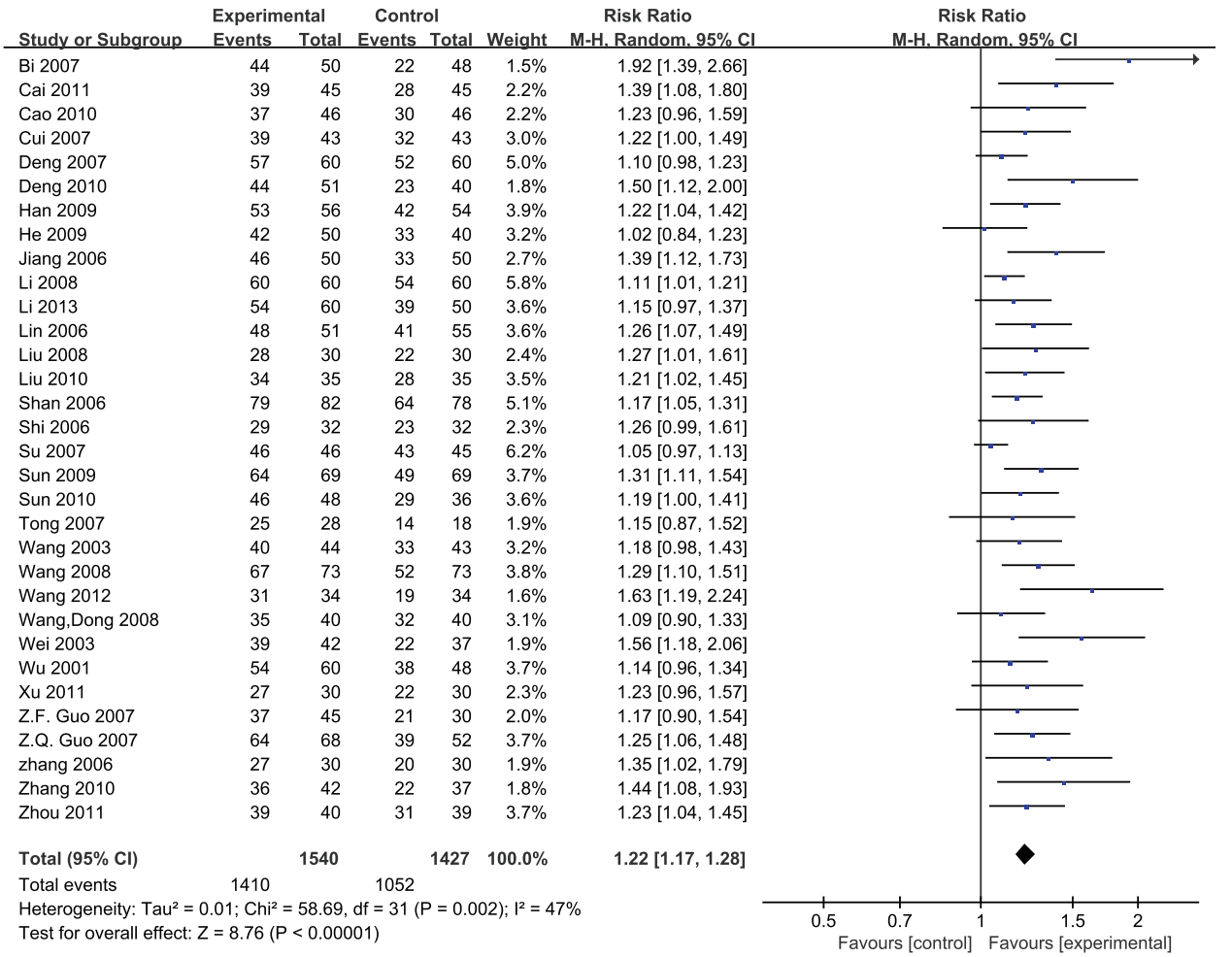

Figure 6. Meta-analyses of the total effective rate.

the random method or allocation concealment, which may produce selection bias. So that, more randomized, double-blind, controlled, multicenter of clinical trials are needed. Though we made effort to find more clinical experiment trails, all the studies were from China mainland. All the adverse reactions were described due to only a few of the included trials reported adverse events and the cases, which was not enough for statistical analysis. In addition, the dose of included trials was different,

