Is adjunctive treatment with medication of liver-soothing-oriented method beneficial for depression after cerebrovascular accident?  
A PRISMA-compliant meta-analysis

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Abstract
Background: Adjunctive treatment with medication of liver-soothing-oriented method (MLSM) is one of the most commonly used approaches for subjects with depression after cerebrovascular accident (DCVA) in China. The purpose of this meta-analysis was to evaluate the outcome of MLSM treatment in subjects with DCVA using relevant published literature.

Methods: The PubMed, Cochrane Library, Embase, Chinese databases of China National Knowledge Infrastructure, WanFang, Sinomed, and VIP were used to collect all publications until March 2016. Randomized controlled trials comparing treatments with and without MLSM for subjects with DCVA were included. The quality of each publication was assessed based on the recent Handbook (5.1 version) for Cochrane Reviewers. Cochrane Collaboration’s software RevMan 5.3 software was applied for data analysis.

Results: Thirty studies, including 2599 cases, were identified and collected. Adjunctive treatment with MLSM noticeably enhanced total effective rates (odds ratio 3.76; 95% confidence interval [CI] 2.92–4.85, I² = 0%, P = 0.96) in comparison to non-MLSM conventional pharmacotherapy. Compared to non-MLSM treatment with MLSM, respectively, decreased and showed beneficial effects after 3 weeks (weighted mean difference [WMD] −4.83; 95% CI −6.82 to −2.83; I² = 86%, P < 0.001), 4 weeks (WMD −4.20; 95% CI −5.06 to −3.33; I² = 78%, P < 0.001), 6 weeks (WMD −3.36; 95% CI −4.05 to −2.68; I² = 54%, P = 0.02), 8 weeks (WMD −4.83; 95% CI −5.62 to −4.04; I² = 73%, P < 0.001), and 12 weeks (WMD −2.88; 95% CI −4.09 to −1.67; I² = 58%, P = 0.09). As for changes in inflammatory cytokine levels, adjunctive treatment with MLSM was associated with a significant decrease in tumor necrosis factor-α, IL-6, and interleukin-1β levels in comparison to non-MLSM treatment. Moreover, there were positive effects on score changes for some scales of daily living, Hamilton Anxiety Scale, Modified Edinburgh Scandinavian Stroke Scale, and Self-Rating Anxiety Scale. No serious adverse events were reported.

Conclusion: MLSM appears to improve symptoms of depressive disorders, enhance immediate responses, and the quality of life in subjects with DCVA. The positive action of MLSM might be potentially connected with its immunoregulating effects. More prospective trials with strict design and larger sample sizes are warranted to clarify its effectiveness and safety.
1. Introduction

Depression after cerebrovascular accident (DCVA) is a common disorder in subjects with stroke and consequently enhances the risks of physical nonparticipation, disability, and mortality. In China, the incidence of DCVA varies between 23.0% and 76.1%. Mortality in stroke subjects with depression has been observed at rates of 3.5- to 10-times higher than those with nondepression; suicide tendencies are also >10% among stroke subjects. A daily rehabilitation regime for stroke sufferers might positively affect depression symptoms; however, most potential patients suffering from depression are ignored. Conversely, only a small proportion of patients have been definitively identified after diagnosis, and even fewer seek help or receive clinical therapy.

Recently, reports have revealed that cerebrovascular diseases—as well as immunosuppression of human body system—contribute to the risks of depression. In addition, subjects with primary immunodeficiency were more susceptible to depressive disorders. However, most subjects diagnosed with DCVA did not manifest immunodeficiency, and only a small portion had a mild reduction in tumor necrosis factor-α (TNF-α), interleukin-6 (IL-6), or interleukin-1β (IL-1β) levels. DCVA patients are typically treated with antidepressant medications and with selective serotonin reuptake inhibitors in particular. Other therapeutic approaches for DCVA include psychotherapy, electroconvulsive therapy, or pharmacotherapy to relieve symptoms. However, there is no established consensus on the efficacy of these treatments. Furthermore, concerns have been presented about the risks of adverse effects or interactions between different drugs while treating subjects with depression in comparison to healthy individuals. Consequently, there is an imperative need to formulate alternative therapeutic agents to effectively manage DCVA.

