Add-On Effects of Chinese Herbal Medicine for Post-Stroke Spasticity: A Systematic Review and Meta-Analysis

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Background: Treatment for post-stroke spasticity (PSS) remains a major challenge in clinical practice. Chinese herbal medicine (CHM) is often administered to assist in routine care (RC) in the treatment of PSS, with increasing numbers of clinical research and preclinical studies suggesting that it has potential benefits. Therefore, we conducted a systematic review and meta-analysis to evaluate the add-on effects and safety of CHM for PSS.

Methods: Five English and four Chinese databases were searched from their respective inception to 28 February 2018. We included randomized controlled trials that evaluated the add-on effects of CHM for PSS, based on changes in the scores of the (Modified) Ashworth Scale (AS or MAS), Fugl-Meyer Assessment of Sensorimotor Recovery (FMA), and Barthel Index (BI).

Results: Thirty-five trials involving 2,457 patients were included. For upper-limb AS or MAS, the estimated add-on effects of CHM to RC were significantly better when using oral (SMD −1.79, 95% CI: −3.00 to −0.57) or topical CHM (SMD −1.06, 95% CI: −1.40 to −0.72). For lower-limb AS or MAS, significant add-on benefits to RC were also detected (SMD −1.01, 95% CI: −1.43 to −0.59 and SMD −1.16, 95% CI: −1.83 to −0.49) using oral and topical CHM, respectively. For FMA and BI, better results were detected when adding CHM to RC, except for the subgroup of oral CHM for upper-limb FMA. Ten of the 35 included studies reported safety information, with two of them mentioning two mild adverse events.

Conclusions: Noting the quality concerns of the included trials, this review suggests that CHM appears to be a well-tolerated therapy for patients with PSS, and the potential add-on effects of CHM in reducing spasticity and improving the daily activities of patients with PSS require further rigorous assessment.

Keywords: herbal medicine, meta-analysis, muscle spasticity, randomized controlled trial, stroke
INTRODUCTION

Spasticity can adversely impact almost half of stroke survivors (Watkins et al., 2002; Kwah et al., 2012; Zorowitz et al., 2013) and may worsen other post-stroke complications, including urinary and fecal incontinence, as well as skin infection (Bravo-Esteban et al., 2013; Martin et al., 2014; Gillard et al., 2015; Milinis and Young, 2015). In particular, spasticity can be a great barrier in rehabilitation for stroke recovery (Nair and Marsden, 2014).

Although there is uncertainty about the effects of specific rehabilitation interventions targeting post-stroke spasticity (PSS) and about the timing of their initiation, control of spasticity as soon as the patient’s posture or mobility is affected is generally encouraged (European Stroke Organization (ESO) Executive Committee and ESO Writing Committee, 2008; Miller et al., 2010; Smith et al., 2010; Stroke Foundation of New Zealand and New Zealand Guidelines Group, 2010; Chinese Society of Neurology and Stroke Prevention Project Committee of National Health and Family Planning Commission in China, 2012; National Institute for Health and Care Excellence, 2013; Nair and Marsden, 2014; Australian National Stroke Foundation, 2017). In terms of spasticity management, non-pharmaceutical intervention is preferred as first-line treatment; these include position management and manual stretching (Nair and Marsden, 2014).

For some alternative therapies, such as shock wave stimulation, electrical stimulation, and repetitive transcranial magnetic stimulation, comprehensive assessment is required to confirm their effectiveness (Mally and Dinya, 2008; Stein et al., 2015; Dymarek et al., 2016; Dymarek et al., 2016b; Dymarek et al., 2016c). When these therapies do not achieve a satisfying response, oral and invasive anti-spasticity medications could be considered (Bensmail et al., 2006; Bensmail et al., 2009; Harned et al., 2011). However, more than half of patients with PSS still suffer from moderate to severe disability after using current therapies (Sze et al., 2000), since the effectiveness is limited by a relatively short maintaining period, high costs, and unwanted adverse events, such as drowsiness and muscle weakness (European Stroke Organization (ESO) Executive Committee and ESO Writing Committee, 2008; Miller et al., 2010; Smith et al., 2010; Stroke Foundation of New Zealand and New Zealand Guidelines Group, 2010; Chinese Society of Neurology and Stroke Prevention Project Committee of National Health and Family Planning Commission in China, 2012; National Institute for Health and Care Excellence, 2013; Nair and Marsden, 2014; Australian National Stroke Foundation, 2017).

From a classical Chinese medicine perspective, PSS is also considered one of the clinical manifestations of stroke. The primarily etiology of PSS is a deficiency of qi, Blood, yin, or yang, that generates internal pathological products, such as Wind, Fire, Phlegm, or Stasis, blocking the meridian and collateral channels and resulting in the failure of nourishing tendons and muscles.

Eventually, spasticity, limb stiffness, and contracture occur (Zhang and Xue, 2012). Therefore, Chinese herbal medicine (CHM) that could either restore the balance of qi, Blood, yin, and yang or clean up internal pathological products would be considered in the treatment of PSS (Zhang and Xue, 2012).

Nowadays, CHM is often administered in clinical practice as an adjunct to routine care (RC) for the treatment of PSS. Clinical research has also been increasingly conducted, with a focus on both orally or topically used CHM formulas, for PSS (Liu et al., 2014b; Zhu et al., 2014). Increasing numbers of preclinical studies have suggested that CHM single herbs and formulas are related to inhibition of certain types of neurotoxicity and certain anti-spasmodic activities (Hu et al., 2013; Huang et al., 2013; Li et al., 2014; Zhu et al., 2015).

In order to provide an overall evaluation of existing clinical evidence regarding CHM for PSS, we conducted a systematic review to address whether 1) CHM (including oral and topical CHM) in combination with RC (including pharmacotherapy and/or rehabilitation therapies) is more effective than RC alone in terms of spasticity severity, motor function, and activities of daily living; and whether 2) the use of CHM is safe.

METHODS

Data Sources and Search Strategies

Five English databases (PubMed, Cumulative Index to Nursing and Allied Health Literature, EMBASE, Cochrane Central Register of Controlled Trials, and Allied and Complementary Medicine Database), four Chinese databases (the Wanfang Database, Chongqing VIP Database, Chinese National Knowledge Infrastructure, and Chinese Biomedical Database), and two online clinical trial registration websites (the International Clinical Trials Registry Platform and the Chinese Clinical Trial Registry) were searched from their respective inception to February 2017, with an updated search conducted in February 2018. Related trials and systematic reviews obtained by searching the references of the included studies were also researched. The detailed search strategy is presented in Table S1; three categories of search terms were used (“Chinese herbal medicine,” “post-stroke spasticity,” and “clinical trials”). Reporting details are available in File S1.

Study Screening and Selection Criteria

Two researchers (YC and CZ) independently screened the titles, abstracts, and full texts to remove duplicates and irrelevant trials after applying the selection criteria. Discussion with a third reviewer (SL) was used to resolve doubt or disagreement about study inclusion. Inclusion criteria were as follows: 1) randomized controlled trials (RCTs) or quasi RCTs; 2) patients with one or multiple strokes that were confirmed by computed tomography or magnetic resonance imaging; 3) Ashworth Scale (AS) or Modified Ashworth Scale (MAS) of any joint ≥1; 4) comparison of any type of RC with or without CHM (oral CHM or topical CHM, such as steaming, compression, baths, and various external application therapies of CHM; CHM injection was not regarded as topical CHM and was not included in this study),
or with placebo, with co-intervention being allowed as long as it was incorporated into all arms; and 5) studies that reported at least one of the following outcome measures: AS or MAS for spasticity severity as the primary outcome measure, Fugl-Meyer Assessment of Sensorimotor Recovery (FMA) for motor function and Barthel Index (BI) for assessment of activities of daily living as secondary outcome measures, and reporting of adverse events as a safety outcome. We excluded studies of patients with stroke symptoms caused by trauma, tumor, infection, and subdural hemorrhage or where the add-on effects of CHM could not be estimated due to the involvement of other interventions (i.e., CHM plus acupuncture plus rehabilitation therapies vs. rehabilitation therapies).

**Data Extraction**

Two investigators (YC and CZ) independently extracted information on the characteristics of participants, study methods, and outcomes using a pre-designed form. A third reviewer (SL) checked all extracted data and corrected inconsistencies. If important data were unclear, unavailable, or suspected of duplication, authors of the trials were contacted via phone or emails for clarification.

**Quality Assessment (Risk of Bias)**

Two researchers (YC and CZ) assessed the methodological quality of the included studies using the Cochrane risk-of-bias tool, following the Cochrane Handbook for Systematic Reviews of Interventions (version 5.1.0). Disagreement was resolved through discussion with a third investigator (SL) when necessary. Seven domains were assessed for each study: random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessors, incomplete outcome data, selective reporting, and other bias.

