Review Article

Chinese herbal medicine for myasthenia gravis: A systematic review and meta-analysis of randomized clinical trials

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A B S T R A C T

Background: Myasthenia Gravis (MG) is a disorder of neuromuscular transmission bringing mild ocular weakness to severe generalized muscle weakness and disability. The conventional treatments have long-term side effects, and Chinese herbal medicines (CHM) have shown possible effect and safety for MG patients, but the existing evidence was not robust enough and the results were out of date.

Methods: Searching for randomized controlled trials (RCTs) was conducted in 7 databases and clinical trial registries until July 2021. The ROB 2 tool was used to assess the study quality and GRADE was used to assess the quality of whole evidence. Meta-analyses were conducted and the results were presented as risk ratio (RR) or mean difference (MD) with 95% confidence interval (CI).

Results: Nineteen RCTs (1283 participants) testing 13 kinds of CHM with adequate randomization were included and six RCTs investigating Compound Huangqi were included in the meta-analyses. In addition to conventional treatment, nine CHMs reduced symptom scores of MG. Compound Huangqi plus conventional treatment (pyridostigmine bromide or prednisone or both) reduced the symptom scores compared with conventional treatment (MD = -3.56, 95%CI -4.86 to -2.26). Less adverse events happened in the CHM groups (3/247 in the CHM groups, 52/245 in the control groups, RR = 0.13, 95%CI 0.06 to 0.30, 9 RCTs, a total of 492 participants). The effect on quality of life was inconsistent.

Conclusion: Nine CHMs could probably bring benefit for MG symptom improvement. Moderate to low certainty of evidence supported Compound Huangqi added-on conventional treatment probably bring extra benefit of improving MG symptoms. Adding CHMs could be safer than giving only conventional treatment.

Study registration: The protocol was registered in PROSPERO (ID: 32718).

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1. Introduction

Myasthenia Gravis (MG) is a disorder of neuromuscular transmission, resulting from binding of auto-antibodies to components of the neuromuscular junction, most commonly the acetylcholine receptor (ACHR). Clinically, the symptoms range from mild ocular symptoms to severe generalized muscle weakness and disability. Because of the severity of the symptoms, the disease has an extensive impact on physical, psychological and social well-being. The Medical Scientific Advisory Board of the Myasthenia Gravis Foundation of America (MGFA) has formed a Task Force to address these issues since 1997. The latest authoritative treatment recommendations in 2020 included thymectomy, rituximab in MG with antibodies to acetylcholine receptors and muscle-specific kinase, eculizumab, and methotrexate. However, pyridostigmine, corticosteroids and immunosuppressive therapy (IS) are still the most common treatments for MG. The use of pyridostigmine and corticosteroids needs to be reduced as much as possible because it is associated with many long-term side effects, often intolerable for patients. Therefore, many studies have been investigating alternative therapies for MG.

Chinese herbal medicine (CHM) has been a popular treatment for MG in China. The possible mechanisms include promoting the expression of transcription factor Forkhead box protein P3 (FoxP3) to up-regulate T regulatory cells (Tregs), and decreasing cytokine expression such as IL-4 and IL-13 (Astragalus membranaceus);
increasing number of Tregs and inhibiting Th17 cell differentiation (Radix Ginseng); a decrease of autoantibodies and immunoglobulin G (IgG) (Bupleurum polysaccharides (BPs) from Radix Bupleuri) and anti-acetylcholinesterase effects (flavonoid derivatives from Buxzhong Yiqi decoction). A systematic review on CHM for MG was published in 2018, which included 14 randomized controlled trials (RCTs) published before 2017. It concluded that CHM could be used for MG patients, but the conclusion was based on pooled data of different kinds of CHMs, the kind of CHM named HQFF (Compound Huangqi in English) was studied by three included RCTs, but the meta-analysis for this specific kind of CHM was not conducted. Giving only the overall effect of all kinds of CHMs induced more clinical bias in the analysis and the certainty of evidence was not assessed. Besides, the evidence was also out of date. To straighten out the current research progress of CHMs for MG, a more comprehensive search was conducted to include RCTs with more rigorous criteria of reporting quality, the included RCTs were assessed with the advanced risk of bias tool (ROB2) and the certainty of evidence was evaluated using the Grading of Recommendations, Assessment, Development and Evaluations (GRADE) tool. This review is to evaluate the effect and safety of CHM for MG patients, compared with conventional treatment.

2. Methods

The protocol was registered in PROSPERO (https://www.crd.york.ac.uk/PROSPERO/display_record.php?RecordID=32718), and the deviation from the protocol was explained in the end of this review.

2.1. Eligibility criteria

Types of studies: All RCTs featuring CHM for MG only with clear illustration on the randomization methods. Types of participants: People of any age or sex with an explicit diagnosis of myasthenia gravis. The diagnostic criteria of MG must contain following conditions: 1. Clinical symptoms: some specific striated muscle weakness showed volatility and easy fatigue, extraocular muscle involvement was most common, muscle weakness symptoms were mild in the morning and severe in the evening, after continuous activity, improved after rest. 2. Positive neostigmine test. 3. The results of Repetitive nerves stimulation (RNS) showed that the amplitude of low-frequency stimulation decreased by more than 10%. Single fiber electromography (SFEMG) results showed “trembling” widening with or without block. 4. Immunological examination: AChR antibody could be detected in the blood of most systemic MG patients, while anti-MusK antibody and anti-LRP4 antibody could be detected in a few MG patients. Based on condition 1, MG could be diagnosed with 2 or 3 or 4. This diagnostic criterion of MG was from the Guidelines for the diagnosis and treatment of myasthenia gravis in China 2015, which was published by China Medical Association. Types of interventions: All traditional CHM treatments for MG were included, with no restrictions on formulation, delivery, dosage, regimen etc. The medicine composition, and method of use should be reported. Trials using CHM combined with any acupuncture treatment would be excluded. Types of comparators: No intervention, placebo, or any conventional treatment for MG patients. The conventional treatment refers to all the recommended therapies from the clinical practice guidelines of MG, such as corticosteroids, immunosuppressive drugs, pyridostigmine bromide, and so on. Trials using any CHM treatment including pharmacotherapies and non-pharmacological therapies in the control group would be excluded. Types of outcomes and outcome measures: The main outcomes were symptom scores (continuous variable) and the effective rates of treatment (dichotomous variable) within 18 months of MG. The most important measures of symptom scores were The Quantitative Myasthenia Gravis (QMG) Test, and the clinical absolute and relative score system (ARS). The QMG test is a standardized quantitative strength scoring system developed specifically for MG. The QMG has been validated and has been used by the investigators in several previous trials. The higher numbers are representative of more severe impairment. It was recommended by the earlier MGFA Task force report in 2000 as the measure of improvement and worsening. Recent data support the use of a 2- or 3-point of change in QMG as a criterion for minimal clinically significant change and depending on MG severity; in mild (QMG 0–9) to moderate disease (QMG 10–16), a 2-point change is clinically significant, and a 3-point change is significant for severe MG (QMG >16). The clinical absolute and relative score system (ARS) was a standardized quantitative strength scoring system developed specifically for MG. It was developed in China and the reliability of this scoring system was proved by being tested in different observers. It was used popularly in clinical trials of MG in China. The scoring system consisted of two parts, the absolute scores, and the relative scores. The absolute scores included 8 items: ptosis, palpebra superior fatigability, disability of ocular motion, fatigability of the upper and lower extremity muscles, disability of the facial muscles, chewing difficulties, dysphagia, and disability of the respiratory muscles. Each item had five possible scores, ranging from 0 (the signs and symptoms being absent) to 4 (the most severe dysfunction). The relative scores were obtained with the scores before treatment subtracted by the scores after treatment and then divided by the scores before treatment. The higher the relative scores, the more significant the changes of the disabilities. Besides these, other objective and clearly illustrated effectiveness evaluation criteria would also be included. The specific calculation methods of the effective rates were defined by authors of included RCTs. The secondary outcomes including improvement in quality of life (QoL), reduction of the dose of hormone, withdrawal, and adverse events. Measures of QoL included any internationally recognized score and any other validated assessment techniques.

