Systematic Review and Meta-Analysis

Medicine

OPEN

Herbal medicine for the treatment of non-erosive reflux disease

A systematic review and meta-analysis

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Abstract

Background: Non-erosive reflux disease (NERD) is the most prevalent gastroesophageal reflux disease. Currently, proton pump inhibitors are the most commonly used treatment for NERD. Recently, the demand for herbal medicines with relatively few side effects is increasing and trials confirming the effectiveness and safety of herbal medicines for the treatment of NERD have been conducted. This study aimed to investigate the effectiveness and safety of herbal medicine in the treatment of NERD through published randomized-controlled trials.

Methods: Ten electronic databases were searched from inception until May 2023. Disease, intervention-related terms, and publication type keywords were combined as search terms. Studies designed as randomized controlled trials, including participants diagnosed with NERD with any type of herbal medicine as a treatment intervention were included. Data extraction and analysis were conducted by 2 independent reviewers. The total clinical efficacy rate was assessed as a primary outcome, while the secondary outcomes were recurrence rate, reflux diagnostic questionnaire score, short-form 36 health survey score, and serum motilin level. The risk of bias in each study and quality of evidence were assessed.

Results: Thirty-four randomized controlled trials involving 3759 patients were analyzed. Herbal medicine was significantly more effective in improving total clinical efficacy, recurrence rate, reflux diagnostic questionnaire score, some domains of short-form 36 health survey, and serum motilin levels in patients with NERD than conventional medical therapy. No severe intervention-related adverse effects were observed. Regarding the quality of evidence, most outcomes were revealed to have moderate to low levels of evidence.

Conclusion: This systematic review and meta-analysis suggests that herbal medicine can be an effective and safe therapy for NERD; however, there are several limitations regarding the methodological quality of the included studies. Further research with high methodological quality is necessary to improve the quality of evidence.

Abbreviations: CI = confidence interval, GERD = gastroesophageal reflux disease, MD = mean difference, MeSH = Medical Subject Headings, NERD = non-erosive reflux disease, PPI = proton pump inhibitor, RCT = randomized controlled trial, RDQ = reflux diagnostic questionnaire, RR = relative risk, SF-36 = short-form 36 health survey, TCE = total clinical efficacy, TCM = traditional Chinese medicine.

Keywords: herbal medicine, meta-analysis, non-erosive reflux disease, systematic review, total clinical efficacy rate

1. Introduction

Gastroesophageal reflux disease (GERD), one of the most common chronic gastrointestinal disorders, has 3 phenotypes, based on endoscopic and histopathological findings.[1] Non-erosive reflux disease (NERD) is the most common type, accounting for more than 70% of all cases, followed by erosive esophagitis and Barrett's esophagus.[2] NERD is defined as negative endoscopy results and presents with typical

This research was supported by the National Research Foundation of Korea (NRF) grant funded by the Korean Government (MSIT) (No. 2022R1C1C1004937) to S-JK.

The authors have no conflicts of interest to disclose.

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

Supplemental Digital Content is available for this article.

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How to cite this article: Kim M, Park C, Park J-W, Kim J, Ko S-J. Herbal medicine for the treatment of non-erosive reflux disease: A systematic review and meta-analysis. Medicine 2024;103:45(e40269).

Received: 20 May 2024 / Received in final form: 7 October 2024 / Accepted: 9 October 2024

http://dx.doi.org/10.1097/MD.0000000000040269

symptoms of heartburn and regurgitation.[3] Currently, medical and surgical therapies and lifestyle modifications, such as avoiding meals before bedtime, changing dietary habits, or cessation of cigarette smoking, are available for symptom management. Medical therapies include oral administration of proton pump inhibitors (PPIs), histamine receptor antagonists, and prokinetic agents.[1] PPI therapy is the first-choice treatment for both erosive and non-erosive GERD with its mucosal healing effect, but the pathogenesis of NERD is not the same as erosive esophagitis, and PPI is known to be effective only in approximately half of NERD patients. Other than acidic gastroesophageal reflux conditions, such as esophageal motility disorders, eosinophilic esophagitis, and functional heartburn, are considered the main causes of symptoms in the remaining 50% of NERD patients. The guideline states that adding rikkunshito, an herbal formulation, is effective for PPI-resistant NERD patients.[4] According to clinical practice guidelines of Korean medicine on functional gastrointestinal disorders, co-administering herbal medicine with conventional Western medicine as an add-on treatment is recommended with strengths of recommendation B.[5,6] In addition, the long-term use of PPIs should be performed with careful attention considering its potential risks such as developing carcinoid tumors, influencing gastrointestinal infections, and intestinal bacteria.[4]

Systematic reviews and meta-analyses have investigated the efficacy and safety of herbal medicines in the treatment of gastrointestinal diseases.[7–11] A systematic review and meta-analysis have suggested that modified *Banxia Xiexin* Decoction, a classical Chinese herbal formula, has positive effect on the management of GERD symptoms compared to conventional Western medicine,[7] and another meta-analysis revealed the efficacy and safety of *Banxia Xiexin* Decoction in the treatment of GERD through gastroscopy results, recurrence rate, and improvement in the symptom measures.[11] As the most recent study reported the effects of herbal medicine on the treatment of NERD, in 2018, a meta-analysis to investigate the therapeutic effects and safety of traditional Chinese medicine (TCM) for NERD was conducted. It was concluded that TCM therapy alone alleviates NERD symptoms and reduces the recurrence rate and side effects.[12] However, the searched databases were limited to English and Chinese language, and studies that co-administered Western medicine in the intervention of the experimental group were excluded from the above study.

In this systematic review and meta-analysis, we investigated the effects of herbal prescriptions in the treatment of NERD. Considering that there is an increasing demand for complementary and alternative methods for diseases in which conventional treatment does not have sufficient effects, especially those relevant to functional problems, and that a high proportion of patients take a combination of herbal medicine and Western medicine,[13] the results of this prior study simply comparing herbal formulation and conventional medicine had limitations for direct application in clinical practice. We included 15 more recent studies published after the search date of the previous study. Cases that used herbal medicine alone or in combination with Western medicine in the experimental groups were included in our analysis. We attempted to compare the effectiveness of herbal medicines to that of Western medicines alone to directly apply them in clinical situations. The effects of herbal medicine alone and in combination with conventional medicine were investigated separately.

2. Methods

This systematic review was conducted in accordance with the Cochrane Handbook for Systematic Reviews of Interventions, version 6.4.[14] No ethical approval was needed because all data in this study were derived from published studies.

2.1. Protocol and registration

The study protocol was registered in the International Prospective Register of Systematic Reviews (PROSPERO). The registration number is CRD42023423052.

2.2. Search strategy and selection criteria

Two independent authors (MK and CP) searched the literature published from inception to May 2023, from 10 electronic databases including MEDLINE (via PubMed), Cochrane Central Register of Controlled Trials (CENTRAL), Embase, Allied and Complementary Medicine Database (AMED), China National Knowledge Infrastructure Database (CNKI), Citation Information by Nii (CiNii), Korean Medical Database (Kmbase), Korean Studies Information Service System (KISS), National Digital Science Library (NDSL), and Oriental Medicine Advanced Searching Integrated System (OASIS). There were no restrictions on the language or publication date.

