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Research article

Traditional herbal medicine for Guillain-Barré syndrome: A systematic review and meta-analysis

Somin Jung [a,b,1], Han-Gyul Lee [b,1], Seungwon Kwon [b,*], Seung-Yeon Cho [c], Seong-Uk Park [c], Woo-Sang Jung [b], Sang-Kwan Moon [b], Jung-Mi Park [c], Chang-Nam Ko [c]

[a] *Department of Clinical Korean Medicine, Graduate School, Kyung Hee University, Seoul, Republic of Korea*
[b] *Department of Cardiology and Neurology, Kyung Hee University College of Korean Medicine, Kyung Hee University Medical Center, Seoul, Republic of Korea*
[c] *Stroke and Neurological Disorders Center, Kyung Hee University College of Korean Medicine, Kyung Hee University Hospital at Gangdong, Seoul, Republic of Korea*

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ABSTRACT

Background: Guillain-Barré syndrome (GBS) is a rapid-onset disease caused by the immune system damaging the peripheral nervous system. Since most standardized treatments for GBS focus on acute phase treatment, there are limitations to the rehabilitation and management of general conditions. In East Asian countries, herbal medicine has been used to treat GBS and aid rehabilitation. Therefore, herbal medicine is considered a complementary treatment for GBS. Hence, the present study was conducted to investigate the clinical evidence of herbal medicine treatment for GBS and to provide a research strategy for the future.

Method: PubMed, Embase, Cochrane, CNKI, CiNii, and Science ON were searched from inception to December 4, 2024. Randomized controlled trials (RCTs) comparing conventional Western medicine (CWM) combined with herbal medicine (treatment group) and only CWM (control group), to evaluate the effects of herbal medicine combined with CWM as a treatment for GBS were included. All bibliographic data from the collected studies were summarized in Endnote X9 (Clarivate Analytics). The meta-analysis was conducted using Review Manager (Revman) 5.4.1. software. Effectiveness was assessed by Total Effective Rate (TER), Modified Barthel Index (mBI) score and Manual Muscle Testing (MMT) score. Safety was evaluated as the occurrence of a significant adverse events (AEs).

Results: Ten RCTs that comprised 764 participants were included. Based on the meta-analysis, TER was found to significantly improve in the treatment group compared with the control group (risk ratios: 1.14, 95 % confidence interval: 1.09 to 1.20, $p < 0.00001$). The mBI score and MMT score of upper limb and lower limb also significantly improved in the treatment group compared with the control group. No significant AEs were reported in any included study.

Conclusions: The results of this study suggest that the combination of CWM and herbal medicine may be a better and safer method of physical function recovery and rehabilitation in patients with GBS. Further qualified studies are required to establish this hypothesis.

* Corresponding author. Department of Cardiology and Neurology, Kyung Hee University College of Korean Medicine, Kyung Hee University Medical Center, Seoul, 02447, Republic of Korea.
E-mail addresses: kkokkottung@hanmail.net, seungwon.kwon@khu.ac.kr (S. Kwon).
[1] These authors are contributed equally as first authors.

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1. Introduction

Guillain-Barré syndrome (GBS) is an autoimmune disease of the peripheral nerves that occurs acutely following an infection, and the most typical symptom of GBS is muscle weakness beginning in the lower extremities and progressing to the upper extremities [1]. The prognosis for GBS varies, with approximately 80 % patients recovering to the point of walking unaided by six months with appropriate acute treatment; in severe cases, disability may persist for more than three years or never recover [2]. In South Korea, the number of patients presenting to healthcare facilities with GBS has been increasing over the past decade, nearly double in 2018 compared to 2002 [3]. Since the World Health Organization declared COVID-19 a pandemic in 2020, several vaccines and treatments have been developed at a rapid pace, raising the possibility of a causal link between COVID-19 and GBS, with reports that both COVID-19 infection and COVID-19 vaccination are likely to cause GBS within two weeks [4–8]. Respiratory infections and vaccines are common precursors of GBS [1], and the increase in infections and vaccinations due to COVID-19 may have contributed to the increased incidence of GBS.

Treatment of GBS centers on high-dose intravenous immunoglobulin and plasmapheresis in the acute phase, followed by rehabilitation, management of systemic conditions, and prevention of complications [2]. Recently, remyelination treatment for demyelinating diseases including GBS has also emerged [9]. However, conventional treatment focuses on the acute phase and is limited in treating long-term sequelae such as muscle weakness, sensory abnormalities, pain, and fatigue [10]. The increased incidence of GBS due to COVID-19 infections and COVID-19 vaccination, as well as the limitations of conventional treatments, suggest a need for alternative treatment options for patients with GBS [11].

Korean medicine, a Traditional East Asian Medicine (TEAM), has been used to treat GBS using its mainstay, herbal medicines. Previous studies have included a literature review of herbal treatments for GBS, focused on the journal Traditional Chinese Medicine [12], a meta-analysis of randomized controlled trials of acupuncture published in Chinese journals [13], and a literature review of case reports published in Korean journals [14]. However, previous studies were limited to reviews in specific national journals, systematic reviews and meta-analyses of randomized controlled trials (RCTs) using herbal medicine as a single treatment intervention have not been conducted, and there is a need to comprehensively evaluate the clinical effects of herbal medicine on GBS to provide evidence. In this study, we conducted a systematic review and meta-analysis to compare the therapeutic effectiveness and safety of herbal medicine with those of conventional Western medicine (CWM), herbal medicine alone, and CWM alone for GBS to determine the potential of herbal medicine as an alternative therapeutic agent for GBS.

2. Methods

2.1. Protocol registration

This systematic literature review and meta-analysis was designed in accordance with the National Evidence-Based Healthcare Collaborating Agency's guidelines for undertaking systematic reviews and meta-analyses for interventions [15]. The study protocol was registered in the Research Registry on December 18, 2023 (registration number: 1757). This study was conducted according to the 2020 Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [16].

2.2. Database and literature search

We reviewed domestic and international literature on herbal medicine treatment for GBS published up to December 4, 2024. Five international databases, including Public/Publisher MEDLINE (PubMed), Excerpta Medica dataBASE (EMBASE), Cochrane Central Register of Controlled Trials (CENTRAL), China National Knowledge Infrastructure (CNKI), Citation Information by the National Institute of Informatics (CiNii), and one domestic database, Science ON. The following terms were used: "Guillain-Barré Syndrome," "GBS" for GBS, "Chinese Herbal," "Chinese Plant Extracts," "Chinese Drug," "Chinese Medicine," "Traditional Medicine," "Korea Medicine," "Korean Medicine," "Oriental Medicine," "East Medicine," "East Asia Medicine," "Alternative medicine," "Complementary medicine," "Kampo," "Herbal Medicine," "Herb," "Herbal," "Decoction" for herbal medicine, 'Randomized controlled trial,' 'RCT, ' 'Randomized,' 'Randomly' for RCT. Supplement 1 presents the specific search terms for each database.

2.3. Inclusion and exclusion criteria

2.3.1. Study design

Only RCTs were included, with no limitations on the year or language of publication. Non-RCTs, case reports, in vivo or in vitro studies, study protocols, and review articles were excluded.