2.2. Searching process

Searching was conducted in the Cochrane Neuromuscular Disease Group Specialized Register, The Cochrane Central Register of Controlled Trials (CENTRAL) (2020, in The Cochrane Library), MEDLINE (January 1966 to September 2020), EMBASE (January 1980 to September 2020), Chinese Bio Medical Database (SinoMed) (1979 to September 2020), Chinese National Knowledge Infrastructure Database (CNKI) (1979 to September 2020), and VIP Chinese Science and Technique Journals Database (1989 to September 2020), and updated in July 2021. We also searched for unpublished literature in the Chinese Conference Papers Database and the Chinese Dissertation Database Ovid Wanfang database (from inception to July 2021). We did not set restriction on the year of dissemination, language, or report status such as unpublished manuscripts and conference abstracts. Other searching resources including the Chinese clinical trial registry and ClinicalTrials.gov for online registration were also searched. We searched searching engines and websites including Microsoft Academic for any missing articles, and opengrey.com for gray literature. We checked the references of studies included in the systematic reviews to identify any missing study. The authors of included RCTs were contacted by email and phone to request further published or unpublished work. The search strategy of PubMed can be reached in https://www.crd.york.ac.uk/PROSPEROFILES/32718_STRATEGY_20210103.pdf.

2.3. Selection and data extraction

Six authors were divided into three groups. In each group, two authors screened each record independently using NoteEx-
pressV3.0 and the disagreements were solved by discussion. Kappa values of each group were calculated to assure the quality of screening and we only started formal screening when the kappa value was above 0.75 in the test. One author (SJZ) collected data from included RCTs and another reviewer (ZYY) checked the extracted data and solved the disagreements by discussion. The data extraction form included study ID, title, first author, type of publication, diagnosis criteria, disease severity of MG, description of participants, complications, number of randomized and completed participants in both groups, drop-out details, type and details of treatment and control, duration of treatment, the measuring methods, and results of all outcomes. When studies reported confusing information including unclear or illogical numbers and figures, we tried to consult the authors to provide raw data.

2.4. Study risk of bias assessment

ROB 2 was used to assess risk of bias in the included studies with the excel tool. We assessed the risk of bias of the symptom scores of MG as the main outcome. All domains were assessed including items of the randomization process, deviations from the intended interventions (effect of assignment to intervention), missing outcome data, measurement of the outcome, selection of the reported result and an overall assessment. Two authors (ZSJ and ZYY) assessed risk of bias independently and solved the disagreements by discussion. In the randomization section, we considered only studies that explicitly reported the correct randomization method to be truly randomization. In the “deviations from the intended intervention” domain, if the deviations were not reported by the published trial, and no evidence had been shown for deviations, and the trial did not use adjusted statistical methods for deviations such as ITT analysis, we considered the trial to have used an appropriate analysis to estimate the effect of assignment to intervention. In the “missing outcome data” domain, if we did not find the published protocol of the RCT, the included RCT did not report drop-out, and there was no evidence to prove the existence of drop-out, we considered that the data of the outcome of the RCT was available for all. In the “measurement of the outcome” domain, we believed that if the scale used had been tested for reliability and validity, and had been used popularly by many trials, it was an appropriate measurement method.

When patients in the CHM group had significantly more visits than those in the control group due to the need to adjust the Chinese herbal medicine formulation, we thought that the measurement or ascertainment of the outcome could have differed between intervention groups. When the study did not report whether the outcome assessors were blinded, we considered they might be aware of the intervention received by participants, because in a hospital environment, outpatients were often treated and evaluated by the same doctor, while the inpatients had daily contact with all the doctors. It was easy for the outcome assessors to know the intervention received by participants. In the “selection of the reported result” domain, we compared reported results with the protocol or the pre-specified analysis plan. If the protocol or the analysis plan was not available, we considered there was no information for this domain. When four or more domains were assessed as “some concerns”, the risk of bias of the RCT was accumulated, we considered the overall evaluation should be “high risk”, even if there was no “high risk” domain.

2.5. Effect measures

Continuous data were presented as mean difference (MD) with 95% confidence interval (CI) in the symptom score and quality of life. Binary data were presented as risk ratio (RR) with 95% CI for the total effective rate and the curative rate. The random-effects model was used for meta-analysis considering potential clinical heterogeneity. For example, the included CHM could be given in different dosage forms and was compared with different kinds of conventional treatments. We conducted meta-analyses on the results of MG symptom scores, the effective rates, and secondary outcomes. The results of symptom scores would be synthesized into MD with 95% CI, the post treatment score between groups were compared when the difference value between before and after treatment were not reported. The effective rates would be synthesized into RR with 95% CI.

2.6. Synthesis methods

Only studies with accessible full text, reporting outcomes of interest clearly were eligible for each synthesis. Only studies investigating on the “CHMs of the same category” were eligible for meta-analysis. The definition of “CHMs of the same category” was based on the treating principles of traditional Chinese medicine for MG. According to the previous study, spleen and kidney deficiency was the main pathogenesis of MG, and invigorating spleen and kidney was the treating principle for MG. The most frequently used herb was Astragalus Radix, which was often used as the sovereign drug (main drug) in the prescription. The common minister drug (adjuvant drug) included Ginseng Radix et Rhizoma, Atractylodis Macrocephalae Rhizoma, Angelicae Sinensis Radix, Lycii Fructus etc. If the sovereign drugs and the minister drugs were the same in the prescriptions studied in different RCTs, we considered these CHMs to be of the same category. When there was add-and-subtract of the kinds of the herbs or changes of the amount of drug dosage in the prescription for syndrome differentiation, we still considered them to be of the same category if the kinds of sovereign drugs and minister drugs were not changed.

Forest plot was used to present the result of meta-analyses. Review Manager 5.4 was used to implement meta-analyses. The I² statistic was referred to judge the heterogeneity among the included RCTs. A smaller I² statistic indicates smaller heterogeneity. When I² > 50%, the accuracy of the data was checked first. If the data was accurate and appropriate, subgroup analysis would be used to explore possible causes of heterogeneity including different kinds of controls and different outcome scoring systems and the results would be carefully interpreted. The sensitivity analysis would include only blinded outcome assessment to see if the result was stable without placebo effect, based on the meta-analysis. The GRADE online tool was used to assess certainty of the body of evidence which was presented by Summary of Findings table. A funnel plot was used to explore the possibility of publication bias, if ten or more trials were included in a meta-analysis.