**Data Synthesis and Analysis**

**Treatment Effects**

Data synthesis was conducted using the Cochrane Review Manager software (RevMan 5.3). Mean difference (MD) and 95% confidence interval (CI) was used for continuous data, whereas the standard mean difference (SMD) was applied where the same outcome was reported using different scale ranges. Changes in AS or MAS, FMA, and BI was extracted or calculated for meta-analyses. Random-effect models were used for meta-analyses. The results of five RCTs (Zhang et al., 2008; Zhao, 2010; Huang et al., 2011; Chen, 2013; Zhao, 2013) could not be synthesized into meta-analyses because their reported data were incorrect or could not be pooled. Six studies (Zhu et al., 2002; Zhu et al., 2007; Zhang, 2009; Xie et al., 2011; Zhu et al., 2013; Weng, 2014) evaluated oral plus topical CHM; their results were not pooled for meta-analysis due to the diversity of interventions.

**Subgroup Analysis and Sensitivity Analysis**

The source of clinical heterogeneity among included trials was assessed through subgroup analyses for baseline differences in terms of stroke onset (1 or >1 times), history of stroke (≤180 or >180 days), treatment duration (≤4 or >4 weeks), and preparation of herbal interventions. In consideration of the methodological quality, sensitivity analyses were performed based on the risk-of-bias judgements. In terms of herb analysis, post hoc subgroup analyses on the primary and secondary outcomes were conducted if sufficient data were available to explore the estimated effects of the individual or combination of the top five most frequently reported oral or topical herbs identified from this review.

**Publication Bias**

Publication bias was assessed with a funnel plot and Egger's linear regression test where more than 10 trials were included in a meta-analysis.

**RESULTS**

**Study Selection**

Using the comprehensive search, 46,304 studies were identified (Figure 1). A total of 2,309 possibly relevant studies were obtained for full-text screening. Thirty-five RCTs meeting our criteria were included in the systematic review, of which 24 were included in meta-analyses. The results of five RCTs (Zhang et al., 2008; Zhao, 2010; Huang et al., 2011; Chen, 2013; Zhao, 2013) could not be synthesized into meta-analyses because their reported data were incorrect or could not be pooled. Six studies (Zhu et al., 2002; Zhu et al., 2007; Zhang, 2009; Xie et al., 2011; Zhu et al., 2013; Weng, 2014) evaluated oral plus topical CHM; their results were not pooled for meta-analysis due to the diversity of interventions.

**Characteristics of Included Studies**

All included RCTs were conducted in China and were published between 2002 and 2016 (Table 1). The study sample size ranged from 29 to 120. A total of 2,457 stroke patients with an average age of 61.72 years were included in these studies.

Fifteen studies (Zhang et al., 2008; Huang et al., 2011; Li and Wang, 2011; Wei et al., 2011; Zhang et al., 2012; Chen, 2013; Wang, 2013; Zhao, 2013; Chen et al., 2014; Liu et al., 2014a; Li et al., 2015; Cai, 2016; He, 2016; Murat, 2016; Zhong, 2016) investigated the add-on effects of oral CHM, 14 studies were on topical CHM (Ou et al., 2007; Shen et al., 2007; Zhang et al., 2007; Li et al., 2008; Chen et al., 2010; Zhao, 2010; Huang, 2011; Jia et al., 2012; Ou et al., 2014; Wang et al., 2014; Cao and Han, 2015; Ding, 2016; Lai, 2016; Zhang, 2016), and six studies were oral plus topical CHM (Zhu et al., 2002; Zhu et al., 2007; Zhang, 2009; Xie et al., 2011; Zhu et al., 2013; Weng, 2014). The stroke history of the included patients was reported from 1 day to 1 year. Eight studies (Ou et al., 2007; Zhang et al., 2012; Chen, 2013; Ou et al., 2014; Weng, 2014; Ding, 2016; Murat, 2016; Zhang, 2016) only enrolled participants with a first-ever stroke. Nine trials (Zhu et al., 2002; Ou et al., 2007; Zhu et al., 2007; Zhao, 2010; Huang, 2011; Huang et al., 2011; Chen et al., 2014; Ou et al., 2014; Ding, 2016) merely included stroke patients whose AS or MAS were ≥2 at baseline. Reported CHM formulas varied greatly among the included studies, with a treatment duration ranging from 20 days to 3 months (Table 2). A variety of rehabilitation therapies were used as co-interventions (Table 3). Placebo was not used in any of the included trials. Twenty-three studies reported data on AS or MAS, 17 reported BI, and 14 reported FMA data (Table 1).

**Risk of Bias of Included Studies**

Eighteen studies (Ou et al., 2007; Shen et al., 2007; Li et al., 2008; Zhang, 2009; Chen et al., 2010; Li and Wang, 2011; Xie et al., 2011; Zhang et al., 2012; Chen, 2013; Zhu et al., 2013; Liu et al., 2014a; Ou et al., 2014; Cao and Han, 2015; Ding, 2016; Lai, 2016; Murat, 2016; Zhang, 2016; Zhong, 2016) were assessed as low risk of bias.
in random sequence generation with adequate methods; two trials (Zhu et al., 2007; Wang, 2013) were assessed as high risk of bias because they allocated patients based on the date of admission; others were of unclear risk due to a lack of information. Allocation was well concealed in only two studies (Chen, 2013; Lai, 2016), whereas another two (Zhu et al., 2007; Wang, 2013) were assessed as high risk of bias because participants were allocated based on their case record number. Blinding of participants and personnel was attempted in none of the included trials, but three trials (Zhang et al., 2007; Liu et al., 2014a; Weng, 2014) performed blinding in outcome assessors. All included trials were assessed as low risk of bias in incomplete outcome data. None of the included studies had prospectively registered protocols, and 10 studies (Zhang et al., 2007; Zhang et al., 2008; Li and Wang, 2011; Jia et al., 2012; Zhao, 2013; Zhu et al., 2013; Li et al., 2015; He, 2016; Murat, 2016; Zhong, 2016) did not report the results of all pre-defined outcomes mentioned in the Methods sections. Risk-of-bias assessment is summarized in Figure 2.

Synthesis of Results
Results of meta-analyses are presented below for oral CHM and topical CHM, separately (Table 4).