The search terms for the English databases were created by combining Medical Subject Headings (MeSH) and free-text words of disease-related, intervention-related terms, and publication type. The terms "gastroesophageal reflux," "herbal medicine," and "randomized controlled trials," which are listed in MeSH terms produced by the National Library of Medicine and synonyms of each, were combined to establish the search terms for each database. For disease-related terms, because the word "Non-erosive reflux disease" was not separately listed in the MeSH term, synonyms used in the titles or abstracts of previous studies were used.[12,15,16] In addition, we referred to the search terms of other studies in the same field to set more detailed search terms.[17,18]

All searched studies were investigated according to the following inclusion criteria: studies designed as randomized controlled trials (RCT); studies including participants diagnosed with NERD; studies involving any type of herbal medicine as a treatment intervention; and studies using one or more outcome measures, such as total clinical efficacy (TCE) rate, recurrence rate, or symptom score. Studies with the following criteria were excluded: (1) studies other than RCTs, such as case reports, retrospective studies, or reviews; (2) animal studies; (3) studies involving patients diagnosed with any organic disease associated with symptoms other than NERD; (4) studies involving only non-adults aged <19 years; (5) studies including herbal medicine as an intervention in both the control and treatment groups; and (6) studies using other traditional treatment methods in the treatment group. Disagreements between the 2 researchers were resolved through discussions with a third researcher (S-JK). The study selection process was performed using the EndNote X20 software.

2.3. Data extraction

Two independent reviewers (MK and CP) extracted information on the first author, publication year, language, intervention methods, treatment period, outcome measures, results, and side effects of the included studies. The data obtained were organized in a pre-established form.

2.4. Quality assessment

The quality of each study was assessed by 2 independent researchers (J-WP and JK) using Cochrane risk-of-bias tool version 2.0. Six domains of randomization process, deviations from intended interventions, missing outcome data, measurement of the outcome, selection of the reported results, and overall bias were assessed and each was determined as one of "low risk," "some concerns," or "high risk."

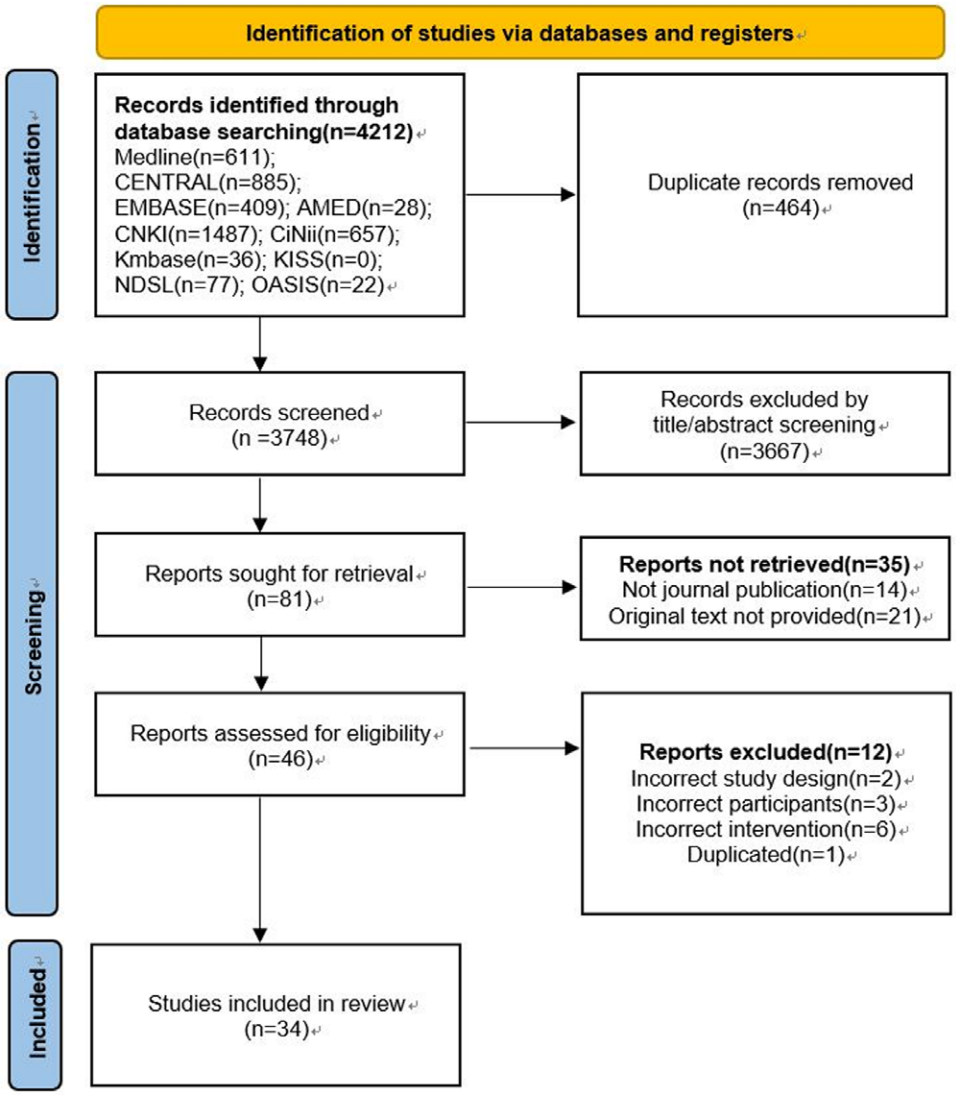

Figure 1. PRISMA flow diagram of study selection.

2.5. Data analysis and synthesis

Review Manager 5.4 software[19] was used for data synthesis and statistical analyses. For TCE and recurrence rate, which are dichotomous data, the results were presented as relative risk (RR) with a 95% confidence interval (CI), and the Mantel-Haenszel estimation method was applied. For the reflux diagnostic questionnaire (RDQ) scores, short-form 36 health survey (SF-36), and serum motilin levels, which are continuous data, results were assessed as the mean difference (MD) with a 95% CI, and the inverse variance estimation method was used. Statistical significance was set at $P < .05$. To assess the heterogeneity of the results, I^2 statistics was used. An I^2 statistic value of >50% was considered to indicate significant heterogeneity, and a random-effects model was used. For I^2 statistical values of or under 50%, a fixed-effects model was applied. For the primary outcome, subgroup analysis was conducted to minimize heterogeneity, and a funnel plot was used to examine publication bias.

2.6. Grading quality of evidence

We assessed the quality of evidence using the Grading of Recommendation, Assessment, Development, and Evaluation approach. The level of evidence was classified as very low, low, moderate, or high according to the risk of bias, inconsistency, indirectness, imprecision, and other considerations such as publication bias.[20]

3. Results

3.1. Study selection

A total of 4212 studies were identified during the first search, of which 464 were initially excluded because of duplications. The titles and abstracts of the remaining 3748 studies were investigated, and 3667 studies were excluded because they were not RCT or irrelevant to NERD and herbal medicine. In the next phase, 46 studies were investigated by full-text review and 12 studies were excluded. Among these, 2 studies were not clinical trials, 3 had inappropriate participants, 6 involved inappropriate interventions, and one was duplicated. Finally, 34 studies that met all the inclusion criteria were selected. All the experiments were conducted by 2 independent researchers (MK, CP, and S-JK) (Fig. 1).

3.2. Study characteristics

All the 34 included studies were designed as parallel RCTs. Only 4 articles[21–24] were written in English and 30 were written in Chinese. A summary of the data extracted from these studies is provided in Table 1.

Table 1

Characteristics of the studies.