In recent years, Chinese herbal medicine has been used as a complementary therapy to safely treat symptoms of depression in patients. Based on the hypothetical theory of ancient Chinese medicine, the etiology and pathogenesis of depression are influenced by Liver-qi stagnation—a comprehensive state exhibited with symptoms of mental strain or stress, pain of hypochondriac or hernal location, abnormal menstruation, or breast distending pain or lumps, and so on. Despite the fact that a series of empirical formulas have been applied in clinical practice, medication that utilizes a medication of liver-soothing-oriented method (MLSM)—a herbal prescription extract of Bupleurum chinense and Rhizoma cyperi—has been chosen for optimized management of DCVA in China. Some herbal treatments have been implicated in enhancing neuroimmunoregulation, including a potential restoration of the network balance of inflammatory cytokines in subjects with DCVA and in animal studies. Also, MLSM and its relevant components have shown to have anti-inflammatory effects in reducing TNF-α, IL-6, IL-1β, and other inflammatory factor levels in preclinical trials, while also suppressing the activity of lipoprotein-associated phospholipase A2 in cultured samples. The findings mentioned above suggest that MLSM may potentially function as a positive modulator of immunoregulation and act as an anti-inflammatory agent.

To date, no previous reviews have focused on the additive effects of MLSM in subjects with DCVA. Therefore, the purpose of this meta-analysis was to evaluate the potential efficacy and safety of adjunctive treatment with MLSM in subjects with DCVA based on published literature.

2. Material and methods

2.1. Search strategy

The review was conducted in accordance with the recommendations from preferred reporting items for systematic reviews and meta-analyses. A systematic search was conducted using the following databases: PubMed, Cochrane Library, Embase, Chinese databases of China National Knowledge Infrastructure, WanFang, Sinomed, and VIP up to March 2016. The terms of retrieval were restricted in randomized controlled trials (RCTs) and using the following keywords: (liver-soothing San OR liver-soothing Tang OR shugansan OR liver-soothing OR Shu-gan OR Liver-soothing-oriented method) AND (depression after cerebrovascular accident OR post-stroke depression OR depression after stroke OR stroke with depressive disorders). The references of included publications were also manually checked to clarify potentially eligible studies.

2.2. Study selection

The inclusion criteria were as follows—trial design: RCTs; recruitment population: subjects with DCVA diagnosis are referred to in the diagnostic criteria; intervention approaches: MLSM plus conventional pharmacotherapy versus conventional pharmacotherapy alone or versus the conventional pharmacotherapy plus placebo (the placebo was a simulated treatment of MLSM with identical dosage forms [i.e., capsule], weight, labeling, etc. in the literature); outcome measurement: the primary outcome indexes were total effective rate based on Hamilton Depression Scale (HAM-D) score changes. The second outcome indexes were based on the levels of inflammatory cytokines (e.g., TNF-α, IL-6, and IL-1β); score changes of National Institute of Health Stroke Scale (NIHSS), activities of daily living (ADL), Hamilton Anxiety Scale (HAM-A), Modified Edinburgh Scandinavian Stroke Scale (MESSS), Self-Rating Anxiety Scale (SAS), and adverse events; and the treatment periods were no less than 3 weeks. The studies were excluded if publications did not use the original formula of MLSM; subjects had taken any antidepressants up to 4 weeks.
before recruitment; and enrolled subjects had liver and renal insufficiency, mental disease, type 2 diabetes mellitus, or other cardiovascular disorders.

2.3. Definition

DCVA diagnosis must be conducted using standards established by the international classification of diseases (ICD-9[51] or ICD-10[52]), Chinese classification of mental disorders-3[53], Diagnostic and Statistical Manual of Mental Disorders (DSM-III,[54] DSM-III-R,[55] DSM-IV,[56] or DSM-5,[57]), or other well recognized criteria. Conventional pharmacotherapy for symptomatic treatment included fluoxetine hydrochloride, deanjit, paroxetine hydrochloride, venlafaxine, or other routine antidepressants. The total effective rate was calculated using the number of subjects who obtained markedly effective responses (≥50% reduction in HAM-D scores) and effective responses (≥25% reduction in HAM-D scores), divided by the total number of subjects.

