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The potential value of traditional Chinese medicine monomers in cerebral ischemia–reperfusion injury: a network meta-analysis based on animal model

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Abstract

Background Cerebral ischemia–reperfusion injury (CIRI) is a complex pathological process, which can further aggravate the damage of ischemic tissues. Traditional Chinese medicine (TCM) monomers, bioactive compounds extracted from Chinese herbal medicines, have been demonstrated to have various protective effects against reperfusion injury. This network meta-analysis (NMA) aimed to investigate the optimal treatment strategy of TCM monomers for CIRI in animal models.

Methods Four databases including PubMed, Embase, Web of Science, and Cochrane were searched up to January 06, 2024. First, prospective registration was done at PROSPERO (ID: CRD42024496289), the quality of the included studies was evaluated with SYRCLE's risk of bias tool, and statistical analysis was conducted with Stata Version 18.0 and RStudio.

Results In total, 26 studies were included, involving 506 animals and 12 TCM monomers. The results of a meta-analysis demonstrated that, compared to the control group, puerarin, paeoniflorin, hydroxysafflor yellow A, sinomenine, and salvianolic acid significantly reduced mNSS scores. Furthermore, ginsenoside, scutellarin, and baicalein significantly reduced Longa scores. In addition, salvianolic acid treatment significantly decreased brain water content. Regarding infarct volume, bilobalide, baicalein and puerarin all demonstrated remarkable effects. The network meta-analysis suggested that paeoniflorin might be the most effective intervention in terms of mNSS score, with a surface under the cumulative ranking curve (SUCRA) value of 92.8%; Scutellarin might be the most effective intervention to reduce Longa score (SUCRA = 87.6%); And salvianolic acid might be the most effective intervention to reduce brain water content (SUCRA = 98.2%); For infarct volume specifically, bilobalide may be the most effective intervention (SUCRA = 95.5%). In our meta-regression, we found that dose and duration of treatment may contribute to heterogeneity among mNSS studies.

Conclusion TCM monomers could provide a favorable neuroprotection on CIRI, with heterogeneous protective effects. Given the small number and the differences in quality of included studies, more high-quality, programmatic animal studies were needed to validate our findings.

Clinical trial number Not applicable.

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Keywords Traditional Chinese medicine monomers, Cerebral ischemia–reperfusion injury, Animal model, Network meta-analysis

Introduction

Stroke is still the second most common cause of death and the third most common cause of disability in the world. Though the incidence has decreased over the past two decades, but it is still a weight-bearing economic burden on families and society [1]. Ischemic stroke accounts for approximately 87% of all strokes, and large vessel occlusion is conservatively estimated to account for 10% – 20% [2]. The final objective of ischemic stroke treatment is to reduce neuronal damage by rapidly opening occlusion vessel (recanalization) to restore cerebral blood flow (reperfusion) [3]. Current reperfusion strategy includes intravenous thrombolysis (IVT) and mechanical thrombectomy (MT), both of which can improve the functional outcomes of patients to some extent [4]. However, their use is limited by the strict time window, the complexity of their implementation, and complex contraindications. It has been reported that in 2016, less than 5% of acute ischemic patients worldwide received IVT within the effective time window, while less than 100,000 patients received MT [2]. The aggravated injury to brain tissue after vessel recanalization, called as cerebral ischemia–reperfusion injury (CIRI) will further deteriorate neurological function. The pathological reactions of CIRI are complex, including but not limited to oxidative stress, inflammation, glutamate neurotoxicity, and cell death [5]. Therefore, it has been a hot topic to explore new neuroprotective therapies to attenuate CIRI. At present, the neuroprotective effect of traditional Chinese medicine (TCM) monomers on CIRI has been widely studied. A lot of preclinical studies showed various neuroprotective effects of TCM monomers, for example, anti-oxidative stress, inhibition of inflammatory response, and inhibition of apoptosis[6–8], repairing the blood–brain barrier and promoting vascular regeneration [9, 10], and reducing neurotoxicity and side effects[11]. TCM monomers such as curcumin and puerarin, protect brain tissues from IRI by modulating multiple signaling pathways [12, 13] and show multiple protective effects in animal models of CIRI.

However, the current research on the protective effect of TCM monomers on CIRI is mainly based on preclinical, animal experiments. As an important carrier of preclinical evidence, these experiments provide unique insights into the pathophysiology and etiology of the disease, and often reveal new targets for targeted therapy[14]. Although the existing literature has examined TCM monomer for the treatment of CIRI, it nevertheless has limitations. Previous meta-analyses have compared only single TCM monomer, without the quantitative calculations for comparisons of multiple monomers in published reviews. Hence, it is not possible to ascertain how comparable TCM monomers are in terms of efficacy or safety. Network meta-analysis (NMA) is a technique that compares multiple intervention options in a systematic review of multiple trials by combining direct evidence (comparison of interventions assessed within the same trials) and indirect evidence (comparisons of interventions across trials using a common comparator) [15]. Therefore, we aim to comprehensively summarize the preclinical evidence for the treatment of CIRI with TCM monomers through this NMA, in order to provide the guiding information for future animal experiments and clinical studies.

Materials and methods

Study registration

The study was conducted according to the Preferred Reporting Items for Systematic Reviews and NMA (PRISMA-NMA) guidelines and prospectively registered with PROSPERO(ID:CRD42024496289)(https://www.crd.york.ac.uk/PROSPERO/#myprospero).

Literature search strategies

Four databases including PubMed, EMbase, Cochrane and Web of Science, were searched with a time frame through January 6, 2024. Search strategy was established based on PICOS principles: (1) Population: Animal models of MCAO/R (middle cerebral artery occlusion/reperfusion); (2) Intervention: Single compounds from traditional Chinese medicine (TCM); (3) Control group: Placebo or other drugs; (4) Outcome measures: Efficacy; (5) Study type: Animal experiments. Details of the search strategy used for each database are provided in Supplementary Table S1.

Inclusion and exclusion criteria

Inclusion criteria

(1) MCAO/R experimental model with in vivo animal study, and no restriction on animal species. (2) In the experimental group, TCM monomer was used as the intervention, with no restrictions on the mode of administration or course of treatment. The optimal dose for therapeutic efficacy was extracted. (3) The control group received placebo or no treatment. Outcome measures: 1. modified neurological severity score (mNSS) [16]:

neurological function, including motor and sensory systems, and reflexes and balance, was graded by using a numerical scale of 0–18 (score 0 for normal, score 18 for maximum severity); 2. Longa score: based on the 5-point scale described by Longa et al. [17] (score 0 for no neurological severity and 4 for maximum severity); 3. brain water content (BWC): based on the formula: H_2O (%) = (wet weight (WW) – dry weight (DW))/WW × 100%; 4. Infarct volume (IV): The infarct area was delineated and analyzed using Image J. The total infarct area was calculated by summing the CT areas of all slices, which was then multiplied by the brain slice thickness to determine the IV [18].

Exclusion criteria

(1) Duplicate publications; (2) In vitro study; (3) No control groups; (4) TCM.

monomers were not the only intervention; (5) Overview, conference abstract, case report, meta-analysis, and clinical trials; (6) Incomplete data or data unable to be analyzed.

Literature screening

Two investigators (X Luo and JY Niu) independently screened the studies, and Endnote software was used to check the imported studies. First, article titles and abstracts were read to complete the preliminary screening, then the articles possibly meeting the inclusion criteria were read and their full text was rescreened, the reasons for exclusion were recorded, and cross-checking was performed after literature screening. In case of differences of opinion, a third investigator (HS Chen) was involved to discuss and decide whether to include them.

Data extraction

Two investigators (X Luo and JY Niu) extracted data according to a pre-established information extraction form, and in cases where numerical data could not be obtained, the authors were contacted up to three times to request the necessary data. In cases where no response was received from the authors, EngaugeDigitizer software (version 12.1) was used to extract the mean, standard deviation, or standard error from the graphs in the articles. Data extracted included the following: (1) characteristics included in the study: first author, country, publication year; (2) animal characteristics: species, sex, body weight, number, modeling method; (3) intervention method: duration of ischemia–reperfusion injury, administration time, drug, administration method, dose, frequency, and intervention duration; (4) outcome measures: data related to mNSS score, Longa score, BWC and IV. If there was any disagreement, the two investigators would discuss or consult with a third investigator (HS Chen).

Assessment of risk of bias

The included studies were assessed by two independent investigators (X Luo and JY Niu) with SYRCLE's risk of bias tool [19]. This tool consists of six domains—selection bias, performance bias, detection bias, attrition bias, reporting bias, and other sources of bias. The tool contains 10 items, with each item being assigned a judgment of "yes", "no", or "unclear". Disagreements were subject to negotiation or adjudication by a third researcher (HS Chen).

Statistical analysis

Meta-analysis (MA): Data synthesis and analysis were performed using Stata 18.0 through conventional pairwise meta-analysis. mNSS, Longa scores, infarct volume, and brain water content were treated as continuous variables and expressed as mean values with standard deviations. The effect size for each outcome measure was pooled using the standardized mean difference (SMD) and its 95% confidence interval (CI), with statistical significance set at $P < 0.05$. Heterogeneity was assessed using the Cochrane Q test and I^2 statistics. Specifically, if $P > 0.1$ and $I^2 \leq 50\%$, the heterogeneity between studies was considered minimal, and thus a fixed-effects model was used; if $P < 0.1$ or $I^2 > 50\%$, the heterogeneity between studies was deemed substantial, and thus a random-effects model was applied.

Network meta-analysis: Bayesian network meta-analysis was conducted using Stata 18.0 and RStudio. I^2 was employed to assess heterogeneity between studies. A random-effects model was adopted when $I^2 > 50\%$, indicative of significant heterogeneity; Otherwise, a fixed-effect model was utilized [20]. First, network evidence diagrams were plotted for each outcome measure to visually represent pairwise comparisons of different interventions, with each node indicating an intervention, the size of the node represents sample size involved, lines connecting nodes indicating direct comparisons between the two interventions, and width of each line indicating study number for comparisons between the two interventions. If there was a closed ring between the interventions, the node splitting method was applied to test the consistency. If the comparison result was $P > 0.05$, it indicated that the consistency of both direct and indirect comparisons was good. The consistency model was applied for statistical analysis, or the non-consistency model was applied for analysis; if there was no closed ring, the consistency model was directly applied for analysis. The effect was ranked according to the surface under the cumulative ranking curve (SUCRA), and the range of SUCRA values

was 0%−100%. A higher SUCRA value indicated a higher probability of ranking the treatment effect top. For outcomes reported in more than ten included studies, publication bias was assessed via funnel plot and Egger's test. Additionally, we also conducted a meta-regression analysis to explore whether dose and duration of treatment were associated with the efficacy of TCM monomers in the treatment of CIRI, and if so, subgroup analyses were performed.

