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## Review Article

## Overview of Cochrane reviews on Chinese herbal medicine for stroke

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## ABSTRACT

**Background:** Stroke is a major health issue worldwide. Since Chinese herbal medicine is widely used for the treatment of stroke, there is a need to evaluate its efficacy as an alternative treatment option. The aim of this paper is to carry out an overview of Chinese herbal medicine for the treatment of stroke by summarizing and evaluating all existing Cochrane reviews.

**Methods:** The Cochrane Database of Systematic Reviews was searched from its inception date to August 2019 using “stroke” and “herbal medicine” or “traditional medicine” as search terms. For the methodological quality assessment of the Cochrane reviews, the Assessment of Multiple Systematic Reviews (AMSTAR) tool was used.

**Results:** Eight Cochrane reviews that evaluated the efficacy of herbal medicine for the treatment of stroke were included in this overview. There were 71 randomized controlled trials, with 5770 patients in total. The AMSTAR scores of the Cochrane reviews included in this study ranged from 9 to 11 with a mean score of 10. Three reviews met all the 11-item criteria of the AMSTAR. All reviews presented potential efficacy of herbal medicine for stroke treatment in terms of improvement of neurological deficit.

**Conclusion:** This overview reveals the potential efficacy of herbal medicines for the treatment of stroke in terms of neurological deficit improvement. However, due to the high risk of bias in the reviews' studies, an affirmative conclusion for the recommendation of herbal medicine for clinical practice could not be drawn.

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## Background

Stroke is a major health issue and is the second leading cause of death worldwide.<sup>1</sup> A stroke occurs when a blood vessel is obstructed by a clot or ruptures, leading to brain cell damage.<sup>2</sup> According to the heart disease and stroke statistics recently released by the American Heart Association, stroke occurs every 40 s on average in the US.<sup>3</sup> It is also one of the deadly diseases in China and the leading cause of death and disability.<sup>4</sup> Stroke is a

serious health problem because it causes disability and requires long-term care and rehabilitation of the survivors.<sup>5</sup>

According to China's Ministry of Health, one of the reasons for China's struggle with stroke prevention and treatment is the lack of national policy and systematic approach to stroke care.<sup>4</sup> By analyzing systematic reviews on Chinese herbal medicine for stroke, this overview attempts to provide valuable information about the use of Chinese herbal medicine in stroke care by addressing the interventions of Cochrane reviews on Chinese medicines for stroke, summarizing their results and promoting the evidence into practice. Several systematic reviews have assessed different types of Chinese medicines for stroke, but further study is required due to poor methodological quality of the included trials and the limitation of the effects of traditional Chinese medicine in ischemic stroke. In this overview, only Cochrane reviews were considered because Cochrane is internationally known for its high-quality evidence of efficacy and safety.

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Chinese herbal medicine is generally considered to be nontoxic and potentially beneficial to patients. In China's clinical practice, Chinese herbal medicine is widely used for patients with stroke, even though limited high-quality evidence exists to support its efficacy. For this reason, there is a need to evaluate the efficacy of Chinese herbal medicine as an alternative treatment for stroke. Therefore, the aim of this study is to carry out an overview of Chinese herbal medicine for the treatment of stroke by summarizing and evaluating all existing Cochrane reviews.

## Methods

### Search strategy

We searched the Cochrane Database of Systematic Reviews from its inception date to August 2019 for potential reviews using the following search terms: "stroke" and "herbal medicine" or "traditional medicine." The completed search strategy applied is provided in the supplementary table (S1).

### Study collection and selection of reviews

Two authors independently performed the searches and screened for eligible reviews. All the Cochrane reviews that assessed the efficacy of Chinese herbal medicine for the treatment of stroke were identified and included in this overview, excluding those on prevention and those that are research protocols.

Reviews were included if herbal medicinal products of any types were used as intervention for stroke regardless of their comparison groups and outcome. Reviews were excluded if the herbal medicine interventions were not natural products but synthetic derivative products. All disagreements observed were resolved through discussion or by a third author when necessary.

### Data extraction and management

Data extraction was conducted by two authors independently using predefined data extraction forms. All data extracted from the included reviews were checked by a third author for accuracy. The data obtained included the last name of the first author, year of publication, type of stroke, the number of articles included in each review, sample size, type of intervention and control, primary and secondary outcomes, overall risk of bias of each review, and intervention effects. We also extracted a narrative text of the authors' conclusions from each review included in the study. Discrepancies observed were resolved through discussions with a third author until consensus were obtained.