2.4. Data extraction and quality assessment

Two reviewers gathered the informative sources from all qualified studies. The extracted items included the publication year, first author, sample size, target subjects’ gender and age, MLSM interventions, control therapies, diagnoses, treatment durations, follow-up periods, outcome measurement, and adverse events. Once incomplete data or potentially duplicated documents were identified, attempts were made to contact the corresponding authors or other potential leading members via telephone or by e-mail. Publications were excluded from the review if the intervention strategy or control group settings were inconsistent with the selection criteria, in addition to other incomplete data that could not be verified by consultation with publication authors. The quality of the eligible studies was estimated based on the tools for risk bias assessment recommended by the Cochrane Collaboration (Revman5.3; www.cochrane.org/training/cochrane-handbook). Key items in the assessment included selection bias, reporting bias, performance bias, attrition bias, detection bias, and other sources of bias.

2.5. Statistical methods

Dichotomous data were presented by odds ratio (OR) with a 95% confidence interval (CI), while the continuous variables were estimated by weighted mean difference (WMD) with a 95% CI. OR values with a total effective rate >1 indicated that MLSM from pooled effects was better in comparison to the control. Using the synthesized results of ADL score changes, WMD values that were >0 indicated that MLSM was superior to those in control. However, WMD values >0 revealed that MLSM was better than those in control, while taking into account pooled effects of score changes of HAM-D, NIHSS, ADL, HAM-A, MESSS, and SAS, and the levels of inflammatory cytokines (TNF-α, IL-6, and IL-1β). Furthermore, that heterogeneity of risk factors among trials was analyzed using the I^2 and Cochrane Q statistical models. The corresponding data were evaluated based on the fixed-effect model (FEM) if there was no statistical heterogeneity observed (I^2 < 50% or P > 0.10). Once certain statistical heterogeneity was determined (I^2 > 50% or P < 0.10), pooled results were analyzed by to the random-effects model (REM). When ≥9 publications presented similar outcome indexes, funnel plots were applied to verify the potential publication bias. Intervention studies that involved different treatment durations or follow-up periods of MLSM, subgroup analyses were also performed. Grading evidence for quality evaluation of this review was conducted using the Grades of Recommendations Assessment Development and Evaluation (GRADE) profiler software (https://gradepro.org). The RevMan 5.3 software recommended by Cochrane Collaboration was utilized for data analyses (http://tech.cochrane.org/revman/).
### Characteristics of trials included in the meta-analysis.