2.3.2. Study participants

Studies that included patients diagnosed with GBS based on clinical symptoms and examination results were also included. The type of GBS, sex, age, race, symptom severity, illness duration, and treatment period were not restricted.

2.3.3. Treatment groups

Studies on treatment groups that received herbal medicines in combination with CWM were included. Herbal medicines only administered orally were also included. The dosage, frequency, duration, and formulation (capsules, tablets, decoctions, pills, and

extracts) were not restricted. Studies that used herbal medicines combined with other TEAM treatments, such as acupuncture, moxibustion, cupping, medicinal needles, or herbal medicine treatments other than oral administration, such as injections, were excluded.

2.3.4. Control groups

Studies with control groups that received CWM alone, CWM with placebo were included. If the control group received a treatment other than the CWM, it was excluded.

2.3.5. Outcome measurements

The outcome measures included all outcomes that assessed the therapeutic effectiveness and safety of the treatment intervention.

2.4. Data collection and analysis

Two researchers (SJ and SK) independently collected and analyzed the data. All bibliographic data from the collected studies were summarized in Endnote X9 (Clarivate Analytics, Philadelphia, USA). In the first screening, we removed duplicates and reviewed titles and abstracts to exclude articles that were not relevant to the study subjects and treatments, or were not RCTs. During the second screening, the full texts of the remaining literature were reviewed to exclude ineligible studies. All selection processes were recorded in the PRISMA flow chart. From the final selected studies, information on the author, year of publication, subject characteristics (number, sex, age, and treatment period), intervention methods, outcome measurements, results, and adverse events (AEs) were extracted. Any disagreements between the two researchers were resolved consensually.

2.5. Quality assessment

Two researchers (SJ and SK) independently evaluated the quality of the included studies using Cochrane's Risk of Bias tool (RoB tool). Seven items were used to assess each study: selection bias (random sequence generation and allocation concealment), performance bias, detection bias, attrition bias, reporting bias, and other biases. Each item was categorized as "low risk," "high risk," or "unclear" based on Cochrane Handbook for Systematic Reviews of Interventions version 5.1.0 [17]. Any disagreements between the

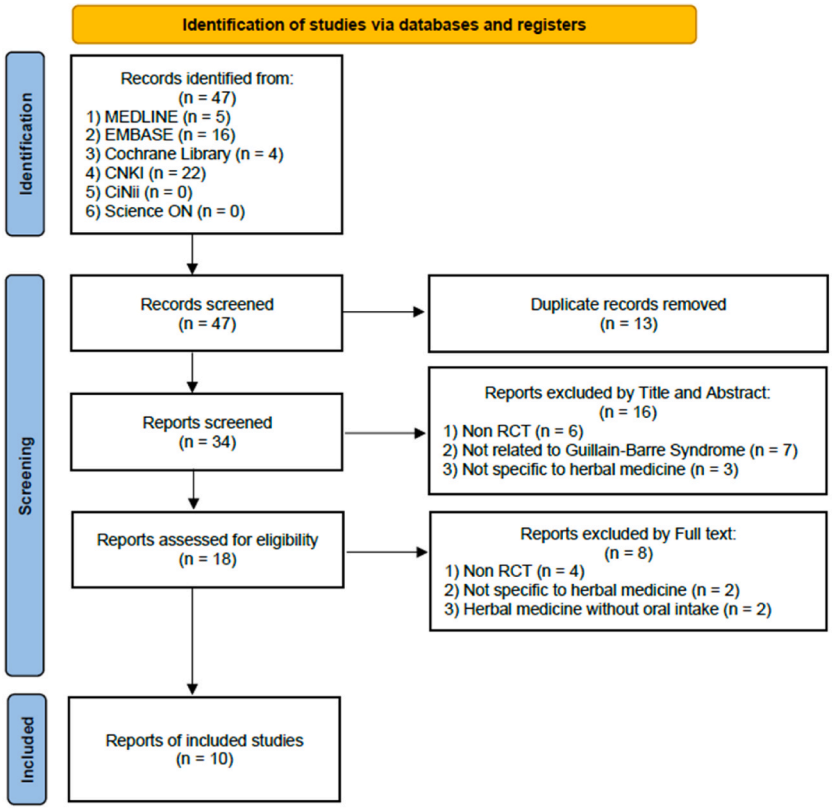

Fig. 1. PRISMA flow chart of the study. PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analysis; EMBASE, Excerpta Medica dataBASE; CNKI, China National Knowledge Infrastructure; CiNii, Citation Information by National Institute of Informatics; RCT, Randomized Controlled Trial.

two researchers were resolved consensually.

2.6. Statistical analysis

Result synthesis and statistical analyses were conducted using Review Manager (RevMan) 5.4.1 software (Cochrane, London, UK). Statistical analyses were performed when a quantitative synthesis was possible. All meta-analyses were performed using the generalized inverse variance estimation method. Risk ratios (RR) and 95 % confidence intervals (CI) were used for dichotomous variables and mean differences (MD) and 95 % CI were used for continuous variables. RR and 95 % CI were used for dichotomous variables and MD and 95 % CI were used for continuous variables. Statistical significance was set at $p < 0.05$. Methodological heterogeneity was assessed based on study design and risk of bias. Studies were excluded from the analysis if they were highly heterogeneous with other studies. For clinical heterogeneity, studies were excluded from the analysis if the treatment intervention was clinically significantly different from that used in the other studies. Statistical heterogeneity among the studies included in the analysis was determined using Higgins' I^2 test, with an I^2 value of 50 % or higher considered statistically heterogeneous [18]. Publication bias was assessed through the asymmetry of the funnel plot.

3. Results

3.1. Study selection

A total of 47 studies were obtained from electronic database searches. After excluding 13 duplicates, 34 studies were selected for eligibility. At the first screening, six non-RCTs, seven studies that were not about GBS, and three studies in which the treatment group was not herbal medicine alone, were excluded based on titles and abstracts. At the second screening, four non-RCTs, two papers in which the treatment group and two studies in which herbal medicine was not administered orally were excluded based on full texts. Ultimately, ten studies [19–28] were selected (Fig. 1).

3.2. Characteristics of included studies

In total, 764 participants (389 and 375 in the treatment and control groups, respectively) were included in this study. No statistically significant differences were observed between the treatment and control groups in any of the studies (Table 1). Nine studies [19–26,28] provided diagnostic criteria for GBS, while one study [27] did not specify the source of the diagnostic criteria (Supplement 2). In the treatment group, Xiaoxuming decoction (Sosokmyungtang, in Korean) was used in two studies [19,23], and Fuzheng Qingre formula (Bujeongcheongyeolbokbang, in Korean) was also used in two studies [20,21]. The most commonly categorized pattern identification in the treatment group was damp-heat, used in five studies [20,21,23,25,28]. The most commonly used constituent herbal medicine was Glycyrrhizae Radix et Rhizoma, which was used in eight studies [19–24,26,28], followed by Astragali Radix [20–22,24,26,28] and Paeoniae Radix Rubra [19–21,23,25,27] in six studies (Supplement 3). When classifying constituent herbal medicines by TEAM efficacy, heat-clearing medicines were used the most at 27 times, followed by qi-tonifying medicines at 15 times, and blood-activating and stasis-dispelling medicines at 12 times (Fig. 2). CWMs were administered to treat GBS in all the studies (Table 2).