Results

Results of literature screening

A total of 3537 studies were retrieved initially, and 2218 records remained after duplicates were excluded. After the review of titles and abstracts, 277 were remained.

After careful reading of the full text, 26 studies were finally included according to the inclusion/exclusion criteria, and the screening process for the included studies is shown in Fig. 1.

Study characteristics

The characteristics of the included studies are provided in Table 1. The table included data on 26 studies, all of which involved mice or rats, with 506 animals in total (252 and 254 in the experimental and control groups, respectively). Twenty-five studies came from China and one from Turkey. Twenty studies used Sprague–Dawley (SD) rats, Wistar rats in four studies, C57BL/6 J mice in one study, and CD1 mice in one study. One of the twenty-six studies used female animals and all the others were male. Twenty-five studies developed middle cerebral artery occlusion (MCAO/R) models, while one study induced stroke by bilateral common carotid artery occlusion (BCCAO/R). Twelve TCM monomers were included: ginsenoside in six studies, salvianolic acid in

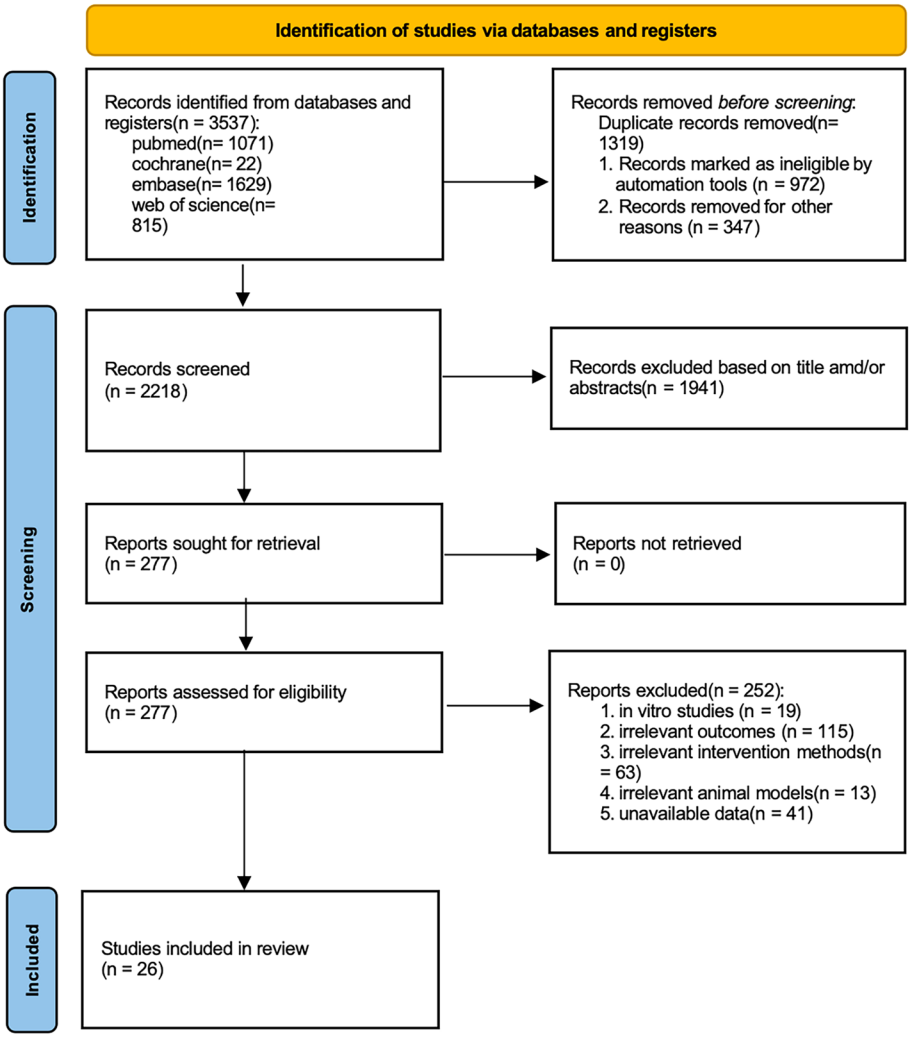

Fig. 1 Guidelines flow diagram

Table 1 Study characteristics of the included studies

Study	Species (sex, weight)	Model	N = experimental/ control group	Ischemia duration	Time of administration	Control group	Experimental group (drug/daily dosage/ frequency, approach, duration)	Outcomes
Yang LX 2016(China) [21]	Rat/SD (M, 270–320 g)	MCAO/R	20/22	2 h	1 h before MCAO	NS	Ginsenoside, 10 mg/kg, qd, i.p., 7 d	Longa
Xie CL 2015(China) [22]	Rat/SD (M, 250–300 g)	MCAO/R	12/12	2 h	3 d before MCAO	NS	Ginsenoside, 40 mg/kg, qd, i.p., 14 d	Longa
Lin M 2015 (China) [23]	Rat/SD (M, 280–320 g)	MCAO/R	10/10	2 h	2 h after I/R	NS	Ginsenoside, 60 mg/kg, bid, i.v., 3 d	Longa
Zhou Y 2014 (China) [24]	Rat/SD (M, 230–280 g)	MCAO/R	12/12	2 h	3 d before MCAO	NS	Ginsenoside, 20 mg/kg, bid, i.p., 14 d	Longa
Wang C 2023 (China) [25]	Rat/SD (M, 140–160 g)	MCAO/R	12/12	1.5 h	0 h after MCAO	NS	Scutellarin, 12 mg/kg, tid, i.v., 12 h	Longa
Xu S 2017 (China) [26]	Rat/Wistar (M, 180–220 g)	MCAO/R	10/10	1 h	NI	NS	Salvianolic acid, 12 mg/kg,/, i.p., 3 d	Longa
Altinay S 2017(Turkey) [27]	Rat/Wistar (female, 400–500 g)	BCCAO/R	8/8	0.5 h	NI	NS	Curcumin, 300 mg/kg, qd, i.p., 3 d	Longa
Li L 2023 (China) [28]	Rat/SD (M, 280–300 g)	MCAO/R	16/16	1.5 h	0 h after I/R	NI	Quercetin, 50 mg/kg, qd, ip, 3 d	Longa
Wu WN 2011 (China) [29]	Rat/SD (M, 220–250 g)	MCAO/R	4/4	2 h	1 h after MACO	distilled water	Sinomenine, 30 mg/kg, qd, i.p., 7 d	Longa
Yang S 2019 (China) [30]	Rat/SD (M, 290–310 g)	MCAO/R	6/6	1.5 h	24 h after I/R	NI	Baicalein, 200 mg/kg, qd, i.g., 7 d	Longa, mNSS
Tang H 2021 (China) [31]	Rat/SD (M, 200–250 g)	MCAO/R	10/10	1.5 h	2 h after MCAO	150 ul saline and 20% DMSO	Paeoniflorin, 10 mg/kg, bid, i.p., 14 d	mNSS
Shi YH 2021 (China) [32]	Rat/SD (M, 250–280 g)	MCAO/R	12/12	2 h	3 d before MCAO	NS	Astragaloside IV, 20 mg/kg, qd, i.p., 7 d	mNSS
Li L 2021 (China) [33]	Rat/SD (M, 280–300 g)	MCAO/R	10/10	1.5 h	NI	NS	Astragaloside IV, 40 mg/kg, qd, i.p., 14 d	mNSS
Wang N 2014 (China) [34]	Rat/SD (M, 250–270 g)	MCAO/R	10/10	2 h	1 h after MCAO	NI	Puerarin, 23.59 mg/kg,/, i.g., 7 d	mNSS, IV
Wu M 2014 (China) [35]	Rat/Wistar (M, 280–320 g)	MCAO/R	18/18	2 h	24 h after MCAO	NS	Puerarin, 100 mg/kg, qd, i.p., 14 d	mNSS
Wu S 2021 (China) [36]	Rat/SD (M, 250–280 g)	MCAO/R	6/6	1.5 h	0.5 h before MCAO	NI	Curcumin, 300 mg/kg,/, i.p., 7 d	mNSS
Wang Y 2019 (China) [37]	Mice/C57BL/6 J (M, 26–28 g)	MCAO/R	5/5	0.5 h	NI	PBS	Curcumin, 25 mg/kg,/, i.v., 3 d	mNSS
Cui Q 2021 (China) [38]	Rat/SD (M, 230–260 g)	MCAO/R	6/6	2 h	NI	NS	Hydroxysafflor yellow A, 10 mg/kg, qd, i.v., 3 d	mNSS
Yan M 2023 (China) [39]	Rat/SD (M, 250–280 g)	MCAO/R	6/6	2 h	6 h after I/R	PBS	Salvianolic acid, 20 mg/kg, qd, i.g., 14 d	mNSS

Table 1 (continued)

Study	Species (sex, weight)	Model	N = experimental/ control group	Ischemia duration	Time of administration	Control group	Experimental group (drug/daily dosage/ frequency, approach, duration)	Outcomes
Yao RQ 2012 (China) [40]	Rat/SD (M, 250–270 g)	MCAO/R	12/12	1.5 h	3 h after MCAO	distilled water	Quercetin, 20 mg/kg, qd, i.g., 28 d	mNSS
Gao XQ 2010 (China) [41]	Rat/Wistar (M, 250–300 g)	MCAO/R	4/4	2 h	0 h after I/R	isotonic saline	Ginsenoside, 40 mg/kg,/, i.p., 10 d	mNSS
Zhu J 2012 (China) [42]	Rat/SD (M, 220–250 g)	MCAO/R	12/12	2 h	7 d before MCAO	NS	Ginsenoside, 12.5 mg/kg, qd,/, 3 d	mNSS
Yang S 2016 (China) [43]	Rat/SD (M, 250–290 g)	MCAO/R	6/6	2 h	1 h before MCAO	NS	Sinomenine, 90 mg/kg,/, i.v., 1 d	mNSS, BWC
Li WH 2020 (China) [6]	Rat/SD (M, 240–260 g)	MCAO/R	3/3	1 h	NI	NS	Baicalein, 100 mg/kg,/, i.g., 7 d	BWC, IV
Zheng XF 2023 (China) [44]	Mice/CD1 (M, 25–30 g)	MCAO/R	10/10	1 h	0 h after MCAO	NS	Salvianolic acid, 30 mg/kg,/, i.p., 3 d	BWC
Zheng YQ 2018 (China) [45]	Rat/M/SD 220–230 g	MCAO/R	12/12	1.5 h	0.5 h before MACO	NS	Bilobalide, 10 mg/kg, qd, d.a., 7 d	IV

Abbreviations: *BCCAO* The bilateral common carotid arteries occlusion, *BWC* Brain water content, *CD1*, CD1 mice, *C57BL/6 J* C57BL/6 J mice, *d* day, *h* Hour, *i.g.* Intragastric gavage, *i.p.* Intraperitoneal, *i.v.*, Intravenous injection, *I/R* Ischemia/reperfusion, *Longa* Zea-Longa neurological deficit scores, *MCAO* Middle cerebral artery occlusion, *M* Male, *mNSS* The modified neurological severity scores, *NS* Normal saline *PBS* Phosphate-buffered saline, *DMSO* Dimethyl sulfoxide, *SD* Sprague–Dawley, *d.a.*, Duodenal administration, *NI* No information

three studies, curcumin in three studies, astragaloside IV in two studies, quercetin in two studies, sinomenine in two studies, baicalein in two studies, puerarin in two studies, scutellarin in one study, paeoniflorin in one study, hydroxysafflor yellow A in one study, and bilobalide in one study. The interventions in the control group were placebo (normal saline (NS), carrier, phosphate buffered saline (PBS) and distilled water).