| Study          | Y | Sample sizes trial/control | Age, y, trial/control | Target group | Control group | Treatment duration, wk | Outcomes interesting | Follow-up duration |
|----------------|---|----------------------------|-----------------------|--------------|---------------|------------------------|----------------------|-------------------|
| Chang et al.   | 2010 | 50/50                      | 42–74/45–75           | MLSM + CPST  | CPST          | 4                      | 1/2/4                | 6 wk              |
| Chen           | 2014 | 58/57                      | 56.8 ± 8.4/58.5 ± 6.7 | MLSM + CPST  | CPST          | 6                      | 1/2                  | NP                |
| Du             | 2013 | 30/40                      | 62.3 ± 6.8            | MLSM + CPST  | CPST          | 8                      | 1/2                  | NP                |
| Fan et al.     | 2010 | 62/60                      | 64.2 ± 2.2            | MLSM + CPST  | CPST          | 8                      | 1/2                  | NP                |
| Gan            | 2012 | 45/46                      | 47.9 ± 3.4/47.8 ± 3.5 | MLSM + CPST  | CPST          | 8                      | 1/2/3/4              | 4 wk              |
| He             | 2007 | 36/18                      | 53.4 ± 6.3/54.3 ± 4.4 | MLSM + CPST  | CPST          | 8                      | 1/2                  | NP                |
| Hu et al.      | 2014 | 48/48                      | 56.8 ± 7.8/56.8 ± 8.2 | MLSM + CPST  | CPST          | 6                      | 1/2                  | NP                |
| Huang et al.   | 2015 | 40/40                      | 63.5 ± 4.3/63.4 ± 4.6 | MLSM + CPST  | CPST          | 4                      | 1/2/3/4              | 12 wk             |
| Huang et al.   | 2012 | 39/39                      | 62.5 ± 7.4/61.9 ± 7.8 | MLSM + CPST  | CPST          | 12                     | 1/2                  | NP                |
| Li             | 2012 | 42/46                      | 46–75/43–79           | MLSM + CPST  | CPST          | 4                      | 1/2                  | NP                |
| Li et al.      | 2013 | 27/27                      | 57.9 ± 6.1/58.2 ± 6.7 | MLSM + CPST  | CPST          | 8                      | 1/2/7                | 8 wk              |
| Li et al.      | 2015 | 81/76                      | 32–52                 | MLSM + CPST  | CPST          | 6                      | 1/2/3/4/5            | NP                |
| Lian et al.    | 2009 | 30/50                      | 56.2 ± 18.6/54.6 ± 17.5 | MLSM + CPST  | CPST          | 8                      | 1/2                  | NP                |
| Liu            | 2010 | 30/30                      | 62.4 ± 2.5/59.9 ± 2.6 | MLSM + CPST  | CPST          | 12                     | 1/2                  | NP                |
| Liu et al.     | 2007 | 60/60                      | 50–79/51–80           | MLSM + CPST  | CPST          | 8                      | 1/2                  | NP                |
| Liu et al.     | 2011 | 35/32                      | 45–74/43–70           | MLSM + CPST  | CPST          | 8                      | 1/2                  | 4 wk              |
| Liu            | 2015 | 65/64                      | 53.6 ± 5.6/53.4 ± 5.5 | MLSM + CPST  | CPST          | 6                      | 1/2                  | NP                |
| Ma et al.      | 2015 | 38/38                      | 57.7 ± 9.6/57.4 ± 2   | MLSM + CPST  | CPST          | 8                      | 2                    | NP                |
| Shen           | 2009 | 30/30                      | 60.02 ± 5.3/58.9 ± 5.7 | MLSM + CPST  | CPST          | 8                      | 1/2                  | 6 wk              |
| Su             | 2013 | 40/40                      | 64.5 ± 6.5/56.9 ± 7.5 | MLSM + CPST  | CPST          | 8                      | 1/2/3                | NP                |
| Sun            | 2015 | 48/48                      | 64.1 ± 2/64.4 ± 4.3   | MLSM + CPST  | CPST          | 6                      | 1/2                  | 4 wk              |

**Note:** (1) Total effective rate; (2) Hamilton Depression Scale (HAMD); (3) Adverse events; (4) National Institute of Health Stroke Scale (NIHSS); (5) Activities of Daily Living (ADL); (6) Hamilton Anxiety Scale (HAMA); (7) Modified Edinburgh Scandinavian Stroke Scale (MESSS); (8) Self-Rating Anxiety Scale (SAS); (9) Detection of inflammatory cytokines. CPST = conventional pharmacotherapy of symptomatic treatment, MLSM = medication of liver-soothing-oriented method, NP = not provided.

### 2.6 Ethical review

The study is a systemic literature review that did not involve experimental participants or human subjects, and there was no collection of any private data or sensitive information during the review process.