Add-On of Oral CHM to RC
Significant add-on effects of oral CHM were found in terms of changes in scores of AS or MAS of the upper limbs (three studies: Zhang et al., 2012; Liu et al., 2014a; Cai, 2016; SMD −1.79, 95% CI: −3.00 to −0.57, \( P = 94% \)) and lower limbs (three studies: Wang, 2013; Liu et al., 2014a; Cai, 2016; SMD −1.01, 95% CI: −1.43 to −0.59, \( P = 55% \)), although with moderate to high heterogeneity (Table 4 and Figure 3).
| Intervention                  | Author, year | Sample size (I/C) | Age (years) | Gender (% male) | Stroke type                                      | First onset of stroke | Time from stroke onset | Spasticity severity | Outcome measures                                                                 |
|------------------------------|--------------|------------------|-------------|-----------------|-------------------------------------------------|-----------------------|------------------------|----------------------|--------------------------------------------------------------------|
| Oral CHM                     | Cai, 2016    | 47/46            | 65.9        | 65.6            | Cerebral infarction and hemorrhage               | N/A                   | ≤3 months              | MAS > 0              | MAS, CSS, ER                                                      |
| Oral CHM                     | Chen et al., 2014 | 25/25            | 59.1        | 68              | Cerebral infarction                              | N/A                   | 10–42 days             | AS ≥ 2               | AS, FMA, BI                                                        |
| Oral CHM                     | Chen, 2013   | 30/30            | 64.6        | 54.9            | Cerebral infarction and hemorrhage               | Yes                   | ≤3 months              | MAS: 1–3             | CSIP, FMA, BI, EMG, TOM syndrome score                             |
| Oral CHM                     | He, 2016     | 50/50            | 60.7        | 61              | N/A                                              | N/A                   | 4–87 days              | MAS > 0              | FMA, BI, ER                                                       |
| Oral CHM                     | Huang et al., 2011 | 20/15            | 68.6        | 57.1            | N/A                                              | N/A                   | ≤3 months              | MAS: 2–3             | FMA, BI, ER, wrist and ankle ROM                                   |
| Oral CHM                     | Li and Wang, 2011 | 40/40            | N/A         | 65              | Cerebral infarction                              | N/A                   | 10–82 days             | MAS > 0              | FMA, BI, ER                                                        |
| Oral CHM                     | Liu et al., 2015 | 40/40            | N/A         | 68              | Cerebral infarction                              | N/A                   | ≤90 days               | MAS > 1              | FMA, BI, ER                                                       |
| Oral CHM                     | Liu et al., 2014a | 34/34            | 67.6        | 55.9            | Cerebral infarction and hemorrhage               | Yes                   | 2–5 weeks              | MAS ≥ 1              | BI, ER, TOM syndrome score                                        |
| Oral CHM                     | Murat, 2016   | 36/36            | 61.5        | 62.5            | Cerebral infarction                              | N/A                   | 30–180 days            | MAS ≥ 1              | MAS, FMA                                                          |
| Oral CHM                     | Wang, 2013    | 35/34            | N/A         | 60.9            | Cerebral infarction                              | N/A                   | 2 weeks–6 months       | MAS ≥ 0              | FMA, FMA, ER                                                      |
| Oral CHM                     | Wei et al., 2011 | 30/30            | 56.2        | 65.0            | Cerebral infarction and hemorrhage               | Yes                   | ≤6 months              | MAS: 1–3             | MAS, Bi, IEMG                                                    |
| Oral CHM                     | Zhang et al., 2008 | 35/31            | 65.8        | 72.7            | Cerebral infarction and hemorrhage               | N/A                   | 2 weeks–6 months       | MAS ≥ 1              | MAS, ER, Swelling score (upper limb), Berg balance score, BI, AS, AE, neurological deficit score, Brunstrom, motor patterns, TCM syndrome score |
| Oral CHM                     | Zhang et al., 2012 | 60/40            | 64.14       | 68.0            | Cerebral infarction                              | Yes                   | 14–180 days            | MAS: 1–3             | MAS, ER, Swelling score (upper limb)                               |
| Oral CHM                     | Zhao, 2013    | 30/30            | 63.5        | 65              | Cerebral infarction                              | N/A                   | N/A                   | N/A                  | MAS ≥ 1                                                          |
| Oral CHM                     | Zhong, 2016   | 41/41            | 62.56       | 56.1            | Cerebral infarction                              | N/A                   | 3–9 days               | MAS ≥ 1              | Bi, ER                                                           |
| Topical CHM                  | Cao and Han, 2015 | 32/32            | 57.7        | 61.3            | Cerebral infarction                              | N/A                   | <365 days              | MAS ≥ 1              | MAS, CSS, BI                                                      |
| Topical CHM                  | Chen et al., 2010 | 25/25            | 60          | 54              | Cerebral infarction                              | N/A                   | <6 months              | MAS: 1–3             | AS, AE                                                            |
| Topical CHM                  | Ding, 2016    | 59/50            | 57.1        | 56.0            | Cerebral infarction                              | Yes                   | 10–100 days            | MAS ≥ 2              | MAS, ROM, ER                                                      |
| Topical CHM                  | Huang, 2011   | 45/45            | 60.8        | 61.1            | Cerebral infarction                              | N/A                   | N/A                   | N/A                  | MAS, Bi, AE                                                       |
| Topical CHM                  | Jia et al., 2012 | 44/42            | 65.5        | 61.6            | Cerebral infarction                              | N/A                   | 6–20 days              | MAS ≥ 1              | MAS, FMA, BI, ER, FMA, BI, IEMG                                   |
| Topical CHM                  | Lai, 2016     | 30/30            | 68.5        | 59.3            | Cerebral infarction                              | N/A                   | N/A                   | N/A                  | MAS ≥ 1                                                          |
| Topical CHM                  | Li et al., 2008 | 30/30            | 57.2        | 58.3            | Cerebral infarction                              | Yes                   | <1 year                | MAS ≥ 2              | MAS, step, walking speed                                         |
| Topical CHM                  | Ou et al., 2007 | 15/14            | N/A         | N/A             | Cerebral infarction                              | Yes                   | <1 year                | MAS ≥ 2              | MAS, FMA, FIM, AE                                                |
| Topical CHM                  | Ou et al., 2014 | 20/21            | 59.4        | 53.7            | Cerebral infaration                              | Yes                   | ≤6 months              | MAS: 1–3             | AS, AE                                                            |
| Topical CHM                  | Shen et al., 2007 | 31/30            | 60          | 55.7            | Cerebral infaration                              | N/A                   | 30–151 days            | MAS ≥ 1              | MAS, Bi                                                           |
| Topical CHM                  | Wang et al., 2014 | 24/24            | 57          | 62.5            | Cerebral infaration                              | Yes                   | 17–180 days            | MAS ≥ 1              | MAS, Bi                                                           |
| Topical CHM                  | Zhang, 2016   | 60/60            | 62.1        | 60.0            | Cerebral infaration                              | Yes                   | 2–12 weeks             | MAS: 1–3             | FMA, FIM, ER                                                      |
| Topical CHM                  | Zhang et al., 2007 | 30/30            | 66.0        | 65.0            | N/A                                              | N/A                   | 30–180 days            | MAS ≥ 1              | MAS, Bi                                                           |
| Topical CHM                  | Zhao, 2010    | 28/27            | N/A         | 63.6            | Cerebral infaration                              | N/A                   | N/A                   | N/A                  | MAS ≥ 2                                                          |
| Oral plus topical CHM        | Weng, 2014    | 35/38            | 55.42       | 47.95           | Cerebral infaration                              | Yes                   | ≤60 days               | MAS > 1              | MAS, FMA, BI                                                     |
| Oral plus topical CHM        | Xie et al., 2011 | 60/60            | 59.25       | 60.83           | Cerebral infaration                              | Yes                   | ≤60 days               | MAS > 1              | MAS, FMA, BI                                                     |
| Oral plus topical CHM        | Zhang, 2009   | 38/36            | 54.49       | 56.76           | Cerebral infaration                              | N/A                   | N/A                   | AS > 0               | FMA, BI, ER, TOM syndrome score, AE                              |
| Oral plus topical CHM        | Zhu et al., 2002 | 30/30            | 63.5        | 71.67           | Cerebral infaration                              | N/A                   | 1–2 months             | MAS ≥ 2              | MAS, ER, AE                                                      |
| Oral plus topical CHM        | Zhu et al., 2007 | 31/31            | 63.1        | 59.68           | Cerebral infaration                              | N/A                   | 1–2 months             | MAS: 2–4             | AS, Bi, ER, AE                                                    |
| Oral plus topical CHM        | Zhu et al., 2013 | 30/30            | 64.35       | 51.67           | N/A                                              | N/A                   | AS: 1–3               | N/A                  | FMA, SEmG                                                        |

**Abbreviations:** CHM: Chinese herbal medicine; CSS: Composite Spasticity Scale; EMG: electromyography; ER: effective rate; FIM: Functional Independent Measure; FMA: Fugl-Meyer Assessment of Sensorimotor Recovery; MAS: Modified Ashworth Scale; RDM: range of motion; sEMG: surface electromyography; TCM: traditional Chinese medicine; VAS: Visual Analogue Scale. Reported data were incorrect or unable to be merged.
## TABLE 2 | Summary of Intervention Treatment

| Author, year | Oral CHM Preparation | Dosage | Frequency | Period | Duration | Frequency | Period | Formula | Ingredients* |
|--------------|----------------------|--------|-----------|--------|----------|-----------|--------|---------|--------------|
| Cai, 2016    | Decoction 200 ml     | bid    | 12 weeks  | N/A    | N/A      | N/A       | Gua Lou Gen, GuiZhi, Bai Shao, Sheng Jiang, Da Zao, Gan Cao |
| Chen et al., 2014 | Decoction 0.5 dose   | bid    | 4 weeks   | N/A    | N/A      | N/A       | Gua Lou Gen, GuiZhi, Bai Shao, Sheng Jiang, Da Zao, Gan Cao |
| Chen, 2013    | Decoction 200 ml     | bid    | 4 weeks   | N/A    | N/A      | N/A       | Gua Lou Gen, GuiZhi, Bai Shao, Sheng Jiang, Da Zao |
| He, 2016      | Decoction 1 dose     | qd     | 28 days   | N/A    | N/A      | N/A       | Tong Luo Jie Jing Tang |
| Huang et al., 2011 | Capsule 3g      | tid    | 3 months  | N/A    | N/A      | N/A       | Wen Jing Shu Jin Jiao Nang |
| Li and Wang, 2011 | Decoction 1 dose   | qd     | 28 days   | N/A    | N/A      | N/A       | Tong Luo Jie Jing Tang |
| Li et al., 2015 | Decoction 1 dose    | qd     | 28 days   | N/A    | N/A      | N/A       | Yi Qi Rou Jin Tang |
| Liu et al., 2014a | Decoction 0.5 dose | bid    | 2 months  | N/A    | N/A      | N/A       | Decoction without a name |
| Murat, 2016   | Decoction 200 ml     | bid    | 4 weeks   | N/A    | N/A      | N/A       | Decoction without a name |
| Wang, 2013    | Capsule N/A         | tid    | 4 weeks   | N/A    | N/A      | N/A       | Bu Chang Nao Xin Tong Jiao Nang |
| Wei et al., 2011 | Decoction 100 ml    | bid    | 4 weeks   | N/A    | N/A      | N/A       | Rou Jin Tang |
| Zhang et al., 2008 | Decoction 1 dose | qd     | 4 weeks   | N/A    | N/A      | N/A       | Decoction without a name |
| Zhang et al., 2012 | Decoction 0.5 dose | bid    | 3 weeks   | N/A    | N/A      | N/A       | Shao Yao Gan Cao Tang |
| Zhao, 2013    | Decoction 250 ml     | bid    | 4 weeks   | N/A    | N/A      | N/A       | Zi Ni Wen Shen Yi Qi HuoXieTang |
| Zhong, 2016   | Decoction 0.5 dose   | bid    | 4 weeks   | N/A    | N/A      | N/A       | Shao Yao Gan Cao Tang |
| Cao and Han, 2015 | N/A             | N/A    | 30 min    | bid    | 30 days  | N/A       | Compression Decoction without a name |
| Chen et al., 2010 | N/A             | N/A    | 30 min    | qd     | 30 days  | N/A       | Compression Decoction without a name |
| Ding, 2016    | N/A                | N/A    | 30 min    | qd     | 8 weeks  | N/A       | Compression Decoction without a name |