Study	Language	Intervention (n)	Control (n)	Treatment period	Outcome measure	Results	Side effects
Zhu et al. (2007)	Chinese	HM + Esomeprazole (32)	Esomeprazole (32)	8 weeks	① TCE	① 90.6% versus 68.8% ($P < .05$)	NR
Chen et al. (2010)	Chinese	HM (42)	Omeprazole + Domperidone (42)	4 weeks	① TCE ② Symptom score ③ Recurrence rate	① 92.9% versus 80.9% ($P > .05$) ② No significant difference between 2 groups. ③ 12.8% versus 73.5% ($P < .01$)	NR
Huang et al. (2010)	Chinese	HM (100)	Omeprazole (100)	4 weeks	① TCE ② Improvement of main symptoms ③ Recurrence rate	① 78.0% versus 52.0% ($P < .001$) ② Treatment group was significantly better than control group in improving regurgitation and bitter mouth. ③ 15.5% versus 40.8% ($P < .01$)	No toxic side effects occurred.
Li et al. (2011)	English	HM + Placebo mosapride (54)	Mosapride + Placebo HM (51)	4 weeks	① Symptom score ② SF-36	① total score 12.85 ± 7.09 versus 17.93 ± 8.34 ($P < .05$) ② Treatment group was significantly better than control group in the domains of RP and GH.	No meaningful adverse reaction.
Zhong et al. (2011)	Chinese	HM (80)	Rabeprazole (80)	8 weeks	① TCE ② Symptom score ③ Recurrence rate	① 93.75% versus 80.00% ($P < .01$) ② heartburn 0.6 ± 0.7 versus 1.2 ± 0.9 ($P < .05$) acid regurgitation 1.0 ± 0.9 versus 1.7 ± 1.2 ($P < .05$) substernal pain 0.4 ± 0.6 versus 1.0 ± 1.1 ($P < .05$) regurgitation 0.7 ± 0.8 versus 1.1 ± 1.1 ($P < .05$) ③ 22.5% versus 55.0% ($P < .05$)	No meaningful adverse reaction.
Chen et al. (2012)	Chinese	HM (45)	Rabeprazole (45)	8 weeks	① TCE ② Recurrence rate	① 91.1% versus 65.0% ($P < .01$) ② 21.9% versus 50.0% ($P < .01$)	NR
Yang et al. (2012)	Chinese	HM (64)	Pantoprazole (63)	8 weeks	① Symptom score ② TCE ③ TCM symptom score ④ Curative effect of single symptom	① total score 6.39 ± 4.33 versus 6.06 ± 3.34 ($P > .05$) ② 92.2% versus 90.5% ($P > .05$) ③ Treatment group was significantly better than control group in improving belching, dry and bitter mouth, decreased appetite. heartburn 1.89 ± 1.99 versus 1.06 ± 1.89 ($P > .05$) acid reflux 1.36 ± 1.84 versus 0.82 ± 1.43 ($P > .05$) belching 1.19 ± 1.13 versus 2.00 ± 1.32 ($P < .01$) epigastric pain 0.85 ± 0.89 versus 0.94 ± 0.90 ($P > .05$) chest pain 0.12 ± 0.53 versus 0.18 ± 0.73 ($P > .05$) dry and bitter mouth 0.27 ± 0.72 versus 0.77 ± 1.07 ($P < .05$) decreased appetite 0.36 ± 0.59 versus 0.76 ± 0.56 ($P < .01$) ④ No significant difference between 2 groups.	NR

(*Continued*)

Table 1

(*Continued*)

Study	Language	Intervention (n)	Control (n)	Treatment period	Outcome measure	Results	Side effects
Li et al. (2013)	Chinese	HM (58)	Omeprazole (56)	4 weeks	① Symptom score ② SF-36 ③ TCE	① total score 20.2 ± 12.5 versus 23.9 ± 33.0 ($P < .01$) ② Treatment group was significantly better than control group. ③ 89.7% versus 78.6% ($P > .05$)	No meaningful adverse reaction.
Yang et al. (2013)	Chinese	HM (64)	Pantoprazole (63)	8 weeks	① RDQ ② TCE ③ PSQI ④ HAD	① total score 8.44 ± 4.22 versus 6.82 ± 3.26 ($P > .05$) frequency 2.82 ± 2.54 versus 1.76 ± 1.99 ($P > .05$) degree 5.62 ± 1.73 versus 5.06 ± 1.30 ($P > .05$) ② 87.5% versus 90.48% ($P > .05$) ③ 4.03 ± 2.74 versus 5.53 ± 3.54 ($P < .05$) ④ 5.36 ± 4.47 versus 7.88 ± 5.48 ($P < .05$)	NR
Wang (2014)	Chinese	HM (68)	Pantoprazole (69)	8 weeks	① RDQ ② SAS ③ SDS ④ SF-36	① frequency 2.8 ± 2.5 versus 1.7 ± 1.9 ($P > .05$) degree 5.6 ± 1.7 versus 5.0 ± 1.3 ($P > .05$) ② 23.1 ± 4.5 versus 38.8 ± 5.7 ($P < .05$) ③ 22.8 ± 4.8 versus 41.2 ± 6.1 ($P < .05$) ④ Treatment group was significantly better than control group.	NR
Tominaga et al. (2014)	English	HM + Rabeprazole (92)	Rabeprazole + Placebo HM (95)	8 weeks	① FSSG ② GSRS ③ SF-8	① No significant difference between 2 groups. ② No significant difference between 2 groups. ③ No significant difference between 2 groups.	No meaningful adverse reaction.
Zhang et al. (2015)	Chinese	HM (20)	Esomeprazole (20)	8 weeks	① Reflux symptom score ② DeMeester score ③ Reflux frequency ④ 5-HT OD value ⑤ LESP ⑥ Contraction amplitude	① No significant difference between 2 groups. ② No significant difference between 2 groups. ③ Treatment group was significantly better than control group. ④ Treatment group was significantly better than control group. ⑤ No significant difference between 2 groups. ⑥ No significant difference between 2 groups.	NR
Pan et al. (2016)	Chinese	HM + Pantoprazole + Domperidone (62)	Pantoprazole + Domperidone (60)	2 weeks	① Symptom score ② TCE	① No significant difference between 2 groups. ② abnormal acid reflux type 90.3% versus 83.3% ($P < .05$) acid hypersensitivity type 86.1% versus 40.0% ($P < .05$)	No meaningful adverse reaction.
Fu et al. (2016)	Chinese	HM (59)	Esomeprazole + Mosapride (59)	8 weeks	① RDQ ② TCE ③ HAMD ④ HAMA ⑤ SF-36 ⑥ TCM symptom score ⑦ Recurrence rate	① 3.56 ± 1.25 versus 7.92 ± 1.69 ($P < .01$) ② 81.36% versus 69.49% ($P < .05$) ③ 10.35 ± 5.73 versus 14.19 ± 6.42 ($P < .01$) ④ 3.56 ± 1.25 versus 7.92 ± 1.69 ($P < .01$) ⑤ Treatment group was significantly better than control group in the domains of PF, RP, GH, RE, and MH. ⑥ total score 5.62 ± 2.96 versus 7.15 ± 3.35 ($P < .05$) ⑦ 13.95% versus 37.50% ($P < .05$)	No meaningful adverse reaction.