Risk of bias assessment results

Of 26 studies included, no study provided specific details of randomization or concealed grouping. Overall, the baseline characteristics of age, sex, and body weight of animals were generally similar across all studies, and all animals were included in the final analysis. In twenty-two studies [6, 21–33, 36, 38–40, 42–45], animals were randomized to animal rooms. Because the information from the included studies was limited, only one [23] of all studies was blinded to the animal keeper and/or investigator, 17 [22–24, 26–28, 30, 32–35, 37, 39, 41, 42, 44, 45] were blinded to the measurement investigator, but it could not be judged whether animals were randomly selected for measurement, and incomplete data reporting was present in four studies [6, 24, 27, 38]. Therefore, the risk of performance bias in the study quality assessment was high. The risk of bias assessment for the included studies is shown in Fig. 2, Table S2.

MA results

mNSS score

Table S3 presents the results of pairwise meta-analysis for direct comparisons of mNSS. Compared with the control group, puerarin (SMD = 2.54, 95% CI [1.82, 3.26], $P < 0.05$), paeoniflorin (SMD = 3.32, 95% CI [1.92, 4.71], $P < 0.05$), hydroxysafflor yellow A (SMD = 2.07, 95% CI [0.62, 3.52], $P < 0.05$), sinomenine (SMD = 1.43, 95% CI [0.14, 2.73], $P < 0.05$), and salvianolic acid (SMD = 3.04, 95% CI [1.29, 4.78], $P < 0.05$) significantly reduced mNSS scores.

Longa score

Table S4 presents the results of pairwise meta-analysis for direct comparisons of Longa scores. Compared with the control group, ginsenoside (SMD = 1.44, 95% CI [0.08, 2.80], $P < 0.05$), scutellarin (SMD = 3.63, 95% CI [2.29, 4.96], $P < 0.05$), and baicalein (SMD = −3.25, 95% CI [−5.07, −1.43], $P < 0.05$) significantly reduced Longa scores.

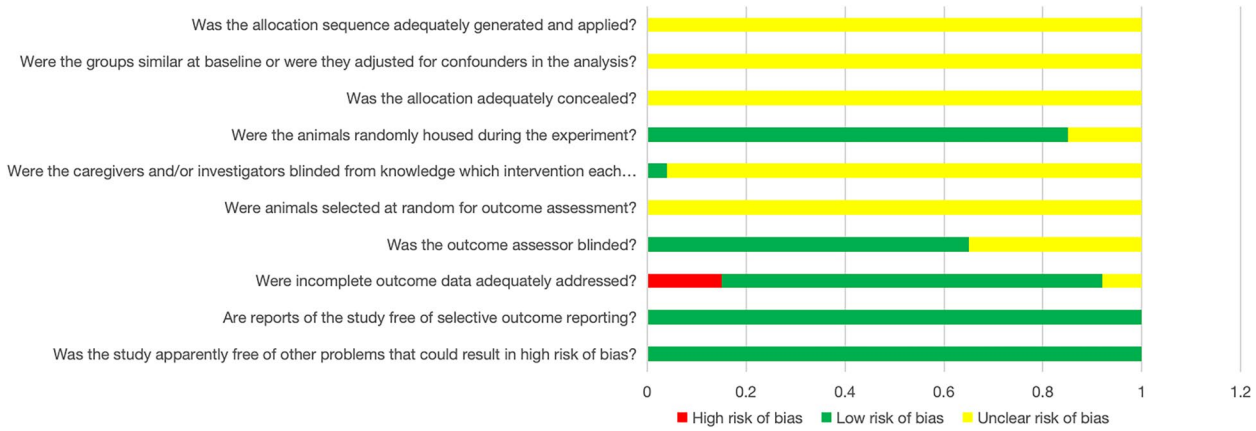

Fig. 2 Results of risk of bias assessment

Brain water content

Compared to the control, salvianolic acid treatment (SMD = 4.21, 95% CI [2.04, 6.37], $P < 0.05$) significantly reduced brain water content (Table S5).

Infarct volume

Compared to the control, bilobalide (SMD = −5.32, 95% CI [−7.08, −3.55], $P < 0.05$), puerarin (SMD = 1.96, 95% CI [0.87, 3.04], $P < 0.05$), and baicalein (SMD = −3.86, 95% CI [−6.97, −0.74], $P < 0.05$) significantly reduced brain infarct volume (Table S6).

NMA results

mNSS score

(1) Association between interventions.

A total of 14 studies [30–43] involving 246 animals and 10 TCM monomers. The network diagram showed no closed loops among studies; therefore, a consistency model was used for analysis. Among them, the number of studies on ginsenoside, astragaloside IV, puerarin, and curcumin were all two, and the rest were all one (Fig. 3).

(2) Analysis results

NMA showed that overall heterogeneity was small ($I^2 = 36\%$). Paeoniflorin (SMD = −3.18, 95% CI [−4.58, −1.78], $P < 0.05$), puerarin (SMD = −2.46, 95% CI [−3.19, −1.74], $P < 0.05$), hydroxysafflor yellow A (SMD = −1.91, 95% CI [−3.37, −0.45], $P < 0.05$), salvianolic acid (SMD = −2.80, 95% CI [−4.56, −1.04], $P < 0.05$), and sinomenine (SMD = −1.32, 95% CI [−2.62, −0.22], $P < 0.05$) were significantly superior to control (Fig. 4). Pairwise comparisons of monomers revealed that paeoniflorin was superior to quercetin (SMD = −2.89, 95% CI [−4.51, −1.28], $P < 0.05$), ginsenoside (SMD = −2.59, 95% CI [−4.16, −1.02], $P < 0.05$), curcumin (SMD = −3.09, 95% CI [−4.73, −1.46], $P < 0.05$), baicalein (SMD = −2.23, 95% CI [−4.09, −0.37], $P < 0.05$), and astragaloside IV (SMD = −2.59, 95% CI [−4.13, −1.06], $P < 0.05$); puerarin was superior to quercetin (SMD = −2.18, 95% CI [−3.26, −1.09], $P < 0.05$), ginsenoside (SMD = −1.88, 95% CI [−2.89, −0.86], $P < 0.05$), curcumin (SMD = −2.38, 95% CI [−3.49, −1.26], $P < 0.05$), baicalein (SMD = −1.51, 95% CI [−2.93, −0.09], $P < 0.05$), and astragaloside IV (SMD = −1.88, 95% CI [−2.83, −0.92], $P < 0.05$); salvianolic acid was superior to quercetin (SMD = −2.51, 95% CI [−4.45, −0.58], $P < 0.05$), ginsenoside (SMD = −2.22, 95% CI [−4.12, −0.32], $P < 0.05$), curcumin (SMD = −2.72, 95% CI [−4.67, −0.76], $P < 0.05$), and astragaloside IV (SMD = −2.22, 95% CI [−4.08, −0.35], $P < 0.05$); hydroxysafflor yellow A was superior to curcumin (SMD = −1.83, 95% CI [−3.51, −0.14], $P < 0.05$). There were no statistically significant differences between the rest TCM monomers (Table 2). Paeoniflorin was probably the most effective intervention (92.8%) according to SUCRA, followed by salvianolic acid (85.6%), and puerarin (82.1%) (Fig. 5).

Longa score

(1) Association between interventions.

A total of 10 studies [21–30] involving 222 animals and 7 TCM monomers. The network diagram showed no closed loops among studies; therefore, a consistency model was used for analysis. At the same time, the number of studies on ginsenoside was the largest (4 studies), and the rest were all one (Fig. 6).

(2) Analysis results.

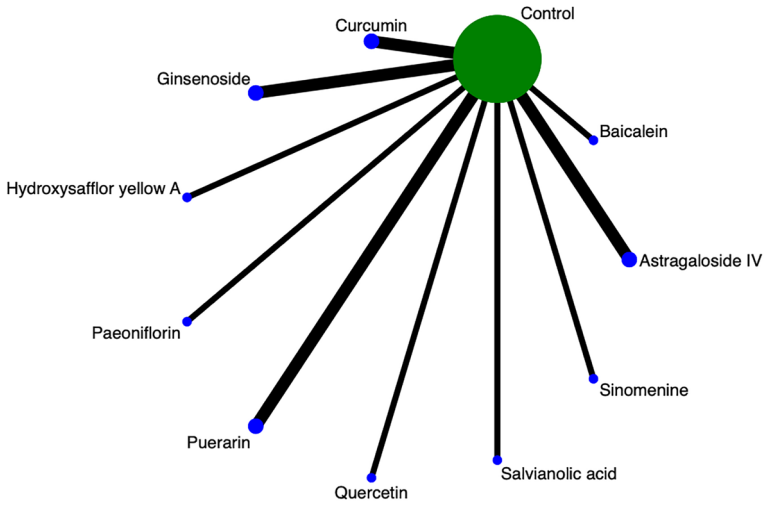

Fig. 3 Evidence network diagram of mNSS

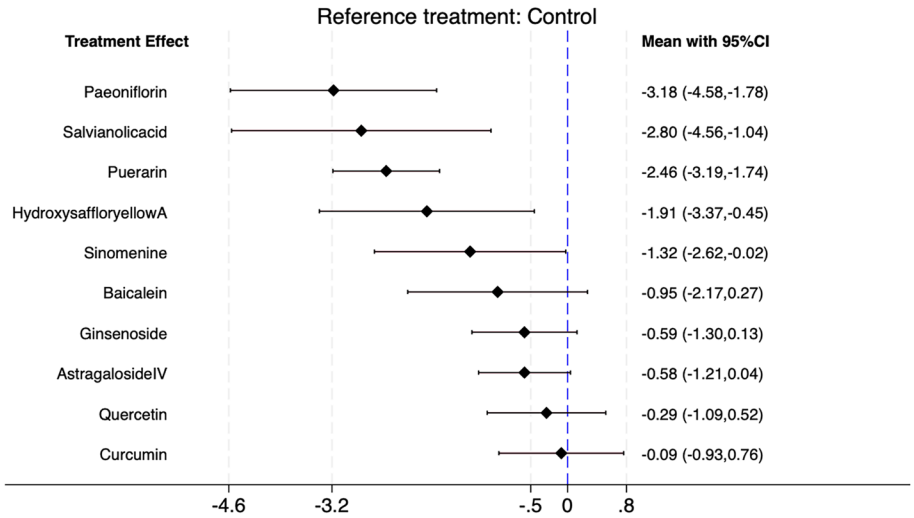

Fig. 4 Forest plot of TCM monomers compared to control group (mNSS)

NMA showed that overall heterogeneity was large (I^2 = 88%). Scutellarin (SMD = −3.49, 95% CI [−6.50, −0.49], P < 0.05) and ginsenoside (SMD = −1.44, 95% CI [−2.86, −0.02], P < 0.05) were significantly superior to control (Fig. 7). There were no statistically significant differences between the TCM monomers (Table 3). The SUCRA rankings for the different interventions (Fig. 8) showed that scutellarin was most effective in lowering Longa score (87.6%), followed by baicalein (81.1%), and ginsenoside (58.6%).