Table 1
Characteristics of included studies.

Author (Year)	Sample size(T:C)	Male/Female	Mean age: M±SD	Duration of disease: M±SD
Wu et al. (2021) [19]	92(46:46)	T: 24/22	T: 7.65 ± 1.06	T: 4.61 ± 1.22y
		C: 25/21	C: 7.46 ± 1.03	C: 4.63 ± 1.29y
Yang and Zhao (2020) [20]	63(35:28)	T: 24/11	T: 40.1 ± 16.9	T: 6.31 ± 4.46d
		C: 19/9	C: 37.8 ± 14.0	C: 6.75 ± 3.82d
Zhao and Gao (2019) [21]	74(37:37)	T: 25/12	T: 40.1 ± 16.9	T: 6.6 ± 3.9d
	*Dropout 11(2:9)	C: 23/14)	C: 37.8 ± 14.0	C: 6.3 ± 3.7d
Wang and Tian (2019) [22]	59(30:29)	T: 19/11	T: NR	T: 5.93 ± 2.12d
		C: 17/12	C: NR	C: 5.34 ± 2.24d
Shen et al. (2018) [23]	104(52:52)	T: 29/23	T: 38.12 ± 5.27	T: 29.48 ± 3.06 h
		C: 31/21	C: 37.85 ± 5.19	C: 28.96 ± 3.02 h
Yang et al. (2016) [24]	60(30:30)	T: 18/12	T: 47.5	1–6m
		C: 16/14	C: 48.1	
Gong et al. (2007) [25]	100(50:50)	T: 30/20	T: NR	1-5d
		C: 28/22	C: NR	
Guo et al. (2004) [26]	72(36:36)	T: 22/14	T: 40.5 ± 4.0	NR
		C: 23/13	C: 41.5 ± 3.8	
Xie (2003) [27]	65(32:33)	T: NR	T: 33	T: 5.6d
		C: NR	C: 32.5	C: 5.8d
Ding et al. (1992) [28]	86(43:43)	T: 30/13	T: 26.5	2-7d
		C: 31/12	C: 27.5	

T, treatment group; C, control group; M, mean; SD, Standard deviation; NR, not reported; h, hours; d, days; m, months; y, years.

3.3. Outcomes of efficacy of herbal medicine on GBS

Nine studies [19–26,28] evaluated treatment effectiveness by calculating the total effective rate (TER) according to the degree of improvement in symptoms before and after treatment. TERs ranged from 83 to 100 % in the treatment group and 53–93.10 % in the control group, with all nine studies showing higher TERs in the treatment group than in the control group, and all but one study [26] showing a significant difference ($p < 0.05$). In all five studies [19–23] that reported the Modified Barthel Index (MBI), the treatment group presented significantly higher scores than the control group ($p < 0.05$). In all four studies [19,22,24,28] that reported Manual Muscle Testing (MMT), the treatment group demonstrated a significant improvement compared to the control group ($p < 0.05$). In all three studies [20,21,24] that reported the Hughes functional grading scale, the treatment group showed improvement compared to the control group, and all but one study [24] showing a significant difference ($p < 0.05$). In all two studies [19,27] that reported recovery time, the treatment group presented significantly less recovery time than the control group ($p < 0.05$). In two studies [20,21] that reported Motor Conduction Velocity (MCV), Sensory Conduction Velocity (SCV), and Distal Motor Latency (DML), the treatment group showed significant improvement compared with the control group ($p < 0.05$) (Table 2).

3.4. Outcomes of safety of herbal medicine on GBS

Two studies [23,28] reported AEs. Ding et al. [28] reported no AEs, and Shen et al. [23] reported one case of nausea and vomiting (1.92 %) in the treatment group, and two cases of mild fever and one case of dizziness and nausea in the control group, a total of three cases (5.77 %) (Table 2).

3.5. Risk of bias evaluation

Fig. 3 shows the risk of bias of the included studies. In the random sequence generation, four studies [21–24] used randomization with a random number table, and one study [19] used randomization by shuffling envelopes, which was judged as low. In the allocation concealment, one study [19] used opaque sealed envelopes with serialized numbers to store and open the allocation order, which was judged as low. Regarding performance bias, all studies were judged as high, as it was assumed that it would be difficult to blind the kind of treatment the participants were receiving and what treatment the researcher performed due to differences in treatment between the groups. Regarding detection bias, all studies were judged as unclear because they did not mention whether blinding was implemented for the outcome evaluation. Regarding attrition bias, all studies except one study [21] had no missing data and were judged to be low. Regarding reporting bias, one study [20] was judged as high because it could not be included in the meta-analysis owing to incomplete outcome reporting. Regarding other biases, all studies were judged to be unclear.

3.6. Meta-analysis

Studies with identical outcome measurements were quantitatively synthesized, and treatment effects were compared and analyzed. Among them, studies that used the same herbal medicine as a treatment intervention were classified into subgroups (Xiaoxuming decoction subgroup and Fuzheng Qingre formula subgroup) and quantitatively synthesized to further compare and analyze their treatment effects.

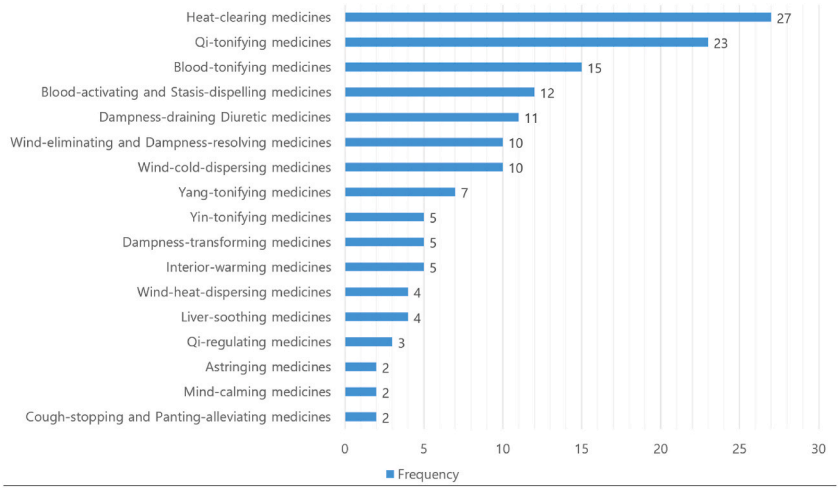

Fig. 2. Frequency of constituent herbal medicines classified by TEAM efficacy. TEAM, Traditional East Asian Medicine.

Table 2
Summary of the randomized controlled trials of herbal medicine for Guillain-Barré syndrome.

