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Review Article

TCM formulas for strengthening the spleen, tonifying Qi, and supplementing the marrow in the treatment of MG: A network meta-analysis

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ABSTRACT

Introduction: Myasthenia gravis is an autoimmune disease that primarily affects the acetylcholine receptors on the postsynaptic membrane at the neuromuscular junction. Traditional Chinese medicine (**TCM**) TSQNM formulas have been widely utilized in clinical practice and have shown effectiveness in treating Myasthenia gravis. There is a broad spectrum of TCM formulas with varying effectiveness, but there is a lack of direct comparative evidence between them. Bayesian network meta-analysis was utilized to evaluate the clinical efficacy and safety of TCM formulations that focus on spleen tonification, qi enhancement, and marrow nourishment (referred to as TSQNM) for treating myasthenia gravis. The results are anticipated to provide valuable insights into the treatment of myasthenia gravis.

Methods: Pertinent randomized controlled trials were retrieved from databases from the inception of the databases to October 17, 2023. The quality of studies was assessed using the risk of bias assessment tool developed by the Cochrane Collaboration. It was also preregistered in PROSPERO (ID: CRD42023482260). Network meta-analysis was conducted using STATA16 and R4.2.3.

Results: Twenty studies were included, involving 1 473 participants, with 739 cases in the experimental group and 734 cases in the control group. These studies examined the effectiveness of eight TCM formulas.

Conclusions: Combining conventional Western medicine treatment with TSQNM formulas has been shown to provide superior therapeutic effects for patients with myasthenia gravis, compared to using prescription drugs alone. Notably, when Buzhong Yiqi Decoction is combined with conventional Western medicine treatment, it has shown remarkable efficacy in reducing hormone-induced obesity and gastrointestinal tract discomfort.

Full botanical plant names

Herbal medicine	Composition (scientific name)
Buzhong Yiqi Decoction	*Astragalus mongholicus* Bunge 60 g, *Elephantopus scaber* L. 10 g, *Codonopsis pilosula* (Franch.) Nannf. 30 g, *Citrus reticulata* Blanco 15 g, *Actaea cimicifuga* L. 10 g, *Dioscorea oppositifolia* L. 10 g, *Atractylodes macrocephala* Koidz. 15 g, *Levisticum officinale* W.D.J.Koch 10 g, *Glycyrrhiza glabra* L. 5 g
Zishen Tiaogan Decoction	*Paeonia lactiflora* Pall. 15 g, *Levisticum officinale* W.D.J.Koch 15 g, *Eucommia ulmoides* Oliv. 15 g, *Conioselinum anthriscoides 'Chuanxiong'* 15 g, *Spatholobus suberectus* Dunn 15 g, *Morus alba* L. 15 g, *Rehmannia glutinosa* (Gaertn.) DC. 10 g, *Cornus officinalis* Siebold & Zucc. 10 g, *Dioscorea oppositifolia* L. 10 g, *Glycyrrhiza glabra* L. 10 g
Jianpi Yishen Juxian Decoction	*Codonopsis pilosula* (Franch.) Nannf. 15 g, *Atractylodes macrocephala* Koidz. 10 g, *Astragalus mongholicus* Bunge 60 g, *Actaea cimicifuga* L. 6 g, *Elephantopus scaber* L. 6 g, *Levisticum officinale* W.D.J.Koch 15 g, *Glycyrrhiza glabra* L. 6 g, *Citrus reticulata* Blanco 10 g, *Eucommia ulmoides* Oliv. 15 g, *Cuscuta chinensis* Lam. 5 g, *Lycium barbarum* L. 15 g,

Abbreviation: CI, Confidence intervals; CWMT, Conventional Western medicine treatment; DIC, Deviance information criterion; LRP4, Low-density lipoprotein receptor-related protein 4; MD, Mean difference; MG, Myasthenia gravis; MuSK, Muscle-specific tyrosine kinase; PRISMA-NMA, Systematic Reviews and Network Meta-Analysis; RCTs, Randomized controlled trials; RR, Relative risk; SUCRA, Cumulative ranking curve; TCM, Combination of traditional Chinese medicine

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	Lycopodiella cernua (L.) Pic.Serm. 15 g, *Rehmannia glutinosa* (Gaertn.) DC. 15 g, *Cyathula officinalis* K.C.Kuan 15 g, *Stephania cephalantha* Hayata 10 g
Shengyang Jutuo Decoction	*Astragalus mongholicus* Bunge 28 g, *Panax ginseng* C.A.Mey. 28 g, *Actaea cimicifuga* L. 28 g, *Atractylodes macrocephala* Koidz. 12 g, *Elephantopus scaber* L. 12 g, *Paeonia lactiflora* Pall. 12 g, *Levisticum officinale* W.D.J.Koch 8 g, *Citrus reticulata* Blanco 8 g, *Carum carvi* L. 8 g, *Glycyrrhiza glabra* L. 8 g, *Citrus* × *aurantium* L. 8 g, *Hansenia weberbaueriana* (Fedde ex H.Wolff) Pimenov & Kljuykov 8 g, *Cinnamomum verum* J.Presl 5 g, *Salvia miltiorrhiza* Bunge 5 g
Yiqi Shengti Decoction	*Astragalus mongholicus* Bunge 30 g, *Atractylodes macrocephala* Koidz. 15 g, *Leonurus japonicus* Houtt. 15 g, *Levisticum officinale* W.D.J.Koch 15 g, *Actaea cimicifuga* L. 6 g, *Elephantopus scaber* L. 10 g, *Smilax glabra* Roxb. 15 g, *Wurfbainia villosa* (Lour.) Škorničk. & A.D.Poulsen 6 g, *Conioselinum anthriscoides 'Chuanxiong'* 10 g, *Glycyrrhiza glabra* L. 10 g
Jiawei Huangqi Renshen Decoction	*Astragalus mongholicus* Bunge 30 g, *Actaea cimicifuga* L. 10 g, *Panax ginseng* C.A.Mey. 10 g, *Citrus reticulata* Blanco 10 g, *Ophiopogon japonicus* (Thunb.) Ker Gawl. 10 g, *Atractylodes macrocephala* Koidz. 10 g, *Phellodendron amurense* Rupr. 10 g, *Levisticum officinale* W.D.J.Koch 15 g, *Glycyrrhiza glabra* L. 6 g, *Dolomiaea costus* (Falc.) Kasana & A.K.Pandey 10 g, *Eucommia ulmoides* Oliv. 10 g, *Dipsacus asper* Wall.ex DC. 10 g, *Hibiscus sabdariffa* L. 20 g
Zini Yiqi Jianpi Decoction	*Codonopsis pilosula* (Franch.) Nannf. 20 g, *Atractylodes macrocephala* Koidz. 30 g, *Dioscorea oppositifolia* L. 20 g, *Smilax glabra* Roxb. 20 g, *Citrus reticulata* Blanco 20 g, *Astragalus mongholicus* Bunge 30 g, *Coix lacryma-jobi* L. 20 g, *Actaea cimicifuga* L. 20 g, *Elephantopus scaber* L. 15 g, *Levisticum officinale* W.D.J.Koch 15 g, *Glycyrrhiza glabra* L. 6 g
Peipi Shugan Decoction	*Atractylodes macrocephala* Koidz. 30 g, *Astragalus mongholicus* Bunge 250 g, *Citrus reticulata* Blanco 10 g, *Magnolia officinalis* Rehder & E.H.Wilson 10 g, *Neolitsea cassia* (L.) Kosterm. 30 g, *Elephantopus scaber* L. 10 g, *Hordeum vulgare* L. 45 g, *Zingiber officinale* Roscoe 30 g, *Paeonia lactiflora* Pall. 15 g, *Dioscorea oppositifolia* L. 45 g, *Kummerowia striata* (Thunb.) Schindl. 30 g, *Ephedra sinica* Stapf 6 g, *Achyranthes bidentata* Blume 10 g