### Methodological quality

Methodological quality assessment was independently conducted by the two authors using the Assessment of Multiple Systematic Reviews (AMSTAR) tool, with a total of 11 items. In AMSTAR a score of 1 was given for each item when it was met and a score of 0 when it was not met. The quality of reviews was categorized into three levels based on the total score: total score of 0–3 for low quality, total score of 4–7 for medium quality, and total score of 8–11 for high quality.<sup>6</sup> We did not assess the quality of the studies in the Cochrane reviews included in this study. Inconsistencies observed were resolved through discussions until consensus were obtained.

### Statistical analysis

Descriptive statistics were used to summarize the characteristics of each Cochrane review included in this study. A summary of

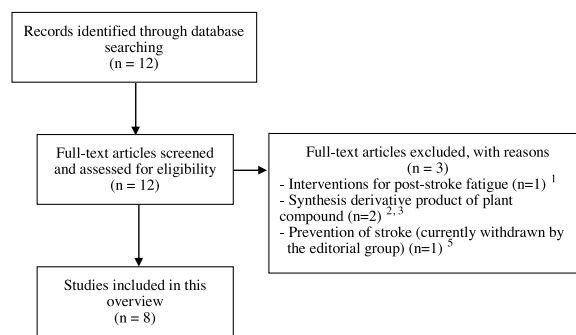


Fig. 1. Flow chart of the review selection process.

the effect estimates for the main outcomes reported in each review included in this study is provided in this overview.

## Results

Eight reviews published in the Cochrane Database of Systematic Reviews were finally included in this overview<sup>7–14</sup>. A flow diagram of the review selection process is provided in Fig. 1.

The reviews included in this study were published between 2005 and 2015 and were up to date. Four reviews<sup>15–18</sup> were excluded according to the pre-defined criteria. In all the reviews, only randomized controlled trials (RCTs) and quasi-RCTs were included. There were 71 RCTs, with 5770 patients in total. The summary of the characteristics of all the included reviews is shown in Table 1.

The herbal interventions studied in the review comprised Ginkgo biloba, Danshen (*Radix salviae miltiorrhiza*), Dengzhanhua (*Erigeron breviscapus*), Sanchi (*Radix notoginseng*), Chuanxiong (*Rhizoma ligustici wallichii*), Tongxinluo (traditional medicine capsule consisting of *Radix ginseng*, *Scorpio* (Chinese scorpion), *Hirudo* (leech), *Eupolyphaga seu steleophaga*, *Scolopendra*, *Periostracum cicadae*, *Radix paeoniae rubra*, and *Borneolum syntheticum*), and *Acanthopanax*, Mailuoning (a compound agent consisting of *Dendrobium*, *Radix scrophulariae*, *Flos lonicerae*, and *Radix achyranthis bidentatae*). All these interventions were compared with placebo or no treatment.

The main outcome considered in all the reviews was the improvement in neurological deficit which is one of the secondary outcomes of stroke treatment. The primary outcomes measured in the included reviews were death and dependency. However, the primary outcomes of only one review<sup>11</sup> was statistically assessed. Out of the eight reviews included in this study, five reviews<sup>11,14,16–18</sup> statistically evaluated the improvement of neurological deficit, whereas one review<sup>15</sup> did not use meta-analysis as a statistical approach.

The methodological qualities of the reviews included in this study were evaluated using the AMSTAR tool. The total scores of the reviews assessed ranged from 9 to 11 (mean score = 10), and three reviews met all the 11-item criteria of the AMSTAR. Two reviews<sup>10,13</sup> did not report the status of publication as an inclusion criterion, three reviews<sup>8,10,14</sup> did not assess the potential publication bias, and three reviews<sup>8,12,13</sup> did not include the potential conflicts of interest. The results of the quality of the reviews included in this study, using the AMSTAR tool, are shown in Table 2.

