Evidence-Based Complementary and Alternative Medicine

Emerging Trends in Evidence-based Traditional Chinese Medicine

Lead Guest Editor: Xing Liao
Guest Editors: Xiao-Yang Hu, Bo Li, Jing Hu, and Zhaolan Liu

Emerging Trends in Evidence-based Traditional Chinese Medicine

Evidence-Based Complementary and Alternative Medicine

Emerging Trends in Evidence-based Traditional Chinese Medicine

Lead Guest Editor: Xing Liao
Guest Editors: Xiao-Yang Hu, Bo Li, Jing Hu, and Zhaolan Liu

Contents

Hindawi
Evidence-Based Complementary and Alternative Medicine
Volume 2023, Article ID 6028554, 7 pages
https://doi.org/10.1155/2023/6028554

Research Article

Effectiveness and Safety of Lianhua Qingwen Capsules for COVID-19: A Propensity-Score Matched Cohort Study

Yun Lu,[1] Meng Zhang,[2] Qing-qing Yang,[2] Wen-jing Li,[1] Kun Yang,[1] Wen Hu,[1] Su-yu Gao,[1] Qiao-li Jiang,[1] Li-kai Lin,[3] Hong Cheng,[1] and Feng Sun[2]

[1]*Department of Pharmacy, Zhongnan Hospital of Wuhan University, Wuhan 430071, China*
[2]*Department of Epidemiology and Biostatistics, School of Public Health, Peking University, Beijing 100191, China*
[3]*Institute of Hospital Management, Wuhan University, Wuhan 430071, China*

Correspondence should be addressed to Hong Cheng; chenghong@znhospital.cn and Feng Sun; sunfeng@bjmu.edu.cn

Received 14 July 2022; Accepted 5 September 2022; Published 17 February 2023

Academic Editor: Xing Liao

As a traditional Chinese medicine, Lianhua Qingwen capsules have been widely used to treat Coronavirus Disease 2019 (COVID-19). This study was aimed to demonstrate the association between treatment with Lianhua Qingwen capsules and the clinical outcomes of hospitalized patients with COVID-19. This retrospective study was conducted at four hospitals in Central China. Data of hospitalized COVID-19 patients were collected between December 19, 2019 and April 26, 2020. Based on whether Lianhua Qingwen capsules were used, patients were classified into Lianhua Qingwen and non-Lianhua Qingwen (control) groups. To control for confounding factors, we used conditional logistic regression in a propensity-score matched (PSM) cohort (1 : 1 balanced), as well as logistic regression without matching as sensitivity analysis. A total of 4918 patients were included, 2760 of whom received Lianhua Qingwen capsules and 2158 of whom did not. In the PSM model, after adjusting for confounders, the in-hospital mortality was similar between the Lianhua Qingwen group and the control group (6.8% vs. 3.3%, adjusted OR, 0.66 [95% CI, 0.38-1.15], $p = 0.138$). The negative conversion rate of Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2) infection was higher in the Lianhua Qingwen group (88.3% vs. 96.1%, adjusted OR, 4.02 [95% CI, 2.58-6.25], $p < 0.001$). The incidence of acute liver injury was comparable between the two groups (14.0% vs. 11.5%, adjusted OR: 0.85 [95% CI, 0.71-1.02], $p = 0.083$), and the incidence of acute kidney injury was lower in the Lianhua Qingwen group (5.3% vs. 3.0%, adjusted OR: 0.71 [95% CI, 0.50-1.00], $p = 0.048$). Treatment with Lianhua Qingwen capsules was not significantly associated with in-hospital mortality in COVID-19 patients. In the Lianhua Qingwen group, the negative conversion rate of SARS-CoV-2 infection was higher and the incidence of acute kidney injury was lower than in the control group.

1. Introduction

While the Coronavirus Disease 2019 (COVID-19) pandemic has been ongoing for nearly three years, the disease epidemic has been moderated in most countries due to the successful development and administration of vaccines. However, severe conditions and death still occur among some people infected with Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2), and effective therapeutic drugs remain scarce [1–4]. Lianhua Qingwen is a traditional Chinese medicine (TCM) with botanical ingredients such as forsythia, honeysuckle, ephedra, bitter almond, and others [5]. It is processed into capsules and granules and was first marketed in China in 2004 to prevent and treat viral infections of the respiratory tract [6].

As early as the 2020 pandemic, Lianhua Qingwen capsules and granules were recommended as therapeutic agents in six successive versions of the diagnosis and treatment guidelines for COVID-19 [4, 7]. On April 14, 2020, the indication that "in the routine treatment of COVID-19, it can be used for fever, cough, and malaise caused by a mild or moderate type of disease" was approved to be added to the usage of Lianhua Qingwen capsules by the National Medical Products Administration of the People's Republic of China

[8]. Several studies have shown the efficacy and safety of Lianhua Qingwen for the treatment of COVID-19. However, the number of cases in these studies was small, which provided insufficient strength of the evidence supporting the effectiveness of Lianhua Qingwen for COVID-19 [8–10].

The extensive use of Lianhua Qingwen for COVID-19 treatment in the Chinese population underscores the urgent need for a comprehensive assessment of its safety and efficacy. Utilizing the COVID-19 database from early 2020, we conducted a retrospective study on the effectiveness and safety of Lianhua Qingwen to provide evidence for the appropriate use of this treatment for COVID-19.

2. Materials and Methods

2.1. Study Design. This multicenter retrospective study was conducted between December 19, 2019 and April 26, 2020 at four hospitals in Wuhan, China. Based on the rapid advice guideline for the diagnosis and management of COVID-19, data on patients with a confirmed diagnosis of COVID-19 were collected [4]. This study was approved by the Medical Ethics Committee of the Zhongnan Hospital of Wuhan University.

After excluding 32 patients aged <18 years, 484 patients without complete records, and 21 pregnant patients, a total of 4918 patients were included in the analysis (Figure 1).

2.2. Outcomes. The primary outcome in our analysis was effectiveness of Lianhua Qingwen including in-hospital mortality and negative conversion rate of SARS-CoV-2 infection which was conducted in terms of progressive disease and was defined as two consecutive negative nucleic acid tests for at least 24 h between samples from respiratory specimens [4].

The secondary outcome was the safety of Lianhua Qingwen including the incidence of acute liver injury (ALI) and acute kidney injury (AKI). ALI was defined as either (1) alanine aminotransferase (ALT) or aspartate aminotransferase (AST) ≥3 upper limit of normal (ULN); (2) alkaline phosphatase (ALP), total bilirubin (TBIL), or gamma-glutamyl transferase (GGT) ≥2ULN [11, 12]. AKI was defined as one of the following: (1) increase in serum creatinine (SCR) by ≥26.5 (μmol/L) within 48 hours, (2) increase in SCR ≥1.5 times baseline within the previous 7 days, or (3) urine volume ≤0.5 ml/kg/h for 6 hours [12].

2.3. Data Extraction and Management. Clinical data on patient characteristics, treatments during hospitalization, and outcomes were extracted from the hospital electronic medical record database consisting of front-pages, progress notes, laboratory testing results, and medication administration records. We included the following covariates: age (years), sex (female or male), time from symptom onset to admission (days), severity at admission (nonsevere group: mild or moderate cases; severe group: severe or critically severe cases) according to the Chinese management guidelines for COVID-19 (six versions), symptoms at admission (fever, cough, dyspnea, fatigue, diarrhea, or vomiting, yes or no), and comorbidities (diabetes, hypertension, cancer, and heart diseases, yes or no). In addition, the drugs (antiviral, adrenocortical hormone, or anticoagulant therapy) used were considered.

2.4. Statistical Analysis. Categorical variables were described as counts and percentages, and continuous variables as means ± standard deviations or medians with interquartile ranges (IQRs). Chi-square (χ^2) or Fisher's exact tests were used to compare categorical variables. The Mann–Whitney U test or t-test was used for continuous variables. Propensity score matching (PSM) was used to adjust for confounding factors and reduce the bias. A propensity score refers to the probability that a patient would be assigned to a certain intervention, given a set of covariates [13].

Patients who did or did not use Lianhua Qingwen were matched 1 : 1 based on similar or identical propensity scores. PSM was achieved using the MatchIt package in R using greedy nearest neighbor matching (maximum caliper distance = 0.1). In our analysis, only variables such as age, sex, time from symptom onset to admission, severity and symptoms at admission, and comorbidities were included in multivariable logistic regression to calculate propensity scores. Equivalence between the two groups was examined using the methods described above for categorical and continuous variables. Then, conditional logistic regressions with or without drug adjustment were used to explore the associations between Lianhua Qingwen capsules and outcomes.

Furthermore, the results of logistic regression based on an unmatched cohort were also compared with PSM [14, 15]. In the logistic regression, the strategies of the adjusted covariates were similar to those used in PSM. Statistical significance was defined as a two-tailed p value <0.05.

3. Results

3.1. Baseline Characteristics. A total of 4918 COVID-19 patients were enrolled. Table 1 shows the patients' characteristics upon admission. Treatment with Lianhua Qingwen capsules was provided to 2760 patients (56.1%) and was not provided to 2158 patients (43.9%). Lianhua Qingwen capsules of 1.4 g were orally administrated three times a day, and the median duration of Lianhua Qingwen treatment was 10 days (IQR: [3–16]). Of them, the median age was 61 years (IQR: [49-69]), and 48.3% (2377) of patients were women. Of the patients, 43.7% (2147) had severe condition at admission, 16.2% (796) had diabetes, 29.1% (1430) had hypertension, 0.9% (45) had cancer, and 6.2% (306) had heart diseases. Patients who received Lianhua Qingwen were older (59 (IQR: [47-68]) vs. 62 (IQR: [51-69]), $p < 0.001$) and spent less time from symptom onset to admission (16 (IQR: [8-30]) vs. 13 (IQR: [7-20]), $p < 0.001$). Compared with control group, Lianhua Qingwen users were easier to have symptoms of fever (51.4% vs. 59.9%, $p < 0.001$), cough (35.4% vs. 43.7%, $p < 0.001$), and fatigue (23.2% vs. 28.2%, $p < 0.001$). We also found that antiviral therapy was more frequently used in the Lianhua Qingwen group (63.9% vs. 87.0%,

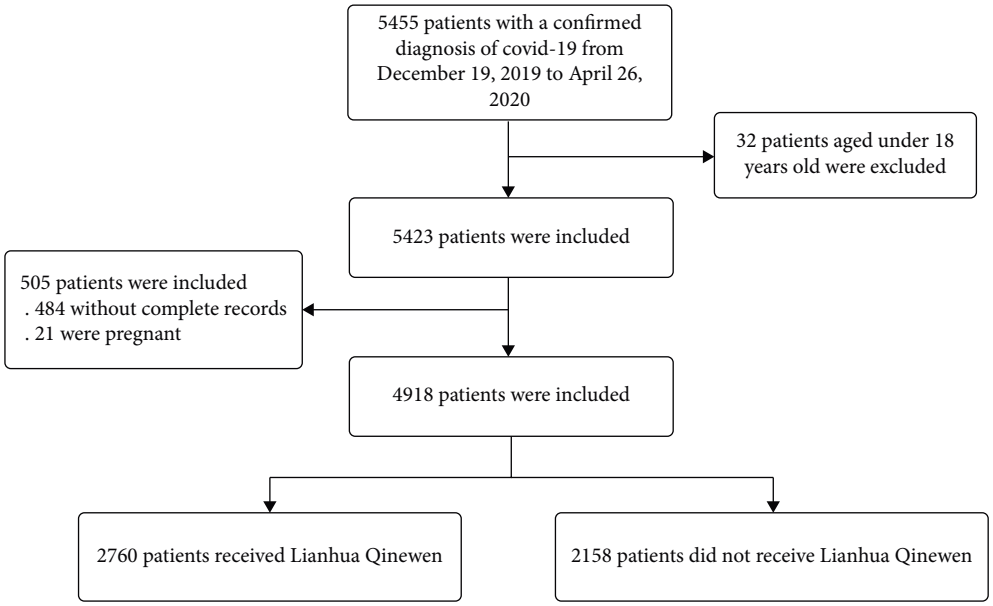


Figure 1: Flowchart of inclusion criteria.

$p < 0.001$), whereas anticoagulant therapy was used less frequently in the Lianhua Qingwen group (16.2% vs. 11.1%, $p < 0.001$) (Table 1).

3.2. Primary Outcomes. A total of 1997 participants from the Lianhua Qingwen group were 1 : 1 matched to the 1997 participants from the control group. Their characteristics were well-balanced (Table S1). In PSM analysis adjusted for age, sex, time from symptom onset to admission, severity and symptoms at admission, and comorbidities, Lianhua Qingwen decreased in-hospital mortality in COVID-19 patients (adjusted OR, 0.46 [95% CI, 0.34-0.63], $p < 0.001$). After further adjusting drug use (antiviral, adrenocortical hormone, and anticoagulant therapy), Lianhua Qingwen was not significantly associated with in-hospital mortality (adjusted OR, 0.66 [95% CI, 0.38-1.15], $p = 0.138$). In a logistic model, the use of Lianhua Qingwen was associated with a lower risk of in-hospital mortality in COVID-19 patients after adjusting for age, sex, time from symptom onset to admission, severity and symptoms at admission, and comorbidities (adjusted OR, 0.45 [95% CI, 0.34-0.59], $p < 0.001$). After further adjustment for drug use, Lianhua Qingwen was also associated with a declined in-hospital mortality in COVID-19 patients (adjusted OR, 0.62 [95% CI, 0.45-0.85], $p = 0.004$) (Figure 2). The Kaplan–Meier curve for survival probability by Lianhua Qingwen use from the day of COVID-19 diagnosis and continued for 21 days or until death in PSM analysis is shown in Figure S1.

Subsequently, after excluding 1804 patients without SARS-Cov-2 RNA date, 117 first used Lianhua Qingwen after SARS-CoV-2 RNA returned to negative, and 2997 patients were included for negative conversion rate of COVID-19 RNA. A total of 1607 patients used Lianhua Qingwen, and 1390 patients were in the control group (Figure S2). Patients who received Lianhua Qingwen were older (57.0 (IQR: [45.3-66.0]) vs. 61.0 (IQR: [50.0-69.0]), $p < 0.001$) and spent less time from symptom onset to admission (20.0 (IQR: [7.0-30.0]) vs. 14.0 (IQR: [7.0-22.0]), $p < 0.001$). Compared with control group, Lianhua Qingwen users were easier to have fever (48.7% vs. 56.4%, $p < 0.001$), cough (48.3% vs. 62.6%, $p < 0.001$), and fatigue symptoms (30.2% vs. 39.3%, $p < 0.001$). We also found that antiviral therapy was more frequently used in the Lianhua Qingwen group (53.6% vs. 83.1%, $p < 0.001$), whereas anticoagulant therapy was used less frequently in the Lianhua Qingwen group patients (14.2% vs. 9.3%, $p < 0.001$) (Table S2).

A total of 1188 participants who used Lianhua Qingwen were matched with 1188 participants from the control group. The characteristics of the two groups were well-balanced (Table S3). In PSM model adjusted for age, sex, time from symptom onset to admission, severity and symptoms at admission, and comorbidities, Lianhua Qingwen treatment was associated with an elevated negative conversion rate of SARS-CoV-2 (88.3% vs. 96.1%, adjusted OR, 3.21 [95% CI, 2.27-4.54], $p < 0.001$) (Figure S3). After further adjustment for drug use, the use of Lianhua Qingwen was also significantly associated with an increased negative conversion rate of SARS-CoV-2 (adjusted OR, 4.02 [95% CI, 2.58-6.25], $p < 0.001$) (Figure S3). Similarly, in a logistic model with age, sex, time from symptom onset to admission, severity and symptoms at admission, and comorbidities, we also found an association between Lianhua Qingwen treatment and an increased negative conversion rate of SARS-CoV-2 (adjusted OR, 3.56 [95% CI, 2.60-4.92], $p < 0.001$). After further adjustment for drug use, Lianhua Qingwen was also associated with an increased negative conversion rate of SARS-CoV-2 (adjusted OR, 3.86 [95% CI, 2.79-5.38], $p < 0.001$) (Figure S3).

Table 1: Baseline characteristics of COVID-19 patients by Lianhua Qingwen use.

Characteristic	Overall ($N = 4918$)	Control ($N = 2158$)	LHQW ($N = 2760$)	p-Value*
Age (years)	61.0 (49.0-69.0)	59.0 (47.0-68.0)	62.0 (51.0-69.0)	**<0.001**
Gender (%)				0.054
Female	2377 (48.3)	1077 (49.9)	1300 (47.1)	
Male	2541 (51.7)	1081 (50.1)	1460 (52.9)	
Time from symptom onset to admission (days)	14.0 (7.0-27.0)	16.0 (8.0-30.0)	13.0 (7.0-20.0)	**<0.001**
Severity at admission (n, %)				0.138
Nonsevere[a]	2771 (56.3)	1242 (57.6)	1529 (55.4)	
Severe[b]	2147 (43.7)	916 (42.4)	1231 (44.6)	
Symptoms at admission (n, %)				
Fever	2763 (56.2)	1110 (51.4)	1653 (59.9)	**<0.001**
Cough	1969 (40.0)	764 (35.4)	1205 (43.7)	**<0.001**
Dyspnea	1279 (26.0)	532 (24.7)	747 (27.1)	0.060
Fatigue	1278 (26.0)	500 (23.2)	778 (28.2)	**<0.001**
Diarrhea or vomiting	1059 (21.5)	457 (21.2)	602 (21.8)	0.615
Comorbidities (n, %)				
Diabetes	796 (16.2)	370 (17.1)	426 (15.4)	0.115
Hypertension	1430 (29.1)	601 (27.8)	829 (30.0)	0.100
Cancer	45 (0.9)	20 (0.9)	25 (0.9)	1.000
Heart diseases	306 (6.2)	133 (6.2)	173 (6.3)	0.927
Medication (n, %)				
Antiviral	3778 (76.8)	1378 (63.9)	2400 (87.0)	**<0.001**
Adrenocortical hormone	1447 (29.4)	666 (30.9)	781 (28.3)	0.054
Anticoagulant	657 (13.4)	350 (16.2)	307 (11.1)	**<0.001**

LHQW, Lianhua Qingwen capsules; [a]including mild and moderate cases. [b]including severe and critical cases.

3.3. Secondary Outcomes. COVID-19 patients who received Lianhua Qingwen had a comparable incidence of ALI (crude rate, 14.0% [95% CI, 12.5%-15.5%] vs. 11.5% [95% CI, 10.3%-12.8%], adjusted OR: 0.85 [95% CI, 0.71-1.02], $p = 0.083$) and a slightly lower incidence of AKI (crude rate, 5.3% [95% CI, 4.4%–6.4%] vs. 3.0% [95% CI, 2.4%–3.8%]; adjusted OR: 0.71 [95% CI, 0.50–1.00], $p = 0.048$) compared with the patients who did not receive Lianhua Qingwen after adjusting for age, sex, time from symptom onset to admission, severity and symptoms at admission, and comorbidities as well as antiviral, adrenocortical hormone, and anticoagulant therapy (Table 2).

4. Discussion

The treatment of COVID-19 remains a pressing issue during the current worldwide pandemic. Although several meta-analyses and systematic reviews have been published on this topic [16, 17], our work represents the first retrospective study examining the effectiveness and safety of the Lianhua Qingwen capsules in a comparatively large number of in-hospital COVID-19 patients from multicenters. Although Lianhua Qingwen treatment was not associated with in-hospital mortality in the present study, the results still revealed that Lianhua Qingwen capsules effectively improved the negative conversion rate of SARS-CoV-2 infection and reduced the incidence of AKI in COVID-19 patients.

In China, TCM has a long history of treating against influenza [18]. Lianhua Qingwen capsule is a Chinese patent medicine composed of eleven herbs. Previous studies on TCM therapy and modern pharmaceuticals have proven that the ingredients in Lianhua Qingwen capsules, such as isatis root, forsythia, herbal houttuynia, and honeysuckle, have a very significant effect on viral respiratory diseases such as SARS, influenza (including H1N1 and H7N9), chronic rhinosinusitis, tonsillitis, and hand-foot-and-mouth disease by relieving the symptoms of fever, headache, dizziness, fatigue, and rhinorrhea [5, 6, 19]. Wu et al. have reported that the combination of Lianhua Qingwen granules and peramivir sodium chloride injection could shorten the progress of the disease and improve C-reactive protein (CRP), procalcitonin (PCT) levels, and interleukin (IL)-6 levels with promising potency in influenza patients [20]. Based on previous clinical experiences, Lianhua Qingwen has been recommended to treat patients with COVID-19 after the pandemic outbreak. Fan et al. have reported that Lianhua Qingwen significantly alleviated the symptoms of respiratory infection in 66 patients with COVID-19 on the basis of routine treatment [9]. Li et al. suggested that a combination therapy consisting of Lianhua Qingwen, umifenovir, ribavirin, and lopinavir/ritonavir could be an optional treatment approach for 151 severe patients with COVID-19 [21].

In our study, Lianhua Qingwen did not appear to affect in-hospital mortality; however, it significantly increased the negative conversion rate of SARS-CoV-2 infection. It has been reported that the active component of Lianhua Qingwen may inhibit viral replication by blocking the binding of SARS-CoV-2 to angiotensin-converting enzyme 2 (ACE2) [22] and could reduce the virions in infected cells, as well as change the surface virions of infected cells

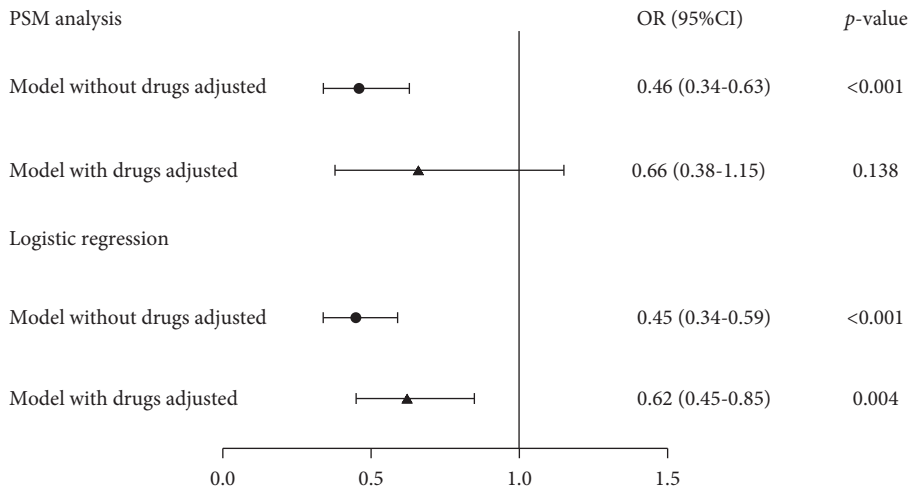


Figure 2: Association between Lianhua Qingwen use and in-hospital mortality.

Table 2: Associations between Lianhua Qingwen and safety outcomes.

Safety outcome	Crude rate (95% CI, %)	Unadjusted		Adjusted*	
		OR (95% CI)	*p*-Value	OR (95% CI)	*p*-Value
Acute liver injury					
Control	**14.0 (12.5-15.5)**	1 (ref)		1 (ref)	
LHQW	**11.5 (10.3-12.8)**	**0.80 (0.68-0.95)**	**0.010**	**0.85 (0.71-1.02)**	**0.083**
Acute kidney injury					
Control	**5.3 (4.4-6.4)**	1 (ref)		1 (ref)	
LHQW	**3.0 (2.4-3.8)**	**0.56 (0.42-0.74)**	**<0.001**	**0.71 (0.50-1.00)**	**0.048**

LHQW, Lianhua Qingwen capsules; OR, odds ratio; Cl, confidence interval, and ref, reference. *Association was adjusted for age, sex, time from symptom onset to admission, severity and symptoms at admission, comorbidities, and antiviral, adrenocortical hormone, and anticoagulant therapy.

conducted by Nanshan Zhong et al.[23]. Meanwhile, research has shown that Lonicera japonica and Forsythia (main components of Lianhua Qingwen capsules) can inhibit the binding of the novel coronavirus to ACE2 [24]. Similarly, Rheum palmatum (another main component of Lianhua Qingwen capsules) can effectively block the interaction between S protein and ACE2 [25]. A network pharmacology analysis suggested that Lianhua Qingwen capsules might potentially treat and prevent COVID-19 by targeting the serine/threonine protein kinase (Akt1) [26], which is involved in viral infection, lung injury, and lung fibrosis [27]. The impact of Lianhua Qingwen capsules on increasing the negative conversion rate of SARS-CoV-2 in our study is supported by the above mechanisms.

Although COVID-19 was first found to target to the respiratory system, growing evidence highlights the wide distribution of ACE2 enables SARS-CoV-2 to cause a systemic disease characterized by multiple organ involvement [28, 29]. The liver and kidney may be among the target organs of SARS-COV-2 [30, 31]. In our study, we found that the incidence of ALI was comparable between Lianhua Qingwen and the control groups. Notably, we first observed a lower risk of AKI in COVID-19 patients taking Lianhua Qingwen capsules. Early recognition and application of preventive and therapeutic measures to limit successive AKI are essential to reduce mortality in COVID-19 patients. Therefore, relevant research is required to investigate the underlying mechanisms.

To this study, there are still potential limitations. First, the sample was limited to a restricted number of hospitalized patients who were crudely classified into Lianhua Qingwen and non-Lianhua Qingwen groups. It is also possible that the comparatively limited sample size in each group led to a lack of power with an increased beta risk. Second, although we used PSM to control for important characteristics, information not included in the analysis may lead to potential confounders. Third, the protocol design of our study was different from that of a randomized control trial. The association between Lianhua Qingwen and clinical outcomes should continue to be clarified through high-quality clinical trials.

5. Conclusions

Our study demonstrated that treatment with Lianhua Qingwen capsules was not associated with in-hospital mortality, but it increased the negative conversion rate of SARS-CoV-2 infection and reduced the incidence of AKI in COVID-19 patients, suggesting that Lianhua Qingwen

combined with other therapeutic drugs may be a promising strategy for COVID-19.

Data Availability

The original data are available from the corresponding author upon request.

Disclosure

Yun Lu and Meng Zhang share the first authorship.

Conflicts of Interest

The authors declare that there are no conflicts of interest regarding the publication of this paper.

Authors' Contributions

Hong Cheng and Feng Sun contributed to the conception and study design and assumed responsibility for data completeness and accuracy of data analysis. Hong Cheng, Li-kai Lin, Kun Yang, Su-yu Gao, Wen Hu, Qiao-li Jiang, and Wen-Jing Li were responsible for the acquisition of data and literature research. Yun Lu, Meng Zhang, and Qing-qing Yang were responsible for data analysis and presentation. Yun Lu and Meng Zhang drafted the manuscript. Yun Lu and Meng Zhang contributed equally to this work.

Acknowledgments

This study was supported by Special Project for Director, China Center for Evidence Based Traditional Chinese Medicine (No. 2020YJSZX-2); TCM scientific research project of Hubei Provincial Health Commission (No. ZY2021Z021); Clinical Characteristics of Drug-Induced Liver Injury in Patients with COVID-19 and its Outcome (No. CXPY2020032) and Special Project of Clinical Toxicology, Chinese Society of Toxicology (CST2020CT605, CST2021CT102).

Supplementary Materials

Figure S1. Kaplan–Meier survival curves for in-hospital mortality by Lianhua Qingwen use. Figure S2. Flowchart of the analysis of negative conversion rate. Figure S3. Association of Lianhua Qingwen use with negative conversion rate. Table S1. Baseline characteristics of COVID-19 patients by Lianhua Qingwen use after propensity score matching. Table S2. Baseline characteristics of COVID-19 patients by Lianhua Qingwen in the analysis of negative conversion rate. Table S3. Baseline characteristics of patients with Lianhua Qingwen in the analysis of negative conversion rate after propensity score matching. (*Supplementary Materials*)

References

[1] S. SeyedAlinaghi, A. Karimi, H. Mojdeganlou et al., "Impact of COVID-19 pandemic on routine vaccination coverage of children and adolescents: a systematic review," *Health Science Reports*, vol. 5, no. 2, Article ID e00516, 2022.

[2] H. Aghamirza Moghim Aliabadi, R. Eivazzadeh-Keihan, A. Beig Parikhani et al., "COVID-19: a systematic review and update on prevention, diagnosis, and treatment," *MedComm*, vol. 3, no. 1, p. e115, 2022.

[3] F. Sun, H. Kou, S. Wang et al., "An analytical study of drug utilization, disease progression, and adverse events among 165 COVID-19 patients," *Annals of Translational Medicine*, vol. 9, no. 4, p. 306, 2021.

[4] Y. H. Jin, L. Cai, Z. S. Cheng et al., "A rapid advice guideline for the diagnosis and treatment of 2019 novel coronavirus (2019-nCoV) infected pneumonia (standard version)," *Military Medical Research*, vol. 7, no. 1, p. 4, 2020.

[5] X. Shen and F. Yin, "The mechanisms and clinical application of traditional Chinese medicine lianhua-qingwen capsule," *Biomedicine & Pharmacotherapy*, vol. 142, Article ID 111998, 2021.

[6] D. Gao, M. Niu, S. Z. Wei et al., "Identification of a pharmacological biomarker for the bioassay-based quality control of a thirteen-component TCM formula (Lianhua qingwen) used in treating influenza A virus (H1N1) infection," *Frontiers in Pharmacology*, vol. 11, p. 746, 2020.

[7] L. T. F. Ho, K. K. H. Chan, V. C. H. Chung, and T. H. Leung, "Highlights of traditional Chinese medicine frontline expert advice in the China national guideline for COVID-19," *European Journal of Integrative Medicine*, vol. 36, Article ID 101116, 2020.

[8] K. Hu, W. J. Guan, Y. Bi et al., "Efficacy and safety of Lianhua Qingwen capsules, a repurposed Chinese herb, in patients with Coronavirus disease 2019: a multicenter, prospective, randomized controlled trial [Phytomedicine 85 (2021) 153242]," *Phytomedicine*, vol. 94, Article ID 153800, 2022.

[9] S. J. Fan, J. K. Liao, L. Wei, B. Y. Wang, L. Kai, and D. X. Tan, "Treatment efficacy of Lianhua Qingwen capsules for eralystage COVID-19," *American Journal of Translational Research*, vol. 14, no. 2, pp. 1332–1338, 2022.

[10] M. Xiao, J. Tian, Y. Zhou et al., "Efficacy of huoxiang zhengqi dropping pills and lianhua qingwen granules in treatment of COVID-19: a randomized controlled trial," *Pharmacological Research*, vol. 161, Article ID 105126, 2020.

[11] W. M. Lee, R. H. Squires, S. L. Nyberg, E. Doo, and J. H. Hoofnagle, "Acute liver failure: summary of a workshop," *Hepatology*, vol. 47, no. 4, pp. 1401–1415, 2007.

[12] P. Zhong, J. Xu, D. Yang et al., "COVID-19-associated gastrointestinal and liver injury: clinical features and potential mechanisms," *Signal Transduction and Targeted Therapy*, vol. 5, no. 1, p. 256, 2020.

[13] J. S. Haukoos and R. J. Lewis, "The propensity score," *JAMA*, vol. 314, no. 15, pp. 1637-1638, 2015.

[14] A. C. Cioci, A. L. Cioci, A. M. A. Mantero, J. P. Parreco, D. D. Yeh, and R. Rattan, "Advanced statistics: multiple logistic regression, cox proportional hazards, and propensity scores," *Surgical Infections*, vol. 22, no. 6, pp. 604–610, 2021.

[15] J. Amoah, E. A. Stuart, S. E. Cosgrove et al., "Comparing propensity score methods versus traditional regression analysis for the evaluation of observational data: a case study evaluating the treatment of gram-negative bloodstream infections," *Clinical Infectious Diseases*, vol. 71, no. 9, pp. e497–e505, 2020.

[16] X. Zhang, D. Cao, J. Liu, Q. Zhang, and M. Liu, "Efficacy and safety of Lianhua Qingwen combined with conventional antiviral Western Medicine in the treatment of coronavirus disease (covid-19) in 2019: protocol for a systematic review

and meta-analysis," *Medicine (Baltimore)*, vol. 99, no. 30, Article ID e21404, 2020.

[17] M. Liu, Y. Gao, Y. Yuan et al., "Efficacy and safety of integrated traditional Chinese and western medicine for corona virus disease 2019 (COVID-19): a systematic review and meta-analysis," *Pharmacological Research*, vol. 158, Article ID 104896, 2020.

[18] Z. J. Zhang, S. L. Morris-Natschke, Y. Y. Cheng, K. H. Lee, and R. T. Li, "Development of anti-influenza agents from natural products," *Medicinal Research Reviews*, vol. 40, no. 6, pp. 2290–2338, 2020.

[19] F. Qi and W. Tang, "Traditional Chinese medicine for treatment of novel infectious diseases: current status and dilemma," *BioScience Trends*, vol. 15, no. 4, 2021.

[20] J. Wu, Q. Wang, L. Yang, Z. Li, and X. Wang, "Potency of Lianhua Qingwen granule combined with paramivir sodium chloride injection in treating influenza and level changes of serum inflammatory factors," *American Journal of Translational Research*, vol. 13, no. 6, pp. 6790–6795, 2021.

[21] X. Li, Y. Yang, L. Liu et al., "Effect of combination antiviral therapy on hematological profiles in 151 adults hospitalized with severe coronavirus disease 2019," *Pharmacological Research*, vol. 160, Article ID 105036, 2020.

[22] W. Niu, F. Wu, H. Cui et al., "Network pharmacology analysis to identify phytochemicals in traditional Chinese medicines that may regulate ACE2 for the treatment of COVID-19," *Evidence-Based Complementary and Alternative Medicine*, vol. 2020, Article ID 7493281, 14 pages, 2020.

[23] L. Runfeng, H. Yunlong, H. Jicheng et al., "Lianhuaqingwen exerts anti-viral and anti-inflammatory activity against novel coronavirus (SARS-CoV-2)," *Pharmacological Research*, vol. 156, Article ID 104761, 2020.

[24] M. Niu, R. L. Wang, Z. X. Wang et al., "[Rapid establishment of traditional Chinese medicine prevention and treatment of 2019-nCoV based on clinical experience and molecular docking]," *Zhongguo Zhongyao Zazhi*, vol. 45, no. 6, pp. 1213–1218, 2020.

[25] T. Y. Ho, S. L. Wu, J. C. Chen, C. C. Li, and C. Y. Hsiang, "Emodin blocks the SARS coronavirus spike protein and angiotensin-converting enzyme 2 interaction," *Antiviral Research*, vol. 74, no. 2, pp. 92–101, 2007.

[26] Q. D. Xia, Y. Xun, J. L. Lu et al., "Network pharmacology and molecular docking analyses on Lianhua Qingwen capsule indicate Akt1 is a potential target to treat and prevent COVID-19," *Cell Proliferation*, vol. 53, no. 12, Article ID e12949, 2020.

[27] V. Callahan, S. Hawks, M. A. Crawford et al., "The pro-inflammatory chemokines CXCL9, CXCL10 and CXCL11 are upregulated following SARS-CoV-2 infection in an AKT-dependent manner," *Viruses*, vol. 13, no. 6, p. 1062, 2021.

[28] M. Lopes-Pacheco, P. L. Silva, F. F. Cruz et al., "Pathogenesis of multiple organ injury in COVID-19 and potential therapeutic strategies," *Frontiers in Physiology*, vol. 12, Article ID 593223, 2021.

[29] M. Dong, J. Zhang, X. Ma et al., "ACE2, TMPRSS2 distribution and extrapulmonary organ injury in patients with COVID-19," *Biomedicine & Pharmacotherapy*, vol. 131, Article ID 110678, 2020.

[30] A. D. Nardo, M. Schneeweiss-Gleixner, M. Bakail, E. D. Dixon, S. F. Lax, and M. Trauner, "Pathophysiological mechanisms of liver injury in COVID-19," *Liver International*, vol. 41, no. 1, pp. 20–32, 2021.

[31] E. Ahmadian, S. M. Hosseiniyan Khatibi, S. Razi Soofiyani et al., "Covid-19 and kidney injury: pathophysiology and molecular mechanisms," *Reviews in Medical Virology*, vol. 31, no. 3, Article ID e2176, 2021.

Hindawi
Evidence-Based Complementary and Alternative Medicine
Volume 2023, Article ID 4612036, 7 pages
https://doi.org/10.1155/2023/4612036

Research Article

Reporting Quality of Oral TCM Systematic Reviews Based on the PRISMA Harms Checklist from 2013 to 2020

Tianying Chang,[1] **Yingzi Cui**,[1] **Ying Zhang**,[2] **Jinhui Ma**,[3] **Jing Tan**,[4] **and Jian Wang**[2]

[1]*EBM Office, The Affiliated Hospital to Changchun University of Chinese Medicine, Changchun 130021, China*
[2]*Neurology Department, The Affiliated Hospital to Changchun University of Chinese Medicine, Changchun 130021, China*
[3]*Department of Health Research, Evidence, and Impact, McMaster University, Hamilton, ON, Canada*
[4]*Chinese Evidence-Based Medicine Center and National Clinical Research Center for Geriatrics, West China Hospital, Sichuan University and Collaborative Innovation Center, Chengdu, Sichuan 610041, China*

Correspondence should be addressed to Jing Tan; jingtan0801@qq.com and Jian Wang; jian-w222@163.com

Received 28 July 2022; Revised 4 August 2022; Accepted 9 October 2022; Published 24 January 2023

Academic Editor: Xing Liao

Background. Systematic reviews focusing on the effectiveness of different kinds of healthcare interventions have been widely published, but there were few guidelines for reporting safety concerns before 2016. The PRISMA harms checklist, which was published in 2016, can standardize reporting quality. *Objectives*. To evaluate the safety information reporting quality of oral traditional Chinese medicine (TCM) in systematic reviews before and after the PRISMA harms checklist was published and to explore factors associated with better reporting. *Methods*. We searched PubMed, the Cochrane Library, and Embase to identify all systematic reviews using oral TCM as interventions published before (from 2013 to 2015) and after (from 2017 to 2020) the PRISMA harms checklist was published. We used the PRISMA harms checklist to assess the quality of reporting of the safety information to included systematic reviews. *Results*. In total, 200 systematic reviews were sampled from eligible studies published between 2013 and 2020. Reviews from 2016 were excluded. Scores on the PRISMA harms checklist (23 items) ranged from 0 to 12. A systematic reviews published after 2016 had better reporting quality compared with studies published before 2016 with regard to the title ($P = 0.03$), results of individual studies ($P = 0.016$), and risk of bias across studies ($P = 0.043$). In all included systematic reviews of our study, the state conclusion in coherence with review findings was reported adequately with the proportion of adherence at 95%; other items had a reporting proportion ranging from 0% to 57%. The four essential reporting items of the PRISMA harms checklist also had a low reporting quality ranging from 0% to 4%. *Conclusions*. Oral TCM systematic reviews reported inadequate safety information before and after the PRISMA harms checklist was published. This survey suggested that the PRISMA harms checklist should be recommended more to both original research and systematic review authors.

1. Introduction

A large number of systematic reviews in the field of traditional Chinese medicine (TCM) are published every year [1]. As the original research's primary purpose was to evaluate the effectiveness of TCM, the leading outcome indicators of most systematic reviews mainly focus on effectiveness. However, randomized controlled trials can also identify common adverse reactions (drug safety events), which is often a secondary aim of these studies. Thus, many original research studies and systematic reviews do not obtain first-hand information on drug safety. Moreover, it is rare and challenging to perform meta-analysis due to the inconsistencies among side effects. This is very unfavorable to the value of existing systematic reviews, which can guide clinical practice regarding safety concerns.

Before the 2016 Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) harms checklist was published [2], most systematic review guidance was directed toward the evaluation of effectiveness. Most systematic reviews focused on the effectiveness of TCM interventions [3–10]. With concerns about drug safety issues, systematic

reviews and meta-analyses of clinical trial safety data have become more important [11–14].

Traditional Chinese herbal medicine refers to the decoction of herbal medicines extracted according to TCM theory, which is based on the notion of harmony and balance [15]. It also includes herb extracts and patented herbal medicines. The drug safety information for these decoctions is essential for clinicians, especially for those TCM interventions that have a complicated effect [16, 17]. Most TCM patent medicine instructions claim the adverse reactions are not clear, and randomized controlled trials of TCM decoctions often report unknown safety issues [18, 19]. This is mainly the case when adverse drug effects are rare [20–22] when assessing drug safety [14].

Four essential reporting elements (whether or not harms were reported in the title, synthesis of results (zero events handling), study characteristics, and results synthesis) have been added to the PRISMA statement to improve harms reporting in reviews since 2016 [2]. The PRISMA-harms checklist identifies and provides a minimal set of items that should be reported when reviewing adverse events. We conducted the survey to investigate the quality of safety reporting among oral TCM systematic reviews before and after the PRISMA harms checklist were published to assess the checklist's effectiveness.

2. Methods

2.1. Eligibility Criteria. We included a study if it was a systematic review that assessed the efficacy/effectiveness of an oral TCM decoction, including granules and extracts, or an oral TCM patent. Other kinds of systematic reviews, such as network meta-analysis, individual participant data meta-analysis, and overviews of systematic reviews were excluded.

A study was defined as a systematic review according to the Cochrane Handbook criteria (version 5.1.0) [23]. Nonrandomized studies in systematic reviews included quasi-randomized clinical trials (quasi-RCTs), cohort studies, and case-control studies.

2.2. Information Sources and Study Selection. Two independent authors systematically searched PubMed, Embase, and the Cochrane Library to identify systematic reviews. We searched studies from 2013 to 2015 to evaluate the quality of safety reporting before the PRISMA harms checklist was published. In addition, we also searched for studies from 2017 to April 2020 to evaluate safety reporting quality after the PRISMA harms checklist was published. The literature screening process is shown in Figure 1. The full search strategy used in Embase is shown as follows:

(1) Traditional Chinese Medicine.mp. or Chinese Medicine.
(2) Chung I Hsueh.mp.
(3) Hsueh, Chung I.mp.
(4) Chinese Medicine/or Traditional Medicine, Chinese.mp.
(5) Chinese Medicine/or Zhong Yi Xue.mp.
(6) Chinese Medicine/or Chinese Traditional Medicine.mp.
(7) Chinese Medicine/or Chinese Medicine, Traditional.mp.
(8) Chinese Medicine/or Traditional Tongue Diagnosis.mp.
(9) Chinese Medicine/or Tongue Diagnoses, Traditional.mp.
(10) Tongue Diagnosis, Traditional.mp. or Chinese Medicine/
(11) Chinese Medicine/or Traditional Tongue Diagnoses.mp.
(12) Chinese Medicine/or Traditional Tongue Assessment.mp.
(13) Tongue Assessment.mp.
(14) Chinese Medicine/or Traditional Tongue Assessments.mp.
(15) Systematic review.mp. or "systematic review".
(16) Meta-analysis.mp. or meta-analysis.
(17) Meta-analysis.mp. or meta-analysis.
(18) 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14,
(19) 15 or 16 or 17.
(20) 18 and 19.
(21) Limit 20 to (English language and yr = "2017–Current").

We conservatively estimated that 200 reports would be sufficient to obtain a robust result [14]. A total of 100 citations were sampled from studies dating from 2013 to 2015. The PRISMA harms checklist was published on 11 December 2015, so another 100 citations were chosen from studies published from 2017 to April 2020. Studies published in 2016 were excluded from the search.

2.3. Data Extraction and Management. Data extraction was performed by reviewer Tianying Chang. Jing Tan, a second independent reviewer, cross-checked the extraction for accuracy. We collected the following information from each included study: [1] author, [2] published year, [3] number of studies included in the review, [4] number of subjects involved in the included systematic review, [5] type of TCM intervention (decoction, extract, or patent), [6] type of control (placebo, standard of care, or other TCM intervention), and [7] type of funding.

The safety information of all included systematic reviews was evaluated by the PRISMA harms checklist [2]; we also assessed the reporting quality of all included studies with PRISMA [24]. The two independent authors assessed whether or not the PRISMA and PRISMA harms checklist items were reported.

The PRISMA harms checklist has 23 reporting items based on the PRISMA statement. Of these 23 items, four are essential, or minimum, reporting items. These four essential items include the title, synthesis of results, study

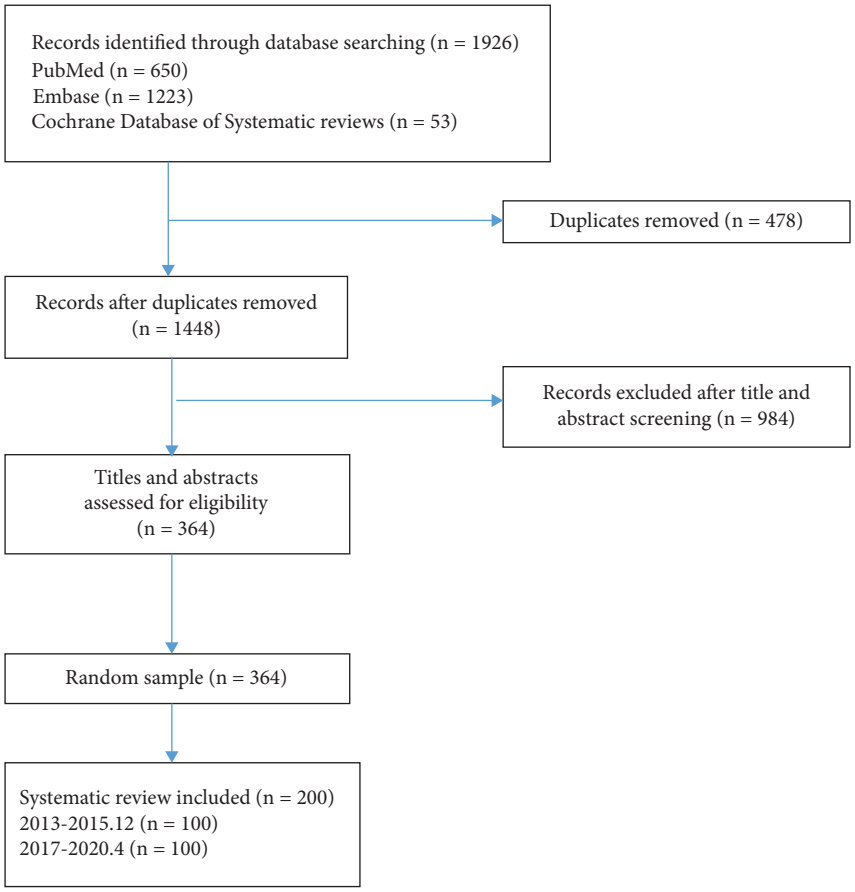


Figure 1: Flow chart of study selection.

characteristics, and synthesis of results. [2] The minimum item of the title (item 1) includes "specifically mention 'harms' or other related terms, or the harm of interest in the review," item of synthesis of results (item 14) includes "specify how zero events were handled, if relevant," item of study characteristics (item 18) includes "define each harm addressed. How it was ascertained," and item of synthesis of results (item 21) includes "describe any assessment of possible causality."

All items from the PRISMA statement and the PRISMA harms checklist were evaluated and reported with "Yes" and "No." To calculate a total score for each assessed study, all "Yes" responses were assigned a value of 1 and all "No" responses were assigned a value of 0.

2.4. Statistical Analysis. We conducted a statistical description for the reporting items of all included systematic reviews. Dichotomous variables were described with frequencies and percentages. Continuous variables were described with means and medians. We compared the characteristics of systematic reviews before and after the PRISMA harms checklist was published. Dichotomous variables were tested with a chi-square test, and continuous variables were tested by the *t*-test when the distribution was normal.

3. Results

The initial systematic search resulted in a total of 1926 citations from PubMed, Embase, and the Cochrane Library. After 478 duplicate publications were removed, the titles and abstracts of 1448 records were screened, and 984 irrelevant records were excluded. After assessing the full texts, 364 systematic reviews satisfied the eligibility criteria and were included in the critical evaluation (Figure 1). We sampled 200 studies from 364 included reviews. Twenty-one Cochrane systematic reviews were chosen before randomization as having better review quality. In total, 100 systematic reviews were published from January 2013 to December 2015, and another 100 systematic reviews were published from January 2017 to April 2020.

The median number of studies included among the eligible systematic reviews was 12 (ranging from 0 to 83). The median number of participants included in the studies was 1081 (ranging from 0 to 8138). All studies assessed the effects of oral TCM preparations [14]. The range of PRISMA scores was 18–27 in publications before 2016, and 11–27 in publications after 2016. The average scores were 23.4 in publications before 2016 and 22.9 in publications after 2016.

Table 1: Adherence of systematic review reporting of the PRISMA harms checklist.

Sections	Items	PRISMA harms checklist			
		Total (%)	Published before 2016 (%)	Published after 2016 (%)	*P* values
Title	1 Title	8 (4)	1 (1)	7 (7)	0.03
Abstract	2 Structured summary	112 (56)	57 (57)	55 (55)	0.78
Instruction	3 Rationale	22 (11)	11 (11)	11 (11)	1.0
	4 Objectives	1 (0.5)	0	1 (1)	0.32
	6 Eligibility criteria	2 (1)	1 (1)	1 (1)	1.0
	8 Search	3 (1.5)	1 (1)	2(2)	0.56
	9 Study selection	0	0	0	—
Methods	11 Data items	2 (1)	0	2 (2)	0.155
	12 Risk of bias in individual studies	2 (1)	0	2 (2)	0.155
	14 Synthesis of results	2 (1)	0	2 (2)	0.155
	15 Risk of bias across studies	2 (1)	0	2 (2)	0.155
	16 Additional analyses	3 (1.5)	0	3 (3)	0.081
Results	17 Study selection	0	0	0	—
	18 Study characteristics-1	1 (0.5)	0	1 (1)	0.316
	18 Study characteristics-2	0	0	0	—
	19 Risk of bias within studies	2 (1)	0	2 (2)	0.155
	20 Results of individual studies	97 (48.5)	40 (40)	57 (57)	0.016
	21 Synthesis of results-1	2 (1)	0	2 (2)	0.155
	21 Synthesis of results-2	0	0	0	—
	22 Risk of bias across studies	4 (2)	0	4 (4)	0.043
Discussion	25 Limitations	1 (0.5)	0	1 (1)	0.316
	26 Conclusions	190 (95)	98 (98)	92 (92)	0.052

3.1. Characteristics of Included Studies. Among the 100 systematic reviews published before 2016, four studies included RCTs and quasi-RCT [25–28]; the remainder of the studies included RCTs. In the 100 systematic reviews published after 2016, one study included RCT and a quasi-RCT [29]. Another study included a controlled trial [30], and the remaining studies included RCTs. The publication distribution of the selected studies was as follows: 38 studies (19%) were from 2013, 21 studies (10.5%) were from 2014, 41 studies (20.5%) were from 2015, 26 studies (13%) were from 2017, 31 studies (15.5%) were from 2018, 36 studies (18%) were from 2019, and 7 studies (3.5%) were from 2020.

There were 22 categories of diseases among the included studies. The top 10 were nervous system diseases (12.5%), digestive system diseases (11.5%), oncological diseases (9%), cardiac diseases (8%), hypertension (7%), dermatological disease (6.5%), endocrine and metabolic diseases (6.5%), urinary system disease (6%), immune system diseases (5.5%), and respiratory diseases (5.5%).

The first authors of all included studies were from 84 hospitals/universities. Methodologists were identified by the co-authors' backgrounds in epidemiology, biostatistics, and evidence-based medicine. Among the 100 systematic reviews published before 2016, methodologists participated in 66 studies (66%). Among the 100 systematic reviews published after 2016, methodologists participated in 82 (82%) studies. Of the included studies, a total of 178 studies were from mainland China, 8 were from Australia, 6 were from Hong Kong, 1 was from Macau, 2 were from Korea, 1 was from Malaysia, 2 were from Singapore, 1 was from the United Kingdom, and 1 was from the Netherlands.

3.2. Adherence to the PRISMA Harms Checklist. Most systematic reviews met a few requirements of the PRISMA harms checklist (Table 1 and Figure 2). Among the 23 items on the PRISMA harms checklist, only one item (conclusions-statement of conclusions in coherence with the review findings) was reported adequately (proportion of adherence = 95%). The proportion of reporting other criteria ranged from 0% to 57%. For the four essential reporting items, 8 (4%) reviews specifically mentioned "harms," other related terms or the harm of interest in the review title. A total of three reviews (1.5%) specified how zero events were handled. Two reviews (1%) defined each harm that how it was ascertained, and over what time period; 0 reviews (0%) described the assessment of possible causality.

In the analysis by the Pearson's chi-squared test, systematic reviews published after 2016 had a better reporting quality with regard to title s(7% vs. 1%, $P = 0.03$), results of individual studies (40% vs. 57%, $P = 0.016$), and risk of bias across studies (0% vs. 4%, $P = 0.043$). In other items, there was no statistical difference.

4. Discussion

In this survey, we found that the reporting quality of safety information among oral TCM systematic reviews was generally low before and after the PRISMA harms checklist was published. We did not include studies from 2016 because the PRSIMA harms checklist was published in December 2015. The four essential PRISMA harm items (proportion and adherence ranging from 0% to 4%) also had a low reporting quality. Our findings for 19 nonessential items showed a proportion of adherence ranging from 0% to

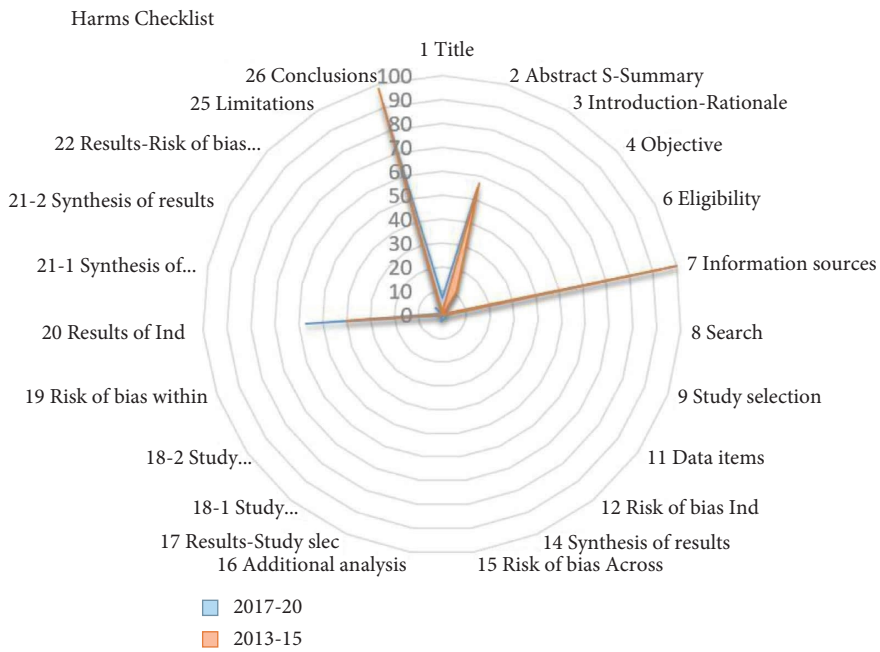


Figure 2: Adherence to the PRISMA harms checklist before and after its publication (%).

95%, which is consistent with surveys of systematic reviews assessing harms reporting for various health care interventions (adherence ranging from 1.7% to 81.6% and from 13% to 62% [14, 31]). The inclusion of safety information is not the primary aim of most oral TCM systematic reviews, and, thus, the safety reporting deficiency can be somewhat attributed to that fact. Twenty-one Cochrane systematic reviews were included, but with the unbalanced number of non-Cochrane systematic reviews, we did not compare the reporting quality between each other.

Item 7 of the PRISMA harms checklist reads, "Report if you only searched for published data or also sought data from unpublished sources, from authors, drug manufacturers, and regulatory agencies. If includes unpublished data, provide the source and the process of obtaining it." Most systematic review authors attempted to acquire all collectable data, but unpublished data were usually unavailable. If an author searched several unpublished databases but obtained no results, we question whether or not item 7 should be considered as included. Should this item be evaluated by search results or search process? The differences in how item 7 may have been considered by different reviewers are a possible question to address in a future examination.

There are several strengths in our survey. First, we systematically surveyed the reporting quality of safety information among reviews of oral TCM, which were obtained from PubMed, Embase, and the Cochrane Library. Second, the included systematic reviews of our survey were chosen over a relatively broad time span (from 2013 to 2020) and sampled, which represents a more robust survey outcome.

Limitations also exist in our survey. First, the interventions were limited to oral TCM, including decoctions (herbs, granules, and extracts) and patent medications. Other routes of TCM administration were excluded, but external TCM and TCM injections also have some adverse effects reported. TCM injections, especially some injections for the purpose of treating cancer, have reported adverse effects [32], although some adverse effects were obviously related to the cancer itself. Second, a reporting guideline requires a considerable period of time to determine if it has been implemented into practice. The implementation of the PRISMA harms checklist was hard to assess in the TCM field because of the relatively short time since implementation. Third, as network meta-analysis, overviews of systematic reviews, and individual participant meta-analysis were excluded, the findings of our survey did not generalize more information to conduct a more comprehensive outcome from these reviews. As we aimed to acquire a better study quality, we only searched for studies published in English, which have been considered to be of better quality.

The consideration of adverse effects is an essential issue in drug trials and meta-analyses [14]. The authors of systematic reviews often focus on the efficacy of interventions but do not consider safety. In TCM clinical studies and meta-analyses, adverse effects are not adequately reported [16], which could have a negative effect on medication and treatment guidance. Inadequate reporting and assessment of safety would also negatively impact guidance for clinical practice.

The reporting of safety information should be guided by well-designed analyses. The PRISMA harms checklist should be more widely promoted to systematic review authors.

5. Conclusions

Systematic reviews of oral TCM published before and after 2016 did not show a significant statistical difference in safety reporting quality. Both time periods demonstrated a poor

usage of the PRISMA harms checklist. Our survey suggests a strong need to use the PRISMA harms checklist for reporting safety information among oral TCM systematic reviews. Systematic review authors should pay more attention to safety information reporting.

Data Availability

The data used to support the findings are available from the corresponding authors upon reasonable request.

Disclosure

Tianying Chang and Yingzi Cui are co-first authors.

Conflicts of Interest

All the authors declare that they have no conflicts of interest.

Acknowledgments

This study was supported by the National TCM Evidence-Based Capacity Building Project (2019XZZX-NB005) and The National Key Research and Development Program of China (2019YFC1709902).

References

[1] M. H. Wang, C. Chen, M. L. Yeh, and J. G. Lin, "Using traditional Chinese medicine to relieve asthma symptoms: a systematic review and meta-analysis," *The American Journal of Chinese Medicine*, vol. 47, no. 8, pp. 1659–1674, 2019.

[2] L. Zorzela, Y. K. Loke, J. P. Ioannidis et al., "PRISMA harms checklist: improving harms reporting in systematic reviews," *BMJ*, vol. 352, p. i157, 2016.

[3] J. Tian, J. Zhang, L. Ge, K. Yang, and F. Song, "The methodological and reporting quality of systematic reviews from China and the USA are similar," *Journal of Clinical Epidemiology*, vol. 85, pp. 50–58, 2017.

[4] J. Y. Wang, J. F. Wang, S. Q. Cheng, G. H. Tian, Y. P. Wang, and H. C. Shang, "Development and current situation analysis of Chinese medicine systematic reviews/meta analysis of 19 years," *Journal of Traditional Chinese Medicine*, vol. 58, no. 11, pp. 919–925, 2017.

[5] H. Y. Sun and A. K. Lv, "Current status in the field of traditional Chinese medicine: a systematic review and meta-analysis," *Hebei Journal of Traditional Chinese Medicine*, vol. 36, no. 9, pp. 1392–1396+401, 2014.

[6] E. S. Y. Chan, D. T. Bautista, Y. Zhu et al., "Traditional Chinese herbal medicine for vascular dementia," *Cochrane Database of Systematic Reviews*, vol. 12, no. 12, Article ID CD010284, 2018.

[7] H. Deng and J. Xu, "Wendan decoction (Traditional Chinese medicine) for schizophrenia," *Cochrane Database of Systematic Reviews*, vol. 6, no. 6, Article ID CD012217, 2017.

[8] R. Qiu, J. Hu, Y. Huang et al., "Outcome reporting from clinical trials of non-valvular atrial fibrillation treated with traditional Chinese medicine or Western medicine: a systematic review," *BMJ Open*, vol. 9, no. 8, Article ID e028803, 2019.

[9] D. Z. Kong, N. Liang, J. P. Liu et al., "Chinese herbal medicine formula, for chronic hepatitis B," *Cochrane Database of Systematic Reviews*, vol. 11, 2018.

[10] N. Liang, D. Z. Kong, C. L. Lu et al., "Radix Sophorae flavescentis versus other drugs or herbs for chronic hepatitis B," *Cochrane Database of Systematic Reviews*, vol. 6, no. 6, Article ID CD013106, 2019.

[11] J. A. Berlin, B. J. Crowe, E. Whalen, H. A. Xia, C. E. Koro, and J. Kuebler, "Meta-analysis of clinical trial safety data in a drug development program: answers to frequently asked questions," *Clinical Trials*, vol. 10, no. 1, pp. 20–31, 2013.

[12] V. R. Cornelius, M. J. Perrio, S. A. Shakir, and L. A. Smith, "Systematic reviews of adverse effects of drug interventions: a survey of their conduct and reporting quality," *Pharmacoepidemiology and Drug Safety*, vol. 18, no. 12, pp. 1223–1231, 2009.

[13] S. Golder, Y. Loke, and H. M. McIntosh, "Poor reporting and inadequate searches were apparent in systematic reviews of adverse effects," *Journal of Clinical Epidemiology*, vol. 61, no. 5, pp. 440–448, 2008.

[14] L. Li, C. Xu, K. Deng et al., "The reporting of safety among drug systematic reviews was poor before the implementation of the PRISMA harms checklist," *Journal of Clinical Epidemiology*, vol. 105, pp. 125–135, 2019.

[15] E. S. Chan, D. T. Bautista, J. T. Long et al., "Traditional Chinese herbal medicine for vascular dementia," *Cochrane Database of Systematic Reviews*, vol. 12, no. 12, Article ID Cd010284, 2013.

[16] R. X. Hu, lZ. Wen, M. K. Yu, Y. M. Ren, H. J. Cao, and J. Q. Gao, "Literature analysis of present situation and reporting quality in TCM safety systematic reviews based on, 2019 PRISMA harms checklist," *Chinese Journal of Pharmacovigilance*, vol. 16, no. 4, pp. 231–238, 2019.

[17] S. K. Hung, S. Hillier, and E. Ernst, "Case reports of adverse effects of herbal medicinal products (HMPs): a quality assessment," *Phytomedicine*, vol. 18, no. 5, pp. 335–343, 2011.

[18] J. J. Guo and H. O. Jin, "Literature analysis on the current research status of adverse reactions of traditional Chinese medicine," *Medical Diet and Health*, vol. 18, no. 17, p. 22+4, 2020.

[19] S. X. Li, "Data analysis of adverse reactions of traditional Chinese medicines in pharmaceutical manufacturers in beijing (2009-2013)," Master,s Degree, Beijing University of Chinese Medicine, 2016.

[20] A. J. Sutton, N. J. Cooper, P. C. Lambert, D. R. Jones, K. R. Abrams, and M. J. Sweeting, "Meta-analysis of rare and adverse event data," *Expert Review of Pharmacoeconomics & Outcomes Research*, vol. 2, no. 4, pp. 367–379, 2002.

[21] D. K. Bhaumik, A. Amatya, S. L. T. Normand et al., "Meta-analysis of rare binary adverse event data," *Journal of the American Statistical Association*, vol. 107, no. 498, pp. 555–567, 2012.

[22] S. Singh and Y. K. Loke, "Drug safety assessment in clinical trials: methodological challenges and opportunities," *Trials*, vol. 13, no. 1, p. 138, 2012.

[23] S. H. J. Green, P. Alderson, M. Clarke, C. D. Mulrow, and A. D. Oxman, "Introduction Cochrane handbook for systematic reveiws of interventions," Edited by J. P. T. Higgins and S. Green, Eds., 2011, http://handbook-5-1.cochrane.org/.

[24] D. Moher, A. Liberati, J. Tetzlaff, and D. G. Altman, "Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement," *PLoS Medicine*, vol. 6, no. 7, Article ID e1000097, 2009.

[25] Z. Gao, Y. Liu, J. Zhang, and H. Upur, "Effect of Jianpi therapy in treatment of chronic obstructive pulmonary disease: a systematic review," *Journal of Traditional Chinese Medicine*, vol. 33, no. 1, pp. 1–8, 2013.

[26] T. Hong, M. Zhang, and J. Fan, "Cordyceps sinensis (a traditional Chinese medicine) for kidney transplant recipients," *Cochrane Database of Systematic Reviews*, vol. 2015, no. 10, Article ID Cd009698, 2015.

[27] T. Li, T. Wang, Y. Fei, X. Xue, and X. Wu, "Chinese herbal medicine combined with nucleotide analogues for compensated HBV-related cirrhosis: a systematic review of randomized controlled trials," *Journal of Traditional Chinese Medical Sciences*, vol. 2, no. 1, pp. 11–24, 2015.

[28] W. J. Li, Q. H. Peng, and H. Y. Tan, "Neuroprotective effects of traditional Chinese medicine in treating glaucoma: a Meta-analysis. [Chinese]," *International Eye Science*, vol. 13, no. 4, pp. 671–673, 2013.

[29] Y. Wang, X. T. Lou, Y. H. Shi, Q. Tong, and G. Q. Zheng, "Erxian decoction, a Chinese herbal formula, for menopausal syndrome: an updated systematic review," *Journal of Ethnopharmacology*, vol. 234, pp. 8–20, 2019.

[30] H. Xu, W. Y. M. Wei, and C. Dong, "Efficacy and safety of Chinese patent medicine (Jinlong capsule) in the treatment of advanced hepatocellular carcinoma: a meta-analysis," *Bioscience Reports*, vol. 40, no. 1, Article ID BSR20194019, 2020.

[31] L. Zorzela, S. Golder, Y. Liu et al., "Quality of reporting in systematic reviews of adverse events: systematic review," *BMJ*, vol. 348, p. f7668, 2014.

[32] X. Y. Zhang, "Retrospective analysis on ADR by anti-tumor traditional Chinese medicine injections and explore on clinical rational drug use," *China Medicine and Pharmacy*, vol. 9, no. 16, pp. 93–96+112, 2019.

Hindawi
Evidence-Based Complementary and Alternative Medicine
Volume 2022, Article ID 6106993, 12 pages
https://doi.org/10.1155/2022/6106993

Review Article

Efficacy of Traditional Chinese Medicine on Animal Model of IgA Nephropathy: A Systematic Review and Meta-Analysis

Tian-ying Chang,[1] **Hong-an Wang**,[2] **Yin-ping Wang**,[2] **Jin-hui Ma**,[3] **Di Zou**,[2] **Shou-Lin Zhang**,[2] **and Lehana Thabane**[3,4]

[1]*EBM Department, The Affiliated Hospital to Changchun University of Chinese Medicine, Changchun 130021, China*
[2]*Nephrology Department, The Affiliated Hospital to Changchun University of Chinese Medicine, Changchun 130021, China*
[3]*Department of Health Research, Evidence, and Impact, McMaster University, Hamilton, ON, Canada*
[4]*Biostatistics Unit, St Joseph's Healthcare-Hamilton, Hamilton, ON, Canada*

Correspondence should be addressed to Shou-Lin Zhang; shoulin-z@163.com and Lehana Thabane; thabanl@mcmaster.ca

Received 17 August 2022; Accepted 23 September 2022; Published 26 December 2022

Academic Editor: Xing Liao

Objective. Traditional Chinese medicine (TCM) has a long history in the treatment of Immunoglobulin A nephropathy (IgAN). A large number of animal experiments focused on the TCM treatment of IgAN are conducted every year. The evidence for these preclinical studies is not clear. This study summarized and evaluated the results of animal experiments on TCM treatment for IgAN. *Methods*. We systematically searched animal studies from 6 databases from inception to August 30, 2022. We included Chinese studies from the key magazine of China technology. The quality of the included studies was evaluated with the SYRCLE animal experimental bias risk assessment tool and the Grading of Recommendations Assessment, Development, and Evaluation (GRADE). *Results*. Out of 832 records identified in the initial search, 30 studies were selected. The results indicated that, compared with the control group, the TCM treatment group improved 24 h urine protein (24 h-UP) level (standardized mean difference (SMD) 3.57, 95% confidence interval (CI) 4.48 to 2.66, $P < 0.001$), urine red blood cell (U-RBC) (SMD 13.66, 95% CI 17.99 to 9.32, $P < 0.001$), serum creatinine (Scr) (mean difference (MD) 10.89, 95% CI 17.00 to 4.77, $P < 0.001$), blood urea nitrogen (BUN) (MD 2.44, 95% CI 3.42 to 1.47, $P < 0.001$), tumor necrosis factor-α (TNF-α) (MD 171.28 to 95% CI 323.68 to 18.88, $P = 0.03$), transforming growth factor-β1 (TGF-β) (SMD 4.02, 95% CI 7.26 to 0.77, $P = 0.02$), matrix metalloproteinase-9/tissue inhibitors of metalloproteinase-1(MMP-9/TIMP-1) (MD 0.03, 95% CI 0.00 to 0.06, $P = 0.02$), nephrin mRNA (SMD 3.39, 95% CI 2.59 to 4.18, $P < 0.001$). However, there is no difference in albumin level (MD 1.10, 95% CI 0.06 to 2.26, $P = 0.06$) and interleukin-6 (IL-6) (MD 170.77, 95% CI 365.3 to 23.75, $P = 0.09$). *Conclusions*. TCM can improve 24 h-UP, U-RBC, Scr, BUN, MMP-9/TIMP-1, TNF-α, TGF-β, and nephrin mRNA of IgAN animal models. Moreover, there is a need for rigorous reporting of preclinical research methodology, which is essential to support the quality of preclinical research. *Registration*. This review was registered with a systematic review record CRD42020171404 in the PROSPERO database.

1. Introduction

IgA nephropathy (IgAN) refers to primary glomerulonephritis with a large number of IgA or IgA-based immune complex granules deposited in the mesangial area. It is the most common primary glomerulonephritis in the world at present. [1] The modern medical treatment for IgAN is limited [2, 3]; Chinese medicine (including herb decoctions under the guidance of TCM theory, extract of herbs or decoctions, and patents) has been widely approved for its positive role in the prevention and treatment of IgAN [4].

The incidence of primary glomerular disease accounts for 30% in Asia, and it is also one of the leading causes of end-stage renal disease (ESRD) in China. Data show that the incidence of this disease has been gradually increasing in recent years. [5] The prognosis of IgAN is not optimistic. After treatment, about 50% of patients still progress to ESRD within 30 years. [6] Patients with ESRD can only rely on

kidney transplantation or dialysis to maintain their lives, which puts a massive psychological and economic burden on individuals, families, and society. Kidney function preservation and remission of proteinuria are the principles for its treatment. [7] Glucocorticoids and immunosuppressants can reduce urinary protein levels in IgAN patients and improve the prognosis. [3] However, severe adverse reactions, insensitivity, and drug resistance occur sometimes. TCM has certain advantages in the treatment of IgAN. It could delay the development of IgAN in the early stage, synergistically treat IgAN with immunosuppressants and glucocorticoids in the middle stage, and improve life quality in the end stage. [8] However, the results of these studies were not systemically evaluated. Systematic evaluation of animal experiments has become a new trend and an essential means to integrate animal experimental results, improve the quality of animal experiments, and guide clinical research. It is also an important channel to connect basic research and clinical trials. To further clarify the mechanism of Chinese medicine in the treatment of IgAN, this study intends to use the meta-analysis method to systematically evaluate the intervention of TCM in experimental IgAN animal models, to expand further the evidence of the mechanism of TCM in the treatment of IgAN, and to provide reference data for follow-up research.

2. Materials and Methods

This review was registered with a systematic review record CRD42020171404 in the PROSPERO database.

2.1. Search Strategy. Databases including PubMed, Cochrane Library, Embase, CNKI, VIP, and Wanfang data were searched for the literature from the inception to 4 April 2020 without language restriction. MeSH terms and keywords ("Immunoglobulin A Nephropathy" OR "Immunoglobulin A") AND ("Chinese Medicine" OR "Chinese Herbal Medicine") AND ("Animal" OR "Rat" OR "Mice") were used to search studies.

2.2. Inclusion and Exclusion Criteria

2.2.1. Eligibility Criteria. (1) Participants: models of IgAN (rats or mice); (2) intervention(TCM herb decoctions, extract, and patents): with all doses and durations; (3) control: distilled water treated, saline water treated, and same solvent or no treatment; (4) outcomes: 24 h-UP, U-RBC, Scr, BUN, Alb, MMP-9/TIMP-1, IL-6, TNF-α, TGF-β, and nephrin mRNA; (5) Study design: randomized controlled research studies.

2.2.2. Exclusion Criteria. (1) Participants: *in vitro* studies and research in humans; (2) intervention: TCM without dose unit or TCM was not given by oral gavage administration; (3) control: other TCM; (4) study design: case reports, crossover studies, and studies without a separate control group; (5) pilot studies; (6) reviews; (7) conference papers; (8) studies without full text. If studies were repeatedly published, we chose the one with the largest sample size.

2.3. Data Extraction. Two reviewers (TYC and HAW) independently extracted the following information according to the predesigned file from selected studies: characteristics of studies (first author, publication year, TCM treatment composition, type of models, modeling method; individual data for each study, including animal number, species, gender, weight, treatment time, and mode of administration). The outcome measurement includes 24 h-UP, U-RBC, Scr, BUN, Alb, MMP-9/TIMP-1, IL-6, TNF-α, TGF-β, and nephrin mRNA. If outcomes were presented at different time points, variables were extracted from the last time point. If studies had more than one experiment group sharing one control group, the control group would be separated into multiple groups (the number was the same as the experiment groups), incorporating these comparisons into this meta-analysis. Any disagreements regarding extracted data were resolved through discussion, if necessary, by a third party (SLZ).

2.4. Quality Assessment. The included studies were evaluated with SYRCLE's Risk of Bias Tool for Animal Studies (8). Ten items were used to analyze the methodological quality: (1) sequence generation; (2) baseline characteristics; (3) allocation concealment; (4) random housing; (5) blinding (performance bias); (6) random outcome; (7) blinding (detection bias); (8) incomplete outcome data; (9) selective outcome reporting; (10) other sources of bias. Two reviewers (TYC and HAW) assessed the risk of bias independently, and if necessary, a third party (SLZ) adjudicated the judgment.

2.5. Statistical Analysis. We used RevMan version 5.3 by the Cochrane Collaboration Network to analyze the data. Continuous data were expressed as the mean difference with a 95% confidence interval (CI). Categorical data were calculated with the risk ratio (RR) and 95% CI. We evaluated heterogeneity with the Higgins I^2 test. If $I^2 > 50\%$, a random-effect model was used for meta-analyses; if not, a fixed-effect model was used. Publication bias was assessed by a funnel plot. The quality of evidence was rated with the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) [9].

3. Results

3.1. Study Inclusion. In the initial search, 832 related studies were obtained and 206 repetitive studies were excluded as duplications by EndNote X9 software. The rest studies were further screened by reviewing titles, abstracts, and the list of Chinese Core Journals. The rest 52 studies were full-text screened, and 19 studies were excluded by a nonunified treatment dose. At last, 30 eligible studies were identified. All

the literature was published in Chinese, and all trials were conducted in China. The literature screening process and results are shown in Figure 1.

3.2. Study Characteristics. The 30 included studies involved 681 animals, the treatment group ($n = 340$), and the control group ($n = 341$). And among these animals, 150 were Wistar rats, 511 were Sprague Dawley rats, and 20 were BALB/C mice. 17 studies [10–26] used male rats, five studies [27–32] used female rats, four studies [32–35] used half male and half female, and 4 studies [16, 33, 36, 37] did not describe. The animal model of IgA nephropathy was established by bovine serum albumin (BSA) + lipopolysaccharide (LPS) + carbon tetrachloride (CCL4) in 22 studies [10, 11, 13–22, 24–26, 32–39], and BSA + staphylococcal enterotoxin-B (SEB) in 8 studies [12, 23, 27–31, 40]. 19 studies [10, 12–15, 17, 18, 21–24, 27, 29, 30, 32, 35, 37–39] used 24 h-UP as a measurement result, 10 studies [11–13, 15, 17, 20, 22, 24, 27, 29] used U-RBC, 15 studies [12, 13, 15, 16, 18, 21, 24, 27, 29, 30, 32, 35, 37–40] used Scr, 12 studies [12, 13, 15, 16, 18, 21, 24, 29, 30, 35, 37, 39, 40] used BUN, six studies [15, 24, 30, 32, 35, 38] used Alb, two studies [14, 38] used nephrin mRNA, two studies [13, 33] used TGF-β1, two studies [11, 14] used MMP9/TIMP-1, three studies [12, 35, 36] used IL-6, and TNF-α was used in 3 studies [18, 20, 36], and these characteristics are shown in Table 1. The quality of evidence was rated with GRADE.

3.3. Methodological Quality of Included Studies. Sequence generation was mentioned in 7 studies. [13, 14, 21, 33, 35, 38, 39] Incomplete outcome data were mentioned in 6 studies. [16, 20, 22, 25, 30, 36] All studies mentioned selective outcome reporting and other sources of bias. All studies did not mention baseline characteristics, allocation concealment, random hosing, blinding (performance bias), random outcome assessment, and blinding (detection bias). The methodological quality of the included studies is shown in Table 2.

3.4. 24-Hour Urinary Protein. 20 studies [10–15, 17, 18, 21–24, 27, 29, 30, 32, 35, 37–39] reported the impact of TCM on 24 h-UP, and results showed significant heterogeneity ($I^2 = 90\%$, $P < 0.001$). A random-effect model was conducted. The meta-analysis revealed that the 24-hour urine protein level was significantly improved compared with the control group treatments (SMD 3.57, 95% CI 4.48 to 2.66, $P < 0.001$) (Figure 2).

3.5. Urinary Red Blood Cell. 10 studies [11–13, 15, 17, 20, 22, 24, 27, 29] reported the impact of TCM on U-RBC, and results showed significant heterogeneity ($I^2 = 96\%$, $P < 0.001$). A random-effect model was conducted. The meta-analysis revealed that the U-RBC level was significantly improved compared with the control group treatments (SMD 13.66, 95% CI 17.99 to 9.32, $P < 0.001$) (Figure 3).

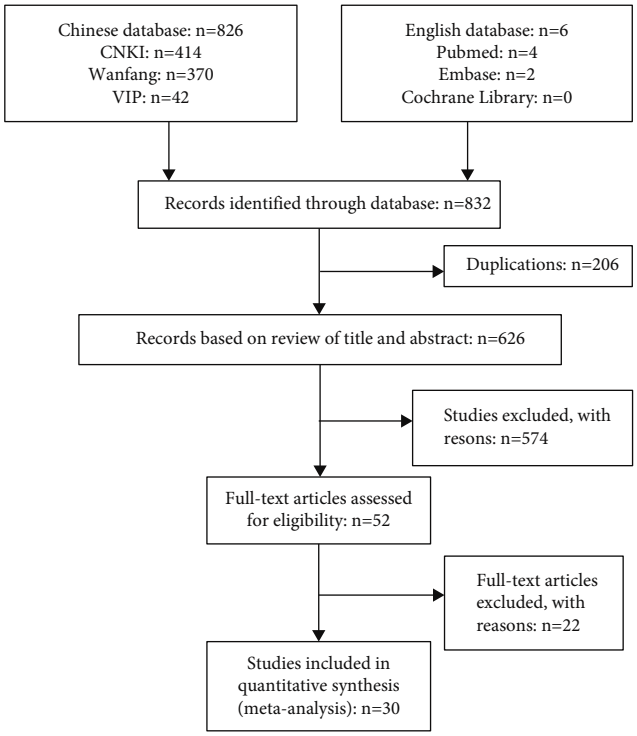


Figure 1: Literature screening process.

3.6. Serum Creatinine. 15 studies [12, 13, 15, 16, 18, 21, 24, 27, 29, 30, 32, 35, 37–40] reported the impact of TCM on Scr, and results showed significant heterogeneity ($I^2 = 97\%$ $P < 0.001$). A random-effect model was conducted. The meta-analysis revealed that the Scr level was significantly improved compared with the control group treatments (MD 10.89, 95% CI 17.00 to 4.77, $P < 0.001$) (Figure 4).

3.7. Blood Urea Nitrogen. 13 studies [12, 13, 15, 16, 18, 21, 24, 27, 29, 30, 32, 35, 37–40] reported the impact of TCM on BUN, and results showed significant heterogeneity ($I^2 = 98\%$, $P < 0.001$). A random-effect model was conducted. The meta-analysis revealed that the BUN level was significantly improved compared with the control group treatments (MD 2.44, 95% CI 3.42 to 1.47, $P < 0.001$) (Figure 5).

3.8. Albumin. 6 studies [15, 24, 30, 32, 35, 38] reported the impact of TCM on Alb, and results showed significant heterogeneity ($I^2 = 66\%$, $P = 0.01$). A random-effect model was conducted. The meta-analysis revealed no difference between the two groups in improving Alb level (MD 1.10, 95% CI 0.06 to 2.26, $P = 0.06$) (Figure 6).

3.9. MMP 9/TIMP-1. 2 studies [11, 22] reported the impact of TCM on MMP-9/TIMP-1, and no significant heterogeneity was tested between these two studies ($I^2 = 0\%$, $P = 0.59$, $P = 0.59$). A fixed-effect model was conducted. The meta-

Table 1: Basic characteristics of the included studies.

Study	Species	Number (T/C)	Gender m/f	Weight (g)	Model method	Interventions		Outcome
						Treatment	Control	
Bian et al., 2016	SD rats	10/10	0/40	150 ± 10	BSA + LPS + CCL4	Decoction	Distilled water	1
Chen et al., 2013	SD rats	12/12	30/30	200 ± 20	BSA + LPS + CCL4	Decoction	Saline	1,3,5,10,19,20,21
Guo et al., 2010	SD rats	12/12	NR	220–260	BSA + LPS + CCL4	Patent	Distilled water	6,22
Huang et al., 2009	SD rats	7/7	NR	145–155	BSA + LPS + CCL4	Patent	Saline	8,9
Jin et al., 2017	Wistar rats	12/12	0/80	200–220	BSA + LPS + CCL4	Patent	Distilled water	1,2,7
Liu et al., 2003	SD rats	10/10	0/50	180 ± 10	BSA + SEB	Patent	Distilled water	1,2,3,4,14
Song et al., 2014	Wistar rats	12/12	0/60	150 ± 10	BSA + LPS + CCL4	Decoction	Distilled water	1,2,3,4,6
Tang et al., 2018	SD rats	20/20	0/80	180 ± 20	BSA + LPS + CCL4	Decoction	Saline	1,10
Wang et al., 2018	SD rats	6/6	0/30	180–220	BSA + LPS + CCL4	Decoction	Saline	1,2,3,4,5,11,12,13
Wang et al., 2010	SD rats	10/10	NR	180–220	BSA + LPS + CCL4	Extract	Distilled water	3,4,23,24
Wang and wang, 2017	Wistar rats	10/11	0/80	180 ± 20	BSA + LPS + CCL4	Patent	Saline	1,2
Xiang et al., 2013	SD rats	10/10	60/0	200 ± 20	BSA + SEB	Patent	Saline	1,2,3
Yang et al., 2019	SD rats	20/20	NR	180 ± 20	BSA + LPS + CCL4	Decoction	Saline	1,3,4
Yang et al., 2017	SD rats	12/12	0/60	180 ± 20	BSA + LPS + CCL4	Decoction	Distilled water	1,3,4,9,26
Zhang et al., 2016	SD rats	12/12	0/72	180 ± 20	BSA + LPS + CCL4	Decoction	Saline	26
Zhang, 2013	Wistar rats	10/10	0/60	240–260	BSA + LPS + CCL4	Decoction	Distilled water	2,8,9
Zhou et al., 2015	SD rats	12/12	0/48	180–200	BSA + LPS + CCL4	Decoction	Distilled water	1,3,4
Zou et al., 2016	Wistar rats	12/12	0/72	160–200	BSA + LPS + CCL4	Patent	Distilled water	1,2,7
Zeng et al., 2004	SD rats	12/12	62/0	140 ± 10	BSA + SEB	Patent	Distilled water	36,37
Hu et al., 1999	SD rats	12/12	60/0	180 ± 10	BSA + SEB	Patent	Distilled water	1,2,3,4,27,28,29
Lin et al., 2016	SD rats	15/15	25/25	130–160	BSA + LPS + CCL4	Patent	Distilled water	1,3,5,14,15,27,30
Liu et al., 2006	SD rats	12/12	0/48	180 ± 10	BSA + SEB	Decoction	Tap water	1,3,4,5,
Sun et al., 2004	SD rats	12/12	60/0	140 ± 10	BSA + SEB	Patent	Distilled water	6
Wang et al., 2017	SD rats	12/12	0/36	200–210	BSA + SEB	Patent	Saline	1
Yan et al., 2015	SD rats	8/8	0/56	180 ± 10	BSA + LPS + CCL4	Extract	Saline	1,2,3,4,5,12,13
Ye et al., 2014	SD rats	10/10	0/60	180–220	BSA + LPS + CCL4	Decoction	Distilled water	31,32,33,34,35
Zhou et al., 2003	BALB/C mice	10/10	0/40	20	BSA + SEB	Decoction	Saline	3,4,23,24,27
Cao et al., 2009	SD rats	12/12	0/48	220–260	BSA + LPS + CCL4	Patent	Distilled water	16,17,18
Yu et al., 2013	SD rats	10/10	29/29	180–220	BSA + LPS + CCL4	Patent	Distilled water	25
Zhang et al., 2022	SD rats	8/8	8/8	200 ± 20	BSA + LPS + CCL4	Patent	Distilled water	1,3,4,5,8

SD: Sprague-Dawley; BSA: albumin from bovine serum; LPS: lipopolysaccharide; SEB: staphylococcal enterotoxin-B; CCL4: carbon tetrachloride; ig:irrigation; h: hour; NR: NO report; D: days; W: weeks; 1: 24-hour urinary protein quantity; 2: urinary red blood cell; 3: serum creatinine; 4: blood urea nitrogen; 5: albumin; 6: transforming growth factor-β; 7: MMP-9 or matrix metallopeptidase 9/matrix metalloproteinase tissue inhibitor 1; 8: IL-6 or interleukin-6; 9: TNF-α or tumor necrosis factor-α; 10: nephrin mRNA; 11: uric acid; 12: alanine aminotransferase; 13: aspartate aminotransferase; 14: cholesterol; 15: triglyceride; 16: nuclear factor kappa-B; 17: monocyte chemotactic protein 1; 18: intercellular cell adhesion molecule-1; 19: nephrin; 20: podocin; 21: podocin mRNA; 22: P38MAPK; 23: superoxide dismutase; 24: malondialdehyde; 25: interleukin-13 mRNA; 26: interleukin-4; 27: immunoglobulin A; 28: immunoglobulin G; 29: immunoglobulin M; 30: C3; 31: prothrombin time; 32: prothrombin time activity; 33: activated partial thromboplastin time; 34: thrombin time; 35: fibrinogen; 36: nitric oxide; 37: nitric oxide synthase.

Table 2: Quality assessment of included studies.

Study	A	B	C	D	E	F	G	H	I	J
Bian et al., 2016	U	U	U	U	U	U	U	U	Y	Y
Chen et al., 2013	Y	U	U	U	U	U	U	U	Y	Y
Guo et al., 2010	Y	U	U	U	U	U	U	U	Y	Y
Huang et al., 2009	U	U	U	U	U	U	U	Y	Y	Y
Jin et al., 2017	U	U	U	U	U	U	U	U	Y	Y
Liu et al., 2003	U	U	U	U	U	U	U	U	Y	Y
Song et al., 2014	Y	U	U	U	U	U	U	U	Y	Y
Tang et al., 2018	Y	U	U	U	U	U	U	U	Y	Y
Wang et al., 2018	U	U	U	U	U	U	U	U	Y	Y
Wang et al., 2010	U	U	U	U	U	U	U	Y	Y	Y
Wang and wang, 2017	U	U	U	U	U	U	U	U	Y	Y
Xiang et al., 2013	U	U	U	U	U	U	U	U	Y	Y
Yang et al., 2018	U	U	U	U	U	U	U	U	Y	Y
Yang et al., 2017	U	U	U	U	U	U	U	U	Y	Y
Zhang et al., 2016	U	U	U	U	U	U	U	U	Y	Y
Zhang, 2013	U	U	U	U	U	U	U	Y	Y	Y
Zhou et al., 2015	Y	U	U	U	U	U	U	U	Y	Y
Zou et al., 2016	U	U	U	U	U	U	U	Y	Y	Y
Zeng et al., 2004	U	U	U	U	U	U	U	U	Y	Y
Hu et al., 1999	U	U	U	U	U	U	U	U	Y	Y
Lin et al., 2016	U	U	U	U	U	U	U	U	Y	Y
Liu et al., 2006	U	U	U	U	U	U	U	Y	Y	Y
Sun et al., 2004	U	U	U	U	U	U	U	U	Y	Y
Wang et al., 2017	U	U	U	U	U	U	U	U	Y	Y
Yan et al., 2015	U	U	U	U	U	U	U	U	Y	Y
Ye et al., 2014	U	U	U	U	U	U	U	Y	Y	Y
Zhou et al., 2003	U	U	U	U	U	U	U	U	Y	Y
Cao et al., 2009	U	U	U	U	U	U	U	U	Y	Y
Yu et al., 2013	U	U	U	U	U	U	U	U	Y	Y
Zhang et al., 2022	U	U	U	U	U	U	U	Y	Y	Y

A, whether the distribution sequence is generated or applied sufficiently; B, whether the baselines of each group are the same; C, whether the distribution hiding is sufficient; D, whether the animals are randomly placed during the experiment; E, whether the researchers are blinded; F, whether the animals are randomly selected in the result evaluation; G, whether the blind method is used for the evaluators of the results; H, whether the incomplete data are reported; I, whether the research report has nothing to do with the selective results report; J, whether there is no other bias; Y, yes; N, no; U, uncertain.

analysis revealed that the MMP-9/TIMP-1 level was significantly improved compared with the control group treatments (MD 0.03, 95% CI 0.00 to 0.06, $P = 0.02$) (Figure 7).

3.10. Interleukin-6. 3 studies [20, 36] reported the impact of TCM on IL-6, and no significant heterogeneity was tested between these two studies ($I^2 = 100\%$, $P < 0.001$). A random-effect model was conducted. The meta-analysis revealed no difference between the two groups in improving IL-6 level (MD 170.77, 95% CI 365.3 to 23.75, $P = 0.09$) (Figure 8).

3.11. Tumor Necrosis Factor-α. Three studies [18, 20, 36] reported the impact of TCM on TNF-α, and no significant heterogeneity was tested between these two studies ($I^2 = 99\%$, $P < 0.001$). A random-effect model was conducted. The meta-analysis revealed that the TNF-α level was significantly improved compared with the control group treatments (MD 171.28 to 95% CI 323.68 to 18.88, $P = 0.03$) (Figure 9).

3.12. Transforming Growth Factor-β1. Two studies [13, 33] reported the impact of TCM on TGF-β1, and no significant heterogeneity was tested between these two studies ($I^2 = 88\%$, $P = 0.004$). A fixed-effect model was conducted. The meta-analysis revealed that the TGF-β1 level was significantly improved compared with the control group treatments (SMD 4.02, 95% CI 7.26 to 0.77, $P = 0.02$) (Figure 10).

3.13. Nephrin mRNA. 2 studies [14, 38] reported the impact of TCM on nephrin mRNA, and no significant heterogeneity was tested between these two studies ($I^2 = 98\%$, $P = 0.39$). A fixed-effect model was conducted. The meta-analysis revealed that the nephrin mRNA level was significantly improved compared with the control group treatments (SMD 3.39, 95% CI 2.59 to 4.18, $P < 0.001$) (Figure 11).

3.14. Subgroup Analyses. We conducted a subgroup analysis by different modeling methods. The TCM can significantly reduce 24 h-UP on the BSA + LPS + CCL4 model (SMD 4.54, 95% CI-5.90 to 3.17, $P < 0.001$) and the BSA + SEB model (SMD-2.34, 95% CI-2.87 to 1.80, $P < 0.001$), and the overall effect is (SMD 3.68, 95% CI 4.66 to 2.71, $P < 0.001$) (Figure 12).

3.15. Publication Bias Test. We conducted a funnel plot to indicate publication bias and potential publication bias observed in Figure 13.

3.16. Sensitivity Analysis. Significant heterogeneity was found in the meta-analysis of 24 h-UP, U-RBC, Scr, BUN, albumin, IL-6, TNF-α, and TGF-β1. We conducted a series of sensitivity tests by excluding better-designed studies to examine the robustness of our results, and we found that the results were consistent.

4. Discussion

The renal protective effect of TCM has been extensively researched in different animal experimental models, and our systematic review and meta-analysis intend to analyze whether TCM treatment exerted an effect on IgAN animal models. The results indicated that oral gavage TCM could significantly lower levels of 24 h-UP, U-RBC, Scr, BUN, albumin, MMP-9/TIMP-1, IL-6, TNF-α, TGF-β1, and nephrin mRNA.

Twenty-one TCM treatments were used in our systematic review, eleven were decoctions, and eight were patent. The main medicinal ingredients of TCM are the following: Rehmannia, Astragalus, Chinese yam, Puhuang,

Study or Subgroup	Experimental Mean	Experimental SD	Experimental Total	Control Mean	Control SD	Control Total	Weight (%)	Std. Mean Difference IV, Random, 95% CI
Bian et al., 2016	13.05	1.45	10	20.06	1.95	10	5.2	−3.91 [−5.52, −2.30]
Chen et al., 2013	55.05	3.65	12	71.21	3.71	12	5.3	−4.24 [−5.78, −2.70]
Hu et al., 1999	0.5	0.75	12	2.1	0.8	12	5.8	−1.99 [−3.00, −0.98]
Ji et al., 2020	7.98	1.45	12	18.16	1.33	12	4.4	−7.06 [−9.39, −4.74]
Jin et al., 2017	10.82	1.48	12	18.65	1.45	12	5.0	−5.16 [−6.95, −3.37]
Lin et al., 2016	36.88	6.11	15	47.69	4.45	15	5.9	−1.97 [−2.86, −1.07]
Liu et al., 2003	96.23	12.317	10	148.25	42.669	10	5.8	−1.59 [−2.62, −0.55]
Liu et al., 2006	45.28	11.9	12	81.31	12.7	12	5.6	−2.83 [−4.01, −1.64]
Song et al., 2014	22.34	0.46	10	96.23	12.317	10	3.8	−8.12 [−11.06, −5.18]
Tang et al., 2018	10.97	2.4	20	17.52	2.16	20	5.9	−2.81 [−3.71, −1.91]
Wang and Wang, 2017	8.77	0.53	11	18.82	1.18	10	3.1	−10.74 [−14.44, −7.03]
Wang et al., 2017	9.11	0.93	12	13.09	1.76	12	5.7	−2.73 [−3.89, −1.57]
Wang et al., 2018	2.3	0.43	6	4.09	1.21	6	5.4	−1.82 [−3.26, −0.38]
Xiang et al., 2013	66.76	15.73	10	146.67	32.83	10	5.5	−2.97 [−4.32, −1.62]
Yan et al., 2015	47	18.8	8	51.3	12.7	8	5.8	−0.25 [−1.24, 0.73]
Yang et al., 2017	19.4	7.88	12	32.28	16.67	12	5.9	−0.95 [−1.81, −0.10]
Yang et al., 2019	10.97	2.4	20	17.52	2.16	20	5.9	−2.81 [−3.71, −1.91]
Zhang et al., 2022	2.53	0.39	8	2.57	0.4	8	5.8	−0.10 [−1.08, 0.88]
Zhou et al., 2015	2.64	0.17	12	10.52	0.34	12	0.9	−28.31 [−37.10, −19.51]
Zou et al., 2016	8	0.53	12	18.82	1.18	12	3.2	−11.42 [−15.04, −7.80]
Total (95% CI)			*236*			*235*	*100.0%*	*−3.57 [−4.48, −2.66]*

Heterogeneity: Tau² = 3.48; Chi² = 182.23, df = 19 (P < 0.00001); I^2 = 90%
Test for overall effect: Z = 7.66 (P < 0.00001)

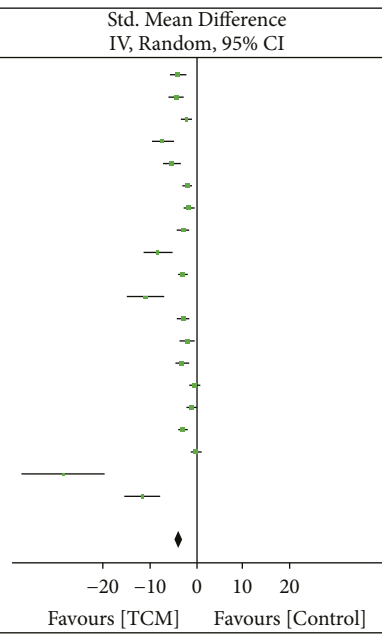


Figure 2: Forrest plot of TCM vs. control for the outcome of 24 h urinary protein.

Study or Subgroup	Experimental Mean	Experimental SD	Experimental Total	Control Mean	Control SD	Control Total	Weight (%)	Std. Mean Difference IV, Random, 95% CI
Hu et al., 1999	10.1	0.49	12	18.5	1.35	12	12.2	−7.99 [−10.58, −5.39]
Jin et al., 2017	89.8	9.81	12	240.68	1.78	12	10.0	−20.66 [−27.11, −14.22]
Liu et al., 2003	5.114	2.035	10	5.75	2.512	10	12.7	−0.27 [−1.15, 0.61]
Song et al., 2014	254.46	15.37	12	851.38	22.39	12	8.0	−30.01 [−39.33, −20.69]
Wang and Wang, 2017	87.32	1.21	11	165.48	1.79	10	4.4	−49.60 [−66.27, −32.94]
Wang et al., 2018	28.6	12.05	6	127.8	21.68	6	12.2	−5.22 [−8.01, −2.43]
Xiang et al., 2013	3.03	1.02	10	13.86	4.37	10	12.6	−3.27 [−4.70, −1.84]
Yan et al., 2015	2	0.6	8	7.5	0.7	8	11.9	−7.98 [−11.31, −4.65]
Zhang, 2013	58.13	4.51	10	235.34	16.45	10	11.0	−14.07 [−19.02, −9.13]
Zou et al., 2016	87.32	1.21	12	165.48	1.79	12	4.9	−49.40 [−64.70, −34.09]
Total (95% CI)			*103*			*102*	*100.0*	*−13.66 [−17.99, −9.32]*

Heterogeneity: Tau² = 38.21; Chi² = 207.75, df = 9 (P < 0.00001); I^2 = 96%
Test for overall effect: Z = 6.18 (P < 0.00001)

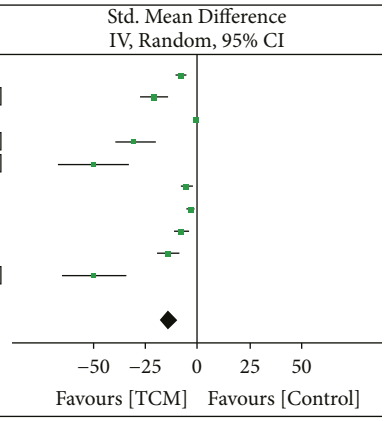


Figure 3: Forrest plot of TCM vs. control for the outcome of urinary red blood cell.