3. Results

3.1. Study selection

Overall, 6058 records were identified from database searching and other resources. 4060 records were screened by checking titles and abstracts, and 232 articles were screened by checking the full texts. After full-text screen, 19 RCTs with 1283 participants (46.4% male and 53.6% female) were included in this systematic review (Fig. 1).

3.2. Study characteristics

All trials were conducted in China and published from 2003 to 2020 with only one study (Jiang C 2014) published in English. Five trials were published in journals and 14 were dissertations. Only one trial (Jiang C 2014) had its protocol published online in the Chinese clinical trial registry, and no other protocols or statistics...
analyses plans were identified. All the studies only included patients with mild MG as Osseman or modified Osseman I, IIa, IIb type. Eight studies used diagnosis criteria from Guidelines for the diagnosis and treatment of myasthenia gravis in China 2015,7 7 used diagnosis criteria from medical textbooks, 2 used the results of academic conference for MG in 1997, 2 used both of guidelines and medical textbooks by combining the criteria. Participants of all ages were covered, only one study focused on the elderly and only one study focused on children. The comparisons between groups were CHM plus conventional treatment versus conventional treatment (15 studies) or CHM plus conventional treatment versus placebo plus conventional treatment (4 studies). Thirteen kinds of CHM were included, comparing with pyridostigmine bromide (PB), prednisone (Pred) or both or dexamethasone acetate. Among them, Compound Huangqi decoction or granules was tested in 6 studies, compared with different conventional treatments and with or without placebo, therefore we conducted meta-analyses on Compound Huangqi. The characteristics of included RCTs were shown in Table 1. The compositions, dosages, dosage forms and treating principles of all the prescriptions of included TCMs were displayed in the supplementary Table S1. We also compared the prescriptions of all the other kinds of CHMs with Compound Huangqi to present the differences between prescriptions of Compound Huangqi given by different RCTs and the similarity between Compound Huangqi and other kinds of CHMs in the supplementary Table S1.

In terms of outcomes, all 19 trials reported the symptom scores and the outcome was evaluated by The Quantitative Myasthenia Gravis (QMG) Test (n = 6) or the clinical absolute and relative score system (ARS) (n = 13). The evaluation of effective rates was reported as the total effective rate (n = 16) and the curative rate (n = 11). The rule to calculate these two rates was based on symptom scores. The relative score = (total symptom score before treatment - total symptom score after treatment)/total symptom score before treatment. The reporting effect was classified as curative, basically curative, significantly improved, improved, and ineffective, respectively, if the relative score is no less than 0.95, between 0.80 to 0.94, between 0.50 to 0.79, between 0.25 to 0.49, and below 0.25. The total effective rate included the curative, the basically curative, the significantly improved and the improved cases. The curative rate included only the curative cases. This calculation rule was applied to both the QMG test and the ARS system. Three trials reported the quality of life evaluated by Busch Qol. score, and 2 trials reported the reduction of the dose of pyridostigmine bromide (PB). The detailed results of main outcomes of all included studies were presented in Table 2.

3.3. Risk of bias in studies

The risk of bias in the outcome of symptom scores was assessed and shown in Table 3. All the trials reported the method of ran-
| Article ID | Type of MG | Male/Female | Age(year) | Duration of disease | Complications | Number of patients (T/C) | Treatment group | Control group | Duration of treatment | Outcome |
|-----------|------------|-------------|-----------|---------------------|---------------|--------------------------|----------------|--------------|----------------------|---------|
| BaoB 2016a | I, Ila, IIb | 28/32 | 28-64 | 3 months-4 years | NR | 30/30 | Compound Huangqi granules + pyridostigmine bromide | Placebo + pyridostigmine bromide | 36 weeks | 1,2 |
| BaoB 2016b | I, Ila, IIb | 110/131 | 27-65 | 11-38 years | No | 121/120 | Compound Huangqi granules + pyridostigmine bromide | Placebo + pyridostigmine bromide | 12 weeks | 1,2 |
| ChenML 2020 | I | 29/37 | 29-53 | 2-4 years | No | 34/32 | Qilin decoction + pyridostigmine bromide | Pyridostigmine bromide | 8 weeks | 1,2 |
| GuoY 2020 | I, Ila | 64/56 | 12-68 | 3 months-7 years | No | 60/60 | Yiqi Jianpi decoction + pyridostigmine bromide | Pyridostigmine bromide | 1 weeks | 1,2 |
| HeT 2016 | I, Ila, IIb | 26/35 | 18-75 | 1-10 months | No | 31/30 | Bupi Yishen decoction + pyridostigmine bromide | Pyridostigmine bromide | 6 months | 1,2,3 |
| JiangC 2014 | II | 35/25 | 17-75 | 1-61 months | No | 30/30 | JNJ granules + pyridostigmine bromide | Pyridostigmine bromide | 6 months | 1 |
| JuGS 2003 | I, Ila | 14/26 | 5-45 | 2 months-2.5 years | No | 30/30 | Tan-wei capsule + prednisone | Prednisone | 4 months | 1,2 |
| LaiJ 2013 | I, Ila, IIb | 29/31 | 7-74 | 1 month-16 years | No | 30/30 | Bupi Qiangli decoction + prednisone + pyridostigmine bromide | Prednisone + pyridostigmine bromide | 3 months | 1,2 |
| LiDF 2012 | I, Ila, IIb | 22/18 | 27-52 | NR | No | 30/30 | Pyridostigmine bromide | Pyridostigmine bromide | 8 weeks | 1,2 |
| LiZQ 2019 | I, Ila, IIb | 28/32 | 22-73 | NR | No | 30/30 | Compound Huangqi decoction + pyridostigmine bromide | Pyridostigmine bromide | 6 months | 1,2 |
| LiuXY 2020 | I, Ila, IIb | 38/30 | 60-80 | Thymoma 19, thymic hyperplasia 22, hyperthyroidism 27 | NR | 34/34 | Buzhong Yiqi decoction + dexamethasone acetate | Dexamethasone acetate | 12 weeks | 1 |
| MaY 2016 | I, Ila, IIb | 23/29 | 28-61 | 2.37 years on average | No | 26/26 | Bupi Yishen decoction + pyridostigmine bromide for type I | Pyridostigmine bromide for type I | 3 months | 1,2,3 |
| NiuGH 2009 | I, Ila, IIb | 24/36 | 24-62 | NR | No | 30/30 | Compound Huangqi granules + prednisone for type II | Placebo + prednisone + pyridostigmine bromide | 3 months | 1,2 |
| OuZh 2005 | I, Ila | 13/23 | 6-60 | 2 months-12 years | No | 18/18 | Qiangji Jianli oral liquid + pyridostigmine bromide | Placebo + pyridostigmine bromide | 60 days | 1,2 |
| ShengWD 2018 | I, Ila | 18/22 | 38-61 | NR | No | 20/20 | Supplemented Buzhong Yiqi decoction + pyridostigmine bromide | Pyridostigmine bromide | 2 months | 1 |
| YuanYK 2017 | I, Ila, IIb | 24/33 | 22-55 | NR | No | 29/28 | Compound Huangqi decoction + pyridostigmine bromide | Prednisone + pyridostigmine bromide | 4 weeks | 1,2,3 |