### 3. Results

#### 3.1. Description of included trials

The initial retrieval of publications resulted in the collection of 768 potential studies. After reviewing the full texts, a total of 30 studies qualified for inclusion based on the predetermined criteria of inclusive recruitment (Fig. 1). In all, 2,599 subjects with DCVA were included in this review. All of the publications included were written in the Chinese language (Mandarin), and the experimental work was performed in China. The duration of therapies was between 4 and 12 weeks. Outcome measures were collected both before and at the end of the relevant treatments. Target subjects in the control groups were given conventional pharmacotherapy of symptomatic treatment, while subjects in the MLSM treatment groups were given MLSM plus routine pharmacotherapy. MLSM was formulated by herbal decoction, particle, powder, capsule, or oral liquid. The baseline characteristics from the 30 studies are presented in Tables 1 and 2. The evaluation of methodological quality for each included trial is listed in Figs. 2 and 3. In general, most of the enrolled studies were observed with obvious bias from unclear to high risks. The grading evidence of quality was calculated using GRADEprofile software (Fig. 4).
3.2. Effects of the interventions: primary outcomes

3.2.1. Total effective rates with or without MLSM. Twenty-six trials\([11–13,15,16,18–27,29–31,33–40]\) reported the total effective rates as key measurement of outcomes. A total of 1126 cases were allocated to MLSM group, while 1099 cases were assigned to the control group based on conventional pharmacotherapy alone. Adjunctive treatment with MLSM significantly enhanced the total effective rate (OR 3.76; 95% CI 2.92–4.85, \(I^2 = 0\%\), \(P = 0.96\)) in comparison to the control in the FEM (Fig. 5).

3.2.2. Publication bias of total effective rates with or without MLSM. In order to evaluate potential publication bias, funnels plot analyses were performed using total effective rates from 26 trials\([11–13,15,16,18–27,29–31,33–40]\) that compared treatment with or without MLSM. Significant asymmetry was observed, indicating the presence of possible publication bias and inclusion of low-quality trials (Fig. 6).

3.2.3. Score changes in HAM-D with or without MLSM. Twenty-eight studies\([11,13–37,39,40]\) that compared with or without MLSM treatment were assessed using the mean change from baseline in HAM-D scores, resulting in substantial heterogeneity (\(P < 0.10, I^2 > 50\%\)) due to variability in the timing point of the synthesized results. Therefore, pooled estimates were conducted based on REM models, with subgroup analyses between studies using different intervention periods of 3, 4, 6, 8, and 12 weeks. Results of subgroup analyses on the changes in HAM-D scores are displayed in Fig. 7. Compared with non-MLSM, there were positive effects on HAM-D score changes after 3 weeks (WMD \(-6.28; 95\%\ CI \(-8.09 \text{ to } -4.43; I^2 = 0\%\), \(P = 0.001\)) in 15 trials,\([11,13,15,16,18–27,29,31,33–40]\) 4 weeks (WMD \(-4.83; 95\%\ CI \(-6.62 \text{ to } -3.04; I^2 = 0\%\), \(P = 0.001\)) in 25 trials,\([11,13,15,16,18–27,29,31,33–40]\) 6 weeks (WMD \(-3.66; 95\%\ CI \(-5.43 \text{ to } -1.90; I^2 = 0\%\), \(P = 0.001\)) in 10 trials,\([11,13,15,16,18–27,29,31,33–40]\) 8 weeks (WMD \(-4.83; 95\%\ CI \(-6.62 \text{ to } -3.04; I^2 = 0\%\), \(P = 0.001\)) in 16 trials,\([11,13,15,16,18–27,29,31,33–40]\) 12 weeks (WMD \(-2.88; 95\%\ CI \(-4.66 \text{ to } -1.10; I^2 = 0\%\), \(P = 0.001\)) (Fig. 7). The outcomes of sensitivity analyses revealed that no changes were observed in effect sizes when any single trial was excluded (data not included), which supported the reliability of these results.

3.2.4. Publication bias of HAM-D comparing with or without MLSM. In order to estimate potential publication bias, a funnel plot analysis of 28 trials\([11,13–37,39,40]\) was performed that compared studies with or without MLSM adopting HAM-D score changes, and significant asymmetry was observed (Fig. 8). This could indicate publication bias among the included studies.