*The ingredients are listed for each formula, but the specific compositions are not detailed in the table. Further research may be necessary to identify the exact ingredients used in each study.
| Author, year | Oral CHM | Topical CHM | Formula | Ingredients* |
|-------------|-----------|-------------|---------|--------------|
| Huang, 2011 | N/A       | N/A         | (steaming) Shu Jin Tong Luo Fang | Bai Shao, Mu Gua, Mu Gui, Xi Xian Cao, Shen Jin Cao, TuBie Chong, ChuanXiong, XueJie, Hong Hua, NiXi, QuanXie, Wu Gong, Dan Shen, Sheng Du Huang, Dang Gui, Tou Gu Cao, Gan Cao |
| Ja et al., 2012 | N/A       | N/A         | (steaming) Decoction without a name | Hong Hua, Dan Shen, Dang Gui, Chuan Xiong, J XuE Ting, Mu Gua, Xi Xian Cao, Shen Jin Cao, Wei Ling Xian, Qiang Huo, Du Huo, Sang Zhi, GuZhi, Cang Zhu, Bai Zhu, Di Long, Bai Shao, Gan Cao |
| Ou et al., 2007 | N/A       | N/A         | (steam) Shu JinHuo Luo Xi Ji | Huang Qi, Dang Gui, Dang Shen, Tan Ren, Hong Hua, Chuan Xiong, Su Wu, Sang Zhi, Shen Jin Cao, Ji XuE Ting, Mu Gua, Wei Ling Xian, Dan Shen, Ma Qian Zi |
| Shen et al., 2007 | N/A       | N/A         | (compression) Decoction without a name | Dang Gui, Chuan Xiong, Bing Plan, Ni Xi, Tou Gu Cao, Wei Ling Xian, Hong Hua, Fang Feng, Ai Ye, GuZhi, Zhe Chong, Huang Ju, Ci Tong You |
| Wang et al., 2014 | N/A       | N/A         | (compression) Decoction without a name | Shen Jin Cao, Bai Shao, Gan Cao, Dang Gui, Di Long, Mai Dong, Fang Feng, Wu Gong |
| Zhang, 2016 | N/A       | N/A         | (steam) Ji Jing She Jun Tang | Tian Ma, Gou Teng, Wu Gong, Fang Feng, Shen Jin Cao, Ji XuE Ting, Wei Ling Xian, Bai Shao, Mai Dong, Dang Gui, Tan Ren, Hong Hua |
| Zhang et al., 2007 | N/A       | N/A         | (steam) Decoction without a name | Bai Shao, Wang Jiang Nan, Shen Jin Cao, Mu Gua, Sang Zhi, GuZhi, Hong Hua, Dang Gui, Gu Xiang, Mo Yao |
| Zhao, 2010 | N/A       | N/A         | (foot bath) Decoction without a name | Hong Hua, Tan Ren, Dang Gui, Dan Shen, Mu Gua |
| Weng, 2014 | Decoction 100 ml bid | 4 weeks | | Bai Shao, Gan Cao, Wang Jiang Nan, Mu Gua, Gu Xiang, Mo Yao, Quan Xie, Dan Shen, Huang Ju |
| Xie et al., 2011 | Decoction 150 ml qd | 28 days | (bath) Rou Jin Tang | Bai Shao, Gan Cao, J XuE Ting, Shen Zhu Yu, Wu Gong |
| Zhang, 2009 | Decoction 150 ml bid | 28 days | (oral+compression) Jie Jing He Ji | Bai Shao, Gan Cao, Shen Jin Cao, Ji Ku Miao, Su Wu, Sang Zhi, Tian Ma, Jia Hong, Wu Tou, Fang Feng, GuZhi, Hua Jiao, Hong Hua, Dang Gui, Huang Qi, Tou Gu Cao, Shen Jin Cao, Wei Ling Xian |
| Zhu et al., 2002 | CHM syrup 10 ml tid | 30 days | (oral+compression) Jie Jing He Ji | Bai Shao, Gan Cao, Wang Jiang Nan, Mu Gua, Quan Xie, Dan Shen, Huang Ju |
| Zhu et al., 2007 | CHM syrup 10 ml tid | 30 days | (oral+compression) Jie Jing He Ji | Bai Shao, Gan Cao, Wang Jiang Nan, Mu Gua, Gu Xiang, Mo Yao, Quan Xie, Dan Shen, Huang Ju |
| Zhu et al., 2013 | CHM syrup 10 ml tid | 30 days | (oral+compression) Shao Yao Gan Cao Tang | Bai Shao, Gan Cao |

*The ingredients of formulas were presented with Chinese pinyin. Correspondent scientific names were available in the book “Dan Bensky. Editor. Chinese Herbal Medicine: Materia Medica. Third Edition. WA: Eastland Press, Inc; 2004”.

bid, twice per day; CHM, Chinese herbal medicine; min, minutes; N/A, not available; qd, once per day; qid, four times per day; tid, three times per day.
In terms of the improvement of overall motor function measured using the FMA, combining oral CHM and RC was estimated to be significantly superior to RC alone (three studies: Li and Wang, 2011; Wang, 2013; He, 2016; MD 12.15, 95% CI: 1.57 to 22.71, $I^2 = 89$%) (Table 4 and Figure 4). Similarly, benefits of adding oral CHM to RC were seen in the FMA score changes for the lower extremities (two studies: two studies; Wei et al., 2011; Chen et al., 2014; MD 4.03, 95% CI: 1.90 to 6.17, $F = 61$%), but not in that of the upper limbs (three studies: Wei et al., 2011; Chen et al., 2014; Li et al., 2015; MD 7.64, 95% CI: −1.29 to 16.57, $F = 97$%).

Seven included trials (Li and Wang, 2011; Chen et al., 2014; Liu et al., 2014; Li et al., 2015; He, 2016; Murat, 2016; Zhong, 2016) reported changes to the BI results and were pooled for meta-analysis. Results showed that the combination of oral CHM and RC yielded more improvement in the BI than RC alone (MD 13.15, 95% CI: 4.37 to 21.93), although with high heterogeneity ($I^2 = 98$%) (Table 4 and Figure 5).

### Add-On of Topical CHM to RC

Compared to RC alone, adding topical CHM further decreased AS or MAS in the upper limbs (eight studies: Shen et al., 2007; Li et al., 2008; Chen et al., 2010; Huang, 2011; Wang et al., 2014; Ding, 2016; Lai, 2016; Zhang, 2016; SMD −1.06, 95% CI: −1.40 to −0.72, $I^2 = 72$%) and lower limbs (five studies: Ou et al., 2007; Shen et al., 2007; Chen et al., 2010; Huang, 2011; Wang et al., 2014; SMD −1.16, 95% CI: −1.83 to −0.49, $I^2 = 84$%) (Table 4), although with high heterogeneity detected in both analyses.