Imperata root, Poria, Alisma, Chinese wolfberry, and Rhubarb. These TCM were taken under the guidance of Nourishing Yin and Qi, tonifying kidney, and hemostasia methods.

IgAN, as primary glomerulonephritis, first identified by Berger and Hinglais in 1968, represents the leading cause of kidney failure among East Asian populations. [41] Aberrant glycosylation of IgA1 elicits an autoimmune response, generating antiglycan antibodies. [42] Consequent immune complexes deposit in the glomerular mesangium, which activates the complement pathway, stimulates mesangial cells, and induces the secretion of cytokines, finally resulting in inflammation and fibrosis. IgAN is an autoimmune disease wherein immune complexes cause renal injury. [43] Studies of animal experiments showed that urinary protein could induce renal tubular epithelial cell damage, so urinary protein has been used as an independent factor in evaluating renal prognosis. [44, 45].

The pathogenesis of IgAN includes environmental factors, genetic factors, and immune factors, among which immune factors have been the primary targets for the study of the treatment of the disease. At present, the cytokines that play an essential role in the pathogenesis and progression of IgAN are IL-6, TNF-α, TGF-β1, and MMP-9/TIMP-1. TNF-α is produced by activated monocytes; under normal conditions, an appropriate amount of TNF-α has a protective effect on the body, and excessive TNF-α causes immune damage to the body. Studies have shown that mononuclear macrophages infiltrate into renal tissue to release TNF-α, resulting in focal glomerular damage, resulting in gross hematuria, [46, 47] consistent with clinical studies. [47, 48] IL-6 can induce B lymphocytes to differentiate and produce immunoglobulin, stimulate the proliferation of glomerular mesangial cells, and produce an extracellular matrix, thus increasing the burden on the kidney and leading to glomerular fibrosis. [49] Glomerulosclerosis is a common

Study or Subgroup	Experimental Mean	Experimental SD	Experimental Total	Control Mean	Control SD	Control Total	Weight (%)	Mean Difference IV, Random, 95% CI
Chen et al., 2013	22.76	6.09	12	23.09	15.33	12	6.3	−0.33 [−9.66, 9.00]
Hu et al., 1999	220.654	49.074	12	293.363	72.76	12	1.3	−72.71 [−122.36, −23.05]
Ji et al., 2020	50.03	3.94	12	51.31	5.89	12	7.2	−1.28 [−5.29, 2.73]
Lin et al., 2016	31.38	6.36	15	28.87	4.46	15	7.2	2.51 [−1.42, 6.44]
Liu et al., 2003	65.4	17.6	10	104	34.3	10	3.5	−38.60 [−62.49, −14.71]
Liu et al., 2006	53.7	10.37	12	78.3	12.54	12	6.3	−24.60 [−33.81, −15.39]
Song et al., 2014	38.29	7.06	12	62.41	8.77	12	6.9	−24.12 [−30.49, −17.75]
Wang et al., 2010	82.92	8.23	10	110.94	10.33	10	6.5	−28.02 [−36.21, −19.83]
Wang et al., 2018	31.62	5.52	6	32.38	3.73	6	7.0	−0.76 [−6.09, 4.57]
Xiang et al., 2013	49.68	6.62	10	53.42	9.21	10	6.7	−3.74 [−10.77, 3.29]
Yan et al., 2015	25.03	4.12	8	30.25	2.25	8	7.3	−5.22 [−8.47, −1.97]
Yang et al., 2017	30.83	6.13	12	46.76	7.71	12	7.0	−15.93 [−21.50, −10.36]
Yang et al., 2019	27.7	2.45	20	28.75	2.05	20	7.4	−1.05 [−2.45, 0.35]
Zhang et al., 2022	100.52	16.78	8	95.29	15.41	8	5.0	5.23 [−10.56, 21.02]
Zhou et al., 2003	42.2	5.12	10	48.7	5.14	10	7.1	−6.50 [−11.00, −2.00]
Zhou et al., 2015	41.16	1.1	12	62.48	2.28	12	7.4	−21.32 [−22.75, −19.89]
Total (95% CI)			*181*			*181*	*100.0*	*−10.89 [−17.00, −4.77]*

Heterogeneity: Tau² = 131.23; Chi² = 549.10, df = 15 (P < 0.00001); I^2 = 97%
Test for overall effect: Z = 3.49 (P = 0.0005)

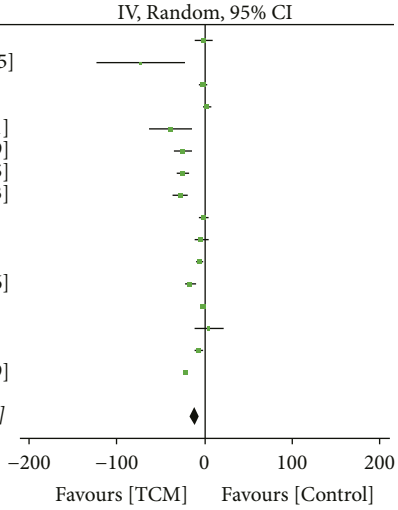


Figure 4: Forrest plot of TCM vs. control for the outcome of serum creatinine.

Study or Subgroup	Experimental Mean	Experimental SD	Experimental Total	Control Mean	Control SD	Control Total	Weight (%)	Mean Difference IV, Random, 95% CI
Hu et al., 1999	24.58	5.02	12	32.631	7.41	12	2.6	−8.05 [−13.12, −2.99]
Ji et al., 2020	6.24	0.44	12	6.3	0.41	12	9.0	−0.06 [−0.40, 0.28]
Liu et al., 2003	18.54	2.35	10	32.2	4.76	10	4.5	−13.66 [−16.95, −10.37]
Liu et al., 2006	7.31	0.87	12	11.13	1.37	12	8.5	−3.82 [−4.74, −2.90]
Song et al., 2014	8.58	1.53	12	12.59	2.16	12	7.5	−4.01 [−5.51 , −2.51]
Wang et al., 2010	9.56	0.8	10	13.24	1.05	10	8.6	−3.68 [−4.50, −2.86]
Wang et al., 2018	4.95	1.61	6	5.82	1.51	6	7.0	−0.87 [−2.64, 0.90]
Yan et al., 2015	6.5	1	8	8.2	1.4	8	8.0	−1.70 [−2.89, −0.51]
Yang et al., 2017	5.78	1.33	12	7.53	1.31	12	8.3	−1.75 [−2.81, −0.69]
Yang et al., 2019	6.56	0.83	20	7.3	0.48	20	9.0	−0.74 [−1.16, −0.32]
Zhang et al., 2022	3.89	0.56	8	4.06	0.74	8	8.8	−0.17 [−0.81, 0.47]
Zhou et al., 2003	4.19	0.41	10	4.21	0.51	10	9.0	−0.02 [−0.43, 0.39]
Zhou et al., 2015	5.83	0.12	12	8.52	0.18	12	9.1	−2.69 [−2.81 , −2.57]
Total (95% CI)			*144*			*144*	*100.0*	*−2.44 [−3.42 , −1.47]*

Heterogeneity: Tau² = 2.72; Chi² = 492.48, df = 12 (P < 0.00001); I^2 = 98%
Test for overall effect: Z = 4.90 (P < 0.00001)

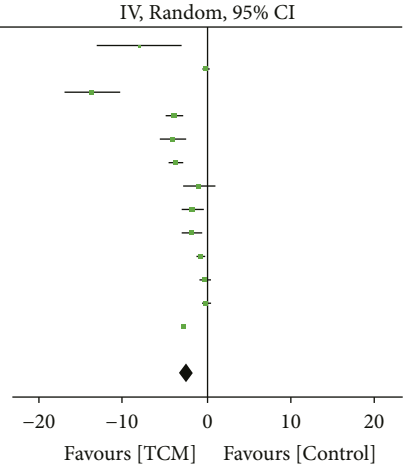


Figure 5: Forrest plot of TCM vs. control for the outcome of blood urea nitrogen.

Study or Subgroup	Experimental Mean	Experimental SD	Experimental Total	Control Mean	Control SD	Control Total	Weight (%)	Mean Difference IV, Random, 95% CI
Chen et al., 2013	30.76	6.09	12	27.82	6.95	12	4.2	2.94 [−2.29, 8.17]
Lin et al., 2016	37.17	4.52	15	34.7	3.46	15	10.5	2.47 [−0.41, 5.35]
Liu et al., 2006	13.28	1.07	12	10.79	1.33	12	24.4	2.49 [1.52, 3.46]
Wang et al., 2018	45.48	1.76	6	45.88	1.66	6	16.2	−0.40 [−2.34, 1.54]
Yan et al., 2015	32.14	1.21	8	31.38	1.06	8	23.1	0.76 [−0.35, 1.87]
Zhang et al., 2022	18.71	1.59	8	18.74	0.97	8	21.6	−0.03 [−1.32, 1.26]
Total (95% CI)			*61*			*61*	*100.0*	*1.10 [−0.06, 2.26]*

Heterogeneity: Tau² = 1.19; Chi² = 14.73, df = 5 (P = 0.01); I^2 = 66%
Test for overall effect: Z = 1.85 (P = 0.06)

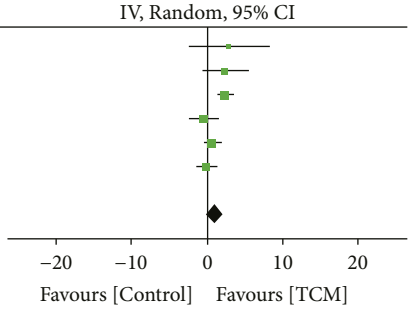


Figure 6: Forrest plot of TCM vs. control for the outcome of albumin.

pathological feature of most immune and nonimmune renal diseases, and TGF-β has been recognized as the target of glomerular sclerotherapy. [50] TGF-β can promote the proliferation of mesangial cells and promote the synthesis and deposition of extracellular matrix and can stimulate glomerulosclerosis. [51] In the animal model of IgAN and patients with IgAN, the level of TGF-β in plasma and renal tissue increased. [52] TIMP-1 and MMP-9 form an

Study or Subgroup	Experimental Mean	Experimental SD	Experimental Total	Control Mean	Control SD	Control Total	Weight (%)	Mean Difference IV, Fixed, 95% CI
Jin et al., 2017	0.69	0.18	12	0.63	0.04	12	7.0	0.06 [−0.04, 0.16]
Zou et al., 2016	0.69	0.027	12	0.66	0.043	12	93.0	0.03 [0.00, 0.06]
Total (95% CI)			*24*			*24*	*100.0*	*0.03 [0.00, 0.06]*

Heterogeneity: $Chi^2 = 0.30$, df = 1 (P = 0.59); $I^2 = 0\%$
Test for overall effect: Z = 2.27 (P = 0.02)

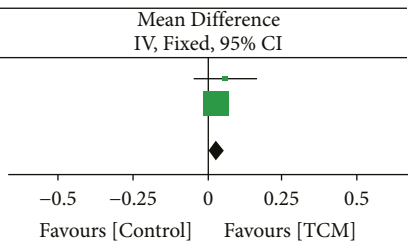


Figure 7: Forrest plot of TCM vs. control for the outcome of MMP-9/TIMP-1.

Study or Subgroup	Experimental Mean	Experimental SD	Experimental Total	Control Mean	Control SD	Control Total	Weight (%)	Mean Difference IV, Random, 95% CI
Huang et al., 2009	31.58	8.42	7	362.25	47.16	7	33.1	−330.67 [−336.16, −295.18]
Zhang et al., 2022	18.17	2.99	8	17.16	1.98	8	33.5	1.01 [−1.48, 3.50]
Zhang, 2013	146.83	23.34	10	331.32	32.36	10	33.3	−184.49 [−209.22, −159.76]
Total (95% CI)			*25*			*25*	*100.0*	*−170.77 [−365.30, 23.75]*

Heterogeneity: $Tau^2 = 29389.94$; $Chi^2 = 544.20$, df = 2 (P < 0.00001); $I^2 = 100\%$
Test for overall effect: Z = 1.72 (P = 0.09)

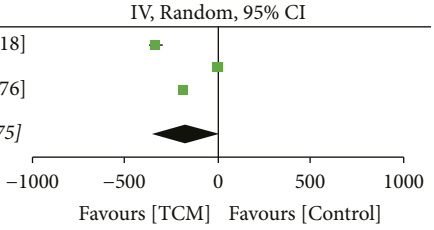


Figure 8: Forrest plot of TCM vs. control for the outcome of IL-6.

Study or Subgroup	Experimental Mean	Experimental SD	Experimental Total	Control Mean	Control SD	Control Total	Weight (%)	Mean Difference IV, Random, 95% CI
Huang et al., 2009	136.55	16.23	7	395.98	27.22	7	33.4	−259.43 [−282.91, −235.95]
Yang et al., 2017	193.2	33.65	12	217.2	28.49	12	33.4	−24.00 [−48.95, 0.95]
Zhang, 2013	203.45	25.58	10	434.06	43.13	10	33.2	−230.61 [−261.69, −199.53]
Total (95% CI)			*29*			*29*	*100.0*	*−171.28 [−323.68, −18.88]*

Heterogeneity: $Tau^2 = 17952.44$; $Chi^2 = 201.85$, df = 2 (P < 0.00001); $I^2 = 99\%$
Test for overall effect: Z = 2.20 (P = 0.03)

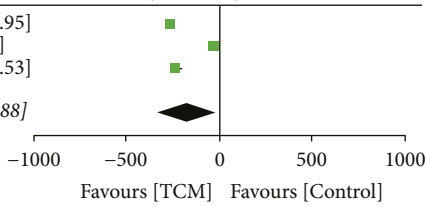


Figure 9: Forrest plot of TCM vs. control for the outcome of tumor necrosis factor-α.

Study or Subgroup	Experimental Mean	Experimental SD	Experimental Total	Control Mean	Control SD	Control Total	Weight (%)	Std. Mean Difference IV, Random, 95% CI
Guo et al., 2010	0.352	0.106	12	0.646	0.124	12	53.1	−2.46 [−3.57, −1.36]
Song et al., 2014	0.421	0.031	12	0.722	0.064	12	46.9	−5.78 [−7.74, −3.82]
Total (95% CI)			*24*			*24*	*100.0*	*−4.02 [−7.26, −0.77]*

Heterogeneity: $Tau^2 = 4.85$; $Chi^2 = 8.36$, df = 1 (P = 0.004); $I^2 = 88\%$
Test for overall effect: Z = 2.43 (P = 0.02)

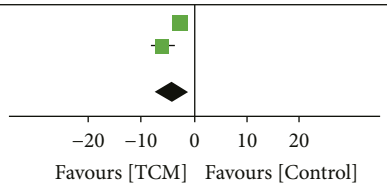


Figure 10: Forrest plot of TCM vs. control for the outcome of transforming growth factor-β1.

Study or Subgroup	Experimental Mean	Experimental SD	Experimental Total	Control Mean	Control SD	Control Total	Weight (%)	Std. Mean Difference IV, Fixed, 95% CI
Chen et al., 2013	28.79	5.77	12	15.26	2.26	12	42.6	2.98 [1.76, 4.20]
Tang et al., 2018	0.106	0.026	20	0.035	0.006	20	57.4	3.69 [2.64, 4.74]
Total (95% CI)			*32*			*32*	*100.0*	*3.39 [2.59, 4.18]*

Heterogeneity: $Chi^2 = 0.74$, df = 1 (P = 0.39); $I^2 = 0\%$
Test for overall effect: Z = 8.32 (P < 0.00001)

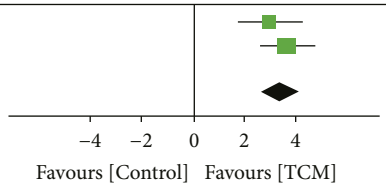


Figure 11: Forrest plot of TCM vs. control for the outcome of nephrin mRNA.

Study or Subgroup	Experimental Mean	Experimental SD	Experimental Total	Control Mean	Control SD	Control Total	Weight (%)	Std. Mean Difference IV, Random, 95% CI
16.1.1 BSA+SEB								
Hu et al., 1999	500	740	12	2,100	800	12	5.9	−2.00 [−3.02, −0.99]
Liu et al., 2003	96.23	12.317	10	148.25	42.669	10	5.9	−1.59 [−2.62, −0.55]
Liu et al., 2006	45.28	11.9	12	81.31	12.7	12	5.8	−2.83 [−4.01, −1.64]
Wang et al., 2017	9.11	0.93	12	13.09	1.76	12	5.8	−2.73 [−3.89, −1.57]
Xiang et al., 2013	66.76	15.73	10	146.67	32.83	10	5.6	−2.97 [−4.32, −1.62]
Subtotal (95% CI)			*56*			*56*	*29.0*	*−2.34 [−2.87, −1.80]*
Heterogeneity: $\tau^2 = 0.03$; $\chi^2 = 4.38$, df = 4 (P = 0.36); $I^2 = 9\%$								
Test for overall effect: Z = 8.63 (P < 0.00001)								
16.1.2 BSA+LPS+CCL4								
Bian et al., 2016	13.05	1.45	10	20.06	1.95	10	5.4	−3.91 [−5.52, −2.30]
Chen et al., 2013	55.05	3.65	12	71.21	3.71	12	5.5	−4.24 [−5.78, −2.70]
Ji et al., 2020	7.98	1.45	12	18.16	1.33	12	4.6	−7.06 [−9.39, −4.74]
Jin et al., 2017	10.82	1.48	12	18.65	1.45	12	5.2	−5.16 [−6.95, −3.37]
Lin et al., 2016	36.88	6.11	15	47.69	4.45	15	6.0	−1.97 [−2.86, −1.07]
Song et al., 2014	7.59	0.46	12	22.34	0.46	12	0.9	−30.96 [−40.57, −21.35]
Tang et al., 2018	10.97	2.4	20	17.52	2.16	20	6.0	−2.81 [−3.71, −1.91]
Wang and Wang, 2017	8.77	0.53	10	18.82	1.18	11	3.4	−10.37 [−13.95, −6.79]
Wang et al., 2018	2.3	0.43	6	4.09	1.21	6	5.6	−1.82 [−3.26, −0.38]
Yan et al., 2015	47	18.8	12	51.3	12.7	12	6.1	−0.26 [−1.06, 0.55]
Yang et al., 2017	19.4	7.88	12	32.28	16.67	12	6.0	−0.95 [−1.81,−0.10]
Yang et al., 2019	10.97	2.4	20	17.52	2.16	20	6.0	−2.81 [−3.71, −1.91]
Zhang et al., 2022	2.53	0.39	8	2.57	0.44	8	5.9	−0.09 [−1.07, 0.89]
Zhou et al., 2015	2.64	0.17	12	10.52	0.34	12	1.0	−28.31 [−37.10, −19.51]
Zou et al., 2016	8	0.53	12	18.82	1.18	12	3.4	−11.42 [−15.04, −7.80]
Subtotal (95% CI)			*185*			*186*	*71.0*	*−4.54 [−5.90, −3.17]*
Heterogeneity: $Tau^2 = 5.77$; $Chi^2 = 203.82$, df = 14 (P < 0.00001); $I^2 = 93\%$								
Test for overall effect: Z = 6.50 (P < 0.00001)								
Total (95% CI)			*241*			*242*	*100.0*	*−3.68 [−4.66, −2.71]*
Heterogeneity: $Tau^2 = 3.93$; $Chi^2 = 208.56$, df = 19 (P < 0.00001); $I^2 = 91\%$								
Test for overall effect: Z = 7.39 (P < 0.00001)								
Test for subgroub differences: $Chi^2 = 8.65$, df = 1 (P = 0.003). $I^2 = 88.4\%$								

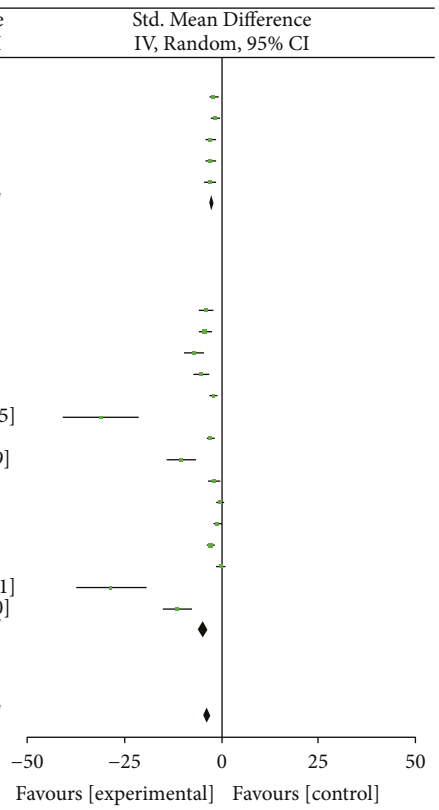


Figure 12: Forrest plot of TCM vs. control for subgroup outcome of 24-hour urinary protein.

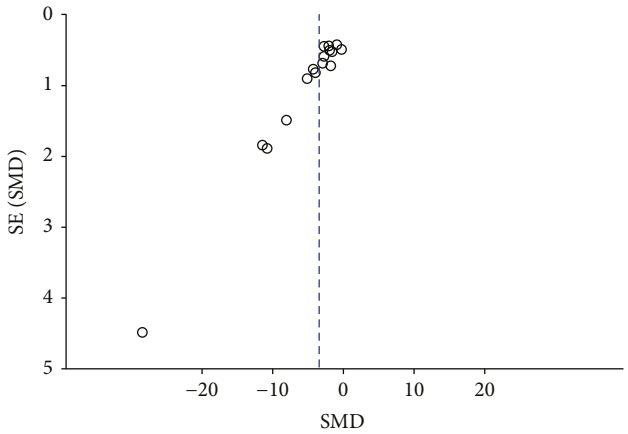


Figure 13: Funnel plot of the SMD in 24 h-UP.

MMP-TIMP complex at 1 : 1, blocking the binding of MMP-9 to the substrate, thus affecting the balance of ECM accumulation and degradation. [53, 54] Any imbalance between TIMP-1/MMP9 and ECM may lead to abnormal accumulation of ECM, glomerular disease, glomerular remodeling, hematuria, and proteinuria. The meta-analysis results showed that after TCM treatment, TNF-α and TGF-β could be reduced, and serum MMP-9/TIMP-1 content could be increased; the difference was statistically significant.

In addition, the study found that there is also podocyte destruction in the occurrence and development of IgAN. [55] Podocyte injury, especially the role of changes in the fissure diaphragm in the occurrence of IgAN proteinuria, has also attracted people's attention. Clinical studies have confirmed that the urinary protein level exceeding 1.0 g/d during renal biopsy indicates that the prognosis of patients is poor. [56, 57] Therefore, stabilizing the podocyte fissure diaphragm will be an important starting point for treating IgAN proteinuria. Nephrin, a sign of mature podocytes, is the first transmembrane protein found on the glomerular filtration barrier of SD, and it is also the "main body" part of SD. The nephrin deficiency in humans and rats will lead to classic SD deficiency and massive proteinuria. The results of the meta-analysis showed that the TCM treatment could significantly reduce the level of urinary protein and downregulate the expression of nephrin mRNA in podocytes in rats with IgA nephropathy, thus playing a role in the treatment of IgAN.

Plenty of animal experiments focused on TCM treatment for IgAN animal models have been conducted for years. For better quality of included studies, we chose studies from the list of Chinese Core Journals if published in Chinese. Animal models for IgAN were established in three kinds of rats/mice. Six studies constructed animal models with Wistar rats, one study constructed an animal model with BALB/C mice, and twenty-three studies used SD rats. Most studies constructed models with two methods. One method is oral gavage with BSA 400 mg/kg every other day, subcutaneous injection of CCL4 0.1 ml/weekly and benne oil 0.5 mL/weekly for nine weeks, and intravenous injection of LPS 0.05 mg at the sixth or eighth

week. The other method is intravenous injection of SEB combined with oral gavage with BSA. IgAN animal experiments conducted outside China usually construct an animal model with a ddY mouse [58] which has an abnormally high concentration of IgA from 10 to 60 weeks, but rare hematuria. The BSA + SEB method usually constructs models with a high mortality rate after modeling. Most included studies used the BSA + LPS + CCL4 method to construct an animal model.

Methodological quality was low among animal experiments. We used GRADE to evaluate the certainty of the main outcomes of this meta-analysis, and all certainty is very low. Insufficient reporting of how these studies were conducted lowers the quality and increases the biases. Six of ten SYRCLE's tool items were reported as unclear in all included studies, which means researchers need more training in methodological ability. Evidence-based medicine ability should be emphasized to TCM researchers and practitioners. The animal modeling method is also a source of heterogeneity. Furthermore, our results were consistent with the sensitivity of excluding studies with different modeling methods.

Through this study, we can find that although there are a large number of IgAN animal experimental studies published, most of them are not fully reported in the methods of model establishment, animal feeding, and model evaluation. High-quality systematic evaluation of animal experiments will help to prevent the waste of laboratory animals and test participants by carrying out unnecessary, ineffective, or less information research [59]. Therefore, a high-quality original research design is essential to provide research evidence for treating IgAN with traditional Chinese medicine.

This study showed that TCM intervention in IgAN animals could reduce levels of 24 h-UP, U-RBC, Scr, BUN, TNF-α and upregulate the contents of serum TGF-β1, nephrin mRNA, and MMP-9/TIMP-1. According to different animal species and modeling methods in the subgroup analysis, the results show that TCM significantly affects IgAN SD and Wistar rats; the results are statistically significant. This meta-analysis reinforces the evidence that TCM has a protective effect in experimental IgAN animal models. However, the methodological quality of these studies needs to be improved.

Data Availability

The datasets used and/or analyzed during the present study are available from the corresponding author upon request.

Conflicts of Interest

The authors declare that they have no conflicts of interest.

Authors' Contributions

TYC, SLZ, and LT planned and designed this systematic review. TYC, SLZ, HAW, DJ, YPW were responsible for data management and analysis. ZD, HAW, and YPW contributed to interpretation of study results. LT and JM provided methodological and guiding for this study. TYC and LT drafted the manuscript. All authors read and approved the final manuscript.

Acknowledgments

This work was supported by the National Natural Science Foundation of China (81673953), Natural Science Foundation of Jilin Province (20210101419JC), and Basic TCM Evidence-Based Capacity Building Project of the Affiliated Hospital of Changchun University of Chinese Medicine.

References

[1] J. Barratt and J. Feehally, "IgA nephropathy," *Journal of the American Society of Nephrology*, vol. 16, no. 7, pp. 2088–2097, 2005.

[2] P. Li, Y. Z. Chen, H. L. Lin et al., "Abelmoschus manihot a traditional Chinese medicine versus losartan potassium for treating IgA nephropathy: study protocol for a randomized controlled trial," *Trials*, vol. 18, no. 1, p. 170, 2017.

[3] C. Pozzi, "Treatment of IgA nephropathy," *Journal of Nephrology*, vol. 29, no. 1, pp. 21–25, 2016.

[4] S. Li and J. P. Li, "Treatment effects of Chinese medicine (Yi-Qi-Qing-Jie herbal compound) combined with immunosuppression therapies in IgA nephropathy patients with high-risk of end-stage renal disease (TCM-WINE): study protocol for a randomized controlled trial," *Trials*, vol. 21, no. 1, p. 31, 2020.

[5] F. D. Zhou, M. H. Zhao, W. Z. Zou, G. Liu, and H. Wang, "The changing spectrum of primary glomerular diseases within 15 years: a survey of 3331 patients in a single Chinese centre," *Nephrology, Dialysis, Transplantation: official publication of the European Dialysis and Transplant Association European*, vol. 24, 2009.

[6] T. Moriyama, K. Tanaka, C. Iwasaki et al., "Prognosis in IgA nephropathy: 30-year analysis of 1, 012 patients at a single center in Japan," *PLoS One*, vol. 9, no. 3, Article ID e91756, 2014.

[7] J. Floege, S. J. Barbour, D. C. Cattran et al., "Management and treatment of glomerular diseases (part 1): conclusions from a kidney disease: improving global outcomes (KDIGO) controversies conference," *Kidney International*, vol. 95, no. 2, pp. 268–280, 2019.

[8] Y. Zhong, M. C. Menon, Y. Deng, Y. Chen, and J. C. He, "Recent advances in traditional Chinese medicine for kidney disease," *American Journal of Kidney Diseases*, vol. 66, no. 3, pp. 513–522, 2015.

[9] G. H. Guyatt, A. D. Oxman, S. Sultan et al., "GRADE guidelines: 9. Rating up the quality of evidence," *Journal of Clinical Epidemiology*, vol. 64, no. 12, pp. 1311–1316, 2011.

[10] D. Bian, H. Liu, and Z. Lv, "Effect of self-made supplementing Qi and nourishing yin-clearing heat and draining dampness formula on renal local KKS of IgA nephropathy rats," *Liaoning Journal of Traditional Chinese Medicine*, vol. 43, pp. 837–839+897, 2016.

[11] D. Jin and S. L. Zhang, "Influence of Bushenjianpi and Lishihuayu on serum MMP-9 and TIMP-1 contents in IgA nephropathy model rats," *Jilin Journal of Chinese Medicine*, vol. 37, pp. 280–284, 2017.

[12] G. Z. Liu, H. Xiao, and Z. Liu, "Experimental study of shenkangling capsule on IgA nephropathy in rats," *Chinese*

Journal of Integrated Traditional and Western Nephrology, vol. 4, pp. 110-111, 2003.

[13] Y. F. Song, J. Z. Zhang, and G. P. Liu, "Intervention effect of yishen tongluo formula on rat model of IgA nephropathy," *Journal of Sichuan of Traditional Chinese Medicine*, vol. 32, pp. 39–42, 2014.

[14] Y. Tang, Y. F. Jiang, H. X. Cao, X. X. Zhang, and L. Q. He, "Effect of guben tongluo formula based on xuanfu theory on rats with IgA nephropathy and CD2AP expression," *Chinese Journal of Integrated Traditional and Western Nephrology*, vol. 19, pp. 388–390, 2018.

[15] Q. Wang, Z. Ye, and D. Y. Xu, "Renal preventive mechanism of ziyin liangxue decoction on rats with IgA nephropathy," *Journal of Guangzhou University of Traditional Chinese Medicine*, vol. 35, pp. 672–678, 2018.

[16] X. Wang, J. Zhou, and Y. Sun, "Effect of kummerowia striata (thunb.) schindl on IgA nephropathy model rats," *Journal of Guangzhou University of Traditional Chinese Medicine*, vol. 27, 2010.

[17] Y. P. Wang, H. A. Wang, H. B. Zhang, and S. L. Zhang, "Impacts of gouqi fushen pills on IgA nephropathy rat model," *World Journal of Integrated Traditional and Western Medicine*, vol. 12, pp. 504–506+523, 2017.

[18] X. J. Yang, F. Liu, and Z. P. Wu, "Experimental study of mahuang lianqiao chixiaodou decoction in the treatment of IgA nephropathy in rats," *Shanghai Journal of Traditional Chinese Medicine*, vol. 51, 2017.

[19] D. M. Zhang, Y. P. Wang, H. A. Wang, H. B. Zhang, and S. L. Zhang, "Effect of tonifying Kidney and invigorating spleen, detoxification and promoting pharynx on Th1/Th2 in IgA Nephropathy Model Rats," *Chinese Journal of Gerontology*, vol. 36, pp. 798–800, 2016.

[20] S. L. Zhang, "Impacts on the contents of TNF-α and IL-6 in serum of IgA nephropathy model rats treated with the therapy for tonifying the kidney, strengthening the spleen, resolving dampness and removing stasis," *World Journal of Integrated Traditional and Western Medicine*, vol. 8, pp. 1114–1116, 2013.

[21] L. X. Zhou, P. H. Xiong, M. Fei, and S. F. Tian, "Therapeutic effect of huoxue yangyin fang on IgA nephropathy rats model," *Chinese Journal of Integrated Traditional and Western Nephrology*, vol. 16, pp. 674–676+753, 2015.

[22] D. Zou, S. L. Zhang, Y. P. Wang, H. A. Wang, and C. J. Cui, "Effect of gouqi fushen pill on MMP-9 and TIMP-1 in IgA nephropathy rats model," *Chinese Journal of Gerontology*, vol. 36, pp. 549–551, 2016.

[23] H. X. Wang, R. Lang, and C. X. Yang, "Effect of xue niaoan tablets on complement regulatory protein CR1 in IgA nephropathy rats," *China Pharmacist*, vol. 20, pp. 2085–2087, 2017.

[24] J. Yan, D. H. Tang, W. D. Xuan, Z. P. Fan, and S. G. Hu, "Therapeutic effects of thesium chinensis extract on IgAN rats," *Journal of Pharmaceutical Practice*, vol. 33, pp. 28–31, 2015.

[25] S. F. Ye, J. B. Wu, J. Y. Zhou, J. M. Lai, J. Lin, and Y. Zhou, "Effect of zhenwu decoction on blood hypercoagulable state in rats with IgA nephropathy," *Journal of Guangzhou University of Traditional Chinese Medicine*, vol. 31, pp. 247–251, 2014.

[26] F. Cao, P. Y. Han, D. Z. Guo, D. Bian, and Y. H. Wang, "Effect of shenyanning on the correlation factors of inflammation reaction in renal tissue of IgA nephropathy rats," *Hebei Journal of Traditional Chinese Medicine*, vol. 31, pp. 1710–1712, 2009.

[27] S. W. Xiang, G. D. Huang, and R. F. Huang, "Experimental study on therapeutic effect of complex xiancao granule on IgA nehpropathy rat model," *Journal of Liaoning University of Traditional Chinese Medicine*, vol. 15, pp. 39–41, 2013.

[28] A. P. Zeng, W. Sun, and G. Wang, "Effects of jianshen tablet on NO and NOS in the renal tissue in the renal tissues in the rat with IgAN," *Chinese Journal of Information on Traditional Chinese Medicine*, vol. 11, pp. 212-213, 2004.

[29] H. X. Hu, H. Y. Jia, and Z. S. Shi, "Experimental study on therapeutic effect of zishen zhixue tablet on experimental IgA nephropathy in rats," *Chinese Journal of Basic Medicine in Traditional Chinese Medicine*, vol. 5, pp. 40–45, 1999.

[30] J. H. Liu, J. P. Zeng, L. Zeng, D. Wang, Z. Y. Zheng, and X. P. Lan, "Study on the effects of qilianmaogentang on the experimental IgA nephropathy rat," *Chinese Journal of Information on Traditional Chinese Medicine*, vol. 13, pp. 28-29, 2006.

[31] W. Sun, A. P. Zeng, and G. Wang, "Effects of jianshen tablet on renal expression of TGF-β-1 in rats with IgAN," *Chinese Journal of Integrated Traditional and Western Nephrology*, vol. 5, pp. 225–257, 2004.

[32] X. Q. Lin, J. Yuan, and Y. P. Song, "Experimental study of artemisinin combined with hydroxychloroquine in treating rats with IgA nephropathy," *Traditional Chinese Drug Research & Clinical Pharmacology*, vol. 27, pp. 608–613, 2016.

[33] D. Z. Guo, Y. H. Wang, D. Bian, Z. Q. Chen, P. Y. Han, and Y. F. Jin, "Influences of Shenyanning on renal signal pathway of TGF-β1 and p38MAPK in rats with IgA nephropathy," *Journal of Beijing University of Traditional Chinese Medicine*, vol. 33, pp. 175–178, 2010.

[34] C. Yu, J. Zhang, S. Z. Wang, and G. Q. Yang, "Effect of QiJiShenkang granule on renal tissue of IL-13 and CIC from serum of rats with IgA nephropathy," *Chinese Journal of Integrated Traditional and Western Nephrology*, vol. 14, pp. 388–391, 2013.

[35] Y. Y. Zhang, P. P. Jin, H. C. Jin, Y. Gu, and D. Z. Guo, "Effect of modified shengjiangsan on Gd-IgA1 in IgA nephropathy rats: based on C1GALT1/C1GALT1C1 signaling pathway," *Chinese Journal of Experimental Traditional Medical Formulae*, vol. 28, pp. 70–80, 2022.

[36] G. D. Huang, H. T. Wen, and X. L. Ma, "The expression of compound xiancao capsule on IL-6 TNF-α of IgA nephropathy tissue," *Liaoning Journal of Traditional Chinese Medicine*, vol. 11, pp. 208–210, 2009.

[37] J. M. Yang, Y. Tang, H. X. Cao, P. C. Shen, and L. Q. He, "Effects of guben tongluo formula on expressions of podocin mRNA and α-actinin-4mRNA in rats with IgA nephropathy based on sweat pore theory," *Journal of Shandong University of Traditional Chinese Medicine*, vol. 43, pp. 301–307, 2019.

[38] H. B. Chen, Y. Zhuang, H. Z. Ma, and Y. S. Fan, "Effect of shenqi dihuang decoction on nephrin mRNA and podocin mRNA in renal tissue of IgA nephropathy rats," *Journal of Traditional Chinese Medicine*, vol. 54, pp. 601–604, 2013.

[39] L. G. Ji, S. Y. Wang, and D. Z. Guo, "Effects of Tongli Sanjiao Qingre Lishi decoction on kidney miRNA-148b and serum IL-4 in rats with IgA nephropathy," *Journal of Jinan University(Natural Science & Medicine Edition)*, vol. 41, pp. 475–484, 2020.

[40] J. J. Zhou, J. D. Gao, L. Q. He, and P. D. Zheng, "The study of gubentongluochongji on experimental IgA nephropathy," *Chinese Journal of Integrated Traditional and Western Nephrology*, vol. 4, pp. 442–444, 2003.

[41] J. Berger and N. Hinglais, "[Intercapillary deposits of IgA-IgG]," *Journal d'Urologie et de Nephrologie*, vol. 74, no. 9, pp. 694-695, 1968.

[42] K. T. Woo, C. M. Chan, Y. M. Chin et al., "Global evolutionary trend of the prevalence of primary glomerulonephritis over the past three decades," *Nephron Clinical Practice*, vol. 116, no. 4, pp. c337–c346, 2010.

[43] H. Trimarchi, J. Barratt, R. C. Monteiro, and J. Feehally, "IgA nephropathy: State of the art: a report from the 15th International Symposium on IgA Nephropathy celebrating the 50th anniversary of its first description," *Kidney International*, vol. 95, no. 4, pp. 750–756, 2019.

[44] K. Kiryluk and J. Novak, "The genetics and immunobiology of IgA nephropathy," *Journal of Clinical Investigation*, vol. 124, no. 6, pp. 2325–2332, 2014.

[45] F. P. Schena and I. Nistor, "Epidemiology of IgA nephropathy: a global perspective," *Seminars in Nephrology*, vol. 38, no. 5, pp. 435–442, 2018.

[46] G. D'Amico, P. Napodano, F. Ferrario, M. P. Rastaldi, and G. Arrigo, "Idiopathic IgA nephropathy with segmental necrotizing lesions of the capillary wall," *Kidney International*, vol. 59, no. 2, pp. 682–692, 2001.

[47] J. C. Davin, I. J. Ten Berge, and J. J. Weening, "What is the difference between IgA nephropathy and Henoch-Schönlein purpura nephritis?" *Kidney International*, vol. 59, no. 3, pp. 823–834, 2001.

[48] L. L. Xing, S. X. Fu, L. Yang, S. M. Li, and J. R. Wang, "Clinicopathological relationship between TNF-α and IgA nephropathy," *Journal of Chinese Physician*, vol. 7, pp. 188–190, 2005.

[49] X. P. Liu, J. S. Hu, and Q. Fang, "Establishment of IgAN model in rats and determination of the serum IL-6, FN and NO," *Chinese Journal of Comparative Medicine*, vol. 84, pp. 5–8, 2008.

[50] X. Y. Shi, Z. X. Hu, and Z. H. Zhu, "Clinical significance of measurement on plasma leptin and serum IL-6, IL-18 and SOD levels in patients with chronic nephritis," *Journal of Radioimmunology*, vol. 25, pp. 125–127, 2012.

[51] W. A. Border, N. A. Noble, and M. Ketteler, "TGF-beta: a cytokine mediator of glomerulosclerosis and a target for therapeutic intervention," *Kidney International Supplement*, vol. 49, pp. S59–S61, 1995.

[52] H. W. Schnaper, T. Hayashida, S. C. Hubchak, and A. C. Poncelet, "TGF-beta signal transduction and mesangial cell fibrogenesis," *American Journal of Physiology Renal Physiology*, vol. 284, no. 2, pp. F243–F252, 2003.

[53] Y. Taniguchi, N. Yorioka, T. Masaki, Y. Asakimori, K. Yamashita, and M. Yamakido, "Localization of transforming growth factors β1 and β2 and epidermal growth factor in IgA nephropathy," *Scandinavian Journal of Urology and Nephrology*, vol. 33, no. 4, pp. 243–247, 1999.

[54] B. Yang, H. Sheng, and C. L. Yuan, "Expression of MMP-9 and TIMP-1 in non-small cell lung cancer and its relationship with clinical pathological features," *Chinese Journal of Laboratory Diagnosis*, vol. 13, pp. 1166-1167, 2009.

[55] Y. Li, J. Yang, C. Dai, C. Wu, and Y. Liu, "Role for integrin-linked kinase in mediating tubular epithelial to mesenchymal transition and renal interstitial fibrogenesis," *Journal of Clinical Investigation*, vol. 112, no. 4, pp. 503–516, 2003.

[56] Y. Y. Liu, H. Liu, and H. Q. Chai, "Research progress on the mechanism of renal injury in IgA nephropathy," *Chinese Journal of Integrated Traditional and Western Nephrology*, vol. 17, pp. 79–81, 2016.

[57] M. Goto, K. Wakai, T. Kawamura, M. Ando, M. Endoh, and Y. Tomino, "A scoring system to predict renal outcome in IgA nephropathy: a nationwide 10-year prospective cohort study," *Nephrology Dialysis Transplantation: official publication of the European Dialysis and Transplant Association European*, vol. 24, pp. 3068–3074, 2009.

[58] H. Suzuki, Y. Suzuki, J. Novak, and Y. Tomino, "Development of animal models of human IgA nephropathy," *Drug Discovery Today: Disease Models*, vol. 11, pp. 5–11, 2014.

[59] J. K. Xu, L. L. Zhao, and X. L. Liao, "Systematic development of a standard process for systematic reviews of animal experimental studies," *Chinese Journal of Evidence-Based Medicine*, vol. 17, pp. 1357–1364, 2017.

Hindawi
Evidence-Based Complementary and Alternative Medicine
Volume 2022, Article ID 6970751, 20 pages
https://doi.org/10.1155/2022/6970751

Review Article

Acupuncture May Be a Potential Complementary Therapy for Alzheimer's Disease: A Network Meta-Analysis

Wenshan Yin,[1,2] Yihan Chen,[1,2] Anping Xu,[1] Yinshan Tang,[3] Qingtao Zeng,[4] Xin Wang,[5] and Zhigang Li[1]

[1]*School of Acupuncture-Moxibustion and Tuina, Beijing University of Chinese Medicine, Beijing, China*
[2]*Second Clinical Medical College, Beijing University of Chinese Medicine, Beijing, China*
[3]*Department of Rehabilitation and Traditional Chinese Medicine, The Second Affiliated Hospital of Zhejiang University School of Medicine, Hangzhou, China*
[4]*Information Engineering Institute, Beijing Institute of Graphic Communication, Beijing, China*
[5]*Beijing Hospital of Traditional Chinese Medicine, Capital Medical University, Beijing, China*

Correspondence should be addressed to Anping Xu; xuanping01@163.com and Xin Wang; xinflare827@126.com

Received 22 April 2022; Revised 23 August 2022; Accepted 30 September 2022; Published 23 November 2022

Academic Editor: Vijaya Anand

With Alzheimer's disease (AD) becoming a worldwide problem, traditional Chinese medicine (TCM), especially acupuncture, stands out as a complementary therapy because of its feature—"treatment based on syndrome differentiation". This systematic review and network meta-analysis (NMA) confirms the complement effect of acupuncture and explores the best combination of therapy for AD based on the total effect and activity of daily living scale (ADL). We searched relevant randomized controlled trials (RCTs) that applied acupuncture for treating AD. 58 studies with 4334 patients were included in accordance with PRISMA guidelines. The results showed that for the total effect, the order of probability for the effect: acupuncture + western medicine > acupuncture + herbal medicine > acupuncture > acupuncture + western medicine + herbal medicine. For the ADL score, the order of probability for the effect: acupuncture + western medicine > acupuncture > acupuncture + western medicine + herbal medicine > acupuncture + herbal medicine. The combination of acupuncture and medicine has a better clinical effect than acupuncture only in a way. Acupuncture + western medicine has an obvious and exact improvement in the curative effect from both total effect and ADL score, but further higher quality studies, which can detail the classification of these interventions, are still needed to verify it.

1. Introduction

Alzheimer's disease (AD), also known as senile dementia, is a common degenerative disease of the central nervous system in the elderly. AD is the most common type of dementia (accounting for 60% to 80% of all dementia types) [1], mainly manifested as memory impairment, aphasia, apraxia, ignorance, executive dysfunction, as well as personality and behavior changes. With the progression of the disease, patients' abilities in cognition, behavior, and other aspects can gradually decline. Their living quality can be much lower and they eventually lose their cognition and self-care abilities. As the aging of the world's population intensifies, the incidence rate of AD has also increased. As of 2017, the prevalence rate of AD in China was 7.5%; the prevalence rate for people over 80 years old was about 30% [2]. From the current situation of clinical treatment, the cure rate of AD is low. Recently, the age of onset has also been getting younger, and the pathogeny of AD has become much more complicated. AD has gradually become a worldwide problem [3].

At present, western medicine is considered the mainstream treatment for AD. Western medicine mainly uses drugs with functions of inhibiting β-amyloid deposition, inhibiting neurofibrillary tangles, increasing cholinergic nerve function, and excitatory neurotransmitters to treat AD

[4], such as nimodipine, donepezil hydrochloride, Oracetam, Carbalatin, etc. Because of the complex pathogenesis of AD, drug therapy has its limitations. Drug therapy can only target certain pathogenesis to treat AD, which is deficient in comprehensive treatment. Therefore, various complementary therapies have been developed recently. Traditional Chinese medicine (TCM) therapies, such as herbal medicine and acupuncture, are complementary treatments with huge development potential that have been proven to be effective. They all follow the principle of "treatment based on syndrome differentiation", which means that clinicians can adjust their selection of herbal medicine or acupoint based on the specific body condition of patients to get a better overall effect. Moreover, previous studies have confirmed that acupuncture has the features of multiple targeting therapy. Moreover, its function of holistic regulation plays an important role in the preventive treatment of AD [5]. The combination of TCM therapies and western mainstream medicine has been constantly innovated and developed, among which the combination of acupuncture and medicine accounts for a certain proportion, and the clinical efficacy of this combination has also been confirmed. However, due to the variation and differences in the prescription of TCM and the selection of acupoints, the clinical efficacy of combined interventions is greatly affected by specific intervention plans. The various intervention plans with great differences in clinical randomized controlled trials (RCTs) may affect the comprehensiveness of therapeutic evaluation because of the limitations on sample size. Clinical studies with large sample sizes are needed to provide evidence for comparing the clinical efficacy of various combinations of acupuncture and medicine for treating AD, to help determine the best combination, and to explore whether acupuncture can complement the mainstream drugs for AD, and provide a reference for the clinical treatment of AD.

Network meta-analysis (NMA) can aggregate data from multiple studies and remedy the limitations on the sample size, allowing us to compare and analyze the clinical efficacy of different interventions for AD based on the network relationships of multiple trials. This study compares and ranks the clinical efficacy of different combination interventions for treating AD (acupuncture + western medicine, acupuncture + herbal medicine, acupuncture, acupuncture + western medicine + herbal medicine, western medicine + herbal medicine, and western medicine) based on NMA to provide more intuitive data evidence for the comparison and application of various combinations of acupuncture and medicine in the clinical treatment of AD.

2. Methods

2.1. Search Strategy. Two researchers searched PubMed, Embase, Cochrane Library, CBM, CNKI, WanFang Data, and CQVIP databases until August 21, 2021, independently. There were no date limits regarding the publication date of the included studies. In addition, the references of the included studies were traced to obtain other relevant studies to supplement the included studies.

The search was carried out by combining subject terms and free words. All RCTs of acupuncture for treating Alzheimer's disease were collected. We searched for articles in both Chinese and English for more comprehensive materials. Search terms: "Alzheimer", "Alzheimer's", "Alzheimer disease", "AD", "ATD", "senile dementia", "Alzheimer type dementia", "Alzheimer-type dementia", "degenerative Alzheimer's disease", "Alzheimer syndrome", "presenile dementia", "Alzheimer sclerosis", "Acupunctural", "Acupuncture", "Acupuncture therapy", "Acupuncture treatment", "Scalp acupuncture", "Needle", "warm needle", "temperature needle", "auricular point sticking", "auricular acupuncture", "Fire-needle acupuncture", "needle warming therapy", etc. Taking PubMed as an example, the retrieval strategy is shown in Table 1.

2.2. Inclusion and Exclusion Criteria. Inclusion and exclusion criteria were formulated based on the principle of PICOS (P-population; I-intervention;C-comparison;O-outcome;S-study design):

The inclusion criteria were as follows: ① Study design: published RCTs. The language of materials was limited to Chinese or English. ② Population: patients who were diagnosed with AD or met the diagnostic criteria, such as "the Diagnostic and Statistical Manual of Mental Disorders, Revised Fourth Edition" (DSM-IVR) [6], which was published by the American Psychiatric Association. There was no limitation in patients' gender, age, nationality, race, occupation, education level, course, and severity of the disease. The baseline of the same RCT was balanced ($P > 0.05$). The participants were allowed to suffer from hypertension, diabetes, hyperlipidemia, and other underlying diseases. ③ Intervention and comparison: The experimental group was treated with various acupuncture methods alone or combined with herbal or western medicine, such as electroacupuncture combined with donepezil hydrochloride, acupuncture combined with Yizhi Jiannao granule, and so on. The control group was treated with herbal medicine, western medicine, or a combination of herbal medicine and western medicine. ④ Outcome: Total effect: According to "Criteria of diagnosis and therapeutic effect of internal diseases and syndromes in traditional Chinese medicine" (issued by the National Administration of Traditional Chinese Medicine), the curative effect can be divided into "cured" (all symptoms disappear), "improved" (symptoms are relieved), and "ineffective" (aggravation or no change in symptoms). "Cured" and "improved" were regarded as effective. The total effect = (the number of "cured" and "improved"/the total sample size)*100%; Activity of Daily Living Scale (ADL). Included studies should address one or both of the outcomes mentioned above.

The exclusion criteria were as follows: ① Repeated publications. ② Studies in the diagnosis of vascular dementia. ③ Studies without relative data or unavailable for researchers. ④ Participants had a malignant tumor, diseases of the blood or immune system, mental illness, or other obvious complications. ⑤ The experimental groups or control groups applied other therapies besides acupuncture,

Table 1: PubMed search strategy.

#1	Alzheimer disease[MeSH]
#2	Alzheimer[Tiab] OR Alzheimer's[Tiab] OR Alzheimer disease[Tiab] OR AD[Tiab] OR ATD[Tiab] OR Senile dementia[Tiab] OR Alzheimer type dementia[Tiab] OR Alzheimer-type dementia[Tiab] OR Degenerative Alzheimer's disease[Tiab] OR Alzheimer syndrome[Tiab] OR Presenile dementia[Tiab] OR Alzheimer sclerosis [Tiab]
#3	#1 OR #2
#4	Acupuncture[MeSH] OR Acupuncture therapy[MeSH]
#5	Acupunctural[Tiab] OR Acupuncture[Tiab] OR Acupuncture therapy[Tiab] OR Acupuncture Treatment[Tiab] OR Scalp Acupuncture[Tiab] OR Needle[Tiab] OR warm Needle[Tiab] OR Temperature needle[Tiab] OR Auricular point sticking [Tiab] OR Auricular Acupuncture[Tiab] OR Fire-needle Acupuncture[Tiab] OR Needle warming Therapy[Tiab]
#6	#4 OR #5
#7	#3 AND #6

herbal medicine, or western medicine, such as doll therapy, hyperbaric oxygen, music-assisted therapy, electric shock therapy, etc. ⑥ The rate of loss to follow-up or drop-off was more than 50%, the data of outcome were missing or wrong obviously, or the efficacy evaluation was unclear.

2.3. Study Selection and Data Extraction. Four trained researchers were divided into two groups to screen studies and extract data independently, and another two researchers cross-checked the data. Any disagreement was resolved by discussion. Subsequently, the data were extracted into a unified spreadsheet, and the extraction contents included the following: ① basic information of included studies: title, name, and nationality of the first author, publication year, source of study, fund status, etc.; ② baseline characteristics of objects: sample size of each group, age, course of the disease, etc.; ③ intervention: acupuncture methods (including acupoint selections, reinforcing and reducing techniques, direction of the needle, retaining time of needle, course of treatment, etc.), drug therapeutic schedule; ④ relative information about bias risk assessment: random method, the situation of drop-off and follow-up, etc.; ⑤ outcome: total effect and ADL.

2.4. Risk of Bias. Two researchers evaluated the quality of included studies independently according to the bias risk assessment tool, namely ROB 2 [7], recommended by Cochrane5.1.0. Subsequently, the results of the assessment were cross-checked and any disagreement was resolved by a discussion.

The assessment was related to five major domains: ① the randomization process; ② deviations from the intended interventions; ③ missing outcome data; ④ measurement of the outcome; and ⑤ selection of the reported results. The answers to questions involved the five domains were provided as Yes (Y), Probably Yes (PY), Probably No (PN), No (N), or No Information (NI). The whole process of assessment was based on the Cochrane Handbook.

2.5. Statistical Analysis. Researchers utilized Stata/SE 16.0 software to construct NMA in a frequentist framework. All the statistical data mentioned below were calculated using Stata/SE 16.0. For dichotomous variables (total effect), odds ratio (OR) was adopted as the effective value. For continuous variables (ADL), mean difference (MD) was adopted as the effective value. The meta-analyses were carried out by calculating the effect values and their 95% credibility interval (CI).

Researchers constructed a network map to depict the comparator arms of various interventions and the relationship between these interventions. Weight the points by the total sample size received for the specific treatment, and weight the lines by the number of researchers, which compared two interventions connected by the line directly.

Researchers calculated the effect values and their standard error (SE) of each research group and constructed a contribution plot to display the contribution of direct and indirect comparison in NMA.

A heterogeneity test was performed through an I^2 test. Higgins [8] considered that I^2 was between 0% and 100%. There was no heterogeneity between studies when $I^2 = 0\%$. The larger the I^2, the higher the possibility of heterogeneity. It indicated that there was mild heterogeneity when $I^2 = 25\%$; it indicated that there was moderate heterogeneity when $I^2 = 50\%$. It indicates a high degree of heterogeneity when $I^2 = 75\%$. The Cochrane manual believed that when $I^2 > 50\%$, the research study was considered to be heterogeneous, and a random effects model should be applied. When $I^2 < 50\%$, the fixed effects model should be applied. If the heterogeneity was high, further subgroup analysis (according to the course of disease and therapy) and meta-regression should be performed to analyze the causes of heterogeneity.

The inconsistency test of each closed loop in the network map was carried out. Researchers calculated the inconsistency factors (IFs), 95% CI, and the heterogeneity parameter t^2 (t = Standard deviation<SD>) of each loop to analyze whether there was an inconsistency in each closed loop. The closer the IF gets to 1, the more consistent between

different studies. If the lower limit of 95% CI was 1, it meant that the direct comparison results were consistent with the indirect comparison results.

Researchers set "Western medicine" as the original control intervention. We construct an interval prediction graph and an inverted triangle diagram to display the direct and indirect comparison results of different interventions. Treatment ranking was related to the area under the curve. The larger the area, the better the effect of the intervention [9].

A comparison correction funnel plot was applied to analyze whether there was a small sample effect between the studies and to assess the publication bias.

Researchers summarized the selection and usage frequency of acupoint and drugs used in the included studies.

3. Results

3.1. Results of the Search Process. The total number of obtained records was 6338, including 421 for PubMed, 146 for Embase, 1098 for the Cochrane Library, 1006 for CBM, 1590 for CNKI, 775 for CQVIP, and 1302 for WanFang Data. Records were imported into NoteExpress 3.2.0; then 4074 records after duplicates removed were obtained. Four researchers simply screened titles and abstracts. 157 records were left after excluding experience summary, reviews, animal experiments, nonrandomized controlled trials, and other irrelevant literature. The remaining full-text articles were further screened, and 58 records were left after excluding those that deviated from required outcomes or treatment, as well as unavailable ones. Ultimately, 58 RCTs [10–30] [31–45] [46–67] were included in our research, and the process is depicted in Figure 1.

3.2. Characteristics of the Included Studies. As demonstrated in Table 2, 58 articles were included in the research, and 4334 AD patients were recruited in the trial, 2190 for experimental groups and 2144 for comparator groups, respectively. Two studies [40, 64] collected outcomes, respectively, at different stages of treatment. Researchers split these two studies according to the course of treatment into five independent studies. Ultimately, 60 studies were included in the final statistical analysis, with 4542 patients. The total effect and ADL were the main outcomes. 54 studies reported total effects, and 25 studies reported ADL. 7 interventions were included, A-herbal medicine; B-western medicine; C-acupuncture;D-acupuncture + herbal medicine; E-acupuncture + herbal medicine + western medicine; F-acupuncture + western medicine; G-herbal medicine + western medicine.

3.3. Risk of Bias and Certainty of Evidence. Researchers used the bias risk assessment tool, named ROB 2, recommended by Cochrane 5.1.0. A total of 5 aspects of the original study were assessed, including the randomization process, deviation from intended interventions, missing outcome data, measurement of the outcome, and selection of the reported result. Included studies were classified as high quality, low quality, or unknown risk bias. The result is depicted in Figure 2 and Table 3.

3.4. Total Effect

3.4.1. Network Structure. A total of 59 studies reported the total effect, involving 129 arms and 4,414 patients. Figure 3 depicts the comparative relationship between different interventions. The dots represent the total number of samples in all studies using this intervention. The lines represent the amount of research evidence that directly compared the two interventions connected. An indirect comparative analysis was carried out based on a network structure for two unconnected interventions. The studies involved included six kinds of interventions: herbal medicine, western medicine, acupuncture, acupuncture + herbal medicine, acupuncture + western medicine, and acupuncture + western medicine + herbal medicine. five closed loops have been formed in the network structure ("herbal medicine, acupuncture, acupuncture + herbal medicine", "herbal medicine, western medicine, acupuncture", "western medicine, acupuncture, acupuncture + herbal medicine", "western medicine, acupuncture, acupuncture + western medicine", "herbal medicine, western medicine, acupuncture + herbal medicine"), to provide direct and indirect comparative evidence for NMA.

3.4.2. Contribution Plot. Figure 3 displays the contribution of each direct comparison result to the comprehensive comparison results of NMA, based on the total effect. "Direct comparisons in the network" refers to the direct comparison evidence included in studies. "Mixed estimates" represent comparisons that combine direct and indirect comparison evidence. "Indirect estimates" represent comparisons that are only based on indirect comparison evidence. For example, 25.9 means that the contribution rate of the direct comparison between intervention A (Herbal medicine) and intervention D (Acupuncture + Herbal medicine) for comparing the efficacy of intervention A (Chinese medicine) and intervention B (Western medicine) is 25.9%.

3.4.3. Testing for Heterogeneity and Inconsistency. According to the results of the heterogeneity test, $I^2 = 16.4\% < 25\%$, $P < 0.05$, regarded as low heterogeneity. NMA was carried out under the fixed effects model; applied the inconsistency model was used for NMA in advance, $P = 0.0946 > 0.05$. According to the inconsistency test for the closed loop, $P > 0.05$ for each closed loop (Table 4), which indicates no inconsistency among the groups. The consistency model was selected for NMA.

3.4.4. Network Meta-Analysis. Figure 4 displays the results of direct and indirect comparisons; _y_A, _y_C, _y_D, _y_E, and _y_F represent comparison results between interventions A, C, D, E, F, and intervention B, respectively. Labels, like_y_C-_y_A, _y_D-_y_A, etc., represent the comparison results between the two interventions mentioned. The results indicate that the curative effects of

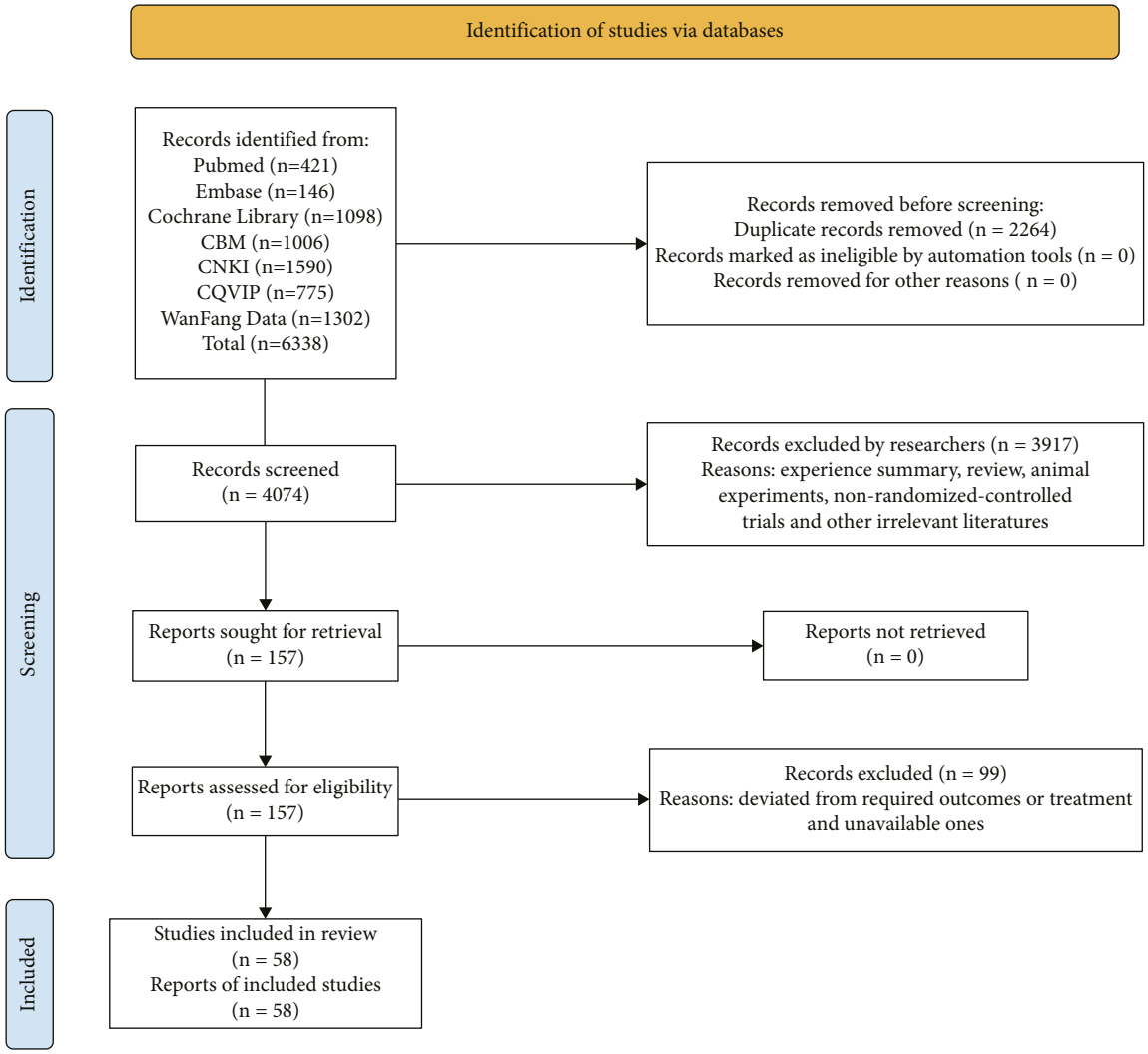


Figure 1: Search process depicted by the PRISMA flowchart.

acupuncture, acupuncture + herbal medicine, acupuncture + western medicine, and acupuncture + herbal medicine + western medicine are better than that of western medicine. The curative effects of acupuncture, acupuncture + herbal medicine, and acupuncture + western medicine are better than those of herbal medicine. The curative effect of acupuncture + western medicine is better than acupuncture + herbal medicine + western medicine. The differences in the remaining comparisons were not statistically significant.

The results mentioned above can also be obtained from the inverted triangle diagram (Table 5). The 95% CI must not contain 1; otherwise, the differences in comparisons are not statistically significant. If the OR value is greater than 1, it means that the interventions sorted by the column have better efficacy than the interventions sorted by the line.

The surface under the cumulative ranking curve (SUCRA) (Figure 4) shows that the combination of acupuncture and western medicine is the most effective intervention for treatment. The order of probability for the effect: acupuncture + western medicine > acupuncture + herbal medicine > acupuncture > acupuncture + western medicine + herbal medicine > herbal medicine > western medicine. the order of the curative effect of the intervention combined with acupuncture: acupuncture + western medicine > acupuncture + herbal medicine > acupuncture > acupuncture + western medicine + herbal medicine.

3.4.5. Small Sample Effect and Bias. The comparison-correction funnel plot (Figure 5) displays that the dots are slightly asymmetrically distributed on both sides of the vertical line of the X = 0. Five studies, including "western medicine" vs "acupuncture + herbal medicine + western medicine", "western medicine" vs "acupuncture + herbal medicine", "herbal medicine" vs "acupuncture + herbal medicine", "western medicine" vs "acupuncture + western medicine" are from the line of 95% CI in Figure 5, which shows that asymmetry may be caused by heterogeneity.

3.5. ADL Score

3.5.1. Heterogeneity Test and Subgroup Analysis. According to the results of the heterogeneity test, $I^2 = 94.4\% > 75\%$, $P < 0.05$, regarded as high heterogeneity.

Table 2: Baseline characteristics included in NMA of the treatment of AD patients.

Study ID	Group		Age (mean ± SD)	Course (Month-M; Year-Y)	Follow times/d	Interventions		Outcome	Acupoints
	Exp	Com				Exp	Com		
Lei [48]	22	20	Average 67.3/66.4	Average 19.2/17.8M	28	D	B	Total effect	EX-HN1, DU20, DU24, HT7, PC6, LI4, SP6, ST36, KI3
Li et al. [28]	35 37	18 14	67 ± 4/66 ± 4 65 ± 6/65 ± 7	3.1 ± 1.1/3.0 ± 1.3y 3.0 ± 1.6/2.7 ± 2.0y	None	D C	A B	Total effect, ADL	DU20/EX-HN1, GB20, BL23
He et al. [43]	32	30	55–69/50–69	None	None	F	B	Total effect	DU20
Ou et al. [23]	16	14	65.53 ± 6.8/64.72 ± 7.6	2.9 ± 1.6/2.7 ± 2.0y	56	C	B	Total effect, ADL	DU20/EX-HN1, BL23
Ou et al.[23]	16	14	65.5 ± 6.8/64.7 ± 3.4	2.9 ± 1.6/2.7 ± 2.0y	56	C	B	Total effect	DU20/EX-HN1, BL23
Xia [38]	30	30	67.93 ± 4.68/16.40 ± 4.26	67.70 ± 5.49/ 16.03 ± 4.00M	7	D	B	Total effect, ADL	DU20, EX-HN1, DU24, HT7, KI3, ST36, GB39, KI4, BL23, SP6
He [55]	30	30	63.83 ± 6.24/66.97 ± 7.34	17.13 ± 4.44/ 18.93 ± 5.05M	28	F	B	Total effect, ADL	DU20, DU14, DU4, DU9
Zhou [67]	50	50	71.30 ± 8.20/ 68.60 ± 10.10	1.80 ± 0.50/1.70 ± 0.20y	28	D	B	Total effect, ADL	EX-HN3, DU20, DU23, KI3, GB39, GB20, LR3, BL18, LI4, BL23, PC6, BL17
Chen et al. [19]	51	51	68.59 ± 4.36/68.59 ± 4.36	2.45 ± 0.71/2.45 ± 0.71y	28	C	B	Total effect, ADL	DU20, DU24, GB20, SP10, RN17, RN12, GB12, ST36, RN6
Li et al. [11]	45	45	(70.52 ± 5.34)/ (70.56 ± 5.32)	(5.46 ± 1.39)/ (5.42 ± 1.35)y	90	E	B	Total effect, ADL	DU26, PC6, SP6, GB20, DU20, HT7, EX-HN1, EX-HN3
Chen et al.[25]	40	40	69.5 ± 10.3/70.1 ± 9.6	6.1 ± 2.9/5.7 ± 3.3y	28	E	B	ADL	EX-HN3, EX-HN1, DU20, DU24, GB20, KI3, GB39, LI4, LR3, BL18, BL23, PC6, BL17
Peng et al. [41]	25	25	69.4 ± 5.4/69.5 ± 5.3	7.5 ± 1.8/7.6 ± 1.7y	10	F	B	Total effect	DU24, DU20, DU14, DU16, DU4, KI1
Guan [18]	30	30/30	70.5 ± 9.3/70.2 ± 9.5/ 69.3 ± 10.2	5.7 ± 3.2/5.6 ± 3.5/ 6.0 ± 6.0y	7	E	B/G	ADL	Scalp acupuncture, BL23, GB39, KI3, ST36, DU26
Wang and Wang [53]	45	45	68.89 ± 3.22/69.18 ± 3.17	8.59 ± 2.02/8.93 ± 2.17Y	28	E	B	Total effect, ADL	DU20, DU24, DU16, DU4
Ni [66]	33	32	73.25 ± 2.70/74.14 ± 2.76	3.90 ± 1.52/3.20 ± 1.30y	28	D	D	Total effect	DU20, DU14
Chen [49]	31	31	48–70/50–73	6M-5y/5m-7y	90	E	B	Total effect	The four-shen points, Three-brain acupuncture, The three-zhi acupuncture, Temporal three-needle
Jia et al. [15]	41	41	5.11 ± 6.53/74.50 ± 6.83	2.42 ± 1.00/2.50 ± 1.02Y	84	C	B	Total effect, ADL	RN17, RN12, RN6, SP10
Tian and Cheng [17]	35	35	50–80	None	5/30	F	B	Total effect	EX-HN1, DU20, DU24, EX-HN3, DU26, DU16, HT7
Geng [10]	36	36	68–87/69–85	5.19/5.31M	7	C	B	Total effect	DU26, PC6, SP6, KI1, DU24, EX-HN1, DU20, LI4, LR3, GB39
Qing [39]	30	30	70.31 ± 5.43/70.27 ± 5.93	12.63 ± 2.94/ 12.30 ± 3.09M	7	D	B	Total effect	DU20, EX-HN1, KI3, KI4, GB39, RN6, ST36
Liang [60]	37	37	73.8 ± 6.7/72.5 ± 5.2	7.1 ± 1.8/6.4 ± 1.3Y	14	F	B	Total effect, ADL	DU20, ST36, GB39, EX-HN1, KI4, KI3
Zhang [24]	41	41	72.19 ± 2.61	24.16 ± 3.08 M	20	E	B	Total effect, ADL	DU26, GB39, ST36, BL23, KI3

Table 2: Continued.

Study ID	Group		Age (mean ± SD)	Course (Month-M; Year-Y)	Follow times/d	Interventions		Outcome	Acupoints
	Exp	Com				Exp	Com		
Wei et al. [26]	33	33	68.37 ± 5.37/68.71 ± 5.77	7.77 ± 1.65/ (7.88 ± 1.67Y	None	F	B	ADL	DU20, KI1
Ben et al. [42]	37	37	71.5 ± 4.7/70.2 ± 4.6	3.2 ± 1.9/3.0 ± 1.4y	84	C	B	Total effect	ST36, ST40
Zhu [57]	40	40	70 ± 2/66 ± 2	9.02 ± 0.31/9.13 ± 0.25y	10	C	B	Total effect	DU20, EX-HN1, ST36, KI3, KI4, GB39
Yao et al. [64]	24	24	76.52 ± 6.365/ 76.43 ± 6.25	3.6 ± 1.65/3.6 ± 1.65Y	30	E	B	Total effect	DU20
Zhang et al. [59]	40	40	average77.6/76.8	average9.5/9.2y	30	E	B	Total effect	DU20, GB39, EX-HN1, LI4, ST36
Lin [35]	30/30	30	69.7 ± 5.36/73.2 ± 4.81/ 71.6 ± 5.22	55.9 ± 6.18/53.7 ± 5.92/ 61.3 ± 8.46d	28	C/F	B	Total effect, ADL	The four-shen points, Three-brain acupuncture, The three-zhi acupuncture, Temporal three-needle
Wang et al. [20]	36	36	72.05 ± 3.70/70.31 ± 3.79	3.33 ± 1.98/2.60 ± 1.51y	84	C	B	Total effect	DU20, DU14
Liu [52]	20	20	72.2 ± 4.8/74.4 ± 4.7	40.6 ± 13.4/ 35.7 ± 12.9 M	84	C	B	Total effect	DU20, DU14
	20	20	73.2 ± 4.9/70.7 ± 4.4	36.5 ± 13.7/ 33.3 ± 12.1 M	84	D	A	Total effect	
Chen et al. [40]	40	40	67.19 ± 10.53/68.32 ± 9.4	5.36 ± 2.84/5.80 ± 3.48Y	20	E	B	ADL	EX-HN3, EX-HN1, DU20, DU24, DU23, GB20, KI3, GB39, LI4, LR3, BL18, BL23, PC6, BL17
Wang and Li [51]	50	50	69.79 ± 6.52/71.47 ± 6.32	5.54 ± 2.25/5.39 ± 2.03y	10/20	F	B	Total effect, ADL	DU26, SP6, PC6, GB20, GB12, EX-HN12, EX-HN13, SJ17
Li [37]	51	51	71.28 ± 2.34/71.25 ± 2.38	4.75 ± 1.33/4.72 ± 1.30y	10	F	B	Total effect, ADL	SP6, ST36, EX-HN1, ST40, HT7, PC6, KI3, DU26, EX-HN3, DU20, GB20, DU16
Wang et al. [63]	27	28	70.7 ± 9.1/70.3 ± 8.0	5.8 ± 0.6/5.0 ± 1.1y	28	F	B	Total effect	None
Ma [58]	30	30	63.83 ± 6.24/66.97 ± 7.34	17.13 ± 4.44/ 18.93 ± 5.05 M	8	C	B	Total effect, ADL	DU20, DU14, DU4, BL23, GB39, KI3
Jin [30]	26	26	63.73 ± 9.12/64.88 ± 8.97	4.91 ± 2.29/4.86 ± 2.32y	180	F	B	Total effect, ADL	The four-shen points
Chen et al. [44]	50/50	50	73.16 ± 7.69/ 72.86 ± 7.23/72.06 ± 6.97	4.02 ± 0.11/3.96 ± 0.15/ 3.84 ± 0.19	90	F/C	B	Total effect	DU20, EX-HN1
Liu [14]	40	40	66.21 ± 3.72/65.65 ± 3.24	3.86 ± 1.23/3.42 ± 1.12y	90	D	A	Total effect	DU20, DU26, PC6, SP6, ST40, KI3
Zhang et al. [46]	30	30	72.36 ± 4.14/72.31 ± 4.12	3.25 ± 1.29/3.18 ± 1.26Y	90	D	B	Total effect	DU20, KI1
Wang et al. [16]	31	31	72.74 ± 8.36/75.77 ± 7.03	2.50(1.00,4.25)/ 3.00(2.00,5.00)y	56	F	B	Total effect	DU20, EX-HN3, GB15, GB8, GB20, LI4, LI11, ST36, LR3
Xia et al. [56]	30	30	49 ± 11/50 ± 12	3.79 ± 0.27/4.07 ± 0.27y	56	F	B	ADL	DU20, DU16
Zhang [65]	25	25	64.23 ± 1.56/65.42 ± 2.45	4.12 ± 1.42/4.23 ± 1.42y	None	D	B	Total effect	PC6, DU26, DU20, SP6, DU14, HT7
Zhang et al. [34]	46	46	72.6 ± 9.2/71.7 ± 8.7	None	90	F	B	Total effect, ADL	(BL23, BL20, DU20)/(BL15, ST36, EX-HN1)

Table 2: Continued.

Study ID	Group		Age (mean ± SD)	Course (Month-M; Year-Y)	Follow times/d	Interventions		Outcome	Acupoints
	Exp	Com				Exp	Com		
Wang and Li [27]	60	60	69.5 ± 3.5/69.2 ± 3.6	3.3 ± 0.8/3.5 ± 0.9y	28	E	B	Total effect, ADL	Temporal three-needle, three-brain acupuncture, The four-shen points, The three-zhi acupuncture, HT7
Li et al. [21]	43	43	76.5 ± 6.3/77.5 ± 6.8	3.1 ± 0.8/2.9 ± 0.7y	None	D	A	Total effect, ADL	DU20, DU14, DU24, DU16
Tao and Li [47]	45	45	64.23 ± 1.56/65.42 ± 2.45	4.12 ± 1.42/4.23 ± 1.43y	None	D	B	Total effect	KI1, DU20
Chen et al. [62]	48	48	74.36 ± 5.47/75.13 ± 5.81	3.42 ± 0.73/3.29 ± 0.68Y	90	F	B	Total effect, ADL	DU20, DU26, PC6, SP6, GB39, ST40, KI3
Liu [36]	20	20/20	67.2 ± 4.2/68.3 ± 5.1/ 68.8 ± 5.6	None	28	D	A/B	Total effect	EX-HN1, DU20, HT7, ST36
Zhang [50]	32	28	51–80	None	15	D	A	Total effect	DU26, PC6, SP6, DU20, DU14, HT7, GB39, Eye acupuncture
Liu et al. [29]	24	22	56–78/55–77	8M-5y	28	D	B	Total effect	EX-HN1, DU20, DU24, HT7, PC6, LI4, SP6, ST36, LR3
Li and Li [33]	40	40	70.24 ± 5.14/69.37 ± 4.67	4.85 ± 1.50/4.82 ± 1.47y	28	D	B	Total effect, ADL	DU20, DU26, DU15, DU24, DU14, DU9
Zhao et al. [45]	16	16	67 ± 2.12	5.17 ± 1.05Y	60	C	B	Total effect, ADL	DU20, DU14
Zhu et al. [12]	20	20	72.3 ± 6	6M-3y	56	C	B	Total effect	DU20, BL23, SP10, BL17
	20	20			56	D	A		
Liu et al. [54]	40	40	69.16 ± 2.12/68.09 ± 6.24	10.05 ± 2.60/9.79 ± 5.22	7	C	B	Total effect	Three-smell acupuncture
Peng and Dong [22]	28	28/28	62–79	1-8Y	84	D	B/A	Total effect, ADL	DU20, EX-HN1, DU14, RN4
Ji et al. [61]	53	53	None	None	30	C	B	Total effect	DU20, PC6
Li et al. [13]	20/20	20	55–80	None	84	C/D	A	Total effect	BL23, BL17, HT7, DU20
Luo et al. [31]	48	48	67.7 ± 7.2	Over 6M	25	C	B	Total effect	DU14, BL23, KI3, ST36

A-herbal medicine; B-western medicine; C-acupuncture. D-acupuncture + herbal medicine; E-acupuncture + herbal medicine + western medicine; F-acupuncture + western medicine; G-herbal medicine + western medicine.

Researchers performed a subgroup analysis of the included materials according to the course of AD (Studies were divided into 4 subgroups: less than 1 year, 1–3 years, 3–5 years, and 5–10 years). I^2 of groups "less than 1 year" and "5–10 years" decreased to 80.6% and 80.3%, respectively, and the I^2 of the remaining groups did not change significantly. Researchers performed a meta-regression based on the course of AD and interventions, but the heterogeneity remained unchanged. Moreover, there was no reason for heterogeneity was found. Since the number of studies in the group "less than 1 year" is too small (2 studies in total) and the groups "1–3 years" and "3–5 years" have high heterogeneity (>90%), only the "5–10 years" group was involved in NMA. NMA was carried out under the random effects model.

3.5.2. Network Structure. A total of 11 studies were involved in the "5–10 years" group, involving 23 arms and 842 patients. Figure 3 depicts the comparative relationship between different interventions. The dots represent the total number of samples in all studies using this treatment. The lines represent the amount of research evidence that directly compared the two treatments connected. An indirect comparative analysis was carried out based on the network structure of two unconnected interventions. The studies involved included six kinds of interventions: herbal medicine + western medicine, western medicine, acupuncture, acupuncture + herbal medicine, acupuncture + western medicine, and acupuncture + western medicine + herbal medicine. One closed loop has been formed in the network structure ("herbal medicine + western medicine–acupuncture—acupuncture + herbal medicine + western medicine") to provide direct and indirect comparative evidence for NMA.

3.5.3. Contribution Plot. Figure 3 displays the contribution of each direct comparison result to the comprehensive comparison results of NMA, based on the ADL score. For example, 44.1 means that the contribution rate of the direct comparison between herbal medicine + western medicine and acupuncture for comparing the efficacy of these two interventions is 44.1%.

3.5.4. Testing for Inconsistency. Applied the inconsistency model for NMA in advance, $P = 0.4132 > 0.05$. According to the inconsistency test for closed loop, $P = 0.279 > 0.05$ (Table 6), which indicated no inconsistency among the groups. A consistency model was selected for NMA.

3.5.5. Network Meta-Analysis. Figure 4 displays the results of direct and indirect comparisons. The results indicate that the curative effects of acupuncture + western medicine and acupuncture + herbal medicine + western medicine are better than those of Western medicine. The differences in the remaining comparisons were not statistically significant. The results mentioned above can also be obtained from the inverted triangle diagram (Table 7).

The SUCRA (Figure 4) shows that Western medicine is the most effective intervention for treatment. The order of probability for the effect: acupuncture + western medicine > acupuncture > acupuncture + herbal medicine + western medicine > acupuncture + herbal medicine > herbal medicine + western medicine > western medicine. The order of the curative effect of the intervention combined with acupuncture: acupuncture + western medicine > acupuncture > acupuncture + western medicine + herbal medicine > acupuncture + herbal medicine.

3.5.6. Small Sample Effect and Bias. The comparison-correction funnel plot (Figure 5) displays that most of the dots are symmetrically distributed on both sides of the vertical line of X = 0, indicating a low possibility of both bias and the small sample effect.

3.6. Usage of Acupoints and Drugs. Most studies selected the Governor vessel, three foot-yang meridians, extra acupoints, and three foot-yin meridians, with few acupoints selected for three hand-yin meridians and three hand-yang meridians relatively. Compared with other parts of the body, the acupoints on the head, face, and neck, including Governor vessel acupoints, extra acupoints, other acupuncture treatment methods (including the four-shen acupuncture, temporal three-needle, the three-zhi Acupuncture, etc.), acupoints of twelve regular meridians and conception vessel acupoints, were chosen mostly among the 57 kinds of literature included. The number of selected lower limb acupoints is the second, including only acupoints of twelve regular meridians (Figure 6). The top ten ranked frequencies of chosen acupoints are DU20, SP6 (confluent acupoint of three foot-yin meridians), ST36 (He-sea point of foot-yangming meridian), KI3 (Shu-stream acupoints of foot-shaoyin meridian), EX- HN1, GB39 (marrow convergence), BL23 (kidney back-shu point), PC6 (connecting point of hand-jueyin meridian), DU24, and DU14 (confluent acupoint of governor vessel, three foot-yang, and hand-yang meridians), most for located acupoints and several for nourishing kidney yin (Figure 7). Herbal medicine of the studies included was mainly for tonifying the spleen and kidney by activating blood circulation to dissipate stasis, while donepezil was mostly for western medicine.

3.7. Adverse Events. Eleven included studies reported the presence of adverse events(Table 8). Due to the limited number of included studies that reported adverse events, it was not analyzed using NMA.

4. Discussion

AD is a common degenerative disease of the central nervous system in the elderly, whose pathogeny is complex and

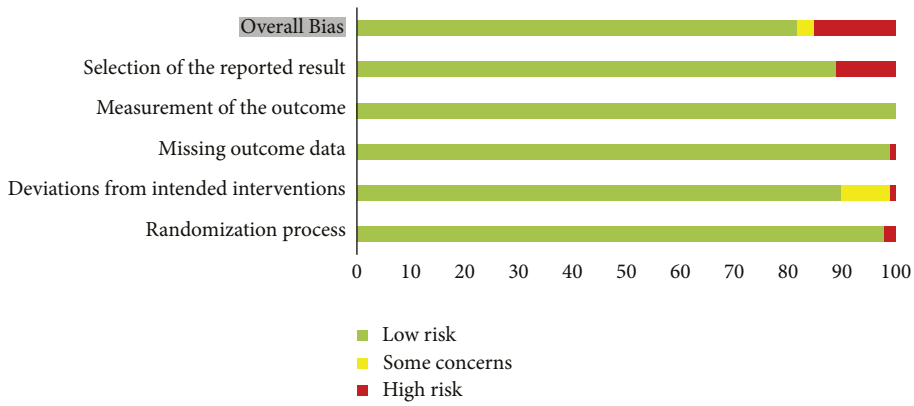


Figure 2: Summary of bias risks based on ROB 2. Over 80% of the included study were assessed as low risk overall.

difficult to be explained. There are many interventions for AD used in clinical settings, such as drug therapy, acupuncture, music therapy, exercise therapy, memory therapy, and so on. Acupuncture has the functions of restoring consciousness and resuscitation, promoting blood circulation, replenishing qi and regulating blood, and replenishing the spleen and kidney [68]. In addition, acupoints can be selected flexibly according to the specific body condition of the patient, to improve the patient's symptoms and overall physical condition in a targeted manner. Also, because of its small side effects and good tolerance [69], acupuncture is widely applied for treating AD. The combined application of acupuncture and medicine (herbal medicine or western medicine) has gradually increased recently, and its efficacy has also been confirmed by clinical research studies.

Researchers searched for relative studies and utilized NMA to evaluate the curative effect of acupuncture and the combined treatment of acupuncture and medicine based on the total effect and ADL score. For the total effect, the curative effects of acupuncture, acupuncture + herbal medicine, acupuncture + western medicine, and acupuncture + herbal medicine + western medicine are all better than those of western medicine. The curative effects of acupuncture, acupuncture + herbal medicine, and acupuncture + western medicine are better than those of Herbal medicine. The curative effect of acupuncture + western medicine is better than acupuncture + herbal medicine + western medicine. The differences in the remaining comparisons were not statistically significant. For the ADL score, the curative effects of acupuncture + western medicine and acupuncture + herbal medicine + western medicine are better than those of western medicine. The differences in the remaining comparisons were not statistically significant. The SUCRA shows that the top two interventions that have the best efficacy for total effect are acupuncture + western and acupuncture + herbal medicine (acupuncture + western > acupuncture + herbal medicine). The top two interventions that have the best efficacy for the ADL score are acupuncture + western medicine and acupuncture (acupuncture + western medicine > acupuncture). Results show that acupuncture combined with medicine has a better clinical effect than acupuncture for treating AD. Acupuncture + herbal medicine is more effective for improving the total effect, but there are certain disadvantages in improving the ADL score. The combination of acupuncture and western medicine has an impressive effect on both the total effect and the ADL score.

Acupuncture + herbal medicine and acupuncture + western medicine both have impressive effects on improving the total effect, but they both have worse effects than only applying acupuncture when adding a variety of medicine (applying acupuncture + herbal medicine + western medicine). Acupuncture + herbal medicine has an impressive effect on improving the total effect, but it has a worse effect on improving ADL scores. Researchers speculated that the reason for this contradiction in the sorting of curative effects may be related to the signaling pathways that various treatments affect the body. The most commonly used herbal medicines for treating AD, such as *Salvia miltiorrhiza*, *Ligusticum chuanxiong*, Noto ginseng, turmeric, *Herba epimedium*, and so on, can treat AD by inhibiting the formation and deposition of amyloid β-protein (Aβ), inhibiting the hyperphosphorylation of the protein tau, antagonizing oxidative stress damage and neuronal apoptosis, or playing an anti-inflammatory effect, etc [70–74]. In particular, herbal medicine for removing blood stasis is closely related to the body's autophagy, which can enhance autophagy and regulate the content of Aβ and protein tau [75]. The most commonly used Western medicine mentioned in the included studies, such as nimodipine, donepezil, and so on, mostly focus on improving symptoms and have a therapeutic effect on AD by inhibiting cholinesterase, regulating the concentration of calcium ions in the brain, and protecting the structure of neurons [9, 76–78]. Acupuncture can promote autophagy at different levels to treat AD by stimulating specific acupoints. The regulating function of acupuncture on autophagy is bidirectional, which can not only promote but also inhibit autophagy. Acupuncture can also adjust the body's oxidative defense system and reduce the toxic effects of excessive free radicals on the nervous system [79, 80]. The mechanisms of acupuncture, herbal medicine, and western medicine for treating AD have their specific parts and similar parts. There is saturation in signal transduction and various physiological processes. Once the signal stimulation of the same pathway reaches saturation, it may have no obvious enhancement of the effect, even produce a degenerative effect. Therefore, the combined application of acupuncture and herbal or western medicine may produce different comprehensive effects due to

Table 3: Quality assessment according to the ROB 2.

Reviewer	*He et al.* [43]		*Zhang* [50]		*Li and Li* [33]		*Chen et al.* [19]		*Geng* [10]		*Liu* [36]		*Xia* [38]		*Tao and Li* [47]		*Ji et al.* [61]		*Li and Li* [33]		*Jia et al.* [15]		*Wang et al.* [20]	
	Assessment	Comments	Assessment	Comments	Assessment	Comments	Assessment	Comments	Assessment	Comments	Assessment	Comments	Assessment	Comments	Assessment	Comments	Assessment	Comments	Assessment	Comments	Assessment	Comments	Assessment	Comments
Selection of the reported result	High	The study did not explain the specific treatment time of each treatment group, and it is suspected that there are possibilities of choosing the results	High	The study did not explain the specific treatment time of each treatment group, and it is suspected that there are possibilities of choosing the results	High	The study did not explain the specific treatment time of each treatment group, and it is suspected that there are possibilities of choosing the results	Low	—	Low	—	High	The study treated adverse events and were suspected of choosing the results	High	The study treated adverse events and were suspected of choosing the results	High	The study treated adverse events and were suspected of choosing the results	Low	—	High	The control group of the study was not treated with specific western medicine for AD, but only treated with conventional western medicine for other diseases.	Low	—	High	The study applied different outcomes from the original outcomes (not the outcomes used in this study).
Measurement of the outcome	Low	—	Low	—	Low	—	Low	—	Low	—	Low	—	Low	—	Low	—	High	The study had an unexplained dropout.	Low	—	Low	—	Low	—
Missing outcome data	Low	—	Low	—	Low	—	Low	—	Low	—	Low	—	Low	—	Low	—	Low	—	Low	—	Low	—	Low	—
Deviations from intended interventions	Low	—	Low	—	Low	—	Some concerns	The study was suspected of including dropout data into the analysis process	Some concerns	The study was suspected of including dropout data into the analysis process	Some concerns	The deviations may not likely to have affected the outcome.	Low	—	Low	—	Low	—	Low	—	Some concerns	The study reduced or stopped the medicine due to the adverse events during the process of treatment.	Low	—
Randomization process	Low	—	Low	—	Low	—	High	The study might take antidepressant and anxiety drugs at the same time in the treatment process and apply random method based on the date of admission.	Low	—	Low	—	Low	—	Low	—	Low	—	Low	—	Low	—	Low	—

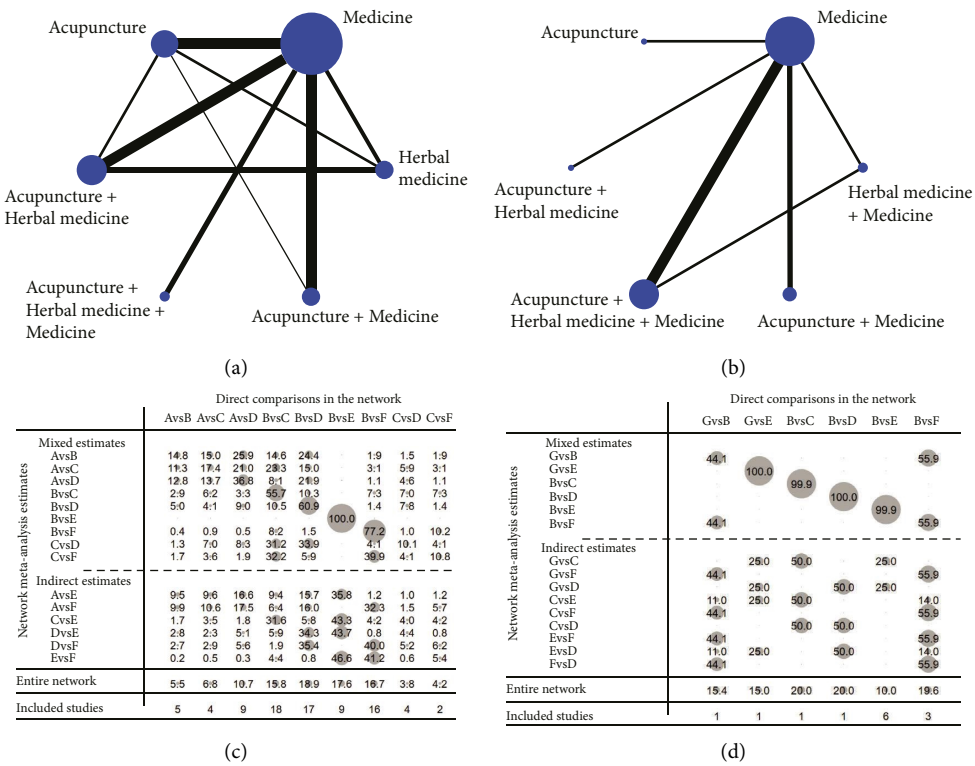


Figure 3: Network diagram comparing treatment outcomes of AD for total effect (a) and ADL (b). The diameter of each dot represents the proportional total weight of all trials in the network that investigated that intervention. The thickness of each line connecting 2 interventions is proportional to the number of trials that investigated that pair of interventions. Contribution plots for treatments of AD for total effect(c) and ADL (d). A-herbal medicine. B-western medicine. C-acupuncture. D-acupuncture + herbal medicine. E-acupuncture + herbal medicine + western medicine. F-acupuncture + western medicine. G-herbal medicine + western medicine. The size of each circle is proportional to the weight attached to each direct or indirect summary effect. The numbers re-express the weights as percentages.

Table 4: Evaluation of inconsistency using loop-specific heterogeneity estimates for total effect.

Loop	ROR	z_value	p_value	CI_95	Loop_Heterog_tau2
A-C-D	1.244	1.622	0.105	(1.00, 1.62)	0.000
A-B-C	1.232	1.641	0.101	(1.00, 1.58)	0.000
B–C-D	1.171	1.652	0.099	(1.00, 1.41)	0.000
B–C–F	1.106	0.994	0.320	(1.00, 1.35)	0.000
A-B-D	1.064	0.522	0.601	(1.00, 1.34)	0.004

A-Herbal medicine. B-Western medicine. C-Acupuncture. D-Acupuncture + Herbal medicine. E-Acupuncture + Herbal medicine + Western medicine. F-Acupuncture + Western medicine.

the compatibility of herbal medicines or acupoints. A combination of multiple medicines may also lead to differences in efficacy. Further research is still needed to verify it.

The results of the usage of acupoints show that the selection of acupoints for treating AD is diverse and complex and distributes in various parts of the body, but all of them have a therapeutic effect on AD indeed. It reflects the treatment principles of combining the main symptoms and concurrent syndromes, treating based on syndrome differentiation, and selecting acupoints based on syndromes. [81] Although compared with western medicine, acupuncture has poor function targeting treating AD, the principle of acupoint selection based on syndrome differentiation and the multidirectional effect of acupuncture makes it not only have the effect of treating AD but also regulates the whole body condition. This may be the reason why the combination of acupuncture and medicine is better than western medicine alone.

A total of 11 included studies mentioned adverse events after treatment. Adverse events mentioned the most frequently were reactions of the digestive system (nausea, vomiting, abdominal distension, diarrhea, loss of appetite) and the central nervous system (dizziness, insomnia). Although the occurrence of adverse events is affected by the patient's age, gender, and other factors [82], interventions must have a certain relationship with the adverse events. We analyzed the types of interventions used in studies with adverse events. We found that the proportion of Western medicines was the highest (81.8%). Among the included studies, donepezil was the western medicine used the most frequently. Studies have shown that adverse events to the digestive system and central nervous system are the most common adverse events of donepezil [83], which is consistent with the adverse events reported in the included studies to some extent. The mechanism of donepezil's

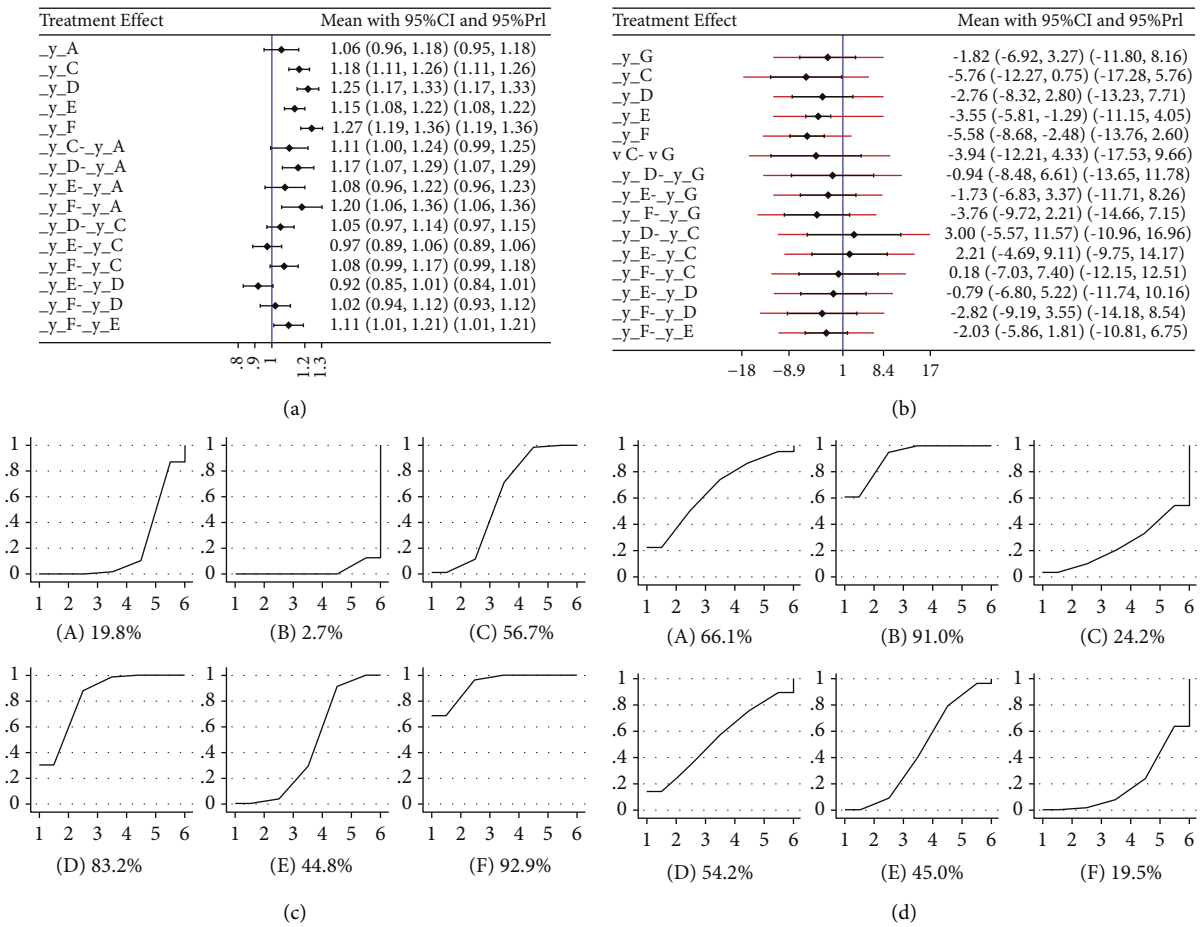


Figure 4: Forest plot of treatment differences on the standard normal scale for total effect (a) and ADL (b). The ineffectiveness line (vertical line, X = 1 or X = 0) means an equal ratio. Each horizontal line connects the upper and lower limits of the 95% confidence interval for study, and the length of lines indicates the range of the confidence interval. If the line crossed X = 1 or X = 0, the study was not statistically significant. If the line totally falls on the left side of X = 1 or X = 0 means worse efficacy and the right side for the opposite. The diamond-shaped blocks are the locations corresponding to the OR values. Surface under the cumulative ranking curves for all interventions for total effect (c) and ADL (d). A-Herbal medicine. B-Western medicine. C-Acupuncture. D-Acupuncture + Herbal medicine. E-Acupuncture + Herbal medicine + Western medicine. F-Acupuncture + Western medicine. G-Herbal medicine + Western medicine. Y axis represents cumulative probability and X axis represents rank. Comparing the cumulative probability of the same control ranking, the higher ranking (6⟶1) with a higher cumulative probability means a better curative effect.