Note: NR means not reported, T/C means treatment group / control group. In the outcome column, 1 means symptom score, 2 means overall evaluation of efficacy, 3 means secondary outcomes including drug withdrawal and quality of life.
| Article ID   | Number of completed and analyzed participants (Treatment group/Control group) | Name of the CHMs and the component herbs                                                                 | Symptom scores Measurement | Total effective rate Risk Ratio (95% CI) | Curative rate Risk Ratio (95% CI) |
|-------------|--------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------|-----------------------------|-----------------------------------------|----------------------------------|
| **Chinese herbal medicine + pyridostigmine bromide + prednisone vs pyridostigmine bromide + prednisone** |                                                                                |                                                                                                          |                             |                                         |                                  |
| Lai 2013    | 30/30                                                                          | Buipi Qiangli decoction: Astragal Radix, Codonopsis Radix, Atractylodis Macrocephalae Rhizoma, Angelicae Sinensis Radix, Epimedi Folioum, Aconiti Lateralis Radix Praeparata, Smilacis Glabrae Rhizoma | ARS −1.13 [−3.33, −1.07]    | 1.07 [0.96, 1.20]                      | 2.00 [0.40, 10.11]                 |
| YuYY 2017   | 30/30                                                                          | Compound Huangqi decoction: Astragali Radix, Cimicifugae Rhizoma, Saponoskiviae Radix, Lycii Fructus, Pseudostellariae Radix, Angelicae Sinensis Radix, Atractylodis Macrocephalae Rhizoma, Corni Fructus | ARS −3.07 [−5.55, −0.59]    | 1.08 [0.88, 1.32]                      | 2.50 [0.53, 11.89]                 |
| YuanYK 2017 | 29/28                                                                          | Yiqi Bushen granules: Ginseng Radix et Rhizoma, Astragal Radix, Citri Reticulatae Pericarpium, Atractylodis Macrocephalae Rhizoma, Scutellariae Radix, Taxilli Herba, Ligustri Lucidi Fructus, Paoniae Radix Rubra | QMG −1.08 [−2.35, 0.19]    | 1.22 [0.90, 1.65]                      | Not Reported                      |
| **Chinese herbal medicine + pyridostigmine bromide + prednisone vs placebo + pyridostigmine bromide + prednisone** |                                                                                |                                                                                                          |                             |                                         |                                  |
| NiuGH 2009  | 30/30                                                                          | Compound Huangqi granules: Astragali Radix, Pseudostellariae Radix, Atractylodis Macrocephalae Rhizoma, Angelicae Sinensis Radix, Lycii Fructus, Corni Fructus | ARS −2.81 [−4.36, −1.26]    | 1.03 [0.94, 1.13]                      | 4.00 [0.47, 33.73]                |
| **Chinese herbal medicine + pyridostigmine bromide vs placebo** |                                                                                |                                                                                                          |                             |                                         |                                  |
| JiangC 2014 | 30/30                                                                          | JIN granules: Astragali Radix, Pseudostellariae Radix, Atractylodis Macrocephalae Rhizoma, Aurantii Fructus, Cimicifugae Rhizoma, Leonuri Herba, Angelicae Sinensis Radix, Lycii Fructus, Polygoni Multiflorei Radix, Corni Fructus | QMG −3.22 [−5.47, −0.97]    | Not Reported                          | Not Reported                      |
| ChenML 2020 | 34/12                                                                          | Qilian decoction: Astragali Radix, Cimicifugae Rhizoma, Bupleuri Radix, Puerariae Lobatae Radix, Copidpis Rhizoma, Scutellariae Radix, Citri Reticulatae Pericarpium, Pinelliae Rhizoma Praeparatum, Bambusae Caulis in Taenias, Nelumbinis Folioum, Chuanxiong Rhizoma, Angelicae Sinensis Radix, Glycyrrhizae Radix et Rhizoma Praeparata Cum Melle | ARS −2.75 [−5.10, −0.40]    | 1.17 [0.94, 1.44]                      | 1.41 [0.44, 4.55]                 |
| GuoY 2020   | 60/60                                                                          | Yiqi Jiaji decoction: Codonopsis Radix, Atractylodis Macrocephalae Rhizoma, Dioscoreae Rhizoma, Poria, Citri Reticulatae Pericarpium, Astragali Radix, Cocis Semen, Cimicifugae Rhizoma, Bupleuri Radix, Angelicae Sinensis Radix, Glycyrrhizae Radix et Rhizoma Praeparata Cum Melle | QMG −2.12 [−2.72, −1.52]    | 1.16 [1.03, 1.31]                      | 2.00 [0.52, 7.63]                |
| HeT 2016    | 31/30                                                                          | Buipi Yishen decoction: Astragali Radix, Panacis Quinquefolii Radix, Dioscoreae Rhizoma, Cimicifugae Rhizoma, Bupleuri Radix, Angelicae Sinensis Radix, Citri Reticulatae Pericarpium, Atractylodis Macrocephalae Rhizoma, Cistanches Herba, Morindae Officinalis Radix, Polygonati Rhizoma, Smilacis Glabrae Rhizoma, Dendrobii caulis, Glycyrrhizae Radix et Rhizoma Praeparata Cum Melle | QMG −0.83 [−1.42, −0.24]    | 1.12 [0.93, 1.35]                      | 2.42 [0.51, 11.53]                |
| LiDF 2012   | 20/20                                                                          | Yiqi Qushao decoction: Astragali Radix, Ginseng Radix et Rhizoma, Atractylodis Macrocephalae Rhizoma, Angelicae Sinensis Radix, Atractylodis Rhizoma, Alismatis Rhizoma, Cimicifugae Rhizoma, Phellodendri Chinensis Cortex | QMG −1.00 [−1.79, −0.21]    | 1.12 [0.91, 1.38]                      | Not Reported                      |
| LiZQ 2019   | 30/30                                                                          | Compound Huangqi decoction: Astragali Radix, Lycii Fructus, Cimicifugae Rhizoma, Saponoskiviae Radix, Angelicae Sinensis Radix etc. | ARS −2.26 [−4.07, −0.45]    | 1.69 [1.18, 2.41]                      | Not Reported                      |
| ShengWD 2018| 20/20                                                                          | Supplemented Buzhong Yiqi decoction: Astragali Radix, Codonopsis Radix, Atractylodis Macrocephalae Rhizoma, Bupleuri Radix, Glycyrrhizae Radix et Rhizoma Praeparata Cum Melle, Curculiginis Rhizoma, Epimedi Folioum, Cimicifugae Rhizoma, Angelicae Sinensis Radix, Citri Reticulatae Pericarpium | ARS −1.70 [−2.59, −0.81]    | NR                                  | Not Reported                      |
| Yanj 2016   | 20/20                                                                          | Supplemented Buzhong Yiqi decoction: Astragali Radix, Codonopsis Radix, Atractylodis Macrocephalae Rhizoma, Bupleuri Radix, Glycyrrhizae Radix et Rhizoma Praeparata Cum Melle, Curculiginis Rhizoma, Epimedi Folioum, Cimicifugae Rhizoma, Angelicae Sinensis Radix, Citri Reticulatae Pericarpium | ARS −3.20 [−4.19, −2.21]    | 1.00 [0.91, 1.10]                      | 3.00 [0.34, 26.45]                |
| YuYY 2018   | 31/31                                                                          | Compound Huangqi: Astragali Radix, Lycii Fructus, Cimicifugae Rhizoma, Saponoskiviae Radix, Angelicae Sinensis Radix etc. | ARS −2.45 [−3.86, −1.04]    | 1.20 [1.00, 1.44]                      | 2.38 [1.23, 4.59]                 |