Author (Year)	Treatment group (T)	Control group (C)	Treatment period	Outcome measurement	Results	Adverse events
Wu et al. (2021) [19]	C-Tx Xiaoxuming decoction (2 times/d, for 2w)	I.V. immunoglobulin 0.4 g/(kg·d) (for 2w) I.V. methylprednisolone 20–30 mg/kg (for 2w)	2w	①Recovery time	①T < C (P < 0.05)	NR
				②MBI score	②T > C (P < 0.05)	
				③NDF score	③T < C (P < 0.05)	
				④MMT score	④T > C (P < 0.05)	
				⑤Inflammatory factor(IL-18, IL-12, IL-1β levels of serum & CSF)	⑤T < C (P < 0.05)	
				⑥Immune Function($CD3^+$, $CD4^+$, CD4+/CD8+ levels of CSF)	⑥T > C (P < 0.05)	
				⑦Immune Function($CD8^+$, CSF protein levels of CSF)	⑦T < C (P < 0.05)	
				⑧TER	⑧T > C (P < 0.05)	
Yang and Zhao (2020) [20]	C-Tx Fuzheng Qingre formula (2 times/d, for 1m)	Conventional treatment (bed rest, V/S monitoring, electrolyte correction, nasal feeding for dysphagia patients, symptomatic treatment for arrhythmia & constipation & urinary retention patients) I.V. gamma globulin 0.4 g/(kg·d) (for 5d) I.V. vitamin B6 0.2 g/d (for 5d) I.M. vitamin B12 0.5 mg/d (for 5d)	1m	①TCM syndrome score	①T < C (P < 0.05)	NR
				②MBI score	②T > C (P < 0.05)	
				③Hughes functional grading scale	③T < C (P < 0.05)	
				④Sensory dysfunction score	④T < C (P < 0.05)	
				⑤MCV of median n. & ulnar n. & common fibular n.	⑤T > C (P < 0.05)	
				⑥DML of median n. & common fibular n.	⑥T < C (P < 0.05)	
				⑦SCV of median n.	⑦T > C (P < 0.05)	
				⑧SNAP of median n. & ulnar n. & common fibular n.	⑧T = C (P > 0.05)	
				⑨TER	⑨T > C (P < 0.01)	
Zhao and Gao (2019) [21]	C-Tx Fuzheng Qingre formula (2 times/d, for 1m)	Conventional treatment (bed rest, V/S monitoring, electrolyte correction, nasal feeding for dysphagia patients, symptomatic treatment for arrhythmia & constipation & urinary retention patients) I.V. immunoglobulin 0.4 g/(kg·d) (for 5d) I.V. vitamin B6 0.2 g/d (for 5d) I.M. vitamin B12 0.5 mg/d (for 5d)	1m	①MBI score	①T > C (P < 0.05)	NR
				②DML of median n.	②T < C (P < 0.05)	
				③MCV of median n. & ulnar n.	③T > C (P < 0.05)	
				④SCV of median n.	④T > C (P < 0.05)	
				⑤Hughes functional grading scale	⑤T < C (P < 0.05)	
				⑥TER	⑥T > C (P < 0.01)	

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Table 2 (*continued*)

Author (Year)	Treatment group (T)	Control group (C)	Treatment period	Outcome measurement	Results	Adverse events
Wang and Tian (2019) [22]	C-Tx Modified Qingzao Tang (2 times/d, for 4w)	Conventional treatment (symptomatic treatment: low-dose β receptor blocker for hypertension patients, abdomen massaging for urinary retention patients, intestinal moisturizers for constipation patients, carbamazepine for neuralgia patients) I.V. immunoglobulin 0.4 g/(kg·d) (for 5d) I.M. vitamin B12 0.5 mg/d (for 2w) I.M. vitamin B1 0.1 g/d (for 2w)	2 courses (1 course of treatment: 2w)	①MMT score ②MBI score ③TER of muscle strength & MBI ④TER of TCM syndrome score	①T > C (P < 0.01) ②T > C (P < 0.01) ③T > C (P < 0.05) ④T > C (P < 0.05)	NR
Shen et al. (2018) [23]	C-Tx Xiaoxuming Tang (2 times/d, for 2w)	Basic treatment (oxygenation, nutritional supplementation, vitamin B, neurotrophic drug, Anti, symptomatic treatment) I.V. immunoglobulin 0.4 g/(kg·d) (for 5d)	2 courses (1 course of treatment: 1w)	①MBI score ②SSS score ③CSF protein content ④TER	①T > C (P < 0.05) ②T < C (P < 0.05) ③T < C (P < 0.05) ④T > C (P < 0.05)	T: 1.92 % nausea & vomiting 1 case C: 5.77 % mild fever 2 cases, dizziness & nausea 1 case
Yang et al. (2016) [24]	C-Tx Qiangjin Tang (3 times/d, for 3m)	Basic treatment (rehabilitation exercises, symptomatic treatment, vitamin B1, vitamin B6, vitamin B12)	3 courses (1 course of treatment: 1m)	①MMT score ②Hughes functional grading scale ③TER	①T > C (P < 0.05) ②T<C (P > 0.05) ③T > C (P < 0.05)	NR
Gong et al. (2007) [25]	<Acute phase> C-Tx Simiao San (for 20d) <Early recovery phase> C-Tx Buyanghuanwu Tang (for 20d) <Late recovery phase> C-Tx Huqian Hwan (for 20d)	Conventional treatment (electrolyte correction, nutritional supplementation, nasal feeding for dysphagia patients) <Acute phase> I.V. ribavirin 0.8 g/d (for 10d) I.V. vitamin C (for 15d) I.V. ATP (for 15d) I.M. vitamin B1 (for 15d) I.M. vitamin B2 (for 15d) I.V. dexamethasone 10–15 mg/d (for 5d) - > P.O. prednisone 30–50 mg/d (gradually reduced for 1m) I.V. Anti (ampicillin or cefotaxime) 6.0–8.0 g/d (for moderate to severe patients) <Recovery phase> I.V. CDP-choline 0.5 g/d (for 15-30d) P.O. dipyridamole 30 mg/d (until the end of treatment)	60d	①Total apparent efficiency after 30 days ②Total apparent efficiency after 60 days ③TER after 30 days ④TER after 60 days	①T > C (P < 0.05) ②T > C (P < 0.05) ③T > C (P < 0.05) ④T > C (P > 0.05)	NR
Guo et al. (2004) [26]	C-Tx Daqinjiao Tang (2 times/d)	Conventional treatment (oxygenation for dyspnea patients, catheterization for urinary retention patients) I.V. dexamethasone 10 mg/d (for less than 2w) I.V. ranitidine hydrochloride 0.2 g/d I.V. vitamin C 3.0 g/d I.V. vitamin B6 0.2 g/d I.M. vitamin B12 0.5 mg/d I.V. 10 % glucose solution 500 mL/d mixed with ATP 40 mg, coenzyme A 100 U, insulin 12 U (for 7d)	T: shortest: 1 course longest: 6 courses C: shortest: 3 courses longest: 10 courses (1 course of treatment: 7d)	①Cure rate ②TER	①T > C (P < 0.01) ②T > C (P < 0.05)	NR
Xie (2003) [27]	C-Tx HM (3 times/d)	Conventional treatment (symptomatic and supportive care) Acute phase treatment (high-dose vitamin B, vitamin C, corticosteroid, antibiotics (such as penicillin))	10d	①Time to cessation of paralysis progression	①T < C (P < 0.01)	NR