Table 5: Inverted triangle diagram for total effect.

B	1.27 (1.19,1.36)	1.15 (1.08,1.22)	1.25 (1.17,1.33)	1.18 (1.11,1.26)	1.06 (0.96,1.18)
0.78 (0.74,0.84)	F	0.90 (0.83,0.99)	0.98 (0.89,1.07)	0.93 (0.85,1.01)	0.83 (0.74,0.94)
0.87 (0.82,0.92)	1.11 (1.01,1.21)	E	1.08 (0.99,1.18)	1.03 (0.94,1.12)	0.92 (0.82,1.04)
0.80 (0.75,0.86)	1.02 (0.94,1.12)	0.92 (0.85,1.01)	D	0.95 (0.87,1.03)	0.85 (0.77,0.94)
0.85 (0.80,0.90)	1.08 (0.99,1.17)	0.97 (0.89,1.06)	1.05 (0.97,1.14)	C	0.90 (0.80,1.00)
0.94 (0.85,1.05)	1.20 (1.06,1.36)	1.08 (0.96,1.22)	1.17 (1.07,1.29)	1.11 (1.00,1.24)	A

The yellow table cells represent interventions. A-Herbal medicine. B-Western medicine. C-Acupuncture. D-Acupuncture +Herbal medicine. E-Acupuncture +Herbal medicine +Western medicine. F-Acupuncture +Western medicine. The blue table cells represent combined effect size which can be referenced to compare the curative effect between the interventions in the column and the line.

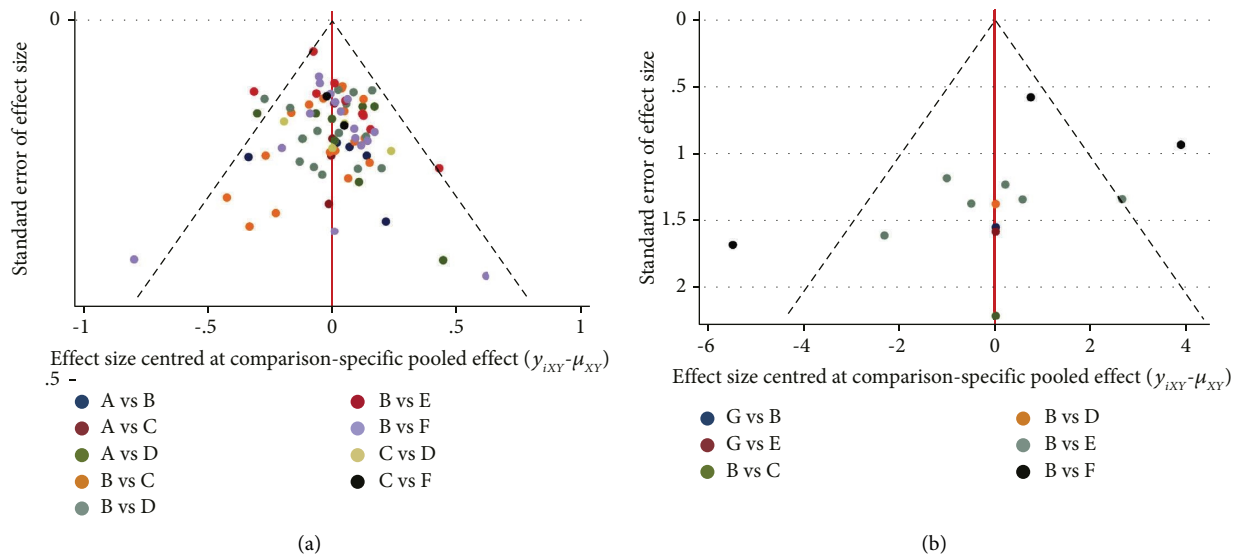


Figure 5: Funnel plot assessment of publication bias for total effect (a) and ADL (b). A-Herbal medicine. B-Western medicine. C-Acupuncture. D-Acupuncture + Herbal medicine. E-Acupuncture + Herbal medicine + Western medicine. F-Acupuncture + Western medicine. G-Herbal medicine + Western medicine. Most of the dots are symmetrically distributed on both sides of the vertical line of the X = 0, indicating a low possibility of both bias and the small sample effect.

Table 6: Evaluation of inconsistency using loop-specific heterogeneity estimates for ADL.

Loop	Ror	seIF	z_value	*p*_value	CI_95	Loop_Heterog_tau2
G-B-E	2.645	2.445	1.082	0.279	(0.00, 7.44)	0.336

B-Western medicine. E-Acupuncture + Herbal medicine + Western medicine. G-Herbal medicine + Western medicine.

Table 7: Inverted triangle diagram for ADL.

B	-5.58 (-8.68, -2.48)	-3.55 (-5.81, -1.29)	-2.76 (-8.32,2.80)	-5.76 (-12.27,0.75)	-1.82 (-6.92,3.27)
5.58 (2.48,8.68)	F	2.03 (-1.81,5.86)	2.82 (-3.55,9.19)	-0.18 (-7.40,7.03)	3.76 (-2.21,9.72)
3.55 (1.29,5.81)	-2.03 (-5.86,1.81)	E	0.79 (-5.22,6.80)	-2.21 (-9.11,4.69)	1.73 (-3.37,6.83)
2.76 (-2.80,8.32)	-2.82 (-9.19,3.55)	-0.79 (-6.80,5.22)	D	-3.00 (-11.57,5.57)	0.94 (-6.61,8.48)
5.76 (-0.75,12.27)	0.18 (-7.03,7.40)	2.21 (-4.69,9.11)	3.00 (-5.57,11.57)	C	3.94 (-4.33,12.21)
1.82 (-3.27,6.92)	-3.76 (-9.72,2.21)	-1.73 (-6.83,3.37)	-0.94 (-8.48,6.61)	-3.94 (-12.21,4.33)	G

The yellow table cells represent interventions. B-Western medicine.C-Acupuncture. D-Acupuncture +Herbal medicine. E-Acupuncture +Herbal medicine +Western medicine. F-Acupuncture +Western medicine. G-Herbal medicine +Western medicine.The blue table cells represent combined effect size which can be referenced to compare the curative effect between the interventions in the column and the line.

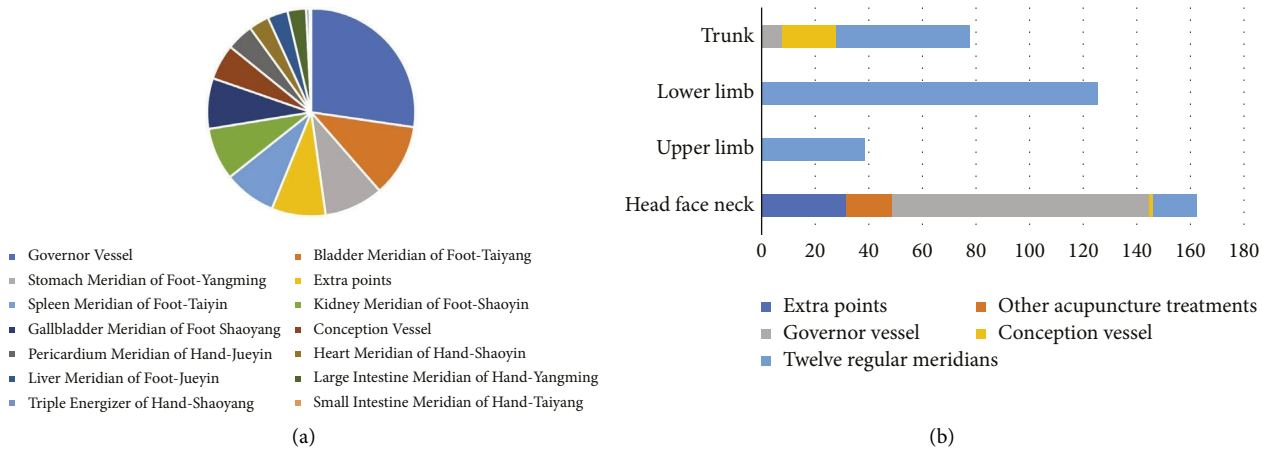


Figure 6: Proportion of meridians chosen by studies included (a). The pie chart area displays application frequency of meridians. Most studies selected Governor the vessel, while few studies select three hand-yin meridians or three hand-yang meridians. Proportion of body parts chosen by studies included (b). The chart shows maximum amount and most abundant meridians of head, face and neck acupoints and opposite for upper limb.

Acupoints	Frequency	Proportion	Acupoints	Frequency	Proportion	Acupoints	Frequency	Proportion
DU20	46	15.70%	DU16	6	2.05%	Three-brain acupuncture (GB19+DU17)	2	0.68%
SP6	22	7.51%	DU4	6	2.05%	DU9	2	0.68%
ST36	21	7.17%	SP10	6	2.05%	LI11	2	0.68%
KI3	21	7.17%	BL18	6	2.05%	GB12	2	0.68%
EX-HN1	20	6.83%	RN12	6	2.05%	BL40	2	0.68%
GB39	17	5.80%	RN6	6	2.05%	SJ17	2	0.68%
BL23	17	5.80%	KI4	5	1.71%	Eye acupuncture	1	0.34%
PC6	16	5.46%	KI1	5	1.71%	Three-tongue acupuncture	1	0.34%
DU24	15	5.12%	RN4	5	1.71%	Three-smell acupuncture	1	0.34%
DU14	13	4.44%	The Four-Shen points	4	1.37%	DU15	1	0.34%
BL17	13	4.44%	BL20	4	1.37%	HT5	1	0.34%
DU26	12	4.10%	Temporal three-needle	3	1.02%	HT1	1	0.34%
ST40	12	4.10%	The Three-Zhi acupuncture (DU24+GB13)	3	1.02%	ST8	1	0.34%
LR3	12	4.10%	DU23	3	1.02%	GB15	1	0.34%
HT7	10	3.41%	SP9	3	1.02%	GB8	1	0.34%
LI4	9	3.07%	RN17	3	1.02%	BL15	1	0.34%
GB20	9	3.07%	EX-HN12、13	2	0.68%	RN23	1	0.34%
EX-HN3	8	2.73%	Scalp acupuncture	2	0.68%	SI19	1	0.34%

Figure 7: Frequency rank of acupoints chosen by studies included. The head, neck, and lower limb acupoints were more selected, which correspond to the local and distal acupoint selection.

adverse reaction may be related to its inhibition of cholinesterase. It can lead to excessive cholinergic action and cause nausea, vomiting, abdominal distension, and other gastrointestinal reactions, or cause a disorder of neurotransmitters in the central nervous system and cause dizziness, insomnia, and other reactions. [82] Among the 11 studies, 3 studies reported similar adverse events under the combined treatment of acupuncture and herbal medicine. Therefore, we believe that although the occurrence of adverse events is closely related to the use of western medicine, it is also affected by acupuncture and herbal medicine.

In the included studies, acupoints on the head were mostly used for treating AD, whereas acupoints correlated with gastrointestinal function were rarely used. Based on the brain-gut axis theory, some active peptides and neurotransmitters exist in both the brain and the gastrointestinal tract. The gastrointestinal function is closely related to the brain function and can interact with each other. [84] Moreover, studies have shown that the dysregulation of intestinal flora may also lead to AD. [85, 86] Due to the high frequency of gastrointestinal reactions in adverse reactions, researchers believe that RN12, BL21, and other acupoints correlated with gastrointestinal function can be appropriately selected in clinical practice to supplement the therapeutic effect of acupoints on the head and to prevent and alleviate adverse events. The original material on adverse events is not adequate enough, so the conclusion about adverse events should be considered comprehensively and carefully used.

5. Limitations

This study has several limitations in the following areas. First, the included studies are mostly small sample studies, and the original data of ADL have high heterogeneity, which may affect the research statistically. More databases need to be searched to increase the number of studies included in the analysis. Second, on account of that western medicine, herbal medicine, and herbal medicine + western medicine were only used as control groups in this study, RCTs, which did not use acupuncture as a study group, but only used western or herbal medicine as study groups, were not included. Therefore, the relative curative effect rankings of western medicine, herbal medicine, and herbal

Table 8: Adverse events in the included studies.

	Treatment	Time	Symptoms (quantity-percent%)
Ou et al. [32]	Western medicine	—	Nausea, dizziness, and dry mouth (2)
Zhou [67]	Western medicine	After 4 weeks of treatment	Nausea, loss of appetite, and diarrhea (3)
	Herbal medicine + acupuncture	—	Diarrhea, loss of appetite and headache (6)
Li et al. [11]	Western medicine	—	Dizziness (1) and abdominal distension (1)
	Western medicine + acupuncture + herbal medicine	—	Anorexia (1)
Wang and Wang [53]	Western medicine	—	Nausea and vomiting (3); diarrhea (3); dizziness and insomnia (2); and muscle spasm (3)
	Western medicine + acupuncture + herbal medicine	—	Nausea and vomiting (2); diarrhea (5); dizziness and insomnia (4); and muscle spasm (2)
Zhang [24]	Western medicine	During the increase of drug dose	6 cases (14.63%)showed adverse drug reactions, including dizziness (3); nausea (1); and decreased appetite (2)
	Western medicine + acupuncture + herbal medicine	—	5 cases (12.20%) had adverse drug reactions, including dizziness(1); vomiting(1); headache(1); and decreased appetite(2)
Wei et al. [26]	Western medicine	—	Abnormal liver function and abdominal distension (1–3.03%); abnormal blood routine (3–9.09%); diarrhea (2–6.06%)
	Western medicine + acupuncture	—	Abnormal liver function, abnormal blood routine, abdominal distension (2–6.06%), and diarrhea (4–12.12%)
Wang and Li [51]	Western medicine	—	Nausea (1), vomiting (1), diarrhea (2), and cough (1)
	Western medicine + acupuncture	—	Nausea (2), diarrhea (1), and cough (1)
Zhang et al. [46]	Western medicine	—	Nausea, vomiting (4); metabolic acidosis (1); diarrhea (3); and pallor (2)
	Herbal medicine + acupuncture	—	Nausea, vomiting(2), and pallor(1)
Xia et al. [56]	Western medicine	—	(8–17.39%): diarrhea (2), nausea or vomiting (5), and insomnia (1)
	Western medicine + acupuncture	—	(2–4.35%): Nausea and vomiting (2)
Zhang et al. [34]	Western medicine	—	Diarrhea (2), nausea or vomiting (5), and insomnia (1)
	Western medicine + acupuncture	—	Nausea and vomiting (1)
Tao and Li [47]	Western medicine	—	(6–13.3%): diarrhea (2), abnormal blood routine (2), abnormal liver function (1), and abdominal distension (1)
	Herbal medicine + acupuncture	—	(5–11.11%): diarrhea (1), abnormal blood routine (1), abnormal liver function (1), and abdominal distension (2)

medicine + western medicine are less of the reference value. Third, interventions in the included studies were only classified into acupuncture, acupuncture + herbal medicine, acupuncture + western medicine, and acupuncture + herbal medicine + western medicine. The therapeutic evaluation might be influenced due to classification, which is not detailed enough. Fourth, the current study compares the efficacy of acupuncture and combined therapy of acupuncture and medicine in the treatment of AD and the complementary effect of acupuncture on drug therapy. Therefore, other treatments for AD, such as music therapy and doll therapy, have not been involved in this study. Subsequent studies can expand the research scope and compare the efficacy of various treatments for AD comprehensively. Fifth, more scales can be included in the analysis to assess the efficacy of interventions more completely.

6. Conclusions

In conclusion, the combination of acupuncture and medicine has a better clinical effect than acupuncture in a way. Acupuncture + western medicine has an obvious and exact improvement in the curative effect from both the total effect and ADL score. Therefore, the researchers believe that the development of the combination therapy of acupuncture and medicine is advantageous and reasonable for treating AD and that acupuncture does have a complementary effect on drug therapy. It has prompted clinicians to practice combination therapy of acupuncture and medicine and use the principle of selecting acupoints based on syndrome differentiation flexibly to improve the therapeutic effect of AD. Acupuncture should be used appropriately to prevent and alleviate the adverse reactions that may occur during the treatment of AD. Researchers can study and compare the clinical efficacy of different combinations of acupuncture and medicine on patients with different syndromes to determine the combinations that can clearly reduce or improve clinical efficacy and to refine the selection of specific acupoints or methods of acupuncture and prescriptions, and to provide more accurate guidance for the clinical treatment of AD.

Abbreviations

AD: Alzheimer's disease
ADL: Activity of daily living scale
ATD: Alzheimer type dementia
CBM: China Biology Medicine Disc
CI: Credibility interval
CNKI: China National Knowledge Infrastructure
CQVIP: Chongqing VIP Database
DSM-IVR: The Diagnostic And Statistical Manual Of Mental Disorders Revised Fourth Edition
IF: Inconsistency factors
MD: Mean difference
NMA: Network meta-analysis
PICOS: P-Population; I-Intervention; C-Comparison; O-Outcome; S-Study design
PRISMA: Preferred reporting items for systematic reviews and meta-analyses
RCTs: Randomized controlled trials
SD: Standard deviation
SE: Standard error
SUCRA: The surface under the cumulative ranking curve
TCM: Traditional Chinese medicine

Conflicts of Interest

The authors declare that they have no conflicts of interest.

Authors' Contributions

Wenshan Yin and Yihan Chen have contributed equally to this work. WY and YC performed data collection and data analysis and prepared the manuscript. AX and XW carried out data analysis and prepared the manuscript. QZ, YT, and ZL guided the study. The authors read and approved the final manuscript.

References

[1] D. S. Knopman, "Alzheimer's disease and other dementias," *Cecil Medicine*, vol. 02, pp. 2274–2283, 2012.
[2] Z. Y. Li and Q. Ning, "Pathogenesis of senile dementia and observation on clinical drug therapy of senile dementia," *Chinese Journal of Modern Drug Application*, vol. 11, no. 04, pp. 131-132, 2017.
[3] J. Gong, J. Y. Qian, Y. X. Wang, K. Qian, Y. Ming, and H. Y. Dong, "Analysis of rule of traditional Chinese medicine in treating Alzheimer's disease," *Journal of Qiqihar Medical University*, vol. 41, no. 16, pp. 2040–2042, 2020.
[4] X. X. Guo, E. C. Guo, and Z. G. Zhong, "Mechanism of traditional Chinese and western medicine research and treatment of senile dementia," *Asia-Pacific Traditional Medicine*, vol. 11, no. 13, pp. 41–44, 2015.
[5] J. Wang, T. Hao, and X. F. Zhao, "Action mechanism of acupuncture in treating AD," *Journal of Clinical Acupuncture and Moxibustion*, vol. 36, no. 12, pp. 87–91, 2020.
[6] C. C. Bell, "DSM-IV diagnostic and statistical manual of mental disorders," *Journal of the American Medical Association*, vol. 272, no. 10, pp. 828-829, 1994.
[7] J. Ma, Y. Liu, and L. P. Zhong, "Comparison between Jadad scale and Cochrane collaboration's tool for assessing risk of bias on the quality and risk of bias evaluation in randomized controlled trials," *China Journal of Oral and Maxillofacial Surgery*, vol. 10, no. 05, pp. 417–422, 2012.
[8] J. P. T. Higgins, S. G. Thompson, J. J. Deeks, and D. G. Altman, "Measuring inconsistency in meta-analyses," *British Medical Journal*, vol. 327, no. 7414, pp. 557–560, 2003.
[9] G. Salanti, A. E. Ades, and J. P. A. Ioannidis, "Graphical methods and numerical summaries for presenting results from multiple-treatment meta-analysis: an overview and tutorial," *Journal of Clinical Epidemiology*, vol. 64, no. 2, pp. 163–171, 2011.
[10] Y. X. Geng, *Clinical Research of Marrow Supplementing and Resuscitation Acupuncture Method on Deficiency of Marrow-Reservoir of Senile Dementia*, Changchun University of Chinese Medicine, Changchun, China, 2017.
[11] L. S. Li, J. J. Feng, D. D. Hei, Y. N. Yue, and L. M. Zhu, "Clinical observation on 45 cases of senile dementia treated by

integrated Traditional Chinese and Western medicine," *Chinese Journal of Ethnomedicine and Ethnopharmacy*, vol. 26, no. 15, 2017.

[12] H. Zhu, K. L. Dong, Y. Wu et al., "Effect of Tonifying kidney and Activating Blood circulation on improving cognitive function in Patients with Alzheimer's disease," *Chinese Journal of Gerontology*, vol. 30, no. 11, pp. 1493–1495, 2010.

[13] R. M. Li, K. L. Dong, and H. Zhu, "Clinical observation on 20 cases of alzheimer disease treated with acupuncture and traditional Chinese medicine," *Hunan Journal of Traditional Chinese Medicine*, vol. 25, no. 4, pp. 1-2, 2009.

[14] Z. Liu, "Effect analysis of Buyuan Congnao Decoction combined with acupuncture on treating senile dementia with kidney deficiency, phlegm and blood stasis," *Journal of Practice Traditional Chinese Medicine*, vol. 36, no. 08, pp. 968-969, 2020.

[15] Y. J. Jia, D. Meng, M. L. Sun et al., "Clinical observation of sanjiao acupuncture on mild to moderate Alzheimer's disease: a randomized controlled trial," *Liaoning Journal of Traditional Chinese Medicine*, vol. 44, no. 09, pp. 1911–1914, 2017.

[16] Y. H. Wang, Y. Wang, X. Zhou, and H. S. Cui, "Clinical observation of needing Qin's eight head acupoints combined with western medicine in the treatment of Alzheimer's disease," *Shanghai Journal of Traditional Chinese Medicine*, vol. 54, no. S1, pp. 69–73, 2020.

[17] D. R. Tian and C. F. Cheng, "Clinical study of olacetam injection combined with acupuncture in the treatment of Alzheimer's disease," *Heilongjiang Medicine and Pharmacy*, vol. 40, no. 02, 2017.

[18] Y. X. Guan, "Clinical study of comprehensive therapy for Alzheimer's disease," *Asia-Pacific Traditional Medicine*, vol. 13, no. 06, pp. 113-114, 2017.

[19] Y. M. Chen, P. Ye, and A. H. Tan, "Clinical observation on acupuncture treatment of Alzheimer's disease," *Cardiovascular Disease Electronic Journal of Integrated Traditional Chinese and Western Medicine*, vol. 5, no. 22, 2017.

[20] K. F. Wang, L. J. Zhang, and X. Y. Chen, "Clinical observation on 36 cases of Alzheimer's disease treated by electroacupuncture Dazhui(GV 14) and Baihui(GV 20)," *China Journal of Traditional Chinese Medicine and Pharmacy*, vol. 30, no. 03, pp. 784–786, 2015.

[21] J. P. Li, Y. H. Ceng, W. Lu, Z. D. Jiang, and L. Yang, "Clinical observation on electroacupuncture combined with compound Danshen tablets in the treatment of Alzheimer's disease," *China Modern Doctor*, vol. 56, no. 23, pp. 64–67, 2018.

[22] X. W. Peng and K. L. Dong, "Clinical observation on acupuncture combined with Yizhi Jiannao Granules for treatment of Alzheimer's disease," *Chinese Acupuncture and Moxibustuon*, vol. 29, no. 04, pp. 269–271, 2009.

[23] Y. Q. Ou, Z. R. Li, Y. Y. Mu, D. Zhao, H. W. Long, and Q. Wu, "Comparative study on the clinical efficacy of acupuncture in the treatment of Alzheimer's disease," *Chinese Acupuncture and Moxibustuon*, vol. 07, pp. 15–17, 1999.

[24] X. F. Zhang, "Clinical study of continuous rivastigmine combined with body acupuncture, xingqiao huoxue decoction in treatment of senile dementia," *Chinese Archives of Traditional Chinese Medicine*, vol. 34, no. 02, pp. 428–430, 2016.

[25] W. Chen, L. F. Jiang, L. Wu, J. E. Xing, and J. F. Liang, "Efficacy of standardized intervention of integrated Traditional Chinese and Western medicine in the treatment of Alzheimer's disease," *Chinese Journal of Gerontology*, vol. 37, no. 06, pp. 1486–1488, 2017.

[26] Y. X. Wei, B. C. Zhang, J. Zhou, and C. G. Gou, "Clinical effect of acupuncture and moxibustion on senile dementia at Baihui(GV 20) and Yongquan(KI 1) points," *Chinese Journal of Gerontology*, vol. 36, no. 12, pp. 2916-2917, 2016.

[27] X. Y. Wang and F. L. Li, "Effect of acupuncture with Maixuekang Capsule on cognitive function of senile dementia patients," *Chinese Journal of Integrative Medicine on Cardio-Cerebrovascular Disease*, vol. 16, no. 05, pp. 640–643, 2018.

[28] Z. R. Li, Y. Y. Mu, and Y. Q. Ou, "Clinic control research of Alzheimer's disease by the combination of acupuncture and Danggui Shaoyao San (DGSYS) of TCM," *Chinese Journal of Tissue Engineering Research*, vol. 19, pp. 2848-2849, 2002.

[29] J. H. Liu, S. W. Ye, and J. H. Huang, "Influence of Xingchi decoction combined with acupuncture on MMSE scale score of senile dementia patients," *Chinese Manipulation and Rehabilitation Medicine*, no. 08, pp. 13–15, 2006.

[30] X. C. Jin, "Clinical comprehensive treatment of senile dementia in 26 cases," *Chinese Medicine Modern Distance Education of China*, vol. 12, no. 01, pp. 57-58, 2014.

[31] D. H. Luo, T. Zou, and Q. Y. Huang, "Clinical observation on the effect of electroacupuncture on senile dementia with kidney deficiency and the effect of β-amyloid protein," *Chronic Pathematology Journal*, vol. 09, pp. 64–66, 2006.

[32] Y. Q. Ou, Z. R. Zhong, Y. Y. Mu, D. Zhao, H. W. Long, and Q. Wu, "A comparative study on the effect of acupuncture on mental retardation in 16 patients with Alzheimer's disease," *Clinical Journal of Traditional Chinese Medicine*, vol. 03, pp. 158-159, 1999.

[33] L. Y. Li and A. M. Li, "Clinical observation on buyuan congnao decoction combined with acupuncture and moxibustion in the treatment of senile dementia(kidney deficiency phlegm and blood stasis type)," *Guangming Journal of Chinese Medicine*, vol. 36, no. 08, pp. 1268–1270, 2021.

[34] K. B. Zhang, Y. H. Yang, and J. Ding, "Clinical observation on fire needle combined with oral donepezil in the treatment of Alzheimer's disease," *Guangming Journal of Chinese Medicine*, vol. 34, no. 02, pp. 291–293, 2019.

[35] H. Lin, *Clinical Study on Treating Alzheimer's Disease with Scalp Acupuncture*, Guangzhou University of Chinese Medicine, Guangzhou, China, 2016.

[36] J. H. Liu, *The Effects of Xingchi Decoction with Acupuncture on MMSE, Hcy and EEG of the Patients of Alzheimer's Disease*, Guangzhou University of Chinese Medicine, Guangzhou, China, 2008.

[37] X. F. Li, "Clinical study of olacetam injection combined with acupuncture in the treatment of Alzheimer's disease," *Health Guide*, vol. 30, p. 55, 2021.

[38] Q. Xia, *Combination of Acupuncture with Medicine Treatment of Senile Dementia Mentla-The Kidney Empty Marrow Suppression of Clinical Observation*, Heilongjiang University of Chinese Medicine, 2013.

[39] H. X. Qing, *Combination of Acupuncture with Medicine Treatment of Alzheimer's Disease-Qi and Blood Deficiency Type of Clinical Research*, Heilongjiang University of Chinese Medicine, Harbin, China, 2013.

[40] W. Chen, L. F. Jiang, L. Wu, J. F. Liang, Y. Q. Hu, and Q. C. He, "Observation on clinical effect of integrated Chinese and Western medicine on Alzheimer's disease," *Internal Medicine*, vol. 10, no. 02, 2015.

[41] J. Peng, X. Chen, A. P. Wang et al., "Efficacy evaluation on electroacupuncture for Alzheimer's disease," *Journal of Acupuncture and Tuina Science*, vol. 15, no. 4, pp. 296–299, 2017.

[42] D. Y. Ben, Q. Liu, Y. X. Chen et al., "Therapeutic observation on electroacupuncture at Zusanli(ST 36) and Fenglong(ST 40)

for senile dementia," *Journal of Acupuncture and Tuina Science*, vol. 14, no. 6, pp. 386–390, 2016.

[43] D. He, R. L. Li, and F. L. Li, "Therapeutic effect of brain regeneration factor acupoint injection therapy on Alzheimer's disease," *Journal of Brain and Nervous Diseases*, no. 02, 2000.

[44] Y. G. Chen, Z. J. Li, and J. Wu, "Clinical research of acupuncture intradermic injection of xueshuantong in the treatment of AD," *Journal of Clinical Acupuncture and Moxibustion*, vol. 36, no. 02, pp. 50–55, 2020.

[45] L. G. Zhao, L. Ma, Y. J. Li et al., "Observation on the curative effect of acupuncturing baihui (GV 20) and Dazhui (GV 14) on senile dementia," *Journal of Clinical Acupuncture and Moxibustion*, vol. 09, pp. 42-43, 2007.

[46] Y. Y. Zhang, Y. F. Yang, and W. L. Liu, "Efficacy of Naolisu Decoction combined with acupuncture in treatment of patients with senile dementia," *Journal of Clinical Medicine in Practice*, vol. 24, no. 17, pp. 45–47, 2020.

[47] S. X. Tao and R. H. Li, "Clinical efficacy and clinical application value of acupuncture Baihui(GV 20) and Yongquan(KI 1) points in senile dementia," *Journal of Frontiers of Medicine*, vol. 8, pp. 334-335, 2018.

[48] L. Lei, "Clinical observation of bushen Huoxue prescription combined with acupuncture in treating senile dementia," *Journal of New Chinese Medicine*, vol. 43, no. 10, pp. 37-38, 2011.

[49] S. Chen, "Clinical observation on treatment of senile dementia with integrated traditional Chinese and western medicine," *Journal of Practical Traditional Chinese Medicine*, vol. 33, no. 10, pp. 1160-1161, 2017.

[50] S. Zhang, *Clinical Observation on Senile Dementia Treated with Acupuncture Combined with Medicine*, Liaoning University of Chinese Medicine, Shenyang, China, 2009.

[51] X. Q. Wang and Y. Y. Li, "Clinical study on the treatment of Alzheimer's disease with rivastigmine combined with xingnao kaiqiao acupuncture," *Medical Innovation of China*, vol. 18, no. 06, pp. 92–96, 2021.

[52] J. Liu, "Effect of Chinese medicine combined with acupuncture on peripheral blood TNF-α and IL-6 expression of patients with Alzheimer's disease," *Medical Innovation of China*, vol. 12, no. 30, pp. 93–95, 2015.

[53] Z. Z. Wang and Z. Wang, "Study on dihuang Yizhi prescription, electroacupuncture combined with donepezil hydrochloride tablets in the treatment of Alzheimer's dementia," *Modern Journal of Integrated Traditional Chinese and Western Medicine*, vol. 26, no. 30, 2017.

[54] Z. B. Liu, W. M. Niu, X. H. Yang, and X. M. Niu, "Clinical study of the influence of "xiusanzhen" on cognitive competence in patients with alzheimer's disease," *Shaanxi Journal of Traditional Chinese Medicine*, vol. 29, no. 06, pp. 711-712, 2008.

[55] X. H. He, *Clinical Research on Warming Moxibustion in the Improvement of Kidney Efficiency and Marrow Insufficiency Typr Alzheimer's Disease Patients with Cognitive Functions*, Shandong University of Chinese Medicine, Jinan, China, 2018.

[56] K. P. Xia, Y. J. Wang, M. Zhang et al., "Effect of electroacupuncture at baihui(GV20) and fengfu(GV16) on the learning and memory abilities in Alzheimer's disease patients," *Shanghai Journal of Acupuncture and Moxibustion*, vol. 39, no. 08, pp. 974–978, 2020.

[57] Y. Y. Zhu, "Observation on the therapeutic effect of warm needling on senile dementia," *Shanghai Journal of Acupuncture and Moxibustion*, vol. 33, no. 11, pp. 996-997, 2014.

[58] H. H. Ma, *Clinical Study of Acupuncture and Moxibustion in the Treatment of Mild to Moderate Alzheimer's Disease Based on the Theory*, Shanxi University of Chinese Medicine, Taiyuan, China, 2021.

[59] W. Zhang, Y. Tian, M. Zhang, Q. Tuo, J. Chen, and D. Liao, "IDOL inducible degrader of low-density lipoprotein receptor, serves as a potential therapeutic target for dyslipidemia," *Medical Hypotheses*, vol. 86, no. 12, pp. 138–142, 2016.

[60] T. Y. Liang, "37 cases of senile dementia treated by warm needle," *Traditional Chinese Medicinal Research*, vol. 29, no. 09, pp. 57–59, 2016.

[61] F. Y. Ji, H. T. Gao, F. Wang, and F. L. Xiong, "Acupuncture baihui(GV 20) and Neiguan(PC 6) point to treat senile dementia," *Western Journal of Traditional Chinese Medicine*, vol. 07, pp. 14-15, 2007.

[62] D. R. Chen, Y. X. Zheng, and M. Z. Chen, "Therapeutic effects of acupuncture on senile dementia and its influence on cytokine and blood lipid metabolism," *World Chinese Medicine*, vol. 13, no. 03, 2018.

[63] Y. Wang, W. G. Qin, and C. D. Yu, "Clinical observation on effect of cranial suture acupuncture combined with donepezil hydrochloride tablets for Alzheimer's disease," *World Journal of Acupuncture-Moxibustion*, vol. 24, no. 2, pp. 19–24, 2014.

[64] A. N. Yao, X. Wang, L. L. Dong, and W. B. He, "Observation on the effect of the treatment of Alzheimer's disease with rehmannia decoction combined acupuncture at baihui point," *World Journal of Integrated Traditional and Western Medicine*, vol. 11, no. 05, pp. 667–670, 2016.

[65] W. S. Zhang, "Effect analysis of acupuncture and moxibustion combined with traditional Chinese medicine for senile dementia," *World Latest Medicine Information*, vol. 19, no. 24, p. 145+147, 2019.

[66] M. Y. Ni, "Observation on clinical effect of acupoint electroacupuncture therapy combined with Modified Zuogui pill on senile dementia," *World Latest Medicine Information*, vol. 17, no. 47, pp. 62-63, 2017.

[67] G. R. Zhou, *Clinical Study on the Treatment of Alzheimer's Disease with Cuzhi Granule Combined with Acupuncture*, Xinxiang Medical University, Xinxiang, China, 2018.

[68] Y. X. Liu, C. Q. Sun, and J. G. Yang, "Study on rules of acupoints selection of acupuncture and moxibustion in treatment of alzheimer disease," *Chinese Journal of Information on Traditional Chinese Medicine*, vol. 24, no. 10, pp. 90–93, 2017.

[69] J. Zhou, W. N. Peng, M. Xu, W. Li, and Z. S. Liu, "The effectiveness and safety of acupuncture for patients with alzheimer disease: a systematic review and meta-analysis of randomized controlled trials," *Medicine*, vol. 94, no. 22, p. 933, 2015.

[70] C. Y. Yuan, S. S. Yuan, D. H. Wu, C. H. Liu, G. L. He, and F. Hou, "Synergistic effect of icariin and panax Notoginseng saponins in inhibiting cell injury in alzheimer's disease models with factorial design," *Geriatrics and Health Care*, vol. 25, no. 03, pp. 355–357+406, 2019.

[71] J. T. Li, Y. Qi, H. Jiang et al., "Study of curcuma aromatica extract on learning and memory function in mice induced by β-amyloid(Aβ25-35)," *Liaoning Journal of Traditional Chinese Medicine*, vol. 44, no. 03, pp. 633–636, 2017.

[72] X. X. Li, X. L. Wu, K. Zhang, L. Su, and Y. X. Sun, "Research progress of tanshinone IIA in prevention and treatment of alzheimer's disease," *Life Science Research*, vol. 21, no. 01, pp. 59–63, 2017.

[73] Y. Qi, R. Liu, D. Jia, H. Jiang, K. Jiang, and Y. B. Wang, "The study of curcuma aromatica volatile oil on the learning and

memory function in mice induced by β-amyloid(Aβ25-35)," *Laboratory Animal Science*, vol. 34, no. 05, pp. 23–27, 2017.

[74] J. J. Zhu and L. H. Wan, "Research progress of the mechanism of tanshinone IIA on alzheimer's disease," *Sichuan Journal of Physiological Sciences*, vol. 37, no. 04, pp. 208–211, 2015.

[75] Y. H. Chen, J. C. Lan, X. Y. Zhang, L. W. Yan, H. M. Zheng, and S. He, "Research progress in the treatment of Alzheimer's disease with traditional Chinese medicine for promoting blood circulation and removing stasis," *Journal of Pharmaceutical Research*, vol. 40, no. 07, 2021.

[76] Z. G. Zhang and X. H. Xu, "The synaptic mechanisms of nimodipine in ameleorating the CaCl2-induced memory dysfunction in brain," *Acta Psychology Sinica*, vol. 03, pp. 436–441, 2006.

[77] S. X. Wan and W. Fang, "Research progress on drugs in treatment of Alzheimer's disease," *Drugs and Clinic*, vol. 33, no. 12, pp. 3406–3410, 2018.

[78] A. E. Roher, Z. Garami, A. V. Alexandrov et al., "Interaction of cardiovascular disease and neurodegeneration transcranial Doppler ultrasonography and Alzheimer's disease," *Neurological Research*, vol. 28, no. 6, pp. 672–678, 2006.

[79] Y. Yang, J. Y. Guo, C. Yang, and Y. K. Du, "Research progress of acupuncture regulating autophagy in Alzheimer's disease," *Guangdong Medical Journal*, vol. 42, no. 04, pp. 404–408, 2021.

[80] L. P. Zhao, L. Q. Miao, L. L. Jiang, K. Liu, Y. Feng, and X. Y. Zhu, "Current situation and thinking of acupuncture improving the mechanism of oxidative stress in alzheimer's disease," *Modernization of Traditional Chinese Medicine and Materia Medica-World Science and Technology*, vol. 22, no. 08, pp. 2670–2678, 2020.

[81] Y. W. Wang and X. M. Ye, "Discussion on several factors improving the clinical effect of acupuncture," *China Journal of Traditional Chinese Medicine and Pharmacy*, vol. 36, no. 05, pp. 3004–3006, 2021.

[82] H. Xie and X. Huang, "Analysis of 35 cases of adverse reactions caused by Donepezil hydrochloride," *Chin J of Clinical Rational Drug Use*, vol. 10, no. 13, 2017.

[83] X. Q. Lv, T. X. Hu, S. Y. Liu, and M. K. Ma, "Statistical analysis of 240 cases of donepezil induced adverse reactions," *Chinese Journal of Clinical Pharmacy*, vol. 27, no. 05, pp. 346–351, 2018.

[84] C. Stasi, M. Rosselli, M. Bellini, G. Laffi, and S. Milani, "Altered neuro-endocrine-immune pathways in the irritable bowel syndrome: the top-down and the bottom-up model," *Journal of Gastroenterology*, vol. 47, no. 11, 2012.

[85] M. Grochowska, M. Wojnar, and M. Radkowski, "The gut microbiota in neuropsychiatric disorders," *Acta Neurobiologiae Experimentalis*, vol. 78, no. 2, pp. 69–81, 2018.

[86] C. Jiang, G. N. Li, P. R. Huang, Z. Liu, and B. Zhao, "The gut microbiota and alzheimer's disease," *Journal of Alzheimer's Disease*, vol. 58, no. 1, pp. 1–15, 2017.

Hindawi
Evidence-Based Complementary and Alternative Medicine
Volume 2022, Article ID 7416448, 16 pages
https://doi.org/10.1155/2022/7416448

Research Article

Exploring the Potential Mechanism of Qi-Shen-Di-Huang Drug Formulary for Myasthenia Gravis (MG) based on UHPLC-QE-MS Network Pharmacology and Molecular Docking Techniques

Yibin Zhang,[1] Tianying Chang,[2] Qi Lu,[3] Yingzi Cui,[2] Dongmei Zhang,[4] Baitong Wang,[1] Peng Xu,[1] Jing Lu,[5] Jinhui Ma,[6] Zhiguo Lv,[1] and Jian Wang[1]

[1]*Department of Neurology, The Affiliated Hospital to Changchun University of Traditional Chinese Medicine, Changchun, China*
[2]*Evidence Based Office, The Affiliated Hospital to Changchun University of Traditional Chinese Medicine, Changchun, China*
[3]*Medical Insurance Office, The Third Affiliated Clinical Hospital of Changchun University of Traditional Chinese Medicine, Changchun, China*
[4]*Scientific Research Office, The Affiliated Hospital to Changchun University of Traditional Chinese Medicine, Changchun, China*
[5]*Research Center of Traditional Chinese Medicine, The Affiliated Hospital to Changchun University of Traditional Chinese Medicine, Changchun, China*
[6]*Department of Health Research, Evidence, and Impact, McMaster University, Hamilton ON, Canada*

Correspondence should be addressed to Zhiguo Lv; lvzhuolunvip@163.com and Jian Wang; jian-w222@163.com

Received 14 July 2022; Accepted 18 August 2022; Published 3 October 2022

Academic Editor: Xing Liao

Myasthenia gravis (MG) is a rare and refractory autoimmune disease, and Qi Shen Di Huang (QSDH) drug formulary is an in-hospital herbal decoction with proven clinical efficacy in treating MG. Currently, most of the research on the QSDH drug formulary has concentrated on its clinical efficacy, and there is a lack of systematic study on the material basis. The active compounds and their mechanism of action have not been entirely determined. Therefore, this study sought to identify the active compounds in the QSDH drug formulary and analyze the key targets and potential mechanisms. We used ultra-performance liquid chromatography Q Exactive-mass spectrometry (UHPLC-QE-MS) and Traditional Chinese Medicine Systems Pharmacology Database and Analysis Platform (TCMSP) database to identify and screen 85 active ingredients corresponding to 59 potential targets (17 herbs) associated with myasthenia gravis, and further identified AKT1 as the primary core target and the PI3K/AKT signaling pathway as the most substantial enriched pathway. Molecular docking and UPLC-MS analysis identified quercetin, luteolin, wogonin, kaempferol, laccasein, and epigallocatechin gallate are the core compounds of the QSDH drug formulary. In vivo rat studies showed that the QSDH drug formulary reduced Lennon's clinical score and decreased acetylcholine receptor antibody levels in peripheral blood rats with experimental autoimmune myasthenia gravis. In addition, the QSDH drug formulary downregulated P-PI3K/PI3K and P-Akt/Akt protein expression. Collectively, these findings describe the role and potential mechanism of the QSDH drug formulary in the treatment of MG, which exerts potential value by acting on AKT targets and regulating the PI3K/AKT signaling pathway and providing a theoretical reference for QSDH drug formulary application in the clinical treatment of MG.

1. Introduction

Myasthenia gravis (MG) is an autoimmune disease with lesions in the postsynaptic membrane of the neuromuscular junction (NMJ). Pathogenic antibodies include the common acetylcholine receptor antibody (AChR-ab) and the less common muscle-specific receptor tyrosine kinase antibody (Musk-ab), and the low-density lipoprotein receptor-related protein4 antibody (LRP4-ab) blocks the aggregation of acetylcholine receptors (AChR) and disrupts the function of AChR and the signaling between NMJ [1]. Fatigue and fluctuating muscle contraction are the core clinical

symptoms, which may involve skeletal muscles throughout the body, including the eyes, medulla oblongata, respiratory, and extremity muscles. The clinical presentation also varies depending on the autoantibody type and a thymoma's presence [2]. The global prevalence of MG is (150~250)/million, and the prevalence of MG in China is about 0.68/per 100,000, slightly higher in women than in men. The whole body's skeletal muscle can be involved, and the symptoms are "light in the morning and heavy in the evening," aggravated by activity and relieved by rest [3]. The treatment of MG is still mainly composed of cholinesterase inhibitors, glucocorticoids, immunosuppressants, intravenous immunoglobulins, and plasma exchange but traditional Chinese medicine has unique advantages in the treatment of MG, improving clinical efficacy while reducing the dosage and side effects of western drugs and improving the immune balance of the body [4].

The QSDH drug formulary is based on the theory of "Fu Xie" and "Nao Sui" which proposes that the fundamental mechanism of this disease is "a deficiency of spleen and kidney and deficiency of brain marrow," and the treatment should be essential in the basic principle of "JianPi YiQi BuSui" [5]. The metabolic profile of TCM is the key to pharmacological research and clinical application. QSDH drug formulary consists of 17 herbs, including Astragalus, Radix Codonopsis, Atractylodes, Radix et Rhizoma, and others.

The current research on the QSDH drug formulary is mainly focused on clinical efficacy, lacking systematic material basis research, in-depth research on its overall chemical composition, the material basis of pharmacological efficacy, activity, and its active ingredients and specific mechanisms not fully understood. TCM research needs some new approaches and various network technologies have been evolving with the development of the information age. Cyberpharmacology has recently been an emerging discipline based on systems biology, multidirectional pharmacology, and proteomics. It combines pharmacology and information networks to construct molecular biological networks of diseases and drugs by analyzing the whole network to elucidate the pharmacological effects of drugs and pathogenesis of diseases through high-throughput histological data analysis and search of network databases [6]. We can directly identify drug and disease targets through network pharmacology from a large amount of data and understand the mechanisms and pathways [7]. Ultrahigh-pressure liquid chromatography coupled with high-resolution mass spectrometry has the advantages of solid separation and structure identification, which can reasonably predict the structure of unknown compounds. The combination of UHPLC-MS and network pharmacology has dramatically promoted the novel pharmacological research and drug development of TCM. Therefore, in our study (Figure 1), we used UHPLC-QE-MS to identify the active ingredients of the QSDH drug formulary and then screened the potential targets of action of the QSDH drug formulary for treating MG by network pharmacology. Finally, molecular docking techniques and animal experiments to validate the key targets and pathways of the QSDH drug formulary and its essential substances acting on MG.

2. Materials and Methods

2.1. Experimental Reagents and Apparatus. Methanol (CAS 67-56-1, CNW Technologies). Acetonitrile (CAS 75-05-8, CNW Technologies). L-2-chlorophenyl alanine (CAS 103616-89-3, Shanghai Hengbai Biotechnology Co., Ltd.). QSDH drug formulary (Jilin Yatai Yongan Tang Pharmaceutical Co., Ltd., lot 210303T). Prednisone acetate tablets (Shanghai Shang-Pharma Xinyi Pharmaceutical Co., Ltd., Lot No. H31020675). Rat-derived AchRα subunit 97–116 peptide fragment (Suzhou QiangYao Biotechnology Co., Ltd., China). Complete Fuchsin adjuvant (CFA), incomplete Fuchsin adjuvant (IFA), (Sigma-Aldrich, lot F5881, F5506, respectively). Dried powder of *Mycobacterium tuberculosis* H37RA (Difco Bacto, USA, lot 231141). Rat antiacetylcholinesterase receptor antibody (AchR-Ab). Enzyme-linked immunosorbent assay (ELISA) kit (Enzyme Immunity, Inc., Lot No. MM-70967R1). Phosphate buffer solution (PBS), (Thermo Fisher Scientific, Item 003002). Phosphatidylinositol 3-kinase (PI3K) antibody, (Abcam, Inc., Item No. Ab 223792). Phosphatidylinositol 3-kinase (p-PI3K) antibody, (Abcam, ab 182651). Phosphorylated protein kinase B (p-Akt) antibody, (Abcam, item #ab38449). Protein kinase B (Akt) antibody (Cell Signaling Technology, Inc., item #4691). Glyceraldehyde-3-phosphate dehydrogenase (GAPDH) internal reference antibody (Proteintech, item #10494-1-AP). RIPA lysate (strong), protein prestain marker, BCA protein quantification kit (P0013 B, P0068, P0010S, respectively). Ultrahigh-performance liquid chromatograph (Model 1290 UPHLC, Agilent). High-resolution mass spectrometer (model Q Exactive focus). Infinite M200 pro multifunctional enzyme standard (Tecan, Switzerland, model InfiniteM200Pro). Power Pac type electrophoresis instrument (Bio-Rad, USA). Fluor chem E alpha chemiluminescence gel imaging system (Protein Simple, USA). Protein Simple.

2.2. Metabolites Extraction. The samples were crushed with a mixer mill for 30 s at 65 Hz. 100 mg of sample was added to 500 μL of an extracted solution containing 1 μg/mL of internal standard and dissolved in 80% methanol. After the 30s vortex, the samples were homogenized at 45 Hz for 4 min and sonicated for 1 hour in an ice-water bath. After 1 hour in −40°C, the sample was centrifuged at 12000 rpm for 15 min at 4°C. Finally, the supernatant was obtained and put in a fresh 2 mL tube for LC-MS/MS analysis, taking 40 *u*l from each sample and pooling it as QSDH samples.

2.3. LC-MS/MS Conditions. LC-MS/MS analysis was performed on an Agilent ultra-high performance liquid chromatography 1290 UPLC system with a Waters UPLC BEH C18 column (1.7 μm 2.1 $*$ 100 mm). The flow rate was set at 0.4 mL/min, and the sample injection volume was set at 5 μL. The mobile phase consisted of 0.1% formic acid in water (A) and 0.1% in acetonitrile (B). The multistep linear elution gradient program was as follows: 0–3.5 min, 95–85% A. 3.5-min, 85–70%A. 6–6.5, 70–70% A. 6.5–12 min, 70–30% A. 12–12.5 min, 30–30% A. 12.5–18 min, 30–0% A. 18–25 min, 0–0% A. 25–26 min, 0–95% A. 26–30 min, 95–95% A.

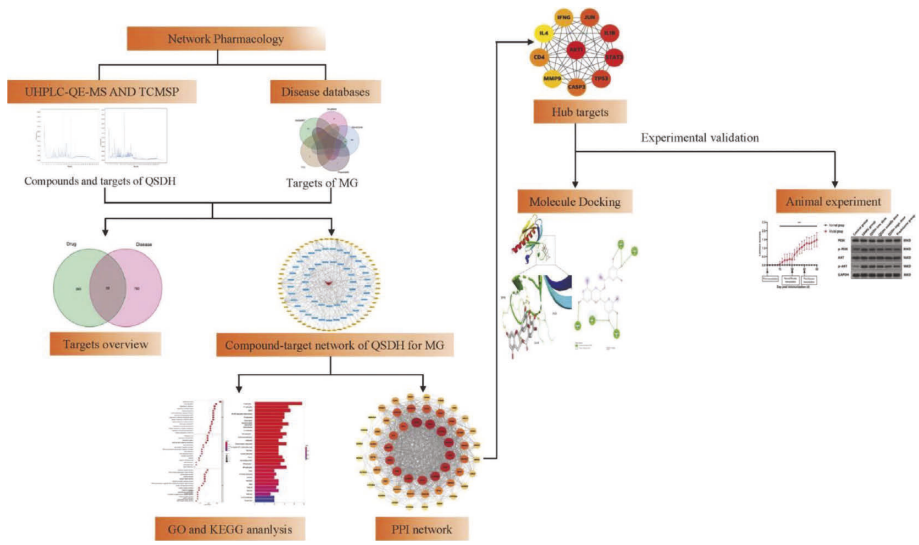


Figure 1: Outline of the study. Exploring the potential mechanism of Qi-Shen-Di-Huang drug formulary for myasthenia gravis (MG) based on UHPLC-QE-MS network pharmacology and molecular docking techniques.

A Q Exactive focus mass spectrometer coupled with an Xcalibur software was employed to obtain the MS and MS/MS data based on the IDA acquisition mode. During each acquisition cycle, the mass range was from 100 to 1500, the top three of every cycle were screened, and the corresponding MS/MS data were further acquired. Sheath gas flow rate: 45 Arb, Aux gas flow rate: 15 Arb, capillary temperature: 400°C, full ms resolution: 70000, MS/MS resolution: 17500, collision energy: 15/30/45 in NCE mode, spray voltage: 4.0 kV (positive) or −3.6 kV (negative).

2.4. QSDH Drug Formulary Screening of Active Ingredients and Targets of Action. According to the principles of toxic pharmacokinetics (ADME), the TCMSP [8] (https://tcmspw.com/tcmspsearch.php) database was used according to the conditions of oral bioavailability (OB) ≥ 30 and drug-like likeness (DL) ≥ 0.18. The active ingredients of QSDH drug formulary detected by UHPLC-QE-MS were screened. The targets corresponding to the chemical composition of the active ingredients were retrieved through the TCMSP database, and the target names were transformed to gene abbreviations through the UniProt (https://www.uniprot.org/) database [9].

2.5. Screening of Targets Related to MG. Using the keyword "myasthenia gravis," enter the Genecards database (https://www.genecards.org/, updated on June 2, 2021) [10]. DrugBank database (https://www.drugbank.ca/, updated on May 3, 2021) [11]. DisGeNET database (https://www.disgenet.org/, updated on August 16, 2021) [12]. TTD database (http://db.idrblab.net/ttd/updated on June 1, 2021) [13]. PharmGKB database (https://www.pharmgkb.org/, updated on October 4, 2021) [14]. Take the intersection and remove duplicate targets to obtain disease targets, input them into the UniProt database to get the corresponding gene names, and finally get all myasthenia gravis disease-related targets.

2.6. Construction Network of the "TCM Active Ingredients - Intersection Target - Disease.". In order to determine the MG target of the QSDH drug formulary, the intersection target of the MG target and the corresponding target of the QSDH drug formulary active compound were obtained by Perl language analysis, and a Wayne diagram was drawn. The data of the intersection targets of the active compounds and their interactions were imported into Cytoscape3.8.2 software to construct a network of "TCM active components-intersectiontarget-disease," and topological analysis was conducted to explore the pharmacological mechanism of the active components of QSDH prescription.

2.7. QSDH Drug Formulary Predictive Target Protein Interaction (PPI) Network Construction and Analysis. After importing the intersection targets obtained above into the STRING database (https://www.string-db.org) [15], multiple proteins were selected to constrain *Homo sapiens*, hide-free nodes, and retain default values for other parameters to obtain the intersection target interaction network. At the same time, the data were set with medium confidence >0.4 to ensure the reliability of the analysis.

2.8. GO and KEGG Enrichment Analysis. The intersection target was imported into the Hiplot database (https://hiplot.com.cn/, updated on May 4, 2021), and the species was *Homo sapiens*. The threshold $P < 0.01$ and the Gene Ontology, GO enrichment analysis, and KEGG (Kyoto Encyclopedia of Genes and Genomes) pathway enrichment analysis were set. R 4.0.3 software was used to draw bubble charts and bar charts from obtaining the biological process (BP), molecular function (MF), cellular components (CC), and main signal pathways involved in the treatment of MG by QSDH drug formulary.

2.9. Molecular Docking Verification of Key Active Ingredients and Core Targets. Based on the above research results, the network analyzer plug-in is used to analyze the network

topology structure. Active components with the most significant degree value and the largest number of targets are selected as ligands, and core key genes are screened as receptors by the Cytohubba plug-in. The PubChem database (https://pubchem.ncbi.nlm.nih.gov/) downloads the 3D structure of active ingredients in the PDB database (http://www1.rcsb.org/) to obtain the target protein 3D structure, AutoDockTools1.5.6, AutoDock Vina and PyMOL software were used for molecular structure processing and molecular docking.

3. Animal Validation

3.1. Experimental Animal Selection. Sixty female SPF Lewis rats, weighing 160~180 g, aged 6~8 weeks, were provided by Beijing Viton Lever Experimental Animal Technology Co., LTD., certificate No. SCXK (Beijing) 2016–0006. They were fed in the SPF barrier laboratory of the Animal Experiment Center of Changchun University of Chinese Medicine with free drinking water, indoor keep $(21 \pm 2)^{\circ}$C, relative humidity 50%–60%, and day and night alternating light and dark for 12 h. The experimental procedure was reviewed and approved by the Experimental Animal Ethics Committee of the Changchun University of Chinese Medicine (NO.2021228).

3.2. Rat Model Preparation and Grouping. Eight of 60 Lewis female rats were chosen randomly as the adjuvant control group, and the remaining 52 were referred to Baggi et al [16]. The EAMG rat model was established by the active immunization method. Each rat was injected with 200 μL of mixed emulsion, and Rα97-116 peptide dry powder and *Mycobacterium tuberculosis* H37RA powder were added to PBS. Each 200μL of PBS contained 50 μg of Rα97-116 dry powder and 1 mg of H37RA dry powder, and the peptide and dry powder were dissolved by ultrasonication on an ice box to make the peptide and dry powder fully fused in PBS until the solution was cloudy. The dissolved liquid is extracted into a 1 mL syringe. Another syringe extracts 200 μL of CFA, and a medical hose connects the two syringes to mix the PBS and CFA of the meaning peptide segment and bacteriophage powder to prevent protein denaturation, the whole process is carried out on the ice, repeatedly pumping two syringes back and forth until milky white liquid appears and the emulsion does not dissolve and does not spread, keeping the spherical shape floating on the water surface for a long time, then the mold-making drug is drug formularyted successfully. The equipped mold-making antigen emulsion was injected subcutaneously at five sites: the tail's base, both hind limbs' foot pads, and both sides of the back. The adjuvant control group was injected with a mixture of CFA and PBS in equal amounts, and the day of the first immunization was recorded as day 0. One booster immunization was given on day 30 and day 45, with the same preparation, injection volume, injection sites, and injection method as the first immunization, except that CFA was replaced with IFA. The adjuvant control group was injected with a mixture of IFA and PBS, with the same injection volume, injection sites, and injection method as the first immunization. The dose, injection site, and injection method were the same as the first immunization. The model was evaluated on day 60, and the change in body mass assessed the success, Lennon's clinical symptom grading method was used [17], and the difference in the level of AChR-Ab in the peripheral serum of the tail vein of rats. Furthermore, Lewis rats meeting the EAMG criteria were divided randomly into eight rats in the model group, the QSDH drug formulary low-dose group (4.8 g/kg/d), the QSDH drug formulary medium-dose group (9.6 g/kg/d), the QSDH drug formulary high-dose group (19.2 g/kg/d), and the prednisone acetate tablet group (5.4 mg/kg/d).

3.3. Western Blot. The removed rat spleen tissue was cut and put into RIPA lysis solution, lysed on ice for 30 min at 12000 r/min, centrifuged at 4°C for 10 min, the supernatant was taken, the protein concentration was measured by BCA method, the sample protein concentration was adjusted to the same, the protein samples were separated by 10% sodium dodecyl sulfate-polyacrylamide gel electrophoresis (SDS-PAGE), and then transferred to polyvinylidene fluoride (PVDF) membranes. After the end of the transfer, PI3K, p-PI3K, Akt, p-AKT primary antibodies (1 : 500), and secondary antibodies were incubated with 5% skimmed milk for 1 hour at room temperature. The transferred protein strips were developed by exposure using a chemiluminescence imaging system, and the images were acquired by quantitative optical density analysis.

3.4. Statistical Analysis. GraphPad Prism 5.0 software was used for statistical analysis, and measures were expressed as mean plus or minus standard deviation ($\overline{x} \pm s$) using one-way ANOVA. $P < 0.05$ indicates that the difference is statistically significant.

4. Results

4.1. UPLC-QE-MS Detection for QSDH Drug Formulary. A total of 930 compounds in 60 categories, including quinones, terpenoids, flavonoids, and phenols, were detected by UPLC-QE-MS. The corresponding pharmacokinetic parameters (ADME) were searched and downloaded from the TCMSP website. According to OB $\geq$ 30% and DL $\geq$ 0.18 as screening conditions, 85 active compounds were obtained, as shown in Table 1.

4.2. Screening for Targets Related to MG. A total of 822 targets related to myasthenia gravis were obtained from the GeneCards, Drugbank, DisGeNET, TTD, and PharmGKB databases using the keyword "myasthenia gravis," as shown in Figure 2.

4.3. Construction of the "TCM Active Ingredients - Intersection Target - Disease Network". Ased on Perl language analysis of 85 targets of active components of QSDH prescription and corresponding targets of MG disease, 59 intersection target proteins were obtained, considered as targets of QSDH drug

Table 1: Active ingredients of QSDH drug formulary.

Mol ID	Molecule Name	OB (%)	DL
MOL000471	Aloeemodin	83.38	0.24
MOL011578	Bilobalide	84.42	0.36
MOL000354	Isorhamnetin	49.6	0.31
MOL000417	Calycosin	47.75	0.24
MOL000471	Emodin	83.38	0.24
MOL002928	Oroxylin a	41.37	0.23
MOL005573	Genkwanin	37.13	0.24
MOL002714	Baicalein	33.52	0.21
MOL001689	acacetin	34.97	0.24
MOL000422	Kaempferol	41.88	0.24
MOL005842	Pectolinarigenin	41.17	0.3
MOL001942	Isoimperatorin	45.46	0.23
MOL003626	Ostruthin	30.65	0.23
MOL000006	Luteolin	36.16	0.25
MOL002341	Hesperetin	70.31	0.27
MOL000392	Formononetine	69.67	0.21
MOL003648	Inermin	65.83	0.54
MOL001297	Eicosenoic acid	30.7	0.2
MOL002881	Flavone base + 3O, 1MeO	31.14	0.27
MOL000098	Quercetin	46.43	0.28
MOL004800	Pelargonidin-3-O-glucoside	38.72	0.71
MOL004903	Liquiritin	65.69	0.74
MOL007274	Cirsimaritin	30.35	0.3
MOL009047	Eudesmin	33.29	0.62
MOL012101	5-hydroxy-6,7-dimethoxyflavone	34.04	0.26
MOL004373	Icaritin	45.41	0.44
MOL005320	Arachidonic acid	45.57	0.2
MOL005190	Eriodictyol	71.79	0.24
MOL008845	Deoxycholic acid	40.72	0.68
MOL004792	Nodakenin	57.12	0.69
MOL004425	Icariin	41.58	0.61
MOL003217	Isoxanthohumol	56.81	0.39
MOL002268	Rhein	47.07	0.28
MOL002776	Baicalin	40.12	0.75
MOL009160	Loureirin A	40.43	0.19
MOL005849	Didymin	38.55	0.24
MOL003378	Demethylwedelolactone	33.94	0.43
MOL004564	Kaempferid	73.41	0.27
MOL002823	Herbacetin	36.07	0.27
MOL004575	Astilbin	36.46	0.74
MOL003908	Strophanthidin	99.94	0.78
MOL004908	Glabridin	53.25	0.47
MOL003759	Iristectorigenin B	63.36	0.34
MOL000492	Cianidanol	54.83	0.24
MOL008698	Dihydrocapsaicin	47.07	0.19
MOL000492	Deoxynivalenol	54.83	0.24
MOL005828	Nobiletin	61.67	0.52
MOL001558	Sesamin	56.55	0.83
MOL002927	Skullcapflavone II	69.51	0.44
MOL004561	Sudan III	84.07	0.59
MOL000173	Wogonin	30.68	0.23
MOL000392	Formononetin	69.67	0.21
MOL010485	Eicosapentaenoic acid	45.66	0.21
MOL001714	5,9-dimethyltetracyclo-dicarboxylic acid	59.94	0.86
MOL000785	Palmatine	64.6	0.65
MOL003950	1-methyl-2-[(6Z)-6-undecen-1-yl]-4(1H)-quinolinone	48.48	0.27
MOL001439	Arachidonic acid (not validated)	45.57	0.2
MOL005658	Periplogenin	36.61	0.74
MOL004759	Napelline	34.48	0.72
MOL002397	Karakoline	51.73	0.73

Table 1: Continued.

Mol ID	Molecule Name	OB (%)	DL
MOL010908	Lindenenol	52.05	0.18
MOL001594	Pisatin	88.05	0.64
MOL007179	Linolenic acid ethyl ester	46.1	0.2
MOL010861	Vitamin D3	45.66	0.48
MOL010828	Cynaropicrin	67.5	0.38
MOL007077	Sclareol	43.67	0.21
MOL008465	Hirsutine	32.75	0.64
MOL001792	Liquiritigenin	32.76	0.18
MOL006821	Epigallocatechin-3-gallate	55.09	0.77
MOL004058	Khellin	33.19	0.19
MOL008400	Glycitein	50.48	0.24
MOL003964	1-methyl-2-undecylquinolin-4-one	47.59	0.27
MOL004827	Semilicoisoflavone B	48.78	0.55
MOL004195	Corydaline	65.84	0.68
MOL013179	Fisetin	52.6	0.24
MOL013276	Poncirin	36.55	0.74
MOL005229	Artemetin	49.55	0.48
MOL005922	Acanthoside B	43.35	0.77
MOL011616	Fortunellin	35.65	0.74
MOL000546	Spirost-5-en-3-ol, (3beta, 25R)-	80.88	0.81
MOL004910	Glabranin	52.9	0.31
MOL004912	Glabrone	52.51	0.5
MOL004949	Isolicoflavonol	45.17	0.42
MOL000830	Alisol B	34.47	0.82
MOL007088	Cryptotanshinone	52.34	0.4

formulary for MG treatment, as shown in Figure 3. Through Cytoscape3.8.2, the "TCM active component-intersectiontarget-disease" network is constructed (Figure 4). The network has 112 nodes and 320 edges. The degree value represents the number of edges connected to this point. The larger the degree value is, the more extensive the effect of this node on other nodes is. The red triangle represents MG disease, the blue rectangle represents active chemical components of the QSDH drug formulary, and the orange ellipse represents the intersection target of active components of herbs and MG. Further topological analysis (based on degree and betweenness centrality of network nodes) shows that the key chemical components in this network are quercetin (MOL000098) and epigallocatechin-3-gallate (MOL006821), luteolin (MOL000006), wogonin (MOL000173), kaempferol (MOL000422), and fisetin (MOL013179). This disease-TCM active ingredient-target network is characterized by complex components, multiple targets, and close interaction between components and targets, forming a complex network for the QSDH drug formulary treatment of MG.

4.4. Construction and Analysis of a PPI Network of Predictive Targets for MG Treatment with the QSDH Drug Formulary. To better explain the mechanisms by which the QSDH drug formulary acts concerning MG, we further evaluated its 59 intersecting targets to analyze their relationship. The 59 intersecting targets were imported into the STRING database to obtain protein interaction information, which was visualized using Cytoscape 3.8.2 software (Figure 5). There are 58 nodes and 1172 edges in the intersection target

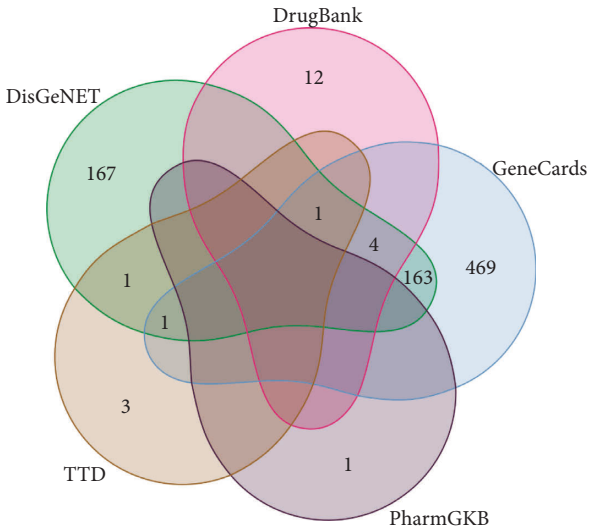


Figure 2: All targets related to MG in various databases.

network. The nodes represent the targets of the active ingredient of the QSDH drug formulary for the treatment of MG, and the larger the mutuality value between the targets, the darker the color of the nodes, indicating the more critical the nodes are. The CytoNCA plug-in was used further to perform core screening by degree centrality (DC), closeness centrality (CC), and betweenness centrality (BC) and to construct a protein interaction network by degree value, see Figure 6, to obtain the final core targets: AKT1, STAT3, IL1B, and TP53. They suggested that the QSDH drug formulary may exert the therapeutic effect of MG by regulating these proteins.

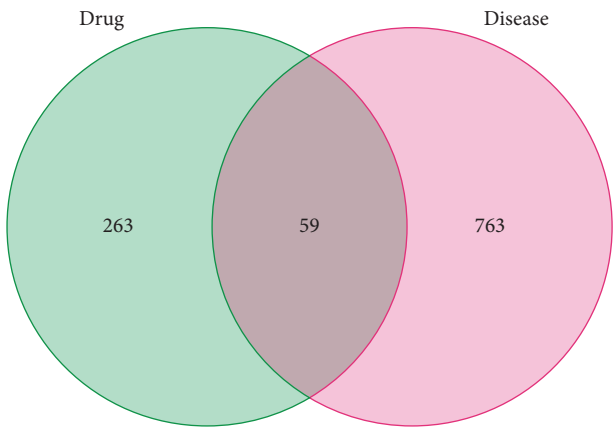


Figure 3: Venn diagram of common targets of TCM active ingredients and diseases.

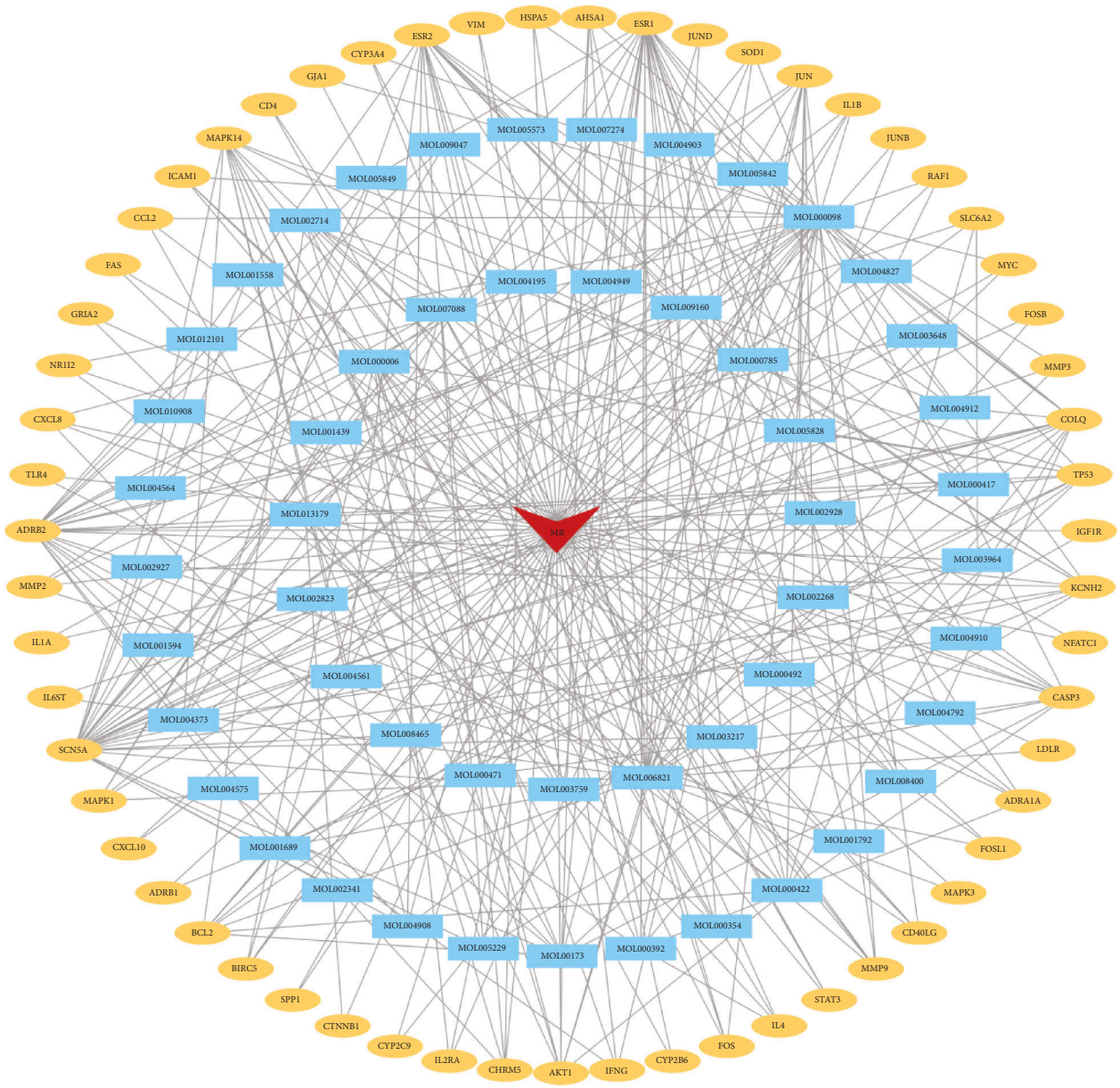


Figure 4: QSDH drug formulary active ingredients-intersectiontarget-disease network. (Red triangles represent diseases, blue rectangles represent active ingredients, and yellow ellipses represent intersection targets).

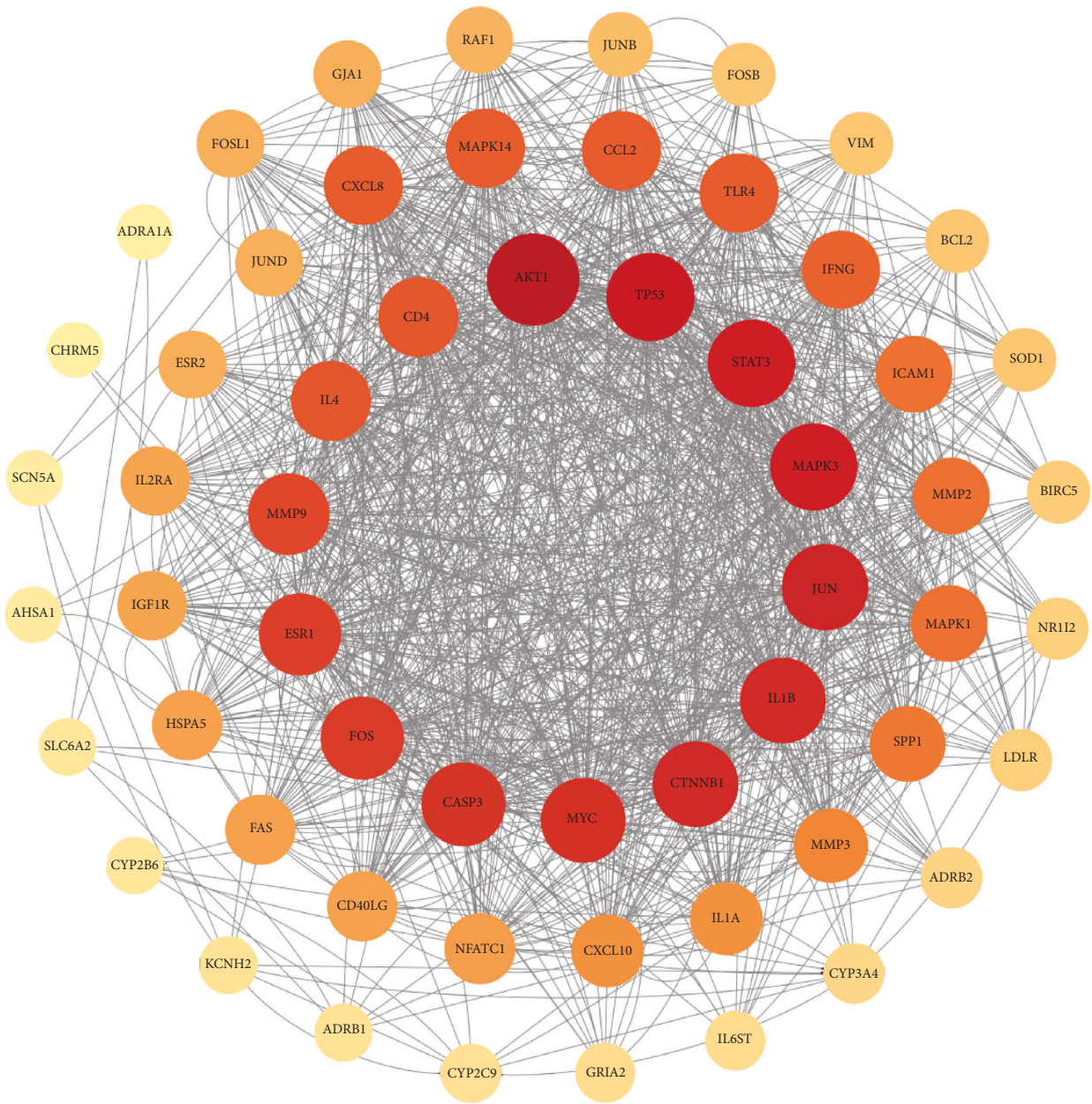


Figure 5: Potential targets of action of QSDH drug formulary for MG treatment PPI network. (Lighter to darker colors and smaller to larger circles represent larger target protein values, representing more important core targets).

4.5. GO Enrichment Analysis. The 59 intersecting targets were entered into the Hiplot online database, set p-value<0.01 and q-value<0.05, The top 10 entries obtained from GO enrichment analysis were performed, and bubble plotted using R4.0.3 software. A total of 1959 items were significantly enriched ($P < 0.05$), of which 1834 were enriched in biological process (BP), 35 in cellular component (CC), and 90 in molecular function (MF), Figure 7. It is mainly related to T cell activation, nutrition level reaction, response to lipopolysaccharide, chemical stress reaction, physical stimulation, oxidative stress, cytokines receptors, cytokine activity, G protein-coupled receptor of neurotransmitter receptor activity, passing the gated ion channel activity involved in the regulation of the postsynaptic membrane potential, and neurotransmitter receptors postsynaptic activity.

4.6. KEGG Signaling Pathway Enrichment Analysis. KEGG signaling pathway enrichment analysis of 59 intersecting targets was performed by Hiplot online database, and the results showed that they were mainly enriched in 157 signaling pathways ($P < 0.05$), and the top 30 pathways were bar charted by R 4.0.3 software (Figure 8). The signaling pathways closely related to MG mainly included the IL-17 signaling pathway, the HIF-1 signaling pathway, the PI3K/AKT signaling pathway, and

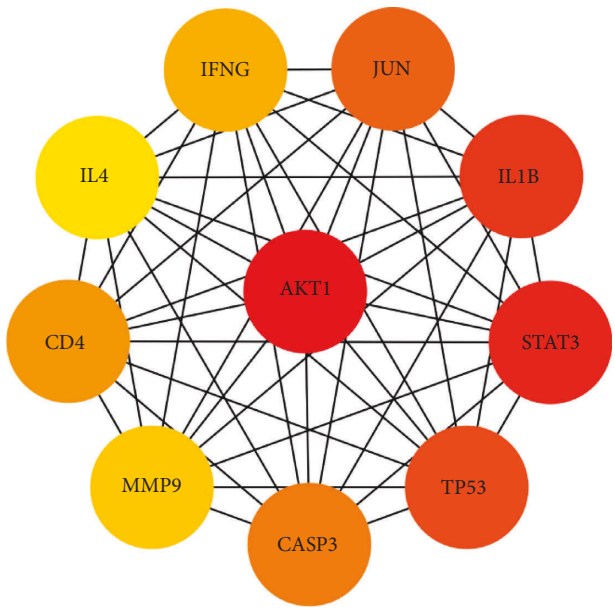


Figure 6: Potential core targets of QSDH drug formulary for MG. (Red represents the most core targets).

the mTOR signaling pathway. The above results suggest that QSDH can be used to treat myasthenia gravis by regulating multiple biological processes and the coordinated action of multiple signaling pathways.

4.7. Molecular Docking Verification. Six central herbal core ingredients in the QSDH drug formulary were quercetin, epigallocatechin-3-gallate, luteolin, wogonin, kaempferol, fisetin, and epigallocatechin-3-gallate, respectively, according to the "active ingredient-intersectiontarget-disease" network analysis. Their binding ability was predicted with AKT1, the top core target screened by the CytoNCA plug-in. See Figure 9 for the chemical structure of the core active components of herbal medicine. Binding energy < −4.25 kcal/mol indicates some binding activity between the small ligand molecule and the receptor protein, binding energy < −5.0 kcal/mol indicates good binding activity between the two, and binding energy < −7.0 kcal/mol indicates that the ligand has binding activity with the receptor binding solid activity [18]. It was suggested that the more stable the binding conformation of the small molecule receptor to the ligand, the lower its energy and the greater the interaction produced [19]. According to the molecular docking binding energy scores (Table 2), it is clear that the binding energy of quercetin, luteolin, wogonin, kaempferol, fisetin, and the above five compounds with the critical core action target AKT1 are all less than −5.0 kcal/mol, indicating an excellent bonding activity between them. The binding energy of AKT1 to epigallocatechin-3-gallate was less than /−7.0 kcal/mol, indicating a solid binding activity between the two. Molecular docking visualization was performed separately using Pymol 2.4.2 software (Figure 10). Epigallocatechin-3-gallate formed hydrogen bonds with five amino acids, ASP-46, GLU-40, LYS-39, ALA-50, and GLN-47, near the active site to bind to AKT1.

4.8. Evaluation of EAMG Rat Models

4.8.1. Lennon Clinical Score. As depicted in Figure 11, during the first 15d after the first immunization, there was still no significant change in Lennon's clinical symptom score. However, the EAMG-modeled rats began to show a gradual decrease in grip strength and activity. From the 15th day after the first immunization, the rats in the model group began to show significantly weaker bilateral forelimb grasping power, reduced antagonism, less flexible body than the adjuvant control group, and preferred to curl up in the corner of the cage. After the second booster immunization (the 30th day after the first immunization), the EAMG symptoms gradually increased ($P < 0.001$).

4.8.2. Changes in Serum AChR-Ab of EAMG Model Rats. On day 60 after the first immunization, the serum AChR-Ab levels of rats were analyzed by ELISA. As shown in Figure 12, the serum AChR-Ab levels of rats in the EAMG modeling group were significantly higher than those in the adjuvant control group ($P < 0.01$).

4.9. Effect of QSDH Drug Formulary on EAMG Rats

4.9.1. Effect of QSDH Drug Formulary on Lennon's Clinical Symptom Score in EAMG Rats. The EAMG model was successfully established and then randomized to group administration of the intervention, with Lennon clinical score tests performed every seven days during treatment. During the administration treatment, the clinical symptoms of rats in the EAMG model group did not improve as the experiment progressed. Even individual rats showed signs of paralysis, convulsions, loose skin, jaws clinging to the bottom of the cage, and inability to eat, and the Lennon clinical score was significantly different from that of the adjuvant control rats ($P < 0.001$), as shown in Figure 13. Indicates that the EAMG model was established stably and did not heal during the administration period. As the experiment continued, the clinical symptoms of the rats in the high, medium, and low doses of QSDH drug formulary and prednisone acetate administration groups were gradually relieved, and the Lennon clinical score tended to decrease and was significantly different from that of the EAMG model group ($P < 0.001$).

4.9.2. Effect of QSDH Drug Formulary on Serum AChR-Ab Levels in EAMG Rats. At the end of the dosing cycle, the rats were anesthetized with gas anesthesia apparatus, taken through the abdominal aorta, and the serum was separated by centrifugation. The ELIAS method detected the peripheral serum AChR-Ab content of the rats in each experiment group. The serum AChR-Ab levels of rats in the EAMG model group were significantly higher than those in the adjuvant control group ($P < 0.01$). After the intervention of each dosing group, the serum AChR-Ab levels of rats in the QSDH drug formulary low, medium, and high-dose groups and the prednisone acetate tablet group were significantly reduced compared with those in the EAMG model group ($P < 0.05$, $P < 0.01$, Figure 14).

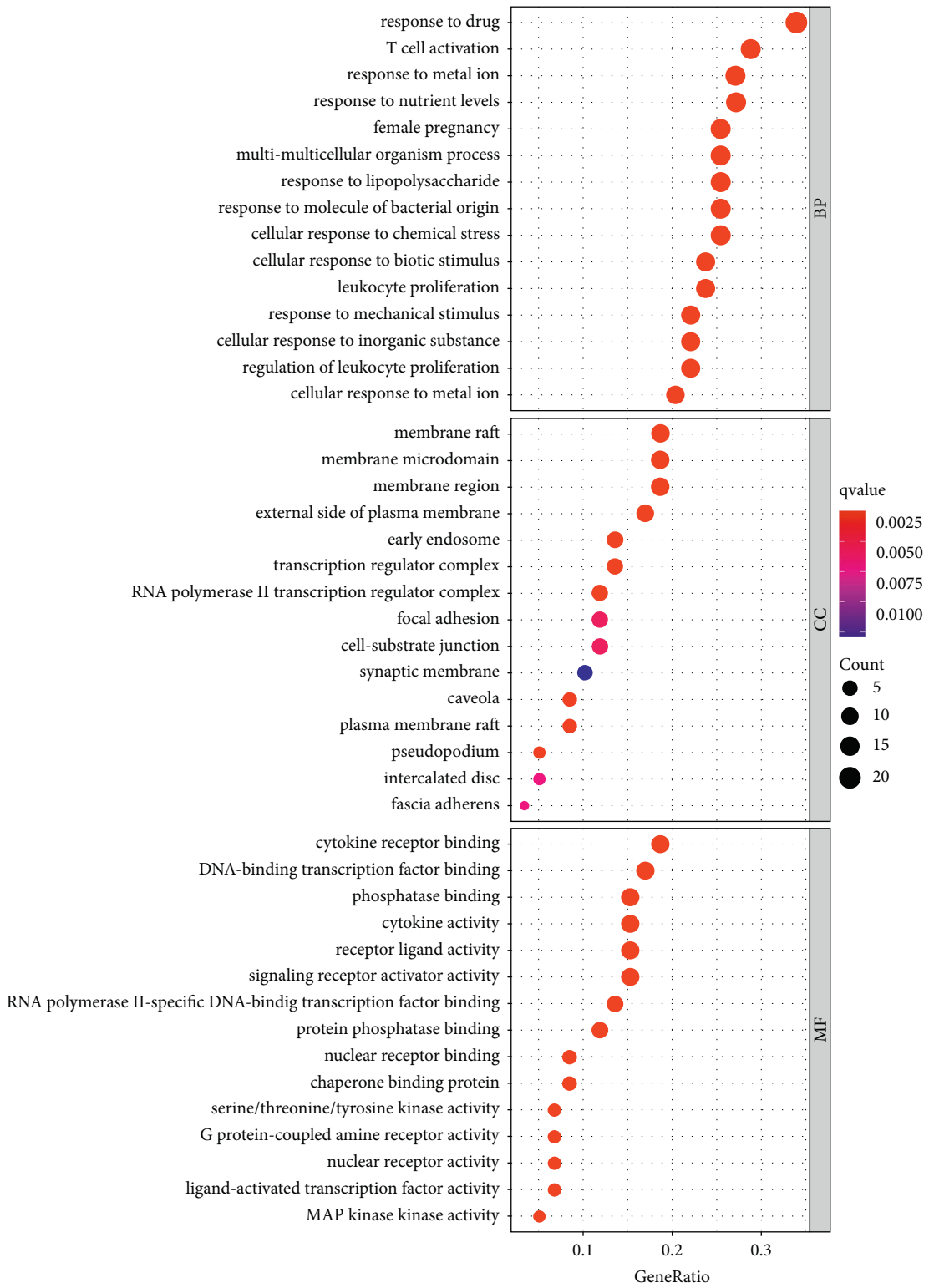


Figure 7: GO enrichment analysis of potential targets of QSDH drug formulary. (The color changes from blue to red, representing smaller P(q.value) values and higher enrichment, and the larger the number of dots, the higher the number of genes, representing higher enrichment).

4.9.3. QSDH can Inhibit the PI3K/AKT Signaling Pathway. Based on the core targets screened by network pharmacology and the results of the KEGG enrichment analysis, we further verified whether the QSDH drug formulary for MG treatment interferes with the PI3K/AKT signaling pathway. Western blot was used to detect the expression of the PI3K/

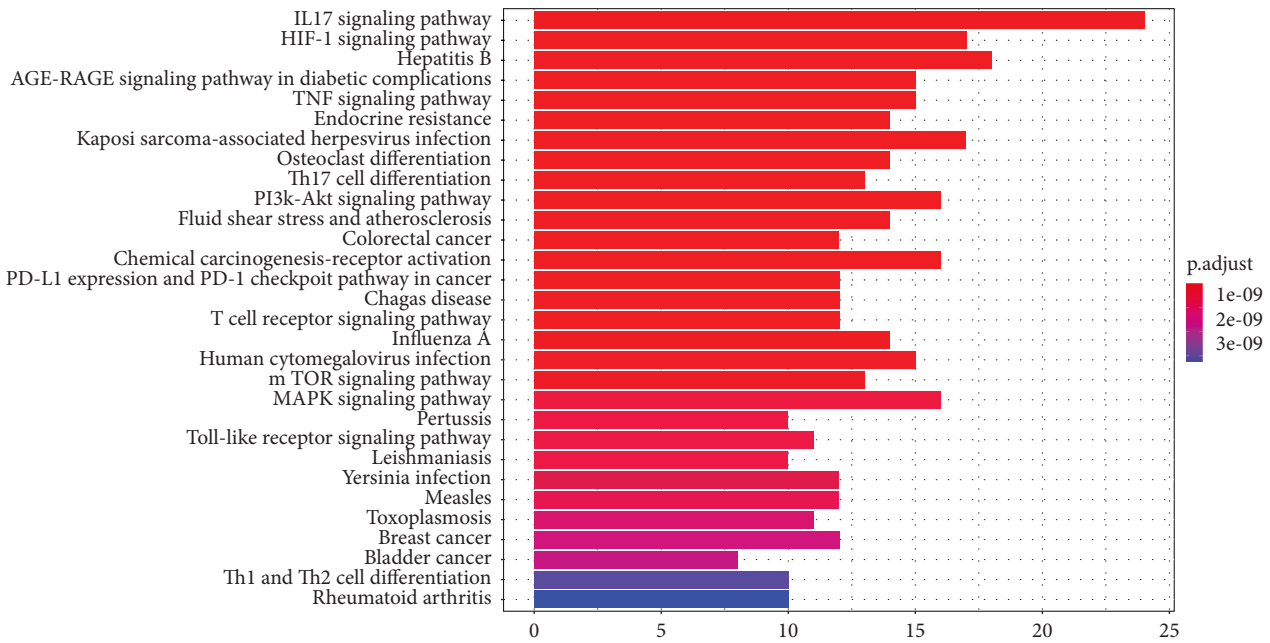


Figure 8: Enrichment analysis of KEGG pathways for potential targets of QSDH drug formulary. (The color changes from blue to red, which means the P–value is getting smaller, and the enrichment level is getting higher. The higher the number of genes, the longer the column shape, and the higher the enrichment).

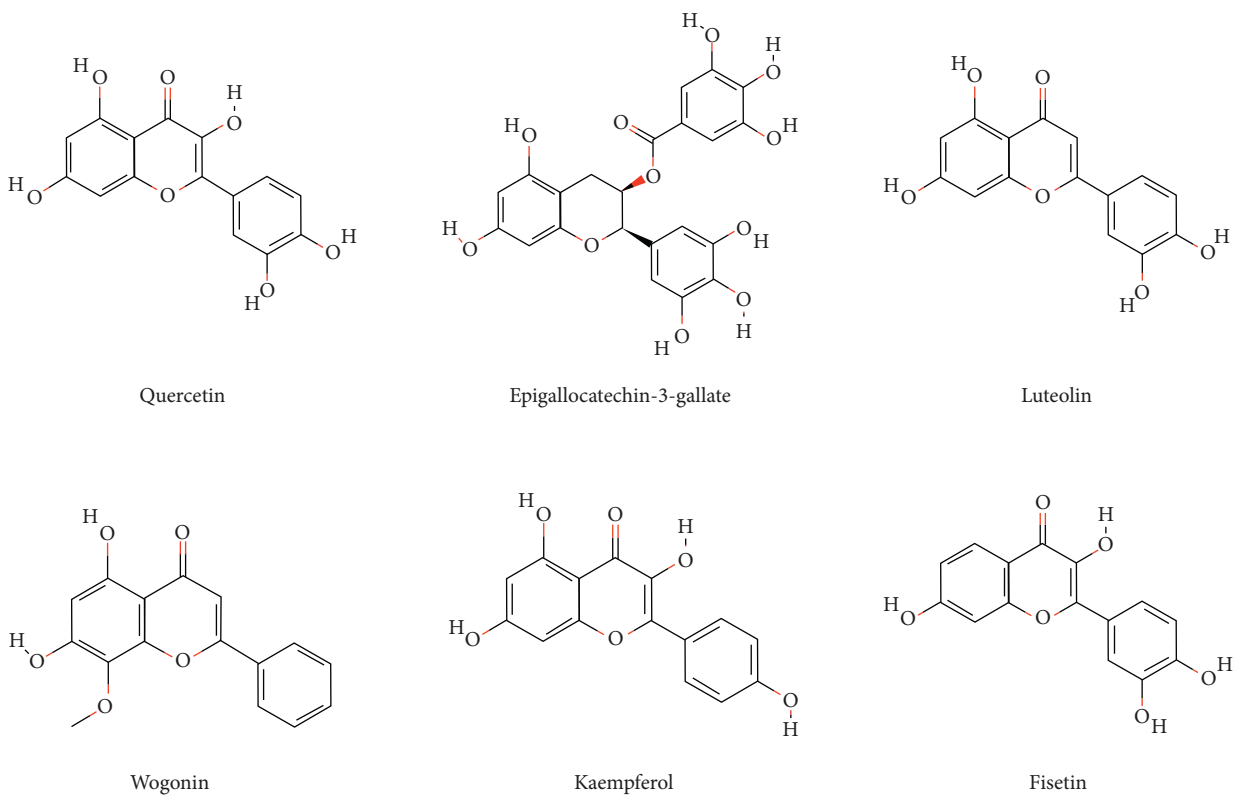


Figure 9: Structural drug formulary of the main active ingredients of QSDH drug formulary.

AKT pathway-related proteins in the spleen tissues of each group of rats. Detection of protein expression of PI3K, phosphorylated PI3K (p-PI3K), AKT, and phosphorylated AKT (p-AKT). As Figures 15(a)–15(b) show, the expression of pathway-related proteins p-PI3K and p-AKT in the spleen tissue of rats in the EAMG model group was significantly higher ($P < 0.01$) than in the adjuvant control group. The pathway-related proteins p-PI3K and p-AKT decreased to

Table 2: Molecular docking score.

Core Targets	PDB ID	Compound Name	Binding energy
AKT1	P31749	Quercetin	−6
		Luteolin	−6.3
		Wogonin	−6
		Kaempferol	−5.9
		Fisetin	−6
		Epigallocatechin-3-gallate	−7.6

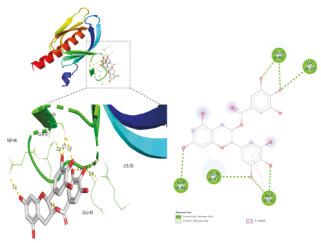


Figure 10: Docking conformation of AKT1 with epigallocatechin-3-gallate.

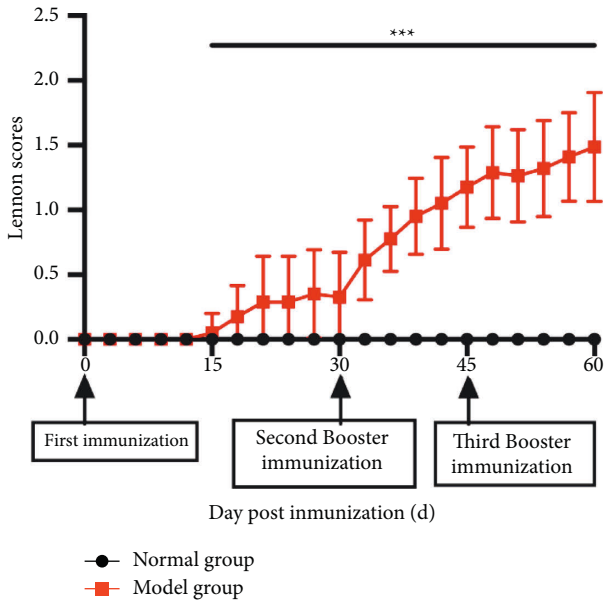


Figure 11: Lennon's clinical score changes in the EAMG model and adjuvant control group (***$P < 0.001$).

different degrees after each dose group of QSDH drug formulary low, medium, and high and positive drug treatment ($P < 0.05$, $P < 0.01$).

5. Discussion

Network pharmacology is based on systems biology theory, integrates pharmacology, high-throughput sequencing, genomics, and other technologies, emphasizing the multichannel regulation of signaling pathways [20]. Our study explores the mechanism of action and potential therapeutic targets of the QSDH drug formulary for MG from the perspective of network pharmacology. Using ultra-

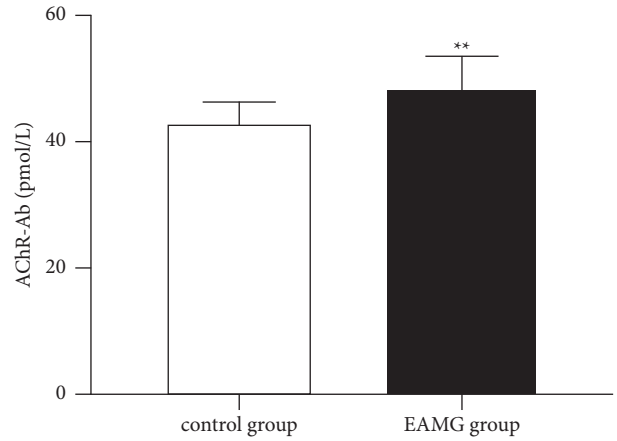


Figure 12: Comparison of serum AChR-Ab levels in EAMG-modeled rats and adjuvant control rats (**$P < 0.01$).

performance liquid chromatography Q Exactive-mass spectrometry, network pharmacology, and molecular docking technology, 930 chemical components were analyzed from the QSDH drug formulary. The "active component-intersectiontarget-disease" network of QSDH drug formulary treatment for MG was constructed. Eighty-five active components and 322 potential targets of quercetin, luteolin, wogonin, kaempferol, fisetin, and epigallocatechin-3-gallate were screened. AKT1, STAT3, IL1B, and TP53 were selected as core targets through the PPI network, and AKT1 was the first and most core target. GO, and KEGG enrichment analysis further explored the biological pathways involved in the expression of potential target proteins, which were enriched in the IL-17 signaling pathway, the HIF-1 signaling pathway, the PI3K-Akt signaling pathway, and the mTOR signaling pathway. PI3K-AKT was the most abundant protein enrichment signaling pathway. The binding activity of the core active ingredient and core target protein in the QSDH drug formulary were verified. Finally, the rat experiment verified that AKT1 might be the main target of QSDH prescription in the treatment of MG, and QSDH prescription can play a role in the treatment of MG by inhibiting the PI3K/AKT signaling pathway.