(continued on next page)
domination generation, but only 4 trials concealed the randomization by using central pharmacy. Only four trials conducted blinding by using the placebo of CHM in the control group. No study reported the blinding the outcome assessor. Three trials reported the existence of drop-out and the details and they all used naive ‘per-protocol’ analyses which may induce bias due to deviations from the intended interventions, but the drop-out rates were all below 5% and the observed events were not rare, so it was unlikely to induce risk of bias due to missing outcome data. The included two scales of MG symptom scores were the most objective and reliable measure assessed by health care professionals, so the assessment of the outcome would be less likely influenced by the knowledge of intervention received. Since only the protocol of one trial was accessible, the risk of bias in selection of the reported result was mostly unclear. But since all the included RCTs reported the important clinical outcomes such as the symptom score, the lack of

| Article ID | Number of completed and analyzed participants (Treatment group/Control group) | Name of the CHMs and the component herbs | Symptom scores | Total effective rate | Curative rate |
|------------|--------------------------------------------------------------------------------|------------------------------------------|----------------|---------------------|--------------|
|            |                                                                                |                                           | Measurement    | Risk Ratio (95% CI) | Risk Ratio (95% CI) |
| **Chinese herbal medicine + pyridostigmine bromide vs placebo + pyridostigmine bromide** |                                       |                                           |                |                     |              |
| BaoB 2016a | 30/10                                           | Compound Huangqi: Astragali Radix, Lycii Fructus, Cimicifugae Rhizoma, Saposhnikoviae Radix, Angelicae Sinensis Radix etc. | ARS −8.20 [−11.91, −4.49] | 3.25 [1.77, 5.98] | Not Reported |
| BaoB 2016  | 121/120                                          | Compound Huangqi: Astragali Radix, Lycii Fructus, Cimicifugae Rhizoma, Saposhnikoviae Radix, Angelicae Sinensis Radix etc. | ARS −4.93 [−6.63, −3.50] | 3.93 [2.71, 5.68] | Not Reported |
| OuZH 2005  | 18/18                                             | Qiangji Jiansi oral liquid: Astragali Radix, Codonopsis Radix, Atractylodis Macrocephalae Rhizoma, Dioscoreae Rhizoma, Angelicae Sinensis Radix, Cimicifugae Rhizoma, Bupleuri Radix, Citri Reticulatae Pericarpium, Glycyrrhizae Radix et Rhizoma Praeparata Cum Melle, Humulus Scandens | ARS −2.41 [−3.33, −1.49] | 1.12 [0.93, 1.36] | 2.00 [0.20, 20.15] |
| **Chinese herbal medicine + prednisone vs prednisone** |                                       |                                           |                |                     |              |
| JuGS 2003  | 20/20                                             | Tan-wet capsule: Astragali Radix, Hominis Placenta, Strychni semen, Glycyrrhiza Radix et Rhizoma Praeparata Cum Melle | ARS −2.40 [−3.28, −1.52] | 1.05 [0.92, 1.20] | 2.00 [0.20, 20.33] |
| **Chinese herbal medicine + dexamethasone acetate vs dexamethasone acetate** |                                       |                                           |                |                     |              |
| LiuXY 2020 | 34/34                                             | Buzhong Yiqi decotion: Polygonyi Multiflore Radix, Atractylodis Macrocephalae Rhizoma, Corni Fructus, Paroniae Radix Alba, Angelicae Sinensis Radix, Glycyrrhiza Radix et Rhizoma Praeparata Cum Melle, Bupleuri Radix, Cuscutae semen, Cimicifugae Rhizoma, Polygonati Rhizoma, Polygonyi Multiflori Caulis | QMG −1.14 [−1.86, −0.42] | Not Reported | Not Reported |
| **Different conventional treatment for different type of MG in one study** |                                       |                                           |                |                     |              |
| MAY 2015   | 26/26                                             | Bupi Yishen decotion: Astragali Radix, Codonopsis Radix, Rehmanniae Radix Praeparata, Angelicae Sinensis Radix, Corni Fructus, Lycii Fructus, Mori Fructus, Atractylodis Macrocephaelae Rhizoma, Poria, Morindae Officinalis Radix, Cistanches Herba, Cuscutae semen, Citri Reticulatae Pericarpium, Bupleuri Radix, Cimicifugae Rhizoma, Platycodonis Radix | QMG Not Reported | 1.14 [0.95, 1.36] | 3.00 [0.33, 26.99] |

ARS, clinical absolute and relative score system; CI, Confidence interval; QMG, Quantitative Myasthenia Gravis Test.
protocol might not induce strong bias. We contacted the authors of 19 included RCTs for more details and any unpublished trials but we did not get any response.

3.4. Meta-analyses of compound Huangqi

We conducted meta-analyses to investigate the effect of Compound Huangqi on all the main outcomes, which were all measured by the clinical absolute and relative score system. The forest plot (Fig. 2) showed that when Compound Huangqi was given added on conventional treatment, the symptom score was reduced, comparing the post treatment score between groups (MD = −3.56, 95% CI −4.86 to −2.26, I² = 66%, 6 RCTs, n = 543). The subgroup analyses were conducted in different control and use of placebo. The results of subgroup analyses were Compound Huangqi plus pyridostigmine bromide (PB) plus prednisone (Pred) versus PB plus Pred (MD = −3.07, 95% CI −5.55 to −0.59, 1 RCT, n = 60); Compound Huangqi plus PB plus Pred versus placebo plus PB plus Pred (MD = −2.81, 95% CI −4.36 to −1.26, 1 RCT, n = 60); Compound Huangqi plus PB versus PB (MD = −2.38, 95% CI −3.49 to −1.27, I² = 0%, 2 RCTs, n = 122); Compound Huangqi plus PB versus placebo plus PB (MD = −6.10, 95% CI −9.17 to −3.03, I² = 61%, 2 RCTs, n = 301). The possible reasons for the heterogeneity in the last subgroup between BaoB 2016 and BaoB 2016a might be that BaoB 2016 was a multi-center RCT with 241 participants, but BaoB 2016a was a single center RCT with only 60 participants.

In terms of other outcomes, the confidence interval of the total effective rate was too wide and overlapped the null (RR=1.71, 95% CI 0.95 to 3.09, I² = 98%, 6 RCTs, n = 543). The heterogeneity was also too high which indicated the calculation of total effective rate might induce statistical bias into the pooled result. But the curative rate was significantly increased in the CHM group (RR = 2.49, 95% CI 1.39 to 4.46, I² = 0%, 3 RCTs, n = 182). However, the result should be interpreted carefully because of its small sample size. Details of the meta-analyses were shown in Fig. 3 and Fig. 4.