### Summary of rehabilitation treatment

| Study ID          | Control method                        | Pharmacotherapy | Dose | Frequency | Treatment period | Rehabilitation therapy | Duration in each treatment section | Frequency (times/day × times/week) | Treatment period |
|-------------------|---------------------------------------|-----------------|------|-----------|------------------|------------------------|------------------------------------|------------------------------------|-----------------|
| Cai, 2016         | Rehabilitation programs and Baclofen   | Increased from 10 mg to 75 mg | qd   | 12 weeks  | 45 min           | 1 × 7                  | 12 weeks                          |                                    |                 |
| Cao and Han, 2015 | Rehabilitation programs               | N/A             | N/A  | N/A       | N/A              | 60 min                 | 1 × 6                             | 4 weeks                            |                 |
| Chen et al., 2010 | Baclofen                               | Increased from 5 mg to 10 mg | tid  | 30 days   | N/A              | N/A                   | 45 min                            |                                    |                 |
| Chen et al., 2014 | Rehabilitation programs               | N/A             | N/A  | N/A       | N/A              | 40 min                 | 1 × 7                             | 8 weeks                            |                 |
| Chen, 2013 (B)    | Rehabilitation programs               | N/A             | N/A  | N/A       | N/A              | 40 min                 | 1 × 7                             | 28 days                           |                 |
| Ding, 2016        | Rehabilitation programs               | N/A             | N/A  | N/A       | N/A              | 60 min                 | 1 × 5                             | 4 weeks                            |                 |
| He, 2016          | Rehabilitation programs               | N/A             | N/A  | N/A       | N/A              | N/A                   | 3 months                          |                                    |                 |
| Huang, 2011       | Rehabilitation programs               | N/A             | N/A  | N/A       | N/A              | N/A                   | 3 months                          |                                    |                 |
| Hu et al., 2016   | Rehabilitation programs               | N/A             | N/A  | N/A       | N/A              | 30 min                 | 1 × 7                             | 2 months                          |                 |
| Li, 2016          | Rehabilitation programs               | N/A             | N/A  | N/A       | N/A              | 1 × 7                  | 30 days                           |                                    |                 |
| Li et al., 2008   | Rehabilitation programs               | N/A             | N/A  | N/A       | N/A              | 40 min                 | 1 × 6                             | 6 weeks                            |                 |
| Li and Wang, 2011 | Rehabilitation programs               | N/A             | N/A  | N/A       | N/A              | N/A                   | N/A                               | 3 months                          |                 |
| Li et al., 2015   | Rehabilitation programs               | N/A             | N/A  | N/A       | N/A              | 30 min                 | 1 × 7                             | 2 months                          |                 |
| Liu et al., 2014a | Rehabilitation programs               | N/A             | N/A  | N/A       | N/A              | N/A                   | 4 weeks                           |                                    |                 |
| Murat, 2016       | Rehabilitation programs               | N/A             | N/A  | N/A       | N/A              | 30–60 min              | (1 to 2) × 7                      | 2 months                          |                 |
| Ou et al., 2007   | Botulinum toxin and rehabilitation    | 100–300 units   | N/A  | N/A       | N/A              | 45 min                 | 1 × 6                             | 4 weeks                            |                 |
| Ou et al., 2014   | Botulinum toxin and rehabilitation    | 20–40 units/injection point | N/A | N/A       | N/A              | N/A                   | N/A                               | 2 months                          |                 |
| Shen et al., 2007 | Rehabilitation programs               | N/A             | N/A  | N/A       | N/A              | 45 min                 | 1 × 6                             | 28 days                           |                 |
| Wang et al., 2014 | Rehabilitation programs               | N/A             | N/A  | N/A       | N/A              | N/A                   | N/A                               | 4 weeks                            |                 |
| Wang, 2013        | Rehabilitation programs               | N/A             | N/A  | N/A       | N/A              | 45 min                 | 1 × 6                             | 4 weeks                            |                 |
| Wei et al., 2011  | Rehabilitation programs               | N/A             | N/A  | N/A       | N/A              | N/A                   | N/A                               | 3 months                          |                 |
| Weng, 2014        | Tizanidine and rehabilitation         | 2–4 mg          | tid  | 4 weeks   | 45 min           | 1 × 5                  | 4 weeks                           |                                    |                 |
| Xie et al., 2011  | Rehabilitation programs               | N/A             | N/A  | N/A       | N/A              | 90 min                 | 2 × 7                             | 28 days                           |                 |
| Zhang, 2016       | Rehabilitation programs               | N/A             | N/A  | N/A       | N/A              | N/A                   | 1 × 5                             | 4 weeks                            |                 |
| Zhang, 2009       | Rehabilitation programs               | N/A             | N/A  | N/A       | N/A              | 45–60 min              | (1 to 2) × 6                      | 28 days                           |                 |
| Zhang et al., 2007| Rehabilitation programs               | N/A             | N/A  | N/A       | N/A              | N/A                   | 45 min                            | 1 × 6                             | 4 weeks            |
| Zhang et al., 2008| Rehabilitation programs               | N/A             | N/A  | N/A       | N/A              | N/A                   | 45 min                            | 1 × 6                             | 3 weeks            |
| Zhang et al., 2012| Rehabilitation programs               | N/A             | N/A  | N/A       | N/A              | N/A                   | 40 min                            | 1 × 7                             | 28 days            |
| Zhao, 2013        | Rehabilitation programs               | N/A             | N/A  | N/A       | N/A              | N/A                   | 30 min                            | 1 × 7                             | 4 weeks            |
| Zhao, 2010        | Rehabilitation programs               | N/A             | N/A  | N/A       | N/A              | N/A                   | 30 min                            | 1 × 6                             | 30 days            |
| Zhong, 2016       | Rehabilitation programs               | N/A             | N/A  | N/A       | N/A              | N/A                   | 30 min                            | 1 × 6                             | 4 weeks            |
| Zhu et al., 2002  | Rehabilitation programs               | N/A             | N/A  | N/A       | N/A              | N/A                   | N/A                               | 30 days                           |                 |
| Zhu et al., 2007  | Rehabilitation programs               | N/A             | N/A  | N/A       | N/A              | N/A                   | N/A                               | 30 days                           |                 |
| Zhu et al., 2013  | Rehabilitation programs               | N/A             | N/A  | N/A       | N/A              | N/A                   | N/A                               | 30 days                           |                 |

bid, twice per day; N/A, not available; qd, once per day; tid, three times per day.
Synthesis of FMA (total motor function) changes from two trials (Zhang et al., 2007; Jia et al., 2012) showed superior effects of topical CHM combined with RC compared to RC alone (MD 5.56, 95% CI: 2.38 to 8.74, \( P = 0\% \)) (Table 4). Similarly, meta-analysis results of another two studies (Ou et al., 2014; Lai, 2016) showed greater improvement in FMA (upper-limb motor function) with topical CHM added to RC (MD 5.88, 95% CI: 4.09 to 7.68, \( P = 0\% \)) than with RC alone (Table 4).

Compared to RC alone, a combination of topical CHM and RC further improved BI results, as shown in a meta-analysis of six studies (Huang, 2011; Jia et al., 2012; Wang et al., 2014; Cao and Han, 2015; Lai, 2016; Zhang, 2016) (MD 12.01, 95% CI: 2.81 to 21.22, \( P = 99\% \)) (Table 4).

Safety Assessment

In total, 10 of the included studies addressed the safety of CHM; the remaining 25 studies did not provide information on adverse events. One study (Lai, 2016) reported one case of skin allergy in the intervention group receiving topical CHM. Although the symptom was evaluated as mild by the physician and was alleviated after 3 days, the patient dropped out of the study due to this event, without further confirmation of causality. Another study reported one patient in the treatment group of topical CHM who experienced transient influenza-like symptoms after Botox injection (Ou et al., 2014), which was considered not related to the use of CHM.

Subgroup Analyses and Sensitivity Analyses

Add-On of Oral CHM to RC

Due to the limited number of included studies, there were insufficient data for subgroup analysis. In terms of sensitivity analysis of BI synthesis results, when only studies with low risk of bias in sequence generation were included, significant results remained and heterogeneity reduced to 66% (four studies: Li and Wang, 2011; Liu et al., 2014a; Murat, 2016; Zhong, 2016; MD 7.81, 95% CI: 4.31 to 11.31) (Table 5).

Add-On of Topical CHM to RC

For AS or MAS in the upper extremity, heterogeneity reduced to 0% in the subgroup where only patients with first-stroke onset were included. Due to the limited number of studies, subgroup analysis on FMA was not possible. With regard to BI, the subgroup where patients were within 180 days after stroke (three studies: Jia et al., 2012; Wang et al., 2014; Zhang, 2016; SMD 19.14, 95% CI: 17.29 to 20.98, \( P = 43\% \)) demonstrated a greater effect than observed in the subgroup of patients with a post-stroke period exceeding 180 days (three studies: Huang, 2011; Cao and Han, 2015; Lai, 2016; SMD 3.53, 95% CI: 0.51 to 6.54, \( P = 43\% \)) (Table 6). In terms of the administration of CHM, an add-on effect was detected when the CHM was used as steaming therapy for the outcomes of lower-limb AS or MAS (SMD −1.22, 95% CI: −2.06 to −0.39, \( P = 82\% \)) and BI (MD 17.12, 95% CI: 11.92 to 22.32, \( P = 82\% \)), while there was no add-on benefit for AS or MAS of lower limb (SMD −1.09, 95% CI: −2.52 to 0.34, \( P = 91\% \)) and BI (MD 8.98, 95% CI: −2.81 to 20.76, \( P = 99\% \)) when CHM was used for compression.
### TABLE 4 | Summary of meta-analyses results.

| Outcome measure                      | No. of studies | Effects                                      | I² (%) |
|--------------------------------------|----------------|----------------------------------------------|--------|
| **Oral CHM**                         |                |                                              |        |
| Upper-limb AS/MAS                    | 3              | SMD −1.79, 95% CI: −3.00 to −0.57*           | 94     |
| Lower-limb AS/MAS                    | 3              | SMD −1.01, 95% CI: −1.43, −0.59*             | 55     |
| Overall motor FMA                    | 3              | MD 12.14, 95% CI: 1.57, 22.71*               | 89     |
| Upper-limb motor FMA                 | 3              | MD 7.64, 95% CI: −1.29, 16.57               | 97     |
| Lower-limb motor FMA                 | 2              | MD 4.03, 95% CI: 1.90, 6.17*                | 61     |
| BI                                   | 7              | MD 13.15, 95% CI: 4.37, 21.93*              | 98     |
| **Topical CHM**                      |                |                                              |        |
| Upper-limb AS/MAS                    | 8              | SMD −1.06, 95% CI: −1.40, −0.72*            | 72     |
| Lower-limb AS/MAS                    | 5              | SMD −1.16, 95% CI: −1.83, −0.49*            | 84     |
| Overall motor FMA                    | 2              | MD 5.56, 95% CI: 2.38, 8.74*                | 0      |
| Upper-limb motor FMA                 | 2              | MD 5.88, 95% CI: 4.09, 7.68*                | 0      |
| BI                                   | 6              | MD 12.01, 95% CI: 2.81, 21.22*              | 99     |

*Significant add-on effect was detected by meta-analysis.