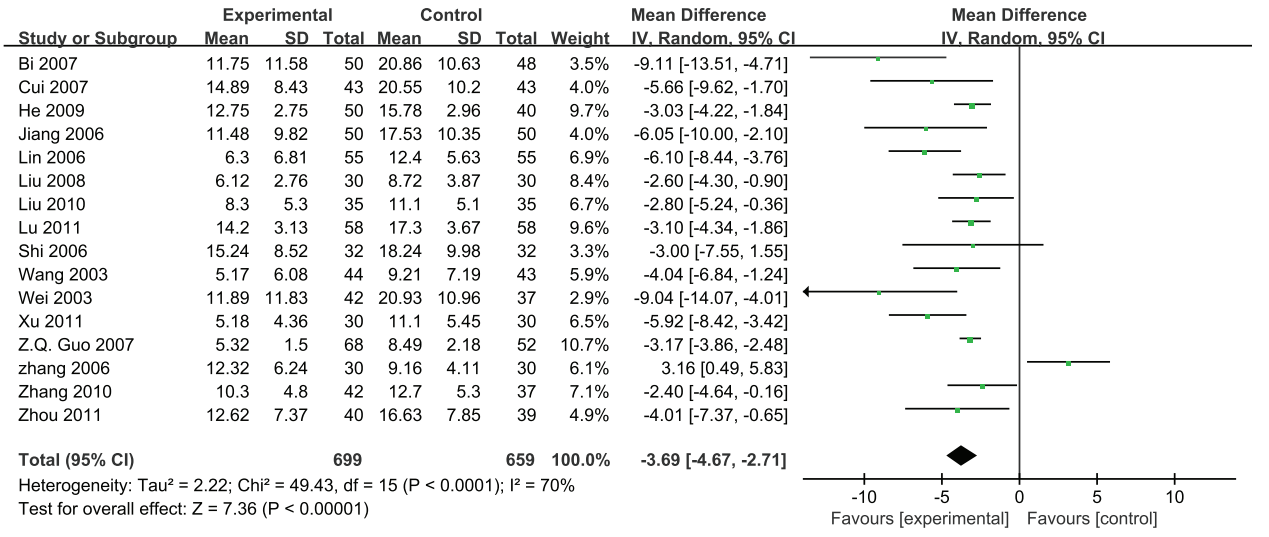

Figure 7. Meta-analyses of the scores of neurological deficits.

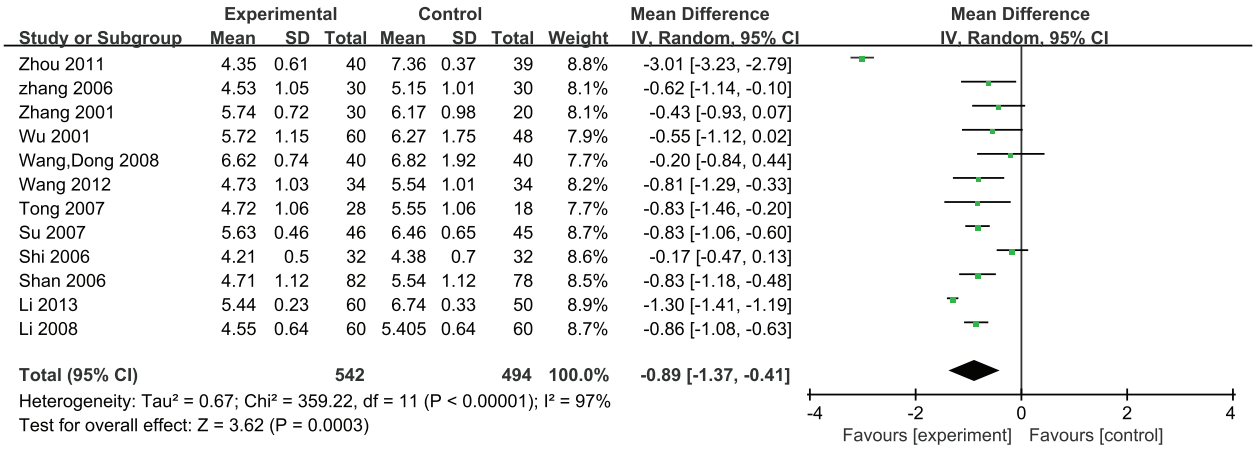

Figure 8. Meta-analyses of the whole blood viscosity scores.