(*continued on next page*)

Table 2 (*continued*)

Author (Year)	Treatment group (T)	Control group (C)	Treatment period	Outcome measurement	Results	Adverse events
				②Time to recovery of muscle strength	②T < C (P < 0.01)	
Ding et al. (1992) [28]	Acute phase treatment Maqianzi San (0.3 g/d: 1st course) (0.8 g/d: 2nd course) (0.75–0.9/d: 3rd, 4th, 5th course) (1 course of treatment: 10d/ treatment for 6d, stop treatment for 4d)	Acute phase treatment (immunosuppressant, vitamin, Anti/tracheotomy if necessary) I.M. loratadine 5 mg/d P.O. isosorbide dinitrate 8 mg/d	5 courses (1 course of treatment: 10d)	①MMT score ②TER	①T > C (P < 0.01) ②T > C (P < 0.01)	None

T, Treatment group; C, Control group; NR, Not reported; C-Tx, Control group treatment; h, hours; d, days; m: months; y, years; I.V., Intravenous; I.M., Intramuscular; P.O., Per oral; TER, Total effective rate; MBI, Modified barthel index; NDF, Neurological deficit score; MMT, Manual muscle testing; SSS, Scandinavian stroke scale; MCV, Motor conduction velocity; SCV, Sensory conduction velocity; DML, Distal motor latency; SNAP, Sensory nerve action potentials; Anti, Antibiotics; CSF, Cerebrospinal fluid; ATP, Adenosine triphosphate; CDP-choline, Cytidine diphosphocholin.

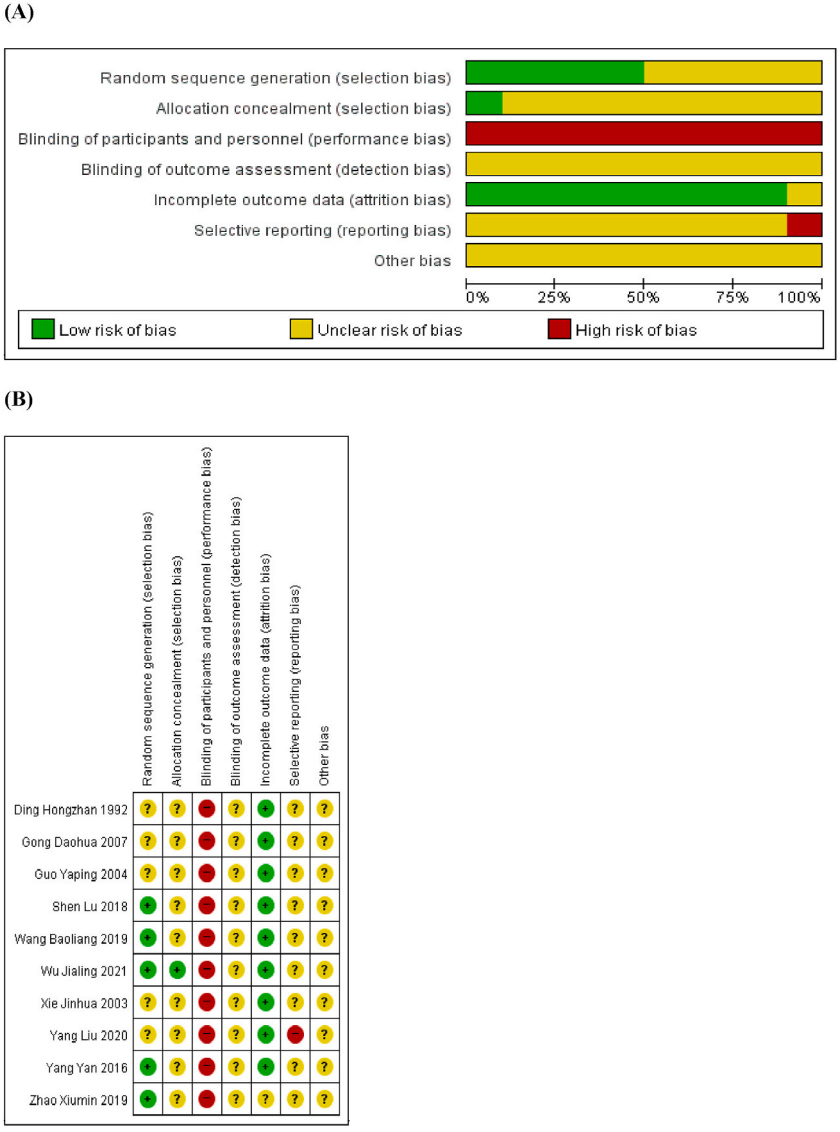


Fig. 3. (A) Risk of bias graph (B) Risk of bias summary ("+" = low risk of bias, "−" = high risk of bias, "?" = unclear risk of bias.).

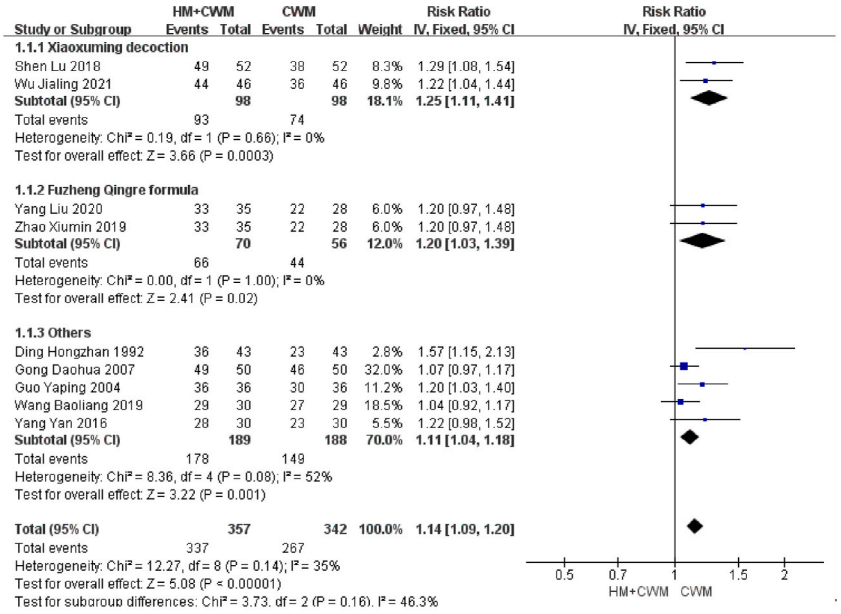
3.6.1. TER

TER was used as an outcome measurement in 9 studies [19–26,28]. The TER result in the treatment group was significantly higher than the control group with low heterogeneity among the studies (RR: 1.14, 95 % CI: 1.09 to 1.20, $p < 0.00001$, $I^2 = 35$ %). The funnel plot was asymmetrical and there was possible evidence of publication bias. In subgroup analysis, Xiaoxuming decoction subgroup was conducted in two studies [19,23] that showed significant improvement in treatment group compared to the control group with no heterogeneity among the studies (RR: 1.25, 95 % CI: 1.11 to 1.41, $p = 0.0003$, $I^2 = 0$ %). Fuzheng Qingre formula subgroup was conducted in two studies [20,21] that showed significant improvement in treatment group compared to the control group with no heterogeneity among the studies (RR: 1.20, 95 % CI: 1.03 to 1.39, $p = 0.02$, $I^2 = 0$ %) (Fig. 4).