(*Continued*)

Table 1

(*Continued*)

Study	Language	Intervention (n)	Control (n)	Treatment period	Outcome measure	Results	Side effects
Zhou et al. (2016)	Chinese	HM + Rabeprazole (80)	Rabeprazole (80)	8 weeks	① RDQ ② GERDQ ③ LESP ④ clearance capacity of distal esophageal body ⑤ TCE	① heartburn 0.62 ± 0.15 versus 0.76 ± 0.13 ($P < .01$) nausea 0.47 ± 0.18 versus 0.65 ± 0.21 ($P < .01$) chest pain 0.51 ± 0.12 versus 0.84 ± 0.14 ($P < .01$) acid reflux 0.32 ± 0.10 versus 0.74 ± 0.21 ($P < .01$) ② 7.42 ± 2.76 versus 8.84 ± 2.85 ($P < .01$) ③ Treatment group was significantly better than control group. ④ Treatment group was significantly better than control group. ⑤ 87.5% versus 61.25% ($P < .01$)	NR
He (2016)	Chinese	HM (44)	Lansoprazole (44)	4 weeks	① TCE ② SF-36	① 90.91% versus 70.45% ($P < .05$) ② Treatment group was significantly better than control group.	NR
Yang (2016)	Chinese	HM (33)	Omeprazole (33)	6 weeks	① TCE ② Symptom score ③ Recurrence rate	① 93.93% versus 72.73% ($P < .05$) ② total score 7.96 ± 1.59 versus 12.33 ± 2.12 ($P < .05$) acid reflux 1.93 ± 0.94 versus 2.90 ± 0.87 ($P < .05$) dysphagia 1.57 ± 0.88 versus 2.92 ± 0.91 ($P < .05$) burning sense in mouth 1.35 ± 0.56 versus 2.84 ± 0.63 ($P < .05$) heartburn 2.52 ± 1.01 versus 3.44 ± 1.14 ($P < .05$) ③ No significant difference between 2 groups.	No meaningful adverse reaction.

(*Continued*)

Table 1

(*Continued*)

Study	Language	Intervention (n)	Control (n)	Treatment period	Outcome measure	Results	Side effects
Du et al. (2017)	Chinese	HM + Pantoprazole + Domperidone (35)	Pantoprazole + Domperidone (33)	6 weeks	① TCE ② TCM symptom score ③ RDQ ④ Recurrence rate	① 94.29% versus 75.76% ($P < .05$) ② total score 6.63 ± 8.17 versus 13.45 ± 11.06 ($P < .01$) acid reflux 1.03 ± 1.12 versus 2.06 ± 1.46 ($P < .01$) heartburn 0.97 ± 1.32 versus 2.06 ± 1.54 ($P < .01$) abdominal pain 0.69 ± 1.08 versus 1.27 ± 1.31 ($P < .05$) belching 0.57 ± 0.92 versus 1.15 ± 1.33 ($P < .05$) pharyngeal discomfort 0.57 ± 0.92 versus 0.79 ± 1.11 ($P = .383$) decreased appetite 0.34 ± 0.77 versus 0.91 ± 1.13 ($P < .05$) depression 0.86 ± 1.40 versus 1.76 ± 1.20 ($P < .01$) bitter mouth 0.69 ± 0.96 versus 1.27 ± 0.40 ($P < .05$) defecation problem 0.51 ± 0.89 versus 1.15 ± 1.23 ($P < .05$) fatigue 0.40 ± 0.95 versus 1.03 ± 1.02 ($P < .05$) ③ total score 5.11 ± 3.90 versus 9.88 ± 6.16 ($P < .01$) frequency 2.46 ± 2.54 versus 4.76 ± 3.59 ($P < .01$) degree 2.66 ± 2.03 versus 5.12 ± 3.08 ($P < .01$) ④ 24.24% versus 48.28% ($P < .05$)	No meaningful adverse reaction.

(*Continued*)

Table 1

(*Continued*)

Study	Language	Intervention (n)	Control (n)	Treatment period	Outcome measure	Results	Side effects
Huang et al. (2017)	Chinese	HM + Omeprazole (43)	Omeprazole (43)	4 weeks	① RDQ ② TCE ③ Gastrointestinal hormone level ④ Symptom score	① total score 6.19 ± 4.80 versus 9.85 ± 4.98 ($P < .05$) ② 86.05% versus 55.81% ($P < .05$) ③ ghrelin 65.05 ± 5.72 versus 63.18 ± 5.90 ($P < .05$) LPO 4.19 ± 1.08 versus 4.52 ± 1.42 ($P < .05$) ④ regurgitation 1.42 ± 1.66 versus 4.29 ± 3.05 ($P < .05$) epigastric fullness 0.39 ± 0.62 versus 1.27 ± 1.06 ($P < .05$) dry and bitter mouth 0.86 ± 1.04 versus 0.68 ± 0.86 ($P < .05$) pharyngeal discomfort 0.59 ± 0.76 versus 0.97 ± 0.82 ($P < .05$) chest pain 0.83 ± 0.94 versus 1.46 ± 1.03 ($P < .05$) irritability 0.29 ± 0.63 versus 1.85 ± 0.63 ($P < .05$) heartburn 1.41 ± 1.33 versus 3.41 ± 3.17 ($P < .05$)	No meaningful adverse reaction.
Niu et al. (2018)	Chinese	HM (60)	Rabeprazole (30)	8 weeks	① TCE ② RDQ ③ TCM symptom score ④ SF-36 ⑤ Symptom score	① 98% versus 90% ($P < .05$) ② 5.60 ± 2.19 versus 7.07 ± 1.31 ($P < .01$) ③ Treatment group was significantly better than control group. ④ Treatment group was significantly better than control group. ⑤ Treatment group was significantly better than control group in improving heartburn and acid reflux.	NR
An et al. (2019)	Chinese	HM (32)	Omeprazole (33)	8 weeks	① TCE ② Symptom score ③ SF-36 ④ Gastrointestinal hormone level	① 87.5% versus 81.8% ($P < .05$) ② No significant difference between 2 groups. ③ Treatment group was better than control group in the domains of RP, GH, VT, SF, RE, and MH. ④ 5-HT 62.57 ± 30.35 versus 78.92 ± 34.28 ($P < .05$) VIP 17.85 ± 2.61 versus 19.61 ± 2.16 ($P < .05$)	No meaningful adverse reaction.

(*Continued*)

Table 1

(*Continued*)

Study	Language	Intervention (n)	Control (n)	Treatment period	Outcome measure	Results	Side effects
Zhang et al. (2019)	Chinese	HM + Rabeprazole (52)	Rabeprazole (48)	8 weeks	① TCE ② Sleep score ③ TCM symptom score ④ Gastrointestinal hormone level ⑤ SF-36	① 90.38% versus 66.67% ($P < .05$) ② Treatment group was significantly better than control group. ③ epigastric fullness 0.35 ± 0.07 versus 0.92 ± 0.11 ($P < .05$) acid reflux 0.52 ± 0.08 versus 0.97 ± 0.11 ($P < .05$) belching 0.42 ± 0.07 versus 0.94 ± 0.13 ($P < .05$) substernal pain 0.87 ± 0.07 versus 1.14 ± 0.14 ($P < .05$) ④ gastrin 64.49 ± 5.41 versus 54.39 ± 8.81 ($P < .05$) motilin 262.37 ± 14.28 versus 210.27 ± 16.71 ($P < .05$) substance P 29.68 ± 4.74 versus 26.39 ± 5.46 ($P < .05$) VIP 53.68 ± 7.28 versus 58.36 ± 9.65 ($P < .05$) ⑤ Treatment group was significantly better than control group.	No meaningful adverse reaction.
Zheng et al. (2019)	Chinese	HM + Lansoprazole (49)	Lansoprazole (49)	8 weeks	① TCE ② GERDQ ③ Symptom score	① 91.84% versus 69.39% ($P < .05$) ② 3.23 ± 0.68 versus 6.05 ± 0.73 ($P < .01$) ③ total score 7.74 ± 1.53 versus 13.08 ± 1.79 ($P < .01$) heartburn 1.98 ± 0.51 versus 3.22 ± 0.75 ($P < .01$) regurgitation 1.84 ± 0.62 versus 2.86 ± 0.69 ($P < .01$) chest pain 1.63 ± 0.58 versus 3.03 ± 0.79 ($P < .01$) acid reflux 1.76 ± 0.71 versus 3.24 ± 0.78 ($P < .01$)	NR
Huang (2019)	Chinese	HM + Mosapride + Flupentixol + Melitracen (60)	Mosapride + Flupentixol + Melitracen (60)	4 weeks	① TCE ② SAS ③ SDS ④ TCM symptom score ⑤ RDQ	① 85% versus 70% ($P < .05$) ② 35.88 ± 6.03 versus 42.64 ± 5.45 ($P < .05$) ③ 36.45 ± 6.12 versus 44.04 ± 5.07 ($P < .05$) ④ total score 10.25 ± 3.03 versus 14.38 ± 4.11 ($P < .05$) ⑤ total score 2.85 ± 0.61 versus 4.33 ± 0.92 ($P < .05$)	NR