3.5. Secondary outcomes

Three studies reported the quality of life measured by Busch QoL score. The MD with 95% CI varied a lot among three studies, including 0.93 (0.24, 1.62), 21 −0.64 (−1.80, 0.52)28 and −2.72 (−4.17, −1.27).25 Because these 3 RCTs studied different kinds of CHMs with different controls, it would be inappropriate to pool the results. In addition, the different directions of results showed that the evidence is very uncertain. No study reported the reduction of the dose of corticosteroids, but 2 studies reported the reduction of PB. Since the evaluation criteria of drug dose reduction were different in these 2 studies, the result cannot be pooled. He T 2016 defined successful drug withdrawal as patients achieving complete remission of symptoms or clinical absolute score of basically curative standard with stable condition and no recurrence after withdrawal for more than one month. Five out of 30 participants achieved successful drug withdrawal, one out of 30 in the control group. Yu YY 2018 reported the change of daily dosage consumption of PB and PB withdrawal. The daily dosage consumption of PB reduced from 88.06±39.95 mg/d (before treatment) to 30.00 ± 36.33 mg/d (after treatment) in the CHM group, and from 89.68 ± 38.94 mg/d to 86.13 ± 42.24 mg/d in the control group (only PB). Seventeen participants achieved PB withdrawal in the CHM group, and only 2 achieved in the control group.

In terms of adverse events (AEs), 3 trials reported no AE in two groups. Seven trials reported no AE in the CHM group, but AEs happened in the control groups. These AEs including gastrointestinal reaction (n = 22), consisting of diarrhea, bloating, nausea, and vomiting; hormone side effects, consisting of moon-shaped face (n = 2), elevated fasting blood glucose (n = 4), and central obesity...
Two trials reported AEs occurred in both groups, but they occurred less in the CHM group. Yu YY 2017 reported 2 cases of stomach discomfort in the Compound Huangqi decoction plus PB group, and 4 cases of stomach cramps, 6 cases of diarrhea, 3 cases of nausea and vomiting, 1 case of bradycardia, 2 cases of increased sputum in the Prednisone Acetate plus PB group. Yuan YK 2017 reported 2 patients in the Prednisone plus PB group and 1 patient in the Yiqi Bushen granules plus Prednisone plus PB group with mild diarrhea and vomiting, which were attributed to unclean diet after medical history inquiry. Seven trials did not reported information about the occurrence of AEs. Overall, nine studies reported adverse events happened in both groups, 3 adverse events happened in the CHM groups (n = 247) and 52 adverse events happened in the control groups (n = 245), and the pooled data of adverse events was RR = 0.13 (95% CI 0.06 to 0.30, 9 RCTs, 492 participants).

3.6. Sensitivity analysis

We did not conduct sensitivity analysis because there was only 1 or 2 included RCTs in each comparison of the meta-analyses. The amount of included RCTs was not enough for us to conduct a meaningful sensitivity analysis.

3.7. Reporting bias

The funnel plot was not conducted as only 6 RCTs were included in the meta-analysis. There were not enough included RCTs to detect reporting bias.
Table 4
The summary of evidence using GRADE method.

**Question 1: Compound Huangqi plus pyridostigmine bromide plus prednisone compared to pyridostigmine bromide plus prednisone for myasthenia gravis patients**

| Certainty assessment | No of patients | Effect | Certainty | Importance |
|----------------------|----------------|--------|-----------|------------|
| **Symptom score (assessed with: the clinical absolute and relative score system)** | | | | |
| 2 RCTs, randomized trials | serious * not serious not serious not serious none | 80 | 60 | - | MO: 2.86 lower (2.2 lower to 3.57 lower) | MODERATE | CRITICAL |
| **The total effective rate (assessed with: the clinical absolute and relative score system)** | | | | | | | |
| 2 RCTs, randomized trials | serious * not serious not serious not serious serious * | 57/68 (59.9%) 54/68 (80.0%) | RR 1.04 (0.99 to 1.13) 36 more per 1,000 (from 20 lower to 117 more) | | | LOW | IMPORTANT |
| **The recovery rate (assessed with: the clinical absolute and relative score system)** | | | | | | | |
| 2 RCTs, randomized trials | serious * not serious not serious not serious serious * | 18/60 (15.0%) 3/60 (5.0%) | RR 2.05 (0.84 to 0.56) 28 more per 1,000 (from 18 lower to 469 more) | | | LOW | IMPORTANT |

**Question 2: Compound Huangqi plus pyridostigmine bromide compared to pyridostigmine bromide for myasthenia gravis patients**

| Certainty assessment | No of patients | Effect | Certainty | Importance |
|----------------------|----------------|--------|-----------|------------|
| **Symptom scores (assessed with: the clinical absolute and relative score system)** | | | | | | |
| 3 RCTs, randomized trials | serious * serious * not serious not serious none | 212 | 211 | - | MO: 4.01 lower (3 lower to 2.02 lower) | LOW | CRITICAL |
| **The total effective rate (assessed with: the clinical absolute and relative score system)** | | | | | | | |
| 3 RCTs, randomized trials | serious * serious * not serious serious * | 178/212 (84.6%) 73/211 (44.6%) | RR 2.22 (0.39 to 13.83) 422 more per 1,000 (from 3 lower to 1,000 more) | | | VERY LOW | IMPORTANT |

Note: a. The protocol of included RCTs were inaccessible, so there were some concerns about reporting bias. b. The confidence interval overlapped the null. c. The confidence interval was wide and the I square is over 50%. GI: GI: GRADE, MI: Mean difference, RR: Risk ratio

3.8. Certainty of evidence

The certainty of the recovery rate in the comparison of CHM plus PB versus PB was not assessed. Because there was only one study included, and GRADE method does not apply to single study. Moderate to low certainty of evidence supported that Compound Huangqi combined with conventional treatment for MG patients probably reduced more symptom scores than conventional treatment (Table 4). However, the certainty of the total effective rate and the curative rate was low to very low.

4. Discussion

According to former studies, CHM as adjunctive therapy for MG could reduce the QMG scores or MG clinical absolute and relative scores and improve total clinical effective rate. In addition, fewer adverse events happened in the CHM groups. But there were still some weaknesses in the primary study. The previous systematic review included 14 RCTs published before March 2017, the conclusion was based on the pooled data of all kinds of CHMs, and the certainty of the evidence was not assessed. This update of systematic review included 19 RCTs, eight of which were published after March 2017 involving 533 participants. This systematic review was conducted with updated methodological tools such as ROB2 and GRADE and the conclusion was based on RCTs studying CHMs of the same category of Compound Huangqi. Twelve kinds of CHM were included, in forms of decoction, granules and oral liquid. We found that most kinds of CHM added on conventional treatment might reduce symptom scores of MG compared with conventional treatment alone. Compound Huangqi showed significantly effect on improving the symptoms of MG, tested by 6 RCTs. As to adverse events, in the newly included RCTs, 3 studies reported adverse events happened in both groups, 3 adverse events happened in the CHM groups (n = 90) and 29 adverse events happened in the control groups (n = 89). Overall, twelve studies reported less AEs in the CHM group and no AE was caused by CHM, which indicated CHM was probably safe to use. Five studies of Compound Huangqi reported none or much less adverse events happened in the treatment group which indicated that Compound Huangqi was safe to use.17,26,29,33,34

In clinical practice, it is important to apply CHM under the guidance of traditional Chinese medicine's theory. In this review, most CHMs were formulated with the principle of tonifying the spleen, nourishing the kidney, dissipating dampness, and rising the Yang. The most used herbs were also well-known to reflect the treatment principles. Among all the tested CHMs, Compound Huangqi has representative characteristics on ingredients and principles of formulated prescription. This formula was invented by Jingsheng Zhang, a well-known traditional Chinese medicine doctor in Liaoning University of Traditional Chinese Medicine, and it was tested for MG in clinical practice for more than 20 years.33 Compound Huangqi decoction was produced by the Pharmaceutical Bureau of the First Affiliated Hospital of Liaoning University of Traditional Chinese Medicine. Compound Huangqi is not on the market yet and it’s only tested in the MG outpatient service of Affiliated Hospital of Liaoning University of Traditional Chinese Medicine in China. This kind of CHM might bring more benefit to MG patients and further clinical trials might unveil the accurate efficacy of Compound Huangqi in the future.