Introduction

Myasthenia gravis (**MG**) is an autoimmune disease that primarily affects the acetylcholine receptors on the postsynaptic membrane at the neuromuscular junction. The pathogenesis of MG involves the complement system and is T cell-dependent, with acetylcholine receptor antibodies playing a major role. In some cases, MG is mediated by muscle-specific tyrosine kinase antibodies and low-density lipoprotein receptor-related protein 4 antibodies. The main clinical manifestations of MG include skeletal muscle weakness and fatigue, which worsen with physical activity and improve significantly with rest and the use of acetylcholinesterase inhibitors. Current treatment options for MG include acetylcholinesterase inhibitors, immunosuppressants, intravenous immunoglobulin, plasma exchange, and thymectomy (Neuroimmunology Group of the Neurology Branch of the Chinese Medical Association, Neuroimmunology Branch of the Chinese Society of Immunology, 2015). However, there is no standardized treatment regimen for MG, and there are various adverse reactions. Some patients have a poor response to treatment, while others cannot tolerate it (Gao et al., 2016). The combination of traditional Chinese medicine (**TCM**) and conventional Western medicine treatment (**CWMT**) has shown significant efficacy in managing MG and effectively reduces the side effects associated with exclusive CWMT. This approach offers notable advantages over exclusive CWMT (Jie et al., 2017).

The study of TCM in the management of MG has been growing. Traditional Chinese medicine TSQNM formulas have been widely utilized in clinical practice and have shown effectiveness in treating MG (Zhao et al., 2014). This therapeutic approach places emphasis on nourishing and regulating the spleen and stomach, recognizing their significance. It has gained recognition from experts (Lv et al., 2017). Consequently, a plethora of studies have increasingly confirmed the beneficial effects of TCM TSQNM formulas in alleviating MG symptoms (Lv et al., 2017).

To address the existing gap in direct comparative evidence among various TCM formulas, this study aims to evaluate the effectiveness and safety of orally administered TCM TSQNM formulas for treating MG using network meta-analysis methods. By ranking these formulas based on their outcomes, the study intends to establish a reference standard for clinical medication in MG treatment. It is important to note that the effectiveness of TCM formulas can vary widely, hence the need for a comprehensive assessment.

Materials and Methods

Study Registration

The study was conducted in accordance with the guidelines provided by the Preferred Reporting Items for Systematic Reviews and Network Meta-Analysis. It was also preregistered in PROSPERO (ID: CRD42023482260).

Inclusion Criteria

Study Type

The researchers required that the studies must be written in Chinese and English, and they had to be clinical randomized controlled trials (**RCTs**).

Study Subjects

MG patients are diagnosed using clinical methods. In the TCM system, the diagnosis follows the Expert Consensus on TCM Syndrome Screening for Myasthenia Gravis (Lv et al., 2017) and the diagnostic criteria for MG caused by spleen-kidney deficiency in Internal Medicine of TCM. Conversely, Western medicine relies on the China Guidelines for the Diagnosis and Treatment of Myasthenia Gravis in 2020 (Chang, 2021) for diagnosis.

Intervention Measures

To ensure homogeneity across the studies, medications were administered according to the *2020 China Guidelines for the Diagnosis and Treatment of Myasthenia Gravis*. In this study, the control group was administered pyridostigmine, prednisone, methylprednisolone, and tacrolimus, either individually or in combination. On the other hand, the experimental group received a combination of TCM formulas that enhance spleen function, boost qi, and nourish the marrow, along with comprehensive whole medical therapy. The initial treatment protocols were identical for both groups, and there were no restrictions on the treatment duration. Furthermore, participants in both groups refrained from using any other TCM remedies, Chinese patent medicines, or non-pharmacological interventions that could potentially influence the efficacy of the treatment.

Outcome Indicators

The study evaluated several outcome measures, including the clinical response rate and adverse reactions. The clinical response rate was calculated using the formula: total effective rate (%) = (number of cured cases + significantly improved cases + improved cases + relieved cases)/total cases × 100%. In the context of conventional Western medicine, methylprednisolone is frequently utilized as an intermediate-acting glucocorticoid. It is known to cause a range of relatively common adverse reactions, which can impact the endocrine, gastrointestinal, musculoskeletal, and immune systems. The severity of these side effects is influenced by the dosage and the method of administration. The impact of methylprednisolone on blood glucose metabolism typically correlates with the dose, with risk factors such as a history of diabetes, advanced age, and obesity increasing the likelihood of complications (Oray et al., 2016). Clinical studies have shown that

pyridostigmine bromide is the preferred first-line treatment for various forms of myasthenia gravis, though it only provides symptomatic relief without addressing the underlying cause. While prednisone can suppress related cell-mediated effects, its long-term use often leads to liver function impairment in patients (Mao, 2011). Therefore, adverse reactions assessed in the study included hepatic impairment, elevated blood sugar levels, gastrointestinal ulcers, and infections.

Exclusion Criteria

We excluded the following studies: (1) studies with incorrect or incomplete data. (2) Studies with outcome indicators that are unrelated. (3) Studies where both the experimental and control groups received other non-drug interventions, etc. (4) Non-RCT, case reports, empirical summaries, and reviews. (5) Preclinical studies, such as animal experiments. (6) Purely descriptive studies. (7) Duplicate publications.

Literature Retrieval Strategy

We conducted a comprehensive search across various databases, such as PubMed, Web of Science, Embase, Cochrane Library, SinoMed, CNKI, Wanfang, and VIP, to gather relevant studies published from the inception of these databases until October 17, 2023. The search was conducted using a combination of subject terms and free-text terms. We customized the retrieval strategies to align with the specific requirements of each database. Table 1 illustrates the literature search strategy, taking Embase as an example.

Selection of Studies and Data Extraction

The retrieved studies were screened, assessed for eligibility, and recorded by two researchers, Guan Chang and Wang Jian, in order to determine the studies to be included. Any disagreements regarding the eligibility of specific studies were resolved through negotiation.

Relevant data were extracted independently by two investigators, Guan Chang and Wang Jian. The data encompassed various parameters such as publication year, first author, country, publication time, subject information including age and gender, sample size, detailed information regarding the treatment group and the control group, as well as comprehensive details about the outcomes and any adverse events that occurred. In cases where the reported data was insufficient or unclear, the investigators diligently reached out to the first author or corresponding author via email or phone to request the missing or clarification of data.

Risk of Bias in the Studies

Two investigators, Guan Chang and Wang Jian, assessed the risk of bias in each included article as stated in the Cochrane Handbook for Systematic Reviews of Interventions (Higgins et al., 2011). The evaluation of methodological quality was based on various factors, including the generation of random sequence, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting, and other potential biases. The risk of bias in each domain of the included studies was categorized as low, high, or unclear.