(*Continued*)

Table 1

(*Continued*)

Study	Language	Intervention (n)	Control (n)	Treatment period	Outcome measure	Results	Side effects
Huang et al. (2020)	Chinese	HM + Lansoprazole (93)	Lansoprazole (93)	8 weeks	① TCE ② TCM symptom score ③ LESP ④ Contraction amplitude ⑤ Gastrointestinal hormone level	① 89.25% versus 65.60% ($P < .05$) ② heartburn 2.02 ± 0.39 versus 2.97 ± 0.68 ($P < .05$) regurgitation 1.23 ± 0.26 versus 2.09 ± 0.43 ($P < .05$) chest pain 2.15 ± 0.45 versus 2.83 ± 0.52 ($P < .05$) acid reflux 1.98 ± 0.36 versus 2.79 ± 0.62 ($P < .05$) ③ Treatment group was significantly better than control group. ④ Treatment group was significantly better than control group. ⑤ motilin 327.92 ± 39.58 versus 289.07 ± 35.72 ($P < .05$) gastrin 158.63 ± 25.77 versus 122.57 ± 23.06 ($P < .05$)	No meaningful adverse reaction.
Yin et al. (2020)	Chinese	HM + Esomeprazole + Flupentixol + Melitracen (44)	Esomeprazole + Flupentixol + Melitracen (43)	8 weeks	① TCE ② RDQ ③ HAMA ④ HAMD	① 90.91% versus 69.77% ($P < .05$) ② total score 7.81 ± 2.22 versus 11.74 versus 3.62 ($P < .05$) ③ Treatment group was significantly better than control group. ④ Treatment group was significantly better than control group.	NR
Zhai et al. (2021)	Chinese	HM + Omeprazole + Mosapride (48)	Omeprazole + Mosapride (48)	8 weeks	① SAS ② SDS ③ PSQI ④ TCE	① 31.07 ± 6.28 versus 37.12 ± 6.71 ($P < .01$) ② 35.08 ± 5.01 versus 40.43 ± 5.81 ($P < .01$) ③ 3.86 ± 0.34 versus 9.13 ± 1.21 ($P < .05$) ④ 95.83% versus 79.17% ($P < .05$)	NR
Cao et al. (2021)	Chinese	HM + Esomeprazole (86)	Esomeprazole + Flupentixol + Melitracen (86)	8 weeks	① GERDQ ② HAMA ③ HAMD-24 ④ TCE ⑤ Number of flora ⑥ Gastrointestinal hormone level	① 7.41 ± 1.62 versus 8.59 ± 2.32 ($P > .05$) ② Treatment group was significantly better than control group. ③ Treatment group was significantly better than control group. ④ 79.27% versus 62.19% ($P < .05$) ⑤ Treatment group was significantly better than control group. ⑥ 5-HT 151.33 ± 31.48 versus 140.57 ± 21.46 ($P < .001$) VIP 29.13 ± 5.36 versus 32.34 ± 3.42 ($P < .001$)	NR

(*Continued*)

Table 1

(*Continued*)

Study	Language	Intervention (n)	Control (n)	Treatment period	Outcome measure	Results	Side effects
Zhang (2021)	Chinese	HM + Rabeprazole + Mosapride (43)	Rabeprazole + Mosapride (43)	6 weeks	① TCE ② TCM symptom score ③ Gastrointestinal hormone level ④ Recurrence rate	① 95.35% versus 81.40% ($P < .05$) ② acid reflux 0.86 ± 0.17 versus 1.13 ± 0.28 ($P < .05$) heartburn 0.91 ± 0.13 versus 1.04 ± 0.15 ($P < .05$) belching 0.73 ± 0.18 versus 1.00 ± 0.22 ($P < .05$) substernal pain 0.61 ± 0.08 versus 0.97 ± 0.10 ($P < .05$) ③ motilin 381.25 ± 54.12 versus 322.69 ± 46.75 ($P < .05$) gastrin 79.28 ± 9.39 versus 58.04 ± 8.92 ($P < .05$) ④ 6.98% versus 41.86% ($P < .05$)	NR
Ma (2021)	Chinese	HM + Rabeprazole (30)	Rabeprazole (30)	4 weeks	① TCE ② TCM symptom score ③ RQS	① 93.33% versus 73.33% ($P < .05$) ② total score 7.73 ± 3.27 versus 11.22 ± 5.18 ($P < .05$) ③ Treatment group was significantly better than control group.	No meaningful adverse reaction.
Zhang et al. (2021)	English	HM + Omeprazole + Placebo omeprazole (93)	Omeprazole + Placebo HM (94)	4 weeks	① GERDQ ② Gastrointestinal microbiota	① No significant difference between 2 groups. ② Treatment group was significantly better than control group in increasing the number and diversity of microbiota.	Reactions such as leukopenia, mild to moderate liver dysfunction, abnormal blood glucose, fecal occult blood, or pruritus were occurred, but no meaningful adverse reaction occurred.
Zhou et al. (2022)	Chinese	HM (30)	Rabeprazole (30)	4 weeks	① EGG ② Gastrointestinal hormone level ③ RDQ ④ SSS ⑤ TCE	① No significant difference between 2 groups. ② PG Ⅰ 104.5 ± 21.2 versus 79.3 ± 15.2 ($P < .05$) G-17 10.5 ± 2.4 versus 8.6 ± 2.9 ($P < .05$) ③ total score 10.2 ± 2.9 versus 13.1 ± 3.3 ($P < .05$) ④ Treatment group was significantly better than control group. ⑤ 93.3% versus 73.3% ($P < .05$)	One case of dizziness and diarrhea in control group, and one case each of dizziness, diarrhea, and burnout in treatment group. No significant difference in the incidence of adverse reaction between 2 groups.