## Discussion

The data from systematic reviews that assessed the efficacy of herbal medicine for the treatment of stroke was evaluated in this review. Most of the systematic reviews included in this study indicated herbal medicine may be an effective treatment for stroke as

**Table 1**  
Summary of the included systematic reviews.

First author (year)	Type of stroke No. of included studies (Total sample size)	Type of herbal medicine	Control	Outcome measures	Effect estimates for main outcomes (meta-analysis)	Overall risk of bias (Low/Unclear/High)	Overall AMSTAR score (Quality)	Authors' Conclusions
Zeng (2005) <sup>7</sup>	Acute ischemic 10 (792)	Ginkgo biloba extract (intravenous injection, tablet)	Placebo/no treatment	1) Death or dependency 2) AEs 3) QoL 4) Neurological deficit	1)-3) No meta-analysis 4) Improvement: OR 2.66; 95% CI 1.79 to 3.94	1/8/1	11 (High)	"No convincing evidence..."
Wu (2007) <sup>8</sup>	Acute ischemic 6 (494)	Dan Shen agents	Placebo/no treatment	1) Death or dependency 2) AEs 3) QoL 4) Neurological deficit	1)-3) No meta-analysis 4) Improvement: OR 3.02, 95% CI 1.73 to 5.26	0/4/2	9 (High)	"... conclusions could not be drawn ..."
Chen (2008) <sup>9</sup>	Acute ischemic 8 (660)	Sanchi agents	Placebo/no treatment	1) Death or dependency 2) AEs 3) QoL 4) Neurological deficit	1) RR 0.63, 95% CI 0.45 to 0.88) 2) RR 1.30, 95% CI 0.47 to 3.54 3) No meta-analysis 4) RR 0.29, 95% CI 0.18 to 0.47	3/5/0	11 (High)	"... a firm conclusion could not be drawn"
Yuan (2008) <sup>10</sup>	Acute ischemic 2 (161)	Chuanxiong	Placebo/no treatment	1) Death or dependency 2) AEs 3) QoL 4) Neurological deficit	1) No meta-analysis 2) RR 1.02, 95% CI 0.35 to 2.95 3), 4) No meta-analysis	0/0/2	9 (High)	"Insufficient evidence..."
Li (2009) <sup>11</sup>	Acute ischemic 13 (962)	Acanthopanax	Placebo/no treatment	1) Death or dependency 2) AEs 3) QoL 4) Neurological deficit	1)-3) No meta-analysis 4) Improvement: RR 1.22, 95% CI 1.15 to 1.29	0/13/0	11 (High)	"... the data were not adequate to draw reliable conclusions..."
Yang (2015) <sup>12</sup>	Acute ischemic 21 (1746)	Mailuoning	Placebo/no treatment	1) Death or dependency 2) AEs 3) QoL 4) Neurological deficit	1) No meta-analysis 2) RR 1.39, 95% CI 0.28 to 6.76 3) No meta-analysis 4) Improvement: RR 0.31, 95% CI 0.23 to 0.42	0/1/20	9 (High)	"Evidence provided was insufficient..."
Cao (2008) <sup>13</sup>	Acute cerebral infarction 9 (723)	Dengzhanhua	Placebo/no treatment	1) Death or dependency 2) AEs 3) QoL	1), 2) No meta-analysis 3) Improvement: RR 1.53; 95% CI 1.36 to 1.72	0/7/2	8 (High)	"... a firm conclusion could not be drawn"
Zhuo (2008) <sup>14</sup>	Acute 2 (232)	Tongxinluo (capsule) alone or tongxinluo plus standard treatment	Placebo/no treatment/standard treatment	1) Death or dependency 2) AEs 3) Neurological deficit	1)-3) No meta-analysis	0/0/2	10 (High)	"Not possible to reliably determine..."

CI, confidence interval; MD, mean difference; QoL, Quality of Life; RR, Relative Risk; WMD, weighted mean difference; Dan Shen, Radix Salviae Miltiorrhizae; Dengzhanhua; Erigeron breviscapus. Sanchi, Radix Notoginseng; Chuanxiong, Rhizoma Ligustici Wallichii; Tongxinluo, traditional medicine capsule (Radix ginseng, Scorpio, Hirudo, Eupolyphaga seu steleophaga, Scolopendra, Periostracum cicadae, Radix paeoniae rubra, and Borneolum syntheticum); Mailuoning, compound agent (Dendrobium, Radix Scrophularia, Flos Lonicerae, and Radix Achyranthis Bidentatae).