3.6.2. MBI

MBI was used as an outcome measurement in 4 studies [19,21–23]. The MBI result in the treatment group was significantly higher than the control group with no heterogeneity among the studies (MD: 4.23, 95 % CI: 2.71 to 5.76, $p < 0.00001$, $I^2 = 0$ %). Since the minimal clinically important difference (MCID) for MBI scores in stroke patients is reported to be 1.85 [29], the mean difference of 4.23 between the treatment and control groups in this study is considered clinically significant. The funnel plot was asymmetrical and there was possible evidence of publication bias. In subgroup analysis, Xiaoxuming decoction subgroup was conducted in two studies [19,23] that showed significant improvement in treatment group compared to the control group with no heterogeneity among the studies (MD: 4.39, 95 % CI: 2.81 to 5.97, $p < 0.00001$, $I^2 = 0$ %) (Fig. 5).

(A)



(B)–

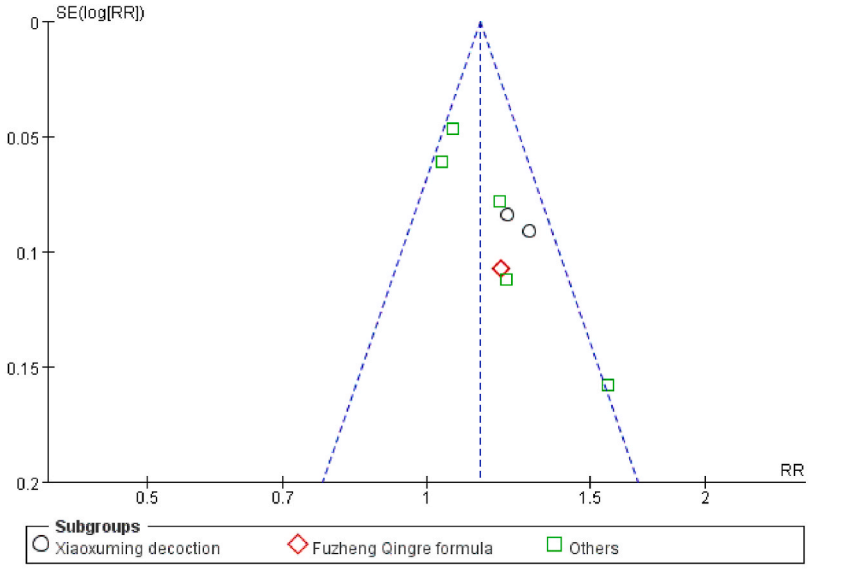


Fig. 4. (A) Forest plot for TER: HM + CWM vs. CWM (B) Funnel plot for TER: HM + CWM vs. CWM. TER, Total Effective Rate; HM, Herbal medicine; CWM, Conventional Western medicine; CI, Confidence Interval; SE, Standard Error.

3.6.3. MMT

MMT for upper and lower limb was used as an outcome measurement in 4 studies [19,22,24,28]. The MMT result in the treatment group was significantly higher than the control group with heterogeneity among the studies in both upper and lower limb (MD: 0.15, 95 % CI: 0.08 to 0.22, $p < 0.0001$, $I^2 = 60$ %, MD: 0.10, 95 % CI: 0.02 to 0.17, $p = 0.01$, $I^2 = 59$ %, respectively). The funnel plots were asymmetrical, and there was possible evidence of publication bias (Fig. 6).

4. Discussion

According to the results of the meta-analysis in this study, the TER and ADL according to MBI of the treatment group was significantly improved than that of the control group. The MCID for the MBI score of stroke patients is reported to be 1.85 points [29], and the difference in the average MBI score between the treatment and control groups in this study was more than 4 points, which can be considered a clinically meaningful result. Also, the degree of improvement in the upper and lower limb muscle strength following MMT in the treatment group was significantly improved compared to the control group. To establish a clinical basis for the use of herbal medicine for the treatment of GBS, we analyzed RCTs that could be quantitatively synthesized and confirmed that herbal medicine has a significant effect on the treatment of GBS.

According to this study, the most commonly categorized symptoms in patients with GBS were damp heat and qi deficiency, and the most commonly prescribed herbal medicines were heat-clearing and qi-tonifying medicines, suggesting that herbal medicines for patients with GBS are mainly focused on clearing damp heat and tonifying qi. GBS is mainly an invasion of inflammatory cells in blood vessels around the endometrium, resulting in abnormalities in the immune system of nerve cells and support structures of the peripheral nervous system [2]. In the acute phase, inflammatory cell invasion is considered an infiltration of damp heat, so the treatment