(*Continued*)

Table 1

(*Continued*)

Study	Language	Intervention (n)	Control (n)	Treatment period	Outcome measure	Results	Side effects
Liu (2022)	Chinese	HM + Omeprazole + Mosapride + Flupentixol + Melitracen (50)	Omeprazole + Mosapride + Flupentixol + Melitracen (50)	12 weeks	① TCM symptom score ② Gastrointestinal hormone level ③ Esophageal motility index ④ SAS ⑤ MUNSH ⑥ SF-36 ⑦ TCE	① epigastric fullness 1.05 ± 0.26 versus 1.52 ± 0.37 ($P < .05$) hiccup and belching 1.18 ± 0.25 versus 1.64 ± 0.46 ($P < .05$) dysphagia 1.14 ± 0.19 versus 1.53 ± 0.26 ($P < .05$) chest fullness 0.91 ± 0.17 versus 1.48 ± 0.35 ($P < .05$) ② G-17 13.25 ± 1.67 versus 16.47 ± 1.73 ($P < .05$) PG Ⅰ 127.18 ± 16.25 versus 102.74 ± 13.56 ($P < .05$) PG Ⅱ 15.44 ± 2.45 versus 20.35 ± 3.41 ($P < .05$) ratio of PG Ⅰ and PG Ⅱ 4.81 ± 0.47 versus 3.68 ± 0.35 ($P < .05$) ③ Treatment group was significantly better than control group. ④ 36.16 ± 4.07 versus 41.72 ± 4.18 ($P < .05$) ⑤ Treatment group was significantly better than control group in improving quality of life and emotional scores. ⑥ Treatment group was significantly better than control group. ⑦ 96% versus 82% ($P < .05$)	NR
Li et al. (2022)	English	HM + Placebo omeprazole (56)	Omeprazole + Placebo HM (53)	8 weeks	① GERDQ ② PRO ③ SF-36	① No significant difference between 2 groups. ② No significant difference between 2 groups. ③ Treatment group was significantly better than control group in the domains of GH and SF.	No meaningful adverse reaction.

5-HT = 5-hydroxytryptamine, EGG = electrogastrogram, FSSG = frequency scale for the symptoms of gastroesophageal reflux disease, GERDQ = gastroesophageal reflux disease questionnaire, GH = general health, GSRS = gastrointestinal symptom rating scale, HAD = hospital anxiety and depression scale, HAMA = hamilton anxiety scale, HAMD = hamilton depression rating scale, HM = herbal medicine, LESP = lower esophagus sphincter pressure, LPO = lipid peroxide, MH = mental health, MUNHS = memorial university of newfoundland happiness scale score, NR = not reported, PF = physiological function, PG = pepsinogen, PRO = patient reported outcome, PSQI = Pittsburgh sleep quality index, RDQ = reflux diagnostic questionnaire, RE = role emotional, RP = physical function, RQS = reflux quality questionnaire, SAS = self-rating anxiety scale, SDS = self-rating depression scale, SF = social functioning, SF-36 = short-form 36 health survey, SF-8 = short-form health survey-8, SSS = somatic symptom self-rating scale, TCE = total clinical efficacy rate, TCM = traditional Chinese medicine, VIP = vasoactive intestinal peptide, VT = vitality.

Table 2

Prescription and composition of herbal medicine.