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**FIGURE 3 | Forest plot of (Modified) Ashworth Scale.**
Sensitivity analysis of studies with low risk of bias for sequence generation showed that the significant treatment effects remained, while heterogeneity reduced for the score changes for upper-limb AS or MAS (six studies: Shen et al., 2007; Li et al., 2008; Chen et al., 2010; Ding, 2016; Lai, 2016; Zhang, 2016; SMD −0.86, 95% CI: −1.14 to −0.58, I² = 50%) (Table 5), as well as that of lower-limb (three studies: Ou et al., 2007; Shen et al., 2007; Chen et al., 2010; SMD −0.61, 95% CI: −0.96 to −0.27, I² = 0%) (Table 5).

Publication Bias
None of the above meta-analyses included more than 10 trials; therefore, publications bias was not evaluated.

Herb Analysis
*Bai Shao* (*Paeonia lactiflora* Pall.) was the most frequently used oral herb, reported by 17 studies, followed by *Gan Cao* (*Glycyrrhiza uralensis* Fisch.) (*Table 7*). *Shen Jin Cao* (*Lycopodium japonicum* Thunb.) and *Dang Gui* [*Angelica sinensis* (Oliv.) Diels] were among the most frequently reported topical herbs in the included studies (*Table 7*). In fact, the combination of *Bai Shao* and *Gan Cao* is a traditional oral CHM formula termed *Shao Yao Gan Cao Tang* (SYGCT), which was reported to have antispasticity activity (Zhang et al., 2015).

For topical herbs, *post hoc* subgroup analysis was conducted to estimate the effects of individual and the combination of the top five most frequently reported herbal ingredients in the included studies. *Table 6* summarizes the results with significant between-subgroup differences in *post hoc* analysis of herbs. Superior effects were detected in the subgroup of studies in which the formulas included *Bai Shao* than in subgroups of studies without *Bai Shao*, in terms of AS or MAS for the lower limbs (SMD −1.55, 95% CI: −2.29 to −0.82, I² = 79%) and BI (MD 18.01, 95% CI: 14.91 to 21.12, F = 75%). Similarly, subgroups of studies using *Dang Gui* might have greater benefits than those without this herb, in terms of upper-limb AS or MAS (SMD −1.21, 95% CI: −1.58 to −0.83, I² = 71%) and BI (MD 18.01, 95% CI: 14.91 to 21.12, F = 75%). It is worth noting that formulas containing three ingredients (*Bai Shao, Dang Gui,* and *Hong Hua*) demonstrated a trend for greater
efficacy in terms of the three outcome measures: AS or MAS in upper limbs (SMD $-1.56$, 95% CI: $-1.94$ to $-1.17$, $I^2 = 43\%$), AS or MAS in lower limbs (SMD $-1.93$, 95% CI: $-2.34$ to $-1.53$, $I^2 = 0\%$), and BI (MD $18.01$, 95% CI: $14.91$ to $21.12$, $I^2 = 75\%$) than the formulas without these herbs, with reduced heterogeneity.

**DISCUSSION**

The results of this systematic review suggested that adding oral or topical CHM to RC for PSS is beneficial for reducing muscle spasticity in the upper and lower extremities. For the overall
TABLE 6 | Subgroup analysis.

| Analysis | Subgroups | Upper-limb AS or MAS* | Lower-limb AS or MAS* | Barthel Index‡ |
|----------|-----------|-----------------------|-----------------------|---------------|
| All studies | | SMD –1.06, 95% CI: –1.10 to –0.72, I² = 72%, 8(200/292) | SMD –1.16, 95% CI: –1.83 to –0.49, I² = 84%, 5(140/138) | MD 12.01, 95% CI: 2.81, 21.22, I² = 99%, 6(231/231) |
| First onset of stroke | Yes | SMD –1.19, 95% CI: –1.48 to –0.91, I² = 0%, 2(119/110) | SMD –1.01, 95% CI: –1.50 to –0.59, I² = 76%, 8(181/182) | N/A |
| Treatment duration | >4 weeks | N/A | N/A | N/A |
| ≤180 days | ≤4 weeks | N/A | N/A | N/A |
| >180 days | Not included | SMD –1.10, 95% CI: –1.48 to –0.71, I² = 67%, 5(199/198) | SMD –0.99, 95% CI: –1.75 to –0.24, I² = 84%, 3(101/103) | MD 19.14, 95% CI: 17.29 to 20.98, I² = 43%, 3(128/128) |
| Preparation | Compressing | SMD –1.12, 95% CI: –1.54 to –0.69, I² = 60%, 4(140/132) | SMD –1.09, 95% CI: –2.52 to 0.34, I² = 91%, 2(65/64) | MD 8.98, 95% CI: –2.81 to 20.76, I² = 99%, 3(82/82) |
| Post hoc analysis | BS | Included | SMD –1.15, 95% CI: –1.69 to –0.61, I² = 82%, 5(184/184) | SMD –1.55, 95% CI: –2.29 to –0.82, I² = 79%, 3(94/94) | MD 18.01, 95% CI: 14.91 to 21.12, I² = 75%, 4(173/171) |
| with herbal ingredients | DG | Included | SMD –0.96, 95% CI: –1.24 to –0.68, I² = 0%, 3(116/108) | SMD –0.50, 95% CI: –0.92 to –0.08, I² = 0%, 2(44/44) | MD 3.79, 95% CI: –0.33 to 7.91, I² = 70%, 2(58/60) |
| Post hoc analysis | BS+DG | Included | SMD –1.30, 95% CI: –1.90 to –0.71, I² = 81%, 4(154/154) | SMD –1.55, 95% CI: –2.29 to –0.82, I² = 79%, 3(94/94) | MD 18.01, 95% CI: 14.91 to 21.12, I² = 75%, 4(173/171) |
| with herbal ingredients | BS+SG | Included | SMD –0.86, 95% CI: –1.13 to –0.59, I² = 16%, 4(146/146) | SMD –0.50, 95% CI: –0.92 to –0.08, I² = 0%, 2(44/44) | MD 3.79, 95% CI: –0.33 to 7.91, I² = 70%, 2(58/60) |
| BS+SJC | Included | SMD –1.15, 95% CI: –1.69 to –0.61, I² = 82%, 5(184/184) | SMD –1.55, 95% CI: –2.29 to –0.82, I² = 79%, 3(94/94) | MD 18.01, 95% CI: 14.91 to 21.12, I² = 75%, 4(173/171) |
| Not included | SMD –0.96, 95% CI: –1.24 to –0.68, I² = 0%, 3(116/108) | SMD –0.50, 95% CI: –0.92 to –0.08, I² = 0%, 2(44/44) | MD 3.79, 95% CI: –0.33 to 7.91, I² = 70%, 2(58/60) |
| DG+SJC | Included | SMD –1.26, 95% CI: –1.70 to –0.82, I² = 75%, 5(23/23) | N/A | N/A |
| Not included | SMD –0.72, 95% CI: –1.02 to –0.41, I² = 0%, 3(87/87) | N/A | N/A |
| BS+DG+HH | Included | SMD –1.56, 95% CI: –1.94 to –1.17, I² = 43%, 3(129/129) | SMD –1.93, 95% CI: –2.34 to –1.53, I² = 0%, 2(69/69) | MD 18.01, 95% CI: 14.91 to 21.12, I² = 75%, 4(173/171) |
| Not included | SMD –0.77, 95% CI: –1.04 to –0.49, I² = 32%, 5(171/163) | SMD –0.61, 95% CI: –0.96 to –0.27, I² = 0%, 3(71/71) | MD 3.79, 95% CI: –0.33 to 7.91, I² = 70%, 2(58/60) |
| BS+DG+SJC | Included | SMD –1.30, 95% CI: –1.90 to –0.71, I² = 81%, 4(154/154) | SMD –1.55, 95% CI: –2.29 to –0.82, I² = 79%, 3(94/94) | MD 18.01, 95% CI: 14.91 to 21.12, I² = 75%, 4(173/171) |
| Not included | SMD –0.86, 95% CI: –1.13 to –0.59, I² = 16%, 4(146/146) | SMD –0.50, 95% CI: –0.92 to –0.08, I² = 0%, 2(44/44) | MD 3.79, 95% CI: –0.33 to 7.91, I² = 70%, 2(58/60) |

Bi, Barthel Index; BS, Bai Shao (Paeonia lactiflora Pall.); CHM, Chinese herbal medicine; DG, Dang Gui (Angelica sinensis (Oliv.) Diels); FMA, Fugl-Meyer Assessment; Hh, Hong Hua (Carthamus tinctorius L.); I/MAS, Modified Ashworth Scale; MG, Mu Gua (Chamaeactes speciosus (Sweet) Nakai); N/A, not applicable; SJC, Shen Jín Cao (Icypodium japonicum Thunb.). *Results were presented in the way of “SMD, 95% CI, I², No. of studies (No. of participants of I/C groups)”; ‡Results were presented in the way of “MD, 95% CI, I², No. of studies (No. of participants of I/C groups)”; §No statistically significant difference; ¶Heterogeneity reduced.

and lower-limb motor score of FMA and BI, significant add-on effects were observed for both oral and topical CHM. In contrast, no significant effects were seen when adding oral CHM to RC for upper-limb motor function. Mild self-healing adverse events were reported in the intervention group receiving topical CHM; the connections of the CHMs to the adverse events had, however, not been explored.