Analysis Methods

The mean difference was used to analyze quantitative data, while the relative risk (**RR**) was employed to assess count data. All effect sizes were reported alongside their respective 95% confidence intervals (**CIs**). To compare the effectiveness of different intervention measures, a Bayesian random effects model was utilized. The modeling process involved the application of the Markov chain Monte Carlo method. Four Markov chains were simultaneously run, with 20 000 annealing cycles and 50 000 simulation iterations. Model fit and overall consistency were assessed using the deviance information criterion. In the case of a closed loop, the node-splitting method would be used to evaluate local consistency. Additionally, intervention measures were ranked based on the surface under the cumulative ranking curve (SUCRA), and a league table was generated to compare the effects of different intervention methods.

Multiple original studies have been conducted to evaluate different dosages and treatment durations for the same intervention measures. In order to compare the effectiveness of drugs versus placebos, we utilized Bayesian network meta-regression analysis to investigate potential differences across various doses and treatment durations. Publication bias was assessed using a funnel plot when there were at least 10 studies reporting the outcome indicator. The software used for the analysis included Stata 15.0 (Stata Corporation, College Station, TX) and R 4.2.0 (R Development Core Team, Vienna, http://www.R-project.org). Statistical significance was defined as a P value < 0.05.

Results

Literature Screening

Initially, a total of 1 222 pieces of literature were collected. These records were imported into EndNote, where 531 duplicate articles were identified and removed. Following this, an additional 432 articles were excluded based on a review of their titles and abstracts. The full texts of the remaining 259 articles were downloaded and thoroughly examined. From this, 237 articles that did not meet the inclusion and exclusion criteria were omitted, resulting in the inclusion of a final set of 20 studies. The complete screening process is visually depicted in Figure 1.

Table 1
Literature search strategy.

No.	Query	Results
#1	'myasthenia gravis'/exp	29 102
#2	'myasthenia gravis':ab,ti OR 'myasthenia gravis, ocular':ab,ti OR 'ocular myasthenia gravis':ab,ti OR 'myasthenia gravis, generalized':ab,ti OR 'generalized myasthenia gravis':ab,ti OR 'muscle-specific receptor tyrosine kinase myasthenia gravis':ab,ti OR 'muscle specific receptor tyrosine kinase myasthenia gravis':ab,ti OR 'muscle-specific tyrosine kinase antibody positive myasthenia gravis':ab,ti OR 'muscle specific tyrosine kinase antibody positive myasthenia gravis':ab,ti OR 'musk mg':ab,ti OR 'musk myasthenia gravis':ab,ti OR 'myasthenia gravis, musk':ab,ti OR 'anti-musk myasthenia gravis':ab,ti OR 'anti musk myasthenia gravis':ab,ti OR 'myasthenia gravis, anti-musk':ab,ti	22 383
#3	#1 OR #2	30 980
#4	'chinese medicine'/exp	75 010
#5	'medicine, chinese traditional':ab,ti OR 'traditional chinese medicine':ab,ti OR 'chung i hsueh':ab,ti OR 'hsueh, chung i':ab,ti OR 'traditional medicine, chinese':ab,ti OR 'zhong yi xue':ab,ti OR 'chinese traditional medicine':ab,ti OR 'chinese medicine, traditional':ab,ti OR tang:ab,ti OR decoction:ab,ti OR pill:ab,ti OR capsule:ab,ti OR granule:ab,ti OR 'chinese herbal medicine':ab,ti	230 337
#6	#4 OR #5	268 568
#7	#3 AND #6	159

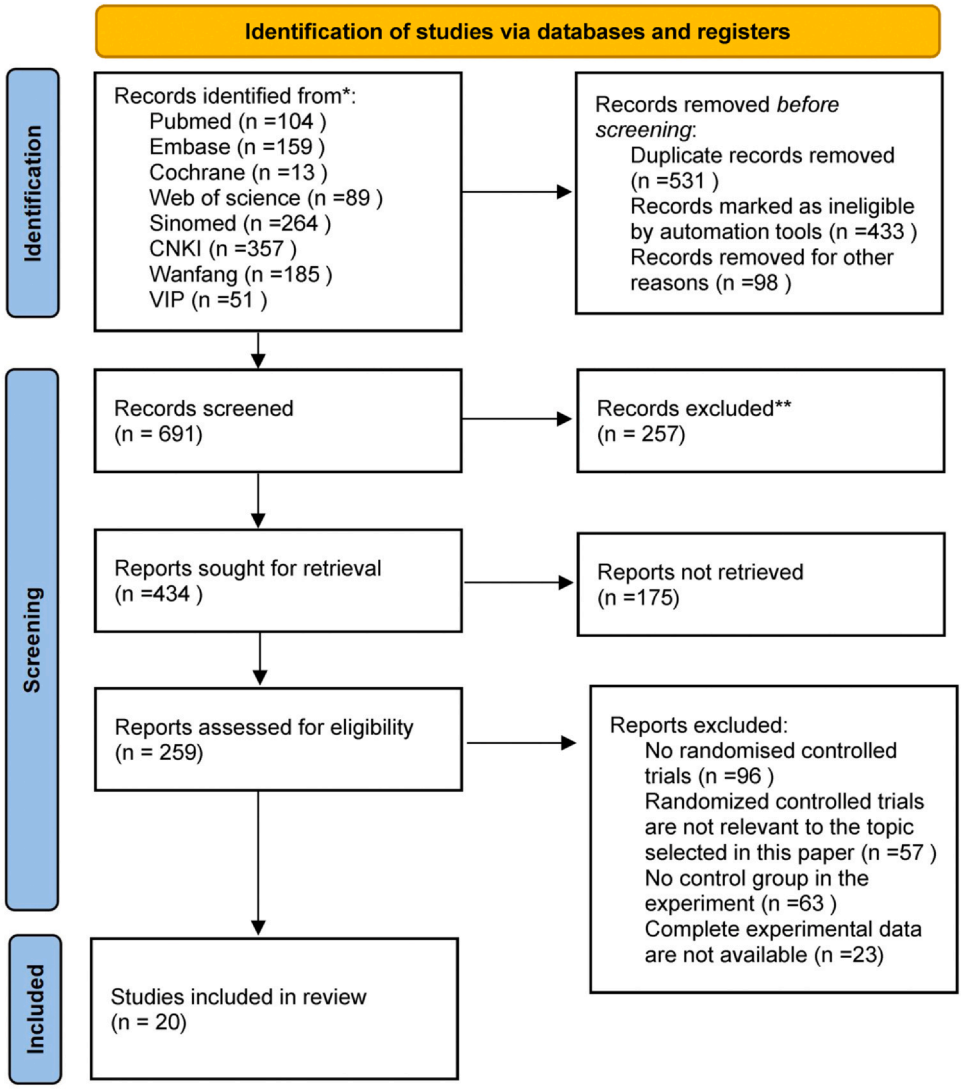

Fig. 1. Literature screening results.