Study	Herbal medicine
Zhu et al. (2007)	*Liuwei anxiao* capsule (Dried root of *Inula helenium* L. 50g, Dried root of *Rheum palmatum* L. 200g, Fruit of *Crataegus pinnatifida* Bunge 150g, Fruit of *Terminalia chebula* Retz. 100g, *Arca inflata* Reeve. 250g, *Gypsum lamelliforme* 300g)
Chen et al. (2010)	*Banxia houpo* decoction plus *Zuojin* pill (Tuber of *Pinellia ternata* (Thunb.) Makino 10g, Stem bark of *Magnolia officinalis* Rehder & E.H.Wilson 10g, Dried rhizome of *Coptis chinensis* Franch. 12g, Fruit of *Tetradium ruticarpum* (A.Juss.) T.G.Hartley 2g, *Poria cocos* F.A.Wolf 15g, Dried rhizome of *Glycyrrhiza uralensis* Fisch. ex DC. 10g, Dried leaf of *Perilla frutescens* (L.) Britton 10g)
Li et al. (2011)	*Tongjiang* granule (mainly composed of Stem of *Perilla frutescens* var. *crispa* (Thunb.) H.Daene, Dried rhizome of *Cyperus rotundus* L., *Sepia esculenta* Hoyle, Dried rhizome of *Glycyrrhiza uralensis* Fisch. ex DC.)
Zhong et al. (2011)	*Jiangni hewei* decoction (*Haematites* 30g, *Arca inflata* Reeve. 30g, Flower of *Inula japonica* Thunb. 10g, Tuber of *Pinellia ternata* (Thunb.) Makino 10g, Stem of *Bambusa tuldoides* Munro 10g, Immature fruit of *Citrus aurantium* L. 10g, Dried root of *Bupleurum falcatum* L. 10g, Dried tuber of *Corydalis yanhusuo* (Y.H.Chou & Chun C.Hsu) W.T.Wang ex Z.Y.su & C.Y.Wu 10g, Stem bark of *Magnolia officinalis* Rehder & E.H.Wilson 10g, Stem of *Perilla frutescens* var. *crispa* (Thunb.) H.Daene 10g, Dried herb of *Taraxacum mongolicum* hand.-Mazz. 20g, Dried aerial parts of *Artemisia capillaris* Thunb. 20g, *Sepia esculenta* Hoyle 15g, Dried ripe pericarp of *Citrus aurantium* f. deliciosa (Ten.) M.Hiroe 6g, Dried rhizome of *Glycyrrhiza uralensis* Fisch. ex DC. 3g)
Chen et al. (2012)	*Jianpi qinggan jiangni* decoction (Dried root of *Astragalus mongholicus* Bunge 25g, Dried root of *Codonopsis pilosula* (Franch.) Nannf. 12g, *Poria cocos* F.A.Wolf 12g, Dried rhizome of *Atractylodes macrocephala* Koidz. [*Asteraceae*; *Atractylodes macrocephala* dried rhizome] 12g, Dried ripe pericarp of *Citrus aurantium* f. deliciosa (Ten.) M.Hiroe 12g, Tuber of *Pinellia ternata* (Thunb.) Makino 12g, Flower of *Inula japonica* Thunb. 12g, Immature fruit of *Citrus aurantium* L.12g, Dried tuber of *Corydalis yanhusuo* (Y.H.Chou & Chun C.Hsu) W.T.Wang ex Z.Y.su & C.Y.Wu 12g, Dried rhizome of *Coptis chinensis* Franch. 6g, Dried root of *Inula racemosa* Hook..f. 6g, Fruit of *Tetradium ruticarpum* (A.Juss.) T.G.Hartley 3g, *Arca inflata* Reeve. 15g, Dried tuber of *Bletilla striata* (Thunb.) Rehh.f. 15g, Dried rhizome of *Glycyrrhiza uralensis* Fisch. ex DC. 5g)
Yang et al. (2012)	modified *Banxia xiexin* decoction (Tuber of *Pinellia ternata* (Thunb.) Makino 9g, Dried root of *Scutellaria baicalensis* Georgi 15g, Dried rhizome of *Coptis chinensis* Franch. 6g, Dried rhizome of *Alpinia officinarum* Hance 10g, Dried bulb of *Fritillaria thunbergii* Miq. 15g, Dried herb of *Taraxacum mongolicum* hand.-Mazz. [*Asteraceae*; *Taraxacum mongolicum* dried herb] 15g, Dried trunk of *Santalum album* Linne [*Santalaceae*; *Santalum album* dried trunk] 5g, Dried ripe fruit of *Trichosanthes kirilowii* Maxim. 10g, Dried rhizome of *Glycyrrhiza uralensis* Fisch. ex DC. 6g)
Li et al. (2013)	*Tongjiang* granule (Dried leaf of *Perilla frutescens* (L.) Britton, Dried rhizome of *Cyperus rotundus* L., Dried rhizome of *Coptis chinensis* Franch., Fruit of *Tetradium ruticarpum* (A.Juss.) T.G.Hartley, *Citrus aurantium* L., *Sepia esculenta* Hoyle, et cetra.)
Yang et al. (2013)	modified *Banxia xiexin* decoction (Tuber of *Pinellia ternata* (Thunb.) Makino 9g, Dried root of *Scutellaria baicalensis* Georgi 15g, Dried rhizome of *Coptis chinensis* Franch. 6g, Dried rhizome of *Alpinia officinarum* Hance 10g, Dried bulb of *Fritillaria thunbergii* Miq. 15g, Dried herb of *Taraxacum mongolicum* hand.-Mazz. 15g, Dried trunk of *Santalum album* L. 5g, Dried ripe fruit of *Trichosanthes kirilowii* Maxim. 10g, Dried rhizome of *Glycyrrhiza uralensis* Fisch. ex DC. 6g)
Wang (2014)	modified *Banxia xiexin* decoction (Tuber of *Pinellia ternata* (Thunb.) Makino 9g, Dried root of *Scutellaria baicalensis* Georgi 15g, Dried rhizome of *Coptis chinensis* Franch. 6g, Dried rhizome of *Alpinia officinarum* Hance 10g, Dried bulb of *Fritillaria thunbergii* Miq. 15g, Dried herb of *Taraxacum mongolicum* hand.-Mazz. 15g, Dried trunk of *Santalum album* L. 5g, Dried ripe fruit of *Trichosanthes kirilowii* Maxim. 10g, Dried rhizome of *Glycyrrhiza uralensis* Fisch. ex DC. 6g)
Tominaga et al. (2014)	*Rikkunshito* (Dried rhizome of *Atractylodes lancea* (Thunb.) DC. 4g, Dried root of *Panax ginseng* C.A. Mey. 4g, Tuber of *Pinellia ternata* (Thunb.) Makino 4g, *Poria cocos* F.A.Wolf 4g, Dried ripe fruit of *Ziziphus jujuba* Mill. 2g, Dried ripe pericarp of *Citrus aurantium* f. deliciosa (Ten.) M.Hiroe 2g, Dried rhizome of *Glycyrrhiza uralensis* Fisch. ex DC. 1g, Dried rhizome of *Zingiber officinale* Roscoe 0.5g)
Zhang et al. (2015)	mainly composed of Immature fruit of *Citrus aurantium* L. and Dried rhizome of *Atractylodes macrocephala* Koidz.
Pan et al. (2016)	*Kangfuxin* liquid (mainly composed of *Periplaneta americana* extraction)
Fu et al. (2016)	*Ningshen qingdan* decoction (Dried root of *Bupleurum chinense* DC. 10g, Dried root of *Scutellaria baicalensis* Georgi 10g, Tuber of *Pinellia ternata* (Thunb.) Makino 10g, Immature fruit of *Citrus aurantium* L. 10g, Dried tuber of *Corydalis yanhusuo* (Y.H.Chou & Chun C.Hsu) W.T.Wang ex Z.Y.su & C.Y.Wu 10g, Dried rhizome of *Coptis chinensis* Franch. 6g)
Zhou et al. (2016)	*Wumei wan* decoction (Almost ripe and dried fruit of *Prunus mume* (Siebold) Siebold & Zucc. 10g, Dried root of *Asarum heterotropoides* F.Schmidt 6g, Dried rhizome of *Alpinia officinarum* Hance 6g, Dried rhizome of *Coptis chinensis* Franch. 10g, Dried bark of *Phellodendron chinensis* C.K.Schneid. 6g, Dried root of *Angelica sinensis* (Oliv.) Diels 10g, Processed daughter root of *Aconitum carmichaelii* Debeaux 6g, *Zanthoxylum armatum* var. *armatum* 4g, Dried bark of *Cinnamomum verum* J.Presl 10g, Dried root of *Panax ginseng* C.A. Mey. 10g)
He (2016)	*Chaihu* plus *Longgu muli* decoction (*Ostrea gigas* Thunberg 30g, Dried root of *Bupleurum chinense* DC. 12g, *Poria cocos* F.A.Wolf 20g, *Fossilia ossis Mastodi* 30g, Dried root of *Scutellaria baicalensis* Georgi 10g, Dried root of *Rheum palmatum* L. 9g, Tuber of *Pinellia ternata* (Thunb.) Makino 12g, Dried rhizome of *Zingiber officinale* Roscoe 3 pieces, Dried bark of *Cinnamomum verum* J.Presl 10g, Dried ripe fruit of *Ziziphus jujuba* Mill. 10 pieces)
Du et al. (2017)	*Tiaowei jiangni* decoction (Dried herb of *Taraxacum mongolicum* hand.-Mazz. 30g, Dried germinated ripe fruit of *Hordeum vulgare* L. 30g, Dried root of *Bupleurum chinense* DC. 15g, Immature fruit of *Citrus aurantium* L. 15g, Dried rhizome of *Atractylodes macrocephala* Koidz. 15g, *Poria cocos* F.A.Wolf 15g, Tuber of *Pinellia ternata* (Thunb.) Makino 15g, *Sepia esculenta* Hoyle 15g, Dried root of *Paeonia lactiflora* Pall. 10g, Dried flower bud of *Syzygium aromaticum* (L.) Merr. & L.M.Perry 10g, Stem of *Bambusa tuldoides* Munro 10g, Dried bulb of *Fritillaria thunbergii* Miq. 10g, Dried ripe fruit of *Wurfbainia villosa* (Lour.) Škorničk. & A.D.Poulsen 10g, Dried rhizome of *Glycyrrhiza uralensis* Fisch. ex DC. 6g)
Niu et al. (2018)	*Jiangni qingqing huazhuo* formula (Dried root of *Bupleurum chinense* DC. 12g, Dried root of *Paeonia lactiflora* Pall. 10g, Immature fruit of *Citrus aurantium* L. 15g, Dried rhizome of *Glycyrrhiza uralensis* Fisch. ex DC.10g, Dried rhizome of *Atractylodes lancea* (Thunb.) DC. 10g, Stem bark of *Magnolia officinalis* Rehder & E.H.Wilson 15g, Dried branch bark of *Fraxinus chinensis* subsp. *Rhynchophylla* (Hance) A.E.Murray 10g, Fruit of *Tetradium ruticarpum* (A.Juss.) T.G.Hartley 3g, Dried rhizome of *Coptis chinensis* Franch. 10g, *Sepia esculenta* Hoyle30g, Dried heart wood of trunk of *Dalbergia odorifera* T.C.Chen 10g, Dried aerial parts of *Eupatorium fortune* Turcz. 10g, Dried ripe fruit of *Gardenia jasminoides* J.Ellis 10g, et cetra.)
An et al. (2019)	*Hegan* granule (Dried root of *Angelica sinensis* (Oliv.) Diels 10g, Dried root of *Paeonia lactiflora* Pall. 10g, Dried root of *Codonopsis pilosula* (Franch.) Nannf. 10g, Dried rhizome of *Atractylodes macrocephala* Koidz. 10g, *Poria cocos* F.A.Wolf 10g, Dried root of *Bupleurum chinense* DC. 9g, Dried aerial parts of *Mentha canadensis* L. 3g, Stem of *Perilla frutescens* var. *crispa* (Thunb.) H.Daene 9g, Dried rhizome of *Cyperus rotundus* L. 9g, Dried rhizome of *Zingiber officinale* Roscoe 3g, Dried ripe fruit of *Ziziphus jujuba* Mill. 4 pieces, Dried rhizome of *Glycyrrhiza uralensis* Fisch. ex DC. 6g)
Zhang et al. (2019)	modified *Sini* powder (Dried root of *Bupleurum chinense* DC. 10g, Dried root of *Paeonia lactiflora* Pall. 10g, Immature fruit of *Citrus aurantium* L. 10g, Dried rhizome of *Glycyrrhiza uralensis* Fisch. ex DC. 10g, Dried root bark of *Paeonia suffruticosa* Andrews 15g, Dried ripe fruit of *Gardenia jasminoides* J.Ellis 15g, Flower of *Inula japonica* Thunb. 15g, *Arca inflata* Reeve. 15g, *Haematites* 15g, *Sepia esculenta* Hoyle 15g, Dried rhizome of *Coptis chinensis* Franch. 6g, Fruit of *Tetradium ruticarpum* (A.Juss.) T.G.Hartley 6g)