The basic mechanism of included CHMs is still not clearly investigated, but it can be inferred from published articles about the mechanisms of the components. In terms of the components of Compound Huangqi, studies have shown that Astragalus radix possesses potent immunomodulation, antioxidant, and anti-inflammation functions.35 Cimicifugae Rhizoma was reported to have anti-inflammatory, antioxidant, anti-complement, and...
anticancer effects. Saposnikoviae Radix may enhance the effectiveness of prescriptions by promoting distribution of other herbs in brain. Pharmacological studies indicated that Atractylodis macrocephalae rhizoma possessed antitumor activities, neuroprotective effect, anti-hepatotoxicity, immune and anti-inflammatory activity, etc. Crude extracts and pure compounds isolated from Radix Bupleuri exhibited various biological activities, such as anti-inflammatory, anticancer, antipyretic, antimicrobial, anti-viral, hepatoprotective, neuroprotective, and immunomodulatory effects. Angelicae sinensis radix played a therapeutic role for asthma with Yin deficiency syndrome and improved airway inflammation by inhibiting the expression of RORγt in lung tissues and regulating the balance of Th1/Th2 and Th17/Treg. Lycii fructus exhibits a cytoprotective effect, possibly through the enhancement of the antioxidant gene expression.

The limitation of RCTs included in this review was that the risk of bias was assessed to be unclear in many domains. There was no information about randomization concealing or the assessor to measure or assess the outcome. Seventeen studies did not publish or register the protocol and the only one study had its protocol registered online but did not mention it in the full text. We tried to contact the authors, but no one answered us. Another limitation is all studies of Compound Huangqi were conducted in the MG outpatient service of Affiliated Hospital of Liaoning University of Traditional Chinese Medicine in China. Compound Huangqi was applied in decoction or granules for 3 to 9 months, combined with pyridostigmine bromide or prednisone. When it was applied as decoction, the prescription was adjusted based on syndrome differentiation, and when it was given to children, the dosage was reduced according to their age. The study design did not adopt stratification of the patients according to their syndrome differentiation. The different treating strategies between children and adults were mixed when reporting the effect. The reduction of pyridostigmine bromide and prednisone was not following the same pattern, which might also induce bias in the meta-analyses.

In general, with the promising effect, if Compound Huangqi can be tested in different experimental environments, with more elaborate study design, it might have a larger and more precise clinical value. The mechanisms of the most used herbs in treating MG are still under investigation. Large, well-designed RCTs with a low risk of bias are still in great need.

Author contributions

Conceptualization: LJP. Methodology: LJP, ZSJ, and WRT. Writing – review & editing: LJP. Writing – original draft: ZSJ and WRT. Investigation: WRT, YZY, LCH, ZRX, ZYY, and FM. Formal analysis: ZSJ, YZY, and HM. Data curation: ZSJ, YZY, and HM.

Conflict of interest

JL is an editorial board member of this journal but the member status had no bearing on editorial consideration. The authors declare that they have no other conflicts of interest.

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Ethical statement

Not applicable.

Data availability

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

Deviation from protocol

We did not search AMED database because of network limits but we added search engines and websites follow the recommendation from Cochrane. Since the protocol has been registered for a long time and the ROB tool recommended by Cochrane has been updated, we decided to use ROB 2 to assess the risk of bias of studies. In terms of the inclusion criteria, since the published systematic review used a limit related to risk of bias to narrow the range of studies included in the meta-analysis, we decided to include studies with clearer reporting of the implementation of studies to achieve more reliable evidence. To give more practical recommendation for clinical practice, we only conducted meta-analysis of RCTs on same kind of CHM and assessed the certainty of evidence with GRADE.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.imr.2021.100806.