Study Characteristics

A comprehensive analysis of 20 studies has been conducted, involving the analysis of eight TCM formulas. These formulas include Buzhong Yiqi Decoction, Zishen Tiaogan Decoction, Jianpi Yishen Juxian Decoction, Shengyang Jutuo Decoction, Yiqi Shengti Decoction, Jiawei Huangqi Renshen Decoction, Zini Yiqi Jianpi Decoction, and Peipi Shugan Decoction. The total sample size for the analysis was 1 473, with 739 cases in the experimental group and 734 cases in the control group. Detailed information regarding the characteristics of the included studies can be found in Table 2.

Quality Assessment of Studies

Of the 20 studies included (Guo and Zhang, 2020; Hao et al., 2017; He and Li, 2013; Hu et al., 2016; Lei, 2012; Li et al., 2018, 2021; Liao, 2017; Liu, 2017; Ma, 2013; Ou, 2007; Sun, 2013; Wang, 2018; Wei et al., 2021; Xia, 2013; Yang, 2008; Yang, 2018; Yin, 2021; Zhao et al., 2017; Zu, 2015), 11 studies (Guo and Zhang, 2020; Hao et al., 2017; Li et al., 2018, 2021; Liu, 2017; Sun, 2013; Wei et al., 2021; Xia, 2013; Yang, 2018; Yin, 2021; Zu, 2015) utilized random number tables for grouping. Seven studies (He and Li, 2013; Hu et al., 2016; Lei, 2012; Ma, 2013; Ou, 2007; Yang, 2008; Zhao et al., 2017) either mentioned 'random' or did not provide details on the grouping method. Two studies (Liao, 2017; Wang, 2018) used treatment sequence for grouping. None of the studies provided information on the use of allocation concealment or the implementation of blinding for subjects, implementers, and outcome evaluators. Despite this, the integrity of the study data was considered to be relatively high, with complete and unbiased data. Therefore, all studies were rated as having a low risk in these areas. The assessment of bias is illustrated in Figures 2 and 3.

Meta-analysis

Effective Rate

Comprehensive Results. A total of 20 studies (Guo and Zhang, 2020; Hao et al., 2017; He and Li, 2013; Hu et al., 2016; Lei, 2012; Li et al., 2018; Li et al., 2021; Liao, 2017; Liu, 2017; Ma, 2013; Ou, 2007; Sun, 2013; Wang, 2018; Wei et al., 2021; Xia, 2013; Yang, 2008; Yang, 2018; Yin, 2021; Zhao et al., 2017; Zu, 2015) have reported the response rate, specifically focusing on eight types of TCM TSQNM formulas. It is important to note that each study solely compared TCM formulas with CWMT, without engaging in pairwise comparisons between these specific TCM formulas. Notably, the Buzhong Yiqi Decoction plus CWMT combination was the most frequently reported intervention in the included studies. Given the absence of closed loops, there is no requirement for conducting an inconsistency test (Fig. 4).

Table 2
Characteristics of the included studies.

First author and year of publication	Intervention measures in the control group	Intervention measures in the observation group	The number of cases in the control group	The number of cases in the observation group	Gender (female/male)	Ages in the control group	Ages in the observation group	Course of treatment	Follow-up time	Outcome indicators
(Ou, 2007)	P	P + B	30	30	35/25	27.5 ± 7 61	28.20 ± 7.56	12 mo	12 mo	①
(Yang, 2008)	P	P + B	28	28	29/27	8–70	9–69	3 mo	6 mo	①
(Lei, 2012)	P	H	52	58	69/41	28.75 ± 6.13	29.25 ± 6.07	2 mo	2 mo	①
(He and Li, 2013)	P	B	20	20	27/13	52.40 ± 2.42	51.32 ± 3.84	1 mo	1 mo	①
(Ma, 2013)	P	P + B	36	36	31/41	March 12	February 12	3 mo	3 mo	①, ②
(Sun, 2013)	P	B	30	30	31/29	40.9 ± 15.50	43.93 ± 15.50	15 d	12 mo	①
(Xia, 2013)	P	P + Y	30	30	37/23	45.87 ± 11.95	44.32 ± 13.33	2 mo	2 mo	①, ②
(Zu, 2015)	P	P + B	25	25	19/31	32.4 ± 2.2	32.4 ± 2.2	2 mo	2 mo	①, ②
(Hu et al., 2016)	P	P + Z	20	20	27/13	18–70	18–70	28 d	1 mo	①
(Hao et al., 2017)	P	P + Y	40	40	37/43	36.3 ± 7.5	35. 5 ± 7. 8	2 mo	3 mo	①
(Liao, 2017)	P	P + S	48	48	55/41	30.4 ± 6.1	30.5 ± 6.7	1 mo	1 mo	①
(Liu, 2017)	P	B	40	40	34/46	42.72 ± 4.18	41.37 ± 4.02	3 mo	3 mo	①
(Zhao et al., 2017)	P	P + Z	40	40	47/33	47.91 ± 12.39	51.09 ± 13.12	3 mo	3 mo	①
(Li et al., 2018)	P	P + B	45	45	43/47	33.13 ± 2. 47	33.67 ± 2.13	3 mo	3 mo	①
(Wang, 2018)	P	G	39	39	35/43	55.32 ± 5.23	55.29 ± 5.30	3 mo	3 mo	①, ②
(Yang, 2018)	P	P + B	52	52	55/49	43.47 ± 7.62	43.54 ± 7.37	18 mo	18 mo	①, ②
(Guo and Zhang, 2020)	P	P + YQ	60	60	56/64	35.21 ± 6.41	36.28 ± 6.29	3 mo	6 mo	①
(Li et al., 2021)	P	P + J	34	28	39/23	58.52 ± 13.96	65.20 ± 10.70	3 mo	3 mo	①, ②
(Wei et al., 2021)	P	P + J	35	40	27/48	45 ± 4	45 ± 6	6 mo	6 mo	①, ②
(Yin, 2021)	P	P + B	30	30	35/25	46.58 ± 2.57	46.61 ± 2.60	6 mo	12 mo	①

Notes: P, Conventional Western medicine treatment; B, Buzhong Yiqi Decoction; Z, Zishen Tiaogan Decoction; J, Jianpi Yishen Juxian Decoction; S, Shengyang Jutuo Decoction; Y, Yiqi Shengti Decoction; H, Jiawei Huangqi Renshen Decoction; YQ, Zini Yiqi Jianpi Decoction; G, Peipi Shugan Decoction; ①: effective rate; ②: adverse reaction.

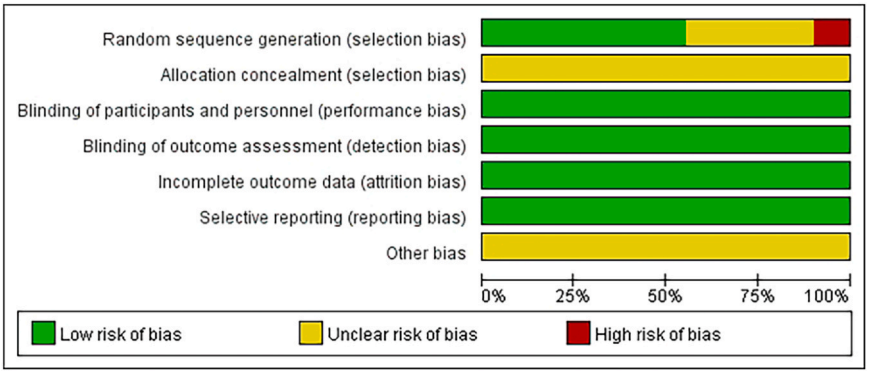

Fig. 2. Assessment of bias.