**Table 2**  
The quality of the included reviews by AMSTAR criteria.

Items	Zeng (2005)	Wu (2007)	Cao (2008)	Chen (2008)	Yuan (2008)	Zhuo (2008)	Li (2009)	Yang (2015)
1 Was an 'a priori' design provided?								
2 Was there duplicate study selection and data extraction?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
3 Was a comprehensive literature search performed?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
4 Was the status of publication (i.e., grey literature) used as an inclusion criterion?	Yes	Yes	No	Yes	No	Yes	Yes	Yes
5 Was a list of studies (included and excluded) provided?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
6 Were the characteristic of the included studies provided?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
7 Was the scientific quality of the included studies assessed and documented?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
8 Was the scientific quality of the included studies used appropriately in formulating conclusion?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
9 Were the methods used to combine the finding of studies appropriate?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
10 Was the likelihood of publication bias assessed?	Yes	No	Yes	Yes	No	No	Yes	Yes
11 Were the conflicts of interest included?	Yes	No	No	Yes	Yes	Yes	Yes	No
Total score	11	9	9	11	9	10	11	10

AMSTAR scoring system: Yes: 1, No: 0.

Low quality score: 0–3; moderate quality score: 4–7; high quality score: 8–11.

an overall conclusion. Only one systematic review did not draw any conclusions or indications. Although most of the reviews indicated that herbal medicine may improve the neurological deficits in stroke patients, there was no clear evidence to support the routine use of herbal medicine for the treatment of stroke. In addition, although the primary outcomes measured in the included reviews were death and dependency, the main outcome considered in all the reviews was the improvement in neurological deficit, which actually was one of the secondary outcomes of stroke treatment. This indicates that mortality rate is not assessed as the primary outcome in most studies, especially trials on the usage of herbal medicine for the treatment of stroke. Therefore, more studies assessing the primary outcome is called for.

Even though the Cochrane reviews present a high quality of evidence, the reviews' studies included in this overview had methodological and reporting issues that could have influenced the validity of the results and conclusions. The common concerns of the studies were inadequate allocation concealment, no blinding of the outcome assessors, short term follow-up, limited available data on the primary outcome, and inadequate or unclear description of herbal medicine preparation method. The risk of bias of the studies included in each review was graded as C (poor) or unclear. As the quality of the studies affects the direction of results, this might have limited the validity of the results, even though meta-analyses were performed. Therefore, all the Cochrane reviews included in this study were inconclusive about the efficacy of herbal medicine in stroke treatment.

In general, the methodological qualities of all the Cochrane reviews were high according to the AMSTAR, with a total score ranging from 9 to 11. This further justified our decision to conduct an overview using only Cochrane reviews, as they have a high quality of evidence.

However, this overview has several limitations that must be taken into consideration. Since systematic reviews from only the Cochrane Database of Systematic Reviews were included, this overview cannot provide evidence on herbal medicines for which no Cochrane systematic review is available. To conclude on the efficacy of herbal medicine for stroke treatment, a more comprehensive review of all the systematic reviews available is needed. Another limitation concerns the inclusion and exclusion criteria of the Cochrane reviews. Several trials conducted on the efficacy

of herbal medicine for the treatment of stroke may have been excluded during the screening process due to different diagnostic criteria or procedures and thus have an influence on the results.

In conclusion, this overview provided the current evidence on the use of Chinese herbal medicine for stroke from Cochrane systematic reviews and showed the potential efficacy of herbal medicines for the treatment of stroke in terms of neurological deficit improvement. However, there is currently no sufficient evidence to recommend herbal medicines for the treatment of stroke as standard therapy, and the overview therefore could not make an affirmative conclusion to recommend herbal medicine for clinical practice. The usage of herbal medicine for stroke treatment still needs to be conclusively explored with better methodological quality RCTs in the future.

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## Conflict of interest

The authors declare no conflict of interest.

## Data availability

Data associated with this article will be provided upon request.

## Author contributions

MW conceived and supervised the work. DW and DK collected the data and performed the analysis. MW drafted the manuscript. MSL provided critical feedback. TYC, LA, and ES updated the Cochrane reviews and the analysis, and revised the manuscript. All authors reviewed and contributed to the final version of the manuscript.

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## Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:<https://doi.org/10.1016/j.imr.2019.11.009>.

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