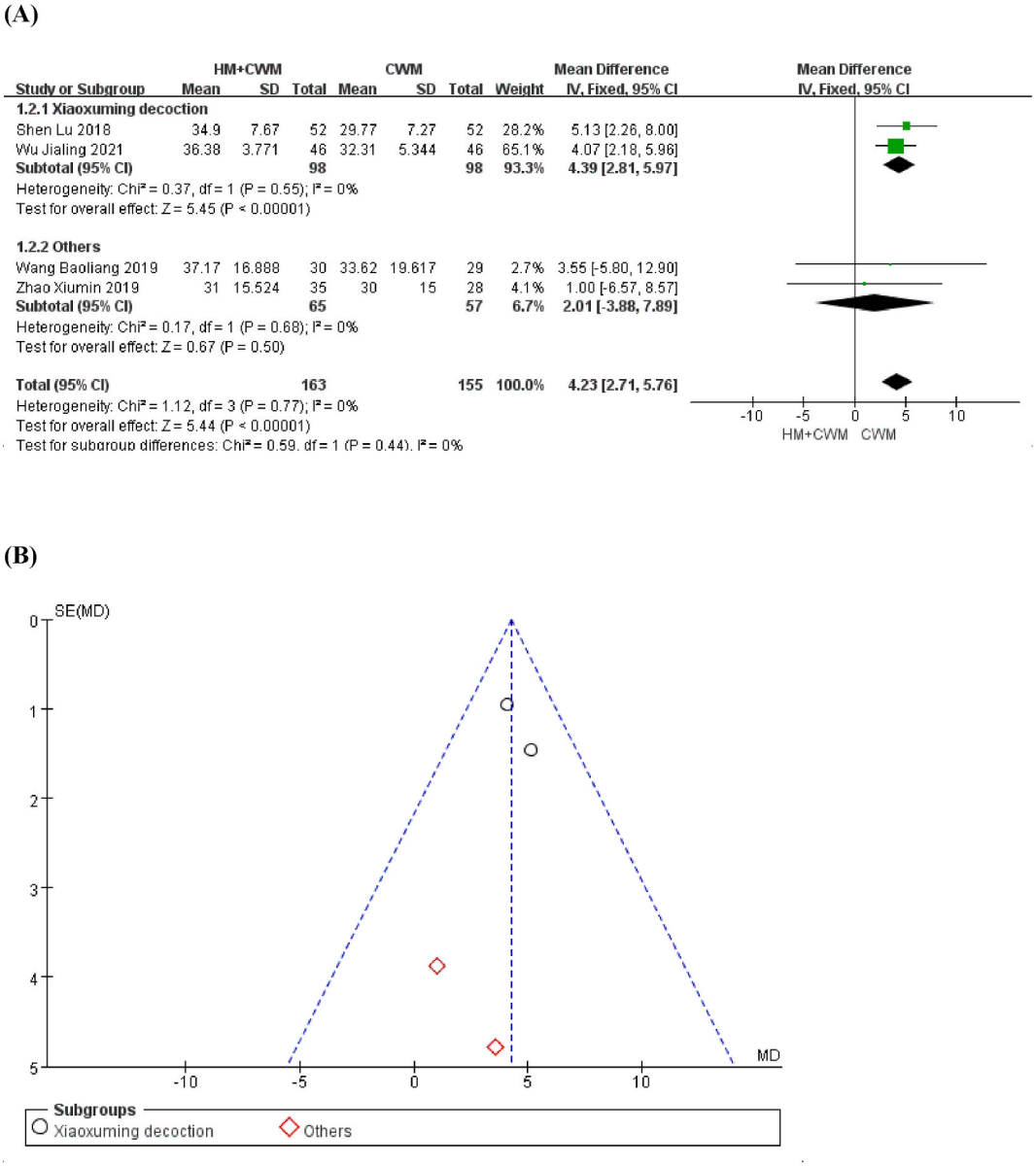


Fig. 5. (A) Forest plot for MBI: HM + CWM vs. CWM (B) Funnel plot for MBI: HM + CWM vs. CWM. MBI, Modified Barthel Index; HM, Herbal medicine; CWM, Conventional Western medicine.

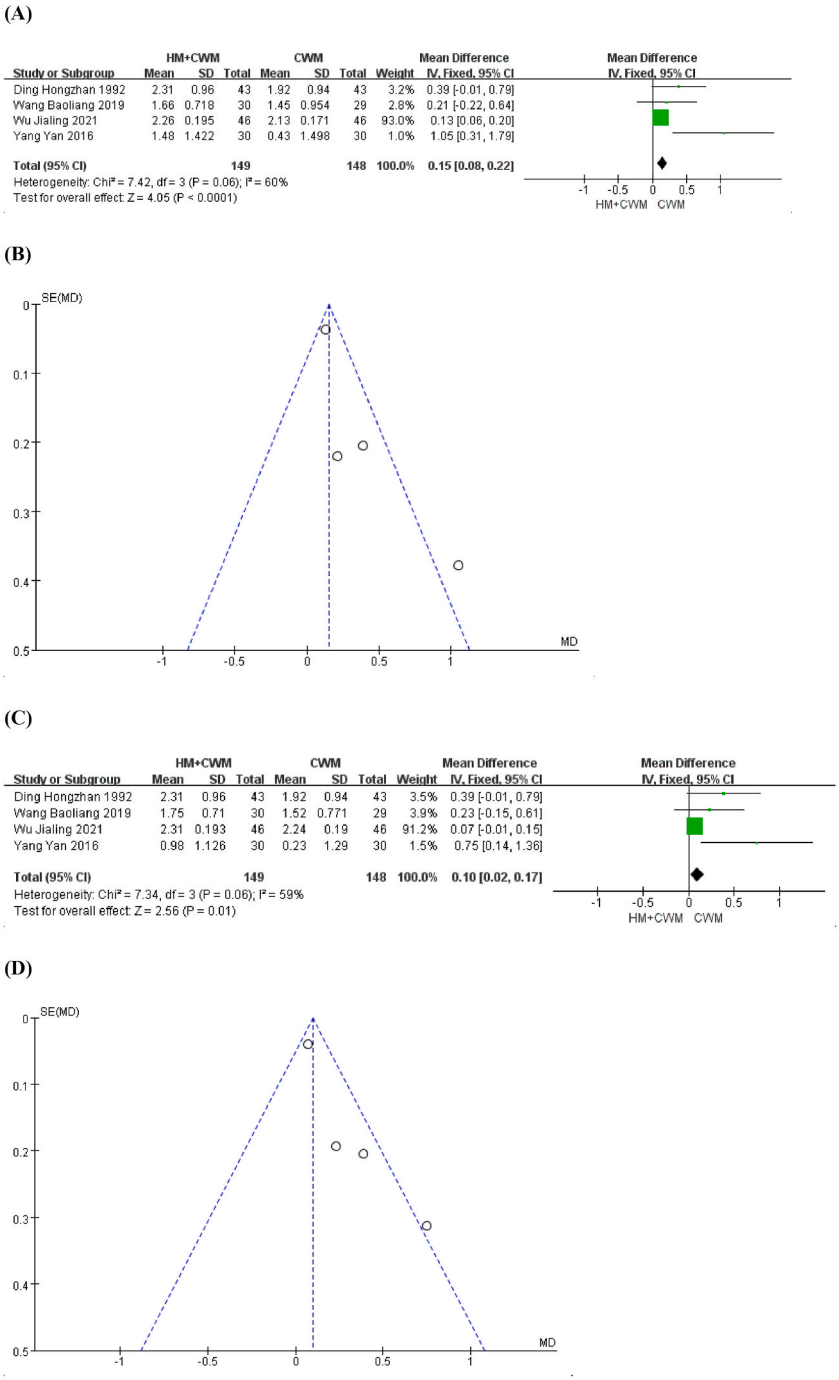


Fig. 6. (A) Forest plot for upper limb MMT: HM + CWM vs. CWM (B) Funnel plot for upper limb MMT: HM + CWM vs. CWM (C) Forest plot for lower limb MMT: HM + CWM vs. CWM (D) Funnel plot for lower limb MMT: HM + CWM vs. CWM. MMT, Manual Muscle Testing; HM, Herbal medicine; CWM, Conventional Western medicine.

focuses on solving damp heat to suppress the immune response [20]. In the early stages of the recovery phase, the focus is on solving the qi deficiency with blood stasis to facilitate blood flow and nourish the nerves, while in the late stages of the recovery phase, the focus is on solving liver kidney deficiency to supplement the regularity of muscle strength recovery [25]. Paeoniae Radix Rubra, the most commonly used heat-clearing medicine in this study, has the ability to clear heat from the blood and relieve pain by dispersing blood stasis. It also has the pharmacological effects of prolonging thrombus formation time, suppressing platelet aggregation, improving red blood cell deformation ability, lowering blood viscosity, and effectively protecting brain cells by increasing brain blood

flow [19,23]. Glycyrrhizae Radix et Rhizoma, the most commonly used qi-tonifying medicine in this study, tonifies qi by strengthening the spleen, detoxifying through clearing heat, and harmonizing. It also exerts anti-inflammatory, antioxidant, and anti-immune effects. Astragali Radix, a qi-tonifying medicine commonly used in this study, tonifies qi and Yang, thereby suppressing sweating by securing the exterior and discharging pus through detoxification. It has the pharmacological effects of promoting angiogenesis and tissue regeneration [20,24].