Network Meta-analysis Results. The network meta-analysis results demonstrated that CWMT + Buzhong Yiqi Decoction, CWMT + Zishen Tiaogan Decoction, Buzhong Yiqi Decoction, and Jiawei Huangqi Renshen Decoction were significantly more effective when compared to CWMT alone (Fig. 5). Additionally, variations in the efficacy of specific TCM formulas were observed (Table 3). Notably, CWMT + Buzhong Yiqi Decoction exhibited superiority over CWMT alone (RR = 1.34, 95% CI [1.21, 1.50], $P < 0.05$), while CWMT + Zishen Tiaogan Decoction showed significant benefits compared to CWMT alone (RR = 1.26, 95% CI [1.02, 1.58], $P < 0.05$). According to the SUCRA probability rankings, the top three effective interventions were CWMT + Buzhong Yiqi Decoction (0.85), Jiawei Huangqi Renshen Decoction (0.74), and CWMT + Zishen Tiaogan Decoction (0.65) (Table 4).

Meta-regression. A meta-regression was conducted to explore the impact of differences in dosages and courses of treatment on the response rate of the included TCM formulas. It was found that the response rate did not show a significant association with the dosage and course of treatment of the TCM formulas, as compared to CWMT, as indicated in Table 5.

Adverse Reactions

Comprehensive Results. Eight studies (Li et al., 2021; Ma, 2013; Wang, 2018; Wei et al., 2021; Xia, 2013; Yang, 2018; Yin, 2021; Zu, 2015) reported adverse reactions related to the use of four different formulas. These reactions included hormone-induced obesity, gastrointestinal issues such as nausea, vomiting, abdominal pain, and diarrhea, as well as gastrointestinal ulcers. Additionally, symptoms of autonomic nervous dysfunction, such as dizziness and palpitations, along with other general symptoms like rash, fever, renal function abnormalities, and liver function abnormalities, were also observed and reported in these studies (Table 6). It is important to note that each study exclusively compared the effects of the TCM formulas with CWMT, without making direct comparisons between the different TCM formulas themselves. Among all the formulas, the Buzhong Yiqi Decoction vs. CWMT was the most frequently studied. Given the absence of a closed loop, inconsistency testing was deemed unnecessary (Fig. 6).

Network Meta-analysis Results. The results from the network meta-analysis indicated that when combined with CWMT, Buzhong Yiqi Decoction, Peipi Shugan Decoction, Jianpi Yishen Juxian Decoction, or Yiqi Shengti Decoction effectively reduced the occurrence of adverse reactions compared to CWMT alone (Table 6). Notably, the treatment with Yiqi Shengti Decoction exhibited significant advantages (Fig. 7), and variations in effectiveness were observed among certain TCM formulas (Table 7). Based on the SUCRA rankings, Yiqi Shengti Decoction (0.91) was associated with the lowest incidence of adverse reactions, followed by Peipi Shugan Decoction (0.83) and Buzhong Yiqi Decoction (0.44) (Table 4).

Meta-regression. We conducted a meta-regression analysis to assess the relationship between dosage, duration of treatment, and the occurrence of adverse reactions, taking into account the variations in dosages and treatment durations. The findings revealed that there was no significant association between the dosage and duration of treatment for TCM formulas, in comparison to CWMT, in terms of the incidence of adverse reactions (Table 5).

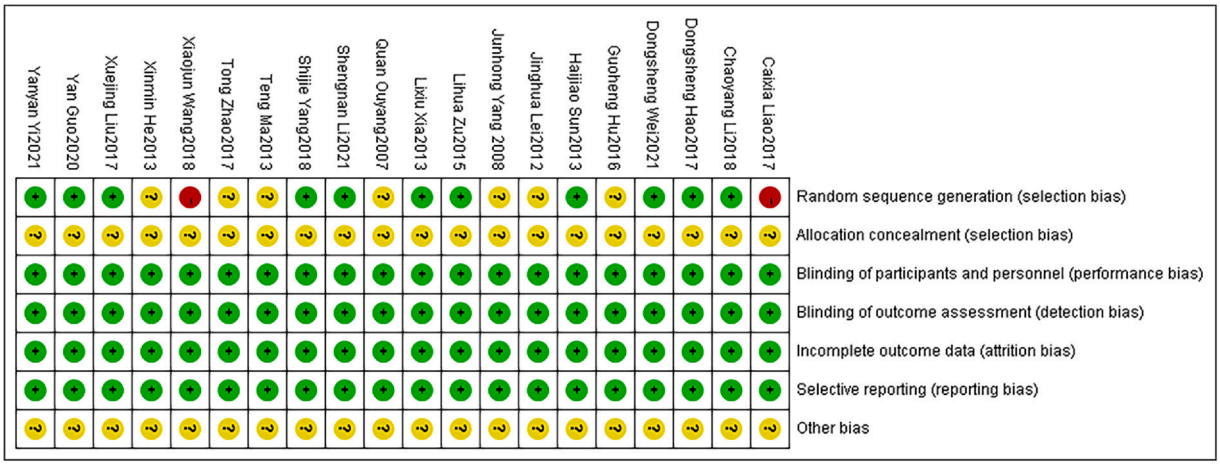

Fig. 3. Assessment of bias.