Brain water content

(1) Association between interventions.

A total of 3 studies [6, 43, 44] involving 38 animals and 3 TCM monomers. The network diagram showed no closed loops among studies; therefore, a consistency model was used for analysis. At the same time, the number of studies of all TCM monomers was one (Fig. 9).

(2) Analysis results.

NMA showed that overall heterogeneity was small (I^2 = 33%). Salvianolic acid (SMD = −3.88, 95% CI [−6.07, −1.70], P < 0.05) was significantly superior to control (Fig. 10). Pairwise comparisons of monomers revealed that salvianolic acid was superior to sinomenine (SMD = −2.74, 95% CI [−5.27, −0.22], P < 0.05), and baicalein

Table 2 Network meta-analysis results of mNSS

Sinomenine										
1.48 [−0.71, 3.67]	Salvianolic acid									
1.14 [−0.35, 2.63]	−0.34 [−2.24, 1.57]	Puerarin								
1.85 [−0.06, 3.76]	0.38 [−1.87, 2.63]	0.72 [−0.86, 2.29]	Paeoniflorin							
−1.04 [−2.57, 0.49]	**−2.51 [−4.45, −0.58]**	**−2.18 [−3.26, −1.09]**	**−2.89 [−4.51, −1.28]**	Quercetin						
0.59 [−1.37, 2.54]	−0.89 [−3.18, 1.40]	−0.55 [−2.18, 1.08]	−1.27 [−3.29, 0.76]	1.62 [−0.04, 3.29]	Hydroxysafflor yellow A					
−0.74 [−2.22, 0.74]	**−2.22 [−4.12, −0.32]**	**−1.88 [−2.89, −0.86]**	**−2.59 [−4.16, −1.02]**	0.30 [−0.78, 1.38]	−1.33 [−2.95, 0.30]	Ginsenoside				
−1.24 [−2.79, 0.31]	**−2.72 [−4.67, −0.76]**	**−2.38 [−3.49, −1.26]**	**−3.09 [−4.73, −1.46]**	−0.20 [−1.37, 0.97]	**−1.83 [−3.51, −0.14]**	−0.50 [−1.61, 0.61]	Curcumin			
−0.37 [−2.16, 1.41]	−1.85 [−3.99, 0.29]	**−1.51 [−2.93, −0.09]**	**−2.23 [−4.09, −0.37]**	0.66 [−0.80, 2.13]	−0.96 [−2.86, 0.94]	0.36 [−1.05, 1.78]	0.86 [−0.62, 2.35]	Baicalein		
−0.74 [−2.18, 0.70]	**−2.22 [−4.08, −0.35]**	**−1.88 [−2.83, −0.92]**	**−2.59 [−4.13, −1.06]**	0.30 [−0.72, 1.32]	−1.33 [−2.91, 0.26]	−0.00 [−0.95, 0.95]	0.50 [−0.55, 1.55]	−0.37 [−1.74, 1.01]	Astragaloside IV	
−1.32 [−2.62, −0.02]	**−2.80 [−4.56, −1.04]**	**−2.46 [−3.19, −1.74]**	**−3.18 [−4.58, −1.78]**	−0.29 [−1.09, 0.52]	**−1.91 [−3.37, −0.45]**	−0.59 [−1.30, 0.13]	−0.09 [−0.93, 0.76]	−0.95 [−2.17, 0.27]	−0.58 [−1.21, 0.04]	Control

Note. The significant findings were displayed in bold

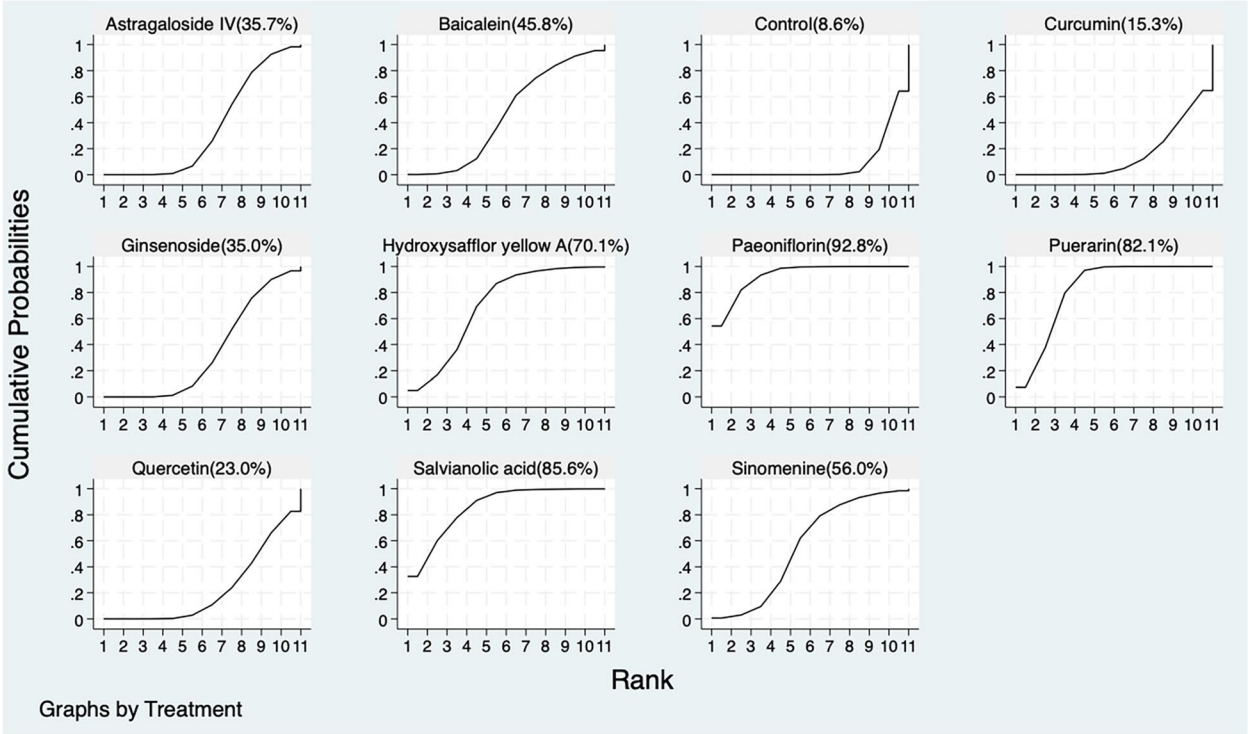

Fig. 5 SUCRA probability ranking of mNSS scores

(SMD = −2.89, 95% CI [−5.75, −0.04], $P < 0.05$). There were no statistically significant differences between the rest TCM monomers (Table 4). According to SUCRA ranking, salvianolic acid was probably the most effective intervention (98.2%), followed by sinomenine (50.7%), baicalein (44.6%) (Fig. 11).

Infarct volume

(1) Association between interventions.

A total of 3 studies [6, 34, 45] involving 50 animals and 3 TCM monomers.The evidence network showed no closed loops among studies; therefore, a consistency model was used for analysis, and the number of studies for all TCM monomers was one. (Fig. 12).

(2) Analysis results.

NMA showed that overall heterogeneity was small ($I^2 = 33\%$). Bilobalide (SMD = − 5.14, 95% CI [− 6.91, −3.36], $P < 0.05$), and puerarin (SMD = −1.88, 95% CI [− 2.96, −0.79], $P < 0.05$) were significantly superior to control (Fig. 13). Pairwise comparisons of monomers revealed that bilobalide was superior to puerarin (SMD = −3.26, 95% CI [−5.34, −1.18], $P < 0.05$). There were no statistically significant differences between the rest TCM monomers (Table 5). According to the SUCRA ranking, bilobalide may be the most effective in reducing infarct volume (95.5%), followed by baicalein (61.5%), and puerarin (41.8%) (Fig. 14).

Meta-regression analysis

As the TCM monomers included in the study had different doses and duration of treatment, we conducted a meta-regression analysis to investigate whether dose and duration of treatment were sources of heterogeneity. Among the mNSS outcome indicators, treatment duration of paeoniflorin (SMD = −3.71, 95% CI [−5.21, −2.22]), puerarin (SMD = −2.78, 95% CI [−3.56, −1.99]), quercetin (SMD = −2.48, 95% CI [−4.74, −0.24]), astragaloside IV (SMD = −0.71, 95% CI [−1.35, −0.08]), and salvianolic acid (SMD = −3.34, 95% CI [−5.16, −1.51]) was significantly associated with heterogeneity, while treatment dose of paeoniflorin (SMD = −2.94, 95% CI [−4.37, −1.51]), salvianolic acid (SMD = −2.60, 95% CI [−4.38, −0.82]), baicalein (SMD = −1.43, 95% CI [−2.81, −0.05]), sinomenine (SMD = −1.39, 95% CI [−2.71, −0.09]), hydroxysafflor yellow A (SMD = −1.68, 95% CI [−3.16, −0.19]), and puerarin (SMD = −2.77, 95% CI [−3.60, −1.94]) was significantly associated with heterogeneity. No statistically significant differences were observed from the meta-regression concerning other outcome