The active ingredient-intersection target network showed that quercetin, epigallocatechin-3-gallate, luteolin, wogonin, kaempferol, and fisetin matched more targets, which may be the core compounds and essential material basis for the QSDH drug formulary to exert its therapeutic effect on MG. Studies have shown that epigallocatechin-3-gallate, quercetin, luteolin, wogonin, kaempferol, and fisetin have anti-inflammatory, antioxidant, immunomodulatory, and neuroprotective effects [21–26]. Epigallocatechin-3-gallate promotes dendritic growth and synaptogenesis through selective inhibition of the AKT/mTOR signaling pathway, inhibits acetylcholinesterase activity, and effectively ameliorates neurological damage in neurodegenerative diseases. In addition, it can regulate immune and inflammatory responses by influencing various aspects of immune cell function in innate and adaptive immunity. It

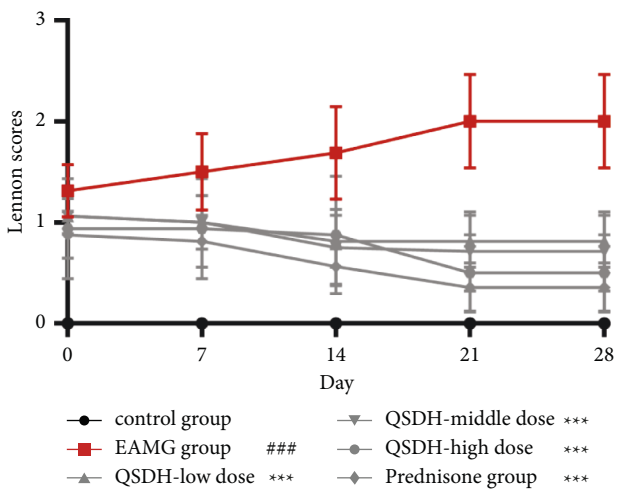


Figure 13: Effect of QSDH drug formulary on Lennon's clinical score in EAMG rats. (Compared with the adjuvant control group $^{\#\#\#\#}P < 0.001$; compared with the EAMG model group $^{***}P < 0.001$).

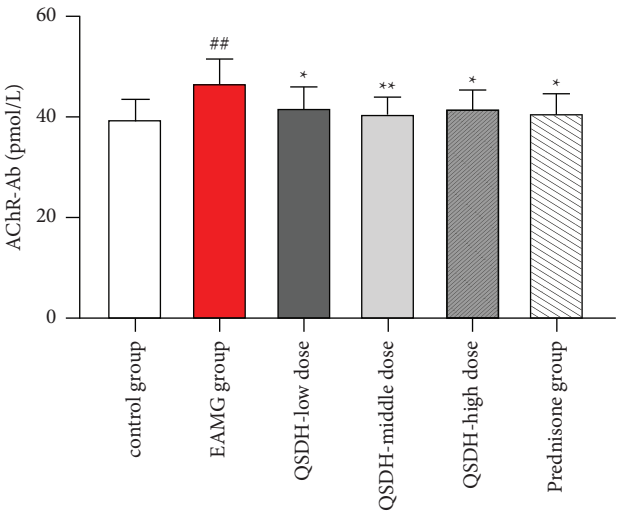


Figure: 14: Effect of QSDH drug formulary on serum AChR-Ab levels in EAMG rats. (Comparison with the adjuvant control group: $^{\#\#}P < 0.01$; comparison with the EAMG model group: $^{*}P < 0.05$, $^{**}P < 0.01$).

can affect the differentiation of initial CD4+T cells to different effector subpopulations and thus treats autoimmune inflammatory diseases [27]. Quercetin has a wide range of pharmacological effects, including anti-inflammatory, antiviral, antibacterial, and immunomodulatory effects, and can significantly upregulate IFN-γ in Th1 and downregulate IL-4 expression in Th2, thereby regulating immune function [28]. Luteolin has antitumor, anti-inflammatory, and cerebrovascular protective effects, and its related mechanism involves the regulation of PI3K/AKT, MAPK, and other signaling pathways as well as the expression of related cytokines and kinases [29]. An experimental study found that kaempferol acts the same way as the immunosuppressant cyclosporine A, mediating calcium-regulated neural phosphatase activity from inhibiting immune cell differentiation [30]. Fisetin reduces IL-17 production by CD4+T lymphocytes through inhibition of the PI3K/AKT/mTOR pathway and decreases Th1/Th17 pro-inflammatory cytokine secretion in human peripheral blood mononuclear cells [31]. The above can indicate that the active ingredients in the QSDH drug formulary can regulate the subpopulation differentiation of CD4+T cells, alter the secretion of related cytokines between Th1/Th2/Th17, and exert anti-inflammatory, immunomodulatory, and neurological function protection effects.

The core targets obtained from screening intersecting targets in the PPI network by Cytohubba and CytoNCA plug-ins, of which the top three occupied by AKT1, STAT3, and TP53, were predicted to be the possible main targets of action of the QSDH drug formulary for the treatment of MG. Studies have reported that AKT1 enhances the differentiation of CD8+T cells, improves the proliferation of CD8+T cells, and inhibits the over-activation of DCs, thus regulating the immune response [32]. The study showed increased expression of Th1 and Th17 cells and their associated cytokines IL-1, IL-6, IL-17, IFN-γ, and TNF-α in the peripheral serum of MG patients [33]. The expression of IL-6 can be regulated by inhibiting the AKT/mTOR signaling pathway to improve the symptoms of muscle fatigue weakness in MG patients [34]. STAT3, which has immunomodulatory effects, modulates the production of Th1 cell-specific cytokines by altering the balance between Th1 and Th2 cells, thereby altering immune function and inflammatory responses [35]. TP53 is currently the most widely studied oncogene. TP53 can be both an activator and an inhibitor of autophagy. Under stress conditions such as nutrient depletion or hypoxia, TP53 promotes autophagy activation by inhibiting the mTOR signaling pathway, thereby suppressing the inflammatory response. Inhibition of TP53 increases IL-6 gene expression while promoting cell proliferation and differentiation [36].

Based on the KEGG pathway enrichment analysis results, we can see that the QSDH drug formulary exerts its effect on the treatment of MG mainly through signaling pathways such as the IL-17 signaling pathway, the HIF-1 signaling pathway, the PI3K-AKT signaling pathway, and the mTOR signaling pathway. The PI3K-AKT signaling pathway regulates cell proliferation, differentiation, apoptosis, and glucose transport and can regulate T cells' development, stability, and function [37]. Studies suggest that PI3K-AKT-specific inhibitors significantly upregulate Th1 and Th17 cells in PBMCs of MG patients, and mTOR/HIF-1α activates the expression of glycolytic genes to provide energy for rapid activation of immune cells, suggesting that the PI3K/AKT signaling pathway regulates immune function in MG [38]. Our in vivo experimental study in rats confirmed that the QSDH drug formulary could alleviate the symptoms of EAMG and reduce the level of acetylcholine receptor antibodies in the peripheral blood of EAMG rats by inhibiting the PI3K/AKT signaling pathway, thus demonstrating that the QSDH drug formulary for MG can work by inhibiting the PI3K/AKT signaling pathway.

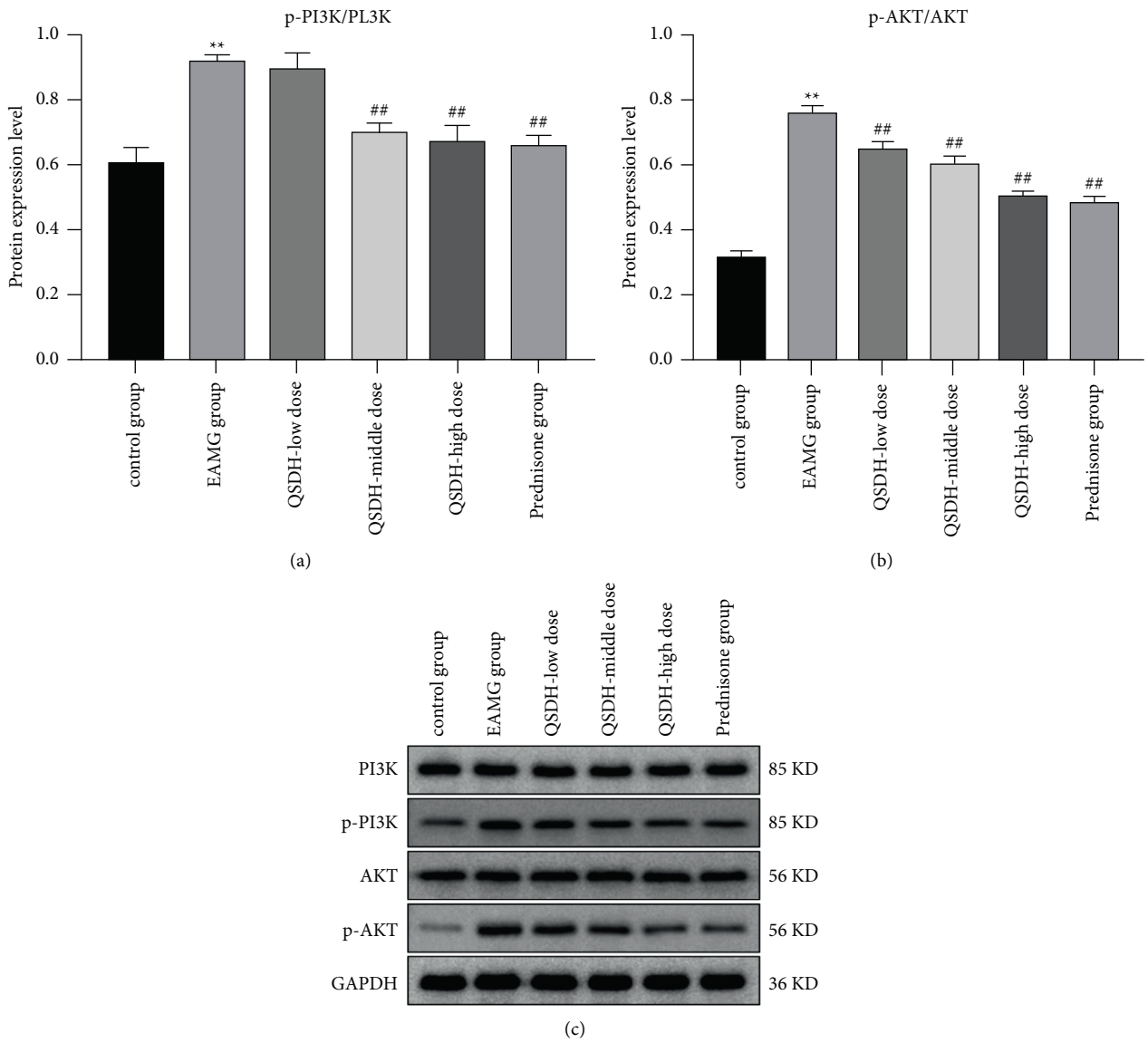


Figure 15: Effect of QSDH drug formulary on the expression level of the PI3K/AKT signaling pathway-related proteins in EAMG rats. (Figure a shows the significant analysis of PI3K and p-PI3K protein expression in the spleen tissues of rats in each experimental group, Figure b shows the significant analysis of AK and p-AKT protein expression in the spleen tissues of rats in each experimental group, and Figure c shows the expression of related proteins in the spleen tissues of rats in each experimental group by Western blot. Comparison of the EAMG model group with adjuvant control group $^{**}P < 0.01$. QSDH drug formulary each dose group compared with the EAMG model group $^{\#}P < 0.05$, $^{\#\#}P < 0.01$).

We selected the core active ingredients quercetin, epigallocatechin-3-gallate, luteolin, wogonin, kaempferol, and fisetin as ligands and the first core target AKT1 as the receptor for molecular docking. Furthermore, we verified the pharmacodynamic substance basis of the QSDH drug formulary for MG treatment. The results showed that the main active compounds could stably bind to the core target AKT1 through hydrogen bonding. Among them, epigallocatechin-3-gallate formed the strongest hydrogen bond to AKT1 with asp-46, Glu-40, LYS-39, AlA-50, and GLN-47 amino acids near the active site. It further indicates that the QSDH drug formulary can treat myasthenia gravis by acting on the AKT1 target protein.

6. Conclusions

In conclusion, 85 active pharmaceutical ingredients of the QSDH drug formulary were identified by UHPLC-QE-MS combined with the network pharmacology method. Preliminary prediction QSDH drug formulary can regulate the PI3K/AKT signaling pathway through quercetin, epigallocatechin-3-gallate, luteolin, wogonin, kaempferol, fisetin, and other active ingredients, acting on AKT1 target protein to inhibit inflammation, immune function, and cell metabolism, to achieve the purpose of treating MG. Provides new insights into the QSDH drug formulary's mechanism to alleviate MG disease's progression.

Data Availability

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Disclosure

Tianying Chang and Qi Lu and yibin zhang are co-first authors.

Conflicts of Interest

The authors declare that they have no conflicts of interest regarding the publication of this paper.

Acknowledgments

This work was supported by the Basic TCM evidence-based capacity building Project of the Affiliated Hospital of Changchun University of Chinese Medicine, the Industrial Technology Research and Development Project of Jilin Province Development and Reform Commission (2020C032-3), the Administration of Traditional Chinese Medicine of Jilin Province (2020017), the Science and Technology Project of Education Department of Jilin Province (JJKH20210978KJ), the Science and Technology Development Project of Jilin Province (20220203152SF), and the Project of Changchun Science and Technology Development (21Z44).

References

[1] N. E. Gilhus, S. Tzartos, and A. Evoli, "Myasthenia gravis," *Nat Rev Dis Primers*, vol. 5, no. 1, p. 30, 2019.

[2] L. Dresser, R. Wlodarski, and K. Rezania, "Myasthenia gravis: epidemiology, pathophysiology and clinical manifestations," *J Clin Med*, vol. 10, no. 11, 2021.

[3] W. Fang, Y. Li, R. Mo et al., "Hospital and healthcare insurance system record–based epidemiological study of myasthenia gravis in southern and northern China," *Neurol Sci*, vol. 41, no. 5, pp. 1211–1223, 2020.

[4] S. Chen, M. B. Xu, X. L. Zhou, P. Q. Rong, T. Y. Jin, and G. Q Zheng, "Chinese herbal medicine for myasthenia gravis: a systematic review and meta-analysis," *Front Pharmacology*, vol. 9, p. 969, 2018.

[5] Y.-B. Zhang, B.-T. Wang, P. Xu et al., "Integrated chemical molecular docking with network pharmacology to study the molecular mechanism of JianPi YiQi BuSui method for treating myasthenia gravis," *Chinese Journal of Analytical Chemistry*, vol. 50, no. 2, pp. 1–12, 2022.

[6] Z. Zhou, B. Chen, and S. Chen, "Applications of network pharmacology in traditional Chinese medicine research [J]," *Evid Based Complement Alternat Med*, vol. 2020, 2020.

[7] X. Wang, Z. Y. Wang, J. H. Zheng, and S. Li, "TCM network pharmacology: a new trend towards combining computational, experimental and clinical approaches," *Chinese Journal of Natural Medicines*, vol. 19, no. 1, pp. 1–11, 2021.

[8] J. Ru, P. Li, J. Wang et al., "TCMSP: a database of systems pharmacology for drug discovery from herbal medicines," *J Cheminform*, vol. 6, no. 1, 2014.

[9] C. Uniprot, "Reorganizing the protein space at the universal protein resource (UniProt) [J]," *Nucleic Acids Res*, vol. 40, no. Database issue, pp. D71–D75, 2012.

[10] N. Rappaport, S. Fishilevich, R. Nudel et al., "Rational confederation of genes and diseases: NGS interpretation via GeneCards, MalaCards and VarElect," *Biomed Eng Online*, vol. 16, no. S1, p. 72, 2017.

[11] D. S. Wishart, Y. D. Feunang, A. C. Guo et al., "DrugBank 5.0: a major update to the DrugBank database for 2018," *Nucleic Acids Research*, vol. 46, no. D1, pp. D1074–D1082, 2018.

[12] J. Pinero, A. Bravo, N. Queralt-Rosinach et al., "DisGeNET: a comprehensive platform integrating information on human disease-associated genes and variants," *Nucleic Acids Res*, vol. 45, no. D1, pp. D833–D839, 2017.

[13] Y. Zhou, Y. Zhang, X. Lian et al., "Therapeutic target database update 2022: facilitating drug discovery with enriched comparative data of targeted agents," *Nucleic Acids Research*, vol. 50, no. D1, pp. D1398–D1407, 2022.

[14] M. Whirl-Carrillo, R. Huddart, L. Gong et al., "An evidence-based framework for evaluating pharmacogenomics knowledge for personalized medicine," *Clin Pharmacol Ther*, vol. 110, no. 3, pp. 563–572, 2021.

[15] D. Szklarczyk, A. L. Gable, K. C. Nastou et al., "The STRING database in 2021: customizable protein–protein networks, and functional characterization of user-uploaded gene/measurement sets," *Nucleic Acids Research*, vol. 49, no. D1, pp. D605–D612, 2021.

[16] F. Baggi, A. Annoni, F. Ubiali et al., "Breakdown of tolerance to a self-peptide of acetylcholine receptor α-subunit induces experimental myasthenia gravis in rats," *Journal Immunology*, vol. 172, no. 4, pp. 2697–2703, 2004.

[17] V. A. Lennon, J. M. Lindstrom, and M. E. Seybold, "Experimental autoimmune myasthenia: a model of myasthenia gravis in rats and Guinea pigs," *Journal of Experimental Medicine*, vol. 141, no. 6, pp. 1365–1375, 1975.

[18] M. Zhou and H. Zhang, "Network pharmacology approach to investigate the mechanism of modified liu jun zi decoction in the treatment of chronic atrophic gastritis," *Evidence-Based Complementary and Alternative Medicine*, vol. 2022, pp. 1–12, 2022.

[19] S. He, T. Wang, C. Shi, Z. Wang, and X. Fu, "Network pharmacology-based approach to understand the effect and mechanism of Danshen against anemia," *Journal of Ethnopharmacology*, p. 282, 2022.

[20] J. Lu, J. Yan, J. Yan et al., "Network pharmacology based research into the effect and mechanism of Xijiao Dihuang decoction against sepsis," *Biomedicine & Pharmacotherapy*, vol. 122, 2020.

[21] Y. Zong, F. Chen, and S. Li, "(-)-Epigallocatechin-3-gallate (EGCG) prevents aminoglycosides-induced ototoxicity via anti-oxidative and anti-apoptotic pathways [J]," *Int J Pediatr Otorhinolaryngol*, p. 150, 2021.

[22] Y. Li, J. Yao, C. Han et al., "Quercetin, inflammation and immunity," *Nutrients*, vol. 8, no. 3, p. 167, 2016.

[23] S. F. Nabavi, N. Braidy, O. Gortzi et al., "Luteolin as an anti-inflammatory and neuroprotective agent: a brief review," *Brain Research Bulletin*, vol. 119, no. Pt A, pp. 1–11, 2015.

[24] D. L. Huynh, T. H. Ngau, N. H. Nguyen, G. B. Tran, and C. T. Nguyen, "Potential therapeutic and pharmacological effects of Wogonin: an updated review," *Mol Biol Rep*, vol. 47, no. 12, pp. 9779–9789, 2020.

[25] H. Feng, J. Cao, G. Zhang, and Y. Wang, "Kaempferol attenuates cardiac hypertrophy via regulation of ASK1/MAPK

signaling pathway and oxidative stress," *Planta Med*, vol. 83, no. 10, pp. 837–845, 2017.

[26] K. Sundarraj, A. Raghunath, L. Panneerselvam, and E. Perumal, "Fisetin inhibits autophagy in HepG2 cells via PI3K/Akt/mTOR and AMPK pathway," *Nutrition and Cancer*, vol. 73, no. 11-12, pp. 2502–2514, 2021.

[27] M. Pae and D. Wu, "Immunomodulating effects of epigallocatechin-3-gallate from green tea: mechanisms and applications," *Food Funct*, vol. 4, no. 9, pp. 1287–1303, 2013.

[28] X. W. Zhang, J. Y. Chen, D. Ouyang, and J. H. Lu, "Quercetin in animal models of alzheimer's disease: a systematic review of preclinical studies," *International Journal of Molecular Sciences*, vol. 21, no. 2, p. 493, 2020.

[29] H. T. Wu, J. Lin, Y. E. Liu et al., "Luteolin suppresses androgen receptor-positivetriple-negative breast cancer cell proliferation and metastasis by epigenetic regulation of MMP9 expression via the AKT/mTOR signaling pathway," *Phytomedicine*, vol. 81, 2021.

[30] H. Wang, C. L. Zhou, H. Lei, S. Zhang, J. Zheng, and Q. Wei, "Kaempferol: a new immunosuppressant of calcineurin," *IUBMB Life*, vol. 60, no. 8, pp. 549–554, 2008.

[31] J. C. Chamcheu, S. Esnault, V. M. Adhami et al., "Fisetin, a 3, 7, 3′, 4′-tetrahydroxyflavone inhibits the PI3K/Akt/mTOR and MAPK pathways and ameliorates psoriasis pathology in 2D and 3D organotypic human inflammatory skin models," *Cells*, vol. 8, no. 9, p. 1089, 2019.

[32] R. Abu Eid, K. M. Friedman, M. Mkrtichyan et al., "Akt1 and -2 inhibition diminishes terminal differentiation and enhances central memory $CD8^+$T-cell proliferation and survival," *Oncoimmunology*, vol. 4, no. 5, 2015.

[33] K. M. Danikowski, S. Jayaraman, and B. S. Prabhakar, "Regulatory T cells in multiple sclerosis and myasthenia gravis," *J Neuroinflammation*, vol. 14, no. 1, p. 117, 2017.

[34] M. Maurer, S. Bougoin, T. Feferman et al., "IL-6 and Akt are involved in muscular pathogenesis in myasthenia gravis," *Acta Neuropathol Commun*, vol. 3, no. 1, 2015.

[35] A. A. Farooqi, G. Butt, S. A. EL-Zahaby et al., "Luteolin mediated targeting of protein network and microRNAs in different cancers: Focus on JAK-STAT, NOTCH, mTOR and TRAIL-mediated signaling pathways," *Pharmacol Res*, vol. 160, 2020.

[36] A. Shoffner, V. Cigliola, N. Lee, J. Ou, and K. D. Poss, "Tp53 suppression promotes cardiomyocyte proliferation during zebrafish heart regeneration," *Cell Reports*, vol. 32, no. 9, 2020.

[37] W. Lv, M. Yu, Q. Yang, P. Kong, and B. Yan, "Total flavonoids of *Rhizoma drynariae* ameliorate steroid-induced avascular necrosis of the femoral head via the PI3K/AKT pathway," *Mol Med Rep*, vol. 23, no. 5, p. 345, 2021.

[38] F. B. Feng and H. Y. Qiu, "Effects of Artesunate on chondrocyte proliferation, apoptosis and autophagy through the PI3K/AKT/mTOR signaling pathway in rat models with rheumatoid arthritis," *Biomedicine & Pharmacotherapy*, vol. 102, pp. 1209–1220, 2018.

Hindawi
Evidence-Based Complementary and Alternative Medicine
Volume 2022, Article ID 1505643, 9 pages
https://doi.org/10.1155/2022/1505643

Research Article

Clinical Practice Pattern of Korean Medicine Doctors in Idiopathic Short Stature Treatment: A Survey Study

Soobin Jang[1] **and Boram Lee**[2]

[1]*Department of Preventive Medicine, College of Korean Medicine, Daegu Haany University, 1 Haanydaero, Gyeongsan-si, Gyeongsangbuk-do 38610, Republic of Korea*
[2]*KM Science Research Division, Korea Institute of Oriental Medicine, 1672 Yuseong-daero, Yuseong-gu, Daejeon 34054, Republic of Korea*

Correspondence should be addressed to Boram Lee; qhfka9357@naver.com

Received 24 January 2022; Accepted 22 July 2022; Published 10 August 2022

Academic Editor: Zhaolan Liu

Background. Korean medicine (KM) interventions are attractive for children with idiopathic short stature (ISS). We investigated the real-world clinical practice patterns of KM doctors in ISS treatment. *Methods*. The survey targeted KM doctors who have treated patients with ISS in KM clinical settings for >3 years. We included questions on the diagnosis and treatment patterns, effects, cost, and opinions of doctors on KM treatment for ISS. A frequency analysis was performed. *Results*. There were 58 respondents, and "heights of parents" ($n = 57$, 98.3%), "height, weight, and growth rate of child" ($n = 55$, 94.8%), and "amount of meals, digestive function" ($n = 52$, 89.7%) were frequently used as indicators for diagnosis and treatment. The most frequently used KM interventions were "herbal medicine" ($n = 58$, 100%), "acupuncture" ($n = 49$, 84.5%), "moxibustion" ($n = 38$, 65.5%), "dry cupping" ($n = 26$, 44.8%), and "physiotherapy" ($n = 22$, 37.9%). Herbal medicines were generally prescribed to tonify the spleen or kidney, and the most frequently used individual herbs were *Acanthopanacis cortex*, *Astragali Radix*, and *Cervi parvum cornu*. The most common acupuncture points were ST36, GB34, SP6, EX-LE5, and LI4. *Conclusions*. This study showed the use of KM for ISS in real-world clinical settings. In the future, well-designed clinical studies to verify the effect of KM treatment on ISS based on real-world clinical practice patterns should be actively performed.

1. Introduction

Idiopathic short stature (ISS) is defined as when the individual's height is two standard deviations or more below the corresponding average height for a given age, sex, and population group, in the absence of any systemic, endocrine, nutritional, or chromosomal abnormality [1]. Approximately 80% of children with short stature are estimated to have ISS [2] and its prevalence is estimated of 16 per 1,000 children [3]. In conventional medicine, recombinant human growth hormone (GH) has been used as the primary standard therapy for ISS since it was approved by the US Food and Drug Administration in 2003 [4]. However, this treatment is rather inconvenient and expensive because it requires daily parenteral administration. Additionally, concerns have been raised regarding the safety of long-term GH treatment, including a decreased sensitivity to insulin, an increased risk of type 2 diabetes, and an adverse effect on peak bone mineralization [5–7].

In South Korea, Korean medicine (KM) treatments, including acupuncture, moxibustion, and herbal medicine, also known as East Asian traditional medicine (EATM), one of the most well-known types of complementary and integrative medicine, have been widely used as an alternative treatment method to support child growth. According to a retrospective study in 2016, growth retardation was the chief complaint among children and adolescents who visited the department of Korean Pediatrics in a KM Hospital [8]. Several preclinical and clinical studies have shown that EATM therapies are effective in treating ISS [9–12].

However, clinical practice guidelines of KM for pediatric growth disorder have not been published. Therefore, an in-depth investigation of the diagnosis and treatment patterns of KM doctors (KMDs), as well as the treatment cost for ISS, may enhance the understanding of the actual healthcare situation and contribute to research that reflects real-world clinical settings.

2. Methods

2.1. Study Aim, Design, and Setting. The aim of this study was to investigate the clinical practice patterns of KMDs in ISS treatment and their therapeutic effects and costs in real-world clinical settings.

This study used a cross-sectional survey design to assess the clinical practice patterns of KMD for ISS treatment in South Korea. The survey was conducted by Mediresearch (https://www.mediresearch.co.kr), which is a professional survey research company. The company sent a questionnaire survey *via* mobile phone to KMDs affiliated with KM clinics or hospitals, based on the cooperation of the Association of Pediatrics of KM. The company recruited participants with consideration of the ratio between specialists in pediatrics and general KM practitioners. The participants were enrolled voluntarily and they were informed that responses were required for all our questions in the questionnaire. The survey was conducted anonymously between November 24 and December 23, 2020.

2.2. Participants. The purpose of this study was to observe the clinical practice patterns of KMD in real-world settings, not to verify the treatment effect; therefore, there was no special method for determining the sample size. We determined the minimum number of respondents as 40, with additional recruitment ongoing until the end of the study period. The inclusion criterion was >3 years of experience of ISS treatment in KM clinical settings.

2.3. Questionnaire. The questionnaire was developed by three traditional KM experts who discussed and selected investigation items. The experts sought to create a concise and easily readable questionnaire to raise the response rate. They conducted a pilot test with a draft questionnaire and feedback was collected. The final version of the questionnaire was developed for respondent convenience using smartphones.

The questionnaire consisted of five categories. Variable descriptions are as follows:

(1) Basic demographic and clinical characteristics of KMD respondents: sex, age, duration of clinical experience, type of KMD license, working institution, monthly number of patients with ISS, and mean age group of patients with ISS.

(2) Diagnosis patterns: indicators used in the diagnosis and treatment of ISS and comorbidities that are checked during ISS diagnosis and treatment.

(3) Treatment patterns: which KM intervention apply, including herbal medicine, acupuncture, moxibustion, dry cupping, physiotherapy, electro-acupuncture, pharmacopuncture, and chuna. Administration duration; frequency of each intervention (except herbal medicine); purpose of herbal prescription; and frequently used individual herbs and acupoint.

(4) Effectiveness and cost: mean height growth (cm) before and after KM treatment, according to sex and age, and cost of each intervention.

(5) Opinions on KM treatment for ISS: Korean-Western medicine collaborations for the treatment of growth disorders; essential KM interventions that should be included in health promotion program for children's growth; limitations of KM treatment for children's growth; and the appropriate herbal medicine for insurance.

2.4. Statistical Analyses. Frequency analysis was conducted for each question, and the ranking was confirmed by indicating the number of responses (n) and percentage (%). Microsoft Excel 2016 (Microsoft Corporation, Redmond, WA, USA) was used for all analyses.

2.5. Ethical Considerations. The study was explained to all participants prior to the initiation of the survey. Only those who voluntarily agreed to participate and for their collected data to be published were enrolled in the study. This study was approved by the Institutional Review Board of Korea Institution of Oriental Medicine (IRB No. I-2010-008-002-01).

3. Results

3.1. Basic Demographic and Clinical Characteristics of Respondents. Fifty-eight KMDs, consisting of 31 (53.4%) men and 27 (46.6%) women, participated in this study. Most respondents were aged between 30 and 49 years (86.2%). In addition, most of their clinical experience was evenly distributed between 5 and 30 years (94.8%). The average monthly number of ISS patients was "<10" ($n = 27$, 46.6%), followed by "≥10 and <30" ($n = 17$, 29.3%). The most frequent average age of ISS patients was prepubertal (≥6 and <10; $n = 28$, 48.3%), followed by preschool (≥3 and <6; $n = 19$, 32.8%) (Table 1).

3.2. Diagnosis Patterns of ISS in Korean Medicine. The most common indices that were referred to when diagnosing ISS were "heights of parents" ($n = 57$, 98.3%), 'height, weight, and growth rate of child' ($n = 55$, 94.8%), and "amount of meal, digestive function" ($n = 52$, 89.7%), followed by "pattern identification" ($n = 38$, 65.5%), "growth plate test (X-ray)" ($n = 37$, 63.8%), "pulse diagnosis" ($n = 36$, 62.1%), "abdominal diagnosis" ($n = 34$, 58.6%), and "tongue diagnosis" ($n = 30$, 51.7%). The top comorbidity that was assessed for when diagnosing and treating ISS was "digestive diseases" ($n = 53$, 91.4%), followed by "respiratory diseases" ($n = 33$, 56.9%), and "allergic diseases" ($n = 23$, 39.7%) (Table 2).

Table 1: Basic demographic and clinical characteristics of respondents.

Basic information		*n* (%)
Sex	Men	31 (53.4)
	Women	27 (46.6)
Age (years)	<30	1 (1.7)
	≥30 to <40	27 (46.6)
	≥40 to <50	23 (39.7)
	≥50 to <60	7 (12.1)
Clinical experience (years)	<5	3 (5.2)
	≥5 to <10	17 (29.3)
	≥10 to <15	13 (22.4)
	≥15 to <20	13 (22.4)
	≥20 to <30	12 (20.7)
Type of KMD license	General practitioner	30 (51.7)
	Specialist	28 (48.2)
Working institution	KM clinic specialized in pediatric care	29 (50.0)
	General KM clinic	13 (22.4)
	Hospital	16 (27.6)
Number of patients with ISS (monthly average)	<10	27 (46.6)
	≥10 to <30	17 (29.3)
	≥30 to <50	6 (10.3)
	≥50	8 (13.8)
Mean age group of patients with ISS (years)	Infancy (<3)	5 (8.6)
	Preschool (≥3 to <6)	19 (32.8)
	Prepubertal (≥6 to <10)	28 (48.3)
	Adolescence (≥10 to <20)	6 (10.3)
Total		58 (100.0)

KM, Korean medicine; KMD, Korean medicine doctor; ISS, idiopathic short stature.

3.3. Treatment Patterns of ISS in Korean Medicine. All KMDs responded that they used "herbal medicine" ($n = 58$, 100%) as an intervention in ISS treatment, followed by "acupuncture" ($n = 49$, 84.5%), "moxibustion" ($n = 38$, 65.5%), "dry cupping" ($n = 26$, 44.8%), and "physiotherapy" ($n = 22$, 37.9%). "Electroacupuncture," "pharmacopuncture," and "chuna" were each selected by 20 respondents (34.5%). The herbal medicine administration period typically ranged from 1 to 6 month: "≥1 and <2 months" ($n = 12$, 20.7%); "≥2 and <3 months" ($n = 20$, 34.5%); and "≥3 and <6 months" ($n = 17$, 27.6%). The frequency of other interventions was generally "once a week" in a clinical setting (Table 3).

The purpose of prescribing herbal medicines were as follows: 51.7% ($n = 30$) for "tonifying the spleen," 19.0% ($n = 11$) for "tonifying the spleen and the kidney," 12.1% ($n = 7$) for "tonifying the kidney," and 10.3% ($n = 6$) for "tonifying the liver and the kidney." The frequently used herbs for ISS treatment were "*Acanthopanacis cortex*" ($n = 23$, 41.8%), "*Astragali Radix*" ($n = 23$, 41.8%), "*Cervi parvum cornu*" ($n = 21$, 38.2%), and "*Rehmanniae Radix preparata*" ($n = 18$, 32.7%). The most frequently used acupuncture points for ISS treatment were "ST36 (Zusanli)" ($n = 48$, 82.8%), "GB34 (Yanglingquan)" ($n = 36$, 62.1%), "SP6 (Sanyinjiao)" ($n = 32$, 55.2%), "EX-LE5 (Xiyan)" ($n = 28$, 48.3%), and "LI4 (Hegu)" ($n = 26$, 44.8%) (Table 4).

3.4. Effectiveness and Cost of Korean Medicine Treatment for ISS. According to the response of KMDs, the mean (standard deviation) of growth height after KM treatment was 6.03 (0.98) cm before puberty and 9.03 (1.56) cm during puberty in boys; and 5.83 (1.05) cm before puberty and 8.36 (1.71) cm during puberty in girls (Table 5).

The distribution of the cost of each intervention is described in Table 6. The cost of moxibustion, dry cupping, and physiotherapy was typically <9 dollars per visit, and acupuncture was <11 dollars per visit. The cost of herbal medicine for the majority of respondents ($n = 45$, 77.6%) ranged from 156 to 268 dollars per 15 days. The daily cost of herbal medicine was between 10.4 and 17.9 dollars.

3.5. Opinions on the Use of Korean Medicine in ISS Treatment. Twenty-eight KMDs (48.3%) responded that 'KM treatment is more cost-effective than GH.' By contrast, 22 KMDs (37.9%) responded that 'It is best to combine herbal medicine, acupuncture, and GH.' Herbal medicine (decoction) was selected the most ($n = 45$, 77.6%) as an essential KM intervention that should be included in a health promotion program for pediatric growth disorders. The top herbal medicines requiring cover by health insurance for ISS treatment were Yukmijihwang-tang ($n = 25$, 43.1%), Sogunjung-tang ($n = 14$, 24.1%), Yukgunja-tang ($n = 8$, 13.8%), Sipjeondaebo-tang ($n = 5$, 8.6%), and Sagunja-tang ($n = 3$, 5.2%) (Table 7).

4. Discussion

This survey investigated the clinical practice patterns of KM treatment for ISS, including a detailed evaluation of diagnosis, treatment, effectiveness, and costs. Furthermore, we sought the opinions of KMDs regarding their use of these

Table 2: Diagnosis pattern of idiopathic short stature in respondents.

Diagnosis pattern		*n* (%)
What indications do you use when ISS treatment? (Duplicate response)	Heights of parents	57 (98.3)
	Height, weight, and growth rate of child	55 (94.8)
	Amount of meal, digestive function	52 (89.7)
	Pattern identification (辨證)	38 (65.5)
	Growth plate test (*X*-ray)	37 (63.8)
	Pulse diagnosis (脈診)	36 (62.1)
	Abdominal diagnosis (腹診)	34 (58.6)
	Tongue diagnosis (舌診)	30 (51.7)
	Growth hormone test (blood test)	13 (22.4)
	Growth plate test (ultrasonography)	3 (5.2)
What accompanied diseases do you check when ISS treatment? (Top 3)	Digestive diseases	53 (91.4)
	Respiratory diseases	33 (56.9)
	Allergic diseases	23 (39.7)
	Underlying disease can cause growth disorder	22 (37.9)
	Precocious puberty	21 (36.2)
	Obesity	12 (20.7)
	Mental illness (i.e. sleep disorder, anxiety)	10 (17.2)

ISS, idiopathic short stature.

Table 3: Treatment pattern of idiopathic short stature in respondents.

	Herbal medicine	Acupuncture	Moxibustion	Dry cupping	Physiotherapy	Electroacupuncture	Pharmacopuncture	Chuna
Yes	58 (100)	49 (84.5)	38 (65.5)	26 (44.8)	22 (37.9)	20 (34.5)	20 (34.5)	20 (34.5)
Frequency (n = 49, no response = 9)								
Once a week		31 (63.3)	22 (57.9)	14 (53.8)	14 (63.6)	14 (70.0)	16 (80.0)	16 (80.0)
Twice a week		17 (34.7)	16 (42.1)	11 (42.3)	8 (36.4)	5 (25.0)	3 (15.0)	4 (20.0)
3 times a week		1 (2.0)	0	1 (3.8)	0	1 (5.0)	1 (5.0)	0
Treatment period (n = 58)								
<1 month	2 (3.4)	3 (6.1)	2 (5.2)	1 (3.8)	0	1 (5.0)	0	0
≥1 and <2 months	12 (20.7)	3 (6.1)	3 (7.9)	3 (11.5)	2 (9.1)	2 (10.0)	2 (10.0)	1 (5.0)
≥2 and <3 months	20 (34.5)	10 (20.4)	7 (18.4)	7 (26.9)	3 (13.6)	5 (25.0)	3 (15.0)	4 (20.0)
≥3 and <6 months	16 (27.6)	15 (30.6)	13 (34.2)	7 (26.9)	12 (54.5)	5 (25.0)	6 (30.0)	7 (35.0)
≥6 and <12 months	4 (6.9)	9 (18.4)	6 (15.8)	6 (23.1)	3 (13.6)	5 (25.0)	5 (25.0)	4 (20.0)
≥1 year	4 (6.9)	9 (18.4)	7 (18.4)	2 (7.7)	2 (9.1)	2 (10.0)	4 (20.0)	4 (20.0)

All data are *n* (%).

treatments. We have also previously reported a network meta-analysis [13] and an observational case series [14] of integrative KM treatment for ISS. The findings suggested that EATM plus GH might have a synergistic effect in comparison with EATM or GH alone [13]. In addition, the changes in growth indicators in children with ISS before and after KM treatment showed the potential of KM for the management of ISS [14]. However, detailed information regarding interventions and costs could not be obtained by both studies because they were secondary research studies using existing data. Therefore, we designed this survey to obtain specific information regarding ISS treatment.

Pattern identification based on KM theory could be a significant method for treating ISS because it is a primary growth disorder with an unknown cause. ISS is typically regarded as a problem with digestive disorders or lack of nourishment in KM [15]. This is consistent with the majority of respondents focusing on "tonifying the spleen (補脾) or the kidney (補腎)" as the purpose of ISS treatment in our study. In EATM, "tonifying the spleen" is

Table 4: Details of interventions for idiopathic short stature.

Intervention		n (%)
Purpose of herbal prescription ($n = 58$)	Tonifying the spleen (補脾)	30 (51.7)
	Tonifying the spleen and the kidney (補脾腎)	11 (19.0)
	Tonifying the kidney (補腎)	7 (12.1)
	Tonifying the liver and the kidney (補肝腎)	6 (10.3)
	Others	4 (6.8)
Frequently used herb ($n = 55$, no response = 3)	Acanthopanacis cortex (五加皮)	23 (41.8)
	Astragali Radix (黃芪)	23 (41.8)
	Cervi parvum cornu (鹿茸)	21 (38.2)
	Rehmanniae Radix preparata (熟地黃)	18 (32.7)
	Atractylodis rhizoma alba (白朮)	16 (29.1)
	Dipsaci Radix (續斷)	14 (25.5)
	Angelicae gigantis Radix (當歸)	12 (21.8)
	Ginseng Radix (人蔘)	12 (21.8)
	Achyranthis Radix (牛膝)	9 (16.4)
	Eucommiae cortex (杜仲)	9 (16.4)
	Citri unshius pericarpium (陳皮)	8 (14.5)
	Dioscoreae rhizoma (山藥)	7 (12.7)
	Corni fructus (山茱萸)	6 (10.9)
Frequently used acupuncture points ($n = 58$)	ST36 (zusanli)	48 (82.8)
	GB34 (yanglingquan)	36 (62.1)
	SP6 (sanyinjiao)	32 (55.2)
	EX-LE5 (xiyan)	28 (48.3)
	LI4 (hegu)	26 (44.8)
	BL60 (kunlun)	16 (27.6)
	KI3 (taixi)	15 (25.9)
	KI4 (dazhong)	12 (20.7)
	GB39 (xuanzhong)	11 (19.0)
	GV20 (baihui)	9 (15.5)
	CV12 (zhongwan)	3 (5.2)

Table 5: Effects of height growth before and after Korean medicine treatment.

		Before KM treatment	After KM treatment
Boys	Before puberty	4.10 (0.71) cm	6.03 (0.98) cm
	Puberty (rapid growth period)	6.50 (1.29) cm	9.03 (1.56) cm
Girls	Before puberty	4.14 (0.78) cm	5.83 (1.05) cm
	Puberty (rapid growth period)	6.14 (1.24) cm	8.36 (1.71) cm

KM, Korean medicine. All data are in mean (standard deviation).

defined as a therapeutic method to treat diminished functional activities of the spleen by using tonifying medicines. "Tonifying the kidney" is a general term for treating deficiency patterns/syndromes of the kidney with tonifying medicines [16].

Taken together, these data show that herbal medicine is regarded as an essential ISS treatment intervention. Furthermore, acupuncture and moxibustion are also necessary for ISS treatment. The administration period for herbal medicines was between 2 and 6 months, and the frequency of other interventions was once a week. Yukmijihwang-tang (六味地黃湯) [17], the most common herbal prescription requiring coverage by health insurance, is a representative herbal medicine for tonifying the kidney. Sogeonjung-tang (小建中湯) [18] and Yukgunja-tang (六君子湯) [19], which were the second and third most commonly recorded, are herbal medicines used to tonify the spleen. In particular, Sogeonjung-tang is a first-line KM treatment for children with a lack of appetite or poor digestion [18].

The most frequently used individual herbs for ISS treatment in clinical settings were *Acanthopanacis cortex* (五加皮), followed by *Astragali Radix* (黃芪) and *Cervi parvum cornu* (鹿茸). The effects of a complex herbal mixture containing *Acanthopanacis cortex*, *Astragali Radix*, and *Dipsaci Radix* (續斷) on height growth have been studied previously and the study showed that height gain was significantly higher in the herbal mixture group than in the placebo group after 24 weeks [12]. Additionally, *Cervi parvum cornu* is the most popular supplement for growth promotion and continues to grow in popularity [20]. In addition, ST36 (Zusanli), the acupuncture point that KMDs reported using most frequently, is actively used in traditional Chinese medicine clinical research, and its positive effect on growth has been studied [21].

Table 6: Cost of each intervention for idiopathic short stature.

	Herbal medicine (15 days) ($n = 58$)	Acupuncture ($n = 49$)	Moxibustion ($n = 38$)	Dry cupping ($n = 26$)	Physiotherapy ($n = 22$)	Electroacupuncture ($n = 20$)	Pharmacopuncture ($n = 20$)	Chuna ($n = 20$)
>USD9	—	22 (44.9)	32 (84.2)	23 (88.5)	19 (86.4)	7 (35.0)	3 (15.0)	1 (5.0)
≥USD9 and >USD11	—	12 (24.5)	3 (7.9)	1 (3.8)	3 (13.6)	7 (35.0)	3 (15.0)	2 (10.0)
≥USD11 and >USD13	—	5 (10.2)	1 (2.6)	—	—	2 (10.0)	3 (15.0)	1 (5.0)
≥USD13 and >USD15	—	2 (4.1)	—	—	—	—	1 (5.0)	1 (5.0)
≥USD15 and >USD17	—	1 (2.0)	—	—	—	—	7 (35.0)	5 (25.0)
≥USD17 and >USD22	—	7 (14.3)	2 (5.3)	2 (7.7)	—	4 (20.0)	2 (10.0)	8 (40.0)
≥USD22	—	—	—	—	—	—	1 (5.0)	2 (10.0)
≥USD44 and >USD134	3 (5.2)	—	—	—	—	—	—	—
≥USD134 and >USD156	3 (5.2)	—	—	—	—	—	—	—
≥USD156 and >USD178	13 (22.4)	—	—	—	—	—	—	—
≥USD178 and >USD223	15 (25.9)	—	—	—	—	—	—	—
≥USD223 and >USD268	17 (29.3)	—	—	—	—	—	—	—
≥USD268	7 (12.1)	—	—	—	—	—	—	—

USD, United States dollar. It was based on the annual average exchange rate in 2020 from the Korea exchange bank. All data are in n (%). Cost of every intervention except herbal medicine were based on 1 visit.

Table 7: Opinions on growth treatment in respondents.

Question	Answer	N (%) 1st rank	N (%) Sum of 1st–3rd rank
Opinion on Korean-Western medicine collaboration for growth disorder treatment	Korean medicine treatment is more cost-effective than growth hormone.	28 (48.3)	—
	It is best to combine herbal medicine, acupuncture and growth hormone.	22 (37.9)	—
	Health promotion program comprising exercise and diet is more effective in case of ISS without underlying diseases.	8 (13.8)	—
Essential interventions that should be included in health promotion program for pediatric growth	Herbal medicine (decoction)	45 (77.6)	52 (89.7)
	Herbal medicine (products)	4 (6.9)	18 (31.0)
	Diet and lifestyle education	3 (5.2)	31 (53.4)
	Chuna	2 (3.4)	8 (13.8)
	Exercise	2 (3.4)	20 (34.5)
	Acupuncture	1 (1.7)	28 (48.3)
	Pharmacopuncture	1 (1.7)	7 (12.1)
	Cupping	—	4 (6.9)
	Moxibustion	—	4 (6.9)
	Physiotherapy	—	2 (3.4)
Limitation of Korean medicine treatment for pediatric growth	High cost	18 (31.0)	44 (75.9)
	Not covered with health insurance	14 (24.1)	37 (63.8)
	No immediate effect	12 (20.7)	29 (50.0)
	Lack of clinical evidence	7 (12.1)	32 (55.2)
	Lack of publicity	7 (12.1)	32 (55.2)
Appropriate herbal medicine for insurance drugs	Yukmijihwang-tang (六味地黃湯)	25 (43.1)	47 (81.0)
	Sogunjung-tang (小建中湯)	14 (24.1)	43 (74.1)
	Yukgunja-tang (六君子湯)	8 (13.8)	31 (53.4)
	Sipjeondaebo-tang (十全大補湯)	5 (8.6)	28 (48.3)
	Sagunja-tang (四君子湯)	3 (5.2)	15 (25.9)

All the acupoints frequently used for the treatment of ISS, except GV20 (Baihui) and CV12 (Zhongwan), were located below the knee to the toes (Table 4). This could stimulate height growth by stimulating the bones of the knee, tibia, and ankle. ST36 (Zusanli) is the most frequently selected acupoint and has been also used for the treatment of short stature in other studies [22, 23]. SP6 (Sanyinjiao)is an acupoint where the three yin meridians of the liver, spleen, and kidney meet, and is used to tonify the liver, spleen, and kidney. GV20 (Baihui) is placed at the top of the head where all yang-qi gathers, and CV12 (Zhongwan), which strengthens digestive functions, is placed at the middle of the umbilicus and the xiphisternal joint.

Several studies have conducted the economic evaluation of GH treatment on ISS [24, 25]. Furthermore, clinical trials have examined the growth effects of herbal medicines in China [26, 27]; however, studies conducting economic evaluation of complementary therapies, such as herbal medicines and acupuncture, for ISS treatment have not been published. We sought to calculate the incremental cost-effectiveness ratio of KM intervention for ISS by extracting the data from systematic reviews, randomized controlled trials, or national secondary data; however, no proper data provided the costs and growth effects of KM interventions.

Accordingly, we collected costs and height growth data in this survey, although it was not sufficient to make any conclusions. Nonetheless, we estimated that three months (the most responsive treatment period) of treatment with herbal medicine, acupuncture, and moxibustion would cost in the range of USD 1,554–1,824. The frequency and cost of acupuncture and moxibustion were assumed to be as once a week and USD 9 per session, respectively. The difference in height growth before and after KM treatment was 1.93 cm (before puberty) and 2.53 cm (puberty) in boys; and 1.69 cm (before puberty) and 2.22 cm (puberty) in girls (Table 5). Therefore, considering the relatively low cost and the effect of height growth of the KM treatment, KM treatment may be cost-effective for ISS treatment. Additionally, almost half of the KMDs who participated in this survey answered that KM treatment was more cost-effective than GH (Table 7). However, the estimated effectiveness and cost of KM treatment were based on the response of a small number of KMDs and not the actual patient data; thus, it was difficult to compare it with GH treatment (currently used treatment). In

addition, as comparison with the untreated control group is impossible due to the nature of the data, the difference in growth rate before and after KM treatment reported by KMDs may not be attributed to the effect of KM treatment. Furthermore, there may be recall errors, and caution is required in interpretation. A study on the effect of KM treatment on the final adult height should be performed to evaluate the cost-effectiveness of KM treatment compared with height monitoring or GH treatment for ISS.

Currently, KM interventions for ISS are not covered by health insurance in South Korea. This is reported as the primary limitation of KM treatment for growth disorders. Several health promotion programs have reported using KM interventions for child growth in public health centers [28]. Health promotion, in contrast to clinical treatment, consists of exercise, education, herbal medicine, and acupuncture. In addition, we are developing a KM health promotion program for children's growth based on the results of this survey. Many KMDs responded that herbal medicine with a type of decoction should be included in a health promotion program; however, it is difficult to provide decoctions because of costs and quality control. Health promotion programs are generally provided free of charge to residents in need; therefore, this could help children with ISS safely and effectively.

There are several limitations in this study. First, the number of participants was small and not representative of the entire KMD population. This survey aimed to recruit KMDs who focused on pediatric care with >3 years of clinical experience with ISS rather than more respondents to investigate clinical patterns in detail. The total number of KMDs is approximately 22,000, and there are only about 130 pediatric specialists focusing on KM in South Korea [29]. In addition, the sample size was small for realistic reasons, such as the study period and funding size. Second, recall bias is likely because the survey depended on the memory of respondents. A future chart analysis study is recommended to extract more accurate data. Additionally, the cost of herbal medicines varies significantly depending on the herb; therefore, the cost effectiveness can only be assessed as reference. Nevertheless, to the best of our knowledge, this study is the first to assess the clinical treatment pattern of ISS in a real-world KM setting.

5. Conclusions

This study analyzed the current KM clinical practice for the treatment of ISS, focusing on diagnosis indices and treatment patterns. The effects and costs of height growth and opinions of KMDs were also investigated. In the future, studies evaluating the efficacy and cost-effectiveness of KM treatment for ISS should be performed based on real-world clinical practice.

Abbreviations

EATM: East Asian traditional medicine
GH: Growth hormone
ISS: Idiopathic short stature
KM: Korean medicine
KMD: Korean medicine doctor.

Data Availability

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Ethical Approval

This survey was approved by Institutional Review Board of Korea Institute of Oriental Medicine (IRB No. I-2010-008-002-01). All participants voluntarily agreed to participate in this survey.

Conflicts of Interest

The authors declare that there are no conflicts of interest regarding the publication of this paper.

Authors' Contributions

SJ drafted the manuscript and extracted the data. SJ and BL managed entire process of survey and conducted the study. BL supervised the study. All authors read and approved the final manuscript.

Acknowledgments

This research was supported by a grant of the Korea Health Technology R&D Project through the Korea Health Industry Development Institute (KHIDI), funded by the Ministry of Health & Welfare, Republic of Korea (grant number: HF20C0103) and the Korea Institute of Oriental Medicine (KSN2022210).

References

[1] M. B. Ranke, "Towards a consensus on the definition of idiopathic short stature," *Hormone Research*, vol. 45, no. 2, pp. 64–66, 1996.

[2] S. Pedicelli, E. Peschiaroli, E. Violi, and S. Cianfarani, "Controversies in the definition and treatment of idiopathic short stature (ISS)," *Journal of Clinical Research in Pediatric Endocrinology*, vol. 1, no. 3, pp. 105–115, 2011.

[3] C. A. Quigley, "Growth hormone treatment of non-growth hormone-deficient growth disorders," *Endocrinology and Metabolism Clinics of North America*, vol. 36, no. 1, pp. 131–186, 2007.

[4] F. D. Administration, "FDA approves humatrope for short stature," *Federal Register*, vol. 68, no. 95, pp. 24003-24004, 2003.

[5] A. Deodati and S. Cianfarani, "Impact of growth hormone therapy on adult height of children with idiopathic short stature: systematic review," *BMJ*, vol. 342, no. mar111, p. c7157, 2011.

[6] A. Grimberg and G. P. Kanter, "USA growth hormone use in the idiopathic short stature era: trends in insurer payments and patient financial burden," *Journal of the Endocrine Society*, vol. 3, no. 11, pp. 2023–2031, 2019.

[7] R. Lanes and L. G. González Briceño, "Alternatives in the treatment of short stature," *Advances in Pediatrics*, vol. 64, no. 1, pp. 111–131, 2017.

[8] E. J. Lee, B. R. Lee, J. H. Lee, and G. T. Chang, "A study on the recent trend of chief complaint of Korean pediatric and adolescent outpatients," *The Journal of Korean Oriental Pediatrics*, vol. 30, no. 1, pp. 45–58, 2016.

[9] S. M. Cho, S. H. Lee, D. Lee et al., "The Korean herbal formulation yukmijih wangtang stimulates longitudinal bone growth in animal models," *BMC Complementary and Alternative Medicine*, vol. 17, pp. 239–248, 2017.

[10] J. Li and E. Yin, "Study on the effect of traditional Chinese medicine intervention on the height and weight of school-age idiopathic short stature," *Medical Innovation of China*, vol. 10, no. 15, pp. 33-34, 2013.

[11] F. Liu, L. Shen, H. Wei, and Y. Chen, "Recent advances in idiopathic short stature," *Clinical Focus*, vol. 34, no. 10, pp. 875–879, 2019.

[12] D. Lee, S. H. Lee, J. Song, H. J. Jee, S. H. Cha, and G. T. Chang, "Effects of astragalus extract mixture HT042 on height growth in children with mild short stature: a multicenter randomized controlled trial," *Phytotherapy Research*, vol. 32, no. 1, pp. 49–57, 2018.

[13] B. Lee, C. Y. Kwon, and S. Jang, "Comparative effectiveness of east Asian traditional medicine for treatment of idiopathic short stature in children: systematic review and network meta-analysis," *IMR*, vol. 11, no. 2, Article ID 100832, 2022.

[14] Y. J. Kim, S. H. Lee, S. Jang, J. Y. Lee, G. T. Chang, and B. Lee, "Integrative traditional Korean medicine treatment for children with idiopathic short stature A STROBE-compliant case series," *Medicine*, vol. 101, no. 28, Article ID e29754, 2022.

[15] Department of Pediatrics and Nationwide Korean Medicine College, *Pediatrics of Korean Medicine*, pp. 814–817, Ui Sung Dang Publishing Co, Seoul, South Korea, 2020.

[16] World Health Organization and Regional Office for the Western Pacific, *WHO International Standard Terminologies on Traditional Medicine in the Western Pacific Region*, WHO Regional Office for the Western Pacific, Manila, Asia, 2007.

[17] J. K. Lee, N. H. Lee, H. Ha et al., "Analysis of studies on yukmijihwang-tang for establishment of evidence based medicine," *Journal of Physiology & Pathology in Korean Medicine*, vol. 23, no. 1, pp. 15–26, 2009.

[18] W. K. Wang, T. L. Hsu, Z. Y. Huang, and Y. Y. L. Wang, "Collective effect of a Chinese formula-a study of xiao-jian-zhong-tang," *The American Journal of Chinese Medicine*, vol. 23, no. 03n04, pp. 299–304, 1995.

[19] Y. S. Shih, C. H. Tsai, T. C. Li et al., "The effect of xiang-sha-liu-jun-zi tang (XSLJZT) on irritable bowel syndrome: a randomized, double-blind, placebo-controlled trial," *Journal of Ethnopharmacology*, vol. 238, Article ID 111889, 2019.

[20] D. J. Lee, M. Hwangbo, K. Kwon, and H. S. Seo, "Review of cervi cornu parvum pharmacopuncture in Korean medicine," *Journal of Pharmacopuncture*, vol. 16, no. 2, pp. 7–14, 2013.

[21] S. G. Park, S. H. Park, S. H. Lee, and J. Y. Lee, "Review of clinical researches in Chinese medical journal for acupuncture, moxibusiton, and manual therapy of pediatric growth," *The Journal of Pediatrics of Korean Medicine*, vol. 33, no. 1, pp. 58–77, 2019.

[22] W. Wang, H. Sun, Y. Ye, Z. Shao, and Y. Xiao, "Influence and effect of acupoint Application of Chinese medicine on height and bone age of children with short stature," *Evidence-based Complementary and Alternative Medicine*, vol. 2021, pp. 1–7, 2021.

[23] K. L. Tan, J. F. He, Y. T. Qu, M. Z. Xie, X. M. Lei, and F. Y. Dai, "Observation on therapeutic effect of moxibustion and exercise for children with short stature of deficience of the kidney essence," *Zhongguo Zhen Jiu*, vol. 29, no. 8, pp. 613–615, 2009.

[24] J. M. Lee, M. M. Davis, S. J. Clark, T. P. Hofer, and A. R. Kemper, "Estimated cost-effectiveness of growth hormone therapy for idiopathic short stature," *Archives of Pediatrics and Adolescent Medicine*, vol. 160, no. 3, pp. 263–269, 2006.

[25] J. Bryant, C. Cave, B. Mihaylova et al., "Clinical effectiveness and cost-effectiveness of growth hormone in children: a systematic review and economic evaluation," *Health Technology Assessment*, vol. 6, no. 18, pp. 1–168, 2002.

[26] L. Wu, T. Yang, and Q. Wang, "Clinical observation on 30 cases of idiopathic short stature with deficiency of both spleen and kidney syndrome treated by growth I prescription combined with tuina," *Journal of Pediatrics of Traditional Chinese Medicine*, vol. 2, pp. 51–54, 2021.

[27] H. Tian and Y. Zeng, "Analysis of short-term curative effect of 35 cases of idiopathic short stature treat with the combination of Chinese and Western medicine," *Journal of Pediatrics of Traditional Chinese Medicine*, vol. 6, pp. 39–43, 2017.

[28] Korea Health Promotion Institute, "Best cases and research status of Korean medicine health promotion programs," *Health Promotion White Paper*, vol. 2, no. 17, 2014.

[29] "Statistics Korea," 2022, https://kosis.kr/statHtml/statHtml.do?orgId=350&tblId=TX_35003_A003&checkFlag=N.

Hindawi
Evidence-Based Complementary and Alternative Medicine
Volume 2022, Article ID 1271205, 12 pages
https://doi.org/10.1155/2022/1271205

Research Article

The Effects of Electroacupuncture as an Adjunct Therapy on Poststroke Aphasia: A Systematic Review and Meta-Analysis

Yao Shi,[1] **Caixia Hu**,[1] **Shuhua Li**,[1] **Tianhua Huang**,[1] **Xingsheng Chen**,[1] **Guifu Li**,[1] **and Xiaohui Qin**[2]

[1]*Department of Neurology, The Second Affiliated Hospital of Guangzhou University of Chinese Medicine (Guangdong Provincial Hospital of Chinese Medicine) Guangzhou, Guangzhou, Guangdong, China*
[2]*Department of Neurosurgery, The Second Affiliated Hospital of Guangzhou University of Chinese Medicine (Guangdong Provincial Hospital of Chinese Medicine) Guangzhou, Guangzhou, Guangdong, China*

Correspondence should be addressed to Xiaohui Qin; 528861777@qq.com

Received 13 March 2022; Revised 6 June 2022; Accepted 27 June 2022; Published 5 August 2022

Academic Editor: Zhaolan Liu

Background. To systematically collate, appraise, and synthesize evidence of electroacupuncture (EA) as an adjunct therapy for poststroke aphasia (PSA) from randomized controlled trials (RCTs) through a systematic review and meta-analysis. *Methods*. An electronic search was conducted in eight databases to identify RCTs evaluating EA adjuvant therapy versus speech and language therapy (SLT). Methodological quality of the included trails was assessed by the Cochrane risk of bias. The software Review Manager 5.4 was used for data analysis. *Results*. Nineteen RCTs enrolling a total of 1263 subjects were identified. The use of EA combined with speech and language therapy (SLT) showed significant improvements in effective rate (RR 1.31, 95% CI [1.21, 1.41]), oral expression score (SMD 1.34, 95% CI [1.13, 1.56]), comprehension score (SMD 1.95, 95% CI [0.88, 3.03]), repetition score (SMD 1.84, 95% CI [0.75, 2.93]), naming score (SMD 1.97, 95% CI [0.81, 3.13]), and reading score (SMD 1.55, 95% CI [1.07, 2.04]) compared to the use of SLT alone. *Conclusions*. The pooled data indicate that EA combined with SLT for the treatment of PSA may improve clinical effectiveness, compared with SLT alone. Future high quality RCTs with large samples are still needed to confirm and expand our findings.

1. Introduction

Stroke is the most common cause of mortality and morbidity worldwide. Globally, more than ten million new cases of stroke are reported each year and at least one third of the affected individuals live with aphasia [1, 2]. Economic and social consequences are highly relevant because poststroke aphasia (PSA) has a serious negative impact on patients' activities of daily living [3]. Furthermore, the impact of PSA on functional communication, everyday activities, and social abilities of patients is dramatic and is, therefore, essential for the effective management and rehabilitation of aphasia [4]. Clinically, speech and language therapy (SLT) remain the gold standard for the treatment of PSA [5]. However, the clinical efficacy of this therapy still cannot meet patients' expectations [5]. In this situation, some patients choose complementary and alternative therapies to treat PSA in an effort to improve their quality of life.

In China, acupuncture is a widely used clinical rehabilitation technique, which is also recommended as an alternative treatment option for poststroke rehabilitation by the Ottawa Panel clinical practice guidelines [6]. As sources of the highest level of evidence for evidence-based medicine, previous systematic reviews/meta-analyses [7–13] have almost all revealed the benefits of acupuncture on PSA. As an extended technique of acupuncture, electroacupuncture (EA) has both the effects of traditional acupuncture and the functions of modern electrotherapy [14]. A recently published network meta-analysis [15] concluded that the efficacy of EA combined with SLT for PSA was superior to that of SLT alone. In addition, a systematic review [16] conducted in Korea concluded that EA could be considered as an

adjunctive therapy for PSA. Nevertheless, the relative effect of EA on PSA could not be assessed because quantitative synthesis was not performed. A preliminary literature search identified a growing number of randomized controlled trials (RCTs) on the effects of EA for PSA, whereas, controversial efficacy was reported. Thus, to systematically collate, evaluate, and synthesize current evidence, we conducted this study.

2. Methods

This meta-analysis was carried out following the guidelines of Cochrane handbook [17] and updated PRISMA checklists [18]. The protocol was registered in the PROSPERO database (no. CRD42021254369).

2.1. Literature Search and Selection. PubMed, the Cochrane Library, Web of Science, Embase, CNKI, Wanfang, VIP, and CBM were systematically searched from database establishment to June 2022. Stroke, aphasia, electroacupuncture, and randomized controlled trials were applied as search keywords. Detailed search strategy in PubMed was given in the supplementary material.

2.2. Inclusion and Exclusion Criteria. Trails met the following inclusion criteria: (I) type of studies: only randomized controlled trials were included; (II) types of participants: stroke was confirmed by neurological examination or by brain scanning, or both. Patients were not limited by gender and age; (III) types of interventions: the intervention was EA plus SLT; (IV) the comparison was SLT alone; (V) types of outcomes: language functions (oral expression, comprehension, repetition, naming, and reading) and effective rate. Language functions were assessed by scales including western aphasia battery (WAB) [19], China rehabilitation research center aphasia examination (CRRCAE) [20], and aphasia battery of Chinese (ABC) [21]. The definition of the effective rate: effective rate = ("total number of patients" - "number of patients with no response") /total number of patients, and "no response" meant no significant change in any aspect of language function or regression of one aspect of language function after treatment [22]; and (VI) it was published in English or Chinese language.

The exclusion criteria were as follows: (I) duplicate studies, duplications; (II) full text cannot be obtained through various approaches or studies in which data cannot be extracted; and (III) aphasia caused by other diseases.

2.3. Data Extraction and Outcome Measures. For literature selection, two independent reviewers read the titles and abstracts in the first screening stage, read the full texts in the final screening stage, and assessed the articles based on the inclusion and exclusion criteria. Information including the first author, publication year, sample size, patient characteristics, interventions, and outcomes were extracted from the included trails.

2.4. Quality Assessment. The risk of bias was independently assessed by two independent reviewers with the Cochrane risk of bias tool from seven domains: (I) randomization process; (II) allocation concealment; (III) blind method; (IV) outcome assessors; (V) missing outcome data processing; (VI) selection of the reported result; and (VII) other bias.

2.5. Statistical Analysis. Data analyses were carried out using Review Manager 5.4 software. The pooled effects were the relative risk (RR) and 95% CI for dichotomous outcomes and the standard mean difference (SMD) with 95% CI for continuous outcomes. Heterogeneity between the trails was determined using I^2 statistics. Fixed effects model was used if $I^2 < 50\%$; otherwise, a random effects model was used ($I^2 \geq 50\%$). Subgroup analyses were performed on the basis of treatment duration. Sensitivity analyses were carried out by removing each study individually to estimate the quality and consistency of the results. Publication bias was carried out with funnel plot.

3. Results

3.1. Literature Search. A total of 814 records were obtained from the eight databases and 184 duplicates were excluded. 630 records were removed after the titles and abstracts were screened. Eventually, 38 records were identified for full-text analysis, and 19 trails [23–41] were deemed eligible finally (Figure 1).

3.2. Characteristics of Included Studies. The included trails with sample sizes ranged from 20 to 120 published between 2000 and 2021. In total, 1263 subjects were included, with 638 in EA groups and 625 in control groups. The treatment cycle lasted 10 to 40 days, and each treatment lasted 15–60 min. More details are shown in Table 1.

3.3. Study Quality. A summary of the risk of biases is presented in Figures 2 and 3. With regards to random sequence generation, four studies [24, 33, 37, 39] had a high risk of bias. To reduce the impact of high risk of bias on the pooled results, these four trails [24, 33, 37, 39] were excluded from the performed meta-analysis. With regards to allocation concealment and blinding, all studies had an unclear risk of bias. All trails had a low risk of bias in incomplete outcome data. With regards to other sources of bias, eight studies had a low risk of bias.

3.4. Meta-Analysis

3.4.1. Effective Rate. 11 studies with a total of 747 subjects used the effective rate to evaluate the efficacy. A random-effect model was applied due to huge clinical heterogeneity in RCT, like acupoints and manipulation. The pooled analysis showed that EA combined with SLT had a higher effective rate (RR 1.31, 95% CI [1.21, 1.41]). In the subgroup analyses based on treatment duration, both subgroups showed statistically significant improvements in the effective rate with combined

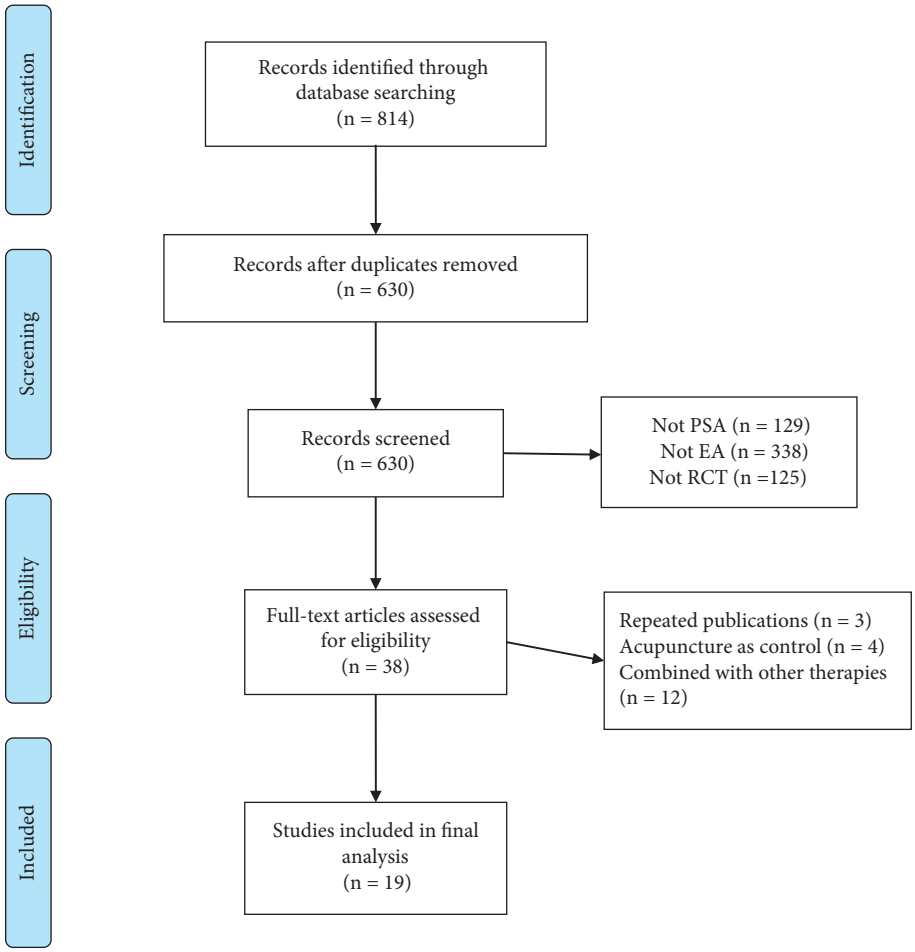


Figure 1: PRISMA flowchart for literature selection.

treatment compared to SLT alone (treatment for 2 weeks: RR 1.24, 95% CI [1.10, 1.40]; treatment for 3 weeks: RR 1.27, 95% CI [1.05, 1.54]; treatment for 4 weeks: RR 1.38, 95% CI [1.22, 1.57]). More details are shown in Figure 4,. The sensitivity analysis performed by the exclusion method showed that the study by Yang et al. [30] was the main cause of heterogeneity. In addition, the funnel plot was not symmetrical (Figure 5), which did not mean that there was a risk of publication bias because the sample size in this study was not small.

3.4.2. Oral Expression Score. Nine studies with a total of 650 subjects used the oral expression score to evaluate the efficacy. A random-effect model was applied, the pooled analysis showed that EA combined with SLT had a higher oral expression score (SMD 1.34, 95% CI [1.13, 1.56]). In the subgroup analysis based on treatment duration, both subgroups showed statistically significant improvements in oral expression score with combined treatment compared to SLT alone (treatment for 2 weeks: SMD 1.30, 95% CI [0.97, 1.63]; treatment for 3 weeks: SMD 1.62, 95% CI [1.22, 2.02]; treatment for 4 weeks: SMD 1.37, 95% CI [1.02, 1.73]; and treatment for 6 weeks: SMD 0.72, 95% CI [0.08, 1.36]). More details are shown in Figure 6.

The sensitivity analysis performed by the exclusion method showed that the study by Nie et al. [25] was the main cause of heterogeneity.

3.4.3. Comprehension Score. Six studies with a total of 456 subjects used the comprehension score to evaluate the efficacy. A random-effect model was applied, the pooled analysis showed that EA combined with SLT had a higher comprehension score (SMD 1.95, 95% CI [0.88, 3.03]). In the subgroup analysis based on treatment duration, both subgroups showed statistically significant improvements in comprehension score with combined treatment compared to SLT alone (treatment for 2 weeks: SMD 1.29, 95% CI [0.27, 2.30]; treatment for 3 weeks: SMD 1.58, 95% CI [0.86, 2.29]; and treatment for 4 weeks: SMD 3.10, 95% CI [0.74, 5.46]). More details are shown in Figure 7.

The sensitivity analysis performed by the exclusion method showed that no significant changes in heterogeneity were observed.

3.4.4. Reading Score. Two studies with 86 subjects used the reading score to evaluate the efficacy. A random-effect model was applied, the pooled analysis showed that EA combined with SLT had a higher reading score (SMD 1.55,

Table 1: Descriptive analysis of the characteristics.

First author; year	Simple		Age		Time post onset		Acupoints	Duration & frequency of trial period	Main outcomes
	I	C	I	C	I	C			
Wang et al. [23]. 2021	40	40	52.25 ± 4.71	52.30 ± 4.76	27.32 ± 3.83d	29.21 ± 3.85	DU16 (风府), DU15 (哑门)	20 min each time, once daily, 4 w	Oral expression score, comprehension score, repetition score, naming score, and ER
Wang [24]. 2021	25	25	Unclear	Unclear	Unclear	Unclear	DU20 (百会), Ex-HN13(金津), HT5 (通里), RN23(廉泉)	30 min each time, once daily, 4 w	Oral expression score, comprehension score, repetition score, naming score, and ER
Nie et al. [25]. 2020	23	23	51.0 ± 2.31	52.0 ± 3.12	Unclear	Unclear	Scalppoints	15 min each time, once daily, 10 d	Oral expression score, reading score, comprehension score, and ER
Ma et al. [26]. 2020	20	20	52.15 ± 9.82	51.36 ± 10.11	60.87 ± 21.43d	59.18 ± 24.21d	Scalppoints	30 min each time, once daily, 3 w	Oral expression score, comprehension score, repetition score, and naming score
Lin et al. [27]. 2019	40	40	52.25 ± 4.71	52.30 ± 4.76	Unclear	Unclear	MS6 (顶颞前斜线), MS10 (颞前线), EX-HN1(四神聪), DU16 (风府), DU20 (百会), EX-HN3(印堂), PC6(内关), DU26(水沟)、HT5(通里)、SP6(三阴, RN23(廉泉)	30 min each time, once daily, 2 w	Oral expression score, comprehension score, repetition score, naming score, and ER
Zheng et al. [28]. 2018	60	60	53.58 ± 1.81	58.38 ± 1.31	69.23 ± 4.32d	79.15 ± 3.53d	RN23(廉泉), GB8 (率谷)	30 min each time, once daily, 4 w	Oral expression score, comprehension score, reading score, repetition score, and naming score
Sun [29]. 2018	50	50	53.7 ± 5.2	52.3 ± 4.9	42.1 ± 12.5d	41.3 ± 11.2d	EX-HN13(玉液), Ex-HN13(金津)	20 min each time, once daily, 4 w	ER
Yang et al. [30]. 2017	45	45	58.4 ± 10.38	60.6 ± 11.57	8.68 ± 3.24d	6.78 ± 3.25d	Scalppoints, DU16 (风府), DU15 (哑门), DU20 (百会)	20 min each time, 5 times weekly, 2 w	Oral expression score, comprehension score, repetition score, naming score, and ER
Li et al. [31]. 2017	30	30	57.10 ± 10.03	58.11 ± 9.96	21.33 ± 5.16 d	22.10 ± 4.89 d	MS6 (顶颞前斜线), MS10 (颞前线), EX-HN1(四神聪), DU20 (百会), RN23(廉泉)	30 min each time, twice daily, 14d	Oral expression score, comprehension score, repetition score, naming score, and ER
Jiang et al. [32]. 2017	10	10	63.7 ± 6.6	58.7 ± 10.4	90.1 ± 58.2d	69.6 ± 43. 5d	MS6 (顶颞前斜线), MS7(顶颞后斜线), DU20 (百会)	60 min each time, twice daily, 2w	Oral expression score and ER
Cui et al. [33]. 2016	33	33	56.1 ± 11.0	56.3 ± 10.7	42.2 ± 19.3d	42.1 ± 19.5d	EX-HN13 (玉液), Ex-HN13 (金津)	20 min each time, once daily, 4w	Repetition score, naming score, and ER
Sheng et al. [34]. 2015	20	20	55.05 ± 9.27	57.10 ± 8.30	24.20 ± 10.95d	23.00 ± 10.40d	Unclear	30 min each time, twice daily, 4w	Oral expression score
Jiang et al. [35]. 2015	30	30	57 ± 10	57 ± 9	42.3 ± 19.2d	40.3 ± 19.4d	Unclear	30 min each time, twice daily, 4w	Repetition score and ER
Zhang et al. [36]. 2014	42	30	62.4 ± 1.4	57.6 ± 1.6	78.0 ± 8.6d	85.0 ± 9.2d	EX-HN13 (玉液), Ex-HN13 (金津)	20 min each time, once daily, 1m	ER
Du [37]. 2012	30	30	42~74	44~74	7~67d	9~66d	RN23 (廉泉)	30 min each time, twice daily, 4w	Oral expression score and ER
Aili et al. [38]. 2012	35	34	Unclear	Unclear	Unclear	Unclear	HT5 (通里), ST36 (足三里), KI6 (照海), PC6 (内关), LI4 (合谷), ST40 (丰隆),	30 min each time, once daily, 1m	ER
LI et al. [39]. 2007	30	30	54 ± 7.8	53 ± 5.6	7 ± 3.2d	7 ± 3.3d	RN23 (廉泉), EX-HN13 (玉液), Ex-HN13 (金津), EX-HN13 (翳明), GB20 (风池)	30 min each time, once daily, 20 d	ER
Zhang et al. [40]. 2005	45	45	56.7 ± 15.6	58.4 ± 13.3	24.4 ± 20.1d	23.4 ± 20.3d	RN23 (廉泉)	30 min each time, once daily, 3w	Oral expression score and ER
Liu et al. [41]. 2000	30	30	Unclear	Unclear	3w-6m	3w-6m	GB8 (率谷), GB13 (本神), DU20 (百会), GB20 (风池)	30 min each time, once daily, 30 d	Oral expression score and ER

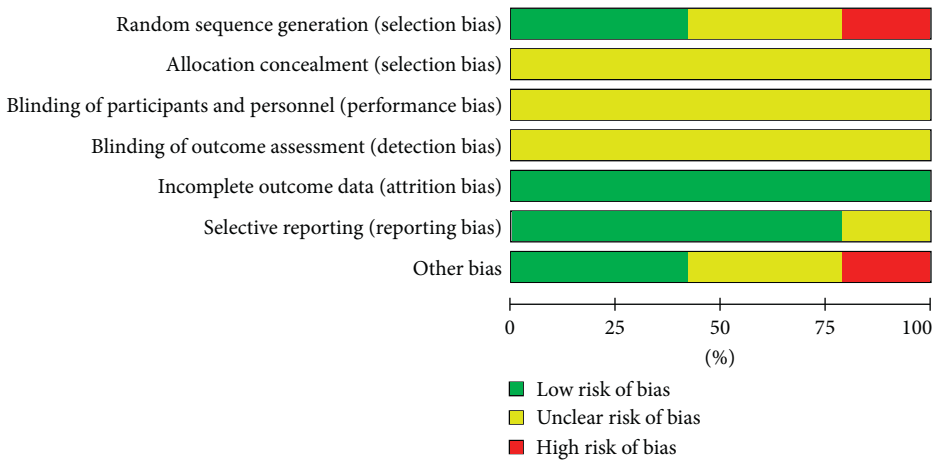


Figure 2: Risk of bias percentage chart.

95% CI [1.07, 2.04]). In the subgroup analysis based on treatment duration, both subgroups showed statistically significant improvements in reading score with combined treatment compared to SLT alone (treatment for 2 weeks: SMD 1.42, 95% CI [0.76, 2.07] and treatment for 4 weeks: SMD 1.73, 95% CI [0.99, 2.47]). More details are shown in Figure 8.

The sensitivity analysis performed by the exclusion method showed that no significant changes in heterogeneity were observed.

3.4.5. Repetition Score. Five studies with 410 subjects used the repetition score to evaluate the efficacy. A random-effect model was applied, the pooled analysis showed that EA combined with SLT had a higher repetition score (SMD 1.84, 95% CI [0.75, 2.93]). In the subgroup analysis based on treatment duration, subgroups showed statistically significant improvements in repetition score with combined treatment compared to SLT alone (treatment for 2 weeks: SMD 1.01, 95% CI [0.69, 1.33] and treatment for 3 weeks: SMD 2.48, 95% CI [1.64, 3.32]), however, with no evidence of benefit from treatment for 4 weeks (SMD 2.40, 95% CI [−0.70, 5.51]). More details are shown in Figure 9.

The sensitivity analysis performed by the exclusion method showed that no significant changes in heterogeneity were observed.

3.4.6. Naming Score. Five studies with 410 subjects used the naming score to evaluate the efficacy. A random-effect model was applied, the pooled analysis showed that EA combined with SLT had a higher naming score (SMD 1.97, 95% CI [0.81, 3.13]). In the subgroup analyses based on treatment duration, subgroups showed statistically significant improvements in naming score with combined treatment compared to SLT alone (treatment for 2 weeks: SMD 1.23, 95% CI [0.48, 1.99] and treatment for 3 weeks: SMD 2.39, 95% CI [1.56, 3.22]), however, with no evidence of benefit from treatment for 4 weeks (SMD 2.54, 95% CI [-0.90, 5.99]). More details are shown in Figure 10.

The sensitivity analysis performed by the exclusion method showed that no significant changes in heterogeneity were observed.

4. Discussion

Aphasia is a common complication following a stroke, often interfering with everyday activities, social abilities, and rehabilitation. In China, acupuncture has a long history of treating PSA, and its efficacy has been supported by evidence-based medical evidence [22]. As an extended technique of acupuncture, EA has both the effects of traditional acupuncture and the functions of modern electrotherapy and is widely used as a complementary therapy for post-stroke rehabilitation. An increasing number of RCTs have begun to investigate the effects of EA in patients with PSA. However, there is no uniform conclusion on whether the combination of EA and SLT has positive clinical efficacy in PSA. To systematically collate, appraise, and synthesize the evidence, we conducted this meta-analysis of RCTs.

4.1. Summary of Main Findings. Comprehensive analysis of this meta-analysis revealed that subjects treated using combined EA and SLT showed significant improvements in effective rate, oral expression score, comprehension score, repetition score, naming score, and reading score compared to those treated by SLT alone. Therefore, we tentatively conclude that EA combined with SLT as an adjunctive for PSA can increase its clinical effectiveness. However, this conclusion must be considered with cautious, given there was too little information in most of these included trails. Firstly, the processes of randomization, allocation concealment, and binding of most trails are unclear, which may have led to a high risk of bias. Secondly, none of the included RCTs applied statistical methods to estimate the sample size, which resulted in the small sample size included in the study and therefore lowering the credibility of the evidence. In addition, all included studies assessed outcomes before and immediately after EA treatment, while the treatment duration was 10–40 days; therefore, this

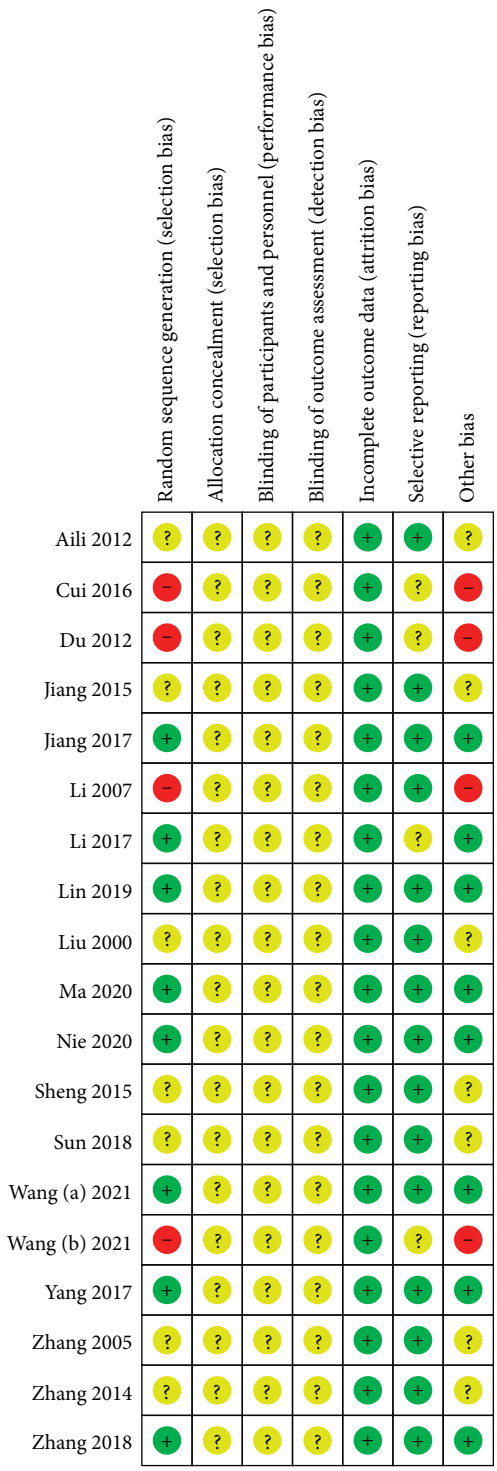


Figure 3: Risk of bias distribution diagram.

present study failed to further assess the long-term effects of EA on PSA. Moreover, the implementation program of EA was not uniform and showed large differences in acupoint selection, stimulation methods, needle retention time, and treatment period and frequency, which might have increased the source of heterogeneity [14]. Furthermore, all of the included trails were conducted in China, which may have led to publication bias.

4.2. Agreements and Disagreements with Other Published Reviews. Previous systematic reviews/meta-analyses [7–13] have almost all revealed the benefits of acupuncture on PSA. Our review agrees with other studies in the aspect that EA as an adjunct therapy on PSA, though with uncertainty. As an extended technique of acupuncture, studies on systematic synthesis of the evidence on EA for PSA are relatively lacking. A network meta-analysis [15] concluded that the

Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight (%)	Risk Ratio M-H, Random, 95% CI
1.1.1 Treatment for 2 weeks						
Li 2017	29	30	22	30	9.5	1.32 [1.05, 1.65]
Lin 2019	39	40	32	40	16.7	1.22 [1.04, 1.43]
Nie 2020	20	23	17	23	6.0	1.18 [0.88, 1.57]
Subtotal (95% CI)		*93*		*93*	*32.2*	*1.24 [1.10, 1.40]*
Total events	88		71			
Heterogeneity: Tau^2 = 0.00; Chi^2 = 0.45, *df* = 2 (*P* = 0.80); I^2 = 0%						
Test for overall effect: *Z* = 3.49 (*P* = 0.0005)						
1.1.2 Treatment for 3 weeks						
Zhang 2005	42	45	33	45	12.6	1.27 [1.05, 1.54]
Subtotal (95% CI)		*45*		*45*	*12.6*	*1.27 [1.05, 1.54]*
Total events	42		33			
Heteogeneity: Not applicable						
Test for overall effect: *Z* = 2.45 (*P* = 0.01)						
1.1.3 Treatment for 4 weeks						
Aili 2012	33	35	19	34	5.3	1.69 [1.24, 2.30]
Liu 2000	28	30	18	30	5.4	1.56[1.14, 2.12]
Sun 2018	49	50	38	50	18.5	1.26 [1.08, 1.46]
Wang (a) 2021	33	40	28	40	8.1	1.18 [0.92, 1.51]
Zhang 2005	42	45	33	45	12.6	1.27 [1.05, 1.54]
Zhang 2014	42	42	17	30	5.3	1.75 [1.28, 2.39]
Subtotal (95% CI)		*242*		*229*	*55.2*	*1.38 [1.22. 1.57]*
Total events	227		154			
Heterogeneity: Tau^2 = 0.01; Chi^2 = 8.48, *df* = 5 (*P* = 0.13); I^2 = 41%						
Test for overall effect: *Z* = 4.96 (*P* < 0.00001)						
Total (95% CI)		*380*		*367*	*100.0*	*1.31 [1.21, 1.41]*
Total events	357		258			
Heterogeneity: Tau^2 = 0.00; Chi^2 = 10.18, *df* = 9 (*P* = 0.34); I^2 = 12%						
Test for overall effect: *Z* = 7.07 (*P* < 0.00001)						
Test for subgroup differences: Chi^2 = 1.51, *df* = 2 (*P* = 0.47); I^2 = 0%						

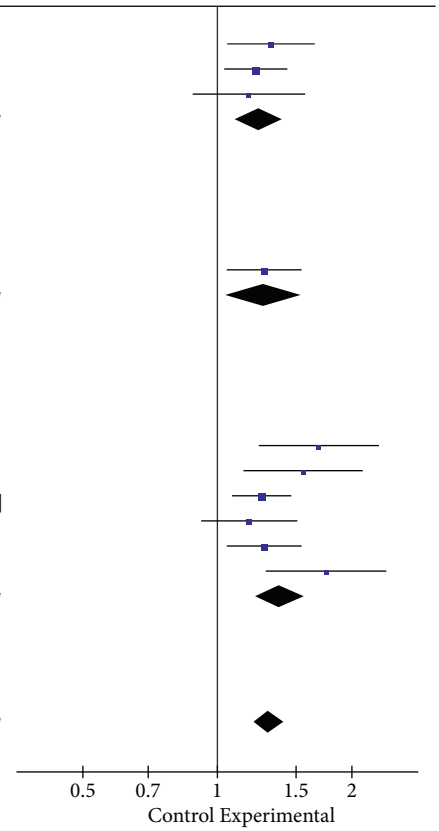


Figure 4: Meta-analysis in effective rate.

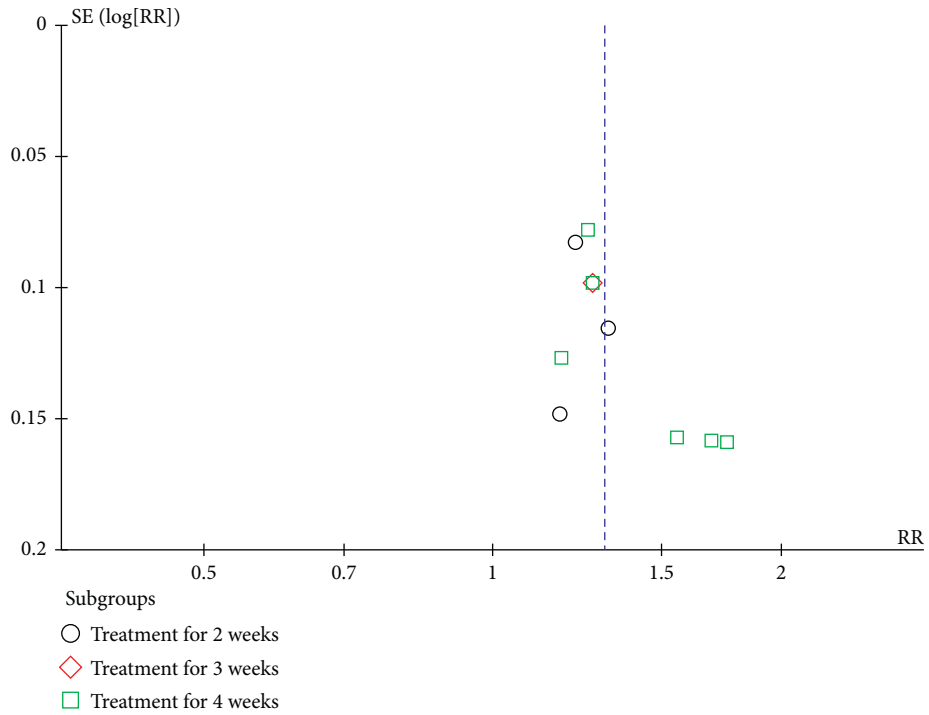


Figure 5: A funnel plot of effective rate.

Study or Subgroup	Experimental Mean	Experimental SD	Experimental Total	Control Mean	Control SD	Control Total	Weight (%)	Std. Mean Difference IV, Random, 95% CI
1.2.1 Treatment for 2 weeks								
Lin 2019	6.84	1.58	40	4.72	1.32	40	12.3	1.44 [0.95, 1.94]
Yang 2017	16.13	3.23	45	12.33	3.13	45	13.9	1.18 [0.74, 1.63]
Subtotal (95% CI)			*85*			*85*	*26.2*	*1.30 [0.97, 1.63]*
Heterogeneity: Tau^2 = 0.00; Chi^2 = 0.57, *df* = 1 (*P* = 0.45); I^2 = 0%								
Test for overall effect: *Z* = 7.67 (*P* < 0.00001)								
1.2.2 Treatment for 3 weeks								
Ma 2020	8.13	1.24	20	6.26	1.08	20	7.0	1.58[0.86, 2.29]
Zhang 2005	67.83	14.38	45	46.27	11.46	45	12.8	1.64 [1.16, 2.12]
Subtotal (95% CI)			*65*			*65*	*19.8*	*1.62 [1.22, 2.02]*
Heterogeneity: Tau^2 = 0.00; Chi^2 = 0.02, *df* = 1 (*P* = 0.88); I^2 = 0%								
Test for overall effect: Z = 7.96 (P < 0.00001)								
1.2.3 Treatment for 4 weeks								
Jiang 2017	99	13.89	10	7.4	19	10	3.9	1.44 [0.43, 2.45]
Wang (a) 2021	10.1	1.2	40	8.3	1.1	40	12.0	1.55 [1.05, 2.05]
Zhang 2005	67.83	14.38	45	46.27	11.46	45	12.8	1.64 [1.16, 2.12]
Zheng 2018	26	1.92	60	24.2	1.66	60	16.9	1.00 [0.62, 1.38]
Subtotal (95% CI)			*155*			*155*	*45.6*	*1.37 [1.02, 1.73]*
Heterogeneity: Tau^2 = 0.06; Chi^2 = 5.37, *df* = 3 (*P* = 0.15); I^2 = 44%								
Test for overall effect: *Z* = 7.60 (*P* < 0.00001)								
1.2.4 Treatment for 6 weeks								
Sheng 2015	37.1	7.14	20	31.25	8.69	20	8.4	
Subtotal (95% CI)			*20*			*20*	*8.4*	*0.72 [0.08, 1.36]*
Heterogeneity: Not applicable								
Test for overall effect: *Z* = 2.20 (*P* < 0.03)								
Total (95% CI)			*325*			*325*	*100.0*	*1.34 [1.13, 1.56]*
Heterogeneity: Tau^2 = 0.03; Chi^2 = 11.52, *df* = 8 (*P* = 0.17); I^2 = 31%								
Test for overall effect: *Z* = 12.46 (*P* < 0.00001)								
Test for subgroup differences: Chi^2 = 5.58, *df* = 3 (*P* = 0.13); I^2 = 46.2%								

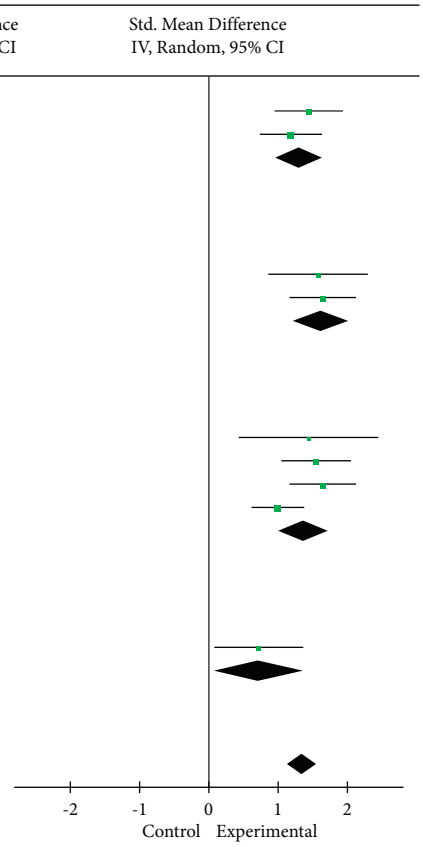


Figure 6: Meta-analysis in oral expression score.