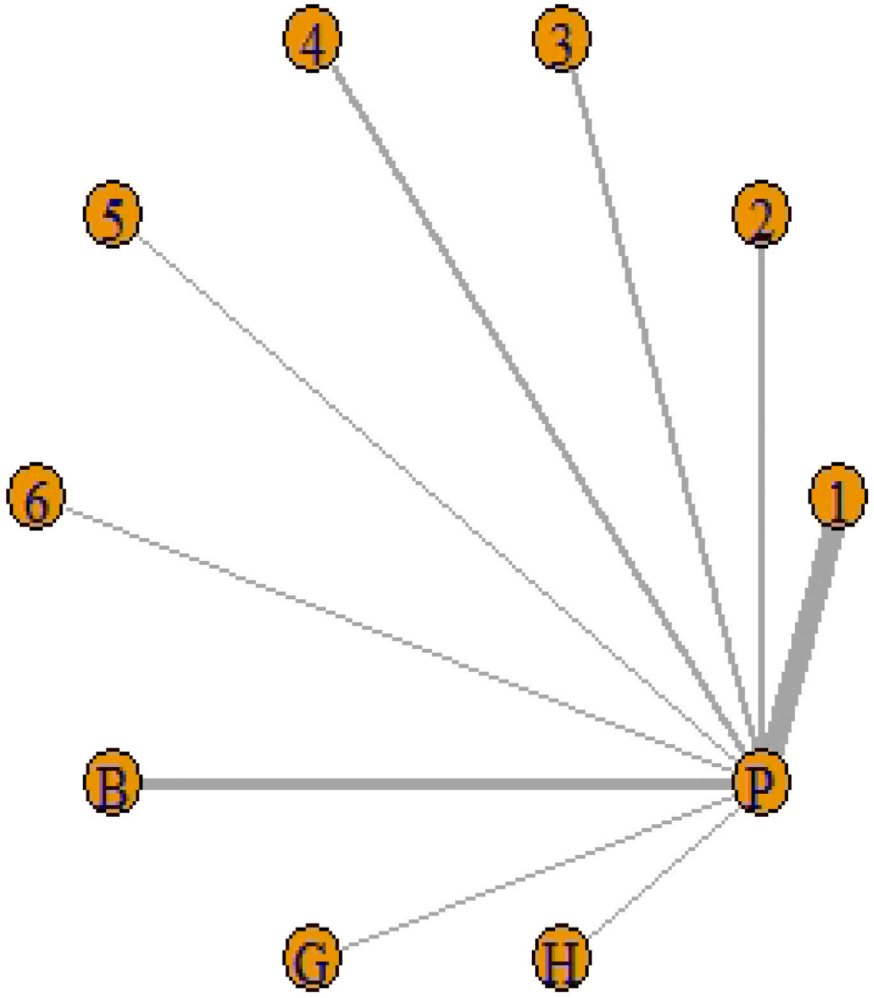

Fig. 4. Efficient network. Notes: 1: conventional Western medicine treatment + Buzhong Yiqi Decoction; 2: Western medicine conventional treatment + Yiqi Shengti Decoction; 3: conventional Western medicine treatment + Jianpi Yishen Juxian Decoction; 4: conventional Western medicine treatment + Zishen Tiaogan Decoction; 5: conventional Western medicine treatment + Shengyang Jutuo Decoction; 6: conventional Western medicine treatment + Zini Yiqi Jianpi Decoction. P, conventional Western medicine treatment; B, Buzhong Yiqi Decoction; H, Jiawei Huangqi Renshen Decoction; G, Peipi Shugan Decoction.

Discussions

Summary of Findings

This study utilizes network meta-analysis to rank the TCM formulas for the treatment of MG. The objective is to provide an evidence-based medicine reference for the integration of TCM into the clinical management of MG. A comprehensive search was conducted to identify relevant studies. A total of 20 studies were included, involving eight TCM formulas: Buzhong Yiqi Decoction, Zishen Tiaogan Decoction, Jianpi Yishen Juxian Decoction, Shengyang Jutuo Decoction, Yiqi Shengti Decoction, Jiawei Huangqi Renshen Decoction, Zini Yiqi Jianpi Decoction, and Peipi Shugan Decoction. The efficacy and safety of combining these formulas with CWMT for MG were meticulously evaluated. Network meta-analysis was employed to indirectly compare the various intervention strategies. The findings suggest that Buzhong Yiqi Decoction exhibited the highest response rate, followed by Jiawei Huangqi Renshen Decoction and Zishen Tiaogan Decoction. Yiqi Shengti Decoction demonstrated the lowest incidence of adverse reactions, followed by Peipi Shugan Decoction and Buzhong Yiqi Decoction. Limited systematic reviews have been conducted on the effectiveness and safety of combining Buzhong Yiqi Decoction with CWMT for MG. Only one meta-analysis report titled 'Meta-analysis of Efficacy and Safety of Buzhong Yiqi Decoction in Treating Myasthenia Gravis (Chen et al., 2019)' included a small number of studies to evaluate the safety of Buzhong Yiqi Decoction alone. Further investigation is warranted. Among the 19 studies included in their analysis, a fixed-effects model was utilized due to low overall heterogeneity (I^2 = 36%). The results demonstrate that compared to CWMT, Buzhong Yiqi Decoction can

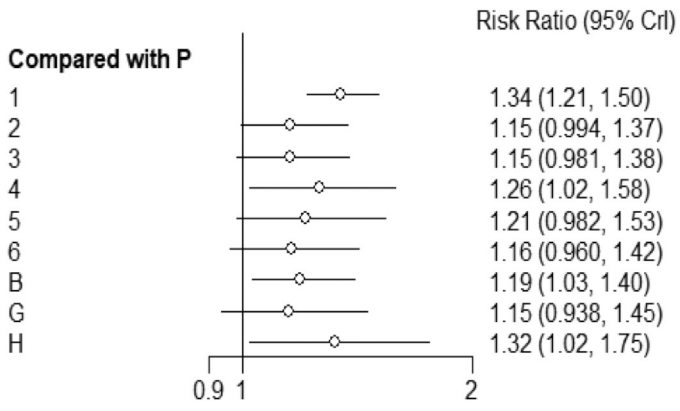

Fig. 5. Forest map of efficacy.

Table 3
League table for response rate.

Intervention measures	1	2	3	4	5	6	B	G	H	P
1	-									
2	1.167 (0.954, 1.403)									
3	1.164 (0.95, 1.419)	0.997 (0.794, 1.268)								
4	1.069 (0.828, 1.359)	0.918 (0.695, 1.211)	0.918 (0.694, 1.209)							
5	1.109 (0.857, 1.407)	0.95 (0.723, 1.253)	0.954 (0.719, 1.251)	1.037 (0.759, 1.424)						
6	1.161 (0.924, 1.444)	0.995 (0.775, 1.281)	0.997 (0.77, 1.29)	1.085 (0.813, 1.463)	1.045 (0.782, 1.41)					
B	1.13 (0.932, 1.36)	0.969 (0.778, 1.216)	0.971 (0.773, 1.229)	1.058 (0.81, 1.396)	1.019 (0.779, 1.339)	0.976 (0.76, 1.246)				
G	1.169 (0.906, 1.472)	1.002 (0.763, 1.308)	1.004 (0.754, 1.319)	1.094 (0.8, 1.492)	1.053 (0.769, 1.436)	1.007 (0.747, 1.341)	1.035 (0.786, 1.34)			
H	1.02 (0.753, 1.352)	0.876 (0.634, 1.199)	0.878 (0.633, 1.196)	0.957 (0.673, 1.348)	0.921 (0.645, 1.301)	0.88 (0.626, 1.222)	0.902 (0.659, 1.227)	0.872 (0.618, 1.234)		
P	1.344 (1.21, 1.505)	1.151 (0.994, 1.372)	1.153 (0.981, 1.379)	1.258 (1.019, 1.583)	1.21 (0.982, 1.533)	1.158 (0.96, 1.419)	1.188 (1.03, 1.4)	1.148 (0.938, 1.453)	1.317 (1.02, 1.751)	

Notes: 1: Conventional Western medicine treatment and Buzhong Yiqi Decoction; 2: conventional Western medicine treatment and Yiqi Shengti Decoction; 3: conventional Western medicine treatment and Jianpi Yishen Juxian Decoction; 4: conventional Western medicine treatment and Zishen Tiaogan Decoction; 5: conventional Western medicine treatment and Shengyang Jutuo Decoction; 6: conventional Western medicine treatment and Zini Yiqi Jianpi Decoction.

Table 4
SUCRA values of various outcome indicators.