**Clinical Implications**

In our analyses, the changes in AS or MAS scores were merged for analysis using SMD; therefore, the minimum detectable difference or minimum clinically important difference (MCID) was not applied to its clinical interpretation (Figure 3). With regard to upper-extremity FMA, both minimum detectable difference and MCID were found to be 5.2 (Wagner et al., 2008; Page et al., 2012). MCID for overall, upper-limb, and lower-limb FMA was found to be 6.0, 4.58, and 3.31, respectively, in another study (Chen et al., 2015). In fact, the changes in the total motor, upper-limb, and lower-limb FMA scores in intervention groups (oral or topical CHM plus RC) and control groups (RC alone) were all greater than the MCID (Figure 4). In terms of BI, the minimum detectable difference (4.02 points) (Hsieh et al., 2007) was established and used for interpretation of our results. The
TABLE 7 | Frequently used herbs.

| Herbs (Chinese Pin Yin) | Academic names | Frequency |
|------------------------|----------------|-----------|
| Oral herbs             |                |           |
| Bai Shao               | Paeonia lactiflora Pall. | 17        |
| Gan Cao                | Glycyrrhiza uralensis Fisch. | 13        |
| Pang Gui               | Angelica sinensis (Oliv.) Diets | 12        |
| Quan Ke                | Ruthus martensii Karsch | 10        |
| Di Long                | Phereetima aspargillum (E.Ferrier) or Phereetima vulgaris Chen or Phereetima guillelmi (Michaelis) or Phereetima pectinifera Michaelen | 9          |
| Mu Gua                 | Chamaomeles speciosa (Sweet) | 9          |
| Jin XueTeng            | Galenaria chuanxiong Hort. | 8          |
| Shen Jin Cao           | Lycopodium japonicum Thunb. | 7          |
| Huang Qi               | Astragalus membranaceus (Fisch.) Bge. var. mongholicus (Bge.) Hsiao or Astragalus membranaceus (Fisch.) Bge. | 7          |
| Tao Ren                | Prunus persica (L.) Batsch or Prunus davidiana (Car.) Franch | 6          |
| Hong Hua               | Carthusium tincturus L. | 6          |
| Topical herbs          |                |           |
| Bai Shao               | Paeonia lactiflora Pall. | 12        |
| Hong Hua               | Carthusium tincturus L. | 12        |
| Mu Gua                 | Chamaomeles speciosa (Sweet) | 11        |
| Gui Zhi                | Cinnamomum cassia Presi | 9          |
| Dan Shen               | Salvia miltiorrhiza Bge. | 9          |
| Gan Cao                | Glycyrrhiza uralensis Fisch. | 9          |
| Chuan Xing             | Ligusticum chuanxiong Hort. | 8          |
| Ji Xue Teng            | Spatholobus suberecctus Dunn | 7          |
| Wei Ling Xian          | Clematis chinensis Osbeck or Clematis hexapetala Pall. or Clematis manshurica Rupr. | 7          |

The use of oral CHM with RC demonstrated clinical advantages for PSS in terms of BI when compared to RC alone (Figure 5). The reasons for inconsistent effects among different outcomes should be cautiously interpreted: first, the relatively small numbers of participants and included studies and high heterogeneity limited our confidence in these results; second, a decrease in spasticity severity might not necessarily lead to improvement in motor function (Li, 2017); third, other factors, such as muscle strength, might also contribute to changes in the results, particularly motor function and activities of daily living (Langhammer et al., 2007; Harvey, 2015; Nunes et al., 2016).

This review attempted to explore the characteristics of PSS patients who would benefit from adding CHM therapies to RC, such as the time of stroke onset and the post-stroke period. The results of subgroup analyses suggested that patients with spasticity within 180 days post-stroke might benefit more from additional topical CHM treatment. As for specific CHM treatment, further exploration of potential formulas was not applicable because of the diversity of formulas used in the included studies (Table 2). Therefore, we summarized the most frequently reported herbs and conducted subgroup analysis for individual and combinations of herbal ingredients used in the included studies. For oral CHM, Bai Shao and Gan Cao were the most frequently used herbs, although a subgroup analysis supporting the use of these two herbs was not possible. In terms of topical CHM, a combination of Bai Shao, Pang Gui, and Hong Hua demonstrated a promising therapeutic add-on effect for spasticity reduction and an improvement in activities of daily living. Specifically, for the preparation of topical CHM, steaming therapy with CHM showed a trend for better improvement than CHM compression therapy (Table 6). It is worth noting that confounding variables might also have an impact on the results, due to the complexity of the application of topical CHM. For instance, the overall treatment effects of steaming may be a combined result of CHM, steaming water, and heat. Therefore, to distinguish and confirm individual therapeutic efficacy of CHM requires further assessment. Treatment duration was reported to range from 20 days to 3 months among the included trials (Table 2). However, subgroup analysis of treatment with a predefined cutoff of 4 weeks' duration was not applicable. Moreover, all participants enrolled in the included studies had already developed spasticity, with AS or MAS ≥ 1. Thus, the effects of CHM on patients at a very early post-stroke stage, when spasticity is not yet detectable with MAS, cannot be known based on the results of this review. Furthermore, all participants enrolled in the included trials were Chinese, and thus the generalizability of the results is not known; additional evidence of using CHM therapy on a non-Chinese population is therefore required.

Potential Pharmacological Mechanisms

Neuroprotective activity, exerted via activation of the adenosine A1 receptor, was observed with paenoniflorin extracted from Bai Shao (Liu et al., 2005; Zhang et al., 2009; Tang et al., 2010; Zhang et al., 2017). In terms of Gan Cao, potential neuroprotection by one of its major ingredients, glycyrrhizin, was mediated by anti-inflammatory effects via inhibition of HMGB1 secretion and inhibition of neurotoxicity by suppression of glutamate-induced apoptosis (Kim et al., 2012b). Triterpene saponins and Licochalcone E in Gan Cao were observed to have protective effects against neurotoxicity through suppression of glutamate-induced apoptosis (Cheng et al., 2006; Hwang et al., 2006) and activation of the Nrf2/antioxidant-response element signaling pathway (Kim et al., 2012a). Another bioactive component, Licochalcone A, was shown to have anti-spasmodic activity alone and when combined with paenoniflorin, potentially through inhibition of phosphodiesterases (Sato et al., 2006; Nagai et al., 2007) and by decreasing excitatory amino acid content, respectively (Kimura et al., 1984; Zhang et al., 2015). The ingredients with anti-neurotoxicity effects in Pang Gui include polysaccharides, organic acids, and pthalides. Potential mechanisms include decreased expression of nicotinic acetylcholine receptors (Gu et al., 2008) and increased brain-derived neurotrophic factor and nerve growth factor protein expression (Chen et al., 2009). Similarly, neuroprotective function could also be observed for ingredients of Hong Hua (He et al., 2012; Yu et al., 2013; Zhang et al., 2016). A combination of topically used Pang Gui, Hong Hua, and Bai Shao demonstrated a promising benefit for PSS (Table 6), but the underlying mechanism is yet to be unveiled. Representative examples of major neurological effects and potential mechanisms are summarized in Table 8.
### TABLE 8 | Representative examples of major neurological effects and potential mechanisms.