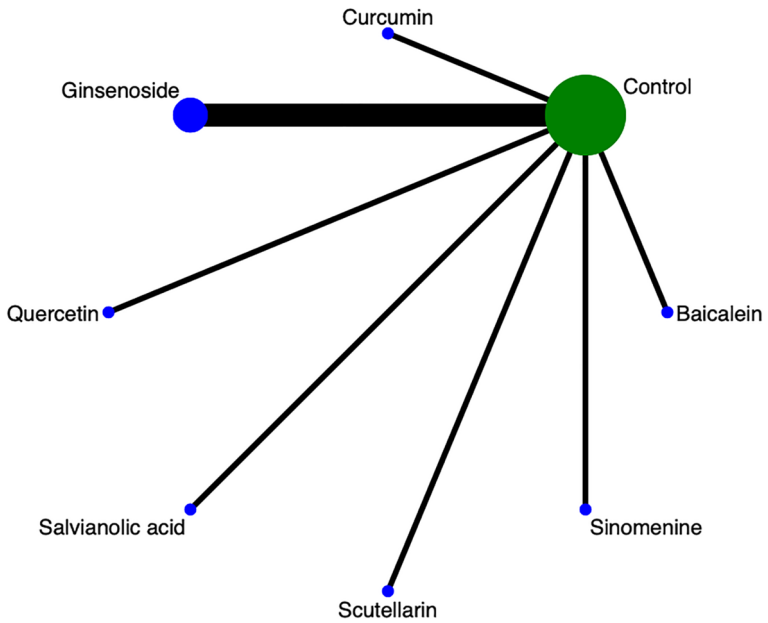

Fig. 6 Evidence network diagram of Longa

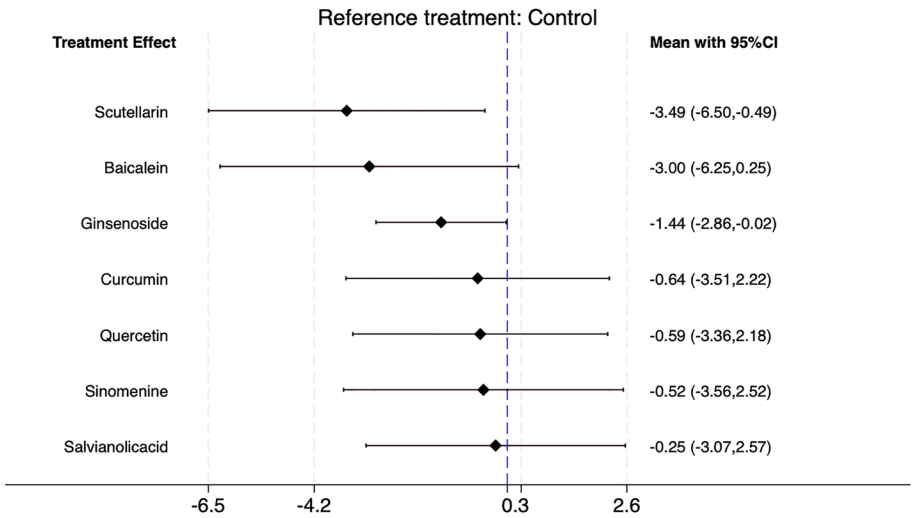

Fig. 7 Forest plot of TCM monomers compared to control group (Longa)

indicators (Table 6), suggesting that these factors might indeed introduce variability among mNSS studies.

Publication bias tests

The funnel plot and Egger's test were used to evaluate potential publication bias. The funnel plots were roughly symmetric (Fig. 15a-b), and Egger's tests yielded *P*-values exceeding 0.05 for both mNSS ($P = 0.131$) and Longa ($P = 0.979$), indicating no presence of publication bias (Fig. 16a-b).

Discussion

In recent years, TCM monomers, as a potential therapeutic drug, have gained much attention in the field of neurological diseases, with significant progress in the animal studies of CIRI. Therefore, it is essential to fully explore the therapeutic potential and optimal therapeutic strategy of different TCM monomers for CIRI in animal studies to provide some guiding information for preclinical experiments and clinical trials. On this basis, we comprehensively evaluated the therapeutic effect of TCM

Table 3 Network meta-analysis results of Longa

Sinomenine							
2.97 [−1.30, 7.25]	Scutellarin						
−0.27 [−4.41, 3.88]	−3.24 [−7.36, 0.88]	Salvianolic acid					
0.07 [−4.05, 4.18]	−2.90 [−6.99, 1.18]	0.33 [−3.62, 4.29]	Quercetin				
0.92 [−2.44, 4.27]	−2.05 [−5.37, 1.27]	1.19 [−1.97, 4.34]	0.85 [−2.26, 3.96]	Ginsenoside			
0.12 [−4.05, 4.30]	−2.85 [−7.00, 1.30]	0.39 [−3.63, 4.41]	0.06 [−3.93, 4.04]	−0.80 [−3.99, 2.40]	Curcumin		
2.48 [−1.97, 6.93]	−0.49 [−4.91, 3.93]	2.75 [−1.55, 7.05]	2.41 [−1.86, 6.68]	1.56 [−1.99, 5.10]	2.36 [−1.97, 6.69]	Baicalein	
−0.52 [−3.56, 2.52]	**−3.49 [−6.50, −0.49]**	−0.25 [−3.07, 2.57]	−0.59 [−3.36, 2.18]	**−1.44 [−2.86, −0.02]**	−0.64 [−3.51, 2.22]	−3.00 [−6.25, 0.25]	Control

Note. The significant findings were displayed in bold

monomers in animal in vivo studies through systematic reviews, MA and NMA, and compared the treatment effect difference between different interventions.

First, we explored the efficacy of TCM monomers on CIRI using MA across different outcome measures. Compared with the control group, 1) in the mNSS outcome, puerarin, paeoniflorin, hydroxysafflor yellow A, sinomenine, and salvianolic acid had significant effects; 2) ginsenoside, scutellarin, and baicalein significantly reduced Longa scores; 3) in terms of lowering cerebral water content, salvianolic acid treatment had a significant effect; and 4) whereas in the infarct volume outcome, bilobalide and puerarin were found to produce a significant effect.

Subsequently, we conducted an NMA, and the results indicated that, regarding mNSS scores, paeoniflorin might be the most effective intervention according to the ranking probability diagram. At present, the primary neuroprotective effects and mechanisms of paeoniflorin are anti-oxidative stress and inhibition of neuroinflammation [46]. It was previously demonstrated that paeoniflorin reduced the degree of lipid peroxidation by increasing SOD levels and decreasing MDA levels in cortical areas in CIRI in rats [47] and secondly, it also has been found to inhibit NF-κB expression in reperfusion injury rats with anti-inflammatory effects [48]. However, due to the limited number of current studies on paeoniflorin and the inclusion of only one relevant study in this analysis, the credibility of evidence may be affected by the small sample size, and the conclusion needs further research. Secondly, there was no significant difference between different TCM monomers in reducing Longa score, and the ranking probability diagram suggested that scutellarin was the most effective intervention. In the rat CIRI

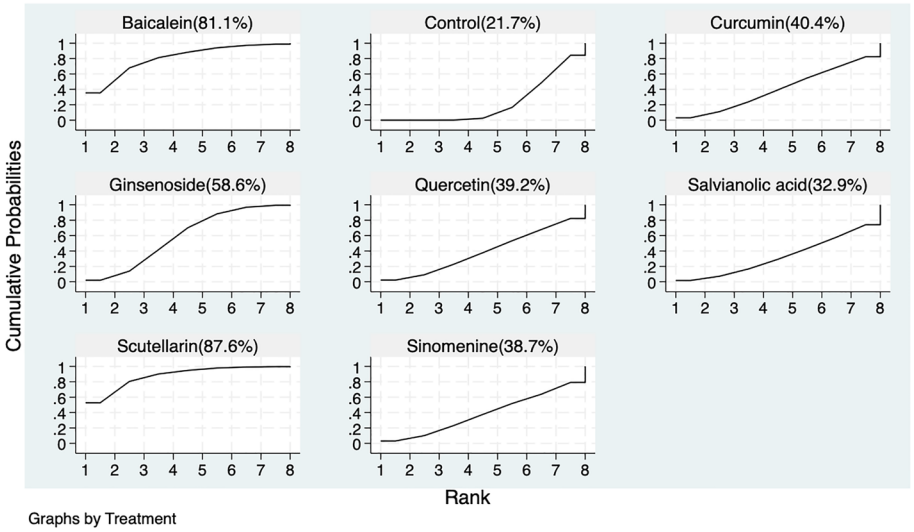

Fig. 8 SUCRA probability ranking of Longa scores

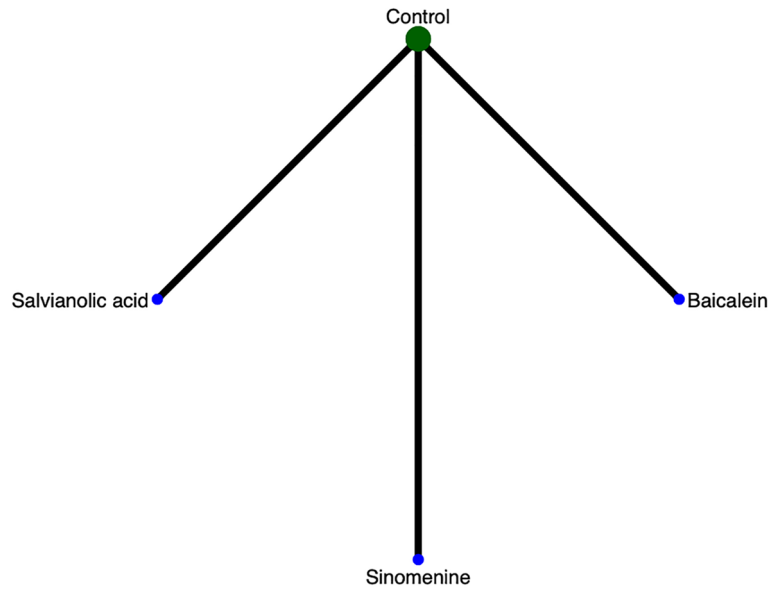

Fig. 9 Evidence network diagram of BWC

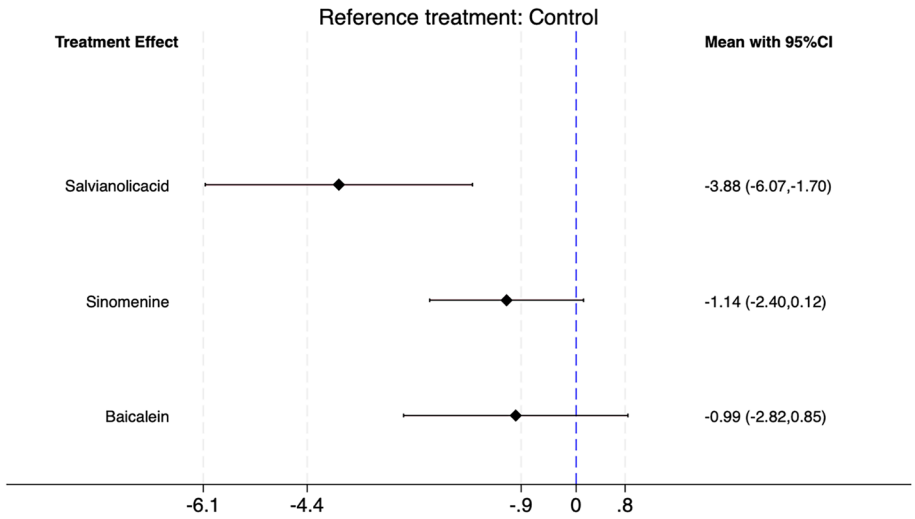

Fig. 10 Forest plot of TCM monomers compared to control group (BWC)