Outcome indicators	Interventions	SUCRA	RANK
Effective rate	P + B	0.85303722	1
	P + Y	0.40874222	9
	P + J	0.41693000	7
	P + Z	0.65284167	3
	P + S	0.55340778	4
	P + YQ	0.42764389	6
	B	0.50243167	5
	G	0.41223556	8
	H	0.74222056	2
	P	0.03050944	10
Adverse reactions	G	0.8370688	2
	P	0.1377550	5
	P + B	0.4426250	3
	P + J	0.1766388	4
	P + Y	0.9059125	1

significantly enhance the overall clinical response rate in individuals with MG (overall odds ratio = 3.85, 95% CI [2.77, 5.35], $P < 0.00001$) (Chen et al., 2019)

The effectiveness of Jianpi Yishen Juxian Decoction in treating Myasthenia Gravis (flaccidity syndrome) has been evaluated through a meta-analysis and network pharmacology studies. (Lu, 2022). Specifically, it improves the clinical response rate and reduces the risk of recurrence. However, there is no significant difference in terms of safety. Furthermore, network pharmacology has been utilized to examine the targets of *Astragalus mongholicus* Bunge. The findings regarding the clinical response rate and safety align with the outcomes of our own study.

Modern pharmacological studies of TCM suggest that the various components in Jiawei Huangqi Renshen Decoction can directly contribute to the repair process of gastric mucosal atrophy. The active ingredients contained in *Atractylodes macrocephala* Koidz. can block the damage caused by inflammatory factors in the CAG process to the mucosa. The combination of *Atractylodes macrocephala* Koidz. and *Panax ginseng* C.A.Mey. can also enhance the expression of gastric mucosal aquaporins AQP3 and AQP4, improving the pathological atrophy of the mucosa. Therefore, it can effectively alleviate the adverse reactions caused by Western medicine related to gastric mucosal damage (Zhang et al., 2019).

Mechanism of Buzhong Yiqi Decoction

The analysis underscores the significant clinical effectiveness of Buzhong Yiqi Decoction in conjunction with CWMT. This approach has the potential to effectively mitigate the adverse reactions induced by hormones, such as obesity and gastrointestinal discomfort. Moreover, the utilization of Yiqi Shengti Decoction in combination with CWMT is less likely to elicit adverse reactions. Contemporary research has established a correlation between the etiology and pathogenesis of MG and spleen deficiency, as well as other implicated organs. Since MG is an autoimmune disorder, the primary CWMT methods encompass the administration of acetylcholinesterase inhibitors to reduce the degradation of acetylcholine, immunosuppressants that target various immune response sites, human immunoglobulin that adheres to antigens in the bloodstream, plasma exchange to eliminate antigen-antibody immune complexes from the blood, and thymectomy or thymoma resection to address excessive thymic hyperplasia. The advantage of employing CWMT based on molecular cytology lies in its precise treatment approach with clearly defined targets. However, there are also apparent drawbacks, as it can easily result in immune disorders and even reciprocal harm. Buzhong Yiqi Decoction contains a novel type of acetylcholinesterase inhibitor (Cui et al., 2015). Some studies propose that this decoction manages MG by inducing changes in both cellular immunity and humoral immunity through its immunosuppressive effects (Dong et al., 2011). Contemporary pharmacological studies have demonstrated that Buzhong Yiqi Decoction reduces

Table 5
Regression coefficients of various influencing factors.

Outcome indicators	Influencing factors	Intervention measures	Regression coefficient
Effective rate	Dosage	P + B	−0.60860 (−1.95287 to 0.7617)
		P + Y	2.64552 (−1.09532 to 23.9973)
		P + J	−0.29219 (−22.30759 to 18.2449)
		P + Z	0.17687 (−18.03563 to 52.1553)
		P + S	0.53462 (−12.41220 to 34.7839)
		P + YQ	−0.056899 (−24.36867 to 16.9593)
		B	2.72241 (−0.49015 to 7.7341)
		G	0.01441 (−20.73046 to 23.6104)
		H	0.43248 (−11.35084 to 55.8888)
	Course of treatment	P + B	0.9042 (−0.27065 to 2.184)
		P + Y	−0.2045 (−31.37105 to 15.062)
		P + J	0.4908 (−5.04062 to 6.943)
		P + Z	0.8223 (−5.07765 to 9.466)
		P + S	0.2217 (−15.36045 to 38.349)
		P + YQ	−0.1573 (−57.85064 to 18.572)
		B	−0.2072 (−2.50947 to 1.897)
		G	−0.1591 (−23.66440 to 28.689)
		H	0.1190 (−16.20974 to 17.602)
Adverse reactions	Dosage	G	0.04690 (−23.02187 to 30.2408)
		P + B	−0.17114 (−2.57001 to 2.1634)
		P + J	0.10485 (−12.06944 to 24.5725)
		P + Y	−0.50520 (−123.79278 to 13.1454)
	Course of treatment	G	0.16255 (−16.53586 to 35.71923)
		P + B	1.17620 (−0.60185 to 2.88870)
		P + J	−0.23403 (−7.38464 to 5.94001)
		P + Y	0.20224 (−18.12605 to 51.21877)

Table 6
Characteristics of the eight studies related to the use of four different formulas.

Literature	Intervention measures	Experimental group	Control group
(Ma, 2013)	P + B	Two cases of hormone-induced obesity and three cases of gastrointestinal reaction	Six cases of hormone-induced obesity and 10 cases of gastrointestinal reaction
(Xia, 2013)	P + Y	-	Two cases of abnormal liver function and one case of hormone-induced obesity
(Zu, 2015)	P + B	One case of rash	Three cases of rash, one case of gastrointestinal ulcer, and two cases of hormone-induced obesity
(Wang, 2018)	G	-	Two cases of nausea and vomiting, one case of fatigue, and one case of dizziness
(Yang, 2018)	P + B	Two cases of dizziness, two cases of hypotension, and one case of fever	Two cases of dizziness, one case of diarrhea, and one case of hypotension
(Li et al., 2021)	P + J	One case of liver dysfunction, one case of renal dysfunction	One case of nausea and vomiting and one case of abdominal pain and diarrhea
(Wei et al., 2021)	P + J	One case of increased blood sugar level, one case of gastrointestinal ulcer, and two cases of infection	One case of liver dysfunction, one case of increased blood sugar level, one case of gastrointestinal ulcer, and one case of infection
(Yin, 2021)	P + B	Two cases of abnormal liver function and one case of hormone-induced obesity	Two cases of nausea and vomiting and one case of abdominal pain and diarrhea

the auxiliary T cells, augments the inhibitory T cells, diminishes the CD4 + /CD8 + ratio, and inhibits the production of acetylcholine receptor antibodies (AChR-Ab) in MG patients (Niu et al., 2009).

The collective findings mentioned above provide evidence that Buzhong Yiqi Decoction has a modulating effect on the immune function of the body, leading to its therapeutic benefits. However, there is a dearth of research on the effectiveness and safety of combining Buzhong Yiqi Decoction with CWMT in the treatment of MG. Only one analysis (Chen et al., 2019) has evaluated the safety of Buzhong Yiqi Decoction as a standalone treatment based on two articles. Therefore, there is a need for further investigation in this area.

The Strengths and Limitations of This Study

This research offers several strengths in comparison to previously published studies. It incorporates clinical RCTs focusing on eight specific types of TCM formulas used in conjunction with cognitive walking and multitasking training (CWMT) for the treatment of MG. Additionally, our study assesses the incidence of adverse reactions and the response rate as outcome measures. Moreover, it is worth noting that the study was prospectively registered in PROSPERO and conducted in adherence to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses Network Meta-Analysis guidelines.