Study or Subgroup	Experimental Mean	Experimental SD	Experimental Total	Control Mean	Control SD	Control Total	Weight (%)	Std. Mean Difference IV, Random, 95% CI
1.3.1 Treatment for 2 weeks								
Lin 2019	7.13	1.8	40	5.59	1.06	40	17.0	1.03 [0.56, 1.50]
Nie 2020	35.18	3.12	23	28.21	2.13	23	16.1	2.56 [1.77, 3.36]
Yang 2017	140.21	22.57	45	130	24.33	45	17.2	0.43 [0.01, 0.85]
Subtotal (95% CI)			*108*			*108*	*50.3*	*1.29 [0.27, 2.30]*
Heterogeneity: Tau^2 = 0.72; Chi^2 = 21.81, *df* = 2 (*P* < 0.0001); I^2 = 91%								
Test for overall effect: *Z* = 2.48 (*P* = 0.01)								
1.3.2 Treatment for 3 weeks								
Ma 2020	8.13	1.24	20	6.26	1.08	20	16.3	1.58[0.86, 2.29]
Subtotal (95% CI)			*20*			*20*	*16.3*	*1.58[0.86, 2.29]*
Heterogeneity: Not applicable								
Test for overall effect: Z = 4.30 (*P* < 0.0001)								
1.3.3 Treatment for 4 weeks								
Wang (a) 2021	11.7	1.4	40	9.1	1.3	40	16.9	1.91 [1.37, 2.44]
Zheng 2018	40.65	1.8	60	32.95	1.75	60	16.5	4.31 [3.65, 4.97]
Subtotal (95% CI)			*100*			*100*	*33.4*	*3.10 [0.74, 5.46]*
Heterogeneity: Tau^2 = 2.80; Chi^2 = 30.86, *df* = 1 (*P* < 0.00001); I^2 = 97%								
Test for overall effect: *Z* = 2.58 (*P* = 0.010)								
Total (95% CI)			*228*			*228*	*100.0*	*1.95 [0.88, 3.03]*
Heterogeneity: Tau^2 = 1.70; Chi^2 = 107.29, *df* = 5 (*P* = 0.00001); I^2 = 95%								
Test for overall effect: *Z* = 3.57 (*P* = 0.0004)								
Test for subgroup differences: Chi^2 = 1.92, *df* = 2 (*P* = 0.38); I^2 = 0%								

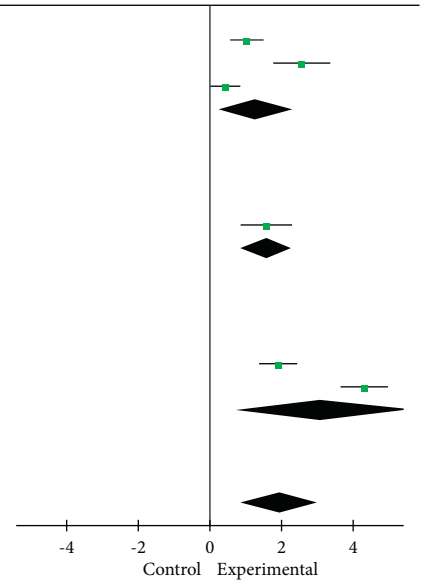


Figure 7: Meta-analysis in comprehension score.

efficacy of EA combined with SLT for PSA was superior to SLT alone in effective rate. The results of this meta-analysis in effective rate are consistent with this network meta-analysis [15]. Furthermore, we also performed subgroup analyses based on treatment duration and assessed the effect of EA on oral expression score, comprehension score,

Study or Subgroup	Experimental Mean	Experimental SD	Experimental Total	Control Mean	Control SD	Control Total	Weight (%)	Std. Mean Difference IV, Random, 95% CI
1.4.1 Treatment for 2 weeks								
Nie 2020	62.67	5.21	23	55.71	4.42	23	56.1	1.42 [0.76, 2.07]
Subtotal (95% CI)			*23*			*23*	*56.1*	*1.42 [0.76, 2.07]*
Heterogeneity: Not applicable								
Test for overall effect: $Z = 4.25$ ($P < 0.0001$)								
1.4.2 Treatment for 4 weeks								
Zheng 2018	28.85	1.96	20	25.68	1.61	20	43.9	1.73 [0.99, 2.47]
Subtotal (95% CI)			*20*			*20*	*43.9*	*1.73 [0.99, 2.47]*
Heterogeneity: Not applicable								
Test for overall effect: $Z = 4.60$ ($P < 0.00001$)								
Total (95% CI)			*43*			*43*	*100.0*	*1.55 [1.07, 2.04]*
Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 0.40$, $df = 1$ ($P = 0.53$); $I^2 = 0\%$								
Test for overall effect: $Z = 6.24$ ($P < 0.00001$)								
Test for subgroup differences: $Chi^2 = 0.40$, $df = 1$ ($P = 0.53$); $I^2 = 0\%$								

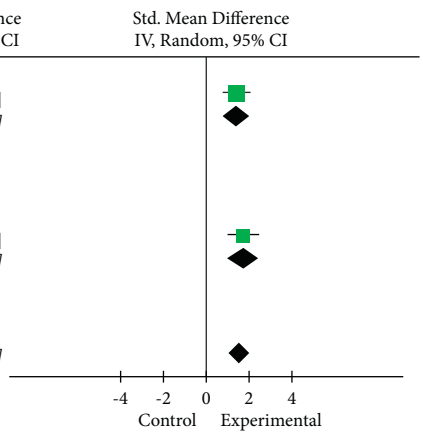


Figure 8: Meta-analysis in reading score.

Study or Subgroup	Experimental Mean	Experimental SD	Experimental Total	Control Mean	Control SD	Control Total	Weight (%)	Std. Mean Difference IV, Random, 95% CI
1.5.1 Treatment for 2 weeks								
Lin 2019	7.94	2.04	40	6.08	1.58	40	20.4	1.01 [0.54, 1.48]
Yang 2017	87.98	11.39	45	77	10.14	45	20.5	1.01 [0.57, 1.45]
Subtotal (95% CI)			*85*			*85*	*40.9*	*1.01 [0.69, 1.33]*
Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 0.00$, $df = 1$ ($P = 1.00$); $I^2 = 0\%$								
Test for overall effect: $Z = 6.18$ ($P < 0.00001$)								
1.5.2 Treatment for 3 weeks								
Ma 2020	6.96	0.92	20	4.86	0.73	20	18.8	2.48 [1.64, 3.32]
Subtotal (95% CI)			*20*			*20*	*18.8*	*2.48 [1.64, 3.32]*
Heterogeneity: Not applicable								
Test for overall effect: $Z = 5.76$ ($P < 0.00001$)								
1.5.3 Treatment for 4 weeks								
Wang (a) 2021	8.7	2.3	40	6.9	2	40	20.4	0.83[0.37, 1.28]
Zheng 2018	47.68	2.19	60	39.67	1.77	60	19.8	4.00 [3.37, 4.62]
Subtotal (95% CI)			*100*			*100*	*40.3*	*2.40 [-0.70, 5.51]*
Heterogeneity: $Tau^2 = 4.95$; $Chi^2 = 64.15$, $df = 1$ ($P < 0.00001$); $I^2 = 98\%$								
Test for overall effect: $Z = 1.52$ ($P = 0.013$)								
Total (95% CI)			*205*			*205*	*100.0*	*1.84 [0.75, 2.93]*
Heterogeneity: $Tau^2 = 1.46$; $Chi^2 = 83.52$, $df = 4$ ($P = 0.00001$); $I^2 = 95\%$								
Test for overall effect: $Z = 3.31$ ($P = 0.0009$)								
Test for subgroup differences: $Chi^2 = 10.76$, $df = 2$ ($P = 0.005$); $I^2 = 81.4\%$								

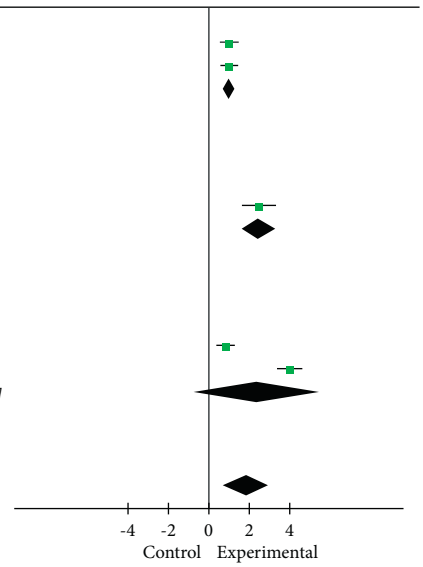


Figure 9: Meta-analysis in repetition score.

repetition score, naming score, and reading score. In addition, a systematic review [16] of 10 RCTs involving 756 patients conducted in Korea concluded that EA could be considered as an adjunctive therapy for PSA. The difference with our meta-analysis was that it did not perform a quantitative synthesis to assess the relative effect of EA on PSA. Our pooled results are more conducive to the certainty of definitive evidence.

4.3. Implications for Research. Of the 19 included trials, only 8 was rated as low risk bias in randomization process, and none of which reported allocation concealment and blinding information. The sample sizes of the studies ranged from 20 to 120, studies with larger sample sizes, clear information about randomization and allocation concealment methods, and statements about whether participants, personnel, and outcome assessors were blinded are needed to assess the effectiveness of EA for PSA. Future studies should pay particular attention to the effects of EA on long-term functional outcomes. It is worth noting that the EA protocols in each study were diverse, including point selection and stimulation duration; therefore, a more standardized and uniform EA treatment protocol should be advocated, which would also facilitate the promotion of EA. In addition, the studies were all conducted in China, and further reliable studies in other ethnic populations are needed to determine population-specific response differences.

4.4. Potential Mechanism of Action. Although there is currently limited evidence of EA for PSA, the mechanism by which EA improve symptoms of PSA is being confirmed. An MRI study [42] revealed that the language-related brain

Study or Subgroup	Experimental Mean	Experimental SD	Experimental Total	Control Mean	Control SD	Control Total	Weight (%)	Std. Mean Difference IV, Random, 95% CI
1.6.1 Treatment for 2 weeks								
Lin 2019	7.99	1.24	40	6.75	1.62	40	20.4	0.85 [0.39, 1.31]
Yang 2017	82.86	9.39	45	69	7.47	45	20.4	1.62 [1.14, 2.10]
Subtotal (95% CI)			*85*			*85*	*40.8*	*1.23[0.48, 1.99]*
Heterogeneity: Tau^2 = 0.24; Chi^2 = 5.16, *df* = 1 (*P* < 0.02); I^2 = 81%								
Test for overall effect: *Z* = 3.21 (*P* = 0.001)								
1.3.2 Treatment for 3 weeks								
Ma 2020	6.39	0.89	20	4.51	0.63	20	19.0	2.39 [1.56, 3.22]
Subtotal (95% CI)			*20*			*20*	*19.0*	*2.39 [1.56, 3.22]*
Heterogeneity: Not applicable								
Test for overall effect: *Z* = 5.65 (*P* < 0.00001)								
1.6.3 Treatment for 4 weeks								
Wang (a) 2021	8.2	1.5	40	6.6	2.4	40	20.4	0.79 [0.34, 1.25]
Zheng 2018	39.35	1.83	60	31.63	1.73	60	19.7	4.31 [3.65, 4.97]
Subtotal (95% CI)			*100*			*100*	*40.2*	*2.54 [-0.90, 5.99]*
Heterogeneity: Tau^2 = 6.10; Chi^2 = 73.85, *df* = 1 (*P* < 0.00001); I^2 = 99%								
Test for overall effect: *Z* = 1.45 (*P* = 0.015)								
Total (95% CI)			*205*			*205*	*100.0*	*1.97 [0.81, 3.13]*
Heterogeneity: Tau^2 = 1.66; Chi^2 = 90.52, *df* = 4 (*P* = 0.00001); I^2 = 96%								
Test for overall effect: *Z* = 3.33 (*P* = 0.0009)								
Test for subgroup differences: Chi^2 = 4.30, *df* = 2 (*P* = 0.12); I^2 = 53.4%								

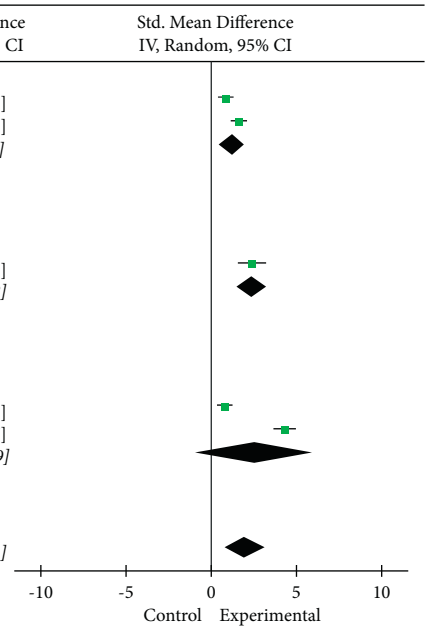


Figure 10: Meta-analysis in naming score.

areas can be activated through EA treatment. A wide range of brain functional areas such as frontal lobe, occipital lobe, parietal lobe, temporal lobe, precuneus, and insula showed active hyperintensity after EA treatment [42]. Similarly, another MRI study also confirmed this finding [43], that stimulation of acupoints associated with language deficits can selectively activate the brain on the lesional side of PSA patients. In addition, it has been found that EA helps to increase blood perfusion in higher speech centers, which in turn improves the ischemic and hypoxic state of brain tissue and awakens nerve cells [44]. The clinical findings were also demonstrated in rat experiments [45]. After receiving EA intervention, the researchers observed significant proliferation of endogenous neural stem cells in rats with cerebral ischemia-reperfusion injury, suggesting that EA can promote the repair of neurological function and reduce secondary nerve injury [45]. Hence, from the potential mechanism of action, EA seems to be a promising method for the treatment of PSA.

4.5. Limitations. There were several potential limitations in this meta-analysis. Firstly, because the included trials lacked follow-up information on EA for PSA, this study could not provide long-term effects of EA for PSA. Secondly, although different acupoint combinations have a significant effect on PSA, our meta-analysis only focused on the overall clinical effect of EA in the treatment of PSA, but did not evaluate the acupoint combination, there it could not provide a basis for specific acupoint selection strategies [46, 47]. Furthermore, the great differences in acupoints pose a challenge to the quantitative findings of this study, so future RCTs should be advocated to adopt standard EA treatment protocols and reduce the generation of heterogeneity to produce more persuasive results.

5. Conclusion

The modality of EA combined with SLT for PSA may improve clinical effectiveness compared to SLT alone, which provides a new option for clinical decision-making. However, limited data, poor methodological quality, and potentially exaggerated effect size evaluation limit the quality of the evidence. More high quality, multi-centers RCTs with large samples are still needed to provide higher evidence.

Abbreviations

PSA: Poststroke aphasia
SLT: Speech and language therapy
RCTs: Randomized clinical trials
ER: Effective rate.

Data Availability

The datasets used in the present review are available from the corresponding author on reasonable request.

Conflicts of Interest

The authors declare that they have no conflicts of interest.

Authors' Contributions

Yao Shi conceived the study and drafted the manuscript. Caixia Hu, Shuhua Li, Tianhua Huang, Xingsheng Chen, Xiaohui Qin, and Guifu Li implemented the study. All authors read and approved the final manuscript.

Acknowledgments

The study was supported by the 13th Chaoyang Talent Project of Guangdong Provincial Hospital of Traditional Chinese Medicine (No. ZY2022YL28), and the Scientific Research Project of Guangdong Provincial Bureau of Traditional Chinese Medicine (No. 20201165).

Supplementary Materials

Supplementary material: detailed search strategy for PubMed. (*Supplementary Materials*)

References

[1] "Correction to: heart disease and stroke statistics-2017 update: a report from the American heart association," *Circulation*, vol. 136, p. e196, 2017.

[2] S. T. Engelter, M. Gostynski, S. Papa et al., "Epidemiology of aphasia attributable to first ischemic stroke: incidence, severity, fluency, etiology, and thrombolysis," *Stroke*, vol. 37, no. 6, pp. 1379–1384, 2006.

[3] K. Hilari, M. Cruice, R. Sorin-Peters, and L. Worrall, "Quality of life in aphasia: state of the art," *Folia Phoniatrica et Logopaedica*, vol. 67, no. 3, pp. 114–118, 2015.

[4] F. Mattioli, "The clinical management and rehabilitation of post stroke aphasia in Italy: evidences from the literature and clinical experience," *Neurological Sciences*, vol. 40, no. 7, pp. 1329–1334, 2019.

[5] M. C. Brady, H. Kelly, J. Godwin, and P. Enderby, "Speech and language therapy for aphasia following stroke," *Cochrane Database of Systematic Reviews*, vol. 5, Article ID CD000425, 2012.

[6] O. Panel, A. Khadilkar, K. Phillips et al., "Ottawa panel evidence-based clinical practice guidelines for post-stroke rehabilitation," *Topics in Stroke Rehabilitation*, vol. 13, no. 2, pp. 1–269, 2006.

[7] Y. Zhang, Z. Wang, X. Jiang, Z. Lv, L. Wang, and L. Lu, "Effectiveness of acupuncture for poststroke aphasia: a systematic review and meta-analysis of randomized controlled trials," *Complement Med Res*, vol. 28, no. 6, pp. 545–556, 2021.

[8] He-Y. Tang, W. Tang, F. Yang, W. Wu, and G. Shen, "Efficacy of acupuncture in the management of post-apoplectic aphasia: a systematic review and meta-analysis of randomized controlled trials," *BMC Complementary and Alternative Medicine*, vol. 19, no. 1, p. 282, 2019.

[9] B. Zhang, Y. Han, X. Huang et al., "Acupuncture is effective in improving functional communication in post-stroke aphasia: a systematic review and metaanalysis of randomized controlled trials, Wien. Klin," *Wiener Klinische Wochenschrift*, vol. 131, no. 9-10, pp. 221–232, 2019.

[10] W. M. Zhu, W. J. Zhong, B. Xu, and X. H. Chen, "Meta-analysis on the clinical efficacy of acupuncture combined with speech rehabilitation for aphasia after stroke," *Lishizhen Med. Mater. Med. Res.*vol. 29, no. 08, pp. 252–257, 2018.

[11] Y. P. Jiang, Y. F. Zhou, and B. Wang, "The efficacy of acupuncture on treating aphasia following stroke: a meta-analysis," *Journal of Xinjiang Medical University*, vol. 46, no. 10, pp. 1237–1241, 2016.

[12] Y. Zhang, L. X. Fu, Y. Zhu, and P. J. Xue, "Acupuncture treatment for aphasia after stroke: a systematic review," *Journal of Clinical Acupuncture and Moxibustion*, no. 11, pp. 66–69, 2014.

[13] Y. Pang, L. B. Wu, and D. H. Liu, "Acupuncture therapy for apoplectic aphasia: a systematic review," *Chinese Acupuncture & Moxibustion*, vol. 30, no. 7, pp. 612–616, 2010.

[14] J. Huang, Y. Shi, X. Qin, M. Shen, M. Wu, and Y. Huang, "Clinical effects and safety of electroacupuncture for the treatment of poststroke dysphagia: a comprehensive systematic review and meta-analysis," *Evidence-based Complementary and Alternative Medicine*, vol. 2020, Article ID 1560978, 9 pages, 2020.

[15] Y. Zhong, W. X. Qin, Z. J. Wang, Q. Yuan, W. T. Zhu, and Y. Zhang, "Efficacy of acupuncture and moxibustion for aphasia after stroke: a network meta—analysis," *Liaoning Journal of Traditional Chinese Medicine*, vol. 48, no. 04, pp. 17–20+222, 2021.

[16] J.-b. Ha, S.-J. Lee, J.-S. Yang, and J. H. Lew, "Electro-acupuncture on aphasia after stroke: a systemic review of randomized controlled trials," *The Journal of Internal Korean Medicine*, vol. 42, no. 3, pp. 323–339, 2021.

[17] P. H. Julian, G. A. Douglas, and A. S. Jonathan, "Assessingrisk of bias in included studies," in *Cochrane Handbook of Systematic Reviewsof InterventionsVersion 5.1.0*, P. H. Julian and G. Sally, Eds., Te Cochrane Collaboration, London, UK, 2011.

[18] M. J. Page, J. E. McKenzie, P. M. Bossuyt et al., "The PRISMA 2020 statement: an updated guideline for reporting systematic reviews," *BMJ*, vol. 372, p. n71, 2021.

[19] M. Dekhtyar, E. J. Braun, A. Billot, L. Foo, and S. Kiran, "Videoconference administration of the western aphasia battery-revised: feasibility and validity," *American Journal of Speech-Language Pathology*, vol. 29, no. 2, pp. 673–687, 2020.

[20] J. Tao, Y. Fang, Z. Wu et al., "Community-applied research of a traditional Chinese medicine rehabilitation scheme on Broca's aphasia after stroke: study protocol for a randomized controlled trial," *Trials*, vol. 15, no. 1, p. 290, 2014.

[21] C. Chen, X. Liu, S. Pan, X. Wu, and J. Wu, "[Neurolinguistic features during recovery of a Chinese patient with pure alexia]," *Nan Fang Yi Ke Da Xue Xue Bao*, vol. 33, no. 5, pp. 713–718, 2013.

[22] J. K. Huang, X. H. Qin, M. Shen, and Y. Huang, "An overview of systematic reviews and meta-analyses on acupuncture for post-stroke aphasia," *European Journal of Integrative Medicine*, vol. 37, Article ID 101133, 2020.

[23] S. Q. Wang, X. Yuan, M. Li, S. Y. Xu, and R. H. Luo, "Clinical study of applying low prequency rTMS associated with electroacupuncture at fengfu and yamen acupoints in the treatment of broca aphasia after stroke," *Journal of Sichuan of Traditional Chinese Medicine*, vol. 39, no. 01, pp. 194–197, 2021.

[24] X. P. Wang, "Effective value of electroacupuncture combined with low frequency repetitive transcranial magnetic stimulation in the treatment of motor aphasia after stroke," *Healthmust-Readmagazine.*vol. 11, pp. 211-212, 2021.

[25] T. Nie, Y. Huang, and C. X. Mo, "An analysis of treating aphasia after stroke by language rehabilitation training plus scalp electroacupuncture," *Clinical Journal of Chinese Medicine*, vol. 12, no. 29, pp. 80–82, 2020.

[26] Y. P. Ma and K. Yang, "Therapeutic effect of scalp electro acupuncture combined with language training on stroke motor aphasia," *Chinese Manipulation & Qi Gong Therapy*, vol. 11, no. 11, pp. 62–64, 2020.

[27] M. Lin and M. J. Lin, "Effect of scalp electroacupuncture combined with speech training in the treatment of aphasia after stroke," *China Modern Medicine*, vol. 26, no. 19, pp. 62–65, 2019.

[28] Y. B. Zheng and S. F. Lin, "A clinical study of electro-acupuncture at lian quan (CV23) and shuai gu (G8) in the treatment of motor aphasia patients after stroke," *Chinese Medicine Modern Distance Education of China*, vol. 16, no. 9, pp. 122–124, 2018.

[29] Y. L. Sun, "Clinical study of speech rehabilitation training combined with electroacupuncture stimulation of nerve trunk therapy in the treatment of stroke speech disorder," *Journal of Practical Traditional Chinese Medicine*, vol. 34, no. 10, pp. 1248-1249, 2018.

[30] L. Yang and Y. G. Guo, "Clinical study of scalp electro-acupuncture combined with language training on post- stroke aphasia patients," *Chinese Journal of Rehabilitation Medicine*, vol. 32, no. 3, pp. 305–308+312, 2017.

[31] T. Li, Y. Wang, and L. Zhang, "Evaluation of scalp electro-—acupuncture combined with speech training on broca language dysfunction after stroke," *Journal of Clinical Acupuncture and Moxibustion*, vol. 33, no. 9, pp. 13–16, 2017.

[32] Y. P. Jiang, Y. F. Zhou, and W. Q. Niu, "Effect of electro-acupuncture combined with aphasia training system on Uygur patients with aphasia," *Chinese Journal of Gerontology*, vol. 37, no. 02, pp. 444–446, 2017.

[33] N. Cui, B. Yu, and J. Jiang, "Observation on therapeutic effect of electroacupuncture stimulation of nerve trunk on apoplectic speech disorder," *Shaanxi Journal of Traditional Chinese Medicine*, vol. 37, no. 07, pp. 915-916, 2016.

[34] G. B. Sheng, X. N. Yin, and Y. Tang, "Clinical observation on treatment of non-fluent aphasia after stroke with electro-acupuncture in temporal area," *Chinese Journal of Traditional Medical Science and Technology*, vol. 22, no. 2, p. 235, 2015.

[35] Y. Jiang, Y. Yang, R. Xiang et al., "Clinical study of post-stroke speech apraxia treated with scalp electric acupuncture under anatomic orientation and rehabilitation training," *Chinese Acupuncture & Moxibustion*, vol. 33, 2015.

[36] S. Y. Zhang and S. B. Liu, "Observation on therapeutic effect of electroacupuncture stimulation of nerve trunk on apoplectic speech disorder," *Chinese Journal of Rehabilitation*, vol. 29, no. 5, p. 336, 2014.

[37] J. Y. Du, *Clinical Observation of Electroacupuncture on Speech and Swallowing Disorders Caused by Pseudobulbar Palsy*, Heilongjiang University of Chinese Medicine, Harbin, China, 2012.

[38] B. Aili, "Clinical effect of electroacupuncture combined with rehabilitation training on dysphagia and speech disorder after stroke," *Chinese Manipulation & Qi Gong Therapy*, vol. 003, no. 009, p. 46, 2012.

[39] H. X. Li, L. R. Liu, and Z. C. Yang, "Clinical study of electroacupuncture on dysphagia and dysphonia after Wallenberg syndrome," *Acta Chinese Medicine and Pharmacology*, vol. 35, no. 5, pp. 24–26, 2007.

[40] X. L. Zhang, A. P. Wang, and J. R. Zhang, "Clinical study of electroacupuncture stimulation combined with language training on aphasia after stroke," *Chinese Journal of Practical Nervous Diseases*, vol. 8, no. 001, pp. 16-17, 2005.

[41] L. A. Liu, N. Mou, and X. He, "Clinical observation on the treatment of apoplectic aphasia by electroacupuncture combined with language training," *Chinese Acupuncture & Moxibustion*, vol. 20, no. 3, pp. 145–148, 2000.

[42] J. Chang, H. Zhang, Z. Tan, J. Xiao, S. Li, and Y. Gao, "Effect of electroacupuncture in patients with post-stroke motor aphasia: neurolinguistic and neuroimaging characteristics," *Wiener Klinische Wochenschrift*, vol. 129, no. 3-4, pp. 102–109, 2017.

[43] G. Li and E. S. Yang, "An fMRI study of acupuncture-inducedbrain activation of aphasia stroke patients," *Complementary Therapies in Medicine*, vol. 19, no. 1, pp. S49–S59, 2011.

[44] J. Huang, M. Wu, S. Liang et al., "A critical overview of systematic reviews and meta-analyses on acupuncture for poststroke insomnia," *Evid Based Complement Alternat Med*, vol. 2020, Article ID 2032575, 7 pages, 2020.

[45] Y. G. Zhang, X. Gong, and H. B. Li, "Effects of electro-acupuncture on the expressions of nestin and glial fibrilliary Acidic protein in dentate gyrus of focal cerebral ischemia-reperfusion rats," *Chinese Journal of Histochemistry and Cytochemistry*, vol. 23, no. 2, pp. 148–153, 2014.

[46] J. Huang, J. Liu, Z. Liu et al., "Reliability of the evidence to guide decision-making in acupuncture for functional dyspepsia," *Frontiers in Public Health*, vol. 10, Article ID 842096, 2022.

[47] J. Huang, M. Lu, Y. Zheng et al., "Quality of evidence supporting the role of acupuncture for the treatment of irritable bowel syndrome," *Pain Research and Management*, vol. 2021, Article ID 2752246, 10 pages, 2021.

Hindawi
Evidence-Based Complementary and Alternative Medicine
Volume 2022, Article ID 6522690, 9 pages
https://doi.org/10.1155/2022/6522690

Research Article

Research on Herbal Therapies for Osteoarthritis in 2004–2022: A Web of Science-Based Cross-Sectional Bibliometric Analysis

Weijiang Song,[1] **Jiaqi Chen**,[2,3] **Guoyan Yang**,[4] **Jiahe Liao**,[2,3] **Hongbo Shen**,[1] **Sai Li**,[1] **Ning Ding**,[1] **and Dong Li**[1]

[1]*Traditional Chinese Medicine Department, Peking University Third Hospital, Beijing, China*
[2]*Graduate School, Beijing University of Chinese Medicine, Beijing, China*
[3]*Traditional Chinese Medicine Department of Rheumatism, China-Japan Friendship Hospital, Beijing, China*
[4]*NICM Health Research Institute, Western Sydney University, Sydney, Australia*

Correspondence should be addressed to Dong Li; lidong6512@sina.com

Weijiang Song and Jiaqi Chen contributed equally to this work.

Received 25 April 2022; Accepted 21 June 2022; Published 30 July 2022

Academic Editor: Xing Liao

Objective. The extent, range, and nature of available research in the field of herbal therapies for osteoarthritis (OA) have not been systematically analyzed. This study aimed to map the literature available on herbal therapies for OA and identify global hotspots and trends in this field. *Methods*. Studies on herbal therapies for OA published between 2004 and 2022 were searched from the Web of Science Core Collection. Microsoft Excel, SPSS Statistics, and CiteSpace software were used to analyze and visualize the quantity and citations of publications, and the research hotspots and trends in research on herbal therapies for OA. *Results*. A total of 1649 publications mainly from 76 countries/regions and 270 institutions were included in this study. From 2004 to 2022, there is an upward trend in the publications of herbal therapies for OA. China ranked first in the number of publications ($n = 568$, 34.45%), followed by the USA ($n = 353$, 21.41%), South Korea ($n = 187$, 11.34%), Germany ($n = 85$, 5.15%), and England ($n = 79$, 4.79%). Kyung Hee University ($n = 46$), Xianxiang Liu ($n = 25$), and *Evidence-Based Complementary and Alternative Medicine* ($n = 74$) were the most prolific affiliation, author, and journal, respectively. Felson DT ($n = 185$) and *Arthritis and Rheumatism* ($n = 1173$) held the record for the most cited papers by an author and journal, respectively. Currently, the hot keywords in the field of herbal therapies for OA include knee OA, traditional Chinese medicine (TCM), differentiation, rosa canina, inflammation, oxidative stress, stem cell, and regenerative medicine. The emerging research trends in herbal therapies for OA are herbal medicinal product, chronic knee pain, mesenchymal stem cell, and clinical pharmacology. *Conclusions*. Research on herbal therapies for OA is flourishing, but communication among countries/regions should be strengthened. Current research on herbal therapies for OA mainly focuses on knee OA, TCM, differentiation, rosa canina, inflammation, oxidative stress, stem cell, and regenerative medicine. The research frontiers are herbal medicinal product, chronic knee pain, mesenchymal stem cell, and clinical pharmacology.

1. Introduction

Osteoarthritis (OA) is the most common degenerative joint disorder that affects one or more diarthrodial joints and is often accompanied by joint pain, stiffness, dysfunction, and structural damages [1]. Age, obesity, genetics, sex, and joint biomechanics are generally considered risk factors for OA [2]. With the ageing and increasing obesity in the global population and the increasing numbers of joint injuries, OA is prevalent, with a worldwide estimate suggesting that 250 million people are currently affected [3]. Moreover, according to the *Global Burden of Disease Study 2019*, OA is the leading cause of disability and source of societal cost in older adults [4].

Recent research has revealed that the mechanism of OA is closely related to inflammation, oxidative stress, apoptosis, and energy metabolism, and these factors can interact with each other [5]. However, the pathogenesis of OA has not

been understood fully, and further research is still needed. To date, no disease-modifying OA drug has received regulatory approval yet. For the main symptoms of joint pain, nonsteroidal anti-inflammatory drugs (NSAIDs), analgesics, and corticosteroids are available as optional drugs. Even so, the cardiovascular and digestive safety issues often surround NSAIDs, and the addictive nature of central analgesics are also concerns of clinicians and patients [6, 7]. Recent case series suggested that negative structural outcomes including accelerated OA progression, subchondral insufficiency fracture, complications of osteonecrosis, and rapid joint destruction may be observed in patients receiving intra-articular corticosteroid injections [8]. Therefore, there is a need to explore effective and safer treatments. Herbs or herbal products have a long history in treating OA and show great potential to generate less adverse events than pharmaceutical drugs [9, 10]. Furthermore, researchers have discovered that herbal therapies can slow down the progression of OA via several mechanisms [11]. At present, there are a large number of literature on herbal therapies for OA, and a bibliometrics is needed.

Bibliometrics is a cross-science that uses mathematical and statistical methods to study documents and bibliometric characteristics [12, 13], such as countries/regions, institutions, journals, authors, and citations. [14]. So far, there are few bibliometric studies on traditional medicine in treating OA, and the majority of them focused on nondrug treatments, such as Tai Chi and acupuncture [15, 16]. However, no bibliometric study has been published on herbal therapies for OA to inform the volume, breadth, and characteristics of research in this area. Hence, we aimed to analyze publications on herbal therapies for OA from 2004 to 2022 and discussed the current hotspots and trends in research.

2. Materials and Methods

2.1. Data Collection. We searched the Web of Science Core Collection (WoSCC) from its inception until 10 February 2022. The search terms were centered on OA and herbs (Figure S1). Articles and reviews reporting herbal therapies in treating OA were eligible for inclusion irrespective of language. Early access, conference proceedings, letters, editorial materials, corrections, book chapters, retracted publications, and editorial materials were excluded. Two authors independently screened all titles and abstracts of the records. The full texts were retrieved for further identification in accordance with eligibility criteria. All uncertainties or discrepancies were resolved through discussion. A total of 1,743 records were identified, of which 94 records were excluded because they did not meet the eligibility criteria. Finally, 1,649 papers were included in this bibliometric study (Figure S1).

2.2. Data Analysis. All included papers retrieved from WoSCC were imported into Microsoft Excel 2019 (Microsoft Corp, Redmond, Washington, USA), which was used to analyze the number of papers published in the year and journal. SPSS Statistics 20 (IBM, Armonk, New York, USA) was used for trend analysis of the number of publications. A $p < 0.05$ was considered statistically significant. CiteSpace V5.8.R3 (Chaomei Chen, Philadelphia, Pennsylvania, USA) was used to perform visual analysis, including the distribution of countries/regions, institutions, authors, co-cited authors, cocited journals, cocited references, keyword cluster, and timeline viewer. CiteSpace is a widely used visualization analysis software, which can combine information visualization methods, bibliometrics, and data mining algorithms in an interactive visualization tool for extraction of patterns in citation data [17, 18] to analyze the structure and distribution of scientific knowledge and the visualizing trends in scientific literature [19].

3. Results

3.1. The Trend of Publication Outputs. A total of 1,649 papers involving 1,285 articles and 364 reviews published between January 2004 and February 2022 were included for analysis in this study. From 2004 to 2022, the total number of published papers on herbal therapies for OA increased year by year (Figure S2, $p < 0.001$). Since 2017, the number of outputs in the field of herbal therapies for OA has exceeded 100, and the number of publications increased significantly in 2020, with a total number of 235 (14.3%). Compared with 2020, the number of publications in 2021 had a slight decrease. However, till February 10, 2022, 19 papers on herbal therapies for OA have been published in 2022, which was similar to a year of outputs in 2006.

3.2. Distribution of Countries/Regions and Institutions. The 1,649 included papers were published mainly by 76 countries/regions involving 270 institutions. As shown in Table 1, China ranked first in the number of publications ($n = 568$, 34.45%), much higher than other countries/regions, followed by the USA ($n = 353$, 21.41%), South Korea ($n = 187$, 11.34%), Germany ($n = 85$, 5.15%), and England ($n = 79$, 4.79%). Kyung Hee University was the most prolific institution ($n = 46$, 2.79%), followed by Shanghai University of Traditional Chinese Medicine ($n = 42$, 2.55%), Fujian University of Traditional Chinese Medicine ($n = 39$, 2.37%), Beijing University of Chinese Medicine ($n = 32$, 1.94%), and Zhejiang University ($n = 27$, 1.64%).

Figure 1 showed the visualization map of publications related to herbal therapies for OA from different countries/regions. Each node represents a country. The lines between two nodes suggest the communication capability between two countries, and the denser lines indicate closer communication. Overall, the centrality of nodes in the knowledge map measures the importance of node position and reflects the communication capability of the nodes, and each node with high centrality has an outer purple circle. Our results showed that among the top 10 countries with the highest number of publications, 6 countries (USA, Italy, England, Canada, Australia, and Germany) had a centrality of more than 0.1, suggesting these are important bridge countries having strong

Table 1: Distribution of publications in the field of herbal therapies for OA from different countries/regions and institutions.

Rank	Country/region	Year	Centrality	Count (%)	Institution	Year	Centrality	Count (%)
1	Peoples R China	2004	0.04	568 (34.45)	Kyung Hee Univ	2005	0.06	46 (2.79)
2	USA	2004	0.51	353 (21.41)	Shanghai Univ Tradit Chinese med	2011	0.14	42 (2.55)
3	South Korea	2004	0.05	187 (11.34)	Fujian Univ Tradit Chinese med	2010	0.02	39 (2.37)
4	Germany	2004	0.12	85 (5.15)	Beijing Univ Chinese med	2015	0.03	32 (1.94)
5	England	2004	0.23	79 (4.79)	Zhejiang Univ	2012	0.06	27 (1.64)
6	India	2004	0.08	71 (4.31)	Shanghai Jiao Tong Univ	2011	0.01	25 (1.52)
7	Australia	2004	0.19	67 (4.06)	Peking Univ	2009	0.07	24 (1.46)
8	Italy	2004	0.31	67 (4.06)	Chinese Univ Hong Kong	2004	0.15	24 (1.46)
9	Canada	2004	0.15	57 (3.46)	Univ Sydney	2011	0.08	23 (1.39)
10	Taiwan	2007	0.05	47 (2.85)	Korea Inst Oriental med	2006	0.05	23 (1.39)

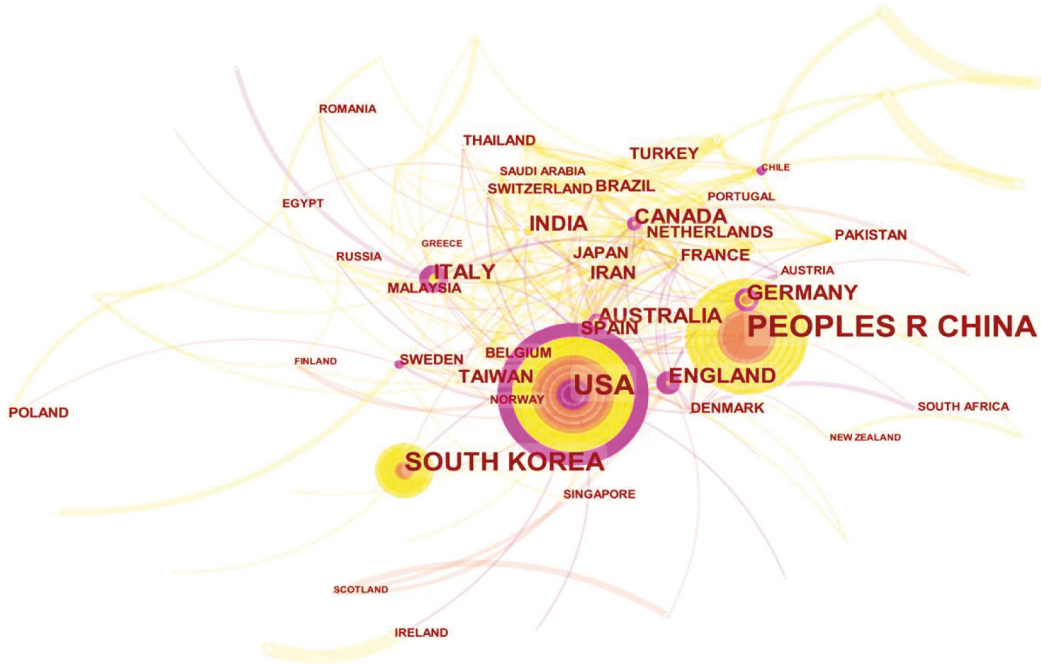


Figure 1: CiteSpace visualization map of publications in the field of herbal therapies for OA from different countries/regions.

communication power all over the world in the field of herbal therapies for OA.

3.3. Authors and Co-Cited Authors. There were 2,038 major authors involved in the 1,649 papers in this study. As shown in Table 2, Xianxiang Liu was the most prolific author in the number of publications on herbal therapies for OA ($n = 25$, 1.52%), followed by Hongzhi Ye ($n = 22$, 1.33%), and Xihai Li ($n = 20$, 1.21%). Cocited authors are two or more authors who are cited by another literature at the same time. There were 1,848 cocited authors in this study. Among these cocited authors, 9 had a frequency of citation over 100 times, and Felson DT was the top cocited author ($n = 185$), followed by Zhang W ($n = 157$).

3.4. Journals and Cited Journals. A total of 586 journals were involved in the 1,649 articles in this study. As shown in Table 3, *Evidence-Based Complementary and Alternative Medicine* was the top journal in the number of publications on herbal therapies for OA ($n = 74$, 4.49%), followed by the *Journal of Ethnopharmacology* ($n = 56$, 3.40%) and *Medicine* ($n = 49$, 2.97%). Cocited journals are two or more journals that are cited simultaneously. Among 924 cocited journals, 5 were cited over 500 times. *Arthritis and Rheumatism* was the top cocited journal, followed by *Osteoarthritis and Cartilage* ($n = 888$), and *Annals of The Rheumatic Diseases* ($n = 667$).

3.5. The Hotspots of Keywords. Keywords often reflect the research topics, and their analysis can indicate the research hotspots in a specific field. The keywords ($n \geq 80$) related to herbal therapies for OA are shown in Table S1. Among these keywords, OA had the highest frequency ($n = 447$), followed by knee OA ($n = 438$), double-blind ($n = 202$), rheumatoid arthritis ($n = 187$), expression ($n = 170$), and pain ($n = 159$). OA, knee OA, and double-blind had a high centrality (>0.10), indicating a great influence of these keywords in the research of herbal therapies for OA.

Table 2: Top authors ($n \geq 10$) and co-cited authors ($n \geq 80$) related to herbal therapies for OA.

Rank	Author	Year	Centrality	Count (%)	Cocited author	Year	Centrality	Citation
1	Xianxiang Liu	2009	<0.01	25 (1.52)	Felson DT	2004	<0.01	185
2	Hongzhi Ye	2009	<0.01	22 (1.33)	Zhang W	2004	0.04	157
3	Xihai Li	2011	0.01	20 (1.21)	Anonymous	2005	<0.01	153
4	Chunsong Zheng	2011	0.01	15 (0.91)	Hochberg MC	2004	0.03	151
5	Dongsuk Park	2008	<0.01	11 (0.67)	Bellamy N	2004	0.01	145
6	Yonghyeon Baek	2008	<0.01	11 (0.67)	Goldring MB	2005	<0.01	143
7	Peijian Tong	2014	<0.01	11 (0.67)	Altman R	2004	0.01	142
8	Jaedong Lee	2008	<0.01	10 (0.61)	Altman RD	2004	<0.01	125
9	Guangwen Wu	2011	0.01	10 (0.61)	Mcalindon TE	2004	0.01	121
10	Xueyong Shen	2013	<0.01	10 (0.61)	Loeser RF	2008	0.01	98
11	Qi Jia	2010	<0.01	10 (0.61)	Ernst E	2004	<0.01	95
12	Ling Zhao	2013	<0.01	10 (0.61)	Hunter DJ	2008	<0.01	88
13	Huifeng Xu	2011	<0.01	10 (0.61)	Lawrence RC	2004	<0.01	82

Table 3: Top 10 journal and cocited journals related to herbal therapies for OA.

Rank	Journal	Count (%)	Cocited journal	Citation
1	Evidence-Based Complementary and Alternative Medicine	74 (4.49)	Arthritis and Rheumatism	1,173
2	Journal of Ethnopharmacology	56 (3.40)	Osteoarthritis and Cartilage	888
3	Medicine	49 (2.97)	Annals of the Rheumatic Diseases	667
4	Phytotherapy Research	29 (1.76)	Journal of Rheumatology	555
5	BMC Complementary and Alternative Medicine	24 (1.46)	Lancet	502
6	Trials	23 (1.39)	Arthritis Research & Therapy	474
7	Frontiers in Pharmacology	21 (1.27)	Rheumatology	431
8	Chinese Journal of Integrative Medicine	20 (1.21)	PloS One	429
9	Osteoarthritis and Cartilage	19 (1.15)	Journal of Ethnopharmacology	421
10	Phytomedicine	19 (1.15)	Annals of Internal Medicine	379

The strong citation burst of keywords represents sharp changes in the number of citations for keywords, which can reflect the rise or fall of research hotspots. As shown in Figure 2, among the top 25 keywords related to herbal therapies for OA, NSAIDS, controlled clinical trial, placebo, and complementary and alternative medicine were popular keywords from 2004 to 2017. Since 2011, interleukin-1β has been a hot keyword. Since 2018, pathogenesis, inflammation, network pharmacology, stem cell, oxidative stress, traditional Chinese medicine (TCM), and differentiation have been hotspots studied in herbal therapies for OA.

The timeline mapping of keywords is the summarization and classification of research keywords, which can show the characteristics of research over time. As shown in Figure 3, keywords on herbal therapies for OA were classified into the following 6 clusters: inflammation, knee OA, celecoxib, rosa canina, scaphoid, and regenerative medicine. Since 2004, inflammation, knee OA, and rosa canina have been in the spotlight. Celecoxib and scaphoid boomed in 2004 but declined in 2010 and 2007, respectively. Regenerative medicine began to garner attention in 2010 and has continued to develop in recent years.

3.6. The Research Frontiers of Herbal Therapies for OA. Cocited papers mean two papers appear in the reference list of another paper, and cocitation analysis can mine the cocitation relationships of papers in the repository. A total of 1,373 articles were cited in papers on herbal therapies for OA in this study, of which 10 papers were cited more than 20 times (table S2). The paper ranked at the top of citations was *OARSI guidelines for the non-surgical management of knee osteoarthritis*. The strongest citation bursts of references, just as the strongest citation bursts of keywords, can reflect changes in research hotspots over a period of time. Figure 4 showed the top 25 references with the strongest citation bursts involved in herbal therapies for OA. Up to now, nearly half of the references remain research hotspots.

On the basis of cocitation analysis, we used CiteSpace to extract cluster labels from papers by cluster analysis, showing the research frontiers in the field of herbal therapies for OA. Silhouette score can evaluate the effect of clustering. When the silhouette score is >0.7, the clustering result is convincing. As shown in Table S3, the following 7 main cluster labels were obtained in the field of herbal therapies for OA: network pharmacology, chronic disorder, mesenchymal stem cell, clinical pharmacology, herbal medicinal product, biological basis, and chronic knee pain.

4. Discussion

4.1. General Information. This is the first bibliometric analysis identifying the global research hotspots and trends in the field of herbal therapies for OA. Our results indicated that the number of publications on herbal therapies for OA

Top 25 Keywords with the Strongest Citation Bursts

Keywords	Year	Strength	Begin	End	2004 - 2022
non-steroidal anti-inflammatory drug	2004	10.02	2004	2017	
controlled clinical trial	2004	8.78	2004	2017	
celecoxib	2004	7.9	2004	2010	
placebo	2004	7.71	2004	2017	
complementary and alternative medicine	2004	6.33	2004	2017	
double blind	2004	6.18	2004	2010	
herbal remedy	2004	5.74	2004	2010	
therapeutic arthritis research	2004	5.59	2004	2010	
low back pain	2004	5.56	2004	2010	
clinical trial	2004	4.99	2004	2017	
alternative medicine	2004	4.7	2004	2017	
rosa canina	2004	4.54	2004	2010	
aqueous extract	2004	4.41	2004	2010	
rofecoxib	2004	4.3	2004	2010	
disability	2004	5.75	2011	2017	
medicine	2004	5.02	2011	2017	
interleukin-1 beta	2004	4.8	2011	2022	
women	2004	4.47	2011	2017	
pathogenesis	2004	6.73	2018	2022	
inflammation	2004	5.99	2018	2022	
network pharmacology	2004	5.69	2018	2022	
stem cell	2004	5.68	2018	2022	
oxidative stress	2004	5.13	2018	2022	
traditional chinese medicine	2004	4.93	2018	2022	
differentiation	2004	4.87	2018	2022	

Figure 2: CiteSpace visualization map of top 25 keywords with the strongest citation bursts involved in herbal therapies for OA.

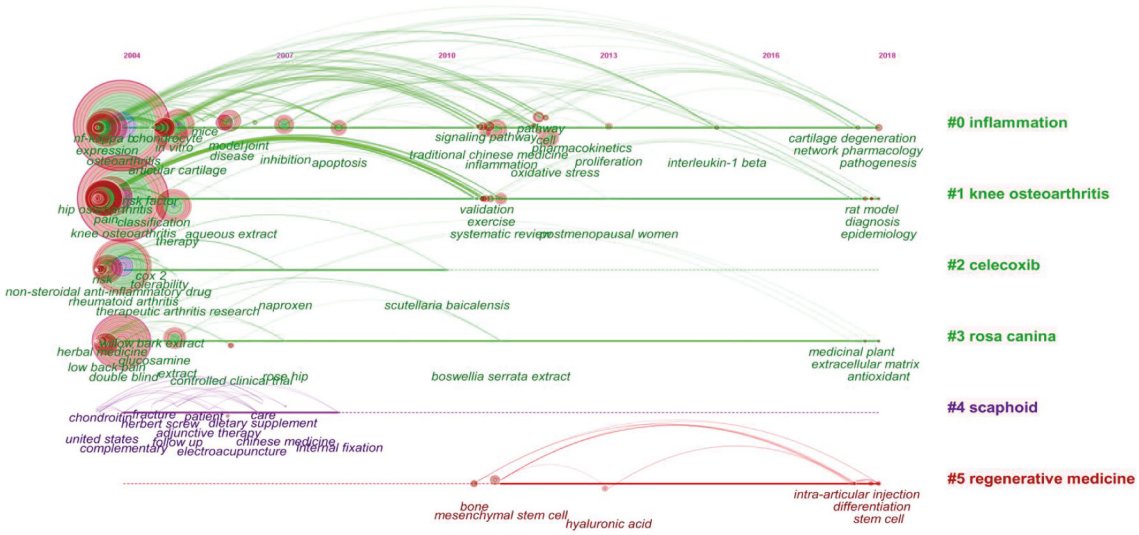


Figure 3: CiteSpace visualization map of timeline viewer related to herbal therapies for OA.

presented an overall upward trend in the field of herbal therapies for OA from 2004 to 2022, suggesting that research on herbal therapies for OA is flourishing. Between 2004 and 2016, the number of publications grew slowly. Since 2016, the growth had accelerated, especially in 2020, suggesting that herbal therapies for OA is attracting increasing attention in recent years.

We found that China ranked first in the number of publications on herbal therapies for OA, followed by the USA, South Korea, Germany, and England. Meanwhile, the centrality of the USA was significantly higher than other countries, indicating that the USA played a bridging role in international cooperation. Seven of the top 10 institutions in the number of publications were from China, with Shanghai

Top 25 References with the Strongest Citation Bursts

References	Year	Strength	Begin	End	2004 - 2022
Clegg DO, 2006, NEW ENGL J MED, V354, P795, DOI 10.1056/NEJMoa052771, DOI	2006	8.76	2006	2017	
Zhang W, 2008, OSTEOARTHR CARTILAGE, V16, P137, DOI 10.1016/j.joca.2007.12.013, DOI	2008	8.3	2008	2017	
Berman BM, 2004, ANN INTERN MED, V141, P901, DOI 10.7326/0003-4819-141-12-200412210-00006, DOI	2004	7.74	2004	2010	
Schniter TJ, 2004, LANCET, V364, P665, DOI 10.106/S0140-6736(04)16893-1, DOI	2004	6.96	2004	2010	
Lawrence RC, 2008, ARTHRITIS RHEUM, V58, P26, DOI 10.1002/art.23176, DOI	2008	6.78	2008	2017	
Silverstein FE, 2000, JAMA-J AM MED ASSOC, v284, P1247, DOI 10.1001/jama.284.10.1247, DOI	2000	6.71	2004	2010	
Ezzo J, 2001, ARTHRITIS RHEUM, V44, P819, DOI 10.1002/1529-0131(200104)44:4<819::AID-ANR138>3.3.CO;2-G, DOI	2001	6.37	2004	2010	
Brinkhaus B, 2006, ARCH INTERN MED, V166, P450	2006	5.88	2006	2017	
McAlindon TE, 2014, OSTEOARTHR CARTILAGE, V22, P363, DOI 10.1016/j.joca.2014.01.003, DOI	2014	19.05	2014	2022	
Hochberg MC, 2012, ARTHRIT CARE RES, V64, P465, DOI 10.1002/acr.21596, DOI	2012	16.47	2012	2017	
Cross M, 2014, ANN RHEUM DIS, V73, P1323, DOI 10.1136/annrheumdis-2013-204763, DOI	2014	12.36	2014	2022	
Bijlsma JWJ, 2011, LANCET, V377, P2115, DOI 10.1016/S0140-6736(11)60243-2, DOI	2011	8.18	2011	2017	
Zhang W, 2010, OSTEOARTHR CARTILAGE, V18, P476, DOI 10.1016/j.joca.2010.01.013, DOI	2010	7.6	2011	2017	
Kuptniratsaikul V, 2014, CLIN INTERV AGING, V9, P451, DOI 10.2147/CIA.S58535, DOI	2014	7.37	2014	2017	
Wojdasiewicz P, 2014, MEDIAT INFLAMM, V2014, P0, DOI 10.1155/2014/561459, DOI	2014	7.35	2014	2022	
Kapoor M, 2011, NAT REV RHEUMATOL, V7, P33, DOI 10.1038/nrrheum.2010.196, DOI	2011	7.28	2011	2017	
Hinman RS, 2014, JAMA-J AM MED ASSOC, V312, P1313, DOI 10.1001/jama.2014.12660, DOI	2014	6.5	2014	2022	
Glyn-Jones S, 2015, LANCET, V393, P1745, DOI 10.1016/S0140-6736(14)60802-3, DOI	2015	16.33	2018	2022	
Hunter DJ, 2019, LANCET, V393, P1745, DOI 10.1016/S0140-6736(19)30417-9, DOI	2019	16.23	2019	2022	
Bannuru RR,2019, OSTEOARTHR CARTILAGE, V27, P1578, DOI 10.1016/j.joca.2019.06.011, DOI	2019	13.52	2019	2022	
TANG X, 2016, ARTHRITIS RHEUMATOL, V68, P648, DOI 10.1002/ART.39465, DOI	2016	11.1	2018	2022	
Kolasinki SL, 2020, ARTHRITIS RHEUMATOL, V72, P220	2020	10.12	2020	2022	
Chen D, 2017, BONE RES, V5, P0, DOI 10.1038/boneres.2016.44, DOI	2017	9.2	2018	2022	
Robinson WH, 2016, NAT REV RHEUMATOL, V12, P580, DOI 10.1038/nrrheum.2016.136, DOI	2016	6.64	2018	2022	
Loser RF, 2016, NAT REV RHEUMATOL, V12, P412, DOI 10.1038/nrrheum.2016.65, DOI	2016	5.9	2018	2022	

Figure 4: CiteSpace visualization map of top 25 references with the strongest citation bursts involved in herbal therapies for OA.

University of Traditional Chinese Medicine and the Chinese University of Hong Kong showing a high level of collaboration. Two Korean institutions, named Kyung Hee University and Korea Institute of Oriental Medicine, were on the top 10 lists, with less international collaboration. Xianxiang Liu and *Evidence-Based Complementary and Alternative Medicine* were the most prolific author and journal, respectively. Simultaneously, Felson DT and *Arthritis and Rheumatism* were the most influential author and journal by holding the most cited papers, respectively. There was no overlap in the top 10 publications and citations by authors and journals, revealing that we still lack author and journal with a high impact on herbal therapies for OA. The *OARSI guidelines for the non-surgical management of knee osteoarthritis* [20] published in 2019 was the most cited reference, while a new guideline published in 2020 named *the 2019 American College of Rheumatology/Arthritis Foundation Guideline for the Management of Osteoarthritis of the Hand, Hip, and Knee* may be a new focus in the future [21].

4.2. The Hotspots and Frontiers

4.2.1. Role of Herbal Therapies for OA. In research on herbal therapies for OA, our results indicated that knee OA has been a research hotspot for a long time (since 2004), and TCM and differentiation also became a research hotspot in 2018. All these suggested that traditional Chinese herbal medicine are research hotspots in the field of herbal therapies for OA. In TCM theories, differentiation refers to syndrome identification, which means the classification of syndrome into a variety of unbalance conditions [22]. Patients with OA could have distinct syndrome classification that dictates different treatment strategies. In this case, traditional Chinese herbal medications will be tailored to the individual patient, which may result in better effects and fewer side effects. However, due to the individualized characteristics of the syndrome, it is difficult to conduct randomized controlled trials and placebo-controlled trials for traditional Chinese herbal medicine. This may account for the decline in randomized placebo-controlled trials since 2018. Due to a lack of high-quality clinical evidence, Chinese herbal medications are often considered complementary or alternative therapies for patients with OA.

Herbal medicinal products and chronic knee pain are research frontiers in herbal therapies for OA. As one of the major symptoms of OA, chronic knee pain seriously impairs the quality of life for patients [23]. Many studies have indicated that herbal therapies can improve pain and slow the progression of OA [24]. Some researchers aim at transforming herbs with potential therapeutic effects into established herbal medicinal products or new clinical medicines. However, the selection of herbs for the treatment of OA is largely empirical, is time-consuming, and lacks high-quality evidence to support it. The complex composition of herbs makes it difficult to explore the exact active ingredient. Furthermore, the interactions between herbal medications with each other are not fully understood. Therefore, there is a long way to elucidate the mechanisms and determine the efficacy and role of herbal therapies for OA.

4.2.2. Main Types of Herbal Therapies for OA. There is a wide range of herbs available for the treatment of OA. Our results showed that rosa canina, a European traditional herb, has been extensively studied since 2004 [25]. A recent meta-analysis included randomized controlled trials that showed that rosa canina powder can alleviate the pain of OA [26], and its mechanism of action is related to antioxidant and anti-inflammatory [27]. TCM mainly includes herbal compounds and herb extracts and has been used in China for over 2,500 years for chronic pain and OA. A famous

TCM compound named *Duhuo Jisheng Tang*, which was invented in the Tang Dynasty, is considered beneficial and widely used in treating OA in China. In addition to compound herbal medicine, many single herbs also showed effects on attenuating symptoms of OA and may be potential therapeutic agents for OA, such as *rhizoma drynariae*, *icariin*, and *curcuma longa* [28–30]. However, current herbal medicines are primarily used as complementary or alternative therapies for OA due to limited evidence [31]. Further long-term, large-sample, high-quality evidence is warranted to support the application of herbal medicines for the treatment of OA.

4.2.3. Mechanisms of Herbal Therapies for OA. For the mechanisms of herbal therapies in treating OA, our results showed that inflammation, oxidative stress, stem cell, regenerative medicine, and network pharmacology were important research hotspots; mesenchymal stem cell and clinical pharmacology were major research frontiers. Understanding the mechanisms of herbal therapies is helpful to maximize the therapeutic effects and develop therapeutic agents. Network pharmacology and clinical pharmacology are research methods aiming at exploring pharmacological actions and therapeutic mechanisms of herbal medicines for OA. It is worth noting that network pharmacology must be analyzed in conjunction with experimental validation to generate trusted evidence.

Inflammation, interleukin-1β, and oxidative stress have been research hotspots in the mechanism study of herbal therapies for OA for a long time. As a proinflammatory factor, interleukin-1β can induce joint inflammation and seems to be associated with cartilage destruction [32]. Interleukin-1β is now often used as a stimulator in cellular experiments. Oxidative stress has been proposed as a driver of the catabolic and anabolic signaling imbalance in cartilage that results in progressive matrix degradation [33]. In addition, oxidative stress can induce senescence in joint cells [34]. There was a correlation between increased oxidative stress and the induction of senescence in cartilage, which might drive OA [33]. Some herbs, such as *curcuma longa*, *vernonia amygdalina*, and *icariin*, can suppress inflammation, decrease oxidative stress, and reduce local symptoms of joints in OA [29, 35, 36].

Stem cell was a research hotpot, and mesenchymal stem cell and regenerative medicine were research frontiers in herbal therapies for OA. Regenerative medicine is an emerging research field in recent years. Recent studies suggested that bone mesenchymal stem cell therapy can relieve local pain and partially repair injured cartilage, with the therapeutic goal of joint regeneration [37]. Some herbs (such as *andrographolide* and *honokiol*) have been shown to improve cell survival and chondrogenesis of mesenchymal stem cells [38, 39], which may be a major potential therapeutic mechanism of herbal therapies for OA.

4.3. Limitations. There are certain shortcomings in this study. Firstly, since we used CiteSpace software for data analysis, which removed some components that were calculated to be insignificant during the analyses, our results may miss some interesting data. Secondly, we only searched one comprehensive English database that could not cover all studies in herbal therapies for OA, so potential bias may exist in the results. Thirdly, as this is a bibliometric analysis, we did not evaluate the methodological quality of included studies and critically analyze the effects of herbal therapies for OA; our results were based majorly on the quantity of publications and citations and may use as a start point for research in this area.

5. Conclusion

Research on herbal therapies for OA is flourishing, but communication among countries should be strengthened. China ranked first in the number of publications, followed by the USA, South Korea, Germany, and England. Current research on herbal therapies for OA mainly focuses on knee OA, TCM, differentiation, rosa canina, inflammation, oxidative stress, stem cell, and regenerative medicine. The emerging research trends in herbal therapies for OA are herbal medicinal product, chronic knee pain, mesenchymal stem cell, and clinical pharmacology.

Data Availability

Data sharing is not applicable to this article as no new data were created in this study. These datasets were derived from the following public domain resources: https://www.webofscience.com/wos/woscc/advanced-search.

Conflicts of Interest

The authors declare that there are no conflicts of interest regarding the publication of this article. The funding agencies had no roles in the study design, collection, analysis, and interpretation of the data, in the report's writing, and in the decision to submit the paper for publication.

Authors' Contributions

Conceptualization was done by D.L.; W.S. and J.C. contributed to the methodology; G.Y., J.L., H.S., S.L., and N.D. investigated the study; W.S. and J.C. wrote the manuscript; and G.Y. and D.L. critically revised the manuscript. W.S. and J.C. contributed equally to the work and share the first authorship.

Acknowledgments

The authors would like to thank Citespace software developers. This work was supported by National Natural Science Foundation of China (81804042).

Supplementary Materials

Figure S1 Flowchart of literature search and selection. Figure S2 Trends of publications in the field of herbal therapies for OA from 2004 to 2022. Table S1 Top keywords ($n \geq 80$) related to herbal therapies for OA. Table S2 Top 10

references related to herbal therapies for OA. Table S3 The clusters of cocited references in herbal therapies for OA. (*Supplementary Materials*)

References

[1] J. Martel-Pelletier, A. J. Barr, F. M. Cicuttini et al., "Osteoarthritis," *Nature Reviews Disease Primers*, vol. 2, no. 1, Article ID 16072, 2016.

[2] S. Glyn-Jones, A. J. R. Palmer, R. Agricola et al., "Osteoarthritis," *Lancet*, vol. 386, no. 9991, pp. 376–387, Jul. 2015.

[3] D. J. Hunter and S. Bierma-Zeinstra, "Osteoarthritis," *Lancet*, vol. 393, no. 10182, pp. 1745–1759, 2019.

[4] GBD 2019 Diseases and Injuries Collaborators, "Global burden of 369 diseases and injuries in 204 countries and territories, 1990-2019: a systematic analysis for the Global Burden of Disease Study 2019," *Lancet*, vol. 396, no. 10258, 2020.

[5] R. Liu-Bryan and R. Terkeltaub, "Emerging regulators of the inflammatory process in osteoarthritis," *Nature Reviews Rheumatology*, vol. 11, no. 1, pp. 35–44, Jan. 2015.

[6] B. R. da Costa, T. V. Pereira, P. Saadat et al., "Effectiveness and safety of non-steroidal anti-inflammatory drugs and opioid treatment for knee and hip osteoarthritis: network meta-analysis," *BMJ*, vol. 375, Article ID n2321, 2021.

[7] A. O. Leopoldino, G. C. Machado, P. H. Ferreira et al., "Paracetamol versus placebo for knee and hip osteoarthritis," *Cochrane Database of Systematic Reviews*, vol. 2, no. 2, Article ID CD013273, 2019.

[8] A. Guermazi, T. Neogi, J. N. Katz et al., "Intra-articular corticosteroid injections for the treatment of hip and knee osteoarthritis-related pain: considerations and controversies with a focus on imaging-radiology scientific expert panel," *Radiology*, vol. 297, no. 3, pp. 503–512, Dec. 2020.

[9] M. Cameron and S. Chrubasik, "Oral herbal therapies for treating osteoarthritis," *Cochrane Database of Systematic Reviews*, vol. 2014, no. 5, Article ID CD002947, 2014.

[10] M. Cameron, J. J. Gagnier, C. V. Little, T. J. Parsons, A. Blumle, and S. Chrubasik, "Evidence of effectiveness of herbal medicinal products in the treatment of arthritis. Part I: Osteoarthritis," *Phytotherapy Research*, vol. 23, no. 12, pp. 1647–1662, 2009.

[11] A. Wang, D. J. Leong, L. Cardoso, and H. B. Sun, "Nutraceuticals and osteoarthritis pain," *Pharmacology & Therapeutics*, vol. 187, pp. 167–179, Jul. 2018.

[12] S.-Q. Wang, J.-X. Wang, C. Zhang et al., "What you should know about osteoarthritis rehabilitation: a bibliometric analysis of the 50 most-cited articles," *Geriatr. Orthop. Surg. Rehabil*, vol. 11, Article ID 215145932097319, 2020.

[13] J.-Q. Chen, Q. He, B.-H. Jiang et al., "Research on primary Sjögren's syndrome in 2004–2021: a Web of Science-based cross-sectional bibliometric analysis," *Rheumatology International*, 2022.

[14] Y. Zhao, L. Huang, M. Liu, H. Gao, and W. Li, "Scientific knowledge graph of acupuncture for migraine: a bibliometric analysis from 2000 to 2019," *Journal of Pain Research*, vol. 14, p. 1985, 2021.

[15] G.-Y. Yang, L.-Q. Wang, J. Ren et al., "Evidence base of clinical studies on Tai Chi: a bibliometric analysis," *PLoS One*, vol. 10, no. 3, Article ID e0120655, 2015.

[16] R. Li, J. Sun, H. Hu et al., "Research trends of acupuncture therapy on knee osteoarthritis from 2010 to 2019: a bibliometric analysis," *Journal of Pain Research*, vol. 13, pp. 1901–1913, 2020.

[17] M. B. Synnestvedt, C. Chen, and J. H. Holmes, "CiteSpace II: visualization and knowledge discovery in bibliographic databases," *AMIA Annual Symposium Proceedings*, vol. 2005, pp. 724–728, 2005.

[18] C. Chen, F. Ibekwe-SanJuan, and J. Hou, "The structure and dynamics of cocitation clusters: a multiple-perspective cocitation analysis," *Journal of the American Society for Information Science and Technology*, vol. 61, no. 7, pp. 1386–1409, 2010.

[19] C. Chen, "Searching for intellectual turning points: progressive knowledge domain visualization," *Proceedings of the National Academy of Sciences of the United States of America*, vol. 101, no. 1, pp. 5303–5310, 2004.

[20] R. R. Bannuru, M. C. Osani, E. E. Vaysbrot et al., "OARSI guidelines for the non-surgical management of knee, hip, and polyarticular osteoarthritis," *Osteoarthritis and Cartilage*, vol. 27, no. 11, pp. 1578–1589, 2019.

[21] S. L. Kolasinski, T. Neogi, M. C. Hochberg et al., "2019 American College of rheumatology/arthritis foundation guideline for the management of osteoarthritis of the Hand, hip, and knee," *Arthritis & Rheumatology*, vol. 72, no. 2, pp. 220–233, 2019.

[22] A. Lu, M. Jiang, C. Zhang, and K. Chan, "An integrative approach of linking traditional Chinese medicine pattern classification and biomedicine diagnosis," *Journal of Ethnopharmacology*, vol. 141, no. 2, pp. 549–556, Jun. 2012.

[23] T. Neogi, "The epidemiology and impact of pain in osteoarthritis," *Osteoarthritis and Cartilage*, vol. 21, no. 9, pp. 1145–1153, 2013.

[24] L. Long, K. Soeken, and E. Ernst, "Herbal medicines for the treatment of osteoarthritis: a systematic review," *Rheumatology*, vol. 40, no. 7, pp. 779–793, 2001.

[25] L. F. Haas, "Rosa canina (dog rose)," *Journal of Neurology, Neurosurgery & Psychiatry*, vol. 59, no. 5, p. 470, 1995.

[26] R. Christensen, E. M. Bartels, R. D. Altman, A. Astrup, and H. Bliddal, "Does the hip powder of Rosa canina (rosehip) reduce pain in osteoarthritis patients: a meta-analysis of randomized controlled trials," *Osteoarthritis and Cartilage*, vol. 16, no. 9, pp. 965–972, 2008.

[27] J. Gruenwald, R. Uebelhack, and M. I. Moré, "Rosa canina—rose hip pharmacological ingredients and molecular mechanics counteracting osteoarthritis—a systematic review," *Phytomedicine*, vol. 60, Article ID 152958, 2019.

[28] G.-Y. Chen, J.-Q. Chen, X.-Y. Liu et al., "Total flavonoids of rhizoma drynariae restore the MMP/TIMP balance in models of osteoarthritis by inhibiting the activation of the NF-κB and PI3K/AKT pathways," *Evidence-based Complementary and Alternative Medicine*, vol. 2021, Article ID 6634837, 14 pages, 2021.

[29] L. Pan, Y. Zhang, N. Chen, and L. Yang, "Icariin regulates cellular functions and gene expression of osteoarthritis patient-derived human fibroblast-like synoviocytes," *International Journal of Molecular Sciences*, vol. 18, no. 12, p. 2656, 2017.

[30] Z. Wang, G. Jones, T. Winzenberg et al., "Effectiveness of curcuma longa extract for the treatment of symptoms and effusion-synovitis of knee osteoarthritis: a randomized trial," *Annals of Internal Medicine*, vol. 173, no. 11, pp. 861–869, 2020.

[31] G. J. Macfarlane, P. Paudyal, M. Doherty et al., "A systematic review of evidence for the effectiveness of practitioner-based complementary and alternative therapies in the management of rheumatic diseases: osteoarthritis," *Rheumatology*, vol. 51, no. 12, pp. 2224–2233, 2012.

[32] M. Kapoor, J. Martel-Pelletier, D. Lajeunesse, J.-P. Pelletier, and H. Fahmi, "Role of proinflammatory cytokines in the pathophysiology of osteoarthritis," *Nature Reviews Rheumatology*, vol. 7, no. 1, pp. 33–42, 2011.

[33] R. F. Loeser, "The role of aging in the development of osteoarthritis," *Transactions of the American Clinical & Climatological Association*, vol. 128, pp. 44–54, 2017.

[34] P. R. Coryell, B. O. Diekman, and R. F. Loeser, "Mechanisms and therapeutic implications of cellular senescence in osteoarthritis," *Nature Reviews Rheumatology*, vol. 17, no. 1, pp. 47–57, 2021.

[35] S. Srivastava, A. K. Saksena, S. Khattri, S. Kumar, and R. S. Dagur, "Curcuma longa extract reduces inflammatory and oxidative stress biomarkers in osteoarthritis of knee: a four-month, double-blind, randomized, placebo-controlled trial," *Inflammopharmacology*, vol. 24, no. 6, pp. 377–388, 2016.

[36] I. N. Madzuki, S. F. Lau, R. Abdullah, N. I. Mohd Ishak, and S. Mohamed, "Vernonia amygdalina inhibited osteoarthritis development by anti-inflammatory and anticollagenase pathways in cartilage explant and osteoarthritis-induced rat model," *Phytotherapy Research*, vol. 33, no. 7, pp. 1784–1793, 2019.

[37] J. J. Hwang, Y. A. Rim, Y. Nam, and J. H. Ju, "Recent developments in clinical applications of mesenchymal stem cells in the treatment of rheumatoid arthritis and osteoarthritis," *Frontiers in Immunology*, vol. 12, Article ID 631291, 2021.

[38] T. Kulsirirat, S. Honsawek, M. Takeda-Morishita et al., "The effects of andrographolide on the enhancement of chondrogenesis and osteogenesis in human suprapatellar fat pad derived mesenchymal stem cells," *Molecules*, vol. 26, no. 7, p. 1831, 2021.

[39] H. Wu, Z. Yin, L. Wang, F. Li, and Y. Qiu, "Honokiol improved chondrogenesis and suppressed inflammation in human umbilical cord derived mesenchymal stem cells via blocking nuclear factor-κB pathway," *BMC Cell Biology*, vol. 18, no. 1, p. 29, 2017.

Hindawi
Evidence-Based Complementary and Alternative Medicine
Volume 2022, Article ID 6933523, 8 pages
https://doi.org/10.1155/2022/6933523

Research Article

Construction of a Meta-Evidence Prototype Database of Traditional Chinese Medicine Splenogastric Diseases and Its Application in an Automatic Meta-Analysis System

Xueqin Zhang, Chunying Wang, Yanning Yao, Wenyu Sun, Yujie Guo, Lin Ma, Xinyuan Lu, and Hongyong Deng

TCM Science and Technology Information Center, Shanghai University of Traditional Chinese Medicine, Shanghai, China

Correspondence should be addressed to Hongyong Deng; denghy@shutcm.edu.cn

Received 16 April 2022; Accepted 21 June 2022; Published 13 July 2022

Academic Editor: Xing Liao

Background. Traditional Chinese medicine splenogastric diseases (TCMSDs) are equivalent to digestive system diseases in modern medicine. The forms of clinical evidence of TCMSDs include clinical trials, such as randomized controlled trials (RCTs) and systematic reviews (SRs). SRs mainly rely on manual operations and have the shortcomings of time consumption and low efficiency; therefore, they cannot meet the needs of rapid clinical decision-making. It is urgent to establish a new and smart form of a database to support the progress of SRs. *Methods*. We searched and screened all TCMSD RCT reports, in both Chinese and English, and extracted them into meta-evidence through predesigned structural Microsoft Excel tables. All meta-evidence was imported into an online clinical meta-evidence collection and management system after data quality checking. The meta-evidence database of traditional Chinese medicine (TCM) splenogastric disease (MED-TCMSD) was then tested as a backend of an automatic meta-analysis system. *Results*. A total of 405 cases of TCMSD RCTs were processed into meta-evidence. The most common diseases were stomach stuffiness disease, epigastralgia, and chronic atrophic gastritis. Banxiaxiexin decoction and its modifications were the most used interventions. More than half of the cases employed TCM in conjunction with regular therapeutics. The top reported outcomes included clinical effects, adverse events, and TCM syndromes. The MED-TCMSD worked well as a part of the automatic meta-analysis system. *Conclusions*. We developed and tested a new form of clinical evidence, meta-evidence, for automatic SR and fast evidence-based decision-making. As an example of the MED, the MED-TCMSD can improve the production and updating efficiency of the evidence of TCMSDs. The methods of constructing the MED-TCMSD can be further applied to the development of MEDs of other diseases.

1. Introduction

Traditional Chinese medicine splenogastric diseases (TCMSDs) are a variety of diseases and symptoms that are related to gastrointestinal functions. Their clinical incidence rate is relatively high. For example, the prevalence of functional dyspepsia in China is 7%–41%, the prevalence of irritable bowel syndrome in China is 5%–25% [1], and the prevalence of gastrointestinal diseases in urban adults is 17.41% [2]. There are numerous therapeutics for these conditions in clinical practice, which can be grouped into three classes: traditional Chinese medicine (TCM) (e.g., TCM decoction [3], Chinese patent medicine [4], and acupuncture [5]), integrated traditional Chinese and Western medicine [ITCWM]) [6, 7], and Western medicine [8]. To help doctors deal with the complicated and variable clinical conditions of TCMSDs quickly and accurately, many scientific research teams have built different kinds of splenogastric disease databases. For example, Huang [9] constructed an online database of irritable bowel syndrome (IBS) with functions of patient data management, statistics, analysis, and data mining. Chen [10] created a database of TCM clinical support for *H. pylori* infection-related diseases. Chen [11] constructed a chronic gastritis database for the

diagnosis and treatment of ITCWM. With the help of the databases, retrospective research can be carried out to explore the connections between TCM and Western medicine. Yan et al. [12] established an online database of the transcriptome of IBS, which integrated and stored 320 IBS gene samples in the Gene Expression Omnibus and ArrayExpress databases. By allowing comparisons of the gene expression levels of IBS patients, this database can help the exploration of the pathogenesis of IBS and the development of drugs. Khanna et al. [13] developed the GI-PRO database, which is an online library of patient-reported outcome measures in gastroenterology. This database can guide clinical decision-making, research, and drug approval. However, most of these databases only include patient case information, and although they can provide a reference for clinical activities, they have limited value in supporting evidence-based clinical decision-making [14, 15]. Therefore, there is a need for databases that can directly support clinicians.

Evidence-based medicine (EBM) databases can be classified into four types [16]: clinical practice guideline (CPG) databases, systematic review (SR) databases, clinical trial databases, and comprehensive EBM databases. They differ in their objective, scope, content, and service target groups but share the same foundations as SRs. The typical processes of SRs include protocol writing, study retrieval, data extraction, evidence synthesis, and evidence evaluation, which are mainly performed manually and are frequently lengthy and inefficient undertakings. The abovementioned four kinds of EBM databases are currently fully developed and have been applied in clinical decision-making. However, they are not designed for rapid evidence-based decision-making based on automatic SRs (ASRs). ASRs employ computer automation techniques, such as natural language processing, text mining, and machine classification, in all phases of an SR to optimize its procedures and improve its efficiency [17, 18]. Data are the essential part of an ASR system. The efficiency requirements of ASRs call for a new form of evidence database besides the current four types of EBM databases.

In this study, we explored a kind of clinical evidence database that is highly standardized and structured to meet the needs of automatic systematic reviewing. We named it the meta-evidence database (MED). It is pre-extracted and stored in a machine-readable data format. We constructed a MED of TCM splenogastric disease (MED-TCMSD) and implemented it in a fast evidence-based decision-making system based on ASRs to test its functions and advantages.

2. Methods

2.1. Data Sources

2.1.1. Databases and Retrieval Strategy. The literature databases that we referred to were four Chinese databases (CNKI, WanFang Data, VIP, and SinoMed) and four English databases (PubMed, Cochrane Library (CENTRAL), Web of Science, and Ebsco Medline). Each database was searched separately for TCM splenogastric disease randomized controlled trials (RCTs) without any time limitations. The search terms were RCT, randomized controlled trial, and a group of specific disease names. We identified 12 TCM diseases corresponding to TCM splenogastric disease: epigastralgia, acid regurgitation, epigastric upset, stomach stuffiness disease, vomiting, hiccup disease, dysphagia disease, regurgitation disease, abdominal pain, diarrhea disease, constipation disease, and dysentery.

2.1.2. Inclusion and Exclusion Criteria. The inclusion and exclusion criteria followed the patient/population, intervention/exposure, comparison/control, outcome, and study design (PICOS) rule [19]. The inclusion criteria were the following: patients diagnosed with TCM splenogastric disease, namely the abovementioned 12 diseases (see 2.1.1); interventions of TCM alone (TCM interventions included herbs, massage, qigong, acupoint-pressing, and acupuncture) or TCM combined with Western medicine; blank control, placebo control, or positive control (add-on study); all outcomes; RCT study design. The exclusion criteria were the following: animal experiment or in vitro experiment; Western medicine-only intervention; non-RCT study design, semi-random, or pseudo-random studies; duplicate literature.

2.1.3. Literature Screening. The screening process was carried out independently by two researchers in three steps: (1) Search results were imported and automatically screened in NoteExpress software to remove the duplicates; they were rechecked manually. (2) The abstracts of the papers were examined carefully according to the selection criteria. Most exclusions were carried out for reasons in this step. (3) The last step was to check all the remaining full texts to make the final inclusion. Two authors completed the screening independently and cross-checked the results for correctness.

2.2. Data Extraction

2.2.1. Extraction Table. A standardized extraction table can facilitate the extraction of data. We created a data sheet for extraction based on Microsoft Excel powered with Visual Basic for Applications (VBAs). The extraction tables of the clinical evidence were designed for data collection, which can be imported into the database in the batch mode. The VBA code built in the table can enable basic data inspection and verification of the input data. Each study was assigned a unique number to identify while storing and citing. The full texts (PDF) of the included studies are attached for reference.

2.2.2. Extracting Content and Methods. Based on the characteristics of RCTs, the extraction table contained six sections: general information, evidence sources, clinical data, trial design, grouping and interventions, and outcomes. (1) The general information section has 10 fields, such as evidence ID, evidence status, creation time, evidence name, clinical trial register number, data editor, and reviewer. (2)

The evidence sources section has 24 fields, such as source type, article title, journal source, author information, author institution, contact information, grant number, and DOI and full-text path or link. (3) The clinical data section has 23 fields, such as diagnosis (both TCM and Western medicine), sample size, age and gender, course of the disease, inclusion criteria, and exclusion criteria. (4) The trial design section has 19 fields, such as study type, randomization type, blindness type, observation time, and risk of bias factors (randomization, allocation concealment, blinding, missing data, selective reporting, and other bias). (5) The grouping and intervention section has 27 fields, such as group name, sample size of each group, age and gender of each group, observation/control type, name of intervention/drug, dosage form, administration, single dose, frequency of administration, and duration of intervention. (6) The outcome section has 19 fields, such as outcome name, endpoint/change value, direction of effect, result data, and data type (continuous or binary). Clinical data extraction requires clinical knowledge of TCM; hence, we trained data extractors before starting the work. We also employed two experienced reviewers to check all input data to ensure completeness and correctness.

2.2.3. Data Standardization. Regarding standardization of the names of diseases, the names of TCMSDs and those of Western medicine were not unified and did not allow us to form a correspondence map. To create a unified standard, the names of diseases diagnosed by TCMSDs were used to frame the names of diseases diagnosed by Western medicine. With reference to the "11th Revision of the International Classification of Diseases (ICD-11) [20], Classification and Code of TCM Diseases and Syndromes, and Clinical Terms of TCM diagnosis and Treatment [21]," we built a mapping table of TCMSD names and ICD-11 codes to construct the corresponding relationship between the TCMSD and the Western medicine names. We also standardized the TCM syndromes of TCMSDs to follow the "Classification and Code of TCM Diseases and Syndromes." Regarding standardization of interventions, the interventions—either the treatment group or the control group—varied in name, dosage form, route of administration, single dose (and unit), and frequency of delivery, among other factors. For example, the intervention of acupuncture could be written as "acupuncture," "acupuncture and moxibustion," or "electro-acupuncture," among others, and the Chinese herb medicine "Guipi decoction" could have different dosage forms such as pills, powder, granules, and capsules. We sorted out these cases and standardized different presentations using common terminologies at the data entry stage. We also applied similar standardization for the outcomes.

2.3. Database Development. MySQL [22] is an open-source database that is widely used and suitable for PHP, Python, and other languages. The MySQL database provides a variety of data types, including integer, floating-point, fixed-point, date and time, string, and binary [23]. The development of a database application program is convenient for users and enables access to and provides security to the data. We developed our database with Python 3.8 and MySQL 8 using Ubuntu 18. Several functional modules such as data input, managing, searching, and output were designed and implemented.

3. Results

3.1. Literature Search and Screening Results. The initial search returned 25,831 papers: 8,428 in Chinese (CNKI: 1,517, WanFang Data: 568, SinoMed: 6,237, and VIP: 106) and 17,403 in English (PubMed: 1,030, Cochrane Library (CENTRAL): 834, Web of Science Core Collection: 7,298, and Ebsco Medline: 8,241). Duplicates were filtered by NoteExpress and manually, resulting in 4,734 papers remaining for the next stage. The inclusion and exclusion criteria were applied to the titles and abstracts of the remaining, and 3,118 papers remained for full-text examination. We downloaded them and read their full text carefully, and finally, 1,600 papers of TCMSDs were included. As the main purpose of this paper was to verify the construction of the meta-evidence database, we chose the most recent five years of RCTs (total 405) for meta-evidence extraction.

3.2. Database Results. A total of 405 cases of TCMSD meta-evidence were collected with Excel tables and imported into the MED.

3.2.1. Population. In the 405 cases of TCMSDs, the TCM diagnoses were mainly stomach stuffiness disease (125), epigastralgia (103), diarrhea disease (35), and constipation disease (18). These four TCM diagnoses accounted for 69% of all the included meta-evidence. The top five TCM syndromes were syndrome of Yang deficiency in the spleen and stomach (36), syndrome of cold and heat complex (16), syndrome of dampness and heat in the spleen and stomach (15), syndrome of spleen and stomach deficiency (15), and syndrome of disharmony of the liver and stomach (13). By comparing Western medicine diagnoses to TCM diagnoses, we found that the distribution was relatively uniform, and the top five occurrences were chronic atrophic gastritis of unknown etiology (65), functional dyspepsia (63), chronic superficial gastritis of unknown etiology (53), localized epigastric pain (33), and diarrhea (21) (Table 1).

3.2.2. Interventions. TCM treatments were mainly herb medicines and Chinese patent drugs, such as banxiaxiexin decoction and its modifications, weifuchun tablets. Weiyan decoction, ziyinyangwei decoction, yiweishengjin decoction, etc., are also occasionally used in clinical use. They are usually combined with Western medicines of gastrointestinal motility drugs and prokinetic agents, such as domperidone, omeprazole, and mosapride citrate tablets (Table 2).

Table 1: Population of included TCMSD RCTs.

TCM diagnosis	Number	TCM syndrome	Number	Western medicine diagnosis	Number
Stomach stuffiness disease	125	Syndrome of Yang deficiency in spleen and stomach	36	Chronic atrophic gastritis of unknown etiology	65
Epigastralgia	103	Syndrome of cold and heat complex	16	Functional dyspepsia	63
Diarrhea disease	35	Syndrome of dampness and heat in the spleen and stomach	15	Chronic superficial gastritis of unknown etiology	53
Constipation disease	18	Syndrome of spleen and stomach deficiency	15	Localized epigastric pain	33
Abdominal pain	6	Syndrome of disharmony of the liver and stomach	13	Diarrhea	21
Regurgitation disease	6	Syndrome of spleen and stomach qi deficiency	9	Functional constipation	16
Acid regurgitation	4	Syndrome of stagnant heat in the liver and stomach	9	Rheumatoid arthritis	15
Dysentery	2	Syndrome of liver depression and spleen deficiency	8	Gastric ulcer	11
Vomiting	1	Syndrome of qi stagnation due to spleen deficiency	5	Gastritis caused by *H. pylori*	8
Epigastric upset	1	Syndrome of dampness and heat	4	Symptomatic diarrhea	7

Table 2: Interventions of included TCMSD RCTs.

Intervention/drug name	Number	Control/drug name	Number
Modified banxiaxiexin decoction	16	Domperidone	24
Banxiaxiexin decoction	7	Omeprazole	21
No. 1 Weiyan decoction	3	Weifuchun tablets	11
Ziyinyangwei decoction	2	Conventional therapy	8
Yiweishengjin decoction	2	Mosapride citrate tablets	8
Yiqihuoxue recipe	2	Montmorillonite powder	6
Xiangsha liujunzi tang	2	Cisapride	6
Xiaopi granules	2	Vitamin tablets	5
Modified sini powder	2	Rabeprazole	4
Qizhiweitong granules	2	Routine nursing	4
Buzhongyiqi decoction	2	Trimebutine maleate tablets	3

3.2.3. Control Types. For TCMSDs, most of the included studies employed add-on tests (211 articles) or positive drugs as control (182 articles). Placebo control (3 articles), dose control (3 articles), and blank control (2 articles) were less common. (1) With respect to add-on trials, the patients both in the intervention group and control group were treated with the same baseline therapeutics, and the patients in the intervention group were further treated with TCM interventions. (2) Regarding positive controls, patients in the intervention group were treated with TCM, and those in the control group were treated with an effective routine approach.

3.2.4. Outcomes. The outcomes of RCTs of TCMSDs include clinical efficacy measures (e.g., number of clinically ineffective, TCM syndrome scores, and number of relapses), safety measures (e.g., number of adverse events), and prognosis measures (e.g., number of relapses). (1) Clinical efficacy measures are quantitative indicators that can objectively describe the clinical treatment effects of interventions. (2) TCM syndrome scores can evaluate the severity and function of the human body. (3) Prognostic measures can reflect the development of disease recovery and outcome after intervention (Table 3).

3.3. Application Demonstration. We tested this database's functionality in a prototype ASR system (https://www.pymeta.com/cdss/). The fast EBM decision-making system, namely the TCM clinical evidence auto-analysis and visualization platform, was designed for rapid (even real-time) clinical and health decision-making (Figure 1). This system includes the MED, automatic meta-analysis, machine-based evidence-labeling, and result visualization modules, in which the MED has the key role of auto-SR support. Based on the TCM splenogastric disease meta-evidence, this platform allows an interesting and different process of SR (Figure 2). A typical application of this system starts from clinical problem (i.e., PICO) querying, matched RCTs (meta-evidence in this system) complete meta-analysis, and a systematic review in the background;

Table 3: Outcomes of included TCMSD RCTs.

Name of outcome measure	Number
Number of clinically ineffective	345
Total number of adverse events	81
TCM syndrome scores (epigastralgia)	77
TCM syndrome scores (fullness)	59
TCM syndrome scores (anorexia)	54
TCM syndrome scores (belching)	47
TCM syndrome scores (total)	43
Number of relapses	40
Serum level (motilin)	30
Symptom scores (stomachache)	30
Serum level (gastrin)	29
Number of adverse events (diarrhea)	26
TCM syndrome inefficiency number	22
TCM syndrome scores (nausea and vomiting)	22
Number of adverse events (dizzy)	20
TCM syndrome scores (loose stool)	20
TCM syndrome scores (sour regurgitation)	20
No improvement of gastroscopy	18
Number of adverse events (rash)	17
TCM syndrome scores (mental fatigue)	17
Number of *H. pylori* positive	16
Symptom scores (fullness)	14
Serum level (IL-6)	14
TCM syndrome scores (noisy stomach)	14
Symptom scores (belching)	13
Number of adverse events (nausea)	13
Number of adverse events (dry mouth)	13
Number of adverse events (astriction)	13
Symptom scores (anorexia)	12
Number of *H. pylori* negative	11

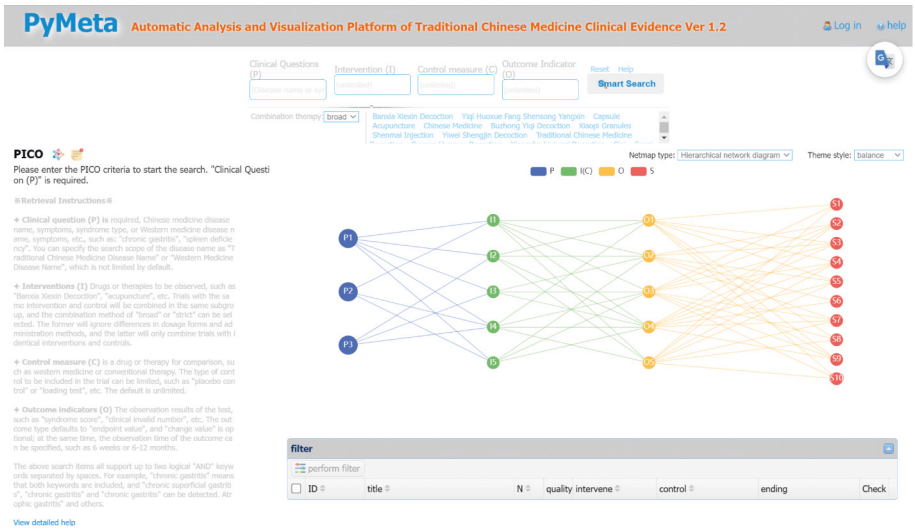


Figure 1: Overview of the TCM Clinical Evidence Auto-analysis and Visualization Platform. (This figure shows the main parts of the platform, the upper input area of PICO, and results area below it, which includes left side of outcoms lists and right side of graphs of PICO-network and evidence-map. The included RCTs show in the bottom table).

the results of the effect and quality of evidence are present in the forms of text, tables, and figures. The platform acts on SR-based decision-making supporting in a fast and efficient way, it provides a new mode for evidence-based selection of drugs for TCMSDs from thousands of candidates.

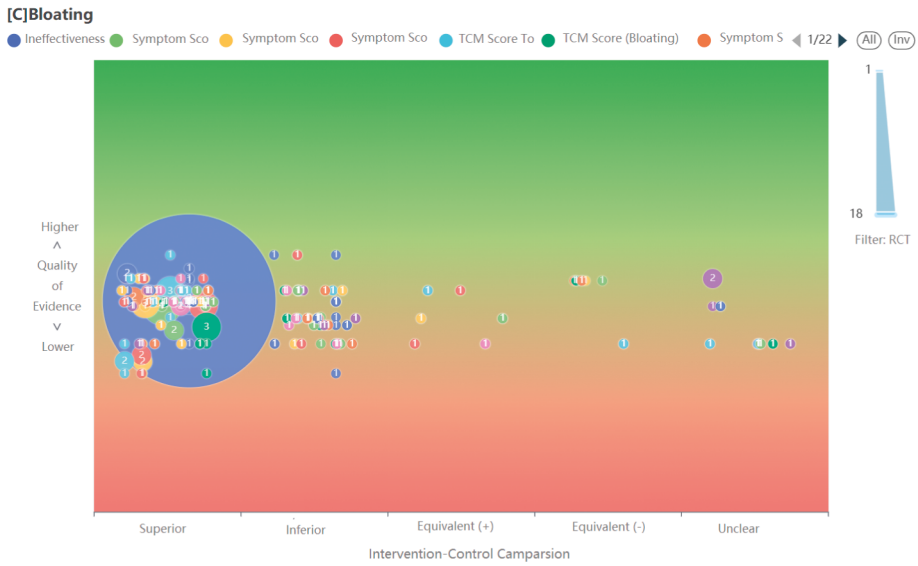


Figure 2: Evidence map based on MED-TCMSD. (Evidence map is the common visualization form of evidence-based decision-making supporting, which present effect (x-axis) and quality (y-axis) of multievidence for the same clinical problem).

4. Discussion and Conclusions

4.1. Main Findings. Meta-evidence is a form of evidence that can meet the needs of rapid evidence-based decision-making. It has the characteristics of standardization, structure, and machine-readability. In this study, we designed an extraction table to collect information of RCTs. All information was grouped in six sections: general information of evidence, source of evidence, clinical data of the study, RCT design, grouping and interventions, and outcomes. A total of 122 data fields within these sections were constructed as a detailed and structured data grid to cover all RCT information and transfer them into the MED. The meta-evidence was stored in a format that was easy for computer processing. As a sample of the MED, 405 cases of RCTs of TCMSDs were collected and extracted. For these studies, patients were diagnosed by TCM as suffering from stomach stuffiness disease and epigastralgia, and most of the TCM syndromes were Yang deficiency in the spleen and stomach, cold and heat complex, and dampness and heat in the spleen and stomach, among others. Regarding the interventions, herb medicine and Chinese patent drugs, such as banxiaxiexin decoction and weifuchun tablet, were the most commonly used. TCM medicines were usually combined with Western medicines of gastrointestinal motility drugs and prokinetic agents and tested in add-on trials. The outcomes of TCMSDs included clinical efficacy, safety, and prognosis measures, such as the number of clinically ineffective, TCM syndrome scores, number of adverse events, and number of relapses. The MED is an essential part of the ASR and rapid EBM decision-making system. The pre-extracted standardized data provide a strong basis for efficient data processing of ASRs. A prototype system of rapid EBM decision-making, namely the TCM clinical evidence auto-analysis and visualization platform, including the component of the MED of TCMSDs, passed the application test and proved the effectiveness and practicability of a MED.

In recent years, there have been many studies on automatic SRs assisted by computer [24], but most of them still adopt the semi-automatic method of "human-machine combination" [25]. Some meta-evidence similar data researches, such as the CISMeF metadata project, based on the Dublin core model, could describe the metadata of EBM resources [26], and Xu et al. [27] established an evidence-based medicine metadata experiment database. Another study [28] reported a web scraping algorithm developed by python language that can automatically extract metadata of published literature (such as title, abstract, keywords, year, author, and DOI). A brief comparison of automatic SR (and/or meta-analysis) and classical manual SR is shown in Table 4.

4.2. Limitations and Outlook. MED-TCMSD was constructed and tested for advancement. However, there are some details that should be improved in the future. (1) Only five years of TCMSD RCT data were included in this sample database. We plan to process the remaining literature in the future. (2) All the extraction work of the meta-evidence was completed by experienced researchers, which consumed substantial manpower and time resources. We are searching for efficient and sustainable solutions, such as computer-aided technologies and crowdsourcing collaboration to replace the current, inefficient manual methods.

4.3. Conclusions. Rapid decision-making based on automatic SR techniques is an interesting direction of evidence-based medicine development. ASR techniques need to be supported by more efficient databases than the classical forms of EBM databases (such as RCT, SR, and CPG). Our new EBM database is highly standardized, structured, and

Table 4: Automatic SR and manual SR.

SRs process	Automatic SR	Manual SR
Literature retrieval	PICOS precise retrieval in multiple databases, subject auto push periodically	Manual indexing and searching in multiple databases
Literature screening	RCT classification based on machine learning	Manual screening based on experience
Data extraction	Full or semi-automatic extraction of PICO information from the paper	Manual extraction and fill the datasheet
Data analysis	Automatic meta-analysis based on modules of statistics and meta-evidence databases	Manual data entry and setup parameters in SR software
Evidence quality assessment	Full or semi-automatic evidence quality assessment	Manual assessment based on expertise and experience

machine-readable, which precisely meets all the requirements of ASRs. A sample of this kind of database, MED-TCMSD, was completed, which has a key role in the ASR and rapid decision-making system. We believe that the meta-evidence approach is a good solution for ASR databases, and the method of constructing MED-TCMSD can be further applied in the development of MEDs for other diseases.

Abbreviations

TCMSDs: Traditional Chinese medicine splenogastric diseases
MED-TCMSD: Meta-evidence database of traditional Chinese medicine splenogastric disease
TCM: Traditional Chinese medicine
RCTs: Randomized controlled trials
SRs: Systematic reviews
IBS: Irritable bowel syndrome
EBM: Evidence-based medicine
CPG: Clinical practice guideline
ASRs: Automatic systematic reviews
VBA: Visual basic for applications
ICD-11: 11th revision of the international classification of diseases
PICOS: Patient/population, intervention/exposure, comparison/control, outcome, study design
IL-6: Interleukin-6.

Data Availability

The data used to support the findings of this study are included within the article. Data are available from the corresponding author upon request.

Conflicts of Interest

The authors declare that they have no conflicts of interest.

Authors' Contributions

X.Z and C.W contributed equally to this work. H.D conceived and designed the study. X.Z collected the data and drafted the manuscript. All the contributors read, corrected, and accepted the final manuscript.

Acknowledgments

The authors would like to thank Comp. Engr Yichen Han for technical support of the extraction table and Professor Hongzhu Wen for guidance of knowledge related to TCMSDs. This research was funded by the National Natural Science Foundation of China (No. 81873183), National key R&D Program Project (No. 2019yfc1709803).

References

[1] Z. Huang, *Establishment and Function Analysis of Functional Gastrointestinal Disorders Database*, Southern Medical University, Guangzhou, China, 2015.
[2] Q. Cai, *Epidemiologic Survey of Gastrointestinal Disorders Among Adults in Wuhan*, Huazhong University of Science and Technology, Wuhan, China, 2008.
[3] X. Hu, L. Chen, S. Yao, Q. Tong, and W. Tang, "Clinical observation of shugan jianpi granule in treating splenogastric disease of liver depression and spleen deficiency," *Lishizhen Medicine and Materia Medica Research*, vol. 17, no. 10, pp. 2030-2031, 2006.
[4] X. Zhou, X. Ma, X. Wang et al., "Clinical observation on 462 cases of bile reflux gastritis treated with traditional Chinese medicine granules," *Journal of Traditional Chinese Medicine*, vol. 43, no. 12, p. 913, 2002.
[5] X. Qi and D. Zhang, "Clinical observations on acupuncture treatment for refractory hiccups in serious patients," *Shanghai Journal of Acupuncture and Moxibustion*, vol. 36, no. 06, pp. 491-492, 2013.
[6] Y. Yang, J. Piao, Y. Zhang, N. Jing, and Y. Lu, "Clinical observation on 38 cases of nausea and vomiting after tumor chemotherapy treated by integrated traditional Chinese and Western medicine," *Journal of New Chinese Medicine*, vol. 39, no. 1, p. 83, 2007.
[7] Z. Yang, H. Wang, and Q. Ma, "Clinical observation on 68 cases of chemotherapy-induced nausea and vomiting treated by integrated traditional Chinese and Western medicine," *Journal of Sichuan of Traditional Chinese Medicine*, vol. 23, no. 11, p. 43, 2005.
[8] X. Liu, B. Chen, J. Shi, B. Ji, and W. Yu, "Clinical observation of domestic azasetron in preventing nausea and vomiting caused by chemotherapy in 43 cases," *Shaanxi Medical Journal*, vol. 4, pp. 477–479, 2005.
[9] M. Huang, *The Construction and Application of Integrated Clinical Database of Irritable Bowel Syndrome*, Guangzhou University of Chinese Medicine, Guangzhou, China, 2019.
[10] Y. Chen, *A Preliminary Study on the Establishment of a Chinese Medicine Database for H.Pylori Infection and a*

Clinical Study on H.Pylori Infection and Tongue Diagnosis, Beijing University of Traditional Chinese Medicine, Beijing, China, 2016.