3.3. Effects of the interventions: secondary outcomes

3.3.1. Changes in inflammatory cytokines levels with or without MLSM. Two trials\([25,32]\) evaluated the change in inflammatory cytokine levels based on TNF-α, IL-6, and IL-1β counts. Adjunctive treatment with MLSM was associated with a significant decrease in TNF-α levels (WMD \(-6.76; 95\%\ CI \(-8.09 \text{ to } -5.43; I^2 = 0\%\), \(P = 0.42\)), IL-6 levels (WMD \(-3.13; 95\%\ CI \(-4.04 \text{ to } -2.22; I^2 = 0\%\), \(P = 0.001\)) in 10 trials,\([11,13,15,16,18–27,29,31,33–40]\) and IL-1β levels (WMD \(-3.42; 95\%\ CI \(-4.66 \text{ to } -2.18; I^2 = 0\%\), \(P = 0.001\)) in 6 trials,\([11,13,15,16,18–27,29,31,33–40]\)
-3.85 to -2.41; I² = 0%, P = 1.00), and IL-1β levels (WMD –4.87; 95% CI –6.07 to –3.66; I² = 0%, P = 0.63) in a FEM when compared to the conventional treatment group (Fig. 9).

### 3.3.2. Score changes of NIHSS with or without MLSM.

Pooled results were calculated using REM model analysis of data from 6 trials[11,16,18,22–24] that compared control versus MLSM treatment by evaluating differences in mean change from baseline in NIHSS scores, and subgroup analyses were performed using follow-up periods of 4, 6, 8, and 12 weeks. There were significant decreases in NIHSS scores in regard to the MLSM group after 4 weeks (WMD –5.81; 95% CI –7.03 to –4.59; I² = 0%, P = 0.48) in 2 trials[11,18] 6 weeks (WMD –2.00; 95% CI –2.80 to –1.20) in 1 trial,[12] 8 weeks (WMD –6.94; 95% CI –7.99 to –5.89; I² = 0%, P = 0.64) in 2 trials,[16,23] 12 weeks (WMD –5.33; 95% CI –7.57 to –3.09; I² = 55%, P = 0.13) in 2 trials,[18,24] and for an overall effect observed (WMD –5.34; 95% CI –7.21 to –3.47; I² = 91%, P < 0.001) (Fig. 10).

### 3.3.3. Score changes of ADL with or without MLSM.

Pooled results were calculated using REM model analysis of data from 4 trials[15,22,30,36] that compared MLSM with non-MLSM by assessing differences in mean change from baseline in ADL scores, and subgroup analyses between trials were performed using
follow-up durations of 4, 6, and 8 weeks. In comparison to non-MLSM treatment, there were significant improvements in ADL scores observed that were in favor of the MLSM group after 4 weeks (WMD 12.95; 95% CI 10.60–15.30; $I^2=24\%$, $P=0.25$) in 2 trials,[15,36] 6 weeks (WMD 17.00; 95% CI 15.59–18.41; $I^2=0\%$, $P=0.43$) in 3 trials,[15,30,36] and an overall effect observed (WMD 15.02; 95% CI 12.98–17.06; $I^2=62\%$, $P=0.02$) (Fig. 11).

3.3.4. Score changes of HAM-A comparing with or without MLSM. Pooled results were calculated using REM model analysis of data from 2 trials[17,34] that compared control versus MLSM treatment by evaluating differences in mean change from baseline in HAM-A scores, and subgroup analyses were conducted between trials that used either 3- or 6-week duration times. In comparison to non-MLSM treatment, there were additive benefits from MLSM in terms of HAM-A scores after 3 weeks (WMD −2.96; 95% CI −4.34 to −1.59; $I^2=0\%$, $P=0.44$) in 2 trials,[17,34] 6 weeks (WMD −2.62; 95% CI −3.74 to −1.50; $I^2=0\%$, $P=0.86$) in 2 trials,[17,34] and for an overall effect observed (WMD −2.76; 95% CI −3.62 to −1.89; $I^2=0\%$, $P=0.86$) (Fig. 12).