Table 4 Network meta-analysis results of BWC

Salvianolic acid			
−2.74 [−5.27, −0.22]	Sinomenine		
−2.89 [−5.75, −0.04]	−0.15 [−2.37, 2.07]	Baicalein	
−3.88 [−6.07, −1.70]	−1.14 [−2.40, 0.12]	−0.99 [−2.82, 0.85]	Control

Note. The significant findings were displayed in bold

model, scutellarin mediates translocation of Nrf2 to the nucleus through the PI3 K/Akt pathway, activates heme oxygenase-1 (HO-1) expression, increases SOD activity and inhibits ROS production in vitro, reduces cellular oxidative stress. Additionally, it reduces NF-κB activity and levels of pro-inflammatory factors, showing antioxidant, anti-inflammatory, and neuroprotective effects [49]. Scutellarin has been made into herbal preparations for clinical use, and a systematic review and meta-analysis of randomized controlled trials reported that scutellarin injection can significantly improve neurological deficits in patients with cerebral infarction [50],

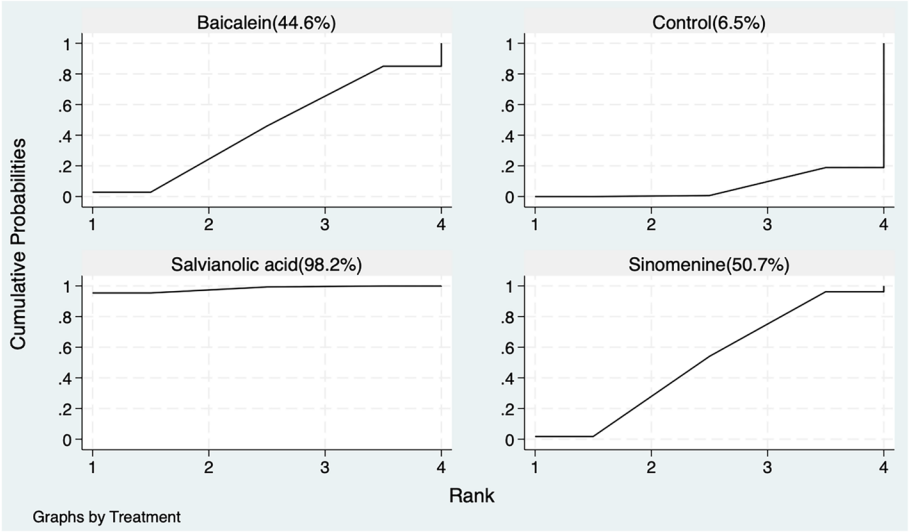

Fig. 11 SUCRA probability ranking of BWC

which seems to further validate our results. In terms of reducing BWC, although the number of included studies was small and there were no statistically significant differences between TCM monomers, and the SUCRA plot provided valuable information, suggesting that salvianolic acid treatment may be the most effective. The protective mechanism of salvianolic acid is mainly related to its anti-inflammatory, antioxidant, anti-or pro-apoptotic, anti-or pro-autophagic functions [51]. In the study, it was found that salvianolic acid has been shown to upregulate the Bcl-2 expression, inhibit the activation of caspase 3, inhibit apoptosis by regulating PKA/CREB/c-Fos signaling pathway, and reduce brain edema to play a neuroprotective role in CIRI [52]. Finally, for IV, based on information provided by the SUCRA ranking, bilobalide might be the most effective intervention. Bilobalide have been clinically shown to act as platelet-activating factor (PAF) antagonists, inhibiting platelet aggregation and promoting increased blood flow, thereby reducing IV [53]. In addition,

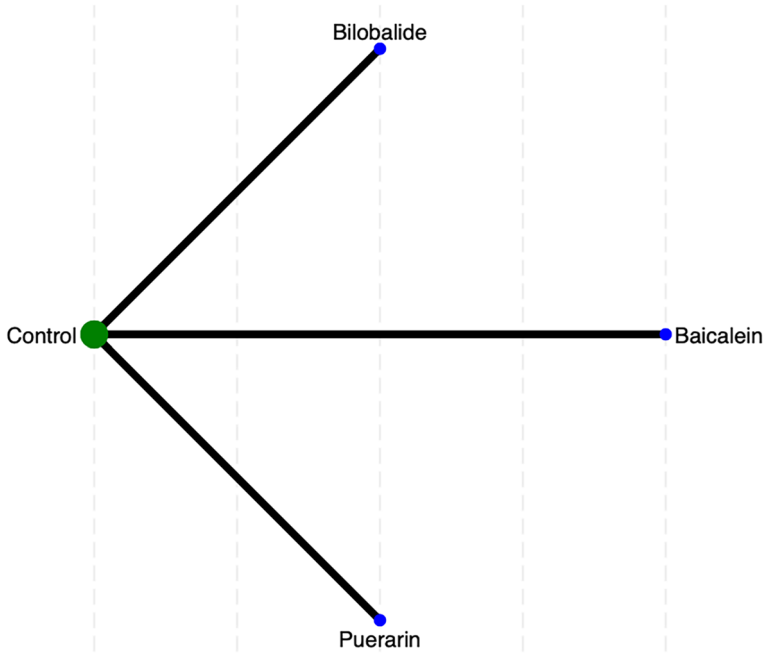

Fig. 12 Evidence network Diagram of IV

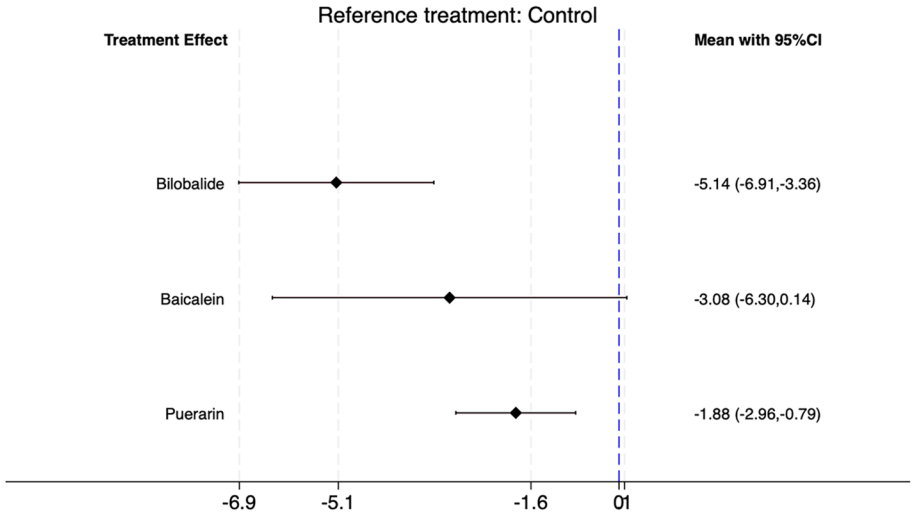

Fig. 13 Forest plot of TCM monomers compared to control group (IV)

pretreatment with bilobalide has been found to significantly reduce the concentrations of MDA, NO, TNF-α, and IL-1β, increase SOD activity, down-regulate the activation of JNK1/2 and p38 MAPK, and produce anti-inflammatory, antioxidant, and anti-apoptotic effects and significantly reduce IV [54]. Given the small sample size in this study and prior studies, the results still need to be further validated in a larger sample of study designs.

Ischemia/reperfusion (I/R) injury is a pathological process in which the damage is exacerbated by the reperfusion of an ischemic organ or tissue. However, both ischemia and reperfusion occur in a series of cellular, biochemical, and metabolic reactions that eventually lead to irreversible damage in brain tissue [55]. Previous preclinical evidence has shown that TCM monomers are effective in treating CIRI due to their various protective effects such as anti-oxidative stress, inhibition of inflammatory response, regulation of programmed cell death, inhibition of glutamate excitotoxicity and protection of blood–brain barrier (BBB) (Table 7) [6, 13, 21, 24, 25, 28, 30, 33, 34, 36, 39, 40, 42, 43, 56–64]. Furthermore, new mechanisms underlying TCM monomers have been discovered, expanding beyond the previously recognized pathways such as anti-inflammation via the NF-κB pathway and antioxidation through the Nrf2 pathway to include emerging pathways such as inhibits pyroptosis and ferroptosis [65]. Nonetheless, most of the studies on TCM monomers in the field of CIRI is still at the cellular or rodent stage, and the number of studies on some TCM monomers is relatively small, so it is difficult to clarify the optimal treatment of TCM monomers for CIRI from the drug target or mechanism level. Even though, our research can still provide some guidance for future animal and clinical studies. Nevertheless, further studies are needed to perform direct comparison between TCM monomers in large sample size animal models or human clinical trials. For instance, in the outcome of cerebral infarction, the analysis suggested that bilobalide may be the most effective intervention. Bilobalide have already been widely applied in the clinical treatment of ischemic stroke. Therefore, we could design randomized controlled trials using commonly prescribed clinical doses with varying courses of treatment, such as 24 h, 48 h, 72 h, 7 days, and 14 days, to determine the optimal treatment duration. Additionally, TCM monomers such as salvianolic acid, scutellarin, panax notoginseng saponins, and tetramethyl pyrazine have demonstrated significant therapeutic effects in clinical practice. we could conduct high-quality clinical studies using multicenter, large-sample, randomized, double-blind design to obtain direct comparative evidence, thereby determining the best approaches for TCM monomer-based treatments for ischemic stroke.