[11] Y. Chen, *The Establishment and Application of the Clinical Database of TCM and Western Medicine Integrated Treatment for Chronic Gastritis*, Guangzhou University of Chinese Medicine, Guangzhou, China, 2020.

[12] J. Yan, Y. Xu, B. Hu et al., "TIBS: a web database to browse gene expression in irritable bowel syndrome," *Journal of Theoretical Biology*, vol. 354, pp. 48–53, 2014.

[13] P. Khanna, N. Agarwal, D. Khanna et al., "Development of an online library of patient-reported outcome measures in gastroenterology: the GI-PRO database," *American Journal of Gastroenterology*, vol. 109, no. 2, pp. 234–248, 2014.

[14] Z. Ji, F. Yang, H. Hu et al., "Construction of evidence base for systematic review/meta analysis of traditional Chinese medicine," *Chinese Journal of Evidence-Based Medicine*, vol. 20, no. 1, pp. 98–101, 2020.

[15] J. H. Elliott, A. Synnot, T. Turner et al., "Living systematic review: 1 Introduction-the why, what, when, and how," *Journal of Clinical Epidemiology*, vol. 91, pp. 23–30, 2017.

[16] X. Zhang and H. Deng, "The current situation and trends of development of evidence-based medicine database," *Chinese Journal of Evidence-Based Medicine*, vol. 21, no. 6, pp. 621–627, 2021.

[17] A. M. O'Connor, G. Tsafnat, S. B. Gilbert et al., "Still moving toward automation of the systematic review process: a summary of discussions at the third meeting of the international collaboration for automation of systematic reviews (ICASR)," *Systematic Reviews*, vol. 8, no. 1, p. 57, 2019.

[18] X. Zhang, W. Zhang, P. Zheng, and H. Deng, "Computer aided systematic review: research and application," *Chinese Journal of Evidence-Based Medicine*, vol. 21, no. 1, pp. 111–116, 2021.

[19] X. Li, "PICOS principles in research design for meta-analysis," *Chinese Journal of Interventional Cardiology*, vol. 24, no. 11, p. 611, 2016.

[20] National Administration of Traditional Chinese Medicine, https://ghs.satcm.gov.cn/gongzuodongtai/2019-05-25/9884.html, 2019.

[21] National Administration of Traditional Chinese Medicine, https://yzs.satcm.gov.cn/zhengcewenjian/2020-11-23/18461.html, 2020.

[22] Z. Xuan, *Design and Implementation of Database Cluster Based on MySQL*, Beijing University of Posts and Telecommunications, Beijing, China, 2013.

[23] W. Zhang, C. Jiang, and J. Wei, "Research and application of MySQL replication technology," *Computer Science*, vol. 39, no. S1, pp. 168–170, 2012.

[24] R. van Dinter, B. Tekinerdogan, and C. Catal, "Automation of systematic literature reviews: a systematic literature review," *Information and Software Technology*, vol. 136, 2021.

[25] T. Papakonstantinou, A. Nikolakopoulou, J. P. T. Higgins, M. Egger, and G. Salanti, "Cinema: software for semi-automated assessment of the confidence in the results of network meta-analysis," *Campbell Systematic Reviews*, vol. 16, no. 1, pp. 1–16, 2020.

[26] Z. Guan, J. Sun, Z. Wang, Y. Geng, and W. Xu, "Development of an open metadata schema for prospective clinical research (openPCR) in China," *Methods of Information in Medicine*, vol. 53, no. 1, pp. 39–46, 2014.

[27] W. Xu and M. Okada, "EBM metadata based on dublin core better presenting validity of clinical trials," *Journal of Medical Systems*, vol. 31, no. 5, pp. 337–343, 2007.

[28] S. González-Toral, R. Freire, R. Gualán, and V. Saquicela, "A ranking-based approach for supporting the initial selection of primary studies in a Systematic Literature Review," in *Proceedings of the 2019 XLV Latin American Computing Conference (CLEI)*, pp. 1–10, Panama City, Panama, September 2019.

Hindawi
Evidence-Based Complementary and Alternative Medicine
Volume 2022, Article ID 8080297, 10 pages
https://doi.org/10.1155/2022/8080297

Review Article

Effectiveness and Safety of Acupoint Catgut Embedding for the Treatment of Poststroke Constipation: A Systematic Review and Meta-Analysis

Mao Guo,[1,2] **Xie Le**,[2] **Wang Qin-yu**,[3] **Mao Ye**,[2] **Zhou Sheng-qiang**,[2] **Xie Yao**,[2] **Wu Da-hua**,[2] **and Liu Bai-yan**[1,4]

[1]*Hunan University of Chinese Medicine, Changsha 410208, Hunan, China*
[2]*Affiliated Hospital of Hunan Academy of Chinese Medicine, Changsha 410006, Hunan, China*
[3]*The People's Hospital of Hunan Province, Changsha 410005, Hunan, China*
[4]*Hunan Academy of Chinese Medicine, Changsha 410006, Hunan, China*

Correspondence should be addressed to Liu Bai-yan; liubaiyan@126.com

Received 23 March 2022; Accepted 18 June 2022; Published 5 July 2022

Academic Editor: Zhaolan Liu

Objectives. Acupoint catgut embedding therapy has shown effectiveness in treating functional constipation; however, relevant, high-quality clinical evidence is scarce. This study aimed to systematically assess the effectiveness and safety of acupoint catgut embedding in treating poststroke constipation. *Methods*. Correlative randomized controlled trials were identified through a comprehensive literature search of PubMed, Cochrane Library/Cochrane Central Register of Controlled Trials, Web of Science, Embase, China National Knowledge Internet, Chinese Biomedical Literature Database, Wanfang, and VIP databases from inception until February 2022. Meta-analysis was performed using RevMan 5.3 software. *Results*. Fifteen trials involving 1084 patients were identified. The meta-analysis revealed that the acupoint catgut embedding group was significantly superior to the non-catgut embedding group with regard to the efficacy rate (RR = 1.27, 95% CI (1.19, 1.37), $P < 0.05$), the first defecation time (MD = −3.08, 95% CI (−4.53, −1.63), $P < 0.05$), the defecation sensation score (MD = −0.44, 95% CI (−0.61, −0.26), $P < 0.05$), the degree of difficulty in defecation (MD = −0.73, 95% CI (−1.10, −0.37), $P < 0.05$), the PAC-QOL scale score (MD = −10.06, 95% CI (−13.47, −6.64), $P < 0.05$), and the symptom integral (MD = −3.15, 95% CI (−3.60, −2.71), $P < 0.05$). However, there was no significant difference in the stool property score (MD = 0.06, 95% CI (−0.39, 0.50), $P > 0.05$) as well as the incidence of adverse reactions (RD = 0.01, 95% CI (−0.01, 0.03), $P > 0.05$) between the two groups. *Conclusions*. The results showed that acupoint catgut embedding is probably an effective and safe acupuncture treatment strategy for poststroke constipation. Nevertheless, more rigorously designed, standardized, large-sample, and multicenter randomized controlled designs are warranted to further verify the findings of this study.

1. Introduction

Stroke is the leading cause of death and disability in many parts of the world. Authoritative research shows that the overall burden of stroke remains high worldwide and it is predicted that stroke will continue to be among the top three causes of death in the world until 2040 [1, 2]. Moreover, many stroke survivors endure physical and mental damage caused by some complications for a long duration after an acute stroke, which seriously affects the quality of life and prognosis of patients [3]. Constipation is a common poststroke complication. Approximately, 30% to 60% of stroke patients develop constipation symptoms after the event, which are mostly related to neurological disorders, dependence, long-term hospitalization, and motor, cognitive, and communication disorders [4, 5]. Constipation markedly harms stroke patients as it can result in symptoms or diseases such as abdominal pain, bad breath, depression, and hemorrhoids. In addition, it can induce another stroke or other cerebrovascular events due

to prolonged squatting and forced defecation, thereby endangering the patient's life.

Thus, maintaining smooth defecation following a stroke is critical for these patients' prognosis. Currently, the clinical treatment of poststroke constipation consists mainly of diet adjustment, drug therapy (laxatives, kinetic agents), enema, and surgery. However, some of these treatments are ineffective, some are rejected because of poor tolerability, and the majority have significant adverse effects. In addition, the recurrence rate of poststroke constipation is high [6, 7]. In supplementary and replacement therapies, acupoint catgut embedding therapy is based on the theory of acupuncture and moxibustion in traditional Chinese medicine and uses absorbable surgical sutures to produce lasting acupoint stimulation in the human body, especially for poststroke constipation [8]. At present, high-quality clinical evidence of the acupoint catgut embedding therapy for the treatment of poststroke constipation is limited and the sample size of most related clinical studies is inadequate. Moreover, the efficacy, safety, and reliability of the acupoint catgut embedding therapy need to be improved. At the same time, there is no systematic evaluation of this problem. In view of this situation, this study used systematic evaluation and meta-analysis methods to evaluate the effectiveness and safety of the acupoint catgut embedding therapy in the treatment of poststroke constipation in order to provide a more reliable reference for clinical practice.

2. Data and Methods

The protocol was prospectively registered with the International Prospective Register of Systematic Reviews (PROSPERO) database on 5 March, 2022, (registration number: CRD42022310504.) and the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 13 February, 2022, (registration number INPLASY202220041). Literature search, data extraction, and quality evaluation were performed independently by two reviewers using the databases mentioned above, and any disagreements were resolved by consensus or by consulting a third experienced reviewer.

2.1. Search Strategy. A comprehensive search was performed in PubMed, Cochrane Library/Cochrane Central Register of Controlled Trials, Web of Science, Embase, China National Knowledge Internet, Chinese Biomedical Literature Database, Wanfang, and VIP databases from inception until February 2022. The following keywords or free-text terms were used: (poststroke or after stroke or after apoplexy) and (constipation or difficult defecation) and acupoint catgut embedding and randomized controlled trial. There were no restrictions on countries, population characteristics, and language for the search process.

2.2. Inclusion and Exclusion Criteria. The inclusion criteria were as follows: (1) the trials had to be RCTs that aimed to evaluate the therapeutic effect of acupoint catgut embedding on constipation after a stroke; (2) the subjects were patients who had poststroke constipation diagnosed according to WHO criteria, not limited by gender and age; (3) the intervention groups received the acupoint catgut embedding therapy, while the control groups received other therapies such as acupuncture, oral drugs, sham catgut embedding therapy, and so on; (4) the observation indices included at least one of the following: efficacy rate, first defecation time, defecation sensation score, degree of difficulty in defecation, stool property score, PAC-QOL scale score [9], symptom integral, and adverse event; and (5) there was a complete and clear treatment course. The exclusion criteria were as follows: (1) literature published repeatedly or published by more than one person in the same study (only the latest and the most comprehensive one was retained) and (2) studies in which the required data were unavailable, or studies for which attempts to contact the author to obtain missing data were unsuccessful.

2.3. Data Extraction. The contents of the data extracted mainly included the author, the year of publication, the country, the intervention measures of the experimental group and the control group, the number of cases in the experimental group and the control group, the course of treatment, the randomization method, and the outcome indicators.

2.4. Literature Quality Assessment. The Cochrane risk of bias tool [10] was used to evaluate the quality of the eligible randomized controlled trials. The tool mainly evaluated the risk of bias from 6 areas: selection bias, implementation bias, measurement bias, follow-up bias, report bias, and other biases. Each index was judged by "low risk," "unclear," and "high risk," and the risk of bias distribution map was drawn.

2.5. Statistical Analysis. Revman5.3 software was used to draw the distribution map of the risk of bias and for meta-analysis. The counting data were expressed by relative risk (RR) and its 95% confidence interval (CI). The measurement data were expressed by mean deviation (MD) and its 95% confidence interval (CI). When $I^2 \leq 50\%$ and $P > 0.10$, the fixed-effect model was used to combine the data. When $I^2 > 50\%$ and $P < 0.10$, the random-effects model was used to combine the data. When there was a large heterogeneity, the sensitivity analysis was carried out using the one-by-one elimination method to explore the source of heterogeneity. When the number of articles included in each outcome index was in the range of 2 to 10 articles, the publication bias among the included studies was evaluated by the Egger test using Stata16.0 software. $P > 0.05$ represents no significant publication bias.

3. Results

3.1. Literature Search Results. A total of 115 articles were initially selected from eight databases after preliminary screening. Then, the inconsistent studies were excluded based on their titles and abstracts and 21 articles were retained. Finally, the full texts of the remaining articles were

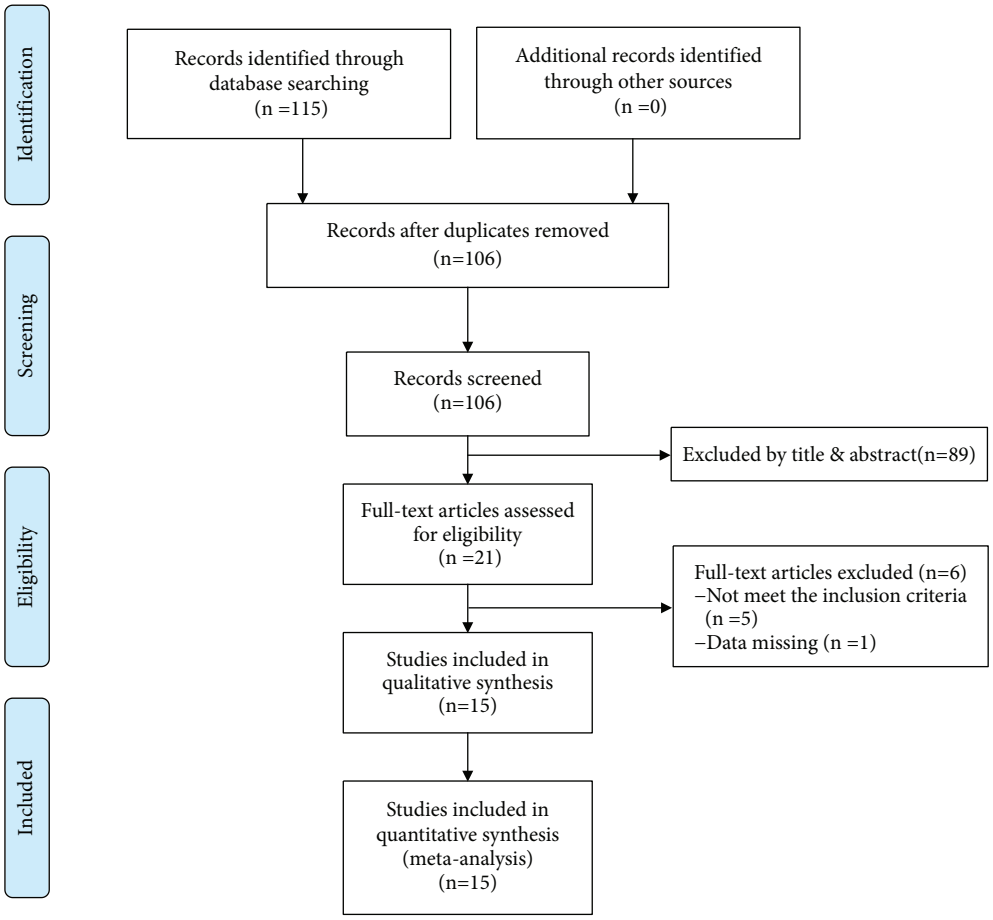


Figure 1: Flowchart of the literature selection process.

evaluated, and the studies not meeting the inclusion criteria were excluded. Thus, 15 studies [11–25]were eligible for our systematic review. The specific search process and study selection are shown in Figure 1, and a detailed description of the general data is shown in Table 1.

3.2. Quality Assessment of the Included Trials. We assessed the risk of bias in all the eligible articles. Randomization was mentioned in all the trials, including the following: 6 studies [12, 16, 20, 22–24] were randomized into groups by the random number table method, 2 studies [13, 14] were randomly divided into groups by statistical software, 2 studies [17, 21] was randomly divided according to the order of enrollment, and 5 articles [11, 15, 18, 19, 25] did not describe the specific method of randomization. Only two studies did not describe the blinding of outcome assessment. Methodological quality evaluation of the risk of bias is shown in Figure 2. The chart shows that there were many studies on low risk of bias, suggesting that the quality of the literature was acceptable.

3.3. Outcome Measures

3.3.1. Efficacy Rate. Twelve studies reported the efficacy rate of acupoint catgut embedding for the treatment of post-stroke constipation. The heterogeneity of the eligible studies was assessed, and the results ($I^2 = 0\%$ and $P > 0.10$) indicated that there was no heterogeneity among the studies. Thus, the fixed-effects model was used to combine the data. The results revealed that the efficacy rate of the acupoint catgut embedding group was higher than that of the control group (RR = 1.27, 95% CI (1.19, 1.37), $P < 0.05$) (Figure 3).

3.3.2. First Defecation Time. Six studies reported the first defecation time of patients who received acupoint catgut embedding for the treatment of poststroke constipation. The heterogeneity of the studies was evaluated, and the results ($I^2 = 94\%$ and $P < 0.10$) revealed a high degree of heterogeneity among the studies; therefore, the random-effects model was adopted. The results showed that the first defecation time of the acupoint catgut embedding group was shorter than that of the control group (MD = −3.08, 95% CI (−4.53, −1.63), $P < 0.05$) (Figure 4).

3.3.3. Defecation Sensation Score [20]. Four studies reported the defecation sensation score of acupoint catgut embedding receivers for the treatment of poststroke constipation. The heterogeneity of the eligible studies was tested, and the results ($I^2 = 0\%$ and $P > 0.10$) showed that there was no heterogeneity among the studies. Hence, the fixed-effects

Table 1: Basic information of the eligible studies.

First author	Year of publication	Country	Type of study	Interventions		Number of cases		Outcome
				Treatment group	Control group	Treatment group	Control group	
LiLi Zeng [11]	2018	China	RCT	ACE	NACE	30	30	①, ⑦
Huiming Deng [12]	2019	China	RCT	ACE	NACE	29	29	①, ⑤
Yonggang Hao [13]	2020	China	RCT	ACE	NACE	30	30	⑦
Jia Du [14]	2020	China	RCT	ACE	NACE	105	105	④, ⑤, ⑥, ⑧
Zhihong Zou [15]	2014	China	RCT	ACE	NACE	50	50	①
Heyi Yang [16]	2012	China	RCT	ACE	NACE	24	20	①, ②
Wenfeng Wu [17]	2011	China	RCT	ACE	NACE	30	30	⑦
Jinying Guo [18]	2012	China	RCT	ACE	NACE	35	35	①, ②
Zipei Zeng [19]	2012	China	RCT	ACE	NACE	40	40	①
Liangyu Huang [20]	2018	China	RCT	ACE	NACE	30	28	①, ②, ③, ④, ⑥, ⑦, ⑧
Xizong Jin [21]	2016	China	RCT	ACE	NACE	20	20	①, ②, ③, ④, ⑤
Xiyang Sun [22]	2019	China	RCT	ACE	NACE	30	30	①, ②, ③, ④, ⑤, ⑥, ⑦, ⑧
Fengyi Guan [23]	2018	China	RCT	ACE	NACE	32	32	①, ⑥, ⑦, ⑧
Ying Gao [24]	2020	China	RCT	ACE	NACE	30	30	①, ③, ④, ⑤, ⑥, ⑦, ⑧
Guifang Luan [25]	2018	China	RCT	ACE	NACE	30	30	①, ②, ⑦

① Efficacy rate; ② first defecation time; ③ defecation sensation score; ④ degree of difficulty in defecation; ⑤ stool property score; ⑥ PAC-QOL scale score; ⑦ symptom integral; ⑧ adverse event; ACE: acupoint catgut embedding; NACE: nonacupoint catgut embedding.

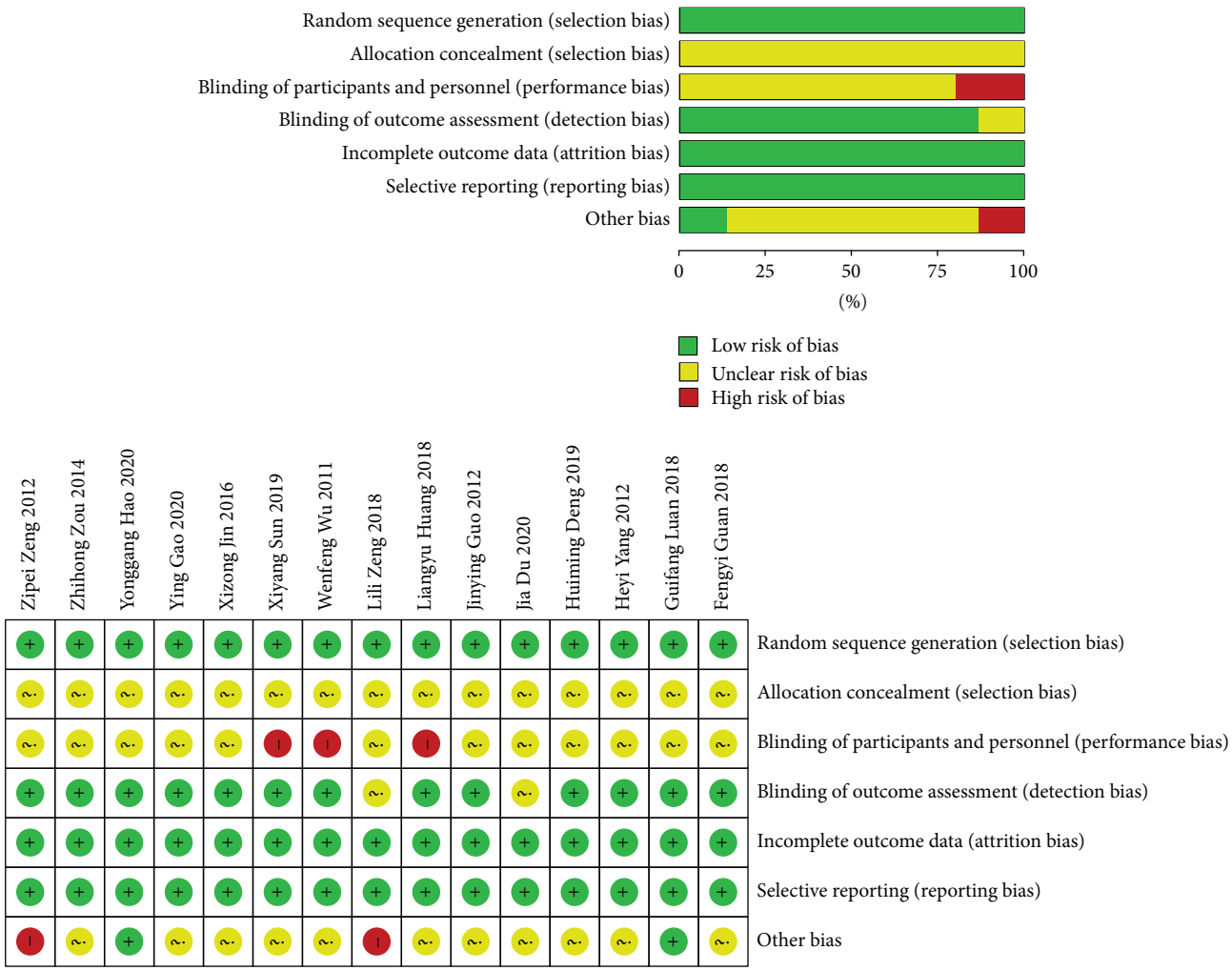
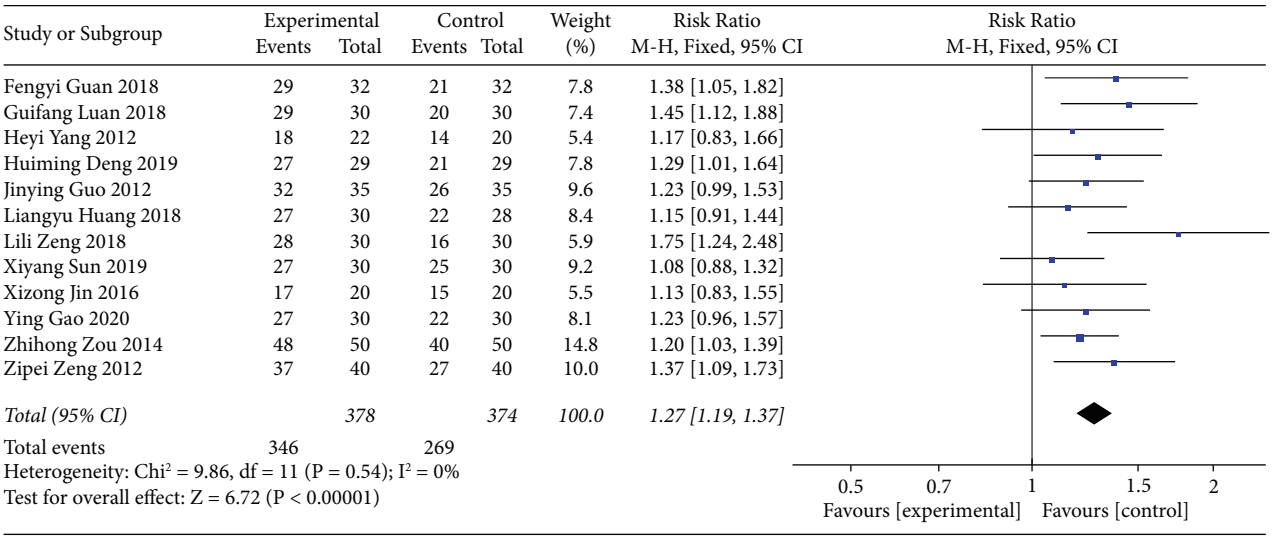


Figure 2: Literature quality risk bias chart.



Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight (%)	Risk Ratio M-H, Fixed, 95% CI
Fengyi Guan 2018	29	32	21	32	7.8	1.38 [1.05, 1.82]
Guifang Luan 2018	29	30	20	30	7.4	1.45 [1.12, 1.88]
Heyi Yang 2012	18	22	14	20	5.4	1.17 [0.83, 1.66]
Huiming Deng 2019	27	29	21	29	7.8	1.29 [1.01, 1.64]
Jinying Guo 2012	32	35	26	35	9.6	1.23 [0.99, 1.53]
Liangyu Huang 2018	27	30	22	28	8.4	1.15 [0.91, 1.44]
Lili Zeng 2018	28	30	16	30	5.9	1.75 [1.24, 2.48]
Xiyang Sun 2019	27	30	25	30	9.2	1.08 [0.88, 1.32]
Xizong Jin 2016	17	20	15	20	5.5	1.13 [0.83, 1.55]
Ying Gao 2020	27	30	22	30	8.1	1.23 [0.96, 1.57]
Zhihong Zou 2014	48	50	40	50	14.8	1.20 [1.03, 1.39]
Zipei Zeng 2012	37	40	27	40	10.0	1.37 [1.09, 1.73]
Total (95% CI)		*378*		*374*	*100.0*	*1.27 [1.19, 1.37]*
Total events	346		269			

Heterogeneity: $Chi^2 = 9.86$, df = 11 (P = 0.54); $I^2 = 0\%$
Test for overall effect: Z = 6.72 (P < 0.00001)

Figure 3: The forest plot of the efficacy rate.

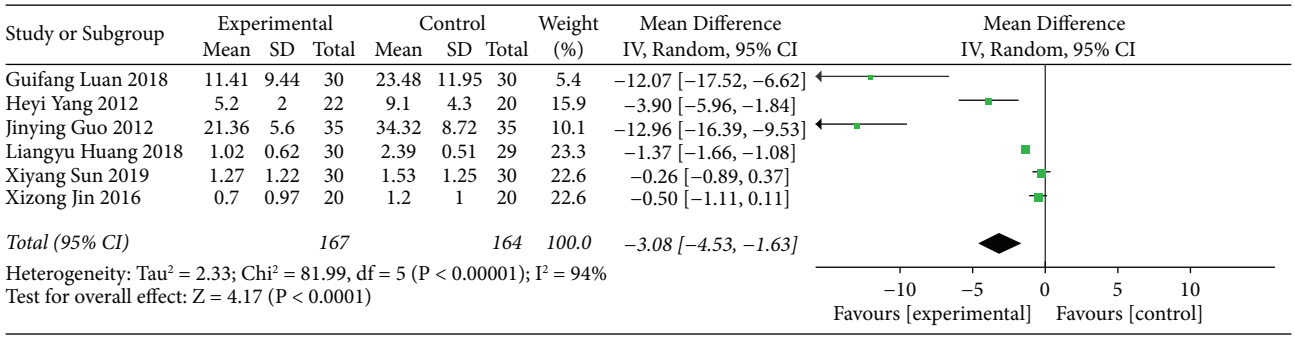


Figure 4: The forest plot of first defecation time.

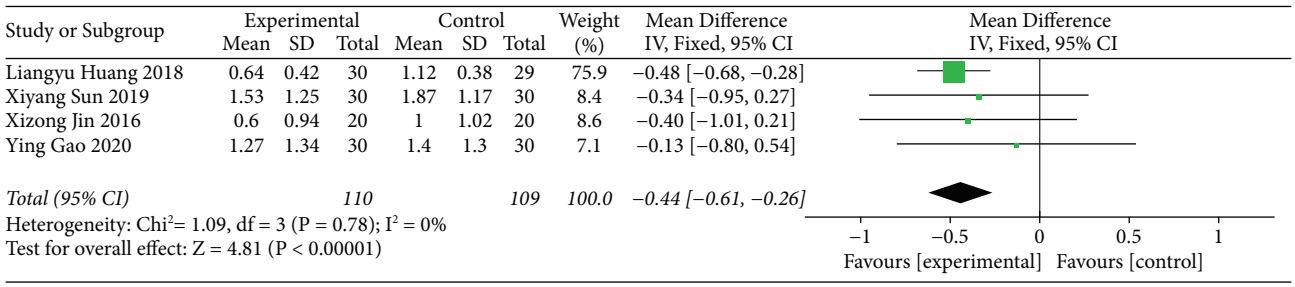


Figure 5: The forest plot of the defecation sensation score.

model was applied to combine the data. The results demonstrated that the defecation sensation score of the acupoint catgut embedding group was lower than that of the control group (MD = −0.44, 95% CI (−0.61, −0.26), $P < 0.05$) (Figure 5).

3.3.4. Degree of Difficulty in Defecation [14]. Five studies reported the degree of difficulty in defecation for patients who received acupoint catgut embedding for the treatment of poststroke constipation and the heterogeneity of the studies was assessed. The results ($I^2 = 78\%$ and $P < 0.10$) revealed a high degree of heterogeneity among the studies. Therefore, the random-effects model was used. The results indicated that the degree of difficulty in defecation of the acupoint catgut embedding group was lower than that of the control group (MD = -0.73, 95% CI (-1.10, -0.37), $P < 0.05$) (Figure 6).

3.3.5. Stool Property Score [14]. Five studies reported the stool property score of acupoint catgut embedding receivers for the treatment of poststroke constipation. There was a high degree of heterogeneity among the studies ($I^2 = 86\%$ and $P < 0.10$), and the random-effects model was applied. The results revealed that there was no significant difference in stool property scores between the two groups. (MD = 0.06, 95% CI (-0.39, 0.50), $P > 0.05$) (Figure 7).

3.3.6. PAC-QOL Scale Score. The PAC-QOL scale score of acupoint catgut embedding receivers for the treatment of poststroke constipation was reported in five studies. The heterogeneity of the studies was determined. Since there was a high degree of heterogeneity among the studies ($I^2 = 84\%$ and $P < 0.10$), the random-effects model was adopted. The results showed that the PAC-QOL scale score of the acupoint catgut embedding group was lower than that of the control group (MD = −10.06, 95% CI (−13.47, −6.64), $P < 0.05$) (Figure 8).

3.3.7. Symptom Integral. Eight studies reported the symptom integral of acupoint catgut embedding for the treatment of poststroke constipation. Heterogeneity assessment revealed that there was little heterogeneity among the studies ($I^2 = 31\%$ and $P > 0.10$). Therefore, the fixed-effects model was used. The results demonstrated that the symptom integral of the acupoint catgut embedding group was lower than that of the control group (MD = -3.15, 95% CI (-3.60, -2.71), $P < 0.05$) (Figure 9).

3.3.8. Adverse Events. The incidence of adverse events of acupoint catgut embedding for the treatment of poststroke constipation was reported in five studies. As there was no heterogeneity among the included studies ($I^2 = 0\%$ and $P > 0.10$), the fixed-effects model was utilized to combine the data. The results revealed that there was no significant difference in the incidence of adverse events between the two groups. (RD = 0.01, 95% CI (-0.01, 0.03), $P > 0.05$) (Figure 10).

4. Sensitivity Analysis

Because of the high heterogeneity among the studies included in the first defecation time, the degree of difficulty in defecation, the stool property score, and PAC-QOL scale

Study or Subgroup	Experimental Mean	Experimental SD	Experimental Total	Control Mean	Control SD	Control Total	Weight (%)	Mean Difference IV, Random, 95% CI
Jia Du 2020	0.92	0.67	101	1.87	0.98	99	25.7	−0.95 [−1.18, −0.72]
Liangyu Huang 2018	0.64	0.42	30	1.84	0.45	29	26.0	−1.20 [−1.42, −0.98]
Xiyang Sun 2019	1.27	1.11	30	1.33	1.21	30	16.4	−0.06 [−0.65, 0.53]
Xizong Jin 2016	0.4	0.82	20	1.1	1.02	20	16.7	−0.70 [−1.27, −0.13]
Ying Gao 2020	1.33	1.21	30	1.67	1.3	30	15.2	−0.34 [−0.98, 0.30]
Total (95% CI)			*211*			*208*	*100.0*	*−0.73 [−1.10, −0.37]*

Heterogeneity: Tau² = 0.12; Chi² = 17.94, df = 4 (P = 0.001); I² = 78%
Test for overall effect: Z = 3.98 (P < 0.0001)

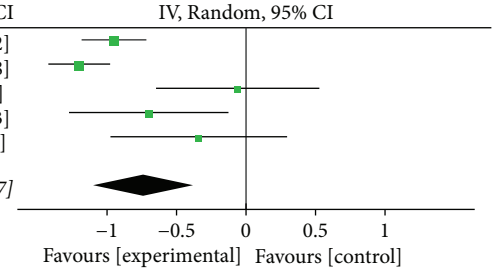


Figure 6: The forest plot of degree of difficulty in defecation.

Study or Subgroup	Experimental Mean	Experimental SD	Experimental Total	Control Mean	Control SD	Control Total	Weight (%)	Mean Difference IV, Random, 95% CI
Huiming Deng 2019	3.28	0.51	29	2.71	0.49	29	18.4	0.57 [0.31, 0.83]
Jia Du 2020	2.37	0.73	105	1.83	0.64	105	18.5	0.54 [0.35, 0.73]
Liangyu Huang 2018	16.28	3.42	30	25.48	3.31	29	11.2	−9.20 [−10.92, −7.48]
Xiyang Sun 2019	1.47	1.04	30	1.33	1.21	30	17.4	0.14 [−0.43, 0.71]
Xizong Jin 2016	0.7	0.97	20	1.3	0.84	20	17.4	−0.60 [−1.16, −0.04]
Ying Gao 2020	1.13	1.25	30	1.87	1.28	30	17.1	−0.74 [−1.38, −0.10]
Total (95% CI)			*244*			*243*	*100.0*	*−1.03 [−1.94, −0.12]*

Heterogeneity: Tau² = 1.15; Chi² = 148.21, df = 5 (P < 0.00001); I² = 97%
Test for overall effect: Z = 2.23 (P = 0.03)

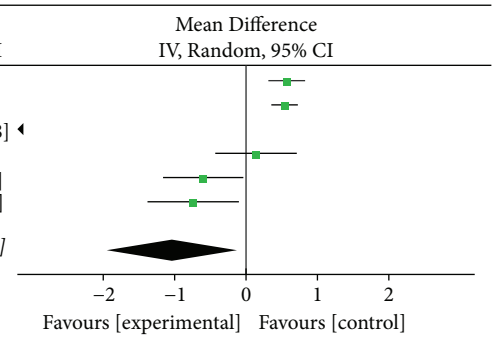


Figure 7: The forest plot of the stool property score.

Study or Subgroup	Experimental Mean	Experimental SD	Experimental Total	Control Mean	Control SD	Control Total	Weight (%)	Mean Difference IV, Random, 95% CI
Fengyi Guan 2018	36.06	12.45	32	43.59	12.27	32	14.9	−7.53 [−13.59, −1.47]
Jia Du 2020	24.29	4.47	105	38.54	6.71	105	26.6	−14.25 [−15.79, −12.71]
Liangyu Huang 2018	16.28	3.42	30	25.48	3.31	29	26.3	−9.20 [−10.92, −7.48]
Xiyang Sun 2019	62.63	14.44	30	73.67	13.94	30	12.5	−11.04 [−18.22, −3.86]
Ying Gao 2020	33.27	8.54	30	40.07	8.35	30	19.6	−6.80 [−11.07, −2.53]
Total (95% CI)			*227*			*226*	*100.0*	*−10.06 [−13.47, −6.64]*

Heterogeneity: Tau² = 10.78; Chi² = 25.42, df = 4 (P < 0.0001); I² = 84%
Test for overall effect: Z = 5.77 (P < 0.00001)

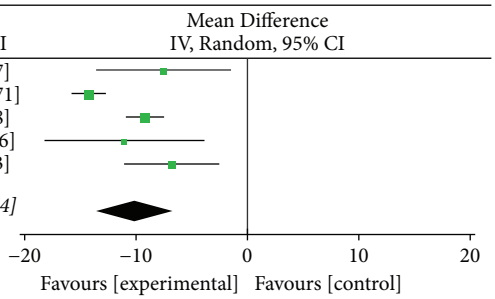


Figure 8: The forest plot of the PAC-QOL scale score.

Study or Subgroup	Experimental Mean	Experimental SD	Experimental Total	Control Mean	Control SD	Control Total	Weight (%)	Mean Difference IV, Fixed, 95% CI
Fengyi Guan 2018	9.05	6.65	32	12.83	8	32	1.5	−3.78 [−7.38, −0.18]
Guifang Luan 2018	13.95	5.34	30	16.43	6.01	30	2.4	−2.48 [−5.36, 0.40]
Liangyu Huang 2018	7.78	1.35	30	11.62	1.16	29	48.4	−3.84 [−4.48, −3.20]
Lili Zeng 2018	3.63	1.56	30	5.97	1.68	30	29.6	−2.34 [−3.16, −1.52]
Wenfeng Wu 2011	6.95	4.77	30	9.87	4.52	30	3.6	−2.92 [−5.27, −0.57]
Xiyang Sun 2019	8.55	2.92	30	10.55	4.54	30	5.3	−2.00 [−3.93, −0.07]
Ying Gao 2020	7.73	4.39	30	10.3	4.53	30	3.9	−2.57 [−4.83, −0.31]
Yonggang Hao 2020	6.12	3.811	30	9.43	3.94	30	5.2	−3.31 [−5.27, −1.35]
Total (95% CI)			*242*			*241*	*100.0*	*−3.15 [−3.60, −2.71]*

Heterogeneity: Chi² = 10.19, df = 7 (P = 0.18); I² = 31%
Test for overall effect: Z = 13.85 (P < 0.00001)

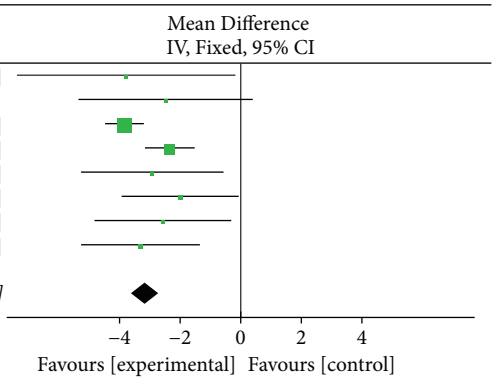


Figure 9: The forest plot of Symptom integral.

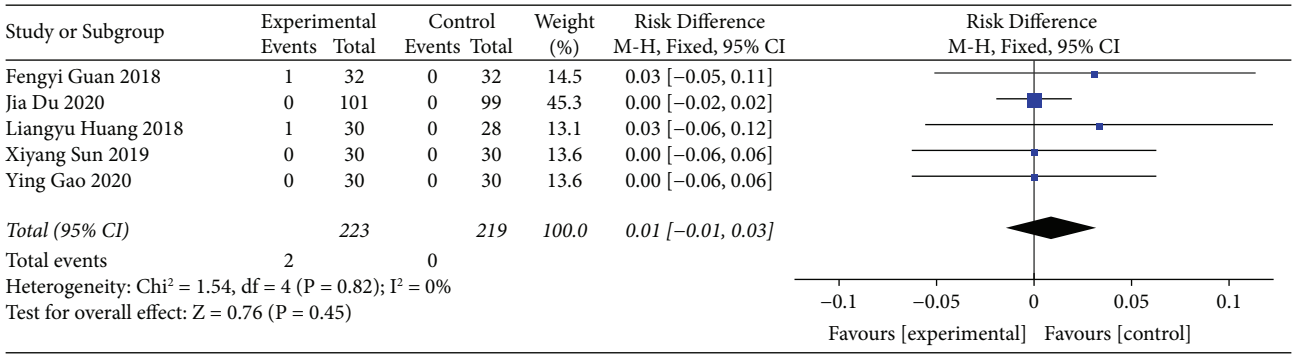


Figure 10: The forest plot of adverse events.

score, were eliminated by the one-by-one method to conduct sensitivity analysis. The main source leading to the increase in heterogeneity was not found in the sensitivity analysis of the stool property score, the first defecation time, and the degree of difficulty in defecation. Therefore, the results obtained were relatively stable and reliable. The literature of Jia Du was found to be the main source of increasing heterogeneity in the sensitivity analysis of the PAC-QOL scale score. After excluding this article, the PAC-QOL scale score of the patients in the experimental group that received the catgut embedding therapy was still lower than that of the control group, and the difference between the two groups was statistically significant ($P < 0.05$). Thus, the result obtained was still relatively stable and reliable.

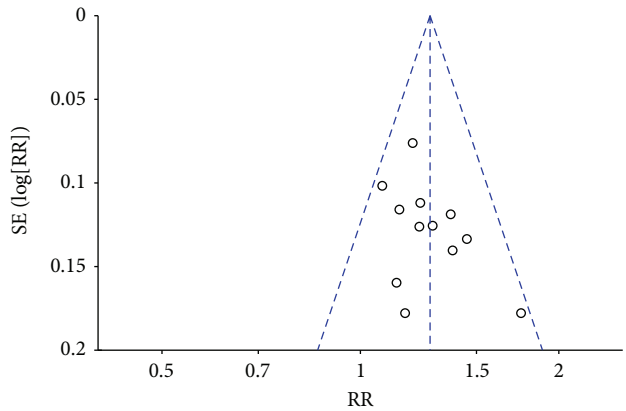


Figure 11: The funnel plot of the efficacy rate.

5. Publication Bias Analysis

The efficacy rate of the outcome indices was included in more than 10 studies. The publication bias was evaluated using a funnel chart. Visually, the points on the funnel chart were scattered and not entirely symmetrical, which indicated the possibility of a publication bias (Figure 11). Since the number of studies with first defecation time, defecation sensation score, degree of difficulty in defecation, stool property score, PAC-QOL scale score, symptom integral, and adverse event as outcomes was less than 10, all outcome indicators could not effectively evaluate the publication bias with a funnel chart. Therefore, the Egger test was used to evaluate the publication bias and the results revealed that there was no publication bias ($P > 0.05$).

6. Discussion

Constipation, a common complication of stroke, seriously threatens the health of stroke patients. Constipation not only affects the quality of life of patients but also induces various diseases. In severe cases, excessive defecation could increase blood pressure and endanger the health of stroke patients. Therefore, alleviating constipation is essential to improving the quality of life of stroke patients [26]. Although drugs are effective in treating poststroke constipation, people are paying increasing attention to adverse drug reactions.

Acupoint catgut embedding is a novel treatment modality. By implanting modern biomedical materials into the patient's acupoint tissues, the catgut can remain in the body. Thus, the process of catgut embedding can be completed promptly, which forms the long-term stimulatory effect of acupuncture points, realizing the long-term therapy mode. Acupoint embedding is similar in principle to acupuncture and moxibustion but has other advantages. In this therapy, the acupuncture effect is substituted with repeated stimulation of acupoints using implanted thread bodies. The selection of acupoints and the number of thread bodies are determined according to disease severity. Following acupoint catgut embedding, the stimulation of acupoints by thread bodies with movement is similar to acupuncture, which can dredge meridians, regulate viscera, strengthen the body's resistance, and eliminate pathogen. Moreover, the curative effect is stable and lasting [27] Reports show [28] that the mechanism of the acupoint catgut embedding therapy for constipation may stimulate related acupoints and parasympathetic nerves, increasing intestinal peristalsis. This therapy can simultaneously inhibit sympathetic nerves, increasing colorectal fluid secretion, and lubrication.

This systematic review and meta-analysis of the effectiveness and safety of acupoint catgut embedding for the treatment of poststroke constipation have some limitations due to the quality of the literature selected. First, the studies used various acupoints. Second, there is no unified standard for the specific operation of acupoint embedding, such as the embedding method and acupoint selection. Third, the efficacy will also be affected by the operator's technical level, the

severity of the patient's condition, and other factors. Fourth, the treatment diversity in the control group of these studies partly affected the consistency of the eligible studies. Finally, the outcome is also affected by factors such as the decision to adopt blinding, the sample size, and the number of centers. Therefore, more rigorously designed, standardized, large-sample, multicenter randomized controlled studies are required to further confirm the results of this study.

7. Conclusion

This study demonstrated that acupoint catgut embedding probably has a remarkable curative effect on poststroke constipation. At the same time, it is a treatment method with a definite curative effect, safety, simplicity, and easy acceptance by patients and hence is worthy of clinical application and further research. Nevertheless, more rigorously designed, standardized, large-sample, and multicenter randomized controlled designs are warranted to further verify the findings of this study.

Data Availability

The data that support the findings of this study are available from the corresponding authors upon reasonable request.

Conflicts of Interest

The authors declare that they have no conflicts of interest.

Authors' Contributions

Guo Mao and Bai-yan Liu selected the topic and conceived the study. Le Xie and Yao Xie were responsible for screening potential studies and extracting data from the eligible studies. Qin-yu Wang and Ye Mao interpreted and edited the result analysis. Da-hua Wu and Sheng-qiang Zhou provided guidance on the overview methodology. Guo Mao assessed the reviews and drafted the manuscript. All authors read, critically reviewed, and approved the final manuscript as submitted.

Acknowledgments

The authors thank all investigators and supporters involved in this study. The study was supported by the Natural Science Youth Fund Project of Hunan Provincial Department of Science and Technology (no. 2021jj40313), the clinical guidance program of Hunan Provincial Department of Science and Technology (no. 2020SK51003), and the Scientific Research Project of Hunan Provincial Bureau of Traditional Chinese Medicine (no. 2021084).

Supplementary Materials

The PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) checklist of this study. (*Supplementary Materials*)

References

[1] GBD 2016 stroke Collaborators, "Global, regional, and national burden of stroke, 1990-2016: a systematic analysis for the global burden of disease study 2016," *The Lancet Neurology*, vol. 18, no. 5, pp. 439–458, 2019.

[2] K. J. Foreman, N. Marquez, A. Dolgert et al., "Forecasting life expectancy, years of life lost, and all-cause and cause-specific mortality for 250 causes of death: reference and alternative scenarios for 2016-40 for 195 countries and territories," *Lancet*, vol. 392, no. 10159, pp. 2052–2090, 2018.

[3] S. A. Chohan, P. K. Venkatesh, and C. H. How, "Long-term complications of stroke and secondary prevention: an overview for primary care physicians," *Singapore Medical Journal*, vol. 60, no. 12, pp. 616–620, 2019.

[4] T. Zhang, G. Wang, B. Li et al., "Effect of acupuncture for constipation after ischemic stroke: study protocol for a randomized controlled trial," *Trials*, vol. 19, no. 1, p. 454, 2018.

[5] H. Pasin Neto and R. A. Borges, "Visceral mobilization and functional constipation in stroke survivors: a randomized, controlled, double-blind, clinical trial," *Cureus*, vol. 12, no. 5, p. e8058, 2020.

[6] J. Zhai, W. Mu, J. Si et al., "Acupuncture for constipation in patients with stroke: protocol of a systematic review and meta-analysis," *BMJ Open*, vol. 8, no. 3, p. e020400, 2018.

[7] S. L. Zhou, X. L. Zhang, and J. H. Wang, "Comparison of electroacupuncture and medical treatment for functional constipation: a systematic review and meta-analysis," *Acupuncture in Medicine*, vol. 35, no. 5, pp. 324–331, 2017.

[8] J. Zhang, L. Lai, L. Liang, X. Bai, and M. Chen, "*Mycobacterium avium* infection after acupoint embedding therapy," *Plastic and Reconstructive Surgery—Global Open*, vol. 5, no. 9, p. e1471, 2017.

[9] P. Marquis, C. De La Loge, D. Dubois, A. McDermott, and O. Chassany, "Development and validation of the patient assessment of constipation quality of life questionnaire," *Scandinavian Journal of Gastroenterology*, vol. 40, no. 5, pp. 540–551, 2005.

[10] J. P. T. Higgins and S. Green, *Cochrane Handbook for Systematic Reviews of Interventions*, john wiley & sons, Hoboken, NJ, USA, 2011.

[11] L. L. Zhen, H. M. Huang, and C. J. Luo, "Jichuan decoction combined with catgut embedding in the treatment of 30 cases of constipation due to spleen and kidney yang deficiency after stroke in the elderly," *Guangxi Journal of Traditional Chinese Medicine*, vol. 41, no. 2, pp. 21–23, 2018.

[12] H. M. Deng, Q. Tian, and K. X. Zeng, "Clinical observation on 29 cases of constipation after apoplexy of Qi deficiency and Blood stasis treated by Catgut embedding," *Hunan Journal of Traditional Chinese Medicine*, vol. 35, no. 1, pp. 64-65, 2019.

[13] Y. G. Hao and L. S. Wang, "Observation on the Therapeutic effect of Sun's abdominal Acupuncture and Catgut embedding in the treatment of Post-apoplectic constipation," *Electronic Journal of Clinical Medical Literature*, vol. 7, no. 15, pp. 81–91, 2020.

[14] J. Du, H. Liu, J. Xu et al., "Post-stroke constipation treated with acupoint embedding therapy: a multi-center randomized controlled trial," *Chinese Acupuncture & Moxibustion*, vol. 40, no. 5, pp. 493–497, 2020.

[15] Z. H. Zou, H. B. Yu, and J. Lu, "Clinical observation of acupoint catgut-embedding therapy combined with abdominal massage in the treatment of post-stroke constipation," *Academic Journal of Guangzhou Medical University*, vol. 42, no. 6, pp. 84–86, 2014.

[16] H. Y. Yang, "Clinical observation on 22 cases of constipation after apoplexy treated by catgut embedding at acupoint," *Forum on Traditional Chinese Medicine*, vol. 27, no. 5, p. 25, 2012.

[17] W. F. Wu, F. Huang, and B. Nie, "Observation on the catgut embedding therapy in treating post-stroke constipation," *Shanghai Journal of Acupuncture and Moxibustion*, vol. 30, no. 4, pp. 225-226, 2011.

[18] J. Y. Guo, "Jin three needles," *Acupoint Catgut Embedding Combined With Huanglong Decoction in the Treatment of 35 Cases of Constipation Of Deficiency Of Both Qi And Yin After Stroke*, vol. 47, no. 11, p. 829, 2012.

[19] Z. P. Zeng, S. H. Wu, and K. X. Zeng, "Clinical observation on abdominal acupuncture combined with catgut embedding in treating constipation in recovery period of stroke," *Inner Mongolia Journal of Traditional Chinese Medicine*, vol. 32, no. 8, pp. 43-44, 2013.

[20] L. Y. Huang, *The Clinical Research of Ba-Liao Acupoints on the Post-stroke Constipation patients*, Guangzhou University of Traditional Chinese Medicine, Guangzhou, China, 2018.

[21] X. Z. Jin, *Clinical Observation on Acupoint Catgut Embedding Therapy in Treatment of Consipation after stroke*, Nanjing University of Traditional Chinese Medicine, Nanjing, China, 2016.

[22] X. Y. Sun, *Clinical Observation on Acupoint Catgut Embedding Therapy in Treatment of Consipation after stroke*, Anhui University of Traditional Chinese Medicine, Hefei, China, 2019.

[23] F. Y. Guan, *Clinical Research on Acupoint Catgut Embedding Therapy in Treatment of Consipation after stroke*, Guangzhou University of Traditional Chinese Medicine, Guangzhou, China, 2018.

[24] Y. Gao, *Clinical Observation on Acupoint Catgut Embedding Therapy for Constipation Due to Qi Deficiency after Stroke and its Influence on Serum SP and VIP content*, Heilongjiang University of Traditional Chinese Medicine, Harbin, China, 2020.

[25] G. F. Luan, *Clinical Observation on Acupuncture Point Embedding Therapy for Constipation after Stroke of Qi Deficiency and Blood Stasis type*, Liaoning University of Traditional Chinese Medicine, Shenyang, China, 2018.

[26] L. Yang, M. Bi, and R. Wang, "General research situation of acupuncture and moxibustion in treatment of functional constipation in recent decade," *Liaoning Journal of Traditional Chinese Medicine*, vol. 42, no. 4, pp. 890–892, 2015.

[27] W. S. Sun and Z. Q. Tan, "New biomedical materials and their application value in creative embedding line," *Shanghai Journal of Acupuncture and Moxibustion*, vol. 29, no. 2, pp. 131-132, 2010.

[28] Y. Z. Wang, "Observation on therapeutic effect and colonic transit activity of catgut embeding for treatment of 28 cases of slow transit constipation," *Lishizhen Medicine and Materia Medica Research*, vol. 17, no. 8, pp. 1545-1546, 2006.

Hindawi
Evidence-Based Complementary and Alternative Medicine
Volume 2022, Article ID 7366320, 8 pages
https://doi.org/10.1155/2022/7366320

Research Article

The Efficacy and Safety of Xinjia Xuanbai Chengqi Granules in Acute Exacerbation of COPD: A Multicentre, Randomised, Double-Blind, Controlled Trial

Ruihan Qi,[1] Hongchun Zhang,[2] Demin Li,[2] Feng Gao,[3] Qing Miao,[4] Sheng Chen,[1] Yan Huang,[5] Lei Wu,[6] Zhenhui Lu,[7] Haibo Hu,[8] Erran Li,[9] and Zhibin Chen[10]

[1]*Department of Respiratory and Critical Care Medicine, Shenzhen Hospital of Traditional Chinese Medicine, Shenzhen 518033, China*
[2]*Center of Respiratory Medicine, China-Japan Friendship Hospital, Beijing 100029, China*
[3]*Department of Respiratory Medicine, Wang Jing Hospital of CACMS, Beijing 100102, China*
[4]*Department of Pulmonary Disease, Xiyuan Hospital of CACMS, Beijing 100091, China*
[5]*Department of Pulmonary Disease, Inner Mongolia Autonomous Region Hospital of Traditional Chinese Medicine, Hohhot 750306, China*
[6]*Department of Respiratory Medicine II, Hebei Hospital of Traditional Chinese Medicine, Shijiazhuang 050011, China*
[7]*Respiratory Research Institute of Longhua Hospital, Shanghai University of Traditional Chinese Medicine, Shanghai 200032, China*
[8]*Department of Respiratory and Critical Care Medicine, Qingdao Haici Medical Group, Qingdao 266033, China*
[9]*Department of Respiratory and Critical Care Medicine, The First Hospital of China Medical University, Shenyang 110002, China*
[10]*Department of Respiratory Medicine, The Second Affiliated Hospital of Fujian University of Traditional Chinese Medicine, Fuzhou 350002, China*

Correspondence should be addressed to Hongchun Zhang; 13701226664@139.com

Received 20 January 2022; Accepted 30 May 2022; Published 23 June 2022

Academic Editor: Talha Bin Emran

Purpose. The study aimed to explore the efficacy and safety of Xinjia Xuanbai Chengqi granules (XJXBCQ) combined with conventional medicine in the treatment of acute exacerbation of chronic pulmonary disease (AECOPD). *Patients and Methods*. This multicentre, double-blind, parallel, placebo-controlled, randomised clinical trial conducted in China from January 2019 to February 2021 recruited 330 participants who were allocated into three groups. All participants underwent conventional basic treatment with oxygen therapy, antibiotics, and a bronchodilator. Besides, group *A* received XJXBCQ granules and budesonide suspension for inhalation; group *B* received XJXBCQ granules and half dosage of budesonide suspension; and group *C* received budesonide suspension and a placebo. All therapies lasted for 5 days, and participants were followed up for 30 days after discharge. The primary outcomes were efficacy, traditional Chinese medicine (TCM) syndrome score, and clinical symptom score. Secondary outcomes included the blood gas analysis, serum inflammatory markers, adverse events, mortality, theoretical discharge time, actual hospitalisation time, proportion of patients requiring invasive mechanical ventilation, proportion of patients transferred to an intensive care unit (ICU), and readmission rate within 30 days after discharge. *Results*. XJXBCQ adjunct with conventional treatment could significantly improve the total efficacy ($P < 0.05$). Meanwhile, group *A* showed significantly better results than group *C* in the TCM syndrome score, phlegm score, and Wexner constipation score ($P < 0.05$). For modified British medical research council (mMRC), on day 3 (−0.17, 95% confidence interval [CI]: −0.33–−0.01) and day 4 (−0.20, 95% CI: −0.39–−0.02), group *A* performed statistically better than group *C*. No significant differences in other secondary outcomes were detected. *Conclusion*. XJXBCQ is beneficial and safe for AECOPD treatment and could be considered an adjunctive therapy for promoting the relief of clinical symptoms. This trial is registered with ChiCTR1800016915.

1. Introduction

Chronic obstructive pulmonary disease (COPD), characterised by persistent respiratory symptoms and airflow limitation, has become the fourth leading cause of death worldwide [1–3]. About 1 million COPD patients die in China every year, accounting for 31.1% of the total COPD deaths in the world [4]. The current incidence of COPD in China has risen from 8.2% to 8.6%, and the incidence in people over 40 years is 13.7%, increasing by about 67% compared with 2002 [5]. Given that COPD can be prevented, effective prevention and treatment will help diminish the acute exacerbation and postpone the disease progression. COPD management is still fundamentally heavily dependent on the use of bronchodilators and corticosteroids. Since long-term use of corticosteroids can result in adverse effects, and inflammation in COPD lungs is often poorly responsive to corticosteroid treatment, bronchodilators can hardly reverse the airflow obstruction. There is an urgent need for an alternative, more effective, and safer therapeutic approach that will not only relieve symptoms but also influence the natural course of COPD by preventing disease progression or even have the ability to reverse the disease [6, 7].

Complementary treatment, whose efficacy was confirmed by many studies, has been widely used in many chronic diseases as an alternative therapy to conventional medicines [8–11]. Traditional Chinese medicine (TCM), characterised by the theory of syndrome differentiation and overall conditioning, implies its potential advantages in the treatment of COPD. A systematic review has revealed that TCM combined with conventional medicines could accelerate the relief of clinical symptoms in COPD patients and improve lung function, modified British medical research council (mMRC), COPD assessment test (CAT), Saint George's respiratory questionnaire (SGRQ), 6-minute walking distance (6MWD), BMI, obstruction, dyspnoea, exercise capacity (BODE) score, and COPD patient-reported outcomes (COPD-PRO) to improve the quality of life and reduce the frequency of acute exacerbations and hospitalisation duration of AECOPD patients [12, 13]. Moreover, studies on TCM syndrome have found that in addition to respiratory symptoms, such as cough, phlegm, and wheezing, patients in acute exacerbation often experience constipation, abdominal distension, and yellow greasy tongue coating. Based on TCM theory, stating that the "lung and the large intestine are interior-exterior," physicians offering the therapeutic approach called Tongfu Xiere, meaning treating both lung and gut, usually achieve good clinical outcomes in AECOPD treatment, and Xinjia Xuanbai Chengqi granules (XJXBCQ) is the representative formula of this kind of therapy. We implemented this rigorously designed clinical trial with the aim of validating the efficacy and safety of XJXBCQ in the treatment of AECOPD and understanding whether TCM therapy works better than conventional treatment.

2. Patients and Methods

2.1. Design. This was a multicentre, double-blind, randomised, placebo-controlled clinical trial conducted in China from October 2018 to March 2020 expectedly, aiming to recruit 360 participants from the respiratory inpatients. In this study, the block randomisation method was adopted, and participants with random numbers, 001–360, were randomly divided into three groups at a ratio of 1 : 1 : 1. The allocated medications of integrated Chinese and Western medicine for group *A* (group *A*), integrated Chinese and Western medicine for group *B* (group *B*), and Western standard medicine for group *C* (group *C*) were exactly the same in appearance, packaging, and specifications and were coded by professionals not participating in the statistical analysis of this project. The trial was registered at the Chinese Clinical Trial Registry (trial registration number: ChiCTR1800016915). Further information could be found in the published study protocol [14].

2.2. Ethics and Consent. Before randomisation, participants were asked to sign informed consent. The study was approved by the leading research unit, the Ethical Committee of China-Japan Friendship Hospital (ethics approval number: 2018-58-K40-4) and another ethical committee of research units participating in the study.

2.3. Inclusion and Exclusion Criteria. As the study protocol reported [14], AECOPD patients of clinical-grade severity of I–II [1, 15] with a syndrome of heat-phlegm and sthenic-fu, in the age range from 40 to 80 years, who volunteered to participate in the study and signed the informed consent were included in this trial. Meanwhile, patients who met any of the following criteria were excluded: (1) patients complicated with asthma, pneumonia, bronchiectasis, cystic fibrosis, pulmonary tuberculosis, lung cancer, or any other airflow-limiting disease with known causes and characteristic pathology; (2) patients complicated with coronary heart disease, hypertensive heart disease, or heart valve disease; (3) patients needing invasive mechanical ventilation; (4) patients with clinically confirmed or highly suspected pulmonary embolism; (5) patients with severe diseases of cardiovascular, cerebrovascular, hepatorenal, haematopoietic, or endocrine system; (6) patients with intestinal obstruction requiring surgical intervention; (7) pregnant or lactating patients; (8) mentally handicapped patients; (9) patients with alanine aminotransferase (ALT) and aspartate aminotransferase (AST) >1.5 times the upper limit of normal reference or serum creatinine (Scr) above the upper limit of normal reference; (10) patients requiring immunosuppressants; (11) patients taking oral or intravenous antibiotics before screening for more than 3 days in the last 3 months; (12) patients allergic to the basic therapeutic drugs, Chinese herbal medicinal ingredient prescription, or other substances prescribed through the research; (14) patients

who have participated in or are participating in other clinical trials in the last 3 months; and (15) patients who were considered inappropriate to participate in this clinical trial by the investigator.

2.4. Intervention and Comparator. According to the protocol [14], all participants underwent conventional basic treatment with oxygen therapy, antibiotics (0.5 g levofloxacin hydrochloride intravenous injection once a day), and bronchodilator (500 ug ipratropium bromide solution for inhalation three times a day). Besides, group *A* received XJXBCQ granules (5 g, three times a day) and budesonide suspension for inhalation (2 mg Pulmicort Respules two times a day); group *B* received XJXBCQ granules (5 g, three times a day) and budesonide suspension for inhalation (1 mg Pulmicort Respules two times a day); and group *C* received the placebo of XJXBCQ granules (5 g, three times a day) and budesonide suspension for inhalation (2 mg Pulmicort Respules two times a day). All therapies lasted for 5 days. XJXBCQ (2.5 g/bag, batch number: 180605) and the related placebo were produced and packaged by Anhui Jiren Pharmaceutical with the China Pharmaceutical Production License (number: Wan 20160083). The details of the components of XJXBCQ are shown in Table 1 [14].

2.5. Measures. As previously reported [14], the primary outcomes were total efficacy (clinical recovery rate, markedly effective rate, and effective rate, explained in the protocol); clinical symptom scores including cough, 24 h phlegm, Wexner constipation score, and mMRC; and TCM syndrome score. The TCM syndrome score consisted of five symptoms: cough, dyspnoea, abdominal distension, constipation, and fever, and the evaluation criteria are available in the protocol [14]. These outcomes would be measured at baseline (day 1 [D1] to day 5 [D5] during the intervention) and day 6 (D6)—the first day after intervention. The evaluation criteria were explained in detail in the protocol [14]. The secondary outcomes were blood gas analysis (pH, PaO_2, and $PaCO_2$), recorded at baseline and day 6, and serum inflammatory markers (procalcitonin [PCT], C-reactive protein [CRP], interleukin [IL]-6, and tumour necrosis factor [TNF]-α) detected on baseline D3 and on D6. The safety outcomes of blood and urine routine; liver function (AST, ALT, total bilirubin [TBil], alkaline phosphatase [ALP], gamma-glutamyl transferase [GGT]), kidney function (blood urea nitrogen [BUN], estimated glomerular filtration rate [eGFR]); and electrocardiogram (ECG) were assessed at baseline and day 6. The adverse events were recorded at any time if they occurred. Other outcomes included mortality, theoretical discharge time, actual hospitalisation time, proportion of patients requiring invasive mechanical ventilation, proportion of patients transferred to an ICU, and readmission rate within 30 days after discharge.

2.6. Administration. As the leading unit of the research, China-Japan Friendship Hospital offered the standard operating procedures (SOPs) for all participating units. Researchers involved underwent a series of training sessions to guarantee a thorough understanding of research protocol and SOPs and ensure the accuracy of recorded data. The clinical data were first recorded in case report form (CRF) and then were electronically dually input into the Electronic Data Capture system. The Beijing Qihuang Pharmaceutical Clinical Research Center was employed as an independent quality inspector for monitoring and managing this trial.

2.7. Statistical Analysis. Statistical analysis was performed by SAS V. 9.4 software. For continuous variables, the paired *t*-test was used to compare the changes in clinical symptom scores before and after intervention, and the covariance analysis model was used for comparison between the groups. The multiplier method was used to calculate the quartiles (25%, 50%, and 75%) of time from enrolment to events occurring, and a bilateral 95% confidence interval (CI) and the incidence rate at each time point after enrolment were calculated. Kaplan–Meier curves were plotted using the log-rank test to compare theoretical hospital stay and actual hospital stay. For the binary variables, such as the recurrence rate of laboratory indicators, the all-cause mortality, the proportion of mechanical ventilation, the proportion of patients transferred to an ICU, and the proportion of readmission within 30 days after discharge, the 95% CI was calculated using a centrally stratified Cochran–Mantel–Haenszel χ^2 test according to the classification, indicators, time points, quantity, and percentage.

3. Results

3.1. Sample Characteristics. The study was conducted between January 2019 and February 2021 in China. The trial had planned to recruit 360 participants, but eventually, a total of 331 eligible patients were screened, and 330 patients were actually enrolled, with 110 patients in group *A*, 109 patients in group *B*, and 111 patients in group *C*. Twenty-two patients failed to complete the trial, and the dropout rate was 5.45% in group *A*, 8.26% in group *B*, and 6.31% in group *C*. Participants accepting at least one time of treatment were included in the full-analysis set (FAS) and safety analysis set (SS), and those who completed all the treatment according to the protocol were admitted in per-protocol set (PPS). The patient enrolment distribution diagram is presented in Figure 1. As shown in Table 2, gender, age, vital signs, past history, and allergic history of allocated participants showed no statistical difference ($P < 0.05$). The three groups were also comparable in terms of acute exacerbation (AE) times within the last year, hospitalisation times for AE, FEV_1%, and efficacy outcomes ($P > 0.05$).

3.2. Primary Outcomes

3.2.1. Efficacy. The total efficacy rate was 90.75% in group *A* (9 clinical recovery, 31 markedly effective, 56 effective, and 10 invalid), 82.24% in group *B* (9 clinical recovery, 27 markedly effective, 52 effective, and 19 invalid), and 71.82% in group *C* (5 clinical recovery, 22 markedly effective, 52 effective, and 31 invalid), showing significant statistical

Table 1: Main components of Xinjia Xuanbai Chengqi granules.

Chinese name	English common name	Scientific name	Amount (grams)
Ku Xing Ren	Bitter almonds	*Armeniacae Semen Amarum*	6
Sheng Shi Gao	Gypsum	*Gypsum Fibrosum*	15
Gua Lou	Snakegourd fruit	*Trichosanthis Fructus*	9
Da Huang	Rhubarb	*Rhei Radix et Rhizoma*	6
Huang Qin	Baikal skullcap root	*Scutellariae Radix*	9
Zi Su Zi	Perilla fruit	*Perillae Fructus*	9
Zhi Gan Cao	Licorice root	*Glycyrrhizae Radix et Rhizoma Praeparata Cum Melle*	6
Jin Qiao Mai	Wild buckwheat rhizome	*Fagopyri Dibotryis Rhizoma*	10
Zi Wan	Tatarian aster root	*Asteris Radix et Rhizoma*	9

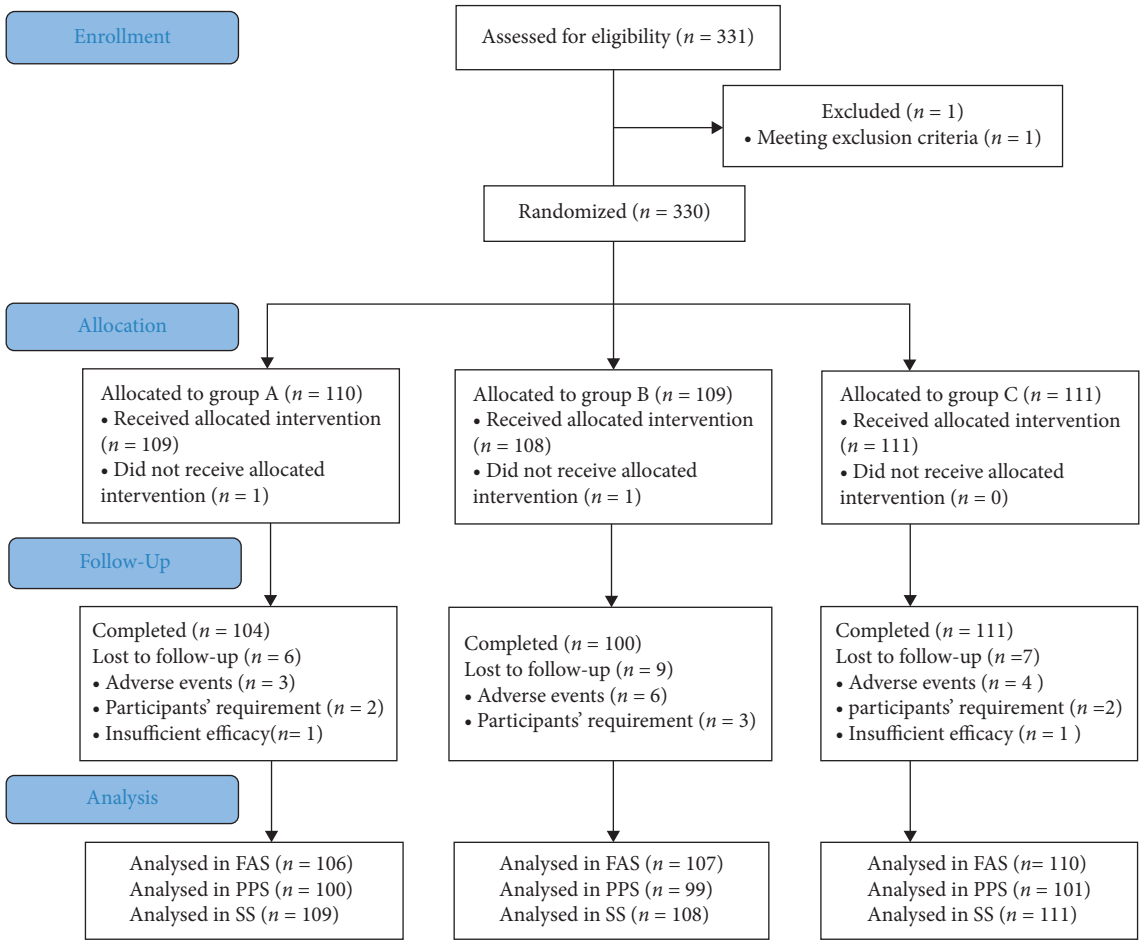


Figure 1: A diagram of the study flow.

difference between the three groups ($P = 0.0038$). Besides, compared with group *C*, the total efficacy rate of group *A* was significantly better ($P < 0.05$). However, there was no statistical difference between group *A* and group *B* (Table 3).

3.2.2. TCM Syndrome Score and Clinical Symptom Score. After a 5-days intervention, the TCM syndrome score and clinical symptom score (phlegm, mMRC, and Wexner score) were significantly improved in all three groups; meanwhile, group A performed significantly better than group C in TCM syndrome score, phlegm score, and Wexner constipation score ($P < 0.05$). For mMRC, there was no statistical difference between the three groups on D6, but on the third and fourth days of the intervention (D3, D4), group *A* performed statistically better than group *C* (D3: −0.17, 95% CI: −0.33–−0.01; D4: −0.20, 95% CI: −0.39–−0.02). Based on conventional Western medicines, adjunctive traditional Chinese medicine was more adept in relieving clinical symptoms of AECOPD patients (Table 3).

Table 2: Demographic characteristics and baseline data of the participants.

Item	Group A ($n = 106$)	Group B ($n = 107$)	Group C ($n = 110$)	Statistics	P value
Gender					
Male	75	86	92	5.86	0.053
Female	31	21	18		
Age (years)	67.17 ± 8.06	68.45 ± 7.28	68.28 ± 8.42	0.82	0.442
Vital signs					
Temperature (°C)	36.52 ± 0.51	36.46 ± 0.37	36.44 ± 0.43	0.91	0.402
Heart rate (times/min)	85.32 ± 13.20	82.70 ± 11.73	84.79 ± 11.34	1.40	0.248
Respiratory rate (times/min)	20.36 ± 1.74	20.31 ± 1.80	20.17 ± 2.18	0.27	0.762
SBP (mmHg)	134.34 ± 17.40	132.09 ± 18.46	133.01 ± 17.32	0.43	0.650
DBP (mmHg)	80.12 ± 9.44	78.51 ± 10.34	78.82 ± 10.97	0.73	0.481
Past history (%)	91 (85.85)	94 (87.85)	97 (88.18)	0.32	0.853
Allergic history (%)	21 (19.81)	26 (24.30)	27 (24.55)	0.89	0.640
AE times within last year	1.18 ± 1.01	1.17 ± 1.33	1.08 ± 1.17	0.22	0.804
Hospitalisation times for AE	0.80 ± 0.83	0.81 ± 0.80	0.78 ± 1.04	0.04	0.962
FEV_1% (numbers)	52.35 ± 14.84 (62)	51.19 ± 14.75 (63)	52.32 ± 13.27 (67)	0.14	0.872
Efficacy outcomes					
Phlegm score	38.08 ± 25.19	41.30 ± 29.78	38.53 ± 50.05	0.24	0.786
Wexner score	7.17 ± 3.56	7.55 ± 3.71	7.05 ± 3.64	0.55	0.577
mMRC	2.35 ± 0.81	2.38 ± 0.75	2.25 ± 0.84	0.76	0.470
pH	7.41 ± 0.03	7.40 ± 0.04	7.40 ± 0.04	0.61	0.545
PaO_2 (mmHg)	75.49 ± 20.79	76.30 ± 21.07	77.19 ± 30.49	0.12	0.886
$PaCO_2$ (mmHg)	41.55 ± 9.44	42.73 ± 9.92	42.54 ± 14.35	0.30	0.741
TCM syndrome score	5.58 ± 2.21	5.47 ± 2.25	5.29 ± 2.15	0.46	0.631

Note. SBP: systolic blood pressure; DBP: diastolic blood pressure; AE: acute exacerbation; TCM: traditional Chinese medicine; mMRC: modified British medical research council.

3.3. Secondary Outcomes

3.3.1. Blood Gas Analysis and Serum Inflammatory Markers. For blood gas analysis measured on day 6 compared with baseline, only group *A* showed improved PaO_2. No statistical difference was shown after intervention for pH and $PaCO_2$ between the three groups (Table 3). Regarding serum inflammatory markers (CRP, IL6, PCT, and TNF-α), only a few patients showed abnormal values at baseline, although the level of inflammatory factors seemed to be lower on D6 after the intervention; however, there were no statistical differences between D6 and baseline (Table 3). Moreover, we used the recovery rate of serum inflammatory markers on D6 to represent the anti-inflammatory effect of the three treatments; however, no difference was observed after intervention or between the three groups (Table 4).

3.4. Adverse Events. Fifteen participants (2 from group *A*, 8 from group *B*, and 5 from group *C*) reported 20 adverse events (4.57%), which were relevant to the given intervention judged by researchers. The most frequent adverse event was diarrhoea, and other event types are listed in Table 5. There were two serious adverse events: a patient in group *A* suspended the trial for severe diarrhoea and vomit that resolved after quitting the drug, and another patient in group *C* suffered drug-induced hypersensitivity, considered to be a severe adverse event by researchers. Other adverse events were mild to moderate (Table 5).

3.5. Other Outcomes. The median length of hospitalisation of the three groups was 8 days, 9 days, and 8 days, respectively, showing no statistical difference ($P = 0.6635$). Two patients (1.89%) in group *A* and two patients in group *B* (1.87%) were readmitted due to AECOPD within 30 days after discharge, and the readmission rate of the three groups was similar ($P = 0.3624$). A patient died in group *A* due to acute cerebral infarction that did not relate to the study intervention. Another patient in group *C* was transferred to an ICU during hospitalisation for requiring invasive mechanical ventilation. Mortality, proportion of patients requiring invasive mechanical ventilation during hospitalisation, and proportion of patients transferred to an ICU during hospitalisation of the three groups showed no statistical difference ($P = 0.3614$; $P = 0.3711$; $P = 0.3711$).

3.6. Discussion. Patients with chronic respiratory disease are two to three times more likely to have gastrointestinal issues, and COPD patients have had higher incidences of inflammatory bowel disease (IBD) compared to non-COPD controls, while over a half of IBD patients, in contrast, show pulmonary involvement [9, 10]. Of COPD patients, 40% have had irregular stools compared to 15% of non-COPD patients when hospitalised, showing statistical difference [16]. Moreover, constipation has been positively correlated with the severity of dyspnoea, acute exacerbation times, and complication of COPD [17]. As for clinical symptoms, these peripheral disease manifestations highlight the immunological crosstalk between the lung and gut, the two mucosal sites, termed the gut-lung axis, whereby the immunological health of the gut impacts the health of the lung [18], similar to the TCM theory arguing that "the lung and the large

Table 3: Comparison of outcomes after intervention.

Variable	Group	$\overline{X} \pm s$		D6–baseline	
		Baseline	D6	$\overline{X} \pm s$	P value
TCM syndrome score	Group A ($n = 106$)	23.32 ± 6.74	9.11 ± 6.18*#	−14.21 ± 7.29	<0.0001
	Group B ($n = 107$)	22.99 ± 7.44	9.84 ± 6.30	−13.15 ± 7.42	<0.0001
	Group C ($n = 110$)	22.53 ± 6.34	11.54 ± 6.52	−10.99 ± 8.36	<0.0001
Phlegm	Group A ($n = 106$)	1.63 ± 0.81	0.64 ± 0.57*	−0.99 ± 0.81	<0.0001
	Group B ($n = 107$)	1.68 ± 0.73	0.71 ± 0.61	−0.97 ± 0.81	<0.0001
	Group C ($n = 110$)	1.57 ± 0.80	0.86 ± 0.77	−0.71 ± 1.09	<0.0001
mMRC	Group A ($n = 106$)	2.35 ± 0.81	1.42 ± 0.99	−0.93 ± 0.89	<0.0001
	Group B ($n = 107$)	2.38 ± 0.75	1.50 ± 0.83	−0.88 ± 0.75	<0.0001
	Group C ($n = 110$)	2.25 ± 0.84	1.56 ± 0.90	−0.69 ± 0.89	<0.0001
Wexner	Group A ($n = 106$)	7.17 ± 3.56	3.25 ± 2.71*	−3.92 ± 2.69	<0.0001
	Group B ($n = 107$)	7.55 ± 3.71	3.75 ± 3.00	−3.80 ± 3.28	<0.0001
	Group C ($n = 110$)	7.05 ± 3.64	4.11 ± 3.48	−2.95 ± 3.03	<0.0001
pH	Group A ($n = 100$)	7.41 ± 0.03	7.40 ± 0.03	−0.00 ± 0.03	0.1212
	Group B ($n = 96$)	7.40 ± 0.04	7.40 ± 0.04	−0.00 ± 0.03	0.4060
	Group C ($n = 104$)	7.40 ± 0.04	7.40 ± 0.04	−0.00 ± 0.03	0.5197
PaO_2	Group A ($n = 100$)	75.49 ± 20.79	80.81 ± 23.28	4.49 ± 18.39	0.0165*
	Group B ($n = 96$)	76.30 ± 21.07	78.63 ± 26.01	1.87 ± 26.44	0.4896
	Group C ($n = 104$)	77.19 ± 30.49	78.53 ± 23.72	0.91 ± 31.60	0.7703
$PaCO_2$	Group A ($n = 100$)	41.55 ± 9.44	42.25 ± 9.10	0.68 ± 4.70	0.1488
	Group B ($n = 96$)	42.73 ± 9.92	43.65 ± 12.62	1.10 ± 7.10	0.1313
	Group C ($n = 104$)	42.54 ± 14.35	43.45 ± 14.11	1.00 ± 5.36	0.0596
CRP	Group A ($n = 101$)	11.98 ± 29.33	8.27 ± 23.02	−3.61 ± 17.50	0.0408
	Group B ($n = 102$)	16.12 ± 33.67	9.35 ± 30.50	−6.60 ± 28.62	0.0218
	Group C ($n = 103$)	15.60 ± 35.21	8.13 ± 23.61	−7.44 ± 24.03	0.0022
PCT	Group A ($n = 102$)	0.09 ± 0.16	0.08 ± 0.15	−0.02 ± 0.28	0.4015
	Group B ($n = 100$)	0.09 ± 0.11	0.08 ± 0.10	−0.02 ± 0.12	0.0926
	Group C ($n = 103$)	0.06 ± 0.06	0.07 ± 0.06	−0.00 ± 0.06	0.4863
IL6	Group A ($n = 93$)	12.35 ± 21.63	11.02 ± 13.91	−0.77 ± 17.53	0.6730
	Group B ($n = 94$)	11.58 ± 17.60	25.41 ± 139.20	15.01 ± 142.62	0.3103
	Group C ($n = 98$)	21.84 ± 101.39	10.14 ± 14.05	−12.72 ± 101.52	0.2177
TNF-α	Group A ($n = 91$)	14.37 ± 29.37	14.04 ± 29.01	−0.30 ± 24.16	0.9044
	Group B ($n = 92$)	72.41 ± 235.71	59.68 ± 210.30	−10.49 ± 209.31	0.6319
	Group C ($n = 100$)	49.39 ± 181.27	32.40 ± 139.82	−15.91 ± 177.03	0.3711

Note. $^{*}P < 0.05$, group A compared with group C; $^{\#}P < 0.05$. D6: the day after intervention; TCM: traditional Chinese medicine; mMRC: modified British medical research council.

Table 4: The recovery rate of serum inflammatory markers.

Groups	CRP			PCT			IL6			TNF-α		
	n	n^*	Rate (%)	n	n^*	Rate (%)	n	n^*	Rate (%)	n	n^*	Rate (%)
Group A	25	12	48.00	12	2	16.67	15	4	26.67	13	3	23.08
Group B	30	13	43.33	18	5	27.78	22	8	36.36	11	2	18.18
Group C	31	17	54.84	8	2	25.00	16	8	50.00	15	2	13.33
P value	0.6373			0.5082			0.4462			0.8747		

Note. n: numbers of participants with abnormal inflammatory markers at baseline; n^*: numbers of participants having abnormal inflammatory markers and returning to normal on the day after intervention (day 6). CRP: C-reactive protein; PCT: procalcitonin; IL6: interleukin-6; TNF-α: tumour necrosis factor-α.

intestine are interior-exterior," which postulates that the disruption of interactive networks (Biao-Li) between these two related organ systems may disrupt the bidirectional gut-lung communication, leading to the onset of a disease. Thus, it has been a common strategy for TCM practitioners to simultaneously treat the lung and gut in respiratory diseases, including AECOPD, which is often accompanied by constipation and abdominal distension. Moreover, XJXBCQ is a representative formula of the gut-lung correlation theory.

The results of this study demonstrated that XJXBCQ significantly reduced clinical symptoms of AECOPD patients compared with conventional medicine. Judging from the Guidelines for TCM Diagnosis and Treatment of COPD (2011) [19] and Guidelines for Clinical Research of New

Table 5: Summary of adverse events.

Event type	Group *A* (no. of cases)	Group *B* (no. of cases)	Group *C* (no. of cases)
Diarrhoea	1	2	1
Vomit	1	1	0
High blood pressure	1	2	0
Insomnia	0	2	0
Dizziness	0	2	1
Dyspnoea	0	3	0
Itchy skin	0	0	1
Stomach upset	0	0	1
Drug-induced hypersensitivity	0	0	1

TCM for Chronic Bronchitis (2002) [20], the total TCM syndrome score and the efficacy rate of combination therapy of XJXBCQ and conventional medicine were superior to using conventional medicine alone, especially in relieving dyspnoea, phlegm, abdominal distension, and constipation. Additionally, the mMRC, the Wexner constipation score, and the 24-hour phlegm score also showed improvement after the combination therapy. However, there were no differences in the recovery rate of IL6, CRP, PCT, and TNF-a, possibly due to the mild degree of inflammation for most AECOPD participants whose inflammatory markers were normal when allocated.

For blood gas analysis, PaO_2 was significantly improved after the intervention involving combination therapy. Although there were no statistical differences, $PaCO_2$ values were slightly elevated in the three groups. We assumed that the diaphragm mobility was limited to some extent as all enrolled patients had a certain degree of abdominal distension and constipation. Once abdominal distension and constipation were relived after the intervention, the diaphragm mobility might have improved, dyspnoea improved, respiratory rates slowed down, and CO_2 emission decreased, leading to an increase in $PaCO_2$ as a consequence.

In this trial, we set three groups to understand whether the combination of XJXBCQ with conventional medicine could reduce the use of corticosteroids as many COPD patients show poor response to the anti-inflammatory benefits of corticosteroids, and the use of inhaled corticosteroids (ICSs) has been associated with an increased risk of pneumonia in patients with COPD [7, 21]. However, although no statistical difference was found in the comparison between group *A* and group *B* for detected outcomes, it should be prudent to reduce corticosteroids while using XJXBCQ due to the lack of rigorous evidence.

Regarding safety, the incidence of drug-related adverse events was similar in the three groups, and the recorded events mainly involved gastrointestinal disorders, including diarrhoea and vomiting. Given that XJXBCQ itself has a laxative effect, which may cause diarrhoea, prudent judgement should be taken regarding whether diarrhoea could be regarded as an adverse reaction.

This multicentre, double-blind, randomised trial was conducted strictly according to the protocol, showing clinical benefits of XJXBCQ in treating AECOPD. Nevertheless, several limitations still exist. We aimed to recruit AECOPD patients with clinical-grade severity of I–II, but actually, most of the patients allocated were mild to moderate and at grade I severity; consequently, many outcomes, such as the blood gas analysis and serum inflammation markers, were normal at baseline, which makes it impossible to assess the effect of the intervention on them, as well as the outcomes of mortality, the proportion of patients requiring invasive mechanical ventilation during hospitalisation, and the proportion of patients transferred to an ICU during hospitalisation.

4. Conclusions

The results of this study demonstrated that the use of XJXBCQ in AECOPD adjunctively with conventional medicine for 5 days could significantly accelerate the recovery of clinical symptoms of dyspnoea and phlegm, the mMRC score, and the specific symptoms of abdominal distension and constipation, as well as improving PaO_2, indicating that XJXBCQ simultaneously treating the lung and gut was effective and safe. Moreover, the results also corroborate the importance of the gut-lung axis in AECOPD treatment. Further basic research is needed to explore the mechanism by which XJXBCQ relieves AECOPD through the gut-lung axis.

Data Availability

The metadata of the trial were uploaded to National Population Health Data Center of China (https://www.ncmi.cn/phda/projectDataDetail.html?id=93e9e1aa-4444-3f78-9d30-17f7bbf93ad7), and it will be accessible from 30 June, 2024.

Conflicts of Interest

The authors report no conflicts of interest in this work.

Authors' Contributions

RQ and HZ contributed to study design, communication, and coordination between research units, quality monitoring of the trial, and manuscript drafting and revision. RQ, HZ, DL, FG, QM, and SC contributed to data acquisition and accuracy. RQ, HZ, and DL contributed to the statistical analysis. All the authors contributed to participants' recruitment and are unanimously accountable for all aspects of the work.

Acknowledgments

The authors appreciate the patients participating in this trial and the Beijing Qihuang Pharmaceutical Clinical Research Center providing quality inspection and management of the trial. The study was supported by the National Key Research and Development Program of China (grant no. 2017YFC1309305); the Science and Innovation Commission of Shenzhen (grant no. KCXFZ20201221173209027); and the Sanming Medical and Health Projects of Shenzhen (SZSM201812063).

References

[1] Global Initiative for Chronic Obstructive Lung Disease (GOLD), "Global strategy for the diagnosis, management and prevention of chronic obstructive pulmonary disease," 2019, https://www.goldcopd.org/.

[2] G. A. Roth, D. Abate, K. H. Abate, and GBD 2017 Causes of Death Collaborators, "Global, regional, and national age-sex-specific mortality for 282 causes of death in 195 countries and territories, 1980–2017: a systematic analysis for the global burden of disease study 2017," *The Lancet*, vol. 392, no. 10159, pp. 1736–1788, 2018.

[3] M. Zhou, H. Wang, X. Zeng et al., "Mortality, morbidity, and risk factors in China and its provinces, 1990–2017: a systematic analysis for the global burden of disease study 2017," *The Lancet*, vol. 394, no. 10204, pp. 1145–1158, 2019.

[4] P. Yin, H. Wang, T. Vos et al., "A subnational analysis of mortality and prevalence of COPD in China from 1990 to 2013: findings from the global burden of disease study 2013," *Chest*, vol. 150, no. 6, pp. 1269–1280, 2016.

[5] C. Wang, J. Xu, L. Yang et al., "Prevalence and risk factors of chronic obstructive pulmonary disease in China (the China pulmonary health [CPH] study): a national cross-sectional study," *The Lancet*, vol. 391, no. 10131, pp. 1706–1717, 2018.

[6] N. Roche, "Stable COPD treatment: where are we?" *COPD: Journal of Chronic Obstructive Pulmonary Disease*, vol. 15, no. 2, pp. 123–129, 2018.

[7] M. G. Matera, M. Cazzola, and C. Page, "Prospects for COPD treatment," *Current Opinion in Pharmacology*, vol. 56, pp. 74–84, 2021.

[8] M. Seyed Hashemi, N. Namiranian, H. Tavahen et al., "Efficacy of pomegranate seed powder on glucose and lipid metabolism in patients with type 2 diabetes: a prospective randomized double-blind placebo-controlled clinical trial," *Complementary Medicine Research*, vol. 28, no. 3, pp. 226–233, 2021.

[9] X. Deng, F. Kang, X. Chen et al., "Comparative effectiveness and safety of seven qi-tonifying Chinese medicine injections for AECOPD patients: a systematic review and network meta-analysis," *Evidence-Based Complementary and Alternative Medicine*, vol. 2021, Article ID 6517515, 15 pages, 2021.

[10] F. Rezayat, M. H. Hashempur, H. Tavahen, H. Salmanroghani, and M. Emtiazy, "The efficacy of ramak (a traditional herbal medicine preparation) for patients with ulcerative colitis: a pilot, randomized, triple-blinded, placebo-controlled clinical trial," *European Journal of Integrative Medicine*, vol. 39, Article ID 101209, 2020.

[11] T. Tan, Y. Meng, J. L. Lyu et al., "A systematic review and meta-analysis of tai chi training in cardiorespiratory fitness of elderly people," *Evidence-Based Complementary and Alternative Medicine*, vol. 2022, Article ID 4041612, 15 pages, 2022.

[12] Y. Jiang, *Systematic Review of Traditional Chinese Medicine Compound in the Treatment of Stable Stage of Chronic Obstructive Pulmonary Disease with Qi Deficiency*, Beijing University of Traditional Chinese Medicine, Chaoyang, China, 2021.

[13] J. Li, H. Zhang, H. Ruan et al., "Effects of Chinese herbal medicine on acute exacerbations of COPD: a randomized, placebo-controlled study," *International Journal of Chronic Obstructive Pulmonary Disease*, vol. 15, pp. 2901–2912, 2020.

[14] J. Jin, H. Zhang, D. Li et al., "Effectiveness of Xin Jia Xuan Bai Cheng Qi decoction in treating acute exacerbation of chronic obstructive pulmonary disease: study protocol for a multicentre, randomised, controlled trial," *BMJ Open*, vol. 9, no. 11, Article ID e030249, 2019.

[15] B. R. Celli and P. J. Barnes, "Exacerbations of chronic obstructive pulmonary disease," *European Respiratory Journal*, vol. 29, no. 6, pp. 1224–1238, 2007.

[16] W. Xu, Y. Liu, Z. Gao, H. Zhao, and W. Pan, "Analysis of the functional status of urine and faece in patients with chronic obstructive pulmonary disease," *Chinese Journal of Experimental Formulas*, vol. 17, no. 12, pp. 227-228, 2011.

[17] P. Han, Z. Xu, Y. Li, X. Lian, and Y. Chao, "Clinical study on chronic obstructive pulmonary disease complicated with constipation," *Medical Forum Magazine*, vol. 30, no. 4, pp. 36–38, 2009.

[18] D. Zhang, S. Li, N. Wang, H. Y. Tan, Z. Zhang, and Y. Feng, "The cross-talk between gut microbiota and lungs in common lung diseases," *Frontiers in Microbiology*, vol. 11, p. 301, 2020.

[19] J. Li, S. Li, and X. Yu, "Guidelines for the diagnosis and treatment of chronic obstructive pulmonary disease in traditional Chinese medicine," *Journal of Traditional Chinese Medicine*, vol. 53, no. 01, pp. 80–84, 2012.

[20] X. Zheng, *Guiding Principles for Clinical Research of New Traditional Chinese Medicines*, China Medical Science and Technology Press, Beijing, China, 2002.

[21] D. Mei, W. S. D. Tan, and W. S. F. Wong, "Pharmacological strategies to regain steroid sensitivity in severe asthma and COPD," *Current Opinion in Pharmacology*, vol. 46, pp. 73–81, 2019.

Hindawi
Evidence-Based Complementary and Alternative Medicine
Volume 2022, Article ID 1500660, 7 pages
https://doi.org/10.1155/2022/1500660

Research Article

Treatment of the Gastroesophageal Reflux Disease with Chinese Herbal Medicine (BanxiaXiexin Decoction): Evidence from Meta-Analysis

Jiali Liu,[1] **Jinke Huang**,[1] **Beihua Zhang**,[1,2] **Xiaolan Yin**,[1,2] **Mi Lv**,[1] **Zhihong Liu**,[3] **Fengyun Wang**,[1,2] **and Xudong Tang**[2]

[1]*Department of Gastroenterology, Xiyuan Hospital, China Academy of Chinese Medical Sciences, Beijing, China*
[2]*Institute of Gastroenterology, Xiyuan Hospital, China Academy of Chinese Medical Sciences, Beijing, China*
[3]*Department of Gastroenterology, Peking University Traditional Chinese Medicine Clinical Medical School (Xiyuan), Beijing, China*

Correspondence should be addressed to Fengyun Wang; wfy811@163.com and Xudong Tang; txdly@sina.com

Received 6 February 2022; Revised 1 April 2022; Accepted 24 May 2022; Published 15 June 2022

Academic Editor: Jing Hu

Objectives. Systematic reviews/meta-analyses (SRs/MAs) are still controversial on the effectiveness of Banxia Xiexin decoction (BXD) to treat gastroesophageal reflux disease (GERD). To assess the evidence reliability and inform the clinical use of BXD, we performed a meta-analysis from previous SRs/MAs to collate, critically appraise, and synthesize the effectiveness of BXD treatment in GERD. *Methods*. SRs/MAs were collected by searching major medical databases. The included studies were evaluated in terms of methodological quality and quality of evidence using criteria from the Assessment of Multiple Systematic Reviews 2 (AMSTAR-2) tool, and the Grades of Recommendation, Assessment, Development, and Evaluation (GRADE) system, respectively. *Results*. Six SRs/MAs were included in this study. The methodological quality of SRs/MAs was generally unsatisfactory. Unregistered protocols, failure to provide a list of excluded trials, and lack of a comprehensive search strategy were the main limitations of previous SRs/MAs. No high-quality evidence was found to support the effect of BXD on GERD patients. The qualitative data synthesis relied on low-quality trials with a small sample size, which was the main factor for evidence degradation. *Conclusions*. BXD seems to have promising efficacy to treat GERD patients. Although the quality of SRs/MAs was generally low and defects were frequent, our study highlights areas where methodologies need to be improved.

1. Introduction

The gastroesophageal reflux disease (GERD) is a functional gastrointestinal disorder characterized by heartburn, chest pain, dysphagia, and abdominal pain due to gastric acid entering the esophagus [1]. The global prevalence of GERD has increased substantially—from 424 million in 1990 to 709 million cases in 2017, a change of 67.2% [2]. The GERD imposes a considerable economic burden, driven by the cost of consulting, examining, and prescribing over the countermedications, surgery, and associated complications such as Barrett's esophagus and esophageal adenocarcinoma [3]. The goal of GERD treatment is to relieve or reduce gastric acid secretion, and therefore, antacids, histamine receptor antagonists, and proton pump inhibitors are the main therapeutic drugs [4]. However, the efficacy of conventional drugs varies widely and most of them require long-term or lifelong administration [5]. Moreover, some patients require surgical treatment when conventional treatment is ineffective [4]. As a result, patients often seek complementary and alternative therapies to alleviate their symptoms [6].

The pathogenesis of GERD has not been fully elucidated. According to available evidence, the development of GERD involves a variety of potential mechanisms, such as transient lower esophageal sphincter relaxation, lower esophageal sphincter pressure, hiatus hernia, crural diaphragmatic

dysfunction, and impaired esophageal clearance [7]. Pharmacological experiments have verified the effectiveness of Banxia Xiexin decoction (BXD) in the treatment of GERD [8]. Animal experiments have shown that BXD helps to reduce esophageal mucosal injury and decreases the expression of intercellular adhesion molecule-1 and L-selectin [9]. Chronic administration of BXD can increase esophageal sphincter pressure, inhibit gastric acid, and promote the repair of damaged mucosa [10]. In addition, BXD may exert a protective effect on the esophageal mucosa by downregulating the mRNA expression of calponin and caldesmon and regulating the synthesis of calcitonin gene-related peptides to reduce gastric acidity [8]. These available evidence support that BXD has good clinical application prospects, given that it is effective to treat GERD acting in multiple pathways.