References

1. Gilhus NE, Verschueren JJ. Myasthenia gravis: subgroup classification and therapeutic strategies. Lancet Neurol. 2015;14:1023–1036. doi:10.1016/S1474-4422(15)00145-3.
2. Sanders DB, Wolfe GI, Benatar M, et al. International consensus guidance for management of myasthenia gravis: executive summary. Neurology. 2016;87:419–425. doi:10.1212/WNL.0000000000002790.
3. Bolding MI, Dekker L, Maniolo AH, et al. An up-date on health-related quality of life in myasthenia gravis -results from population based cohorts. Health Qual Life Outcomes. 2015;13:115. doi:10.1186/s12955-015-0286-1.
4. Nacqyanavami P, Sanders DB, Wolfe G, et al. International consensus guidance for management of myasthenia gravis: 2020 update. Neurology. 2021;96(3):114–122 Epub 2020 Nov 3. PMID: 33144515; PMCID: PMC7884897. doi:10.1212/WNL.0000000000011224.
5. Menon D, Barnett C, Bril V. Novel treatments in myasthenia gravis. Front Neurol. 2020;11:538. PMID: 32714266; PMCID: PMC7344308. doi:10.3389/neurol.2020.00538.
6. Chen S, Xu MB, Zhou XL, Rong PQ, Jin TY, Zheng GQ. Chinese herbal medicine for myasthenia gravis: a systematic review and meta-analysis. Front Pharmacol. 2018;9:969. PMID: 30214409; PMCID: PMC6125412. doi:10.3389/fphar.2018.00969.
7. Sterne JAC, Savović J, Page MJ, et al. ROB 2: a revised tool for assessing risk of bias in randomised trials. BMJ. 2019;366;14888. PMID: 31462531. Can be reached at https://www.rob2.info/welcome. doi:10.1136/bmj.14888.
8. Schünemann HJ, Higgins JPT, Vist GE, et al. Cochrane handbook for systematic reviews of interventions version 6.2 (updated February 2021). Chapter 14: completing ‘Summary of findings’ tables and grading the certainty of the evidence. Cochrane; 2021 Available from .
9. Li DY. Neuroimmunology group, Chinese medical association neurology branch; neuroimmunology branch of Chinese society of immunology Chinese guidelines for the diagnosis and treatment of myasthenia gravis 2015. Chinese J Neurol. 2015;48(11):934–940. doi:10.3760/cma.j.issn.1006-7876.2015.11.002.
10. Bedlack RS, Sineil DL, Bosworth H, Samsa G, Tucker-Lipcsick B, Sanders DB. Quantitative myasthenia gravis score: assessment of responsiveness and longitudinal validity. Neurology. 2005;64(11):1968–1970. PMID: 15955957. can be reached at https://myasthenia.org/Professionals/Resources-for-Professionals . doi:10.1212/01.WNL.0000163988.28892.79.
11. Wang XY, Xu XL, Sun H, Han X, Zhang H, Guo H. A clinical absolute and relative score system for myasthenia gravis. Chinese J Neurol. 1997:02:24–27.
12. Deeks JJ, Higgins JPT, Altman DG, et al. Cochrane handbook for systematic reviews of interventions version 6.2 (updated February 2021). Chapter 10: analysing data and undertaking meta-analyses, Cochrane; 2021 Available from .
13. Higgins JP, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. BMJ. 2003;327(7414):557–560 PMID: 12958120; PMCID: PMC192859. doi:10.1136/bmj.327.7414.557.
14. Page MJ, Higgins JPT, Sterne JAC, et al. Cochrane handbook for systematic reviews of interventions version 6.2 (updated February 2021). Chapter 13: assessing risk of bias due to missing results in a synthesis. Cochrane; 2021 Available from .
15. Xu Xian-hao. Neuroimmunology. Beijing: Beijing Medical University, China Union Medical University. 2001;100–155.
16. Busch C, Machens A, Pichineur U, et al. Long-term outcome and quality of life after thymectomy for myasthenia gravis. Ann. Surg. 1996;224(2):225–232. doi:10.1097/00000658-199608000-00017.
17. Bao B. Observation of clinical curative effect of Engelhardtia compound granules in treating myasthenia gravis. Liaoning University of Traditional Chinese Medicine; 2016.
18. Bao B, Zhang JS, Qiao WJ. Clinical observation on treatment of myasthenia gravis with engelhardtia compound granules. J Guangxi Univ Chinese Med. 2016;19(01):13–15.
19. Chen ML. The clinical efficacy observation of qilian prescription in the treatment of ocular myasthenia gravis with spleen-deficiency and dampness-heat type. Fujian University of Traditional Chinese Medicine; 2020.
20. Guo Y, Zhang LY. Clinical observation of self-made Yiqianji decoction combined with bropixigenine in the treatment of patients with myasthenia gravis. China's Naturopathy. 2020;28(03):57–60.
21. He T. Clinical Observation On the Treatment of Myasthenia Gravis With Reinforcing Spleen and Nourishing Kidney. Chengdu University of Traditional Chinese Medicine; 2016.
22. Jiang C, Liu P, Zhang J, et al. Clinical study of effects of Jian Ji Ning, a Chinese herbal medicine compound preparation, in treating patients with myasthenia gravis via the regulation of differential MicroRNAs expression in serum. Evid Based Complement Alternat Med. 2014;2014 Epub 2014 Jan 5. PMID: 24734107; PMCID: PMC3956408. doi:10.1155/2014/2518942.
23. Ju GS. Tanwei capsule and prednisone in the treatment of myasthenia gravis: a randomized controlled trial. Chengdu University of Traditional Chinese Medicine; 2003.
24. Lai J. Study on the immunoregulatory effect of the Bupiquangji decoction on myasthenia gravis with spleen and kidney deficiency. Guyang University of Traditional Chinese Medicine; 2013.
25. Li DF. Clinical observation of QJ and dampness treatment of myasthenia gravis and research of the immune regulation mechanism. Shandong University of Traditional Chinese Medicine; 2012.
26. Li ZQ. The clinical efficacy of compound Huangqi decoction in the treatment of Type I and II myasthenia gravis patients after thymoma operation. Liaoning University of Traditional Chinese Medicine; 2019.
27. Liu XY, Fan L. Effects of Buzhong Yiqi decoction on Treg cells, lymphocyte subsets and therapeutic effect in elderly patients with myasthenia gravis. World J Traditition Chinese Med. 2020;15(21):3326–3339.
28. Ma Y. Clinical observation of the reinforcing kidney and spleen theory for treating myasthenia gravis. Henan University of Traditional Chinese Medicine; 2016.
29. Niu GH. The complex recipe of astragalus membranaceus’s clinical effect in treating myasthenia gravis. Liaoning University of Traditional Chinese Medicine; 2009.
30. Ou ZS. Clinical study on Qiangji Jiuji Yin in treating myasthenia gravis. Guangzhou University of Traditional Chinese Medicine; 2005.
31. Sheng WD. Nerve electrophysiological effect of the adjusted prescription of Buzhong Yiqi decoction on myasthenia gravis (faciality syndrome) two spleen and kidney deficiency. Henan University of Traditional Chinese Medicine; 2018.
32. Yan J. The effect of the flavored Buzhongyiqi decoction on clinical curative and humoral immune factors in patients with myasthenia gravis. Henan University of Traditional Chinese Medicine; 2016.
33. Yu YY. The clinical curative effect of compound Huangqi decoction combined with pyridostigmine for juvenile ocular myasthenia gravis. Liaoning University of Traditional Chinese Medicine; 2018.
34. Yu Y, Qiao WJ. Observation of effect of modified compound Huangqi decoction on myasthenia gravis of spleen and kidney deficiency. Shanxi J Tradition Chinese Med. 2012;33(10):20–22 .
35. Yuan YK. The clinical observation of Qi-supplementing kidney-tonifying recipe on myasthenia gravis. Henan University of Traditional Chinese Medicine; 2017.
36. Guo Z, Lou Y, Kong M, Luo Q, Liu Z, Wu J. A systematic review of photochemistry, pharmacology and pharmacokinetics on astragali radix: implications for astragali radix as a personalized medicine. Int J Mol Sci. 2019;20(6):1463 PMID: 30909474; PMCID: PMC6470777. doi:10.3390/jcm20061463.
37. Lee JE, Kim BB, Ko Y, Jeong SH, Park JB. Effects of Cimicifugae Rhzoma on the osteogenic and adipogenic differentiation of stem cells. Exp Ther Med. 2017;13(2):443–448 Epub 2016 Dec 29. PMID: 28352313; PMCID: PMC5348703. doi:10.3892/etm.2016.4010.
38. Liang RF, Ge WJ, Wei Z, et al. [Effect of Saposhnikoviae Radix on pharmacokinetics and tissue distributions of active components in Tongue Yaeling in rats]. Zhongguo Zhong Yao Za Zhi. 2017;42(19):3802–3808 ChinesePMID: 29325298. doi:10.19540/j.cnki.cjcm.20170901.005.
39. Ruqiao L, Yueli C, Xuelan Z, et al. Rhizoma Atractylodis macrocephalae: a review of photochemistry, pharmacokinetics and pharmacology. Pharmazie. 2020;75(2):42–55 PMID: 32213324. doi:10.1691/ph.2020.9738.
40. Yang F, Dong X, Yin X, Wang W, You I, Ni J. Radix Bupleuri: a review of traditional uses, botany, phytochemistry, pharmacology, and toxicology. Biomed Res Int. 2017;2017 Epub 2017 May 16. PMID: 28593178; PMCID: PMC5448051. doi:10.1155/2017/7597596.
41. Ma TT, Feng XZ, Wang XY. [Effects and mechanism of Angelicae Sinensis radix on Th1/Th2 and Th17/Treg in mice with asthma and Yin deficiency syndrome]. Zhongguo Zhong Yao Za Zhi. 2017;42(4):758–762 ChinesePMID: 28959849. doi:10.19540/j.cnki.cjcm.20170121.037.
42. Xu W, Saiki S, Myojin T, et al. Lycii fructus extract ameliorates hydrogen peroxide-induced cytotoxicity through indirect antioxidant action. Biosci Biotechnol Biochem. 2018;82(10):1812–1820 Epub 2018 Jun 18. PMID: 29912670. doi:10.1080/09168451.2018.1487274.