Additionally, to explore potential sources of heterogeneity, we conducted a meta-regression analysis on dose and course of treatment. Within the mNSS outcomes,

Table 5 Network meta-analysis results of IV

Bilobalide			
−3.26 [−5.34, −1.18]	Puerarin		
−2.06 [−5.74, 1.62]	1.20 [−2.20, 4.60]	Baicalein	
−5.14 [−6.91, −3.36]	**−1.88 [−2.96, −0.79]**	−3.08 [−6.30, 0.14]	Control

Note. The significant findings were displayed in bold

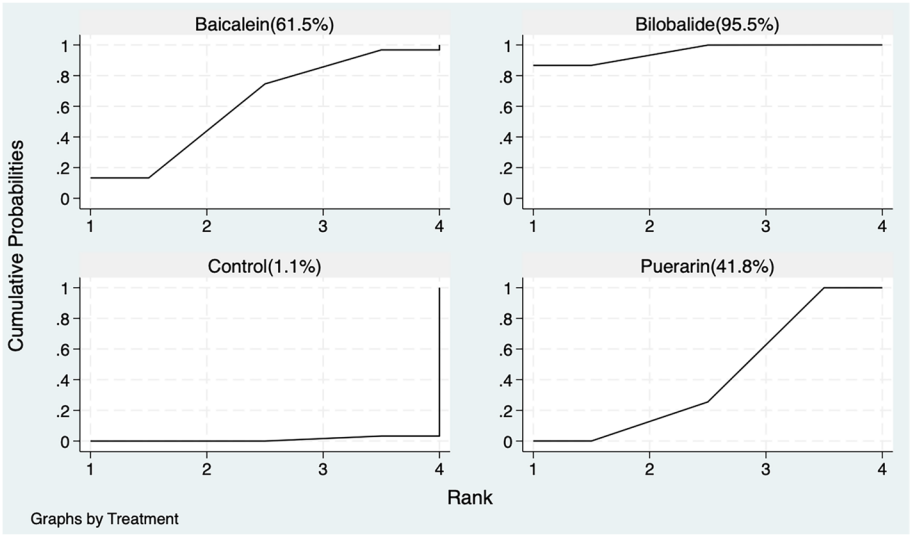

Fig. 14 SUCRA probability ranking of IV

Table 6 Results of meta-regression analysis of dose and course of treatment

Outcomes	TCM monomers	Regression coefficients SMD [95% CI]	
		Dose	Duration
mNSS	Astragaloside IV	−0.42 [−1.08, 0.23]	**−0.71 [−1.35, −0.08]**
	Baicalein	**−1.43 [−2.81, −0.05]**	−0.67 [−1.92, 0.58]
	Curcumin	−0.49 [−1.49, 0.51]	0.41 [−0.56, 1.39]
	Ginsenoside	−0.38 [−1.14, 0.38]	−0.02 [−0.91, 0.87]
	Hydroxysafflor yellow A	**−1.68 [−3.16, −0.19]**	−1.15 [−2.77, 0.48]
	Paeoniflorin	**−2.94 [−4.37, −1.51]**	**−3.71 [−5.21, −2.22]**
	Puerarin	**−2.77 [−3.60, −1.94]**	**−2.78 [−3.56, −1.99]**
	Quercetin	−0.09 [−0.93, 0.76]	**−2.48 [−4.74, −0.24]**
	Salvianolic Acid	**−2.60 [−4.38, −0.82]**	**−3.34 [−5.16, −1.51]**
	Sinomenine	**−1.39 [−2.71, −0.09]**	−0.33 [−1.93, 1.29]
Longa	Baicalein	−3.83 [−12.00, 4.07]	−3.00 [−7.75, 1.74]
	Curcumin	−2.16 [−15.58, 10.03]	−0.55 [−5.21, 4.09]
	Ginsenoside	−1.17 [−4.16, 1.80]	−1.55 [−4.07, 0.99]
	Quercetin	−0.43 [−4.83, 3.72]	−0.48 [−5.11, 4.10]
	Salvianolic Acid	0.15 [−5.18, 5.31]	−0.17 [−4.78, 4.38]
	Scutellarin	−3.09 [−8.55, 2.13]	−3.33 [−8.35, 1.65]
	Sinomenine	−0.23 [−5.14, 4.51]	−0.55 [−5.13, 4.08]
BWC	Baicalein	−1,17 [−12.61, 8.46]	−1.65 [−17.76, 8.78]
	Salvianolic Acid	−3.56 [−19.08, 15.14]	−3.75 [−6.64, 0.11]
	Sinomenine	−1.25 [−8.44, 4.77]	−0.61 [−8.92, 12.29]
IV	Baicalein	−2.68 [−29.69, 29.82]	-
	Bilobalide	−5.39 [−25.64, 11.31]	-
	Puerarin	−2.02 [−14.28, 8.10]	-

Note. The significant findings were displayed in bold. Regarding IV, the course of treatment was the same in all studies, and as a result, meta-regression was not performed

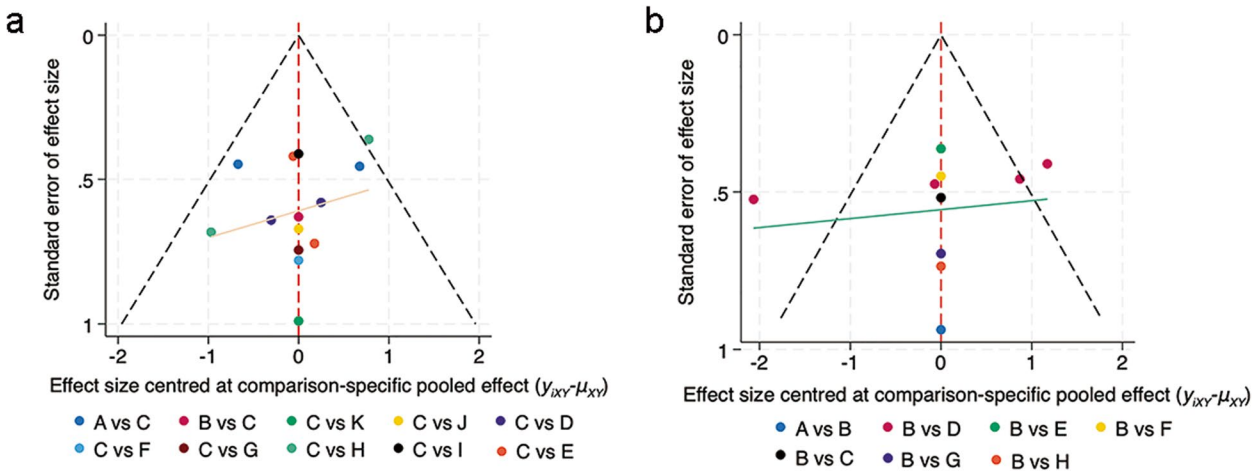

Fig. 15 **a**: Funnel plot of mNSS (**A**: Astragaloside IV; **B**: Baicalein; **C**: Control; **D**: Curcumin; **E**: Ginsenoside; **F**: Hydroxysafflor yellow A; **G**: Paeoniflorin; **H**: Puerarin; **I**: Quercetin; **J**: Sinomenine; **K**: Salvianolic acid). **b**: Funnel plot of Longa (**A**: Baicalein; **B**: Control; **C**: Curcumin; **D**: Ginsenoside; **E**: Quercetin; **F**: Salvianolic acid; **G**: Scutellarin; **H**: Sinomenine)

certain statistically significant findings related to TCM monomers were observed regarding dose and duration of treatment. However, network meta-analysis revealed small overall heterogeneity in mNSS. Furthermore, only a handful of TCM monomers showed statistically significant differences in meta-regression outcomes. Consequently, while treatment dose and duration appear to be potential sources of heterogeneity, their definitive role cannot be conclusively established based on the current results. Unfortunately, due to the limited number of included studies, we were unable to perform further subgroup analyses. Nevertheless, we speculate that the heterogeneity observed across studies in our analysis may partly be attributed to slight differences in behavioral scoring criteria among studies. Furthermore, the scoring results may be influenced by subjective biases of the evaluators, as substantial differences could exist among researchers applying the same scoring system. Additionally, different administration routes may also be a potential source of heterogeneity. Second, the assessment with SYRCLE's risk of bias tool indicated that the methodological quality of the included studies was low, particularly with regard to selection bias, performance bias and measurement bias, and that these studies were unclear on the principles of randomization and blinding, mainly in terms of experimental allocation, implementation of interventions, and assessment of outcome measures. None of the studies described a specific method of random assignment in allocation sequence, and only one study was blinded for performance bias[23]. Although this is common in meta-analyses of preclinical studies, it still highlights the need for randomization and blinding. Therefore, future research should standardize core design procedures to provide higher-quality preclinical evidence.

Overall, the effects currently observed in animal models are promising, but there are still many challenges that need to be addressed before TCM monomers can be applied to clinical trials. First, the meta-regression results indicated statistical significance exclusively for specific TCM monomers in terms of mNSS scores. However, some studies have found that the dose and duration of TCM monomers may be an influencing factor in CIRI [66], and as a next step, more preclinical studies are necessary to determine the optimal dose and duration of treatment in order to maximize the efficacy of the therapy. Additionally, with regard to the clinical translation of some TCM monomers, an appropriate route of drug delivery should be explored given the key role of administration route in the efficacy and safety of drugs [67]. Moreover, the safety and side effects of TCM monomers remain another matter of discussion [68]. Comprehensive preclinical pharmacological and toxicological testing is necessary to reduce the risk of preclinical findings being pushed to the clinical setting. Therefore, it is necessary to further explore the efficacy and safety of TCM monomers in CIRI in preclinical studies to provide the guidance for future clinical translational applications.

Strengths and limitations

To our knowledge, this is the first NMA that uses preclinical evidence to indirectly compare the efficacy of different TCM monomers against CIRI. First, using the internationally accepted SYRCLE risk of bias tool, the internal risk of bias in animal studies was rigorously

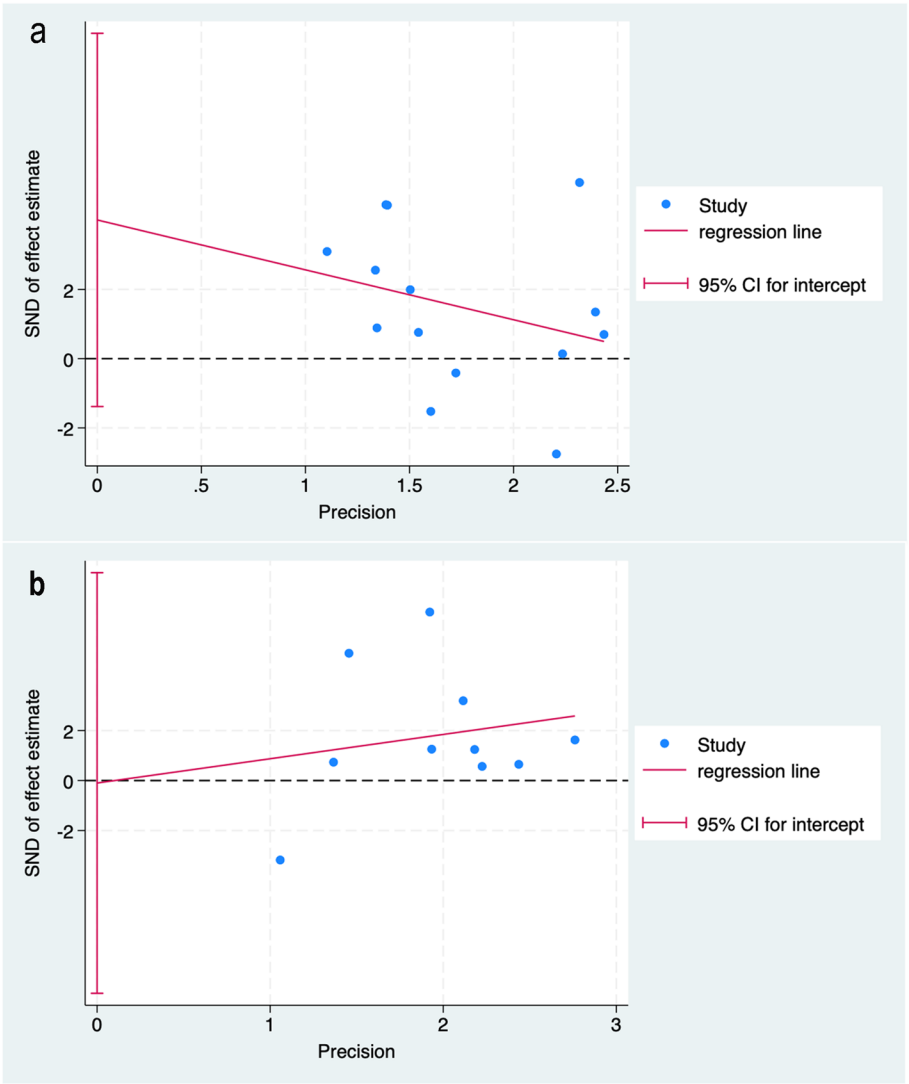

Fig. 16 **a**: Egger's test of mNSS. **b**: Egger's test of Longa

assessed, and suggestions were put forward for future research strategies of TCM monomers in this field. Second, we performed a meta-regression analysis on the duration and dose of different TCM monomers treatments to explore whether these factors influence outcomes, adding to the rigor of our results. Additionally, this study can help improve the accuracy of the estimation of the effect of animal studies and provide an evidence-based guidance for future research.