Systematic reviews (SRs)/meta-analyses (MAs) are considered the highest level of evidence in evidence-based medicine, yet inconsistent results may interfere with evidence-based decision-making [11,12]. BXD has been widely used in the treatment of GERD in China and is highly effective due to its multicomponent and multitarget characteristics [13]. Numerous SRs/MAs have evaluated the effect of BXD on GERD, but the conclusions of these studies were not consistent, which created a need to ascertain the reliability of previous evidence. Thus, we conducted this overview to systematically evaluate the available evidence for the use of BXD in the treatment of GERD.

2. Methods

The protocol of this study was registered in PROSPERO (http://www. crd. York.ac.uk/prospero), and the registration number was CRD42022287497. The methodology was performed following the criteria of the Cochrane Handbook [14].

2.1. Search Strategy. Sources of the Cochrane Library, PubMed, Web of Science, Embase, the Chinese database of Chinese Biomedical Database, ChineseVIP, Wanfang, and China National Knowledge Infrastructure were identified from their inception to January, 2022. Gastroesophageal reflux disease, Chinese medicine, Banxia Xiexin decoction, and systematic review were used as search keywords. The strategy used for the PubMed search is shown in Table 1.

2.2. Criteria for Considering Studies. Inclusion criteria were as follows: (a) SRs/MAs studies; (b) patients diagnosed with GERD; (c) experimental group treated with BXD and control group treated with Western medicine (WM); and (d) outcomes included effective rate, recovery rate, efficacy under gastroscope, recurrence rate, acid regurgitation, heartburn, and adverse events.

The comprehensive efficacy assessment criteria were as follows [15]: (a) cure: clinical symptoms completely disappeared, gastroscopy showed that the esophageal mucosa was completely restored to normal; (b) effective: clinical symptoms were reduced and gastroscopy showed improvement of esophageal mucosal lesions; and (c) ineffective: clinical symptoms and endoscopy showed no improvement in esophageal mucosal lesions. Effective rate was defined as follows: effective rate = (total number of patients - number of patients with no response)/total number of patients. Efficacy under the gastroscope was classified as follows [16]: (a) cured: gastroscope grade 0 seen by endoscopy; (b) significantly effective: gastroscope grading reduced by more than 2 grades compared with the grade before treatment; but not reaching grade 0; (c) effective: gastroscope grading reduced by more than 1 grade compared with the grade before treatment; and (d) ineffective: gastroscope grading reduced by less than 1 grade, unchanged, or aggravated. Efficacy under the gastroscope was defined as follows: effective rate = (total number of patients - number of patients with no response)/total number of patients. Recurrence was defined as the appearance of clinical symptoms and changes in the gastroscopic esophageal mucosal pathology during the follow-up period in completely cured patients [15]. Recurrence rate was defined as follows: recurrence rate = number of patients with recurrence/total number of follow-up patients.

2.3. Exclusion Criteria. Exclusion criteria were as follows: (a) repeated publications; (b) graduate dissertation; and (c) meeting abstracts.

2.4. Study Identification. Study identification and data extraction were carried out independently by two authors. Studies were first identified by screening titles and abstracts, after which the full text was read for papers that possibly met the criteria. Items of the included studies were extracted as follows: authors, sample size, interventions, outcomes, relative effect, and main findings.

2.5. Quality Assessment. Methodological and evidence quality of the enrolled studies were carried out independently by two authors using the AMSTAR-2 tool and GRADE system, respectively. The methodological quality was ranked as high, moderate, low, or critically low [17]. Evidence quality with GRADE was considered from five aspects (risk of bias, inconsistency, indirectness, imprecision, and publication bias) and given a rating of high to critically low [18].

2.6. Data Synthesis and Presentation. A narrative synthesis was performed in this overview. The characteristics and results of each SR/MA as well as the results of AMSTAR 2 were summarized by tabulation. The GRADE evidence profile and summary of findings table were generated by using the GRADE pro GDT online software.

3. Results

3.1. Literature Screening. The literature search identified 202 relevant records, of which 191 records were removed after screening titles and abstracts. The remaining 11 papers were

Table 1: The search strategy for PubMed.

Query	Search term
#1	Gastroesophageal reflux (mesh)
#2	Gastroesophageal reflux (Title/Abstract) or gastroesophageal reflux disease (Title/Abstract) or Gastric acid reflux (Title/Abstract) OR gastro-oesophageal reflux (Title/Abstract) or gastroesophageal reflux (Title/Abstract) or Barrett esophagus (Title/Abstract) or esophagitis (Title/Abstract)
#3	#1 OR #2
#4	Traditional Chinese medicine (mesh)
#5	Chinese medicine (Title/Abstract) or Banxia Xiexin decoction (Title/Abstract) OR herbal medicine (Title/Abstract)
#6	#4 OR #5
#7	Meta-analysis as topic (mesh)
#8	Systematic review (Title/Abstract) or meta-analysis (Title/Abstract) or meta-analysis (Title/Abstract) or meta-analyses (Title/Abstract) or meta-analysis (Title/Abstract)
#9	#7 OR #8
#10	#3 AND #6 AND #9

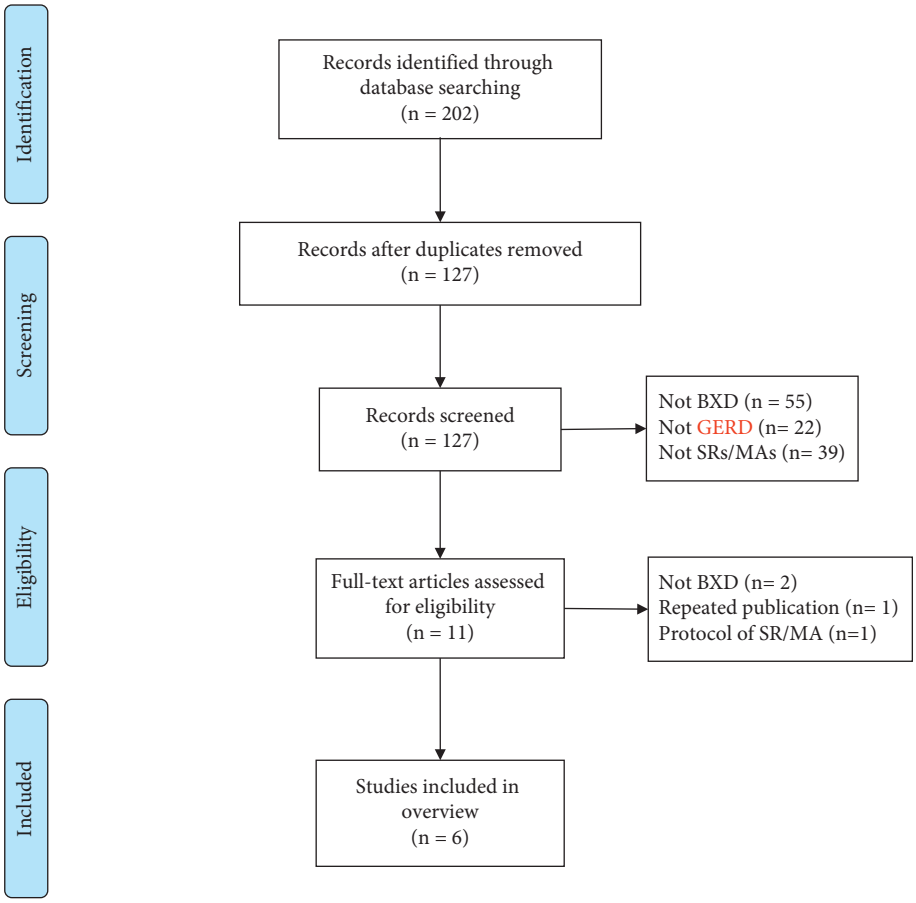


Figure 1: Literature screening flowchart.

evaluated through full-text reading. Finally, five records were excluded, and the remaining six SRs/MAs [19–24] met the inclusion criteria (Figure 1).

3.2. General Characteristics. Features of included SRs/MAs are outlined in Table 2. All SRs/MAs were written by Chinese researchers and published from 2015 to 2020. The number of enrolled trials ranged from 11 to 31, while the sample size ranged from 914 to 2300. The experimental group received BXD while the control groups received WM.

3.3. Methodological Quality Assessment. All included SRs/MAs failed to register protocols and to provide a list of excluded trials. Therefore, previous SRs/MAs were graded critically low for their methodological quality. Furthermore, search strategies, funding source, and conflicts of interest statement displayed different degrees of errors (Table 3).

3.4. Evidence Quality Assessment. Due to limitations of the enrolled trails, the evidence strength was weakened for all outcomes. Inconsistency, imprecision, and publication bias

Table 2: General characteristics of the included reviews.

Studies	Diagnostic criteria	Trials (subjects)	GERD Classification	Experimental Intervention	Control Intervention	Duration	Follow-up period	Quality assessment	Results summary
Yu [19]	①, ②	13 (1089)	NERD, RE	BXD	WM	4–8 weeks	NA	Cochrane Criteria	BXD was more effective to treat GERD than the optimal combination of WM.
Chen [20]	NA	24 (2002)	NERD, RE	BXD	WM	Unclear	NA	Jada scale	BXD was superior to WM alone in the treatment of GERD, but there was no significant difference in gastroscopy results or on the occurrence of adverse reactions.
Dai [21]		31 (1210)	NERD, RE	BXD	WM	4 weeks- 8 months	NA	Cochrane Criteria	BXD showed a potential benefit to GERD patients, but further research is needed due to methodological quality and sample size limitations.
Zheng [22]	NA	11 (1305)	NERD, RE	BXD	WM	4–8 weeks	NA	Cochrane Criteria	BXD treatment improved total effective and recurrence rates for GERD as compared with those of the control group .
Qi [23]	NA	27 (2300)	NERD, RE	BXD	WM	4–8 weeks	3 or 6 months	Cochrane Criteria	The use of BXD tin the treatment of GERD was superior to WM alone in terms of cure rate and total effective rate.
Guo [24]	NA	12 (914)	NERD, RE	BXD	WM	4–8 weeks	NA	Cochrane Criteria	BXD was superior than conventional WM to treat GERD without inducing severe adverse reactions.

①: Consensus Opinion on GERD in China [25]; ②: Chinese Herbal Medicine New Medicine ClinicalResearch Guiding Principle [26]. BXD : Banxia Xiexin decoction; NERD: nonerosive reflux disease; RE: reflux esophagitis; WM : Western medicine; NA: not applicable.

Table 3: Results of the AMSTAR-2 assessments.

Author, Year	AMSTAR-2																Quality
	Q1	Q2	Q3	Q4	Q5	Q6	Q7	Q8	Q9	Q10	Q11	Q12	Q13	Q14	Q15	Q16	
Yu [19]	Y	PY	Y	PY	Y	Y	N	Y	Y	Y	Y	Y	Y	Y	Y	Y	CL
Chen [20]	Y	PY	Y	Y	Y	Y	N	Y	Y	Y	Y	Y	Y	Y	Y	Y	CL
Dai [21]	Y	PY	Y	Y	Y	Y	N	Y	Y	Y	Y	Y	Y	Y	Y	Y	CL
Zheng [22]	Y	PY	Y	PY	Y	Y	N	Y	Y	N	Y	Y	Y	Y	Y	N	CL
Qi [23]	Y	PY	Y	PY	Y	Y	N	Y	Y	N	Y	Y	Y	Y	Y	N	CL
Guo [24]	Y	PY	Y	PY	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	CL

Y : Yes; PY: partial Yes; N : No; CL : Critically low; L : Low; H : High.

Table 4: Results of evidence quality.

Studies	Outcomes	Limitations	Inconsistency	Indirectness	Imprecision	Publication bias	Relative effect (95% CI)	Quality
Yu [19]	Recovery rate	−1	0	0	0	0	RR 1.55 (1.17, 2.05)	M
	Effective rate	−1	0	0	0	0	RR 1.15 (1.10,1.21)	M
	Efficacy under gastroscope	−1	0	0	0	0	RR 1.21 (1.09, 1.35)	M
Chen [20]	Recurrence rate	−1	0	0	−1	0	RR 0.25 (0.09, 0.72)	L
	Effective rate	−1	0	0	0	0	OR 3.96 (2.96, 5.28)	M
	Efficacy under gastroscope	−1	0	0	−1	0	OR 1.99 (0.99, 3.65)	L
	Adverse events	−1	−1	0	0	−1	OR 0.26 (0.06, 1.07)	CL
Dai [21]	Effective rate	−1	0	0	0	−1	OR 3.25 (2.15, 4.94)	L
	Efficacy under gastroscope	−1	−1	0	0	0	OR 1.96 (1.21, 3.18)	L
	Acid regurgitation	−1	−1	0	0	0	SMD 0.51 (-0.90, 1.92)	L
	Heartburn	−1	−1	0	0	0	SMD -0.68 (-1.25, -0.12)	L
	Recurrence rate	−1	−1	0	−1	0	OR 0.35 (0.11, 1.16)	CL
Zheng [22], 2016	Effective rate	−1	−1	0	0	0	OR 4.16 (2.91,5.59)	L
	Recurrence rate	−1	−1	0	0	0	OR O.27 (0.15,0.48)	L
Qi[23], 2016	Effective rate	−1	−1	0	0	−1	OR 3.31 (2.57,4.27)	CL
	Recovery rate	−1	−1	0	−1	−1	OR 1.88 (1.53, 2.31)	CL
Guo[24], 2015	Effective rate	−1	0	0	0	−1	OR 3.41 (2.22, 5.23)	L
	Efficacy under gastroscope	−1	0	0	−1	−1	OR 1.58 (1.04, 2.41)	CL
	Recurrence rate	−1	0	0	0	−1	OR 0.23 (0.14,0.40)	L

-1: downgrade; 0: not downgrade; CL: critically low; L : Low; M: moderate; RR: relative risk; OR: odds ratio; SMD : SMD: standardized mean difference.

also limited the strength of evidence for some outcomes. Four outcomes were deemed of moderate evidence quality, ten outcomes were considered of low quality, and five were of critically low quality. Details are outlined in Table 4.

3.5. Results of Meta-Analyses

3.5.1. Effects of BXD on GERD Patients. Two SRs/MAs [19, 23] compared the effects of BXD with those of WM using recovery rate, and the meta-analysis results revealed that the BXD group was superior to the WM group. All SRs/MAs [19–24] compared BXD vs WM using the effective rate as outcome, and the pooled results revealed that the BXD group was also superior to the WM group. Efficacy under the gastroscope was reported in four studies [19–21, 24]; three of which [19, 21, 24] showed that the BXD group was superior to WM-treated patients. The other study [20] reported no significant differences between these two groups. Four SRs/MAs [19, 21, 22, 24] compared BXD and WM using the recurrence rate of GERD; three of which [19, 22, 24] showed that the BXD group was superior to the WM group, while one study [21] found no significant difference between these two groups. In addition, BXD was reported to be superior to WM in relieving heartburn, but showed no advantage in relieving acid reflux [21].

3.5.2. Safety of BXD for GERD. The pooled results of adverse events were reported in only one study [20], and the results showed that there was no statistical difference between BXD and WM groups.

4. Discussion

SRs/MAs are considered the highest level of evidence in evidence-based medicine [11]. However, low quality SRs/MAs may instead mislead decision makers [25]. Therefore, to collate, critically appraise, and synthesize the clinical evidence of the use of BXD to treat GERD, we conducted an overview of previous SRs/MAs on the matter.

After a systematic review and synthesis, it was found that the gap between evidence and its implementation in clinical practice stems from the low quality and uncertain characteristics of previous evidence. There are several notable findings from this study. First, all included SRs/MAs were published in recent years (2015 to 2020), suggesting that BXD is starting to gain attention as a complementary alternative therapy for GERD. Second, based on results from the AMSTAR-2 tool and the GRADE system, the methodological and evidence qualities of the included studies were limited, which means current evidence cannot provide a reliable basis for clinical decision-making. Third, almost all SRs/MAs yielded positive results. Of note, most authors did not tend to draw firm conclusions about the effects of BXD on GERD patients due to small sample size and low quality of randomized controlled trials.

The AMSTAR-2 tool highlighted several challenges of SRs/MAs that should be addressed. First, studies did not register their protocols. The pre-registration protocol helps to improve transparency, minimize potential risk of bias, reduce duplicated work, and keep the study up to date. It is advocated and recommended that authors register protocols in public databases such as PROSPERO to avoid the risk of bias. Second, authors did not account for publication bias when selecting literature for their SRs/MAs. Therefore, SRs/MAs should provide a comprehensive search strategy for all databases, as a comprehensive and precise search helps to avoid the inclusion of ineligible studies and reduces the risk of publication bias. Furthermore, a list of excluded trials and exclusion criteria improves transparency and can be presented by direct reference or as a supplementary file. Finally, funding sources should be fully reported, as results from commercially funded research might be biased toward funders. Based on the GRADE system, the risk of bias of the enrolled trials was the most common downgrading factor, indicating that the main cause of the reduced quality of evidence came from the quality of the original trials. Only well-designed and rigorously conducted trials can reduce or avoid bias. Specific methods of randomization should be clearly described to reflect whether randomization has been successfully achieved. Moreover, the allocation concealment and blinding method should be fully reported, while large sample sizes and high-quality trials are the basis for high-quality evidence sources.

Numerous SRs/MAs have evaluated the use of BXD to treat GERD, but the quality of these studies is limited and their results are not fully consistent, which is not conducive to the use their evidence. Compared with traditional SRs/MAs, an overview facilitates a comprehensive evaluation of current evidence on multiple identical topics, provides more focused high-quality evidence, and identifies key flaws in evidence use. To our knowledge, this is the first overview of SRs/MAs exploring the effect of BXD on GERD patients using AMSTAR-2 and GRADE. Results herein presented on the methodological and evidence qualities of previous SRs/MAs might help to inform evidence-based decision making and guide future high-quality studies [27, 28].

Some limitations must be acknowledged. First, SRs/MAs lacked detailed characteristics of participants and observation time points. These can hinder the analysis and interpretation of data and reduce the translation of evidence into clinical practice. Second, only eight commonly used public databases were searched in this study. There might be eligible literature in other databases, which were not identified, thus limiting the comprehensiveness of this study. Furthermore, the on standards used in each included study were not fully reported, so it was not possible to determine if they were suitable to be reported together on effectiveness. Future studies are recommended to fully report the details of the inclusion criteria to minimize any potential risk of bias.

5. Conclusion

BXD seems to have a promising efficacy in the treatment of GERD patients. Although the quality of included SRs/MAs was generally low and defects were frequent, our study highlights areas where methodologies need to be improved.

Abbreviations

BXD:	Banxia Xiexin decoction
GERD:	Gastroesophageal reflux disease
SR:	Systematic review
MA:	Meta-analysis
AMSTAR-2:	Assessment of multiple systematic reviews 2
GRADE:	Grading of recommendations, assessment, development, and evaluation
WM:	Western medicine.

Data Availability

All analyses were based on previously published studies.

Disclosure

Jiali Liu and Jinke Huang are the co-first authors.

Conflicts of Interest

The authors declare that there are no conflicts of interest.

Authors' Contributions

Jiali Liu initiated the study design and drafted the manuscript. Jinke Huang, Beihua Zhang, Xiaolan Yin, Mi Lv, and Zhihong Liu helped with the implementation of this work. Fengyun Wang and Xudong Tang contributed to the methodology, review, and editing of the manuscript. All authors read and approved the final manuscript.

Acknowledgments

This work was supported by the National Key R&D Program in the thirteenth Five-year Plan (No. 2019YFC1709600) from the Chinese Ministry of Science and Technology, State Administration of Traditional Chinese Medicine Digestive Refractory Disease Inheritance and Innovation Team Project (No. ZYYCXTD-C-C202010), National Natural Science Foundation of China (Nos. 82004355, 82004356, and 82104850), China Academy of Chinese Medical Sciences Innovation Fund (No. CI2021A01001), and China Academy of Chinese Medical Sciences Excellent Young Talent Cultivation Fund (Nos. ZZ14-YQ-002, ZZ14-YQ-005, and ZZ15-YQ-014).

References

[1] J. Maret-Ouda, S. R. Markar, and J. Lagergren, "Gastroesophageal reflux disease," *JAMA*, vol. 324, no. 24, p. 2565, 2020.

[2] GBD 2017 Gastro-oesophageal Reflux Disease Collaborators, "The global, regional, and national burden of gastro-oesophageal reflux disease in 195 countries and territories, 1990-2017: a systematic analysis for the Global Burden of Disease Study 2017," *Lancet Gastroenterol Hepatol*, vol. 5, no. 6, pp. 561–581, 2020.

[3] L. H. Eusebi, R. Ratnakumaran, Y. Yuan, M. Solaymani-Dodaran, F. Bazzoli, and A. C. Ford, "Global prevalence of, and risk factors for, gastro-oesophageal reflux symptoms: a meta-analysis," *Gut*, vol. 67, no. 3, pp. 430–440, 2018.

[4] R. Badillo and D. Francis, "Diagnosis and treatment of gastroesophageal reflux disease," *World Journal of Gastrointestinal Pharmacology and Therapeutics*, vol. 5, no. 3, pp. 105–112, 2014.

[5] J. Chen and P. Brady, "Gastroesophageal reflux disease: pathophysiology, diagnosis, and treatment," *Gastroenterology Nursing*, vol. 42, no. 1, pp. 20–28, 2019.

[6] J. Zhang, H. Che, B. Zhang et al., "JianpiQinghua granule reduced PPI dosage in patients with nonerosive reflux disease: a multicenter, randomized, double-blind, double-dummy, noninferiority study," *Phytomedicine*, vol. 88, Article ID 153584, 2021.

[7] Z. Zheng, Y. Shang, N. Wang et al., "Current advancement on the dynamic mechanism of gastroesophageal reflux disease," *International Journal of Biological Sciences*, vol. 17, no. 15, pp. 4154–4164, 2021.

[8] X. N. Liu, X. D. Jin, Y. Z. Li, G. L. Liu, and W. Sun, "Study on the treatment effect of BX decoction on rat models of reflux esophagitis," *Journal of Radioimmunology*, vol. 21, no. 4, pp. 312–314, 2008.

[9] S. Pan, Q. Q. Lan, S. N. Lin, Y. P. Zhu, and Z. F. Xu, "Research of pinelliae decoction for purging stomach-fire on immune function of Esophagus Mucous membrane in rat model of reflux esophagitis," *Shanxi Journal of Traditional Chinese Medicine*, vol. 28, no. 4, pp. 49–51, 2012.

[10] Y.-P. Tang, S.-M. Liu, W. Wei et al., "Effect of pungent dispersion bitter purgation method on the esophageal mucosal intercellular space of reflux esophagitis model rats," *Zhongguo Zhong xi yi jie he za zhi Zhongguo Zhongxiyi jiehe zazhi = Chinese journal of integrated traditional and Western medicine*, vol. 34, no. 11, pp. 1335–1341, 2014.

[11] J. Huang, M. Lu, Y. Zheng et al., "Quality of evidence supporting the role of acupuncture for the treatment of irritable bowel syndrome," *Pain Research and Management*, vol. 2021, pp. 1–10, 2021.

[12] J. Huang, J. Zhang, Y. Wang et al., "Scientific evidence of Chinese herbal medicine (gegen qinlian decoction) in the treatment of ulcerative colitis," *Gastroenterology Research and Practice*, vol. 2022, Article ID 7942845, 8 pages, 2022.

[13] S. Gao, X. Lin, C. Fan, X. Zhang, M. Huang, and G. Huang, "Potential molecular mechanism of Banxia Xiexin decoction in treatment of reflux esophagitis based on network pharmacology and molecular docking," *Hunan Journal of Traditional Chinese Medicine*, vol. 38, no. 03, pp. 130–138, 2022.

[14] S. Green, "Cochrane handbook for systematic reviews of interventions: cochrane book Series," *Naunyn-Schmiedebergs archiv für experimentelle pathologie und pharmakologie*, Springer, Berlin, Germany, 2011.

[15] Y. H. Chen, X. H. Hou, Y. L. Xiao et al., "Expert consensus opinion on gastroesophageal reflux disease in China in 2014," *Chinese Journal of Gastroenterology*, vol. 20, no. 03, pp. 155–168, 2015.

[16] X. H. Lu and T. C. Zhang, "Guidelines for the diagnosis and treatment of reflux esophagitis (2003)," *Chinese Journal of Digestive Endoscopy*, vol. 5, no. 04, pp. 4-5, 2004.

[17] B. J. Shea, B. C. Reeves, G. Wells et al., "AMSTAR 2: A critical appraisal tool for systematic reviews that include," *Research Methods & Reporting*, vol. 358, 2017.

[18] A. Pollock, S. E. Farmer, M. C. Brady et al., "An algorithm was developed to assign GRADE levels of evidence to comparisons within systematic reviews," *Journal of Clinical Epidemiology*, vol. 70, pp. 106–110, 2016.

[19] Y. F. Yu, X. D. Lan, M. Y. Jin, S. Q. Xu, Y. Liang, and W. X. Jian, "Meta-analysis and trial sequential analysis of modified Banxia Xiexin decoction in the treatment of gastroesophageal reflux disease," *Journal of Yunnan University of Traditional Chinese Medicine*, vol. 43, pp. 28–35, 2020.

[20] J. K. Chen, H. J. Wei, and S. Xie, "Meta-analysis of Banxia Xiexin decoction in treating gastroesophageal diseases," *Asia-Pacific Traditional Medicine*, vol. 13, pp. 53–56, 2017.

[21] Y. Dai, Y. Zhang, D. Li, J. Ye, W. Chen, and L. Hu, "Efficacy and safety of modified Banxia Xiexin decoction (pinellia decoction for draining the heart) for gastroesophageal reflux disease in adults: a systematic review and meta-analysis," *Evidence-Based Complementary and Alternative Medicine*, vol. 201717 pages, 2017.

[22] M. Zheng and Y. P. Tang, "Meta-analysis of Banxia Xiexin decoction in treating gastroesophageal diseases," *World Journal of Integrated Traditional and Western Medicine*, vol. 0, no. 5, pp. 610–614, 2016.

[23] Y. Qi and X. G. Wan, "Meta-analysis of curative effect of Banxia Xiexin decoction and western medicine on esophagitis," *Hunan Journal of Traditional Chinese Medicine*, vol. 32, pp. 158–161, 2016.

[24] Z. L. Guo, Z. N. Su, Z. F. Wang, and X. M. Luo, "Meta-analysis of Reflux esophagitis treated by modified," *Banxia Xiexin Tang*, vol. 21, pp. 219–224, 2015.

[25] S. Lin, G. Xu, and P. Hu, "Chinese consensus opinion on gastroesophageal disease," *Journal of Digestive Diseases*, vol. 22, no. 4, pp. 233–239, 2007.

[26] X. Y. Zheng, *Chinese Herbal Medicine New Medicine ClinicalResearch Guiding Principle*, China Medical Science Press, Beijing, China, 2002.

[27] J. Huang, J. Liu, Z. Liu et al., "Reliability of the evidence to guide decision-making in acupuncture for functional dyspepsia," *Frontiers in Public Health*, vol. 10, Article ID 842096, 2022.

Hindawi
Evidence-Based Complementary and Alternative Medicine
Volume 2022, Article ID 2425851, 32 pages
https://doi.org/10.1155/2022/2425851

Research Article

Chinese Herbal Medicine for Cervicogenic Dizziness: A Systematic Review and Meta-Analysis

Hyunjoo Oh,[1] **Seungwon Shin**,[1,2] **Euiju Lee**,[3] **and Won-Seok Chung**[4]

[1]*Department of Clinical Korean Medicine, Graduate School, Kyung Hee University, Seoul, Republic of Korea*
[2]*National Agency for Development of Innovative Technologies in Korean Medicine, National Development Institute of Korean Medicine, Seoul, Republic of Korea*
[3]*Department of Sasang Constitutional Medicine, College of Korean Medicine, Kyung Hee University, Seoul, Republic of Korea*
[4]*Department of Rehabilitation Medicine of Korean Medicine, College of Korean Medicine, Kyung Hee University, Seoul, Republic of Korea*

Correspondence should be addressed to Euiju Lee; sasangin@hanmail.net

Received 17 January 2022; Revised 6 April 2022; Accepted 12 April 2022; Published 9 May 2022

Academic Editor: Xing Liao

Background. Chinese herbal medicines (CHMs) have been widely used in the treatment of cervicogenic dizziness (CGD) based on their empirical effectiveness and safety. Herein, we reviewed and evaluated the clinical evidence of the efficacy and safety of CHMs for CGD. *Methods*. Among the relevant studies published in 11 electronic databases up to December 2021, only randomised controlled trials were included. Methodological quality was assessed using the revised Cochrane risk-of-bias tool for randomised trials, and the strength of evidence for the main outcomes was evaluated using the grading of recommendations assessment, development, and evaluation system. *Results*. All 35 included randomised controlled trials with 3,862 participants were conducted with six types of modified CHM and four types of active controls. More than half of the included studies were of low quality because of the high risk of bias due to deviations from intended interventions. CHM plus active control was more effective in the treatment of CGD than active control alone. CHM plus anti-vertigo drugs, CHM plus manual therapy, CHM plus acupuncture therapy, and CHM plus manual and acupuncture therapy were all effective in treating CGD, with CHM plus manual and acupuncture therapy showing the most reliable effect. All CHMs were effective for specific patterns of CGD when administered with active controls, with Dingxuan Tang and Yiqi Congming Tang demonstrating the most reliable effects. No serious adverse events were reported in any of the included studies. *Conclusion*. The current evidence suggests that CHM may enhance the treatment of CGD when combined with other treatments without serious adverse events. Further high-quality evidence is needed to draw definitive conclusions.

1. Introduction

Cervicogenic dizziness (CGD), a major cause of dizziness, is associated with a variety of symptoms, such as headache, unsteadiness, light-headedness, perception of spinning, nausea, and general disorientation, coexisting with neck pain or stiffness [1–4]. Its prevalence is estimated to be 6.4–8.5% [5–7]; however, CGD is common in older patients, especially those with cervical spine dysfunction. Therefore, there is growing apprehension that the number of patients with CGD will increase in accordance with a worldwide ageing population [8–10].

Although it is known that CGD originates from the cervical spine, its pathogenesis remains unclear [11]. Until now, the most prevalent hypothesis is that CGD is caused by disharmonic hyperactivity of the cervical mechanoreceptors located in the joints, ligaments, and muscle spindles, which occurs when the proprioceptive system of the neck is damaged due to muscular fatigue, degeneration, or trauma [10, 12–14]. In a recent review, CGD was classified according to the aetiopathological mechanisms into neural types, comprising degenerative cervical spine disorder, whiplash-associated disorder, and Barré–Liéou syndrome, and vascular types, comprising Bow Hunter's syndrome and Beauty

Parlour syndrome. However, these diseases also overlap because they do not have completely distinct mechanisms [15]. Because there are no established diagnostic criteria for CGD, physicians usually diagnose CGD when the patients' symptoms are not related to other neurological or neuro-otological causes of dizziness [16, 17].

The treatment of CGD has not yet been standardised. Previous studies have explored a variety of treatments to improve the severity and frequency of dizziness by relaxing muscles and ameliorating abnormal proprioceptive sensitivity or impaired blood flow in the cervical region. Treatment strategies include physical therapy [1, 3, 7, 10, 18–22], surgery [10, 16], topical drug injection [9, 23], acupuncture therapy [24, 25], and medications, such as muscle relaxants, opioids, nonsteroidal anti-inflammatory drugs, and anxiolytics, in combination with Chinese herbal medicines (CHMs). CHMs have been widely used for CGD, either alone or in combination with other treatments, based on their empirical effectiveness to suppress pain and improve blood circulation in the human body [24, 26]. However, there has been no systematic verification of their efficacy and safety in the treatment of CGD based on clinical evidence.

Therefore, we aimed to review and evaluate the clinical evidence on the efficacy and safety of CHM as monotherapy or adjunctive therapy for CGD, which would promote evidence-based decision-making in clinical practice.

2. Methods

2.1. Study Registration. The study protocol for this systematic review was registered with the International Prospective Register of Systematic Reviews (registration number: CRD42020199222; registration date: October 27, 2020) and the Research Registry (Review Registry Unique Identifying Number: reviewregistry1036; registration date: November 19, 2020). The study protocol was published [27], and there have been no subsequent amendments that could result in a significant change in the study design. This systematic review is reported in accordance with the Preferred Reporting Items for Systematic Review and Meta-Analyses statement [28]. A preprint has previously been published in Research Square (DOI: https://doi.org/10.21203/rs.3.rs-364098/v1; registration date: March 31, 2021) [29].

2.2. Data Sources and Search Strategy. One researcher (HO) comprehensively searched the following 11 electronic databases for relevant studies published up to December 2021 without language or publication status restrictions: three English databases (Medical Literature Analysis and Retrieval System Online (MEDLINE) via PubMed, Excerpta Medica Database (EMBASE) via Elsevier, and the Cochrane Central Register of Controlled Trials (CENTRAL)), six Korean databases (KoreaMed, Korean Studies Information Service System, Research Information Sharing Service, National Digital Science Library, Korean Medical Database, and Database Periodical Information Academic), one Chinese database (China National Knowledge Infrastructure), and one Japanese database (Citation Information by NII). A manual search on Google Scholar was also performed to identify additional eligible studies among those listed in the reference sections of included studies. The search strategies were tailored to the language and search systems of the databases. The search strategies used in the three English databases (MEDLINE, EMBASE, and CENTRAL) are presented in Additional file 1.

2.3. Eligibility Criteria

2.3.1. Types of Studies. All randomised controlled trials (RCTs) related to the use of CHMs for CGD were included. All other study designs, including quasi-RCTs, were excluded.

2.3.2. Participants. All patients with CGD were included as subjects in this study, with no restrictions on ethnicity, nationality, sex, age, or biological status.

2.3.3. Interventions and Comparisons. CHMs with any formulation administered orally, such as decoction, capsules, tablets, pills, and powders, were considered experimental interventions. There was no limitation on the number or combination of herbs, CHM dose, or the frequency or duration of treatment. If the composition of CHMs used in the included studies differed from the original prescription, "modified" was indicated in front of the CHM name. No treatment and placebo were considered as control interventions to determine the efficacy of CHM as monotherapy. Active controls, such as anti-vertigo drugs, manual therapy, and acupuncture therapy, were also considered as control interventions to determine the efficacy of CHM as adjunctive therapy only when CHMs were equally applied to both the experimental and control groups. Studies comparing different combinations of CHMs or CHM alone with other active controls were excluded because they could not rigorously determine the efficacy of CHMs.

2.3.4. Outcomes. The primary outcomes were as follows:

(1) The change in the patients' overall functional score measured by validated scales (e.g., functional scale for cervical spondylosis of vertebral artery type)

(2) The change in the patients' simple score for dizziness (e.g., the numerical rating scale)

(3) The change in mean blood flow velocity in the vertebrobasilar artery, as evaluated using transcranial Doppler

The secondary outcomes were as follows:

(1) The total effective rate, strictly calculated by counting only the number of patients completely cured, to exclude researcher subjectivity and improve the reliability of the results

(2) The changes in haematological parameters, such as fibrinogen levels, endothelin, total cholesterol (TC), and calcitonin gene-related peptide (CGRP)

(3) Adverse events

2.4. Study Selection Process. Two reviewers (HO and SS) independently screened and assessed all retrieved studies for eligibility based on the aforementioned criteria. After duplicates were removed, the titles and abstracts of the remaining studies were screened using EndNote X9 (Clarivate Analytics, London, UK). Next, the full-text review of the eligible studies was conducted for final inclusion. Any divergence in the agreement was resolved through discussion with a third researcher (EL) at each step of the study selection process.

2.5. Data Extraction. Two reviewers independently extracted data from the included studies (HO and SS) using a predefined data acquisition form. This form included four main domains: general information (title, authors, year of publication, country of the study, and study design), participants' characteristics (age, sex, diagnostic criteria, and CGD duration), intervention and comparison details (sample size; CHM formulation and prescription name; number of herbs; CHM dose; CHM daily dose; comparison, frequency, or duration of the treatment; and follow-up information), and outcomes (primary and secondary outcomes and adverse events). Any discrepancies were resolved through discussion with a third researcher (EL).

2.6. Quality Assessment. The methodological quality of the included studies was assessed using the revised Cochrane risk-of-bias tool for randomised trials [30]. The bias domain for risk-of-bias assessment included the following: (1) bias arising from the randomisation process, (2) bias due to deviations from intended interventions, (3) bias due to missing outcome data, (4) bias in the measurement of the outcome, and (5) bias in the selection of the reported result. The risk of bias was independently evaluated by two reviewers (HO and SS) as "low," "high," or "some concerns." Any divergence in the agreement was resolved through discussion with other reviewers (EL and WSC). Studies evaluated as "low-risk" in all domains were defined as high-quality studies, whereas those evaluated as "high-risk" in at least one domain were defined as low-quality studies.

Subsequently, the strength of evidence for the main outcomes was evaluated using the grading of recommendations assessment, development, and evaluation system [31]. The risk of bias; inconsistency, indirectness, and imprecision of the results; and publication bias were assessed, and the quality of the evidence was graded on a four-point scale as "high," "moderate," "low," or "very low."

2.7. Data Synthesis. When the included studies were sufficiently homogenous, quantitative synthesis was performed using RevMan software (version 5.3; Cochrane, London, UK) to analyse the efficacy of CHMs in the treatment of CGD. Subgroup analyses were conducted according to (1) the comparison types and (2) the CHM prescription names. Dichotomous outcomes were pooled using risk ratios (RRs), and continuous outcomes were pooled using mean differences (MDs), or standardised mean differences (SMDs), with 95% confidence intervals (CIs).

The statistical heterogeneity among studies was assessed by computing I^2 statistics. Data were pooled using a random-effects model, if the included studies had significant heterogeneity (I^2 values ≥50% indicated substantial heterogeneity and I^2 values ≥75% indicated considerable heterogeneity (both were considered significant)). Otherwise, a fixed-effects model was applied [32]. Sensitivity analysis was performed to increase the robustness of the results by excluding studies with a high risk of bias and outliers. If the number of studies was sufficient ($n \geq 10$), a visual inspection of the funnel plot was performed to assess publication bias. Data on the safety of CHMs in the treatment of CGD were described qualitatively.

3. Results

3.1. Study Selection. A total of 8,746 studies were identified through the database searches, and 1 additional study was identified through other sources. After removing 305 duplicates, 8,442 studies were excluded by screening the titles and abstracts. Through a review of the full texts, a further 659 studies were excluded: 17 studies with unavailable full texts, 31 nonclinical studies, 21 case reports, 164 noncomparative studies, 13 nonrandomised controlled trials, 258 studies not related to CGD, 49 studies not related to eligible intervention, and 106 studies not related to the clinical question. Finally, 35 RCTs with 3,862 participants were included in the analysis (Figure 1).

3.2. Study Characteristics. All included studies were RCTs conducted in China. They were classified according to the comparison types, as follows: (1) studies comparing CHMs plus anti-vertigo drugs with anti-vertigo drugs alone ($n = 14$), which were subdivided according to the anti-vertigo drugs used into studies using flunarizine ($n = 6$), betahistine ($n = 5$), both flunarizine and betahistine ($n = 1$), diphenidol ($n = 1$), or nimodipine ($n = 1$); (2) studies comparing CHMs plus manual therapy with manual therapy alone ($n = 7$); (3) studies comparing CHMs plus acupuncture therapy with acupuncture therapy alone ($n = 13$); and (4) studies comparing CHMs plus manual and acupuncture therapy with manual and acupuncture therapy alone ($n = 1$). None of the studies assessed the efficacy of CHM as monotherapy for CGD.

The included studies were also classified according to the CHM prescription names, as follows: (1) studies on Banxia Baizhu Tianma Tang (BBTT; $n = 9$), (2) studies on Buzhong Yiqi Tang (BYT; $n = 2$), (3) studies on Dingxuan Tang (DXT; $n = 8$), (4) studies on Gegen Tang (GGT; $n = 7$), (5) study on Gegen Jieji Tang (GJT; $n = 1$), and (6) studies on Yiqi Congming Tang (YCT; $n = 8$). All CHMs in the included studies were modified prescriptions. In summary, the studies

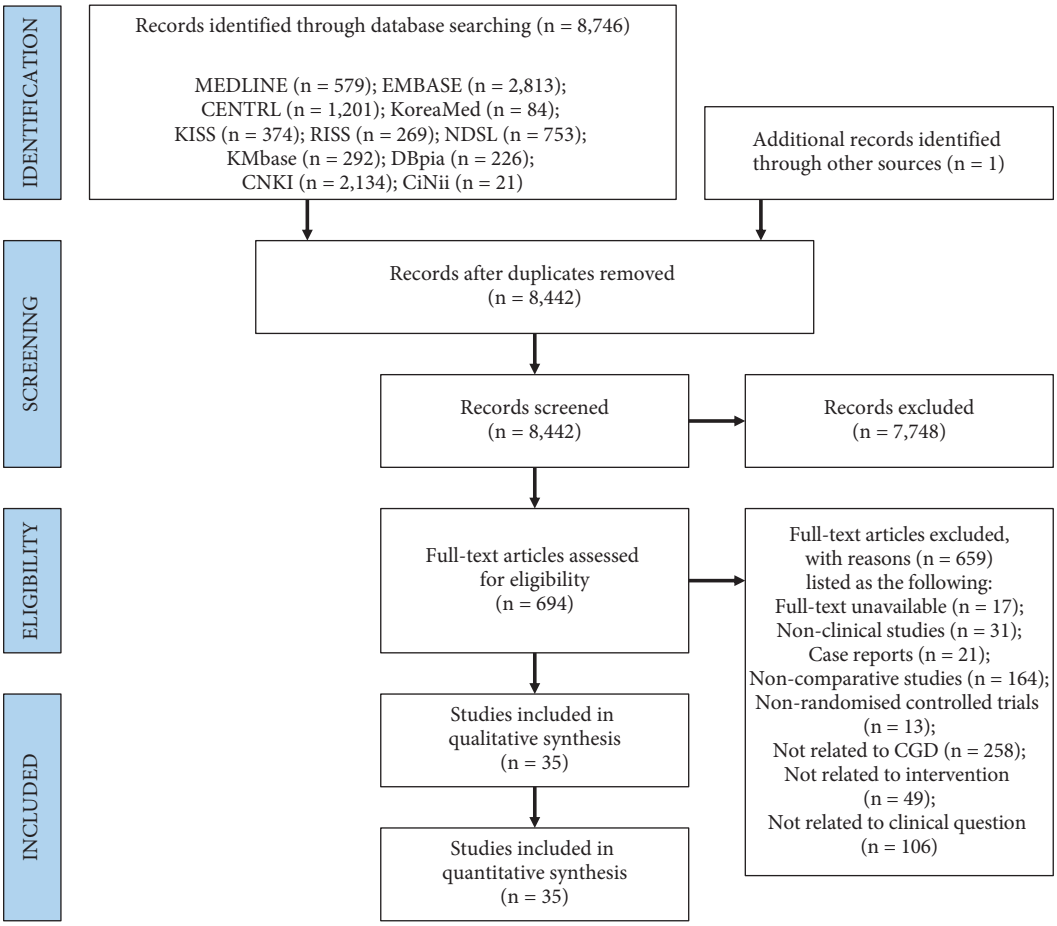


Figure 1: PRISMA flow diagram of the literature screening and selection process. CENTRAL, Cochrane Central Register of Controlled Trials; CGD, cervicogenic dizziness; CiNii, Citation Information by NII; CNKI, China National Knowledge Infrastructure; DBpia, Database Periodical Information Academic; EMBASE, Excerpta Medica Database; KISS, Korean Studies Information Service System; KMbase, Korean Medical Database; MEDLINE, Medical Literature Analysis and Retrieval System Online; NDSL, National Digital Science Library; PRISMA, Preferred Reporting Items for Systematic reviews and Meta-Analyses; and RISS, Research Information Sharing Service.

included in this review were conducted with six types of modified CHMs (BBTT, BYT, DXT, GGT, GJT, and YCT) and four types of active controls (anti-vertigo drugs, manual therapy, acupuncture therapy, and manual and acupuncture therapy).

In addition, 10 types of outcome measurements were identified: 5 studies evaluated overall functional scores, 22 studies evaluated simple scores, 17 studies assessed the mean blood flow velocity in the vertebral arteries, 18 studies assessed the mean blood flow velocity in the basilar artery, 33 studies evaluated the total effective rate, three studies measured endothelin levels, and four studies measured CGRP, fibrinogen and TC levels. The incidence of adverse events was reported in three studies. The study characteristics and the main outcomes are summarised in Table 1.

Each CHM prescription was applied to a specific pattern of symptoms in traditional Chinese medicine: BBTT to the wind-phlegm type or phlegm stasis type; BYT to qi and blood deficiency type; DXT to spleen deficiency and dampness type, qi deficiency and blood stasis type, or hyperactivity of liver yang type; GGT to wind type with disharmony between ying and wei; GJT to collateral stasis type; and YCT to qi and blood deficiency type or qi deficiency and sputum silting up type. All modified CHMs included at least one-third of the original prescriptions. The duration of administration ranged from 10 days to 8 weeks, with 2- and 4-week regimens being the most frequent. The details of the CHMs prescribed in the included studies are summarised in Tables 2 and 3.

3.3. Risk-of-Bias Assessment. For bias arising from the randomisation process, 18 studies were evaluated as "low-risk" because the randomisation process for the allocation sequence was clearly described. The remaining 17 studies were evaluated as "some concerns" because insufficient relevant information was provided. For bias due to deviations from intended interventions, 21 studies, most of which included manual or acupuncture therapy as active controls, were evaluated as "high-risk" because it was unclear whether blinding of participants and trial personnel had been sufficiently performed using sham-massage or sham-acupuncture. The remaining 14 studies were evaluated as "some concerns." For bias due to missing outcome data, 30 studies

Table 1: General characteristics of the included studies.

Study ID	Sample size (A : B)	Study of the country	Mean age (range; yr)	CGD duration (range)	Intervention group (A)	Control group (B)	Treatment duration	Follow-up	Outcome	Results	AE (n)
Bai [33]	80 (40 : 40)	China	(A) 35.6 ± 6.4 (22~54) (B) 36.2 ± 7.2 (22~55)	(A) NR (1.5 days~4 yr) (B) 1.0 ± 0.6 yr (2 days~4 yr)	Modified BYT + (B)	AT (1 time/day)	20 days	NR	(1) SS (2) RVA-BF (3) LVA-BF (4) BA-BF (5) TER	(1) (A) > (B)* (2) N.S. (3) (A) > (B)* (4) (A) > (B)* (5) (A) > (B)*	NR
Chen [34]	120 (60 : 60)	China	(A) 43.81 ± 5.57 (25~58) (B) 43.75 ± 5.61 (22~57)	(A) 7.65 ± 1.79 mon (2~11 mon) (B) 7.63 ± 1.82 mon (2~11 mon)	Modified GGT + (B)	AD: flunarizine (10 mg bid)	1 month	NR	(1) SS (2) RVA-BF (3) LVA-BF (4) BA-BF (5) TER	(1) (A) > (B)* (2) (A) > (B)* (3) (A) > (B)* (4) (A) > (B)* (5) (A) > (B)*	NR
Cheng [35]	84 (42 : 42)	China			Modified DXT + (B)	AD: flunarizine (10 mg qd)	2 weeks	NR	(1) SS (2) TER (3) CGRP level	(1) (A) > (B)† (2) (A) > (B)* (3) (A) > (B)†	NR
Dai [36]	82 (41 : 41)	China	46.2 ± 5.1 (24~65)	NR (3~11 mon)	Modified YCT + (B)	AT (1 time/day)	4 weeks	NR	(1) TER (2) Fib level (3) TC level	(1) (A) > (B)* (2) (A) > (B)* (3) (A) > (B)*	NR
Gao [37]	106 (53 : 53)	China	(A) 54.3 ± 5.6 (24~62) (B) 55.4 ± 5.2 (23~63)	(A) 5.4 ± 0.6 yr (3.0~10.5 yr) (B) 5.6 ± 0.5 yr (3.5~11.0 yr)	Modified BBTT + (B)	AD: flunarizine (5~10 mg·qd)	2 weeks	NR	(1) RVA-BF (2) LVA-BF (3) BA-BF (4) TER	(1) (A) > (B)* (2) (A) > (B)* (3) (A) > (B)* (4) (A) > (B)*	NR

Table 1: Continued.

Study ID	Sample size (A : B)	Study of the country	Mean age (range; yr)	CGD duration (range)	Intervention group (A)	Control group (B)	Treatment duration	Follow-up	Outcome	Results	AE (n)
Gu [38]	70 (35 : 35)	China	52.17 ± 6.34 (24~65)	3.08 ± 0.41 mon (2~6 mon)	Modified YCT + (B)	AT (1 time/2 day)	4 weeks	NR	(1) SS (2) OFS (3) RVA-BF (4) LVA-BF (5) BA-BF (6) TER (7) Fib level (8) TC level	(1) (A) > (B)† (2) (A) > (B)† (3) (A) > (B)* (4) (A) > (B)* (5) (A) > (B)* (6) (A) > (B)* (7) (A) > (B)† (8) (A) > (B)†	NR
Gu [39]	80 (40 : 40)	China	(A) 41.9 ± 5.6 (20~64) (B) 41.3 ± 5.3 (21~63)	NR	Modified BBTT + (B)	AD: flunarizine (10~20 mg·qd)	2~8 weeks	NR	(1) TER	(1) (A) > (B)†	NR
Hu [40]	200 (120 : 80)	China	(A) 55.71 ± 6.93 (B) 56.43 ± 7.34	(A) 10.37 ± 3.23 yr (B) 10.53 ± 4.12 yr	Modified GJT + (B)	AD: betahistine (6 mg tid)	2 weeks	NR	(1) SS (2) TER	(1) (A) > (B)* (2) (A) > (B) †	NR
Huagn [41]	98 (49 : 49)	China	(A) 67.82 ± 5.95 (B) 65.26 ± 5.43	(A) 3.28 ± 0.69 yr (B) 3.34 ± 0.75 yr	Modified GGT + (B)	AD: betahistine (6 mg·tid)	2 weeks	NR	(1) OFS (2) RVA-BF (3) LVA-BF (4) BA-BF (5) TER	(1) (A) > (B)† (2) (A) > (B)† (3) (A) > (B)† (4) (A) > (B)† (5) (A) > (B)*	NR
Huang [42]	120 (60 : 60)	China	(A) 43.63 ± 4.72 (25~57) (B) 43.72 ± 4.54 (27~58)	(A) 5.70 ± 1.14 yr (4 mon~10 yr) (B) 5.65 ± 1.21 yr (3 mon~10 yr)	Modified BBTT + (B)	MT: Tuina (1 time/2 days)	1 month	NR	(1) SS (2) OFS (3) TER	(1) (A) > (B)* (2) (A) > (B)* (3) (A) > (B)*	NR

Table 1: Continued.

Study ID	Sample size (A : B)	Study of the country	Mean age (range; yr)	CGD duration (range)	Intervention group (A)	Control group (B)	Treatment duration	Follow-up	Outcome	Results	AE (*n*)
Ji [43]	60 (30 : 30)	China	NR (40~70)	NR	Modified DXT + (B)	AD: flunarizine (5 mg·qd)	2 weeks	NR	(1) SS (2) TER	(1) (A) > (B)* (2) (A) > (B)*	NR
Ju [44]	120 (60 : 60)	China	(A) 67.82 ± 2.41 (60~75) (B) 67.91 ± 2.37 (64~74)	(A) 5.12 ± 0.82 yr (1~9 yr) (B) 5.30 ± 0.85 yr (1~10 yr)	Modified GGT + (B)	AT (6 times/week)	4 weeks	6 months	(1) SS (2) RVA-BF (3) LVA-BF (4) BA-BF (5) TER	(1) (A) > (B)* (2) (A) > (B)* (3) (A) > (B)* (4) (A) > (B)* (5) (A) > (B)*	NR
Li [45]	68 (34 : 34)	China	(A) 52.60 ± 2.58 (25~68) (B) 42.58 ± 2.65 (24~65)	(A) 3.95 ± 0.78 mon (2~8 mon) (B) 3.92 ± 0.85 mon (1~8 mon)	Modified YCT + (B)	AT (1 time/day)	4 weeks	NR	(1) SS (2) TER	(1) (A) > (B)† (2) (A) > (B)*	NR
Li [46]	116 (58 : 58)	China	(A) 42.98 ± 9.21 (33~63) (B) 42.91 ± 9.45 (32~62)	(A) 5.37 ± 0.65 yr (1 mon~10 yr) (B) 5.32 ± 0.61 yr (1 mon~10 yr)	Modified DXT + (B)	AD: diphenidol (tid)	1 month	NR	(1) SS (2) RVA-BF (3) LVA-BF (4) BA-BF (5) TER (6) ET level (7) CGRP level	(1) (A) > (B)* (2) (A) > (B)* (3) (A) > (B)* (4) (A) > (B)* (5) (A) > (B)* (6) (A) > (B)* (7) (A) > (B)*	NR

Table 1: Continued.

Study ID	Sample size (A : B)	Study of the country	Mean age (range; yr)	CGD duration (range)	Intervention group (A)	Control group (B)	Treatment duration	Follow-up	Outcome	Results	AE (n)
Liu [47]	126 (63 : 63)	China	(A) 52.64 ± 8.25 (26~68) (B) 52.47 ± 8.14 (22~65)	(A) 3.98 ± 1.02 yr (0.6~5 yr) (B) 3.94 ± 1.05 yr (0.8~6 yr)	Modified DXT + (B)	MT: Tuina (1 time/day)	4 weeks	NR	(1) SS (2) OFS (3) RVA-BF (4) LVA-BF (5) BA-BF (6) TER (7) ET level (8) CGRP level	(1) (A) > (B)* (2) (A) > (B)† (3) (A) > (B)* (4) (A) > (B)* (5) (A) > (B)* (6) (A) > (B)* (7) (A) > (B)* (8) (A) > (B)†	NR
Lyu [48]	54 (27 : 27)	China	(A) 35.24 ± 2.15 (20~59) (B) 31.17 ± 1.53 (18~60)	NR	Modified BYT + (B)	AT (1 time/day)	20 days	NR	(1) SS (2) RVA-BF (3) LVA-BF (4) BA-BF (5) TER	(1) (A) > (B)* (2) N.S. (3) (A) > (B)* (4) (A) > (B)* (5) (A) > (B)*	NR
Pan [49]	100 (50 : 50)	China	(A) 42.41 ± 5.93 (B) 40.87 ± 6.25	(A) 3.91 ± 0.74 mon (B) 4.18 ± 0.81 mon	Modified BBTT + (B)	MT: Tuina (1 time/day)	2 weeks	NR	(1) SS (2) TER (3) ET level (4) CGRP level	(1) (A) > (B)† (2) (A) > (B)* (3) (A) > (B)† (4) (A) > (B)†	Gastrointestinal discomfort (1)
Qin [50]	163 (79 : 84)	China	54.78 ± 10.36	NR	Modified YCT + (B)	AD: betahistine (6 mg·tid)	2 weeks	3 months	(1) SS	(1) (A) > (B)*	NR

Table 1: Continued.

Study ID	Sample size (A : B)	Study of the country	Mean age (range; yr)	CGD duration (range)	Intervention group (A)	Control group (B)	Treatment duration	Follow-up	Outcome	Results	AE (*n*)
Qiu [51]	110 (55 : 55)	China	(A) 53.8 ± 5.5 (43~65) (B) 52.6 ± 4.7 (42~63)	(A) 4.5 ± 0.7 mon (1~8 mon) (B) 4.4 ± 0.8 mon (2~9 mon)	Modified YCT + (B)	AT (1 time/day)	1 month	NR	(1) SS (2) BA-BF (3) TER (4) Fib level (5) TC level	(1) (A) > (B)* (2) (A) > (B)* (3) (A) > (B)* (4) (A) > (B)* (5) (A) > (B)*	NR
Shang [52]	82 (41 : 41)	China	40.2 ± 1.7 (31~67)	3.1 ± 0.5 yr (0.33~8 yr)	Modified GGT + (B)	MT (qd)	2 weeks	NR	(1) SS (2) TER	(1) (A) > (B)* (2) (A) > (B)*	NR
Shang [53]	134 (67 : 67)	China	(A) 36.21 ± 4.74 (19~63) (B) 36.51 ± 4.43 (18~64)	(A) 1.35 ± 0.82 yr (2 mon~5 yr) (B) 1.21 ± 0.78 yr (1 mon~4 yr)	Modified GGT + (B)	AD: nimodipine (4 mg/day)	2 weeks	NR	(1) RVA-BF (2) LVA-BF (3) BA-BF (4) TER	(1) (A) > (B)† (2) (A) > (B)† (3) (A) > (B)† (4) (A) > (B)*	NR
Shen [54]	120 (60 : 60)	China	(A) 54.22 ± 5.31 (42~67) (B) 54.53 ± 5.07 (43~66)	NR	Modified YCT + (B)	AT (1 time/day)	NR	NR	(1) SS (2) TER	(1) (A) > (B)† (2) (A) > (B)†	NR
Shi [55]	74 (37 : 37)	China	(A) 54.8 ± 8.9 (B) 55.6 ± 8.4	(A) 3.3 ± 0.9 days (B) 3.5 ± 0.6 days	Modified DXT + (B)	AD: betahistine (12 mg·tid)	2 weeks	NR	(1) RVA-BF (2) LVA-BF (3) BA-BF (4) TER	(1) (A) > (B)* (2) (A) > (B)* (3) (A) > (B)* (4) (A) > (B)*	NR
Tan [56]	154 (77 : 77)	China	23.6 ± 2.5 (18~30)	37.6 ± 7.9 days (7~60 days)	Modified BBTT + (B)	AD: betahistine (8 mg·bid)	10 days	NR	(1) TER	(1) (A) > (B)†	NR
Wang [57]	66 (34 : 32)	China	(A) 35.34 ± 3.24 (20~64) (B) 35.63 ± 2.89 (20~65)	(A) 3.63 ± 1.45 yr (0.2~10 yr) (B) 3.74 ± 1.63 yr (0.8~12 yr)	Modified DXT + (B)	MT: Tuina (5 times/week)	4 weeks	NR	(1) SS (2) TER	(1) (A) > (B)† (2) (A) > (B)†	NR
Wang [58]	160 (80 : 80)	China	49.37 ± 7.48 (33~78)	3.29 ± 1.44 yr (0.5~9.5 yr)	Modified BBTT + (B)	AD: flunarizine (5 mg·qd)	4 weeks	NR	(1) TER	(1) (A) > (B)*	NR

Table 1: Continued.

Study ID	Sample size (A : B)	Study of the country	Mean age (range; yr)	CGD duration (range)	Intervention group (A)	Control group (B)	Treatment duration	Follow-up	Outcome	Results	AE (*n*)
Wang [59]	86 (43 : 43)	China	(A) 44.76 ± 3.69 (23~67) (B) 45.01 ± 3.12 (22~68)	(A) 1.04 ± 0.63 yr (4 mon~2 yr) (B) 1.13 ± 0.64 yr (3 mon~2 yr)	Modified YCT + (B)	AT (1 time/day)	4 weeks	NR	(1) RVA-BF (2) LVA-BF (3) BA-BF (4) TER (5) Fib level (6) TC level	(1) (A) > (B)† (2) (A) > (B)† (3) (A) > (B)† (4) (A) > (B)* (5) (A) > (B)† (6) (A) > (B)†	NR
Wang [60]	80 (40 : 40)	China	(A) 54.23 ± 9.09 (25~73) (B) 54.71 ± 9.91 (25~72)	3.29 ± 1.44 yr (7 days~3 mon)	Modified BBTT + (B)	AT (5 times/week)	2 weeks	NR	(1) TER	(1) (A) > (B)*	Abdominal pain (1) Fainting during acupuncture (1)
Xu [61]	112 (56 : 56)	China	(A) 41.12 ± 3.24 (18~65) (B) 40.92 ± 3.38 (18~67)	(A) 2.67 ± 3.24 yr (1~4 yr) (B) 2.71 ± 0.92 yr (1~5 yr)	Modified GGT + (B)	MT: Tuina (3 times/day)	4 weeks	NR	(1) SS (2) RVA-BF (3) LVA-BF (4) BA-BF	(1) (A) > (B)* (2) (A) > (B)* (3) (A) > (B)* (4) (A) > (B)*	NR
Yang [62]	146 (73 : 73)	China	(A) 35.72 ± 6.66 (18~54) (B) 35.37 ± 6.51 (19~55)	(A) 3.14 ± 0.75 mon (1~5 mon) (B) 3.37 ± 0.81 mon (2~5 mon)	Modified YCT + (B)	AT (1 time/day)	2 weeks	NR	(1) RVA-BF (2) LVA-BF (3) BA-BF (4) TER	(1) (A) > (B)* (2) (A) > (B)* (3) (A) > (B)* (4) (A) > (B)*	NR
Yang [63]	143 (73 : 70)	China	(A) 37.4 ± 1.5 (20~70) (B) 36.5 ± 1.2 (18~69)	(A) 2.4 ± 0.3 yr (0.5 mon~8 yr) (B) 2.5 ± 0.2 yr (1 mon~7 yr)	Modified DXT + (B)	AD: flunarizine (10 mg·qd) and betahistine (20 mg/day)	2 weeks	6 months	(1) SS (2) RVA-BF (3) LVA-BF (4) BA-BF (5) TER	(1) (A) > (B)* (2) (A) > (B)* (3) (A) > (B)* (4) (A) > (B)* (5) (A) > (B)*	Rash (1) Gastrointestinal discomfort (1) Diarrhea (1) Fatigue (2)

Table 1: Continued.

Study ID	Sample size (A : B)	Study of the country	Mean age (range; yr)	CGD duration (range)	Intervention group (A)	Control group (B)	Treatment duration	Follow-up	Outcome	Results	AE (n)
Yao [64]	78 (39 : 39)	China	(A) 42.17 ± 4.35 (22~58) (B) 42.59 ± 5.38 (23~62)	(A) 5.86 ± 1.35 yr (0.04~9 yr) (B) 6.19 ± 1.34 yr (0.04~11 yr)	Modified BBTT + (B)	AT (1 time/5 days)	6 weeks	NR	(1) RVA-BF (2) LVA-BF (3) BA-BF (4) TER	(1) (A) > (B)† (2) (A) > (B)† (3) (A) > (B)† (4) (A) > (B)†	NR
Zhang [65]	290 (145: 145)	China	(A) 57.97 ± 3.54 (47~76) (B) 58.45 ± 3.36 (46~76)	(A) 2.56 ± 1.42 yr (1.5~4.5 yr) (B) 2.85 ± 1.36 yr (1.5~5 yr)	Modified BBTT + (B)	AT + MT (AT: 1 time/day, MT: Tuina, 1 time/2 days)	4 weeks	NR	(1) OFS (2) TER	(1) (A) > (B)* (2) (A) > (B)*	NR
Zhu [66]	120 (60 : 60)	China	(A) NR (31~59) (B) NR (33~58)	(A) NR (10 days~3 yr) (B) NR (7 days~4 yr)	Modified DXT + (B)	MT: Tuina (1 time/day)	2 weeks	NR	(1) SS (2) RVA-BF (3) LVA-BF (4) BA-BF (5) TER	(1) (A) < (B)† (2) (A) > (B)† (3) (A) > (B)† (4) (A) > (B)* (5) (A) > (B)*	NR
Zhu [67]	60 (30 : 30)	China	(A) 45.5 ± 3.4 (20~67) (B) 42.3 ± 2.1 (21~65)	(A) NR (5 days~9 yr) (B) NR (7 days~10 yr)	Modified GGT + (B)	AT (1 time/day)	2 weeks	NR	(1) SS (2) TER	(1) (A) > (B)* (2) (A) > (B)*	NR

Significant differences between the two groups are indicated as follows: $^{*}p < 0.05$ and $^{\dagger}p < 0.01$. Insignificant differences between the two groups ($p > 0.05$) are indicated by N.S. AD, anti-vertigo drug; AE, adverse events; AT, acupuncture therapy; BA-BF, basilar artery blood flow; BBTT, Banxia Baizhu Tianma Tang; BYT, Buzhong Yiqi Tang; CGD, cervicogenic dizziness; CGRP, calcitonin gene-related peptide; DXT, Dingxuan Tang; ET, endothelin; Fib, fibrinogen; GGT, Gegen Tang; GJT, Gegen Jieji Tang; LVA-BF, left vertebral artery blood flow; MT, manual therapy; NR, not reported; OFS, Overall functional score; RVA-BF, right vertebral artery blood flow; SS, simple score; TC, total cholesterol; TER, total effective rate; and YCT, Yiqi Congming Tang.

Table 2: Details of the Chinese herbal medicines BBTT, BYT, and DXT in the included studies.

Study ID	Gao [37]	Gu [39]	Huang [42]	Pan [49]	Tan [56]	Wang [58]	Wang [60]	Yao [64]	Zhang [65]	Bai [33]	Lyu [48]	Cheng [35]	Ji [43]	Li [46]	Liu [47]	Shi [55]	Wang [57]	Yang [63]	Zhu [66]
CHM	BBTT									BYT					DXT				
Administration duration and frequency	2 wks, NR	2~8 wks, tid	1 mon, bid	2 wks, bid	10 dys, bid	4 wks, bid	2 wks, bid	6 wks, bid	4 wks, bid	2 dys, bid	20 dys, bid	2 wks, bid	2 wks, bid	1 mon, bid	4 wks, bid	2 wks, bid	4 wks, bid	2 wks, bid	2 wks, bid
Atractylodis Rhizoma Alba	12	7.5	15	10	9	15	12	10	18	15	10		20	10	20	15		10	
Citri Reticulatae Pericarpium	12	6		10			10		12	10	6		10		10	10			
Glycyrrhizae Radix et Rhizoma			9	6	9	9	5	6	3	10	9		5	10	9				10
Citrus reticulata Blanco			9		9	9		10											
Gastrodiae Rhizoma	12		12	9	9	12	20	10	15					15	10		12	15	10~15
Pinelliae Tuber	10	5	10	9	9	10	15	6	12				9	18				10	
Poria Sclerotium	30	7.5	12	10	9	12	30	20	9				15	25	30			10	30
Poria Sclertum Cum Pini Radix																10			
Zingiberis Rhizoma Recens		5	9	10	6	9	9		6					10					
Zizyphi Fructus			3EA	2EA	3EA	3EA	10		9										
Angelicae Gigantis Radix										10	10	15	10		15	10			
Bupleuri Radix										10	12				10				
Cimicifugae Rhizoma										10	6								
Codonopsis Pilosulae Radix										10	10		20	25	30	15			
Astragali Radix										30	60	30				20			
Uncariae Ramulus Cum Uncus								10									12	15	30
Salviae miltiorrhizae Radix																	9	15	15~30
Polygoni Multiflori Radix																10		10	
Scorpio								3									12	5	
Lumbricus												10				15			
Paeoniae Radix		7.5								10	10	10	10	10	15			10	30

Table 2: Continued.

Study ID	Gao [37]	Gu [39]	Huang [42]	Pan [49]	Tan [56]	Wang [58]	Wang [60]	Yao [64]	Zhang [65]	Bai [33]	Lyu [48]	Cheng [35]	Ji [43]	Li [46]	Liu [47]	Shi [55]	Wang [57]	Yang [63]	Zhu [66]
CHM					BBTT					BYT					DXT				
Administration duration and frequency	2 wks, NR	2~8 wks, tid	1 mon, bid	2 wks, bid	10 dys, bid	4 wks, bid	2 wks, bid	6 wks, bid	4 wks, bid	2 dys, bid	20 dys, bid	2 wks, bid	2 wks, bid	1 mon, bid	4 wks, bid	2 wks, bid	4 wks, bid	2 wks, bid	2 wks, bid
Cinnamomi Ramulus														10	10				
Puerariae Radix										20	30	10		20		20	20	20	30~60
Osterici seu Notopterygii Radix et Ehizoma								10											
Phellodendri Cortex										10	12								
Viticis Fructus	12																		
Cnidii Rhizoma	12							10				10	10	10	15	10	9		15~30
Alismatis Rhizoma	10								9	20	30		20		20				
Arisaematis Rhizoma	10																		
Magnoliae Cortex	12																		
Phyllostachyos Caulis in Taeniam		7.5														10			
Aurantii Fructus Immaturus		6																	
Myrrha								10											
Olibanum								10											
Fossilia Ossis Mastodi													30		30				
Ostreae Testa													30		30		30		
Nelumbinis Folium															15				
Zingiberis Rhizoma															9				
Margaritiferae Usta Concha																	30		
Loranthi Ramulus et Folium																	12		

Table 2: Continued.

Study ID	Gao [37]	Gu [39]	Huang [42]	Pan [49]	Tan [56]	Wang [58]	Wang [60]	Yao [64]	Zhang [65]	Bai [33]	Lyu [48]	Cheng [35]	Ji [43]	Li [46]	Liu [47]	Shi [55]	Wang [57]	Yang [63]	Zhu [66]
CHM	BBTT									BYT					DXT				
Administration duration and frequency	2 wks, NR	2~8 wks, tid	1 mon, bid	2 wks, bid	10 dys, bid	4 wks, bid	2 wks, bid	6 wks, bid	4 wks, bid	2 dys, bid	20 dys, bid	2 wks, bid	2 wks, bid	1 mon, bid	4 wks, bid	2 wks, bid	4 wks, bid	2 wks, bid	2 wks, bid
Chrysanthmi Flos									10										
Batryticatus Bombyx														6				10	
Notoginseng Radix et Rhizoma												6							
Carthami Flos												10							
Persicae Semen												10							
Aconiti Lateralis Radix Preparata												5							
Rehmanniae Radix Preparata																15			
Cuscutae Semen																15			
Cistanchis Herba																15			
Eucommiae Cortex																15			

BBTT, Banxia Baizhu Tianma Tang; BYT, Buzhong Yiqi Tang; CHM, Chinese herbal medicine; DXT, Dingxuan Tang.

Table 3: Details of the Chinese herbal medicines GGT, GJT, and YCT in the included studies.

Study ID	Chen [34]	Huagn [41]	Ju [44]	Shang [52]	Shang [53]	Xu [61]	Zhu [67]	Hu [40]	Dai [36]	Gu [38]	Li [45]	Qin [50]	Qiu [51]	Shen [54]	Wang [59]	Yang [62]
CHM				GGT				GJT				YCT				
Administration duration and frequency	1 mon, bid	2 wks, bid	4 wks, bid	2 wks, bid	2 wks, bid	4 wks, bid	2 wks, bid	2 wks, tid	4 wks, bid	4 wks, tid	4 wks, bid	2 wks, bid	1 mon, bid	NR, bid	4 wks, bid	2 wks, NR
Atractylodis Rhizoma Alba									12	20		NR	12	12	20	
Glycyrrhizae Radix et Rhizoma	6	10	6		6	6	10		6	10	6		13	13	10	6
Citrus reticulata Blanco										15		NR			15	
Gastrodiae Rhizoma			15	15												
Pinelliae Tuber									12				11	11		
Zingiberis Rhizoma Recens		10	10		6	9	10									
Zizyphi Fructus		15			3EA	9	10									
Angelicae Gigantis Radix										15					15	
Bupleuri Radix								NR								
Cimicifugae Rhizoma									9	10	9	NR	7	7	10	9
Codonopsis pilosulae Radix										20	15	NR			20	
Ginseng Radix											15		11	11		15
Astragali Radix							15		15	30		NR	12	12	30	15
Salviae miltiorrhizae Radix	30								12				14	14		
Polygoni Multiflori Radix									12				11	11		
Scorpio	10							NR								
Lumbricus	15															
Paeoniae Radix	15	20	10	9	12	15	12	NR	15		10		11	11		10
Cinnamomi Ramulus		15	10	9	6	6	12	NR								
Puerariae Radix	30	30	20	15	30	30	60	NR	12	15	10	NR	10	10	15	9
Osterici seu Notopterygii Radix et Rhizoma			10					NR								
Angelicae Dahuricae Radix				10				NR								
Phellodendri Cortex											3		8	8		3
Viticis Fructus									15	15	15	NR	13	13	15	6
Cnidii Rhizoma	15		10	10	9	9		NR		20		NR			20	
Alismatis Rhizoma										10		NR			10	
Ephedrae Herba		5			9		6									
Ostreae Testa					30											
Polygalae Radix								NR								
Ligustici Tenuissimi Rhizoma et Radix								NR								
Batryticatus Bombyx			6			6										
Notoginseng Radix et Rhizoma							3									
Achyranthis Radix	15															
Chaenomelis Fructus						15										

Table 3: Continued.

Study ID	Chen [34]	Huagn [41]	Ju [44]	Shang [52]	Shang [53]	Xu [61]	Zhu [67]	Hu [40]	Dai [36]	Gu [38]	Li [45]	Qin [50]	Qiu [51]	Shen [54]	Wang [59]	Yang [62]
CHM				GGT				GJT				YCT				
Administration duration and frequency	1 mon, bid	2 wks, bid	4 wks, bid	2 wks, bid	2 wks, bid	4 wks, bid	2 wks, bid	2 wks, tid	4 wks, bid	4 wks, tid	4 wks, bid	2 wks, bid	1 mon, bid	NR, bid	4 wks, bid	2 wks, NR
Lycopodii Herba							15									
Coicis Semen							30									
Lycopi Herba							12									
Eleocharitis Rhizoma												NR				

CHM, Chinese herbal medicine; GGT, Gegen Tang; GJT, Gegen Jieji Tang; NR, not reported; YCT, Yiqi Congming Tang.

were evaluated as "low-risk," and 1 study was evaluated as "high-risk" because there were missing data (only the results of the per-protocol analysis were reported). The remaining 4 studies were evaluated as "some concerns" because insufficient relevant information was provided. For bias in the measurement of the outcome, 20 studies were evaluated as "low-risk," and the remaining 15 studies were evaluated as "some concerns" because it was difficult to judge whether the outcome measures used in the studies were affected by the awareness of the outcome assessors. For bias in the selection of the reported result, 3 studies were evaluated as "low-risk" because there was no suspicion of deliberate nonreporting, and 3 studies were evaluated as "high-risk" because selective outcome reporting was suspected. The remaining 29 studies were evaluated as "some concerns" because there was no basis for bias assessment (e.g., study protocols). Finally, for the overall risk of bias, 23 studies assessed as "high-risk" were considered low-quality studies; 2 were considered high-quality studies; and the remaining 10 studies were evaluated as "some concerns" (Figure 2).

The risk of bias was evaluated as "low," "high," or "some concerns," represented by the following symbols: "L," "H," and "C," respectively. *D*, bias due to deviations from intended interventions; *Me*, bias in the measurement of the outcome; *Mi*, bias due to missing outcome data; *O*, overall risk of bias; *R*, bias arising from the randomisation process; and *S*, bias in the selection of the reported result.

3.4. Efficacy. In the total analysis of all included studies, compared with the active controls alone, CHMs plus active controls significantly reduced the overall functional scores (five studies: SMD, 2.31 (95% CI: 1.48–3.14); $I^2 = 94\%$), endothelin (three studies: MD, 14.57 (95% CI: 6.81–22.32); $I^2 = 96\%$), fibrinogen (four studies: MD, 0.31 (95% CI: 0.12–0.50); $I^2 = 97\%$), and TC levels (four studies: MD, 0.56 (95% CI: 0.31–0.82); $I^2 = 71\%$). In addition, CHMs plus active controls significantly increased the simple scores (22 studies: SMD, 1.82 (95% CI: 1.26–2.38); $I^2 = 97\%$), the blood flow velocity in the left vertebral artery (17 studies: MD, 5.70 (95% CI: 4.18–7.22); $I^2 = 97\%$), right vertebral artery (17 studies: MD, 4.83 (95% CI: 3.37–6.29); $I^2 = 97\%$), basilar artery (18 studies: MD, 5.58 (95% CI: 4.24–6.92); $I^2 = 96\%$), CGRP levels (four studies: MD, 6.24 (95% CI: 4.37–8.11); $I^2 = 96\%$), and total effective rate (33 studies: RR, 1.55 (95% CI: 1.42–1.69); $I^2 = 0\%$).

3.4.1. CHMs plus Anti-Vertigo Drugs versus Anti-Vertigo Drugs Alone. In the subanalysis of the 14 studies using anti-vertigo drugs as active controls, compared with the anti-vertigo drugs alone, CHMs plus anti-vertigo drugs significantly reduced the overall functional scores (one study: MD, 7.80 (95% CI: 6.02–9.58)) and endothelin levels (one study: MD, 11.14 (95% CI: 9.49–12.79)). In addition, CHMs plus anti-vertigo drugs significantly increased the simple scores (seven studies: SMD, 2.45 (95% CI: 1.32–3.58); $I^2 = 98\%$), the blood flow velocity in the left vertebral artery (seven studies: MD, 5.39 (95% CI: 3.33–7.45); $I^2 = 98\%$), right vertebral artery (seven studies: MD, 5.28 (95% CI: 3.38–7.18); $I^2 = 97\%$), and basilar artery (seven studies: MD, 5.28 (95% CI: 3.97–6.59); $I^2 = 92\%$). CHMs plus anti-vertigo drugs also significantly improved the total effective rate (13 studies: RR, 1.53 (95% CI: 1.35–1.73); $I^2 = 21\%$). However, the changes in the CGRP levels (two studies: MD, 8.89 (95% CI: −0.76–18.54); $I^2 = 98\%$) did not show a significant difference between the intervention and control groups.

In the additional subanalysis of the components of anti-vertigo drug, the combination of CHMs and flunarizine significantly increased the simple scores (three studies: SMD, 2.16 (95% CI: 0.44–3.87); $I^2 = 97\%$), the blood flow velocity in the left vertebral artery (two studies: MD, 3.96 (95% CI: 1.91–6.01); $I^2 = 94\%$), right vertebral artery (two studies: MD, 4.80 (95% CI: 4.23–5.38); $I^2 = 0\%$), basilar artery (two studies: MD, 4.85 (95% CI: 4.04–5.65); $I^2 = 0\%$), CGRP levels (one study: MD, 13.89 (95% CI: 11.48–16.30)), and the total effective rate (six studies: RR, 1.48 (95% CI: 1.16–1.90); $I^2 = 50\%$). The combination of CHMs and betahistine significantly reduced the overall functional scores (one study: MD, 7.80 (95% CI: 6.02–9.58)) and increased the blood flow velocity in the left vertebral artery (two studies: MD, 8.73 (95% CI: 5.49–11.97); $I^2 = 94\%$), right vertebral artery (two studies: MD, 7.77 (95% CI: 7.17–8.37); $I^2 = 25\%$), basilar artery (two studies: MD, 5.70 (95% CI: 5.15–6.24); $I^2 = 0\%$), and the total effective rate (four studies: RR, 1.68 (95% CI: 1.27–2.23); $I^2 = 0\%$). However, the changes in the simple scores (two studies: SMD, 1.29 (95% CI: −0.34–2.91); $I^2 = 98\%$) did not show a significant difference between the intervention and control groups. The combination of CHMs with flunarizine and betahistine significantly increased the simple scores (one study: MD, 6.98 (95% CI: 6.48–7.48)), the blood flow velocity in the left vertebral artery (one study: MD, 4.59 (95% CI: 3.28–5.90)), right vertebral artery (one study: MD, 5.04 (95% CI: 3.85–6.23)), basilar artery (one study: MD, 6.92 (95% CI: 5.74–8.10)), and the total effective rate (one study: RR, 1.97 (95% CI: 1.29–3.00)). The combination of CHMs and diphenidol significantly increased the simple scores (one study: MD, 2.67 (95% CI: 2.41–2.93)), the blood flow velocity in the left vertebral artery (one study: MD, 5.51 (95% CI: 4.39–6.63)), right vertebral artery (one study: MD, 4.69 (95% CI: 3.77–5.61)), basilar artery (one study: MD, 6.23 (95% CI: 4.42–8.04)), CGRP levels (one study: MD, 4.04 (95% CI: 3.68–4.40)), and reduced endothelin levels (one study: MD, 11.14 (95% CI: 9.49–12.79)). However, the changes in the total effective rate (one study: RR, 1.40 (95% CI: 0.80–2.44)) did not show a significant difference between the intervention and control groups. The combination of CHMs and nimodipine significantly increased the blood flow velocity in the left vertebral artery (one study: MD, 2.40 (95% CI: 1.90–2.90)), right vertebral artery (one study: MD, 1.82 (95% CI: 1.35–2.29)), and basilar artery (one study: MD, 2.74 (95% CI: 2.19–3.29)). However, the changes in the total effective rate (one study: RR, 1.32 (95% CI: 0.85–2.04)) did not show a significant difference between the intervention and control groups.

3.4.2. CHMs plus Manual Therapy versus Manual Therapy Alone. In the subanalysis of the seven studies using manual

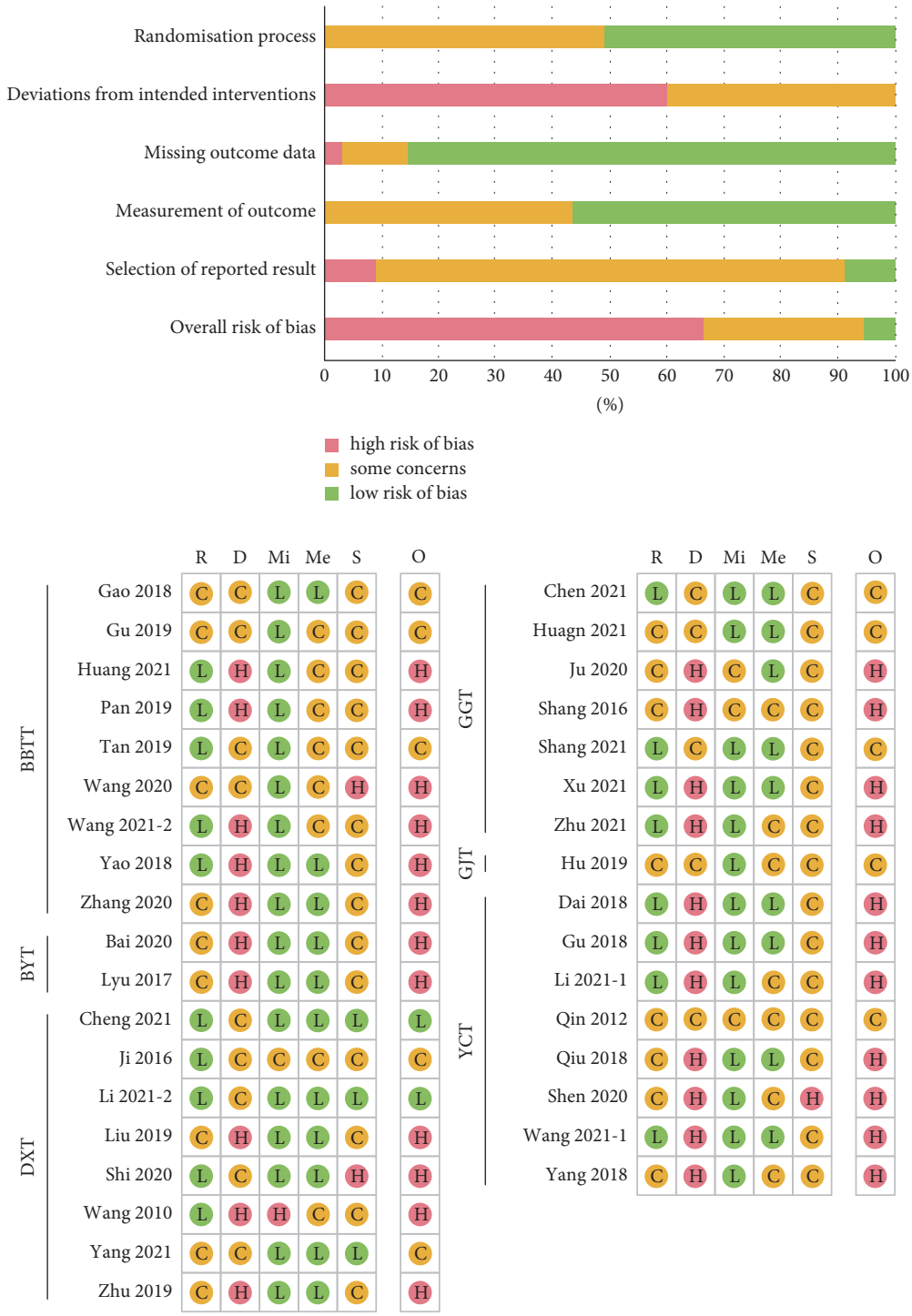


Figure 2: Risk of bias summary for all included studies.

therapy as an active control, compared with the manual therapy alone, CHMs plus manual therapy significantly increased the simple scores (seven studies: SMD, 1.33 (95% CI: 0.12–2.54); $I^2 = 98\%$), the blood flow velocity in the left vertebral artery (three studies: MD, 6.24 (95% CI: 1.36–11.12); $I^2 = 98\%$), right vertebral artery (three studies: MD, 5.62 (95% CI: 1.03–10.21); $I^2 = 98\%$), basilar artery (three studies: MD, 4.62 (95% CI: 0.32–8.91); $I^2 = 97\%$), and CGRP levels (two studies: MD, 4.63 (95% CI: 2.25–7.00); $I^2 = 93\%$). Furthermore, CHMs plus manual therapy significantly improved the total effective rate (six studies: RR, 1.71 (95% CI: 1.36–2.16); $I^2 = 0\%$). However, the changes in the overall functional scores (two studies: SMD, 3.17 (95% CI: −0.15–6.48); $I^2 = 98\%$) and endothelin levels (two studies:

MD, 16.48 (95% CI: −0.34–33.31); $I^2 = 98\%$) did not show significant differences between the intervention and control groups.

3.4.3. CHMs plus Acupuncture Therapy versus Acupuncture Therapy Alone. In the subanalysis of the thirteen studies using acupuncture therapy as an active control, compared with the acupuncture therapy alone, CHMs plus acupuncture therapy significantly reduced the overall functional scores (one study: MD, 1.91 (95% CI: 1.37–2.45)), fibrinogen (four studies: MD, 0.31 (95% CI: 0.12–0.50); $I^2 = 97\%$), and TC levels (four studies: MD, 0.56 (95% CI: 0.31–0.82); $I^2 = 71\%$). In addition, CHMs plus acupuncture therapy significantly increased the simple scores (eight studies: SMD, 1.72 (95% CI: 1.33–2.11); $I^2 = 79\%$), the blood flow velocity in the left vertebral artery (seven studies: MD, 5.81 (95% CI: 2.92–8.70); $I^2 = 95\%$), right vertebral artery (seven studies: MD, 4.03 (95% CI: 1.05–7.01); $I^2 = 96\%$), basilar artery (eight studies: MD, 6.43 (95% CI: 2.97–9.89); $I^2 = 97\%$), and the total effective rate (thirteen studies: RR, 1.54 (95% CI: 1.32–1.78); $I^2 = 0\%$).

3.4.4. CHMs plus Manual and Acupuncture Therapy versus Manual and Acupuncture Therapy Alone. In the subanalysis of the one study using manual and acupuncture therapy as an active control, CHMs plus manual and acupuncture therapy significantly reduced the overall functional scores (one study: MD, 7.06 (95% CI: 6.27–7.85)) and improved the total effective rate (one study: RR, 1.40 (95% CI: 1.02–1.94)), compared with the active control alone.

3.4.5. BBTT plus Active Controls versus Active Controls Alone. In the subanalysis of the nine studies using BBTT as CHM, compared with the active controls alone, BBTT plus active controls significantly reduced the overall functional scores (two studies: SMD, 3.44 (95% CI: 0.69–6.20); $I^2 = 98\%$) and endothelin levels (one study: MD, 25.13 (95% CI: 21.29–28.97)) and increased the simple scores (two studies: MD, 5.15 (95% CI: 4.81–5.50); $I^2 = 0\%$), the blood flow velocity in the left vertebral artery (two studies: MD, 4.44 (95% CI: 3.18–5.69); $I^2 = 71\%$), right vertebral artery (two studies: MD, 3.85 (95% CI: 2.29–5.41); $I^2 = 84\%$), basilar artery (two studies: MD, 3.48 (95% CI: 0.04–6.92); $I^2 = 95\%$), and CGRP levels (one study: MD, 5.89 (95% CI: 4.78–7.00)). BBTT plus active controls also significantly improved the total effective rate (nine studies: RR, 1.48 (95% CI: 1.29–1.70); $I^2 = 33\%$).

3.4.6. BYT plus Active Controls versus Active Controls Alone. In the subanalysis of the two studies using BYT as CHM, compared with the acupuncture therapy alone, BYT plus acupuncture therapy significantly increased the simple scores (two studies: MD, 2.04 (95% CI: 1.35–2.72); $I^2 = 0\%$) and the blood flow velocity in the left vertebral artery (two studies: MD, 1.72 (95% CI: 0.57–2.87); $I^2 = 0\%$). However, the changes in the blood flow velocity in the basilar artery (two studies: MD, 0.43 (95% CI: −0.68–1.55); $I^2 = 0\%$) and the total effective rate (two studies: RR, 1.27 (95% CI: 0.70–2.28); $I^2 = 0\%$) did not show significant differences between the intervention and control groups. Notably, the blood flow velocity in the right vertebral artery (two studies: MD, −1.80 (95% CI: −2.88–0.72); $I^2 = 0\%$) showed a significant increase in the control group compared with the intervention group.

3.4.7. DXT plus Active Controls versus Active Controls Alone. In the subanalysis of the eight studies using DXT as CHM, compared with the active controls alone, DXT plus active controls significantly reduced the overall functional scores (one study: MD, 5.68 (95% CI: 4.36–7.00)) and endothelin levels (two studies: MD, 9.71 (95% CI: 6.61–12.81); $I^2 = 76\%$) and increased the simple scores (seven studies: SMD, 1.67 (95% CI: 0.20–3.14); $I^2 = 98\%$), the blood flow velocity in the left vertebral artery (five studies: MD, 5.13 (95% CI: 3.87–6.40); $I^2 = 78\%$), right vertebral artery (five studies: MD, 5.12 (95% CI: 3.42–6.83); $I^2 = 90\%$), basilar artery (five studies: MD, 5.14 (95% CI: 2.66–7.62); $I^2 = 92\%$), and CGRP levels (three studies: MD, 6.41 (95% CI: 4.15–8.67); $I^2 = 97\%$). Moreover, DXT plus active controls significantly improved the total effective rate (eight studies: RR, 1.61 (95% CI: 1.33–1.95); $I^2 = 0\%$).

3.4.8. GGT plus Active Controls versus Active Controls Alone. In the subanalysis of the seven studies using GGT as CHM, compared with the active controls alone, GGT plus manual therapy significantly reduced the overall functional scores (one study: MD, 7.80 (95% CI: 6.02–9.58)) and increased the simple scores (five studies: SMD, 1.92 (95% CI: 0.99–2.85); $I^2 = 94\%$), the blood flow velocity in the left vertebral artery (five studies: MD, 7.29 (95% CI: 3.51–11.07); $I^2 = 99\%$), right vertebral artery (five studies: MD, 6.18 (95% CI: 3.12–9.24); $I^2 = 99\%$), and basilar artery (five studies: MD, 5.19 (95% CI: 3.50–6.88); $I^2 = 96\%$). Moreover, GGT plus active controls significantly improved the total effective rate (six studies: RR, 1.62 (95% CI: 1.32–1.99); $I^2 = 0\%$).

3.4.9. GJT plus Active Controls versus Active Controls Alone. In the subanalysis of the one study using GJT as CHM, compared with the betahistine alone, GJT plus betahistine significantly increased the simple scores (one study: MD, 2.00 (95% CI: 1.75–2.25)). However, the total effective rate (one study: RR, 2.19 (95% CI: 0.99–4.86)) was not significantly different between the intervention and control groups.

3.4.10. YCT plus Active Controls versus Active Controls Alone. In the subanalysis of the eight studies using YCT as CHM, compared with the active controls alone, YCT plus active controls significantly reduced the overall functional scores (one study: MD, 1.91 (95% CI: 1.37–2.45)), fibrinogen (four studies: MD, 0.31 (95% CI: 0.12–0.50); $I^2 = 97\%$) and TC levels (four studies: MD, 0.56 (95% CI: 0.31–0.82); $I^2 = 71\%$) and increased the simple scores (five studies: SMD, 1.79 (95% CI: 0.93–2.64); $I^2 = 94\%$), blood flow velocity in the left

Table 4: Summary of findings.

Outcomes	No. of participants (RCTs)	Anticipated absolute effects (95% CI)		Relative effect (95% CI)	I^2 value	Quality of evidence (GRADE)	Comments
		Risk with control group	Risk with CHM group				
Total analysis							
OFS	704 (5)	—	SMD 2.31 lower (1.48–3.14 lower)	—	94%	⊕⊕○○ Low	Risk of bias (−1) Inconsistency (−1)
SS	2,289 (22)	—	SMD 1.82 higher (1.26–2.38 higher)	—	97%	⊕○○○ Very low	Risk of bias (−1) Publication bias (−1) Inconsistency (−2)
LVA-BF	1,778 (17)	—	MD 5.70 higher (4.18–7.22 higher)	—	97%	⊕⊕○○ Low	Risk of bias (−1) Inconsistency (−2) Strong association (+1)
RVA-BF	1,778 (17)	—	MD 4.83 higher (3.37–6.29 higher)	—	97%	⊕○○○ Very low	Risk of bias (−1) Inconsistency (−2) Publication bias (−1) Strong association (+1)
BA-BF	1,888 (18)	—	MD 5.58 higher (4.24–6.92 higher)	—	96%	⊕○○○ Very low	Risk of bias (−1) Inconsistency (−2) Publication bias (−1) Strong association (+1)
TER	3,582 (33)	295 per 1,000	450 per 1,000 (419–499)	RR 1.55 (1.42–1.69)	0%	⊕⊕⊕○ Moderate	Risk of bias (−1)
ET level	342 (3)	—	MD 14.57 lower (6.81–22.32 lower)	—	96%	⊕○○○ Very low	Risk of bias (−1) Inconsistency (−2)
CGRP level	426 (4)	—	MD 6.24 higher (4.37–8.11 higher)	—	96%	⊕○○○ Very low	Risk of bias (−1) Inconsistency (−2)
Fib level (vs. AT)	348 (4)	—	MD 0.31 lower (0.12–0.50 lower)	—	97%	⊕○○○ Very low	Risk of bias (−1) Inconsistency (−2)
TC level (vs. AT)	348 (4)	—	MD 0.56 lower (0.31–0.82 lower)	—	71%	⊕⊕○○ Low	Risk of bias (−1) Inconsistency (−1)
Subgroup analysis according to the comparison types							
			CHM plus AD vs. AD				
OFS (vs. betahistine)	98 (1)	—	MD 7.80 lower (6.02–9.58 lower)	—	N/A	⊕○○○ Very low	Risk of bias (−1) Imprecision (−2)
SS	886 (7)	—	SMD 2.45 higher (1.32–3.58 higher)	—	98%	⊕⊕○○ Low	Risk of bias (−1) Inconsistency (−1)
SS (vs. flunarizine)	264 (3)	—	SMD 2.16 higher (0.44–3.87 higher)	—	97%	⊕⊕○○ Low	Risk of bias (−1) Inconsistency (−1)

Table 4: Continued.

Outcomes	No. of participants (RCTs)	Anticipated absolute effects (95% CI)		Relative effect (95% CI)	I^2 value	Quality of evidence (GRADE)	Comments
		Risk with control group	Risk with CHM group				
SS (vs. betahistine)	363 (2)	—	SMD 1.29 higher (0.34 lower–2.91 higher)	—	98%	⊕○○○ Very low	Risk of bias (−1) Inconsistency (−1) Imprecision (−1)
SS (vs. flunarizine and betahistine)	143 (1)	—	MD 6.98 higher (6.48–7.48 higher)	—	N/A	⊕⊕○○ Low	Risk of bias (−1) Imprecision (−1)
SS (vs. diphenidol)	116 (1)	—	MD 2.67 higher (2.41–2.93 higher)	—	N/A	⊕⊕⊕○ Moderate	Imprecision (−1)
LVA-BF	791 (7)	—	MD 5.39 higher (3.33–7.45 higher)	—	98%	⊕⊕○○ Low	Risk of bias (−1) Inconsistency (−1)
LVA-BF (vs. flunarizine)	226 (2)	—	MD 3.96 higher (1.91–6.01 higher)	—	94%	⊕○○○ Very low	Risk of bias (−1) Inconsistency (−1) Imprecision (−1)
LVA-BF (vs. betahistine)	172 (2)	—	MD 8.73 higher (5.49–11.97 higher)	—	94%	⊕○○○ Very low	Risk of bias (−1) Risk of bias (−1) Inconsistency (−1) Imprecision (−1)
LVA-BF (vs. flunarizine and betahistine)	143 (1)	—	MD 4.59 higher (3.28–5.90 higher)	—	N/A	⊕⊕○○ Low	Risk of bias (−1) Imprecision (−1)
LVA-BF (vs. diphenidol)	116 (1)	—	MD 5.51 higher (4.39–6.63 higher)	—	N/A	⊕⊕⊕○ Moderate	Imprecision (−1)
LVA-BF (vs. nimodipine)	134 (1)	—	MD 2.40 higher (1.90–2.90 higher)	—	N/A	⊕⊕○○ Low	Risk of bias (−1) Imprecision (−1)
RVA-BF	791 (7)	—	MD 5.28 higher (3.38–7.18 higher)	—	97%	⊕⊕○○ Low	Risk of bias (−1) Inconsistency (−1)
RVA-BF (vs. flunarizine)	226 (2)	—	MD 4.80 higher (4.23–5.38 higher)	—	0%	⊕⊕○○ Low	Risk of bias (−1) Imprecision (−1)
RVA-BF (vs. betahistine)	172 (2)	—	MD 7.77 higher (7.17–8.37 higher)	—	25%	⊕⊕○○ Low	Risk of bias (−1) Imprecision (−1)
RVA-BF (vs. flunarizine and betahistine)	143 (1)	—	MD 5.04 higher (3.85–6.23 higher)	—	N/A	⊕⊕○○ Low	Risk of bias (−1) Imprecision (−1)
RVA-BF (vs. diphenidol)	116 (1)	—	MD 4.69 higher (3.77–5.61 higher)	—	N/A	⊕⊕⊕○ Moderate	Imprecision (−1)
RVA-BF (vs. nimodipine)	134 (1)	—	MD 1.82 higher (1.35–2.29 higher)	—	N/A	⊕⊕○○ Low	Risk of bias (−1) Imprecision (−1)
BA-BF	791 (7)	—	MD 5.28 higher (3.97–6.59 higher)	—	92%	⊕⊕○○ Low	Risk of bias (−1) Inconsistency (−1)
BA-BF (vs. flunarizine)	226 (2)	—	MD 4.85 higher (4.04–5.65 higher)	—	0%	⊕⊕○○ Low	Risk of bias (−1) Imprecision (−1)
BA–BF (vs. betahistine)	172 (2)	—	MD 5.70 higher (5.15–6.24 higher)	—	0%	⊕⊕○○ Low	Risk of bias (−1) Imprecision (−1)
BA–BF (vs. flunarizine and betahistine)	143 (1)	—	MD 6.92 higher (5.74–8.10 higher)	—	N/A	⊕⊕○○ Low	Risk of bias (−1) Imprecision (−1)
BA-BF (vs. diphenidol)	116 (1)	—	MD 6.23 higher (4.42–8.04 higher)	—	N/A	⊕⊕⊕○ Moderate	Imprecision (−1)
BA-BF (vs. nimodipine)	134 (1)	—	MD 2.74 higher (2.19–3.29 higher)	—	N/A	⊕⊕○○ Low	Risk of bias (−1) Imprecision (−1)

Table 4: Continued.