In subgroup analysis, Xiaoxuming decoction and Fuzheng Qingre formula were included in multiple studies. Xiaoxuming decoction, a prescription based on Paeoniae Radix Rubra, TER of the treatment group was statistically significantly higher than that of the control group, and the ADL according to the MBI in the treatment group was statistically significantly improved compared to the control group. It is reported that Xiaoxuming decoction has the pharmacological effects of dilating blood vessels, inhibiting thrombogenesis, improving intravascular blood coagulation, suppressing oxidative stress, alleviating nitric oxide-induced damage, regulating lipid metabolism, and protecting the blood-brain barrier and neurovascular unit [30]. Specifically, the vasodilating effect of Xiaoxuming decoction is related to its effects on various vasomotor-related G protein-coupled receptor (GPCR) targets, influenced by serotonin 1A, 1B receptors (5-HT1AR, 5-HT1BR), Angiotensin II type 1 receptor (AT1R), β2 adrenergic receptor β2-AR), Urotensin II receptor (hUTR), and Endothelin receptor B (ETB) [31]. The neuroprotective effect of Xiaoxuming decoction is related to an increase in the ratio of B-cell lymphoma-2 (Bcl-2)/Bax-apoptosis-related genes in the brain and suppressing the steps of caspase-induced apoptosis [32]. Additionally, the anti-inflammatory effect of Xiaoxuming decoction is related to a decrease in the expression of inflammatory cytokines [33] and regulating several signal transduction pathways such as IL-17, TNF, and AGE-RAGE [34]. Therefore, in terms of traditional East Asian medicine, Xiaoxuming decoction treats paralysis caused by Damp-heat by clearing heat and removing dampness from the blood. It has been experimentally shown to improve symptoms of patients with GBS by protecting the neurovascular unit through its antiapoptotic, antioxidant, and anti-inflammatory effects. Fuzheng Qingre formula, a prescription based on Astragali Radix, is consisted of Heat-clearing medicines and Dampness-resolving medicines. Astragali Radix has been reported to exert pharmacological effects that promote angiogenesis and tissue regeneration, Glycyrrhizae Radix et Rhizoma has anti-inflammatory and estrogen-like pharmacological effects and Salviae Miltiorrhizae Radix and Paeoniae Radix Rubra have pharmacological effects that improve blood supply [20,21]. Therefore, the Fuzheng Qingre formula can be used for patients with GBS and abnormalities in the immune system of cells and supporting structures by improving the nerves of the peripheral nervous system.

This study had certain limitations. First, the Strychni Semen used in Ding et al. [28] study is highly toxic, and when used in large quantities, it excites the respiratory and vasomotor centers of the medulla oblongata and causes convulsions; therefore, caution is required when using it clinically. Therefore, safety issues may arise when replicating this study in the future. Second, unified diagnostic criteria related to GBS were not applied when selecting the studies. Third, although accurate diagnosis should be a priority when using herbal medicines, most of the selected studies did not clearly establish a diagnostic method for appropriate diagnosis in patients with GBS. Fourth, only two papers [23,28] reported adverse reactions; therefore, there is insufficient evidence to evaluate the safety of herbal medicine treatment compared with CWM. Fifth, the number of studies included is small, with a total of 10, and the research methods are sometimes not clearly specified, so it is difficult to say that the research quality is high. Sixth, there were many uncertainties in evaluating the quality of the studies, which limited the accuracy of interpretation and comparative analysis. Seventh, all the selected studies were conducted in China, and according to a previous study [35], clinical studies conducted in China have been reported to have a high success rate; therefore, there is a possibility of regional and linguistic publication bias. Eighth, as a result of the meta-analysis conducted in this study, all funnel plots were observed to be asymmetric, leading to suspicion of publication bias. If the distribution of effect sizes in the funnel plot is asymmetric, the trim-and-fill method can be used to estimate an unbiased effect size by creating a symmetrical distribution by estimating and filling in unreported effect sizes [36]. However, analysis of publication bias and interpretation of whether the funnel plot is asymmetric are not recommended for studies with fewer than ten studies owing to low power [37,38], and funnel plots are used to measure study quality, heterogeneity, and chance. Because asymmetry can be observed for other reasons as well, publication bias cannot be accurately predicted [15]. Additionally, the trim-and-fill method has a limitation in that it cannot explain factors other than publication bias for the asymmetry of the funnel plot [16]. Considering that the number of studies in which meta-analysis was performed in this study was less than 10, there was a practical problem in that it was not possible to test publication bias in studies where publication bias was suspected due to the small number of included studies.

Despite these limitations, this study has clinical significance. Through a systematic literature review and meta-analysis, the combination of herbal medicine and CWM in patients with GBS was found to be effective in terms of the TER, MBI, and MMT. Therefore, we established the basis for this. Based on this study, we believe that it will be possible to actively combine herbal medicine treatment with CWM in patients with GBS. To compensate for future limitations, additional clearly designed, high-quality randomized controlled studies using a high level of evidence and highly reliable evaluation indicators are required.

5. Conclusions

The use of herbal medicine combined with CWM for GBS resulted in significant improvements in motor function and strength, rehabilitative outcomes, and activities of daily living compared with CWM alone, with no significant AEs. Based on these results, we present the possibility of using herbal medicine as a novel alternative for GBS. Large-scale, higher-quality research is required to solidify this evidence.

CRediT authorship contribution statement

Somin Jung: Writing – original draft, Investigation, Formal analysis, Conceptualization. **Han-Gyul Lee:** Writing – original draft,

Investigation, Formal analysis. **Seungwon Kwon:** Writing – review & editing, Supervision, Investigation, Funding acquisition, Conceptualization. **Seung-Yeon Cho:** Writing – review & editing. **Seong-Uk Park:** Writing – review & editing. **Woo-Sang Jung:** Writing – review & editing. **Sang-Kwan Moon:** Writing – review & editing. **Jung-Mi Park:** Writing – review & editing. **Chang-Nam Ko:** Writing – review & editing.

Ethics declarations

This systematic review and meta-analysis was adhered to the Preferred Reporting Items for Systematic Reviews & Meta-Analysis (PRISMA) guidelines (supporting file 1).

Availability of data and materials

The data are available from the corresponding author upon request.

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Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Abbreviations

AEs	adverse events
CENTRAL	Cochrane Central Register of Controlled Trials
CI	confidence intervals
CiNii	Citation Information by the National Institute of Informatics
CNKI	China National Knowledge Infrastructure
CWM	conventional Western medicine
EMBASE	Excerpta Medica dataBASE
GBS	Guillain-Barré syndrome
mBI	Modified Barthel Index
MCID	minimal clinically important difference
MD	mean differences
MMT	Manual Muscle Testing
Pubmed	Public/Publisher MEDLINE
RCTs	randomized controlled trials
RR	risk ratios
TEAM	Traditional East Asian Medicine
TER	Total Effective Rate

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.heliyon.2024.e41455.

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