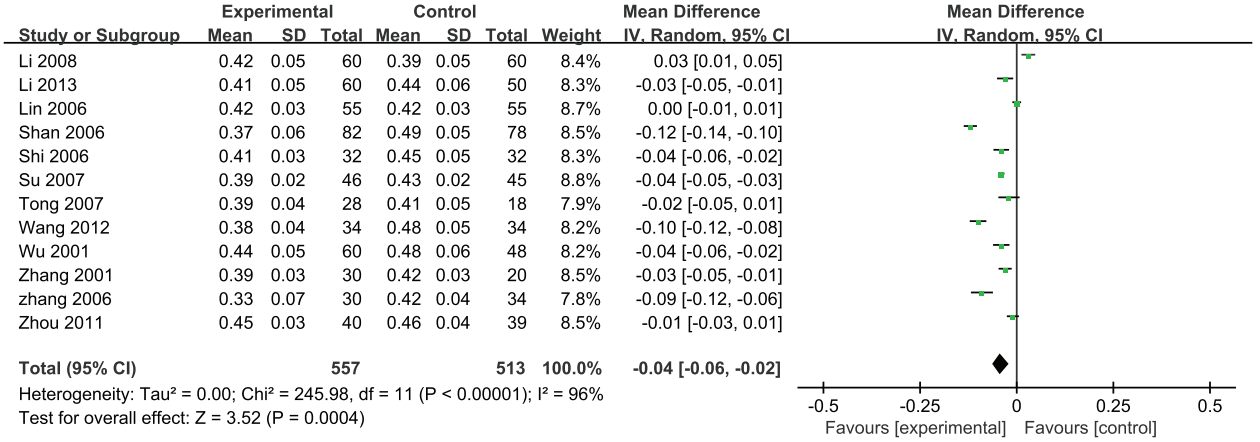

Figure 9. Meta-analyses of HCT. HCT = hematocrit.

which varied from 0.2 g to 0.6 g, and no standard dose delivered to the acute ischemic stroke target was obtained.

In conclusion, the meta-analysis indicates that the puerarin injection is more effective than WCM and provides evidence-based approach for treating ischemic stroke. However, more high quality-RCTs are needed to provide reliable evidence on the effectiveness of puerarin injection for treating acute ischemic stroke.

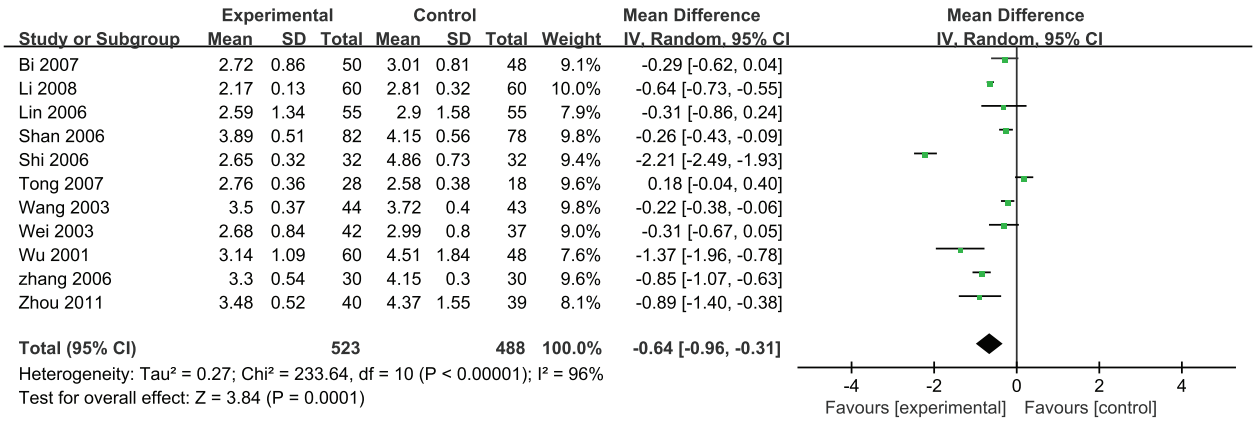

Figure 10. Meta-analyses of the fibrinogen.

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