Outcomes	No. of participants (RCTs)	Anticipated absolute effects (95% CI)		Relative effect (95% CI)	I^2 value	Quality of evidence (GRADE)	Comments
		Risk with control group	Risk with CHM group				
TER	1,529 (13)	311 per 1,000	461 per 1,000 (420–538)	RR 1.53 (1.35–1.73)	21%	⊕⊕⊕○ Moderate	Risk of bias (−1)
TER (vs. flunarizine)	610 (6)	407 per 1,000	590 per 1,000 (472–773)	RR 1.48 (1.16–1.90)	50%	⊕⊕○○ Low	Risk of bias (−1) Inconsistency (−1)
TER (vs. betahistine)	526 (4)	206 per 1,000	322 per 1,000 (262–459)	RR 1.68 (1.27–2.23)	0%	⊕⊕⊕○ Moderate	Risk of bias (−1)
TER (vs. flunarizine and betahistine)	143 (1)	286 per 1,000	562 per 1,000 (369–858)	RR 1.97 (1.29–3.00)	N/A	⊕⊕○○ Low	Risk of bias (−1) Imprecision (−1)
TER (vs. diphenidol)	116 (1)	259 per 1,000	362 per 1,000 (207–632)	RR 1.40 (0.80–2.44)	N/A	⊕⊕○○ Low	Imprecision (−2)
TER (vs. nimodipine)	134 (1)	328 per 1,000	433 per 1,000 (279–669)	RR 1.32 (0.85–2.04)	N/A	⊕○○○ Very low	Risk of bias (−1) Imprecision (−2)
ET level (vs. diphenidol)	116 (1)	—	MD 11.14 lower (9.49–12.79 lower)	—	N/A	⊕⊕⊕○ Moderate	Imprecision (−1)
CGRP level	200 (2)	—	MD 8.89 higher (0.76 lower–18.54 higher)	—	98%	⊕○○○ Very low	Risk of bias (−1) Inconsistency (−1) Imprecision (−2)
CGRP level (vs. flunarizine)	84 (1)	—	MD 13.89 higher (11.48–16.30 higher)	—	N/A	⊕⊕○○ Low	Imprecision (−2)
CGRP level (vs. diphenidol)	116 (1)	—	MD 4.04 higher (3.68–4.40 higher)	—	N/A	⊕⊕⊕○ Moderate	Imprecision (−1)
CHM plus MT vs. MT							
OFS	246 (2)	—	SMD 3.17 lower (6.48 lower–0.15 higher)	—	98%	⊕○○○ Very low	Risk of bias (−1) Inconsistency (−1) Imprecision (−2)
SS	726 (7)	—	SMD 1.33 higher (0.12–2.54 higher)	—	98%	⊕⊕○○ Low	Risk of bias (−1) Inconsistency (−1)
LVA-BF	358 (3)	—	MD 6.24 higher (1.36–11.12 higher)	—	98%	⊕⊕○○ Low	Risk of bias (−1) Inconsistency (−1)
RVA-BF	358 (3)	—	MD 5.62 higher (1.03–10.21 higher)	—	98%	⊕⊕○○ Low	Risk of bias (−1) Inconsistency (−1)
BA-BF	358 (3)	—	MD 4.62 higher (0.32–8.91 higher)	—	97%	⊕⊕○○ Low	Risk of bias (−1) Inconsistency (−1)
TER	614 (6)	235 per 1,000	406 per 1,000 (320–508)	RR 1.71 (1.36–2.16)	0%	⊕⊕⊕○ Moderate	Risk of bias (−1)
ET level	226 (2)	—	MD 16.48 lower (33.31 lower–0.34 higher)	—	98%	⊕○○○ Very low	Risk of bias (−1) Inconsistency (−1) Imprecision (−2)
CGRP level	226 (2)	—	MD 4.63 higher (2.25–7.00 higher)	—	93%	⊕○○○ Very low	Risk of bias (−1) Inconsistency (−1) Imprecision (−1)
CHM plus AT vs. AT							
OFS	70 (1)	—	MD 1.91 lower (1.37–2.45 lower)	—	N/A	⊕○○○ Very low	Risk of bias (−1) Imprecision (−2)
SS	677 (8)	—	SMD 1.72 higher (1.33–2.11 higher)	—	79%	⊕⊕○○ Low	Risk of bias (−1) Inconsistency (−1)

Table 4: Continued.

Outcomes	No. of participants (RCTs)	Anticipated absolute effects (95% CI)		Relative effect (95% CI)	I^2 value	Quality of evidence (GRADE)	Comments
		Risk with control group	Risk with CHM group				
LVA-BF	629 (7)	—	MD 5.81 higher (2.92–8.70 higher)	—	95%	⊕⊕○○ Low	Risk of bias (–1) Inconsistency (–1)
RVA-BF	629 (7)	—	MD 4.03 higher (1.05–7.01 higher)	—	96%	⊕⊕○○ Low	Risk of bias (–1) Inconsistency (–1)
BA-BF	739 (8)	—	MD 6.43 higher (2.97–9.89 higher)	—	97%	⊕⊕○○ Low	Risk of bias (–1) Inconsistency (–1)
TER	1,149 (13)	307 per 1,000	471 per 1,000 (405–546)	RR 1.54 (1.32–1.78)	0%	⊕⊕⊕○ Moderate	Risk of bias (–1)
CHM plus MT plus AT vs. MT plus AT							
OFS	290 (1)	—	MD 7.06 lower Risk of bias (–1) Imprecision (–1; 6.27–7.85 lower)	—	N/A	⊕⊕⊕○ Moderate	Risk of bias (–1)
TER	290 (1)	290 per 1,000	407 per 1,000 (296–563)	RR 1.40 (1.02–1.94)	N/A	⊕⊕⊕○ Moderate	Risk of bias (–1)
Subgroup analysis according to the CHM prescription names							
BBTT plus active controls vs. active controls							
OFS	410 (2)	—	SMD 3.44 lower (0.69–6.20 lower)	—	98%	⊕⊕○○ Low	Risk of bias (–1) Inconsistency (–1)
SS	220 (2)	—	MD 5.15 higher (4.81–5.50 higher)	—	0%	⊕⊕○○ Low	Risk of bias (–1) Imprecision (–1)
LVA-BF	184 (2)	—	MD 4.44 higher (3.18–5.69 higher)	—	71%	⊕○○○ Very low	Risk of bias (–1) Inconsistency (–1) Imprecision (–1)
RVA-BF	184 (2)	—	MD 3.85 higher (2.29–5.41 higher)	—	84%	⊕○○○ Very low	Risk of bias (–1) Inconsistency (–1) Imprecision (–1)
BA-BF	184 (2)	—	MD 3.48 higher (0.04–6.92 higher)	—	95%	⊕○○○ Very low	Risk of bias (–1) Inconsistency (–1) Imprecision (–1)
TER	1,168 (9)	329 per 1,000	486 per 1,000 (424–559)	RR 1.48 (1.29–1.70)	33%	⊕⊕⊕○ Moderate	Risk of bias (–1)
ET level	100 (1)	—	MD 25.13 lower (21.29–28.97 lower)	—	N/A	⊕⊕○○ Low	Risk of bias (–1) Imprecision (–1)
CGRP level	100 (1)	—	MD 5.89 higher (4.78–7.00 higher)	—	N/A	⊕⊕○○ Low	Risk of bias (–1) Imprecision (–1)
BYT plus active controls vs. active controls							
SS	134 (2)	—	MD 2.04 higher (1.35–2.72 higher)	—	0%	⊕⊕○○ Low	Risk of bias (–1) Imprecision (–1)
LVA-BF	134 (2)	—	MD 1.72 higher (0.57–2.87 higher)	—	0%	⊕⊕○○ Low	Risk of bias (–1) Imprecision (–1)
RVA-BF	134 (2)	—	MD 1.80 lower (0.72–2.88 lower)	—	0%	⊕⊕○○ Low	Risk of bias (–1) Imprecision (–1)
BA-BF	134 (2)	—	MD 0.43 higher (0.68 lower–1.55 higher)	—	0%	⊕○○○ Very low	Risk of bias (–1) Imprecision (–2)

Table 4: Continued.

Outcomes	No. of participants (RCTs)	Anticipated absolute effects (95% CI)		Relative effect (95% CI)	I^2 value	Quality of evidence (GRADE)	Comments
		Risk with control group	Risk with CHM group				
TER	134 (2)	224 per 1,000	284 per 1,000 (157–511)	RR 1.27 (0.70–2.28)	0%	⊕○○○ Very low	Risk of bias (−1) Imprecision (−2)
DXT plus active controls vs. active controls							
OFS	126 (1)	—	MD 5.68 lower (4.36–7.00 lower)	—	N/A	⊕⊕○○ Low	Risk of bias (−1) Imprecision (−1)
SS	715 (7)	—	SMD 1.67 higher (0.20–3.14 higher)	—	98%	⊕⊕⊕○ Moderate	Inconsistency (−1)
LVA-BF	579 (5)	—	MD 5.13 higher (3.87–6.40 higher)	—	78%	⊕⊕○○ Low	Risk of bias (−1) Inconsistency (−1)
RVA-BF	579 (5)	—	MD 5.12 higher (3.42–6.83 higher)	—	90%	⊕⊕○○ Low	Risk of bias (−1) Inconsistency (−1)
BA-BF	579 (5)	—	MD 5.14 higher (2.66–7.62 higher)	—	92%	⊕⊕○○ Low	Risk of bias (−1) Inconsistency (−1)
TER	789 (8)	265 per 1,000	431 per 1,000 (352–517)	RR 1.61 (1.33–1.95)	0%	⊕⊕⊕○ Moderate	Risk of bias (−1)
ET level	242 (2)	—	MD 9.71 lower (6.61–12.81 lower)	—	76%	⊕○○○ Very low	Risk of bias (−1) Inconsistency (−1) Imprecision (−1)
CGRP level	326 (3)	—	MD 6.41 higher (4.15–8.67 higher)	—	97%	⊕⊕○○ Low	Risk of bias (−1) Inconsistency (−1)
GGT plus active controls vs. active controls							
OFS	98 (1)	—	MD 7.80 lower (6.02–9.58 lower)	—	N/A	⊕○○○ Very low	Risk of bias (−1) Imprecision (−2)
SS	489 (5)	—	SMD 1.92 higher (0.99–2.85 higher)	—	94%	⊕⊕○○ Low	Risk of bias (−1) Inconsistency (−1)
LVA-BF	579 (5)	—	MD 7.29 higher (3.51–11.07 higher)	—	99%	⊕⊕○○ Low	Risk of bias (−1) Inconsistency (−1)
RVA-BF	579 (5)	—	MD 6.18 higher (3.12–9.24 higher)	—	99%	⊕⊕○○ Low	Risk of bias (−1) Inconsistency (−1)
BA-BF	579 (5)	—	MD 5.19 higher (3.50–6.88 higher)	—	96%	⊕⊕○○ Low	Risk of bias (−1) Inconsistency (−1)
TER	609 (6)	299 per 1,000	485 per 1,000 (395–595)	RR 1.62 (1.32–1.99)	0%	⊕⊕⊕○ Moderate	Risk of bias (−1)
GJT plus active controls vs. active controls							
SS	200 (1)	—	MD 2.00 higher (1.75–2.25 higher)	—	N/A	⊕⊕○○ Low	Risk of bias (−1) Imprecision (−1)
TER	200 (1)	88 per 1,000	187 per 1,000 (87–425)	RR 2.19 (0.99–4.86)	N/A	⊕○○○ Very low	Risk of bias (−1) Imprecision (−2)
YCT plus active controls vs. active controls							
OFS	70 (1)	—	MD 1.91 lower (1.37–2.45 lower)	—	N/A	⊕○○○ Very low	Risk of bias (−1) Imprecision (−2)
SS	531 (5)	—	SMD 1.79 higher (0.93–2.64 higher)	—	94%	⊕⊕○○ Low	Risk of bias (−1) Inconsistency (−1)

Table 4: Continued.

Outcomes	No. of participants (RCTs)	Anticipated absolute effects (95% CI)		Relative effect (95% CI)	I^2 value	Quality of evidence (GRADE)	Comments
		Risk with control group	Risk with CHM group				
LVA-BF	302 (3)	—	MD 7.63 higher (4.69–10.57 higher)	—	80%	⊕⊕○○ Low	Risk of bias (−1) Inconsistency (−1)
RVA-BF	302 (3)	—	MD 7.34 higher (6.02–8.66 higher)	—	0%	⊕⊕⊕○ Moderate	Risk of bias (−1)
BA-BF	412 (4)	—	MD 11.01 higher (4.46–17.56 higher)	—	96%	⊕⊕○○ Low	Risk of bias (−1) Inconsistency (−1)
TER	682 (7)	328 per 1,000	504 per 1,000 (420–604)	RR 1.54 (1.28–1.84)	0%	⊕⊕⊕○ Moderate	Risk of bias (−1)
Fib level	348 (4)	—	MD 0.31 lower (0.12–0.50 lower)	—	97%	⊕⊕○○ Low	Risk of bias (−1) Inconsistency (−1)
TC level	348 (4)	—	MD 0.56 lower (0.31–0.82 lower)	—	71%	⊕⊕○○ Low	Risk of bias (−1) Inconsistency (−1)

If the evidence of more than 10 studies showed MD <4 for the change in the blood flow velocity in the vertebrobasilar artery or RR >2 for the total effective rate, it was considered that there was a strong association for a treatment effect. AD, anti-vertigo drugs; AT, acupuncture therapy; BA-BF, basal artery blood flow; BBTT, Banxia Baizhu Tianma Tang; BYT, Buzhong Yiqi Tang; CHM, Chinese herbal medicine; CI, confidence interval; CGRP, calcitonin gene-related peptide; DXT, Dingxuan Tang; ET, endothelin; Fib, fibrinogen; GGT, Gegen Tang; GJT, Gegen Jieji Tang; GRADE, the grading of recommendations assessment, development, and evaluation; LVA-BF, left vertebral artery blood flow; MD, mean difference; MT, manual therapy; OFS, overall functional score; RCT, randomised controlled trial; RR, risk ratio; RVA-BF, right vertebral artery blood flow; SMD, standardised mean difference; SS, simple score; TC, total cholesterol; TER, total effective rate; YCT, Yiqi Congming Tang.

vertebral artery (three studies: MD, 7.63 (95% CI: 4.69–10.57); $I^2 = 80\%$), right vertebral artery (three studies: MD, 7.34 (95% CI: 6.02–8.66); $I^2 = 0\%$), and basilar artery (four studies: MD, 11.01 (95% CI: 4.46–17.56); $I^2 = 96\%$). Furthermore, YCT plus active controls significantly improved the total effective rate (seven studies: RR, 1.54 (95% CI: 1.28–1.84); $I^2 = 0\%$).

Summarizing the results of the subanalysis according to CHM prescription names, BBTT, DXT, GGT, and YCT showed significant treatment effects on various primary and secondary outcomes and had relatively more clinical evidence compared with the remaining CHM prescription names. GJT was investigated in only one RCT and demonstrated a significant effect on only one primary outcome (change in the simple scores), without statistically significant effects on the other outcome (total effective rate). In the two RCTs investigating BYT, there were significant effects on two primary outcomes (change in the simple scores and blood flow velocity in the left vertebral artery), while the effects on the remaining outcomes were either not significant (blow flow velocity in the basilar artery and total effective rate) or were significant in the control group (the blood velocity for the right vertebral artery). The results of the total analysis and the subanalyses of the efficacy of CHMs are shown in Table 4.

3.5. Safety. Three of the thirty-five included studies reported adverse events. There was one case of gastrointestinal discomfort in the BBTT plus manual therapy group; one case of abdominal pain; one case of fainting during acupuncture therapy in the BBTT plus acupuncture therapy group; one case of rash, diarrhea, and gastrointestinal discomfort each, and two cases of fatigue in the DXT plus anti-vertigo drugs (flunarizine and betahistine) group. All reported adverse events were mild and transient and were evaluated as "not serious" (Table 1).

3.6. Quality of Evidence. In the comparison of CHMs plus active controls versus active controls alone, the quality of evidence for the primary outcomes ranged from "very low" to "low." For the secondary outcomes, the quality of evidence for the total effective rate was graded as "moderate," while that for the other outcomes was graded as "very low" or "low." The overall quality of evidence in the total analysis was graded as "low." In the subanalysis based on the type of active control, the overall quality of evidence was graded as "moderate" for CHMs plus manual and acupuncture therapy and as "low" for CHMs plus any other active control (anti-vertigo drugs, manual therapy, or acupuncture therapy). In the subanalysis based on the CHM prescription name, the overall quality of evidence was evaluated as "low" for all CHM prescriptions. However, its quantitative and qualitative levels were highest for DXT and YCT and lowest for BYT and GJT, respectively. The main reason for the downgrade was the high risk of bias in the included studies, the imprecision of the results due to the small sample size, and the inconsistency of the results due to the high heterogeneity among them (Table 4).

Table 5: Adjusted quality of evidence derived by sensitivity analysis.

Outcomes	Before SA		After SA		
	Anticipated absolute effects (95% CI)	I^2 value	Anticipated absolute effects (95% CI)	I^2 value	Adjusted quality of evidence (GRADE)
Total analysis					
OFS	SMD 2.31 (1.48–3.14)	94%	SMD 1.81 (1.61–2.00)	49%	⊕⊕⊕○ Moderate
TC level (vs. AT)	MD 0.56 (0.31–0.82)	71%	MD 0.43 (0.27–0.60)	0%	⊕⊕⊕○ Moderate
Subgroup analysis according to the comparison types					
CHM plus AD vs. AD					
BA-BF	MD 5.28 (3.97–6.59)	92%	MD 5.65 (5.24–6.06)	48%	⊕⊕⊕○ Moderate
CHM plus MT vs. MT					
LVA-BF	MD 6.24 (1.36–11.12)	98%	MD 3.81 (2.84–4.79)	0%	⊕⊕○○ Low
RVA-BF	MD 5.62 (1.03–10.21)	98%	MD 3.48 (2.52–4.44)	0%	⊕⊕○○ Low
BA-BF	MD 4.62 (0.32–8.91)	97%	MD 6.67 (4.73–8.62)	43%	⊕⊕○○ Low
CHM plus AT vs. AT					
RVA-BF	MD 4.03 (1.05–7.01)	96%	MD 7.28 (6.33–8.22)	0%	⊕⊕⊕○ Moderate
Subgroup analysis according to the CHM prescription names					
DXT plus active controls vs. active controls					
LVA-BF	MD 5.13 (3.87–6.40)	78%	MD 4.56 (3.92–5.20)	48%	⊕⊕○○ Low
RVA-BF	MD 5.12 (3.42–6.83)	90%	MD 4.33 (3.75–4.91)	41%	⊕⊕○○ Low
BA-BF	MD 5.14 (2.66–7.62)	92%	MD 6.45 (5.62–7.28)	0%	⊕⊕○○ Low
CGRP level	MD 6.41 (4.15–8.67)	97%	MD 3.87 (3.57–4.17)	66%	⊕⊕○○ Low
GGT plus active controls vs. active controls					
SS	SMD 1.92 (0.99–2.85)	94%	SMD 1.39 (1.16–1.62)	74%	⊕⊕○○ Low
LVA-BF	MD 7.29 (3.51–11.07)	99%	MD 10.33 (9.76–10.90)	0%	⊕⊕⊕○ Moderate
BA–BF	MD 5.19 (3.50–6.88)	96%	MD 5.46 (5.00–5.93)	45%	⊕⊕⊕○ Moderate
YCT plus active controls vs. active controls					
SS	SMD 1.79 (0.93–2.64)	94%	SMD 2.13 (1.87–2.38)	0%	⊕⊕⊕○ Moderate
LVA-BF	MD 7.63 (4.69–10.57)	80%	MD 3.47 (3.19–3.75)	0%	⊕⊕○○ Low

AD, anti-vertigo drugs; AT, acupuncture therapy; BA-BF, basal artery blood flow; CHM, Chinese herbal medicine; CI, confidence interval; CGRP, calcitonin gene-related peptide; DXT, Dingxuan Tang; GGT, Gegen Tang; GRADE, the grading of recommendations assessment, development, and evaluation; LVA-BF, left vertebral artery blood flow; MD, mean difference; MT, manual therapy; OFS, overall functional score; RVA-BF, right vertebral artery blood flow; SA, sensitivity analysis; SMD, standardised mean difference; SS, simple score; TC, total cholesterol; YCT, Yiqi Congming Tang.

3.7. Sensitivity Analysis. For the outcomes with considerable heterogeneity among studies, we performed sensitivity analysis and adjusted the quality of evidence based on the results. After heterogeneity was eliminated by removing one to two outliers considered to have a high risk for selection and reporting biases, the quality of evidence for the efficacy of CHMs for CGD was similar to that obtained before the sensitivity analysis. Therefore, the findings in this systematic review are considered robust to the decisions made in the process of obtaining them (Table 5).

3.8. Publication Bias. For seven outcomes included in more than ten studies, we examined publication bias using funnel plot analysis. For the comparisons of CHMs plus active controls, anti-vertigo drugs, or acupuncture therapy versus active controls, anti-vertigo drugs, or acupuncture therapy alone, respectively, the funnel plots of the total effective rate were symmetrical for all (Figures 3–5). Conversely, for the comparison of CHMs plus active controls versus active controls, the funnel plots of the simple scores and the blood flow velocity in the vertebrobasilar arteries showed

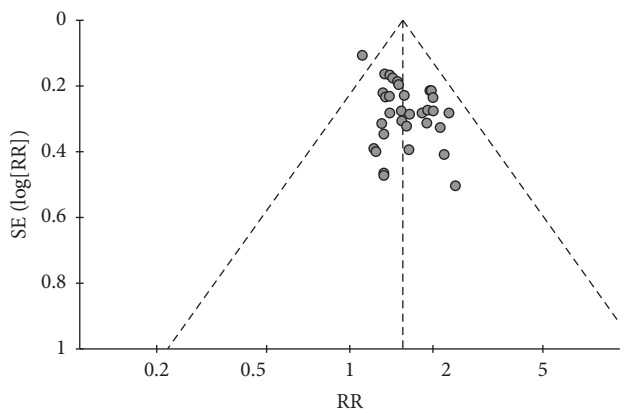


Figure 3: Funnel plot of the effects of CHMs plus active controls on the total effective rate.

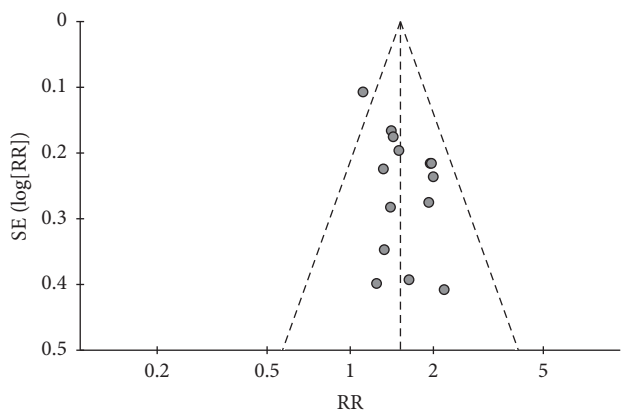


Figure 4: Funnel plot of the effects of CHMs plus anti-vertigo drugs on the total effective rate.

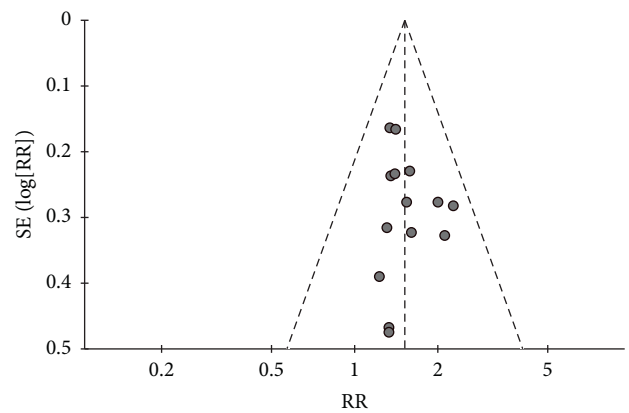


Figure 5: Funnel plot of the effects of CHMs plus acupuncture therapy on the total effective rate.

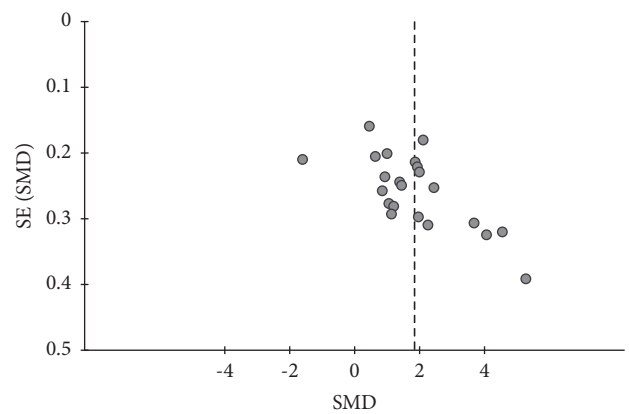


Figure 6: Funnel plot of the effects of CHMs plus active controls on the simple scores.

asymmetry. In the funnel plot of the blood flow velocity in the left vertebral artery, the asymmetry was presumed to be due to considerable heterogeneity. The asymmetry for the remaining outcomes suggested potential publication bias; thus, there may be negative results not published in the literature (Figures 6–9).

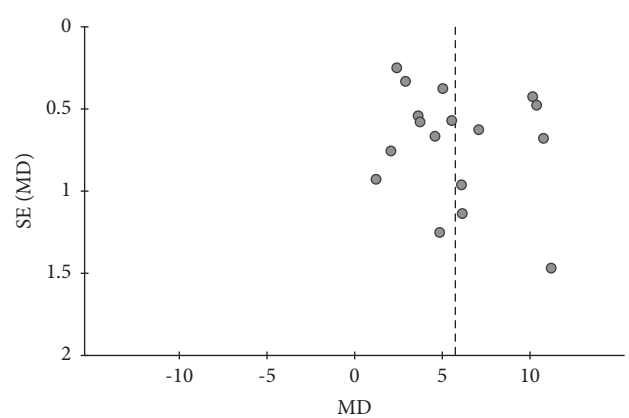


Figure 7: Funnel plot of the effects of CHMs plus active controls on the blood flow velocity in the left vertebral artery.

4. Discussion

4.1. Summary of Findings. In this study, we reviewed and evaluated the available clinical evidence on the efficacy and safety of CHM as monotherapy or adjunctive therapy in the treatment of CGD to promote evidence-based decision-making in clinical practice. As none of the 35 included RCTs [33–67] assessed the efficacy of CHM as monotherapy for CGD, we evaluated its efficacy as adjunctive therapy in combination with other active controls. The included studies were conducted with 6 types of modified CHMs and 4 types of active controls. In the risk-of-bias assessment, more than half of the included studies were considered to be of low quality because of the high risk of bias due to deviations from intended interventions. The results of the efficacy analyses of CHMs plus active controls indicated the following. First, CHMs plus active controls were more effective in treating CGD than active controls alone (the duration of administration ranged from 10 days to 8 weeks). Second, CHMs plus anti-vertigo drugs (flunarizine/betahistine/flunarizine and

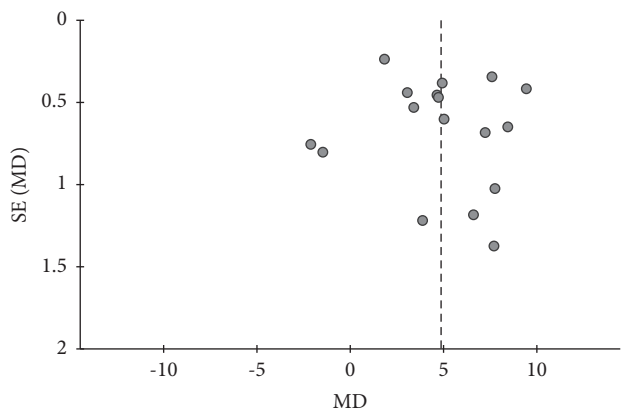


Figure 8: Funnel plot of the effects of CHMs plus active controls on the blood flow velocity in the right vertebral artery.

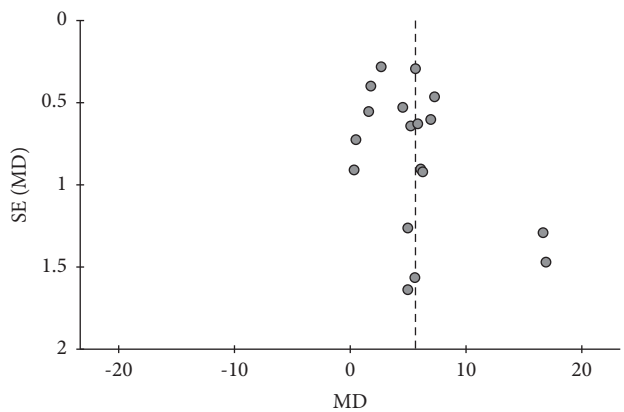


Figure 9: Funnel plot of the effects of CHMs plus active controls on the blood flow velocity in the basilar artery.

betahistine/diphenidol/nimodipine), CHMs plus manual therapy, CHMs plus acupuncture therapy, and CHMs plus manual and acupuncture therapy were all effective in treating CGD. Among all, CHMs plus manual and acupuncture therapy showed the most reliable effect. Third, BBTT, BYT, DXT, GGT, GJT, and YCT were effective for specific patterns in patients with CGD, when administered with active controls. Among the CHM prescriptions, DXT and YCT exhibited the most reliable effects, when combined with active controls. Regarding the safety of CHMs plus active controls in the treatment of CGD, no serious adverse events were reported in any of the included studies.

4.2. Implications for Clinical Practice. In traditional Chinese medicine, CHMs are prescribed to match the specific pattern of the patients' signs and symptoms. It is reasonable to select and prescribe the most appropriate CHM for a specific pattern in each patient with CGD, as opposed to consistently prescribing one CHM to all patients with CGD, even if it is the most evidence-based prescription for CGD. Thus, although DXT and YCT had the highest level of clinical evidence for the treatment effect on CGD in this review, it may be more effective to use other CHMs for specific patterns in some patients with CGD. In traditional Chinese medicine, wind, fire, phlegm, blood stasis, and deficiency are considered the main pathogenetic factors for CGD [25]. DXT is usually prescribed for CGD syndromes of spleen deficiency and dampness, qi deficiency and blood stasis, or hyperactivity of liver yang. DXT has the effect of removing a pathogenic mass as the original prescription, and it can be prescribed for both deficiency and excess syndromes by modification of the original prescription. CHMs can be modified for better efficacy and fewer side effects [68]. In cases of combined excess and deficiency syndromes, such as spleen deficiency and dampness type or qi deficiency and blood stasis type, DXT was modified by the addition of herbs that have effects on invigorating the qi and spleen (*Codonopsis pilosulae* Radix and *Atractylodis* Rhizoma Alba), regulating qi-flowing (Citri Reticulatae Pericarpium), enriching the blood (*Angelicae* Gigantis Radix), and soothing the nerves (Fossilia Ossis Mastodi), but with subtraction of other herbs from the original prescription, which have effects on suppressing hyperactive liver for calming endogenous wind (*Uncariae* Ramulus Cum Uncis and Scorpio) and promoting blood circulation while removing blood stasis (*Salviae miltiorrhizae* Radix) [43, 47]. Conversely, in cases of excess syndrome only, such as hyperactivity of liver yang type, DXT was modified by adding *Puerariae* Radix, which has the effect of dispelling wind-heat [57, 66]. For the combination of DXT and other treatments, quantitative clinical evidence has been reported for the use of DXT with manual therapy [47, 57, 66]. Both YCT and BYT are usually prescribed for CGD syndromes of qi and blood deficiency, while YCT is also used for the sputum silting up type. The clinical evidence for YCT is better than that for BYT because the latter showed low precision for outcomes. For the combination of YCT and other treatments, the majority of quantitative clinical evidence was reported for the use of YCT with acupuncture therapy [36, 38, 45, 51, 54, 59, 62]. BBTT, which has the effect of dispelling pathogenic wind and eliminating phlegm, is usually prescribed for CGD syndromes of wind-phlegm or phlegm stasis [37, 39, 56]. GGT is usually prescribed for CGD syndromes of wind with disharmony between ying and wei [52]. Both BBTT and GGT were used with various active controls and showed reliable treatment effects. GJT was used for the collateral stasis type with betahistine [40]. Through this review, we gain a clue about the relationship between specific patterns of CGD and CHM prescriptions; however, it remains unknown which CHM prescription is most effective for specific patterns of CGD because all included studies used only one CHM prescription with one specific pattern of CGD. Furthermore, studies are needed to confirm which CHM prescription is most effective for specific patterns of CGD.

4.3. Implications for Research. In this review, we identified fibrinogen, endothelin, TC, and CGRP as haematological parameters used in clinical studies on CGD. Endothelin and CGRP were used as indicators to determine the efficacy of

CHMs plus anti-vertigo drugs and CHMs plus manual therapy. Fibrinogen and TC were used to determine the efficacy of CHMs plus acupuncture therapy. Endothelin is an endogenous vasoconstrictor that reduces the perfusion of brain tissues by constricting the blood vessels in the brain [69, 70]. CGRP is a vasodilator, mainly distributed in the central nervous system [71]. In a previous study, endothelin and CGRP were reported as important factors affecting the development of CGD with vertebrobasilar arteriospasm [72]. Fibrinogen also promotes the formation of atherosclerotic plaques [73], and TC accelerates atherosclerosis and causes lipid metabolism disorders [74]. In summary, control of endothelin and CGRP levels improves the prognosis of patients with CGD, and evaluation of fibrinogen and TC levels helps predict CGD progression. Therefore, it is recommended to use them as outcomes when conducting further clinical trials of CGD.

This research is valuable as the first systematic review to comprehensively evaluate the efficacy and safety of CHMs in treating CGD, to guide clinicians in selecting and prescribing suitable CHMs for specific patterns of CGD based on evidence-based decision-making. Furthermore, it provides knowledge of which treatments will be effective in combination with CHMs. This review may contribute to the development of effective strategies for the treatment and management of an increasing number of patients with CGD due to population ageing. Nonetheless, further high-quality evidence from rigorously conducted clinical studies, preferably conducted outside China, is required to support the clinical recommendations regarding the use of CHMs for CGD. In addition, placebo-controlled RCTs are needed to evaluate the efficacy of CHMs as monotherapy for CGD. Furthermore, experimental studies of the mechanism of action and the dose-response relationship of CHMs are necessary to determine the optimal dose.

5. Limitations

This review has some limitations. First, some of the major Chinese databases, such as Wanfang and VIP, were not included in the search process. Additionally, grey literature was not considered. Thus, there is a possibility that relevant studies were omitted. Second, the quality of the included RCTs was generally poor, in particular, because of the high risk of bias due to deviations from intended interventions. Third, most meta-analyses showed high heterogeneity among studies. Fourth, potential publication bias could not be ruled out because the assessment of publication bias was not conducted in the meta-analyses in which the number of included studies was less than 10, and all RCTs were conducted in China and published in Chinese. Fifth, there is the possibility of attrition bias because few studies presented dropout or withdrawal statistics. Sixth, it is unknown whether the treatment effect of CHMs plus active controls was maintained after completion of the intervention because most studies did not perform follow-up assessments. Finally, the safety of CHMs in patients with CGD remains unknown because few studies clearly reported that there were no adverse events.

6. Conclusions

Current evidence suggests that CHMs may have the potential to enhance the treatment effect on CGD when combined with other treatments without serious adverse events. As the overall quality of the studies included in this review was generally low, additional high-quality evidence is needed to draw definitive conclusions.

Abbreviations

BBTT: Banxia Baizhu Tianma Tang
BYT: Buzhong Yiqi Tang
CENTRAL: Cochrane central register of controlled trials
CGD: Cervicogenic dizziness
CHM: Chinese herbal medicine
CGRP: Calcitonin gene-related peptide
CI: Confidence interval
DXT: Dingxuan Tang
EMBASE: Excerpta medica database
GGT: Gegen Tang
GJT: Gegen Jieji Tang
MD: Mean difference
MEDLINE: Medical literature analysis and retrieval system online
RCT: Randomised controlled trial
RR: Risk ratio
SA: Sensitivity analysis
SMD: Standardised mean difference
TC: Total cholesterol
YCT: Yiqi Congming Tang.

Data Availability

All data generated or analysed during this study are included in this article (and its supplementary information files).

Disclosure

The funding bodies had no role in the design of the study and collection, analysis, and interpretation of data and in writing the manuscript.

Conflicts of Interest

The authors declare that they have no conflicts of interest.

Authors' Contributions

HO was responsible for the conceptualisation of the study, funding acquisition, methodology, drafting the manuscript, and critical revision of the manuscript for important intellectual content. EL was responsible for funding acquisition, study supervision, and critical revision of the manuscript for important intellectual content. WSC was responsible for funding acquisition and critical revision of the manuscript for important intellectual content. SS was responsible for the methodology and critical revision of the manuscript for important intellectual content. All authors read and approved the final manuscript.

Acknowledgments

HO was supported by a scholarship from Kyung Hee University. SS and EL were supported by a grant from the National Research Foundation of Korea funded by the Korean Government (grant number: 2020R1F1A1068808). EL and WSC were supported by a grant from the Korea Health Technology R&D Project through the Korea Health Industry Development Institute, funded by the Ministry of Health and Welfare, Republic of Korea (grant number: HI20C1405).

Supplementary Materials

Supplementary materials are given in the .docx file format. *Appendix A*. Search strategies used in English databases. Description of data: search strategies used in three English databases (MEDLINE, EMBASE, and CENTRAL). (*Supplementary Materials*)

References

[1] S. A. Reid and D. A. Rivett, "Manual therapy treatment of cervicogenic dizziness: a systematic review," *Manual Therapy*, vol. 10, no. 1, pp. 4–13, 2005.

[2] T. C. Hain, "Cervicogenic causes of vertigo," *Current Opinion in Neurology*, vol. 28, no. 1, pp. 69–73, 2015.

[3] K. Yaseen, P. Hendrick, A. Ismail, M. Felemban, and M. A. Alshehri, "The effectiveness of manual therapy in treating cervicogenic dizziness: a systematic review," *Journal of Physical Therapy Science*, vol. 30, no. 1, pp. 96–102, 2018.

[4] A. Thompson-Harvey and T. C. Hain, "Symptoms in cervical vertigo," *Laryngoscope Investigative Otolaryngology*, vol. 4, no. 1, pp. 109–115, 2019.

[5] F. N. Ardç, B. Topuz, and C. O. Kara, "Impact of multiple etiology on dizziness handicap," *Otology & Neurotology*, vol. 27, no. 5, pp. 676–680, 2006.

[6] M. Lüscher, S. Theilgaard, and B. Edholm, "Prevalence and characteristics of diagnostic groups amongst 1034 patients seen in ENT practices for dizziness," *Journal of Laryngology and Otology*, vol. 128, no. 2, pp. 128–133, 2014.

[7] S. A. Reid, R. Callister, S. J. Snodgrass, M. G. Katekar, and D. A. Rivett, "Manual therapy for cervicogenic dizziness: long-term outcomes of a randomised trial," *Manual Therapy*, vol. 20, no. 1, pp. 148–156, 2015.

[8] T. Kim, K. T. Kim, and H. Ko, "Clinical analysis on the positional vertigo patients treated in an oriental medical center," *Korean Journal of Internal Medicine*, vol. 32, pp. 371–386, 2011.

[9] J. Y. Kim, W. H. Kim, J. S. Lee, H. M. Oh, D. W. Kim, and D. J. Choi, "The diagnosis and treatment of the cervical vertigo," *Korean Journal of Otorhinolaryngology-Head and Neck Surgery*, vol. 58, 2015.

[10] B. Peng and Y. Li, "Pathogenesis, diagnosis, and treatment of cervical vertigo," *Pain Physician*, vol. 18, no. 4, pp. E583–E595, 2015.

[11] A. Yenigun, M. E. Ustun, S. Tugrul, R. Dogan, and O. Ozturan, "Classification of vertebral artery loop formation and association with cervicogenic dizziness," *Journal of Laryngology and Otology*, vol. 130, no. 12, pp. 1115–1119, 2016.

[12] J. M. Furman and S. P. Cass, *Balance Disorders: A Case-Study Approach*, F A Davis, Philadelphia, PA, USA, 1996.

[13] V. Grgić, "Cervicogenic proprioceptive vertigo: etiopathogenesis, clinical manifestations, diagnosis and therapy with special emphasis on manual therapy," *Lijecnicki Vjesnik*, vol. 128, pp. 288–295, 2006.

[14] M. Magnusson and E.-M. Malmström, "The conundrum of cervicogenic dizziness," *Handbook of Clinical Neurology*, vol. 137, pp. 365–369, 2016.

[15] K. Devaraja, "Approach to cervicogenic dizziness: a comprehensive review of its aetiopathology and management," *European Archives of Oto-Rhino-Laryngology*, vol. 275, no. 10, pp. 2421–2433, 2018.

[16] D. M. Wrisley, P. J. Sparto, S. L. Whitney, and J. M. Furman, "Cervicogenic dizziness: a review of diagnosis and treatment," *Journal of Orthopaedic and Sports Physical Therapy*, vol. 30, no. 12, pp. 755–766, 2000.

[17] M. K. Knapstad, S. H. G. Nordahl, and F. K. Goplen, "Clinical characteristics in patients with cervicogenic dizziness: a systematic review," *Health Science Reports*, vol. 2, no. 9, p. e134, 2019.

[18] M. Karlberg, M. Magnusson, M. Eva-Maj, M. Agneta, and U. Moritz, "Postural and symptomatic improvement after physiotherapy in patients with dizziness of suspected cervical origin," *Archives of Physical Medicine and Rehabilitation*, vol. 77, no. 9, pp. 874–882, 1996.

[19] S. A. Reid, D. A. Rivett, M. G. Katekar, and R. Callister, "Sustained natural apophyseal glides (SNAGs) are an effective treatment for cervicogenic dizziness," *Manual Therapy*, vol. 13, no. 4, pp. 357–366, 2008.

[20] R. P. Lystad, G. Bell, M. Bonnevie-Svendsen, and C. V. Carter, "Manual therapy with and without vestibular rehabilitation for cervicogenic dizziness: a systematic review," *Chiropractic and Manual Therapies*, vol. 19, no. 1, p. 21, 2011.

[21] I. M. Moustafa, A. A. Diab, and D. E. Harrison, "The effect of normalizing the sagittal cervical configuration on dizziness, neck pain, and cervicocephalic kinesthetic sensibility: a 1-year randomized controlled study," *European Journal of Physical and Rehabilitation Medicine*, vol. 53, no. 1, pp. 57–71, 2017.

[22] S.-H. Shin, K.-J. Min, E.-B. Kim, W.-B. Ha, and Y.-S. Ko, "Chuna manual therapy alone for cervicogenic dizziness: a systematic review," *Journal of Korean Medicine Rehabilitation*, vol. 29, no. 1, pp. 1–6, 2019.

[23] Y. Kim and S.-H. Cho, "Pharmacopuncture for cervicogenic dizziness," *Journal of Pharmacopuncture*, vol. 21, no. 4, pp. 241–248, 2018.

[24] H. Heikkilä, M. Johansson, and B.-I. Wenngren, "Effects of acupuncture, cervical manipulation and NSAID therapy on dizziness and impaired head repositioning of suspected cervical origin: a pilot study," *Manual Therapy*, vol. 5, no. 3, pp. 151–157, 2000.

[25] Z. Hou, S. Xu, Q. Li et al., "The efficacy of acupuncture for the treatment of cervical vertigo: a systematic review and meta-analysis," *Evidence-Based Complementary and Alternative Medicine*, vol. 2017, Article ID 7597363, 13 pages, 2017.

[26] S. Takahashi, "Importance of cervicogenic general dizziness," *Journal of Rural Medicine*, vol. 13, no. 1, pp. 48–56, 2018.

[27] H. Oh, S. Shin, and E. Lee, "Herbal medicine for cervicogenic dizziness," *Medicine*, vol. 99, no. 51, Article ID e23852, 2020.

[28] D. Moher, A. Liberati, J. Tetzlaff, and D. G. Altman, "PRISMA group: preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement," *PLoS Medicine*, vol. 6, no. 7, Article ID e1000097, 2009.

[29] H. Oh, S. Shin, E. Lee, and W. S. Chung, "Herbal medicine for cervicogenic dizziness: a systematic review and meta-

analysis," 2021, https://www.researchsquare.com/article/rs-364098/v1.

[30] J. A. C. Sterne, J. Savović, M. J. Page et al., "RoB 2: a revised tool for assessing risk of bias in randomised trials," *BMJ*, vol. 366, Article ID l4898, 2019.

[31] H. Balshem, M. Helfand, H. J. Schünemann et al., "GRADE guidelines: 3. Rating the quality of evidence," *Journal of Clinical Epidemiology*, vol. 64, no. 4, pp. 401–406, 2011.

[32] M. Borenstein, L. V. Hedges, J. P. T. Higgins, and H. R. Rothstein, "A basic introduction to fixed-effect and random-effects models for meta-analysis," *Research Synthesis Methods*, vol. 1, no. 2, pp. 97–111, 2010.

[33] R. Bai, "Clinical observation on the treatment of cervical vertigo by acupuncture combined with Buzhong Yiqi decoction," *Chinese Journal of Ethnomedicine and Ethnopharmacy*, vol. 20, pp. 113–116, 2020.

[34] J. Chen, "Efficacy of Danqi Gegen decoction combined with flunarizine hydrochloride in the treatment of cervical vertigo patients with qi deficiency and blood stasis type," *Journal of Chengde Medical University*, vol. 6, pp. 494–496, 2021.

[35] B. Cheng, S. He, M. Wang, and Y. He, "Effect of Yiqi Dingxuan decoction on NPY and IL-1β in patients with cervical vertigo treated with flunarizine hydrochloride capsule," *Chinese Archives of Traditional Chinese Medicine*, vol. 10, pp. 101–103, 2021.

[36] J. Dai, "Acupuncture and moxibustion combined with modified Yiqi Congming decoction for treatment of qi and blood deficiency type cervical clinical observation of vertigo," *Biped Health*, vol. 2, pp. 184–186, 2018.

[37] E. Gao, Y. Chen, Z. Chi, and M. Wang, "The clinical effect of western medicine combined with Bonxia Baizhu Tianma decoction in the treatment of cervical vertigo," *Chinese Journal of Ethnomedicine and Ethnopharmacy*, vol. 27, pp. 98-99, 2018.

[38] W. Gu and J. Min, "Clinical study on effect of Yiqi Wenzhong acupuncture and moxibustion treatment combined with Yuqicongming decoction in treatment of qi and blood deficiency type cervical vertigo," *Acta Chinese Medicine*, vol. 33, pp. 1359–1363, 2018.

[39] C. Gu, "Evaluation of clinical efficacy of western medicine combined with Banxia Baizhu Tianma decoction on patients with cervical vertigo," *Heilongjiang Journal of Traditional Chinese Medicine*, vol. 6, pp. 25-26, 2019.

[40] X. Hu, L. Li, J. Li, and J. Wang, "Clinical effect of Gegen Jieji capsule in treating cervical vertigo of collateral stasis type," *Clinical Research in Practice*, vol. 20, pp. 92-93, 2019.

[41] T. Huagn, X. Li, and W. Huang, "Observation on the curative effect of modified gegen decoction combined with acupuncture on cervical vertigo," *Journal of Baotou Medical College*, vol. 6, pp. 87–89, 2021.

[42] X. Huang, Z. Hua, Z. Feng, and K. Liao, "Clinical observation on the treatment of cervical vertigo with the addition and subtraction of Banxia Baizhu Tianma decoction and Longshi Zhenggu massage," *Chinese and Foreign Medical Research*, vol. 2, pp. 1–3, 2021.

[43] C. Ji and L. Cheng, "Clinical observation on Dingxuan decoction in treating 30 cases of cervical vertigo," *Human Journal of Traditional Chineses Medicine*, vol. 32, pp. 44-45, 2016.

[44] J. Ju and C. Wang, "Clinical effect of Guizhi Gegen decoction combined with acupuncture in treatment of cervical vertigo in the aged and its effect on prognosis," *Chinese Archives of Traditional Chinese Medicine*, vol. 11, pp. 154–158, 2020.

[45] A. Li, S. Liu, and H. Liu, "The efficacy of the Yiqi Congming decoction plus acupuncture on the Qixue Kuixu type cervical vertigo," *Clinical Journal of Chinese Medicine*, vol. 5, pp. 113–115, 2021.

[46] B. Li, L. Chen, and D. Wang, "Effect of electroacupuncture combined with guizhi gegen decoction on cervical vertigo and its influence on TCD of vertebrobasilar artery, blood rheology indexes, and quality of life," *Evidence-Based Complementary and Alternative Medicine*, vol. 2021, Article ID 2676485, 7 pages, 2021.

[47] S. Liu and X. Yuan, "A clinical study on cervical vertigo by acupoint massage combined with Yiqi Dingxuan decoction," *Guiding Journal of Traditional Chinese Medicine and Pharmacology*, vol. 25, pp. 111–114, 2019.

[48] Y. Lyu and W. Li, "Clinical study on treatment of cervical vertigo with Buzhong Yiqi tang combined with acupuncture," *Acta Chinese Medicine*, vol. 32, pp. 1515–1518, 2017.

[49] M. Pan, J. Zhang, B. Rong, and J. Li, "Clinical study on treatment of patients with cervical vertigo with Banxia Baizhu Tianma decoction combined with acupoint manipulation massage," *Journal of Basic Chinese Medicine*, vol. 25, pp. 1285–1288, 2019.

[50] X. Qin, J. Wang, S. Yang, and A. Lu, "Effective estimation research on cervical vertigo patients with qi deficiency and sputum silting up which were treated by Yiqi Congming decoction of Yan's," *Journal of Sichuan Traditional Chinese Medicine*, vol. 30, pp. 73–75, 2012.

[51] K. Qiu and Y. Ren, "Effect of modified Yiqi Congming decoction combined with acupuncture on qi and blood deficiency type of cervical vertigo," *Clinical Research in Practice*, vol. 29, pp. 130-131, 2018.

[52] G. Shang and L. Ren, "Clinical observation of Guizhi Gegen decoction on cervical dizziness," *Cardiovascular Disease Journal of Integrated Traditional Chinese and Western Medicine*, vol. 4, pp. 179-180, 2016.

[53] Y. Shang, S. Hao, and A. Chen, "Clinical study of modified gegen decoction combined with nimodipine in the treatment of cervical vertigo," *Journal of Practical Traditional Chinese Medicine*, vol. 3, pp. 398-399, 2021.

[54] A. Shen, "Clinical study of modified gegen decoction combined with nimodipine in the treatment of cervical vertigo," *Inner Mongolia Journal of Traditional Chinese Medicine*, vol. 12, pp. 120-121, 2020.

[55] D. Shi, "Rongnao Dingxuan decoction combined with betahistine in the treatment of 37 cases of cervical vertigo," *Chinese Journal of Traditional Medical Science and Technology*, vol. 5, pp. 825-826, 2020.

[56] Y. Tan and Z. Peng, "Treatment of cervical vertigo with Banxia Baizhu Tianma decoction combined with western medicine," *Chinese Journal of Modern Drug Application*, vol. 13, pp. 159-160, 2019.

[57] J. Wang and B. Cao, "Clinical study of integration therapy of Tuina and Dingxuan decoction on cervical vertigo," *Liaoning Journal of Traditional Chinese Medicine*, vol. 37, pp. 294–296, 2010.

[58] Y. Wang, "Clinical efficacy analysis of Banxia Baizhu Tianma decoction in the treatment of cervical vertigo," *Guide of China Medicine*, vol. 5, p. 178, 2020.

[59] Z. Wang, "Clinical observation on treatment of cervical vertigo with modified Yiqi Congming decoction and acupuncture," *Guangming Journal of Chinese Medicine*, vol. 9, pp. 1452–1454, 2021.

[60] Q. Wang, C. Meng, and Z. Chen, "Clinical observation of Banxia Baizhu Tianma decoction combined with acupuncture

and moxibustion in the treatment of cervical vertigo of phlegm turbidity type," *China Practical Medicine*, vol. 18, pp. 167–169, 2021.

[61] L. Xu and R. Wu, "Clinical study of Guizhi Gegen decoction combined with exercise therapy on cervical vertigo," *Research of Integrated Traditional Chinese and Western Medicine*, vol. 2, pp. 89–91, 2021.

[62] X. Yang, "The clinical observation of 73 cases of vertigo with the combination of acupuncture and Yiqi and smart decoction," *Chinese Journal of Ethnomedicine and Ethnopharmacy*, vol. 27, pp. 96–98, 2018.

[63] X. Yang, C. Zhu, and W. Lian, "Clinical observation of Dingxuan decoction on the treatment of patients with cervical vertigo," *Inner Mongolia Journal of Traditional Chinese Medicine*, vol. 10, pp. 7–10, 2021.

[64] G. Yao, R. Chen, Q. Li, H. Deng, and G. Huang, "Therapeutic analysis of small needle knife combined with Banxia Baizhu Tianma decoction in the treatment of cervical vertigo," *Heilongjiang Journal of Traditional Chinese Medicine*, vol. 6, pp. 127-128, 2018.

[65] Y. Zhang and X. Wei, "Clinical effect of Banxia Baizhu Tianma decoction combined with acupuncture and massage in the treatment of cervical vertigo," *Clinical Research Practice*, vol. 23, pp. 149–151, 2020.

[66] K. Zhu, "60 Cases of cervical vertigo treated by Shujing Dingxuan decoction combined with cervical traction and massage," *Traditional Chinese Medical Research*, vol. 32, pp. 21–23, 2019.

[67] J. Zhu, "Clinical efficacy of modified *Puerariae* decoction combined with acupuncture and moxibustion on patients with cervical vertigo," *China Modern Doctor*, vol. 14, pp. 151–154, 2021.

[68] F. F. B. Iris and W. G. Sissi, *Herbal Medicine: Biomolecular and Clinical Aspects*, CRC Press, Boca Raton, FI, USA, 2nd edition, 2011.

[69] F. Liang, D. Wei, Y. Wang, K. Huang, and Q. Huo, "Research on the effect of Jingfutang on the level of plasma ET-1 and CGRP in cervical vertigo patients," *Modern Journal of Integrated Traditional Chinese and Western Medicine*, vol. 22, pp. 343–345, 2013.

[70] A. Kowalczyk, P. Kleniewska, M. Kolodziejczyk, B. Skibska, and A. Goraca, "The role of endothelin-1 and endothelin receptor antagonists in inflammatory response and sepsis," *Archivum Immunologiae et Therapiae Experimentalis*, vol. 63, no. 1, pp. 41–52, 2015.

[71] S. Liu and L. Su, "Effect of Xuanyunning on plasma ET and CGRP in patients with cervical vertigo," *Chinese General Practice*, vol. 13, pp. 199-200, 2010.

[72] J. Wei, J. Xu, and S. Zhang, "Relationship among plasma endothelin, calcitonin gene-related peptide and blood flow rate of bilateral vertebral arteries in patients with cervical vertigo," *Journal of Nan Jing Medical University*, vol. 22, no. 3, pp. 168–171, 2008.

[73] J. Levenson, P. Giral, M. Razavian, J. Gariepy, and A. Simon, "Fibrinogen and silent atherosclerosis in subjects with cardiovascular risk factors," *Arteriosclerosis, Thrombosis, and Vascular Biology*, vol. 15, no. 9, pp. 1263–1268, 1995.

[74] H. H. Wang, G. Garruti, M. Liu, P. Portincasa, and D. Q.-H. Wang, "Cholesterol and lipoprotein metabolism and atherosclerosis: recent advances in reverse cholesterol transport," *Annals of Hepatology*, vol. 16, pp. S27–S42, 2017.

Hindawi
Evidence-Based Complementary and Alternative Medicine
Volume 2022, Article ID 8334397, 12 pages
https://doi.org/10.1155/2022/8334397

Review Article

Dissemination of Acupuncture-Moxibustion Clinical Practice Guidelines among Clinical Practitioners: A Systematic Review of Quality Assessment Studies

Ying Wang,[1] **Qin Wang**,[2] **Yalan Peng**,[3] **Yonggang Zhang**,[4,5] **and Nian Li**[1]

[1]*Department of Medical Administration, West China Hospital, Sichuan University, Chengdu 610041, China*
[2]*Department of Evidence-Based Medicine and Clinical Epidemiology, West China Clinical School of Medicine, Sichuan University, Chengdu 610041, China*
[3]*Hospital Infection Management Department, West China Hospital, Sichuan University, Chengdu 610041, China*
[4]*Department of Periodical Press, West China Hospital, Sichuan University, Chengdu 610041, China*
[5]*Chinese Evidence-Based Medicine Center, West China Hospital, Sichuan University, Chengdu 610041, China*

Correspondence should be addressed to Nian Li; linian@wchscu.cn

Received 28 January 2022; Accepted 23 March 2022; Published 7 April 2022

Academic Editor: Xing Liao

Acupuncture clinical practice guidelines are authoritative medical recommendations developed by evaluating and integrating acupuncture-related evidence. However, their synthesis and dissemination are not integrated, and clinical practitioners require more credible effective evidence. The study aim was to systematically review problems disseminating acupuncture clinical practice guidelines to clinical practitioners, to facilitate evidence dissemination. This systematic review included searches of PubMed, EBSCO, Web of Science, and four major Chinese electronic databases (CNKI, VIP, Wanfang Database, and SinoMed) from inception to October 26, 2021. Two independent reviewers screened the literature, extracted information, and evaluated the quality of included studies. A systematic review was subsequently performed. Eleven studies were reviewed: nine (81.8%) cross-sectional surveys and two (18.2%) systematic reviews. The evaluated clinical practice guidelines differed across studies; seven studies (63.6%) evaluated guidelines for a specific disease, one (9.1%) evaluated guidelines for acupuncture therapies (e.g., moxibustion and fire acupuncture), one (9.1%) evaluated US acupuncture guidelines and recommendations, and two (18.2%) did not describe the guideline content. The included studies used different evaluation indicators. Guideline dissemination problems included lack of guideline standardization, unclear target population, mismatch between guidelines and application environment, lack of reliable health economics evaluation, poor quality content of the recommendations, lack of linkage between recommendations and evidence, and disassociation of recommendations from clinical practice et al. The development and publishing of credible acupuncture clinical practice guidelines is urgently needed to improve the usability of guidelines and standardize and disseminate tools for analysing information to clinical practitioners and to help the domestic and international acupuncture community to apply evidence to practice. Recommendations for promoting the dissemination of acupuncture clinical practice guidelines are to define clinical events suitable for the target population, to develop recommendations relevant to clinical practice, to improve the evidence evaluation index system, and to further standardize the method and process of formulating guidelines.

1. Introduction

Acupuncture-moxibustion is a method of preventing and treating various diseases [1–4]. Numerous clinical studies have provided good evidence that acupuncture-moxibustion has effects on respiratory [5], gastrointestinal [6], neurological diseases [7, 8], and pain [9]. With the development of Chinese medicine, acupuncture-moxibustion is now widely used in more than 180 countries [10]. The application of acupuncture-moxibustion is no longer determined solely by the personal experience of the physician but is supported by scientific evidence. For example, the Guideline for Clinical Practice of

Acupuncture-Moxibustion (group standards) [10], developed and published by the Chinese Acupuncture and Moxibustion Society, comprises authoritative medical recommendations developed by systematically evaluating and integrating evidence related to acupuncture-moxibustion, considering the balance of pros and cons, then making the most appropriate recommendations.

Clinical practitioners need effective ways to obtain more credible evidence to ensure that patients receive effective diagnosis, treatment, and follow-up. These measures should be decided by a consensus between practitioners and patients and should be tailored to each patient's specific needs. However, links in the evidence chain, which includes production, synthesis, dissemination, and implementation, are not currently integrated [11]. There remains a large gap between the production/synthesis of evidence and its dissemination and use among clinical practitioners [12] as a basis for clinical decision-making or policy development. This poses a key challenge to the clinical efficacy of acupuncture-moxibustion. Systematic evaluation is needed to consider the quality of evidence, the pros and cons of different interventions, and patients' preferences and costs. This would help to produce clinical practice guidelines that provide optimal recommendations and disseminate evidence to clinical practitioners [13].

Studies on problems with the dissemination of acupuncture-moxibustion clinical practice guidelines to clinical practitioners have increased; however, such studies use inconsistent methods, tools, participants, and outcomes [13]. This systematic review re-evaluated the literature on relevant assessment tools and research methods (e.g., AGREE II, questionnaires, and Delphi method) to assess the problems with clinical guideline dissemination to clinical practitioners. We summarized and analyzed the quality of clinical practice guidelines and reporting standards, clinical practitioners' attitudes and views toward guidelines, problems encountered during the use of the guidelines, and factors that affect the use of acupuncture-moxibustion guidelines in clinical practice. We present suggestions for future development of acupuncture-moxibustion clinical practice guidelines to address current problems and obstacles in guideline dissemination and clinical practice. We hope that this will help to improve the quality of evidence, disseminate evidence, help clinical practitioners to make appropriate decisions about clinical problems, improve the clinical efficacy of acupuncture-moxibustion, reduce medical costs, and promote the rapid development of acupuncture-moxibustion.

2. Materials and Methods

2.1. Registration. The current systematic review is part results of a systematic review, and the systematic review registration [CRD42021279104] was completed on October 17, 2021.

2.2. Search Strategy. This systematic review included searches of Chinese and English articles in PubMed, EBSCO, Web of Science, and four major Chinese electronic databases (CNKI, VIP, Wanfang Data, and SinoMed) from inception to October 26, 2021 (Appendix 1). Additional search of unpublished literature (including conference papers, master's and doctoral theses, and gray literature) was also conducted.

2.3. Inclusion and Exclusion Criteria

2.3.1. Inclusion Criteria. Inclusion criteria were as follows: studies using various methods/tools for quality assessment of dissemination and application of clinical practice guidelines for acupuncture-moxibustion in clinical practice.

2.3.2. Exclusion Criteria. Exclusion criteria were as follows: literature in languages other than English and Chinese; duplicate publications; publications for which the data could not be obtained, such as conference abstracts; clinical practice guidelines; literature related to the interpretation of guidelines, consensus, standards, procedures, and norms; studies on acupuncture-moxibustion methodology in addition to acupuncture-moxibustion guidelines; and studies on acupuncture-moxibustion service processes.

2.4. Literature Screening. Two researchers independently screened the literature and cross-checked the data. In the event of disagreement, a third researcher was invited to adjudicate. The literature screening was carried out by first reading each source's title and abstract. After excluding obviously irrelevant sources, the full text was read to determine the final inclusion. Literature management and duplication removal were performed using NoteExpress 3.4.0.8878 software.

2.5. Data Extraction. The literature was independently extracted and cross-checked by 2 researchers. Disagreements were resolved by discussion, and a consensus was reached through a third researcher. For sources with incomplete information, the authors of the source were contacted if possible. Data were extracted using a pre-developed data extraction form. Before performing the formal extraction, the researchers involved received training and participated in a practice extraction exercise. The extracted data mainly included baseline characteristics: authors, year of publication/update, country or region, study design, study population, study institution, and publication journal. The guideline evaluation examined evaluation subjects, evaluation/methodological tools, evaluators, problems identified, and recommendations made.

2.6. Quality Assessment of Included Literature. Because no specific checklist has been developed to assess the quality of articles evaluating acupuncture-moxibustion guidelines, we referred to the Joanna Briggs Institute (JBI) checklist for evaluating cross-sectional studies [14] to evaluate the quality of included cross-sectional studies. The following evaluation criteria were used: 1. Were the criteria for inclusion of evaluators clearly defined? 2. Were the guidelines and

settings studied described in detail? 3. Was the evaluation of the guidelines performed in a valid and reliable manner? 4. Was the situation measured using objective criteria? 5. Were confounding factors affecting the practice of the guidelines identified? 6. Were strategies in place to address confounding factors? 7. Were the results obtained in a valid and reliable manner? 8. Was appropriate statistical analysis used? For overview studies, we referred to the AMSTAR II (Appraisal of Guidelines for Research and Evaluation II) to evaluate the scope and purpose, participants, rigorous, clarity, applicability, and independence of the included overview studies [15]. The following evaluation criteria were used: the overall assessment results of the comprehensive evaluation included inclusion, exclusion, or requirement for more information. The quality of the literature was separately evaluated by two researchers. In the event of disagreement, a third researcher was consulted to obtain consensus.

2.7. Systematic Review. A systematic review was performed to assess the problems in dissemination of acupuncture-moxibustion clinical practice guidelines among clinical practitioners.

3. Results

3.1. Literature Screening Process and Results. An initial review of 4,044 relevant sources was conducted. After removing duplicates, 3,087 studies were identified. After screening the titles and abstracts, 100 studies were retained. After browsing the full-text articles, we further excluded 89 records. A final total of 11 studies [10, 13, 16–24] were reviewed (Figure 1).

3.2. Basic Characteristics and Quality Evaluation of the Included Studies. The basic characteristics of the included studies are shown in Table 1. Of studies, 11 (100%) [10, 13, 16–24] were from China, and the earliest [20] was published in 2014. Seven (63.6%) [10, 13, 17–20, 23] studies were from the Chinese Academy of Traditional Chinese Medicine and four were from Nanjing University of Traditional Chinese Medicine [21], Tianjin University of Traditional Chinese Medicine [22], Beijing University of Traditional Chinese Medicine [16], and Hubei University of Traditional Chinese Medicine [24]. Six studies (54.5%) [10, 16–18, 20, 23] were from the journal Chinese Acupuncture and Moxibustion, one (9.1%) [22] was a symposium proceeding, one (9.1%) [24] was published in the Chinese Journal of Integrative Medicine, two (18.2%) [19, 22] were master's theses and one [13] was a doctoral dissertation. Nine studies (81.8%) [13, 16, 18–24] were cross-sectional surveys and two (18.2%) [10, 17] were overviews of systematic reviews. The evaluated guidelines were different in each study: seven (63.6%) [13, 16, 19–23] were practice guidelines for a specific disease, one study (9.1%) [19] evaluated clinical practice guidelines for acupuncture therapies such as moxibustion and fire acupuncture, one (9.1%) [24] examined acupuncture guidelines and recommendations published in the United States, and two (18.2%) [13, 17] did not provide a description of the content of the evaluated guidelines. The results of the quality evaluation of the included studies are shown in Table 2 and Table 3. All studies were included in the systematic review.

AMSTAR II: Appraisal of Guidelines for Research and Evaluation II.

3.3. Problems in the Dissemination of Acupuncture Guidelines to Clinical Practitioners. Because of the different evaluation indicators used in the included studies, we evaluated 10 aspects of the clinical guidelines and problems in dissemination to practitioners identified in the included studies: clinical events defined by the guidelines, target population, application setting, health economics evaluation, content of recommended protocols, association of recommended protocols with evidence, association of recommended protocols with clinical practice, acupuncture-related practice norms, promotion methods and efforts, and methods and theories of guideline writing.

Clinical events defined by the guidelines. A total of three studies [10, 17, 19] reported problems defining clinical events in clinical guidelines. All three studies mentioned unclear and inconsistent criteria for the clinical problems/diseases targeted by the guidelines [10, 17, 19], and one mentioned that the process of identifying clinical events in guidelines was unclear [10] and that the guideline diagnostic criteria were not applicable to the clinical setting [19].

Target population of the guideline. Five studies [10, 13, 17, 19, 20] reported problems defining the target population of the guidelines, two studies reported that the target population of the guidelines was unclear and that some guidelines did not differentiate between population subgroups [10, 13], and one study mentioned that the process of identifying the target population of the guidelines was unclear [10]. Regarding clinical practitioners and patients in the target population, two studies mentioned low trust in acupuncture guidelines among clinical practitioners [19, 20]; two mentioned that the guidelines did not take patients' wishes, preferences, and values into account [13, 20]; one study reported a lack of attention to patients' healthy lifestyles and self-care [17]; and one mentioned that the guidelines did not take into consideration doctor-patient interactions or patients' personality traits or allow for individualization [13, 20].

Application environment of the guidelines—three studies [16, 18, 19] indicated that the dissemination of guidelines may be affected by the regions in which they were applied. Two of these studies also mentioned that the focus on guidelines varies by region within a country [16, 18]; one mentioned that it was limited by local legislation and health insurance payment [18], and one mentioned that it may be affected by the way clinical practitioners learn to apply new knowledge, their habits, traditions, and preferences [19].

Health economics evaluation in the guidelines—four publications referred to the lack of guideline health economics evaluation supported by reliable data, such as cost-effectiveness ratios of recommended interventions [13, 21, 22, 24].

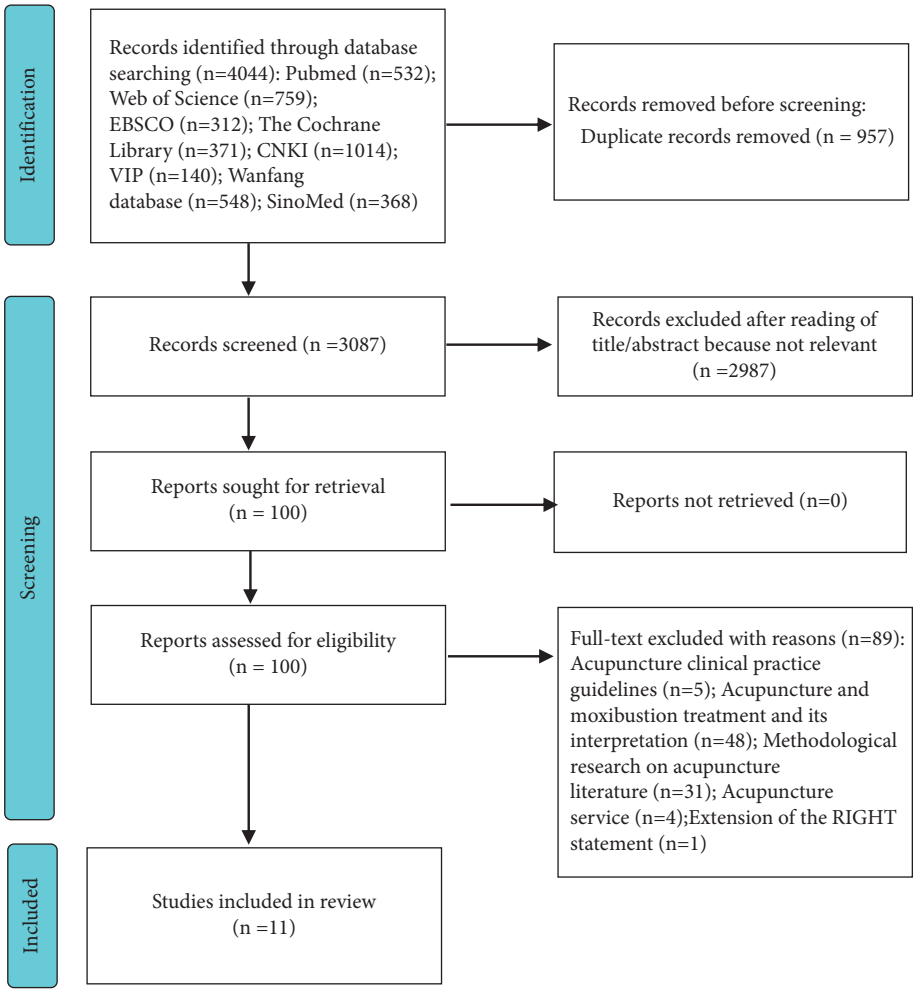


Figure 1: Literature screening process and results.

Table 1: Basic characteristics of the included studies.

Study	Country	Research organization	Publication journal	Study design	Guidance evaluated	Evaluation methods/ evaluation dimensions	Evaluator	Issues*
Hu, Jing [17]	China	Institute of Acupuncture and Moxibustion, China Academy of Chinese Medical Sciences	Chinese Acupuncture and Moxibustion	General narrative	Clinical Practice Guidelines for Evidence-Based Acupuncture: Insomnia	Guideline development: "Define the disease," "Formulate the clinical problem," "Formulate the recommended protocol"	Authors	1, 2, 3, 4, 5, 6, 7
Zhao, Nanqi [10]	China	Institute of Acupuncture and Moxibustion, China Academy of Chinese Medical Sciences	Chinese Acupuncture and Moxibustion	General narrative	35 Evidence-based Acupuncture Clinical Practice Guidelines (Group Standards) published in China 2010–2021	"Purpose and scope," "Rigor of formulation," "Clarity of expression," "Applicability" of the evaluation guide	35 lead drafters of the guide	1, 3, 5, 8, 11, 10, 12. 13, 52

Table 1: Continued.

Study	Country	Research organization	Publication journal	Study design	Guidance evaluated	Evaluation methods/ evaluation dimensions	Evaluator	Issues*
Hu, Jing [18]	China	Institute of Acupuncture and Moxibustion, China Academy of Chinese Medical Sciences	Chinese Acupuncture and Moxibustion	Cross-sectional survey	Clinical Practice Guidelines for Acupuncture: Migraine	Questionnaire: current status of acupuncture application abroad and demand for international standard development, priority of disease types for international standard development, need for international standard translation, key clinical issues to be addressed by international standards, correlation between professional level and demand intention	Top international experts in the field of acupuncture, clinical practitioners, experts in policy-making and acupuncture education, research institutions, experts in the field of acupuncture standards, experts in evidence-based medicine and methodology, patient representatives	14, 15
Guo, Lihua [19]	China	China Academy of Chinese Medical Sciences	Master's thesis	Cross-sectional survey	2019 publication of moxibustion therapy, fire acupuncture, cupping therapy, acupuncture and bloodletting, acupuncture and knife therapy, electroacupuncture, acupuncture point application Evidence-Based Clinical Practice Guidelines for Acupuncture	Questionnaire + n-depth interview: evaluation of guideline quality, barriers to application, and applicability of acupuncture clinical practice guidelines	Guideline developers, evaluators, and relevant researchers	1, 2, 9, 12, 13, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28
Chen, Chao [20]	China	Institute of Acupuncture and Moxibustion, China Academy of Chinese Medical Sciences	Chinese Acupuncture and Moxibustion	Cross-sectional survey	Not specified	Questionnaire: clinical use of acupuncture guidelines, clinical practitioners' perceptions of guidelines, clinical recourse, most needed clinical guidance, how to improve guideline implementability	Clinicians, university teachers, medical students	2, 3, 4, 13, 26, 27, 29, 30, 31, 32, 33

Table 1: Continued.

Study	Country	Research organization	Publication journal	Study design	Guidance evaluated	Evaluation methods/ evaluation dimensions	Evaluator	Issues*
Chen, Chao [13]	China	China Academy of Chinese Medical Sciences	Doctoral dissertation	Systematic evaluation of health economics, cross-sectional surveys	Evidence-Based Clinical Practice Guidelines for Acupuncture: Diabetic Peripheral Neuropathy	Systematic evaluation: health economics evidence Tools for acupuncture: the AGREE II, RIGHT statement, GLIA evaluation of methodological quality, quality of reporting and implementability evaluation questionnaire: use of guidelines and their implementability issues	Author, clinical practitioner of acupuncture	8, 9, 10, 13, 34, 35, 31, 36, 37, 38, 39, 16, 40, 34, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50, 17, 51, 3,
Chen, Hao [21]	China	Nanjing University of Chinese Medicine	Proceedings of the 2014 Annual Meeting of the Clinical Branch of the Chinese Society of Acupuncture and Moxibustion and the 21st National Clinical Symposium on Acupuncture and Moxibustion	Cross-sectional survey	the 2011 publication of Evidence-Based Clinical Practice Guidelines for Acupuncture in Chinese Medicine	AGREE II	Authors	50, 34, 3
Lingling, Zhang [22]	China	Tianjin University of Traditional Chinese Medicine	Master's thesis	Cross-sectional survey	20 clinical practice guidelines (2019) for acupuncture	RIGHT Statement, AGREE-China Tools	Two researchers	3, 52, 34, 26
Guo, Lihua [23]	China	Institute of Acupuncture and Moxibustion, China Academy of Chinese Medical Sciences	Chinese Acupuncture and Moxibustion	Cross-sectional survey	20 evidence-based clinical practice guidelines for acupuncture	AGREE II	Two researchers	26

Table 1: Continued.

Study	Country	Research organization	Publication journal	Study design	Guidance evaluated	Evaluation methods/ evaluation dimensions	Evaluator	Issues*
Yang Xingyue [16]	China	School of Acupuncture-Moxibustion and Tuina, Beijing University of Chinese Medicine	Chinese Acupuncture and Moxibustion	Cross-sectional survey	35 acupuncture guidelines for low back pain	—	Authors	15, 22
Guo, Y [24]	China	College of Acupuncture and Orthopaedics, Hubei University of Chinese Medicine	Chinese Journal of Integrative Medicine	Cross-sectional survey	39 acupuncture guidelines and 80 recommendations published in the USA	AGREE II	Two researchers	4, 3, 52, 34

*Appendix 2. AGREE II: Appraisal of Guidelines for Research and Evaluation II; RIGHT, Reporting Items for practice Guidelines in HealThcare; GLIA, GuideLine Implementability Appraisal.

Content of the recommended programs in the guidelines—nine [10, 13, 16, 17, 19–22, 24] publications identified problems with the content of the recommended protocols in the guidelines; seven of these studies concluded that the guidelines generally did not state outcome indicators or indicators for evaluating the efficacy of interventions to determine the effectiveness of the treatment [10, 13, 17, 20–22, 24], and three studies concluded that the guidelines did not provide an analysis of the pros and cons of interventions [10, 13, 17]. Two studies reported that the acupuncture guidelines stated the strength of recommendations, but the process of reaching conclusions was unclear [13, 19], and four studies concluded that it was not possible to determine the difference in prognostic outcomes between strong and weak recommendations [10, 13, 19, 20]. Three studies reported that the description of the "content of recommendations" was unclear and that the "form of expression of recommendations" was unclear and could be improved [13, 16, 19]. One study concluded that the guideline recommendations did not clearly describe whether acupuncture could be used for both primary and comorbid conditions [13], and three studies concluded that the guidelines rarely considered the safety of acupuncture, including complications and adverse events [10, 22, 24].

Linking recommendations to evidence—four studies identified problems with the association between recommendations and evidence [10, 13, 16, 19]; two studies suggested that the guideline "process for developing recommendations" was unclear and that neither the process nor the rationale for developing recommendations was clear [10, 13]. Two studies suggested that the "association between recommendations and supporting evidence" was not rigorous and that it was unclear how the evidence affected recommendations [9, 11]. One study considered that the guidelines did not describe updates sufficiently, did not present differences between current status and research evidence, and did not explain whether the temporal characteristics of recommendations allowed for revision, while noting that the types of research evidence included were confusing [13]. Two studies considered that the quality of evidence supporting recommendations was poor [13]. Two studies mentioned the poor quality of the evidence for the recommendations [16, 19].

Discrepancies between recommendations and clinical reality—four studies [13, 17, 19, 20] concluded that there were substantial discrepancies between guideline recommendations and clinical practice. For example, three studies considered the evaluated guidelines difficult to apply in practice and unlikely to address practical problems of real clinical concern [17, 19, 20]. One study considered that there was a lack of emphasis on the importance of the timing of acupuncture interventions [17], and one study considered that the recommendations were not in line with routine clinical practice, difficult to practice, or posed an underlying risk [19]. One study considered that the guidelines were not naturally integrated with modern medical examination and treatments [20]. One study considered that the guidelines did not describe the facilitators and hindrances associated with their practical application [13].

Code of practice related to acupuncture—three [17, 20, 24] studies mentioned the lack of guidance on acupuncture techniques and standardized practices in the guidelines, and one study also pointed out that specific treatment recommendations for selecting and matching acupuncture points and identifying diseases and symptoms should be reflected in the recommendations [20].

Modalities and intensity of promotion of the guidelines—five studies [13, 19, 20, 22, 23] reported low accessibility, inadequate promotion, and limited access to clinical practice guidelines for acupuncture, pointing out that

Table 2: Quality assessment of the included studies (cross-sectional study).

Study	Evaluation tools	1. Were the criteria for inclusion of evaluators clearly defined?	2. Were the guidelines and settings studied described in detail?	3. Was the evaluation of the guidelines performed in a valid and reliable manner?	4. Was the situation measured using objective criteria?	5. Were confounding factors affecting the practice of the guidelines identified?	6. Were strategies in place to address confounding factors?	7. Were the results obtained in a valid and reliable manner?	8. Was appropriate statistical analysis used?	Overall assessment
Hu, jing [18]	Evaluation transect study (JBI) inventory (last revised in 2017)	Yes	Yes	Not applicable	Yes	Unclear	Unclear	Yes	Yes	Inclusion
Guo, lihua [19]		Yes	Yes	Not applicable	Yes	Unclear	Unclear	Yes	Yes	Inclusion
Chen, chao [20]		No	No	Yes	Yes	Unclear	Unclear	Yes	Yes	Inclusion
Chen, chao [13]		Yes	Yes	Yes	Yes	Yes	Unclear	Yes	Yes	Inclusion
Chen, hao [21]		Yes	Yes	Yes	Unclear	Unclear	Unclear	Yes	Yes	Inclusion
Lingling, zhang [22]		Yes	Yes	Yes	Yes	Unclear	Unclear	Yes	Yes	Inclusion
Guo, lihua [23]		Yes	Yes	Yes	Yes	Unclear	Unclear	Yes	Yes	Inclusion
Duan, yutin [16]		Yes	Yes	No	No	Unclear	Unclear	Yes	Yes	Inclusion
Guo, Y [24]		Yes	Yes	Yes	Yes	Unclear	Unclear	Yes	Yes	Inclusion

JBI: Joanna Briggs Institute.

Table 3: Quality assessment of the included studies (overview studies).

Study	Evaluation tools	Domain 1 scope and purpose (%)	Domain 2 participants (%)	Domain 3 rigorous (%)	Domain 4 clarity (%)	Domain 5 applicability (%)	Domain 6 independence (%)	Overall assessment	Is it recommended
Hu, Jing [17]	AMSTAR II	72.2	58.3	65.6	80.6	52.1	8.3	3	Yes (used after revision)
Zhao, Nanqi [10]	AMSTAR II	69.4	38.9	26.0	80.6	39.6	8.3	5	Yes (used after revision)

guidelines often did not mention guideline access and related appendices or documents [13].

Methodology and theory for the preparation of the guideline. One study concluded that current guideline development methods were not applicable to acupuncture and that guideline developers lacked an appropriate understanding of the methods and content of acupuncture guideline development [19], such as a lack of in-depth or even erroneous understanding of the GRADE framework [13], problems with the content and presentation of acupuncture guidelines, and lack of clarity of guideline levels [19]. One study concluded that acupuncture clinical practice guidelines do not report members' specialties and that the titles and positions of the individuals who developed the guidelines were not clearly reported, which potentially limits the representation of experts in reviews of acupuncture guidelines. It was also reported that the lack of oversight or audit criteria for some guidelines, lack of information related to sponsorship and funds, lack of documentation and publication of conflicts of interest of guideline development team members, lack of description of publication dates, and failure to provide the limitations of current guidelines and recommendations for future research may all limit guideline dissemination to clinics [13].

4. Discussion

4.1. Summary of Findings. A total of 11 studies were included in this systematic review and evaluation of the quality of evidence for the dissemination of acupuncture clinical practice guidelines to clinical practitioners. The studies reported problems with the Clinical Practice Guidelines for Evidence-Based Acupuncture: Insomnia [17]; 35 Evidence-Based Acupuncture Clinical Practice Guidelines (Group Standards) published in China 2010–2021 [10]; Clinical Practice Guidelines for Acupuncture: Migraine [18]; 2019 publication of moxibustion therapy, fire acupuncture, cupping therapy, acupuncture and bloodletting, acupuncture and knife therapy, electroacupuncture, acupuncture point application Evidence-Based Clinical Practice Guidelines for Acupuncture [19]; Evidence-Based Clinical Practice Guidelines for Acupuncture: Diabetic Peripheral Neuropathy [13]; the 2011 publication of Evidence-Based Clinical Practice Guidelines for Acupuncture in Chinese Medicine [21]; 20 clinical practice guidelines (2019) for acupuncture (five on nervous system diseases; four on musculoskeletal system or connective tissue diseases; two on mental, behavioural, or neurodevelopmental disorders; two on digestive system diseases; two on endocrine, nutritional, or metabolic diseases; two on respiratory diseases; one on genitourinary system diseases; one on skin diseases; and one on ear or mastoid diseases) [22]; 35 acupuncture guidelines for low back pain [16]; and 39 acupuncture guidelines and 80 recommendations published in the USA [24]. We examined other issues regarding guideline dissemination to clinical practitioners; for example, one study described the innovative use of the concept of an evidence ecosystem cycle [11]. The research sources, research institutions, and publications of the included studies were relatively concentrated, and the overlap and credibility of the issues raised by each study were high.

4.2. Differences from Previous Studies. Owing to the inclusion of 5 studies published after 2019, when the 2019 acupuncture group standard "Acupuncture and Moxibustion Clinical Practice Guidelines Formulation and Evaluation Standards" (CAAM-2019 [001]) was issued by the Chinese Society of Acupuncture and Moxibustion [10], the present review supplemented and extended previous findings on the organization, personnel, and process of guideline formulation; the use of evidence quality evaluation; recommendation plan classification; methods of creating expert consensus; guideline formulation and content; and other dimensions of guideline development. A more comprehensive summary of the problems existing in the dissemination of clinical practice guidelines for acupuncture and moxibustion included a lack of standardization in acupuncture clinical practice guidelines in defining clinical events, unclear target population, mismatch between the guidelines and the application environment, lack of reliable health economics evaluation, poor quality content of recommendations, lack of linkage between recommendations and evidence, disassociation of recommendations from clinical practice, lack of acupuncture methodological guidance, limited transmission channels, and insufficient methodological and theoretical application in formulating guidelines. After many years of development, acupuncture is now widely used internationally; however, the technical level and clinical effects obtained by different clinical practitioners vary [25]. This current study showed a more systematic summary of how to improve the credibility, usability of acupuncture clinical practice guidelines, and standard methods for disseminating the guidelines to clinical practitioners. It will help the domestic and international acupuncture community to apply evidence that would facilitate appropriate decision-making about clinical events [3].

4.3. Recommendations for Acupuncture Clinical Practice Guidelines. It is recommended that acupuncture clinical practice guidelines more precisely define clinical events suitable for the target population [26, 27]. Clinical events, diagnostic criteria, treatment methods, and criteria for evaluating clinical effects should be defined. Patient preferences should be integrated, and international guideline standards should be developed. Guidelines should be suitable for practitioners in different regions and at different levels and address differences in the scope of application and key clinical events [28].

It is recommended that acupuncture clinical practice guidelines are relevant to clinical practice [26]. It is important to fully consider the characteristics of acupuncture clinical treatment and the complexity of acupuncture practice, and to not only rely on evidence but to also take into consideration the opinions of acupuncture clinicians and expert consensus. In-depth studies of common clinical acupuncture methods and therapies should be conducted. Guidelines should fit all roles of acupuncture in clinical practice. Guideline recommendation could be classified according to acupuncture methods and should include specific practice guidelines (e.g., for acupoint selection, stimulation methods, and acupuncture duration) [29]. Before a guideline is published, the opinions of clinical practitioners should be solicited to determine the clinical consensus on technical acupuncture skills, such as diagnosis, acupoint selection, use of acupuncture/moxibustion therapy, and other manipulative contents. Alternatively, clinical consistency tests could be conducted to test the development of acupuncture clinical practice guidelines. Clinical practice guidelines should be based on full consideration of the characteristics of the discipline of acupuncture and moxibustion, comprehensive evaluation of modern literature evidence, and integration of ancient literature and the experience of medical practitioners. Recommendations should be developed using appropriate clinical guidance. Attention should be paid to integration of guidelines with the results of modern tests and imaging examinations and to strengthening the study of health economics evaluation in the field of acupuncture and moxibustion.

There is a need to improve the evidence evaluation index system of acupuncture clinical practice guidelines. The selection of efficacy evaluation indicators and targeted data analysis should be combined with clinical needs to ensure the measurability of the recommendations. It is recommended that a detailed guideline update plan be developed and that targeted requirements are introduced into the guideline development process to promote greater clarity in the development process, greater methodological rigor in research, stronger associations, and more scientific evidence in the included studies. The clinical characteristics of the evidence should be based on real-world clinical problems that are of substantial interest or that need to be resolved. High-quality clinical trials appropriate to the practice of acupuncture and moxibustion, as well as multidisciplinary and interdisciplinary collaborative studies, would facilitate the development of guidelines that meet real clinical needs. It is also important to explore the methods of nonclinical trial findings, such as those found in ancient literature and the experiences of famous doctors, in evidence synthesis and other guideline aspects.

Guideline methodology recommendations are to further standardize the method and process of guideline formulation [30]. Close multidisciplinary collaboration, especially between methodologists and clinical experts, is needed. Methodologists should be involved throughout the guideline development process. The guideline development methodology could be enhanced by improving methodological quality control in clinical study design; reporting of members' specialties; clear reporting of titles, positions, and contributions of individuals to guideline development; oversight or audit criteria; information related to sponsorship and use of funds; publications and updates of practice; limitations of the current guidelines; pros and cons of interventions; and recommendations for future research [31]. To strengthen methodological research on guideline development for acupuncture practice, evidence-based acupuncture guidelines need to be reasonably informed by international guideline development methods, combined with a consideration of the unique characteristics of acupuncture clinical practice. The quality and completeness of guideline reporting could be improved by comparing the entries in guideline evaluation tools such as AGREE II and RIGHT to evaluate guidelines [32]. It would be useful to establish an acupuncture clinical practice guideline application-feedback platform to actively track, investigate, and collect clinical users' opinions and suggestions about guidelines. This would facilitate timely identification of problems in acupuncture guidelines and prompt appropriate updates.

5. Limitations

The limitations of this study were that all included studies were from China (no relevant literature was published outside China) and that the research institutions and researchers were limited to the Chinese Academy of Traditional Chinese Medicine and domestic traditional Chinese medicine universities. This may have led to publication bias and results bias. Additionally, all the included studies were reviews or cross-sectional surveys; there was a lack of studies using high-quality experimental designs.

6. Conclusions

There is an urgent need to improve the credibility, usability, and standardization of acupuncture clinical practice guidelines, to standardize and disseminate tools for analysing information to clinical practitioners, and to develop and publish credible guidelines to help the domestic and international acupuncture community to apply evidence. Recommendations for promoting the dissemination of acupuncture clinical practice guidelines are to define clinical events suitable for the target population, to be relevant to clinical reality, to improve the evidence evaluation index system, and to further standardize the method and process of acupuncture clinical practice guideline development.

Future systematic reviews are needed that include new studies.

Disclosure

Ying Wang and Qin Wang are co-first authors.

Conflicts of Interest

The authors declare that there are no conflicts of interest regarding the publication of this paper.

Acknowledgments

The development of this guideline was supported by the National Natural Science Foundation of China (Grant no. 82004213) and the Project of Sichuan Provincial Department of Science and Technology (no. 2021YFH0191).

Supplementary Materials

Appendix 1: search strategy. Table 1: CNKI (1014). Table 2: VIP (140). Table 3: Wanfang (548). Table 4: SinoMed (368). Table 5: PubMed (532). Table 6: Web of Science (759). Table 7: EBSCO (312). Table 8: Cochrane Database (371). Appendix 2: problem description (52 items). (*Supplementary Materials*)

References

[1] W. He, Y. Tong, Y. Zhao, P. Rong, and H. Wang, "Analysis of acupuncture indications based on foreign literature," *Acupuncture Research*, vol. 37, no. 05, pp. 428–430, 2012, [in Chinese].

[2] Q. Wang, N. Li, J. Li et al., "A protocol of a guideline to establish the evidence ecosystem of acupuncture," *Frontiers of Medicine*, vol. 8, Article ID 711197, 2022.

[3] Y. He, J. Li, Y. Li et al., "Strengthening the quality of clinical trials of acupuncture: a guideline protocol," *BMJ Open*, vol. 12, no. 1, Article ID e053312, 2022.

[4] B. Liu, B. Chen, Y. Guo, and L. Tian, "Acupuncture- a national heritage of China to the world: international clinical research advances from the past decade," *Acupuncture and Herbal Medicine*, vol. 1, no. 2, pp. 65–73, 2021.

[5] Y.-M. Chen, X.-L. Xie, P.-Y. Xiao et al., "Acupuncture on treating asthma," *Medicine*, vol. 99, no. 1, Article ID e18457, 2020.

[6] H. Li, T. He, Q. Xu et al., "Acupuncture and regulation of gastrointestinal function," *World Journal of Gastroenterology*, vol. 21, no. 27, pp. 8304–8313, 2015.

[7] L.-Y. Xiao, X.-R. Wang, Y. Ye et al., "Applications of acupuncture therapy in modulating plasticity of central nervous system," *Neuromodulation: Technology at the Neural Interface*, vol. 21, no. 8, pp. 762–776, 2018.

[8] Y. X. Li, X. L. Xiao, D. L. Zhong et al., "Effectiveness and safety of acupuncture for migraine: an overview of systematic reviews," *Pain Research & Management*, vol. 2020, Article ID 3825617, 14 pages, 2020.

[9] A. J. Vickers, E. A. Vertosick, G. Lewith et al., "Acupuncture for chronic pain: update of an individual patient data meta-analysis," *The Journal of Pain*, vol. 19, no. 5, pp. 455–474, 2018.

[10] N. Zhao, J. Yuan, L. Guo, G. F. Dong, X. Wang, and X. D. Wu, "Thinking of the problems in the formulation of domestic acupuncture clinical practice guidelines," *Chinese Acupuncture and Moxibustion*, vol. 41, no. 04, pp. 445–448, 2021, [in Chinese].

[11] Z. Zhu, Y. Hu, Y. Zhou, and W. Xing, "Building a data-based and credible evidence ecosystem: a report on the first global evidence-based summit forum," *Chinese Journal of Evidence-Based Medicine*, vol. 17, no. 12, pp. 1378–1380, 2017, [in Chinese].

[12] Y. Zhou, J. Zhong, L. Li, N. Huang, and X. Pan, "Building an evidence ecosystem to promote the development of evidence-based nursing practice," *Journal of Nurses Training*, vol. 34, no. 03, pp. 193–197, 2019, [in Chinese].

[13] C. Chen, *Research on the Key Factors of Transforming Acupuncture Clinical Evidence into Recommendations*, China Academy of Chinese Medical Sciences, Beijing, China, 2019.

[14] JBI, *Checklist for analytical cross sectional studies*, JBI, Adelaide, Australia, 2021.

[15] B. J. Shea, B. C. Reeves, G. Wells et al., "Amstar 2: a critical appraisal tool for systematic reviews that include randomised or non-randomised studies of healthcare interventions, or both," *BMJ*, vol. 358, Article ID j4008, 2017.

[16] X. Yang, H. Zhao, J. Liu, L. Y. He, and B. Y. Liu, "Application status of acupuncture in low back pain guidelines at home and abroad," *Chinese Acupuncture and Moxibustion*, vol. 39, no. 08, pp. 908–912, 2019, [in Chinese].

[17] J. Hu, J. Yang, and S. Hu, "Based on the "Evidence-based acupuncture clinical practice guidelines: insomnia" to explore the problems and countermeasures of acupuncture clinical research," *Chinese Acupuncture and Moxibustion*, vol. 41, no. 04, pp. 435–438, 2021, [in Chinese].

[18] J. Hu, J. Wang, L. Liu et al., "Acupuncture clinical practice guidelines: migraine" international demand survey results analysis," *Chinese Acupuncture and Moxibustion*, vol. 41, no. 07, pp. 799–804, 2021, [in Chinese].

[19] L. Guo, *Research on the Influencing Factors of the Feasibility of Clinical Practice Guidelines for Acupuncture and Moxibustion*, China Academy of Chinese Medical Sciences, Beijing, China, 2020.

[20] C. Chen, W. Liu, J. Han, X. F. Zhang, D. Wu, and H. C. Wang, "Questionnaire survey and analysis of the feasibility of clinical practice guidelines for acupuncture and moxibustion," *Chinese Journal of Acupuncture and Moxibustion*, vol. 39, no. 12, pp. 1347–1350, 2019, [in Chinese].

[21] H. Chen, G. Li, W. Xu, and B. Xu, "Current status and challenges of domestic evidence-based clinical practice guidelines for acupuncture and moxibustion," in *Proceedings of the 21st National Symposium on Clinical Acupuncture and Moxibustion*, pp. 116–118, Chinese Acupuncture and Moxibustion Society, Tianjin, China, 2014.

[22] L. Zhang, *Evaluation of Clinical Practice Guidelines/consensus Quality of Traditional Chinese Medicine Acupuncture and Moxibustion Based on RIGHT Statement and AGREE-China Tool*, Tianjin University of Traditional Chinese Medicine, Tianjin, China, 2020.

[23] L. Guo, Y. Ma, and X. Wu, "AGREE II evaluation and content analysis of evidence-based acupuncture clinical practice guidelines," *Chinese Journal of Acupuncture and Moxibustion*, vol. 39, no. 11, pp. 1223–1228, 2019, [in Chinese].

[24] Y. Z. H. W. Guo, "Recommendations for acupuncture in clinical practice guidelines of the national guideline clearinghouse," *Chinese Journal of Integrative Medicine*, vol. 11, no. 23, pp. 964–870, 2017.

[25] C. Li, *Formulation of Recommendation Grading Standards in Clinical Guidelines/Consensus of Traditional Chinese*

Medicine, Beijing University of Chinese Medicine, Chaoyang, China, 2019.

[26] Y.-X. Chen, N. Liang, X.-L. Li, S.-H. Yang, Y.-P. Wang, and N.-N. Shi, "Diagnosis and treatment for mild cognitive impairment: a systematic review of clinical practice guidelines and consensus statements," *Frontiers in Neurology*, vol. 12, Article ID 719849, 2021.

[27] W.-C. Xiu, W.-J. Gang, R.-M. Jiao et al., "Effect of acupuncture on outcomes of in vitro fertilisation: a scoping review," *Chinese Journal of Integrative Medicine*, 2021.

[28] Y. He, Y. Li, J. Li, N. Li, Y. Zhang, and N. Li, "Analysis of the most-cited systematic review or meta-analysis in acupuncture research," *Evidence-based Complementary and Alternative Medicine*, vol. 2021, Article ID 3469122., 14 pages, 2021.

[29] S. Chen, S.-n. Guo, F. Marmori et al., "Clinical practice guideline for allergic rhinitis treatment with acupuncture," *Chinese Journal of Integrative Medicine*, vol. 27, no. 2, pp. 83–90, 2021.

[30] L. Ge, H. Zhu, Q. Wang et al., "Integrating Chinese and western medicine for COVID-19: a living evidence-based guideline (version 1)," *Journal of Evidence-Based Medicine*, vol. 14, no. 4, pp. 313–332, 2021.

[31] J. Li, Y. Chen, X. Yu, Y. Xie, and X. Li, "Diagnosis and treatment guideline for Chinese medicine on acute tracheabronchitis," *Journal of Evidence-Based Medicine*, vol. 14, no. 4, pp. 333–345, 2021.

[32] M. Yan, L. Chen, M. Yang et al., "Evidence mapping of clinical practice guidelines recommendations and quality for depression in children and adolescents," *European Child and Adolescent Psychiatry*, vol. 98, 2022.