Currently, there is a shortage of meta-analyses focusing on other TCM formulas. TCM encompasses a wide range of formulas, each with different therapeutic effects. Direct evidence for comparing the efficacy of various TCM formulas is lacking. Consequently, this study utilizes network meta-analysis to assess the effectiveness and safety of different oral TCM formulas, specifically targeting the treatment of MG. The aim is to offer a clinical reference that can aid in the management of MG.

There are still several limitations to consider in this study. Firstly, the quality of the included studies is unsatisfactory. Only 11 studies utilized random number tables for grouping, and none of them provided information on the implementation of allocation concealment and

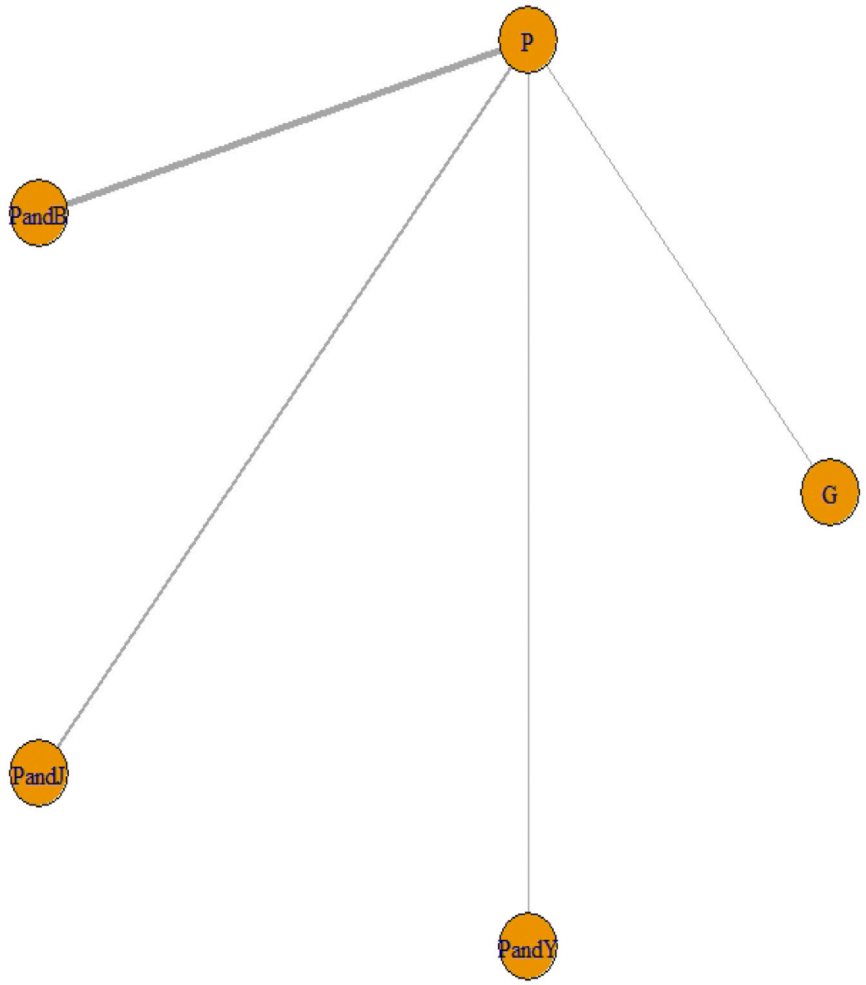

Fig. 6. A network of adverse reactions.

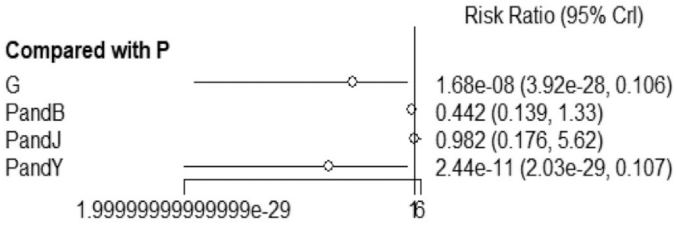

Fig. 7. Forest map of adverse reaction.

blinding. To address these limitations, future studies should prioritize the design of research protocols, clearly define the utilization of randomization methods, and implement allocation concealment and blinding to enhance reporting quality and mitigate bias risks. Secondly, the statistical power of this study may be compromised due to the predominance of small-sample studies. Additionally, the included studies did not specify the methods utilized for sample size estimation, which could impact the credibility of the research findings. Hence, it is crucial to develop precise techniques for calculating sample sizes to conduct robust, large-sample clinical studies and generate high-quality evidence. Lastly, the absence of direct comparative evidence between TCM formulas is a notable limitation, as it may influence the reliability of the research results obtained.

Table 7
League table for adverse reactions.

	G	**P**	P + B	P + J	P + Y
G	-				
P	0 (0, 0.106)				
P + B	0 (0, 0.258)	2.262 (0.75, 7.197)			
P + J	0 (0, 0.124)	1.019 (0.178, 5.675)	0.45 (0.055, 3.363)		
P + Y	1 136.804 (0, 3.13862620397968e + 21)	40 916 045 924.663 (9.369, 4.92731604320708e + 28)	18 426 227 837.053 (3.939, 2.13299728658048e + 28)	43 290 353 874.869 (8.239, 5.02402322643433e + 28)	

Conclusion

Combining TCM TSQNM formulas with CWM has been shown to have superior therapeutic effects in treating MG compared to CWMT alone. This combination treatment has a relatively low risk of adverse reactions. When Buzhong Yiqi Decoction is added to CWMT, it demonstrates the most significant clinical efficacy and effectively reduces adverse reactions such as hormone-induced obesity and gastrointestinal discomfort. On the other hand, the combination of Yiqi Shengti Decoction and CWMT is less likely to cause adverse reactions. With the ongoing advancements in TCM for treating myasthenia gravis, a diverse array of herbal formulations with differing efficacies has emerged, yet direct comparative evidence among these treatments remains scarce. This study aims to evaluate the clinical effectiveness and safety of TCM therapies that focus on strengthening the spleen, enhancing qi, and nourishing the bone marrow in patients with myasthenia gravis. The objective is to develop a comprehensive framework for clinical practice, grounded in existing efficacy data, which will open new avenues for future clinical research and provide novel perspectives for modern pharmacological analysis. These results are anticipated to contribute valuable insights for the management of myasthenia gravis. Future research should focus on exploring the benefits of combining different TCM formulas with CWMT in terms of TCM syndrome scores, serum AChR-Ab levels, daily life abilities, and safety to provide better guidance for clinical practice. In conclusion, the combination of TCM TSQNM formulas with CWMT is an effective treatment for MG. However, the included studies have low methodological quality, so these conclusions should be further verified through high-quality research.

Ethical approval

Not applicable.

CRediT authorship contribution statement

Chang Guan: Writing – original draft, Methodology, Investigation, Formal analysis, Conceptualization. **Jian Wang:** Writing – review & editing, Supervision, Resources. **Peng Xu:** Resources, Funding acquisition.

Informed consent statement

Not applicable.

Clinical trial registration number

Not applicable.

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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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Not applicable.

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