However, our research also has limitations. First, only studies published in English were included to minimize the heterogeneity of the included studies, which could lead to language bias. Second, due to relatively little studies about some TCM monomers, the inadequate available data might ignore the potential therapeutic effects of these TCM monomers and limit the certainty of the evidence. Third, two different behavioral scores might cause some bias in the results, because the score results were largely limited subjectively by the reviewers. Fourth, the differences between drug doses and duration of treatment between studies may have some potential impact on the results, however, the number of studies included with different doses or duration in the same outcome was small, and the TCM monomers were too different between different subgroups to be analyzed by subgroup. We hope that future studies with larger sample sizes can include these two measures into subgroups to minimize heterogeneity among the

Table 7 Effect and mechanism of TCM monomer on cerebral ischemia–reperfusion injury

TCM monomers	References	Model	Dose	Mechanisms	Effects
Paeoniflorin	Wu W 2020 [47]	MCAO	60, 120, 240 mg/kg	SOD↑,MDA↓	Anti-oxidative stress
Scutellarin	Xie X 2023 [49]	MCAO/R,OGD/R	5, 10, 20 mg/kg	SOD↑,ROS↓,Nrf2↑,HO-1↑,TNF-α↓,IL-1β↓,IL-6↓	Anti-oxidative stress and Anti-inflammatory response
Puerarin	Zhang Q 2023 [13]	MCAO/R,OGD/R	25, 50, 100 mg/kg	AKT/Nrf2↑,SOD↑, GPX↑, ROS↓,MDA↓, CAT↑	Anti-oxidative stress
Paeoniflorin	Tang NY 2010 [48]	MCAO/R	10, 15, 20 mg/kg	TNF-α↓,IL-1β↓	Anti-inflammatory response
Curcumin	Huang L 2017 [56]	MCAO/R	200 mg/kg	TLR4↓,IL-1↓,p-Akt↑,p-mTOR↑,LC3-II/LC3-I↓	Anti-inflammatory response and Inhibit autophagy
Salvianolic acid	Zhang W 2020 [57]	MCAO/R,OGD/R	1, 3, 15 mg/kg	TLR4/NF-κB↓, TNF-α↓,IL-1β↓,IL-6↓, caspase-3↓	Inhibits inflammation and apoptosis
Berberine	Maleki SN 2018 [58]	MCAO/R	40 mg/kg	TNF-α↓,IL-1β↓,IL-6↓, IL-10↑	Anti-inflammatory response
Puerarin	Hongyun H 2017 [59]	MCAO/R	4.2 mg/kg	LC3-II↓, LC3-II/LC3-I↓	Inhibit autophagy
Vitexin	Jiang J 2018 [60]	MCAO/R	2 mg/kg	mTOR↑, Ulk1↓, Beclin1↓,p62↑,LC3II↓	Inhibit autophagy
Astragaloside IV	Xiao L 2021 [61]	MCAO/R,OGD/R	10 mg/kg	Nrf2↓, NLRP4↓, IL-18↓,IL-1β↓, MMP-9↓	Inhibit pyroptosis and maintain BBB
Ginkgolide	Gu JH 2012 [62]	MCAO/R,OGD/R	10, 20,40 mg/kg	TNF-α↓,IL-1β↓,iNOS↓,Bcl-2↑,Bax↓, caspase-3↓	Anti-inflammatory and Anti-apoptosis
Baicalein	Yang S 2019 [30]	MCAO/R	200 mg/kg	TNF-α↓,IL-1β↓,IL-6↓,Bax↓, caspase-3↓,p62↑,LC3-II↓	Anti-inflammatory and Anti-apoptosis and Inhibit autophagy
Hydroxysafflor yellow A	Chen L 2013 [63]	MCAO/R	2,4,8 mg/kg	Bcl-2/Bax↑	Anti-apoptosis
Oxymatrine	Jiao-Yan Y 2021 [64]	MCAO/R,OGD/R	1, 10,100 mg/kg	MMP9↓, AQP4↓	Maintain BBB
Ginsenoside	Yang LX 2016 [21]	MCAO/R	10 mg/kg	NEIL 1↑,NEIL 3↑,caspase-3↓	Anti-apoptosis
Ginsenoside	Zhou Y 2014 [24]	MCAO/R	20 mg/kg	AQP4↓	Maintain BBB
Scutellarin	Wang C 2023 [25]	MCAO/R	12 mg/kg	EAAT 2↑,nNOS↓,CAM↓	decreases glutamate excitotoxicity
Quercetin	Li L 2023 [28]	MCAO/R,OGD/R	50 mg/kg	TNF-α↓,IL-1β↓,IL-6↓,iNOS↓	Anti-inflammatory response
Astragaloside IV	Li L 2021 [33]	MCAO/R	40 mg/kg	TNF-α↓,IL-1β↓,IL-6↓,iNOS↓,VEGF↑,IGF-1↑	Anti-inflammatory and Promote angiogenesis
Puerarin	Wang N 2014 [45]	MCAO/R,OGD/R	23.59 mg/kg	BDNF↑,caspase-3↓,Bcl-2/Bax↑	Anti-apoptosis
Curcumin	Wu S 2021 [36]	MCAO/R	300 mg/kg	ZO-1↑,pNF-κBp65↓,MMP-9↓	Anti-inflammatory and Maintain BBB
Salvianolic acid	Yan M 2023 [39]	MCAO/R	20 mg/kg	TNF-α↓,IL-1β↓,IL-6↓,SOD↑,MDA↓	Anti-oxidative stress and Anti-inflammatory response
Quercetin	Yao RQ 2012 [40]	MCAO/R	10, 20 mg/kg	BDNF↑,p—Akt↑,caspase-3↓	Anti-apoptosis
Ginsenoside	Zhu J 2012 [42]	MCAO/R	12.5 mg/kg	TNF-α↓,IL-6↓	Anti-inflammatory response
Sinomenine	Yang S 2016 [43]	MCAO/R	90 mg/kg	IL-1β↓,IL-6↓	Anti-inflammatory response
Baicalein	Li WH 2020 [6]	MCAO/R,OGD/R	100 mg/kg	cytochrome C↓,MCP-1↑,TIMP-1↑	Anti-oxidative stress and Anti-apoptosis

Abbreviations: *MCAO* Middle cerebral artery occlusion, *OGD* Oxygen–glucose deprivation, *R* reperfusion, *ROS* Reactive oxygen species, *iNOS* Inducible nitric oxide synthase, *MDA* malondialdehyde, *MMP-9* Matrix metallopeptidase 9, *HO-1* Heme Oxygenase-1, *SOD* Superoxide dismutase, *ZO-1* Zonula occludens-1, *CAT* Catalase, *IL-1 β* Interleukin-1 β, *IL-6* Interleukin-6, *IL-10* Interleukin-10, *NF- κB* Nuclear factor kappa B, *AKT* Protein kinase B, *AQP4* Aquaporin4, *BAX* BCL-2, associated X, *BBB* Blood–brain barrier, *BCL-2* B-cell lymphoma-2, *TNF-α* Tumor necrosis factor-α, *GPX* Glutathione peroxidase, *VEGF* Vascular endothelial growth factor, *TIMP-1* Tissue inhibitors of metalloproteinase, *TLR 4* Toll-like receptor 4, *TLR 2* Toll Like Receptor 2, *MCP-1* Monocyte chemoattractant protein-1, *BDNF* Brain-derived neurotrophic factor, *IGF-1* Insulin like growth factor, *Nrf2* Nuclear factor erythroid 2–related factor 2, *mTOR* Mammalian target of rapamycin, *EAAT 2* Excitatory amino acid transporter 2, *NEIL* Endonuclease VIII-like, *CAM* Calmodulin, *LC3* Light chain 3, *p62* Sequestosome 1, *ULK1* UNC51-like kinase-1

included studies and enhance the reliability of findings. In summary, the current results should be viewed with caution, and more rigorous and large-sample animal studies are needed to validate the findings in the future.

Conclusion

In this NMA, it was found that TCM monomers have neuroprotective effects on CIRI, and different TCM monomers exhibited significant differences in efficacy. Notably, paeoniflorin was found to be the most

effective intervention to lower mNSS score, scutellarin might be the most effective to lower Longa score, while salvianolic acid treatment might be the most effective intervention to lower BWC, while bilobalide may be the most effective intervention for reducing IV. In order to obtain more reliable evidence in preclinical studies and safely generalize these findings to clinical trials, more high-quality animal experiments are needed in the future to further validate our findings.

Abbreviations

CIRI	Cerebral ischemia–reperfusion injury
TCM	Traditional Chinese medicine
NMA	Network meta-analysis
MA	Meta-analysis
CI	Confidence interval
SUCRA	Surface under the cumulative ranking curve

Supplementary Information

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Supplementary Material 1. Table S1: Search strategies and results details for different databases

Supplementary Material 2. Table S2: Results of quality assessment for each study using SYRCLE's risk of bias tool

Supplementary Material 3. Table S3: Meta-analysis results of mNSS

Supplementary Material 4. Table S4: Meta-analysis results of Longa

Supplementary Material 5. Table S5: Meta-analysis results of BWC

Supplementary Material 6. Table S6: Meta-analysis results of IV

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Authors' contributions
X. L. and J.Y. N. searched the literatures and performed analysis. X. L. wrote the original draft of the manuscript. H.S. C. designed the study and critically revised the manuscript.

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Data availability
The original contributions presented in the study are included in the article/Supplementary Material. Further inquiries can be directed to the corresponding author.

Declarations

Ethics approval and consent to participate
Not applicable.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

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