3.3.5. Score changes of MESSS with or without MLSM. Two trials[21,40] reported a change in MESSS scores during the treatment periods. Adjunctive treatment with MLSM significantly decreased the MESSS scores (WMD −4.04; 95% CI −5.49 to −2.59; $I^2=0\%$, $P=0.55$) when compared to the conventional treatment alone (Fig. 13).

3.3.6. Score changes of SAS with or without MLSM. Two trials[14,31] reported a change in SAS scores during the treatment period. The pooled results suggested that changes in SAS scores (WMD −1.82; 95% CI −2.60 to −1.03; $I^2=0\%$, $P=0.51$) were significantly lower in MLSM-treated subjects during the follow-up duration (Fig. 14).

3.3.7. GRADE quality of evidence. GRADE profiler software was utilized to evaluate the evidence used for this meta-analysis. The quality of present evidence, based on the GRADE profiler analysis, revealed that the results were “Low/Very low”. This occurred due to relatively high risk of bias between studies and low-quality trials with small sample sizes (Fig. 4).

3.3.8. Adverse events. Four trials[15,18,38,39] reported the safety evaluation as outcome indexes. The Treatment Emergent Symptom Scale was mentioned in 1 trial,[15] while the other 3 trials[18,38,39] only covered the number of adverse events. For the MLSM treatment group, 1 trial[15] reported 2 cases with dry mouth and 1 case with dizziness. One trial[18] reported 4 cases with loss of appetite and 2 cases with mild diarrhea. One trial[38] reported 5 cases with epigastric discomfort. One trial[39] reported 2 cases with palpitation, 1 case with dry mouth, and 1 case with...
dizziness. For the conventional pharmacotherapy group, 1 trial reported 5 cases with nausea and vomiting, 3 cases with insomnia, 2 cases with dry mouth, and 2 cases with dizziness. One trial reported 8 cases with stomach upset, 3 cases with dizziness, and 1 case with headache. One trial reported 9 cases with dry mouth, 8 cases with loss of appetite, 5 cases with nausea, 3 cases with fatigue, and 2 cases with headache. One trial reported 3 cases with palpitation, 2 cases with dry mouth, 2 cases with stomach upset, and 2 cases with dizziness. No serious or frequently occurring adverse effects were reported among the literature reviewed.

4. Discussion

The review revealed that adjunctive treatment with MLSM could improve total effective rates, as well as HAM-D score changes in DCVA subjects when compared to non-MLSM treatments. Despite the fact that most of the included literatures were of...
relatively poor methodological quality, the pooled outcomes suggested beneficial effects of MLSM when combined with conventional pharmacotherapy as demonstrated by score changes in NIHSS, ADL, HAM-A, MESSS, and SAS when comparing to the conventional treatment group. Furthermore, stratified analyses indicated that the positive actions of MLSM regarding score changes of HAM-D, NIHSS, ADL, and HAM-A were found in similar magnitudes among the subgroups. In addition, significant differences were noted in the decreased levels of TNF-α, IL-6, and IL-1β in subjects with or without MLSM.

When a patient with stroke attacks found a higher susceptibility to depression, the etiology and pathology of primary immunodeficiency might be taken into account initially. A vital approach for therapies is to enhance the positive immune responses or restore innate defense mechanisms of patients’ themselves. Immune system modulated through proper channels, to some extents, could decrease the risks of progression and recurrence of target conditions. In this review, apart from enhancing the total effective rates, and reducing the score changes of HAM-D or other self-rating indexes during the follow-up period, adjunctive treatment with MLSM also obviously lower the levels of TNF-α as well as levels of IL-6 and IL-1β counts, which in turn improved anti-inflammatory actions. Recent literatures claimed that certain domains in MLSM enhanced the immune effects based on subjects’ active self-functions involved immune organs, specific immunity, and nonspecific immunity. In all, the findings abovementioned revealed that the antidepressive effects of MLSM might be associated with its immunomodulating effects. Unfortunately, no consensus has been drawn on the levels of immunoglobulin or inflammatory cytokines and conditions of recurrence or symptom enhancement in subjects with DCVA.