| Herbs                        | Bioactive ingredients | Related formulations | Beneficial effects | Potential mechanisms                                                                                                                                                                                                 | Experimental models | Ref               |
|------------------------------|-----------------------|----------------------|--------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------|------------------|
| **Dang Gui (Angelica sinensis** | Polysaccharides       | 1) Ji Wei Bu Yang Huan | Neuroprotective     | Increasing brain-derived neurotrophic factor and nerve growth factor protein expression                                                                                                                                  | Rats                | Nunes et al., 2016 |
| *(Oliv. Diels)*               | Organic acids         | Wu Tang              | effects            | Decreased expression of nicotinic acetylcholine receptors induced by β-amyloid protein                                                                                                                                     | Human neuroblastoma | Langhammer et al., 2007 |
|                              | Phthalides            | 2) Tong Luo Jie Jing Tang | Inhibit            | Activating adenosine A1 receptor: 1) scavenging superoxide anions, inhibiting microglial activation and IL-1β, TNF-α expressions 2) attenuated neuronal apoptosis by regulating the Ca²⁺/CaMKII/CREB signaling pathway | Rats                | Liu et al., 2005, Tang et al., 2010, Zhang et al., 2017 |
| **Bai Shao (Paeonia lactiflora** | Paeoniflorin          | 1) Shao Yao Gan Cao Tang | Neuroprotective     | Anti-spasmodic activity (Combined with paeoniflorin and glycyrrhizin): 1) decrease excitatory amino acids content 2) inhibit muscle contraction | Rats                |                   |
| *Pali.*                      |                       | 2) Gua Lou GuZhi Tang | activity           | Analgesic activity Preoniflorin (180 mg/kg): inhibiting the extracellular signal-regulated protein kinase (ERK) pathway                                                                                                           |                    |                   |
|                              |                       | 3) Tong Luo Jie Jing Tang |                   |                              | Rats                |                   |
|                              |                       | 4) Jie Jing He Ji     |                   |                              | Rats                | Zhang et al., 2009 |
| **Gan Cao (Glycyrrhiza uralensis: Fisch).** | Glycyrrhizin | 1) Shao Yao Gan Cao Tang | Neuroprotective     | Anti-inflammatory effects by inhibiting HMGB1 secretion, anti-excitotoxic, and anti-oxidative                                                                                                                                  | Rats                | Kim et al., 2012b  |
| *Pali.*                      | (glycyrrhizin acid)   | 2) Gua Lou GuZhi Tang | effects            |                          |                    |                   |
|                              |                       | 3) Shu Jin Tong Luo Fang |                   |                              | Rats                |                   |
|                              |                       | 4) Jie Jing He Ji     |                   |                              | Rats                |                   |
| **Gan Cao**                  | Triterpene saponins   | 1) Shao Yao Gan Cao Tang | Inhibit            | Suppression of the glutamate-induced apoptosis by: 1) inhibiting the Ca²⁺ influx activated through NMDA receptor by glutamate 2) diminishing DNA fragmentation and cleavage of PARP 3) inhibiting the binding activity of NF-κB 4) maintaining the SOD1 levels | Rat neuronal cultures and merionesugucilactus | Cheng et al., 2006, Hwang et al., 2006 |
| *(Glycyrrhiza uralensis: Fisch).** | LicorhcaloneA       | 2) Gua Lou GuZhi Tang | activity           |                          |                    |                   |
|                              | LicorhcaloneE        | 3) Shu Jin Tong Luo Fang |                   |                              | Rats                |                   |
|                              |                       | 4) Jie Jing He Ji     |                   |                              | Rats                |                   |
| **Hong Hua**                 | Hydroxysaffloweryellow | 1) Bu Yang Huan Wu Tang | Neuroprotective     | Anti-spasmodic activity Inhibit PDEs, especially isozyme 3, followed by the accumulation of intracellular cAMP Activates N12/antioxidant response element signaling pathway | Mouse jejunum       | Nagai et al., 2007, Sato et al., 2006, Kim et al., 2012a |
| *(Carthamustinctiorum L.)*   | A                    | 2) Yi Qi Rou Jin Tang | function           |                          | Mouse cells         |                   |
|                              | Kaempferol-3-O-      | 3) Shu JinHuo Luo Xi Ji |                   | Neuroprotection Suppression of apoptosis by the regulation of Bcl-2 and Bax protein expression Inhibit the activation of NF-κB and STAT3 | Rats                | Yu et al., 2013    |
|                              | rutinoside           | 4) Jie Jing He Ji     |                   |                              | Rats                | Chen et al., 2009 |
| **Mu Gua**                   | Oleandric acid       | 1) Tong Luo Jie Jing Tang | Inhibit            | Neuroprotection Inhibit neuronal death by elevating intracellular Ca²⁺ concentration, and generation of ROS                                                                                                                  | Rat cortical neurons | Zhang et al., 2016 |
| *(Chaenomeles speciosa (Sweet) Nakai)* | Ursolic acid    | 2) Rou Jin Tang       | activity           |                          |                     |                   |
|                              |                      | 3) Shu JinHuo Luo Xi Ji |                   |                              |                     |                   |
|                              |                      | 4) Jie Jing He Ji     |                   |                              |                     |                   |

Bax protein, Bcl-2-associated X protein; Bcl-2, B-cell lymphoma 2; Ca²⁺, calcium ion; CaMKII, calmodulin-dependent protein kinase II; cAMP, Cyclic adenosine monophosphate; CREB, cAMP response element-binding high mobility group box 1; protein; L-1β, interleukin-1beta; NF-κB, nuclear factor-kappa B; NMDA, N-methyl-D-aspartate; NF2, nuclear factor E2-related factor 2; PARP, poly-ADP-ribose polymerase; PDE, phosphodiesterase; Ref, references; ROS, reactive oxygen species; SOD1, superoxide dismutase 1; STAT3, signal transducer and activator of transcription 3; TNF-α, tumor necrosis factor-alpha. Australian National Stroke Foundation (2017).
However, various formulas with complex compounds were used in the included studies, and the potentially active ingredients isolated from CHM usually act on different mechanisms and pathways. There is no direct research evidence from studies on human skeletal muscles using these bioactive ingredients to exploring the underlying mechanisms of the effects on spasticity specifically; spasticity is characterized by a velocity-dependent increase in tonic stretch reflexes (Lance, 1980). Therefore, the causal relationship between the observed therapeutic effects on PSS and the individual components or monomolecular substance targeting at a few known cellular or molecular pathways could not be confirmed. Further mechanistic and clinical studies are needed to elucidate how the bioactive CHM ingredients work individually and interactively, to optimize and even standardize CHM components and treatment protocols in future.

Limitations
Safety and long-term tolerance of therapy are a concern in the treatment of PSS (Nair and Marsden, 2014). Our systematic review suggested that oral and topical CHM were well tolerated during a treatment period as long as 3 months, with mild adverse events among 10 studies (Zhu et al., 2002; Shen et al., 2007; Zhu et al., 2007; Zhang, 2009; Chen et al., 2010; Huang, 2011; Zhao, 2013; Ou et al., 2014; Weng, 2014; Lai, 2016) (Table 1). However, the remaining 25 studies did not address the safety issue and none of the included studies covered a follow-up period, making the assessment of long-term safety inapplicable based on the results of our systematic review.

Proper randomization and allocation are essential for reducing selection bias in RCTs. However, in this systematic review, only 51.4% of the included studies applied appropriate methods for sequence generation, and only 5.7% did so for allocation concealment (Figure 2). Both of these deficits might lead to underestimation or overestimation of the treatment effects (Pildal et al., 2007). It is worth noting that none of the included trials attempted to blind participants or personnel with the use of an appropriate placebo, and outcome assessors were blinded in only three studies (Zhang et al., 2007; Liu et al., 2014a; Weng, 2014). Admittedly, there is no easy way to perform double-blinding with oral or topical CHM therapies, whose preparation, appearance, taste, and smell are so diverse that placebo control might be difficult. In the context of this challenge with decoction, other forms of oral CHM could be considered if applicable, such as granule, capsule, or dropping pills. In addition, given the improvement in the preparation of CHM and the extraction technique of active components, lipophilic compounds of herbs, such as Tanshinone, that could not be efficiently extracted through traditional decoction, might be available with supercritical carbon dioxide (Esquivel-Hernandez et al., 2016; Sulniute et al., 2017). With such techniques, the effective compounds can be extracted more efficiently, and the quality control of CHM products can be improved. Moreover, the use of more advanced CHM products may make the double-blinded, placebo-controlled trial design feasible. Furthermore, tests of blinding with placebo are needed before conducting a randomized control trial, and evaluation of addition of CHM efficacy as compared with placebo, added to rehabilitation therapies or pharmacotherapies, are required, especially for non-objective outcome assessments.

Another limitation of the synthesis results is the reporting quality of the included studies. None of the included studies reported all key items recommended by CONSORT 2010 and its Extension for Herbal Intervention and Chinese Herbal Medicine Formulas (Gagnier et al., 2006; Schulz et al., 2010; Cheng et al., 2017). Even among those reported in original studies, ambiguous terms were frequently seen (Table 2). For example, instead of specific volume, “dose” was frequently used in the reporting of oral CHM interventions. The reported oral solutions in the included studies are difficult to distinguish clearly from decoction, whose scope is yet to be specifically defined. Therefore, future trials need to improve reporting quality, and specific definitions and standardization of CHM interventions require further research and agreement.

Disagreement With Existing Reviews
We identified one published systematic review and meta-analysis investigating the effects of the oral CHM formula SYGCT for PSS (Chen and Tan, 2016). Ten RCTs involving 732 participants were included in that meta-analysis through a database search from January 1990 to November 2015. The Jadad scale was used to assess the methodological quality of the included studies. Based on the synthesis results of FMA and BI, the review concluded that the decoction SYGCT had potential benefits for patients with PSS. However, because different comparisons, such as SYGCT vs. RC, and SYGCT add-on to RC vs. RC, were pooled into one meta-analysis, this conclusion was not confirmed. Moreover, that review did not evaluate the outcome related to the severity of spasticity. Our systematic review and meta-analysis differed from this previous systematic review in the following ways: First, our review focused specifically on the add-on effects of CHM, including oral and topical CHM for PSS; second, comprehensive outcome measures were evaluated in terms of spasticity severity, motor function, and activities of daily living; third, our research provided up-to-date evidence by performing a search from database inception to February 2018; fourth, the Cochrane risk-of-bias tool was used for methodological quality assessment, since the validity of the total score of the Jadad scale has increasingly been challenged (Emerson et al., 1990; Schulz et al., 1995; Juni et al., 1999).
AUTHOR’S NOTE

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AUTHOR CONTRIBUTIONS

CL and CX initiated the research. YC, CZ, and SL conducted the database search, study screening, data extraction, and data analyses. AZ, ZW, and XG were involved in data analysis and interpretation and in resolving disagreements. YC and CZ drafted the manuscript. All authors contributed to manuscript revision and read and approved the submitted version.

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SUPPLEMENTARY MATERIAL

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Conflict of Interest Statement: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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