Figure 8. Funnel plot showing for changes of Hamilton Depression Scale comparing with or without medication of liver-soothing-oriented method.

Figure 9. Forest plots showing weighted mean difference with 95% confidence interval for changes of detection of inflammatory cytokines comparing with or without medication of liver-soothing-oriented method in a fixed-effect model: (A) TNF-α, (B) IL-6, and (C) IL-1β.
Figure 10. Forest plots showing weighted mean difference with 95% confidence interval for changes of National Institute of Health Stroke Scale comparing with or without medication of liver-soothing-oriented method in a random-effect model.

Figure 11. Forest plots showing weighted mean difference with 95% confidence interval for changes of Activities of Daily Living comparing with or without medication of liver-soothing-oriented method in a random-effect model.
with DCVA. Despite the additive benefits of MLSM for DCVA, an increasing concern for decision-making of doctors and patients is the possible toxic or side effects of MLSM. In this review, MLSM appeared to be safely applied and widely tolerable for subjects with DCVA. This situation occurred because few studies included reported relevant adverse events during the treatment or follow-up. Instead, there were just 4 studies\textsuperscript{[15,18,38,39]} that mentioned adverse events of MLSM as outcome measurements for safety. Furthermore, combined uses of medicinal products regarding biological and pharmacological activities might produce a series of potentially synergistic actions or side effect–neutralizing responses. Thus, the safety of MLSM calls for further study with strict designs.

There are some potential limitations as follows. First, the methods of randomization could not found details in most the included studies. Second, traditional clinical medicine in China was connected with pattern or syndrome differentiation. However, the studies included did not clarify subjects’ syndrome diagnosis, which could contribute to selection bias of participants. Third, definitions of DCVA are conformed to patients’ reported outcomes of symptoms or other self-rating scales of emotional disorders. Thus, misclassification in a proportion of subjects could not be ruled out. Fourth, previous data on the distribution of apathy, or other similar psychological disorders were not mentioned in the original documents, differences in severity of DCVA could also have biased effects for the reliable results. Last but not the least, substantial heterogeneities were found in the process of pooling results. In the subgroup analyses, treatment periods (dosage of MLSM), follow-up durations, formula of MLSM (herbal decoction, particle, powder, capsule, or oral liquid), and MLSM combined with immunomodulating or other active components only interpreted partial causes of heterogeneity in this review. The subjects’ severity of DCVA, characteristics of each study at baselines, or other potential confounders might result in the additional heterogeneity.

Given the methodological limitations of the studies included, there were some implications of improvement for further research as follows: informative descriptions of study design, methods of randomization, concealment of allocation, and other specified data should be provided; withdrawal, dropout, and adverse effects also should be attempted to clarify; mean number of episode periods, reduction of symptom, inflammatory cytokines, and adverse effects should also be included in the measurement of outcome indexes; and syndrome or pattern differentiation should be taken into account while conducting the diagnostic process, especially MLSM is better matching for the type of Liver-qi stagnation.

5. Conclusion

The review indicates that adjunctive treatment with MLSM could improve symptoms of depressive disorders, enhance immediate response and quality of life in subjects with DCVA. The positive

![Figure 12](https://example.com/fig12.png)

**Figure 12.** Forest plots showing weighted mean difference with 95% confidence interval for changes of Hamilton Anxiety Scale-A) comparing with or without medication of liver-soothing-oriented method in a fixed-effect model.

![Figure 13](https://example.com/fig13.png)

**Figure 13.** Forest plots showing weighted mean difference with 95% confidence interval for changes of Modified Edinburgh Scandinavian Stroke Scale comparing with or without medication of liver-soothing-oriented method in a fixed-effect model.
Acknowledgments

We thank Prof Patrick Wall and other editors/reviewers for the helpful comments and suggestions. We thank LetPub (www.letpub.com) for its linguistic assistance during the proofreading of this manuscript.

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Figure 14. Forest plots showing weighted mean difference with 95% confidence interval for changes of Self-Rating Anxiety Scale comparing with or without medication of liver-soothing-oriented method in a fixed-effect model.
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