(*Continued*)

Table 2

(*Continued*)

Study	Herbal medicine
Zheng et al. (2019)	*Hewei tongjiang* decoction (*Arca inflata* Reeve. 30g, *Poria cocos* F.A.Wolf 20g, Dried ripe fruit of *Trichosanthes kirilowii* Maxim. 20g, Tuber of *Pinellia ternata* (Thunb.) Makino 15g, Dried leaf of *Perilla frutescens* (L.) Britton 15g, Stem of *Bambusa tuldoides* Munro 15g, Stem bark of *Magnolia officinalis* Rehder & E.H.Wilson 10g, Dried rhizome of *Zingiber officinale* Roscoe 10g, Dried rhizome of *Coptis chinensis* Franch. 10g, Dried ripe pericarp of *Citrus aurantium* f. deliciosa (Ten.) M.Hiroe 10g, Immature fruit of *Citrus aurantium* L. 10g, Dried stem bark of *Melia azedarach* L. 10g, Dried root of *Bupleurum chinense* DC. 10g, Fruit of *Tetradium ruticarpum* (A.Juss.) T.G.Hartley 5g)
Huang (2019)	*Weisu* granule (Immature fruit of *Citrus aurantium* L., Dried ripe fruit of *Citrus medica* L., Dried rhizome of *Cyperus rotundus* L., Dried branch bark of *Fraxinus chinensis* subsp. *Rhynchophylla* (Hance) A.E.Murray, Dried pericarp of *Areca catechu* L., Dried leaf of *Perilla frutescens* (L.) Britton)
Huang et al. (2020)	*Hewei tongjiang* decoction (Dried root of *Bupleurum chinense* DC. 10g, Dried ripe seed of *Aesculus chinensis* Bunge 30g, Dried root of *Codonopsis pilosula* (Franch.) Nannf. 12g, Dried root of *Paeonia lactiflora* Pall. 12g, Dried receptacle of *Nelumbo nucifera* Gaertn. 12g, Tuber of *Pinellia ternata* (Thunb.) Makino 10g, Immature fruit of *Citrus aurantium* L. 10g, *Sepia esculenta* Hoyle 20g, Stem of *Bambusa tuldoides* Munro 15g, Dried rhizome of *Dioscorea oppositifolia* L. 15g, Dried tuber of *Corydalis yanhusuo* (Y.H.Chou & Chun C.Hsu) W.T.Wang ex Z.Y.su & C.Y.Wu 9g, *Galli Stomachichum* Corium 3g)
Yin et al. (2020)	*Chaihu wendan* decoction (Dried root of *Bupleurum chinense* DC. 12g, Dried tuber of *Arisaema erubescens* (Wall.) Schott 15g, Dried rhizome of *Coptis chinensis* Franch. 12g, *Arca inflata* Reeve. 20g, Immature fruit of *Citrus aurantium* L. 12g, *Sepia esculenta* Hoyle 20g, Dried branch bark of *Fraxinus chinensis* subsp. *Rhynchophylla* (Hance) A.E.Murray 15g, Tuber of *Pinellia ternata* (Thunb.) Makino 12g, Dried rhizome of *Cyperus rotundus* L. 15g, Dried rhizome of *Zingiber officinale* Roscoe 9g, *Poria cocos* F.A.Wolf 12g, Dried rhizome of *Atractylodes macrocephala* Koidz. 12g, Dried rhizome of *Glycyrrhiza uralensis* Fisch. ex DC. 6g)
Zhai et al. (2021)	*Qizhi weitong* granule (Dried root of *Paeonia lactiflora* Pall., Dried root of *Bupleurum chinense* DC., Dried rhizome of *Cyperus rotundus* L., Dried tuber of *Corydalis yanhusuo* (Y.H.Chou & Chun C.Hsu) W.T.Wang ex Z.Y.su & C.Y.Wu, Immature fruit of *Citrus aurantium* L., Dried rhizome of *Glycyrrhiza uralensis* Fisch. ex DC.)
Cao et al. (2021)	*Guipi* decoction (Dried root of *Codonopsis pilosula* (Franch.) Nannf. 12g, Dried root of *Astragalus mongholicus* Bunge 15g, Dried rhizome of *Atractylodes macrocephala* Koidz. 12g, *Dimocarpus longan* Lour. 15g, Dried rhizome of *Glycyrrhiza uralensis* Fisch. ex DC. 6g, *Poria cocos* F.A.Wolf 12g, Dried root of *Angelica sinensis* (Oliv.) Diels 12g, Dried root of *Dolomiaea souliei* (Franchet) C.Shih 6g, Dried ripe fruit of *Ziziphus jujuba* Mill. 6g, Dried rhizome of *Zingiber officinale* Roscoe 6g, Dried root of *Polygala tenuifolia* Willd. 12g)
Zhang (2021)	*Shensang banfo* decoction (Dried root of *Astragalus mongholicus* Bunge 15g, Dried root tuber of *Pseudostellaria heterophylla* (Miq.) Pax 10g, Dried ripe fruit of *Citrus medica* L. 10g, Dried root of *Platycodon grandifloras* (Jacq.) A. DC. 6g, Tuber of *Pinellia ternata* (Thunb.) Makino 10g, Dried young branch of *Morus alba* L. 10g, Resin containing wood of *Aquilqria sinensis* (Lour.) Spreng. 2g, Fruit of *Tetradium ruticarpum* (A.Juss.) T.G.Hartley 2g)
Zhou et al. (2022)	*Jianzhong jiangni* decoction (Dried root of *Vincetoxicum mukdenense* Kitag. 30g, *Arca inflata* Reeve. 30g, *Ostrea gigas* Thunberg 30g, *Sepia esculenta* Hoyle 30g, Dried root of *Codonopsis pilosula* (Franch.) Nannf. 20g, Dried tuber of *Corydalis yanhusuo* (Y.H.Chou & Chun C.Hsu) W.T.Wang ex Z.Y.su & C.Y.Wu 20g, Dried rhizome of *Atractylodes macrocephala* Koidz. 10g, *Poria cocos* F.A.Wolf 10g, Tuber of *Pinellia ternata* (Thunb.) Makino 10g, Dried root of *Paeonia lactiflora* Pall. 10g, Dried rhizome of *Cyperus rotundus* L. 10g, Flower of *Inula japonica* Thunb. 10g, Dried heart wood of trunk of *Dalbergia odorifera* T.C.Chen 5g, Dried rhizome of *Glycyrrhiza uralensis* Fisch. ex DC. 3g)
Liu (2022)	*Yueju* pill plus *Xuanfu daizhe* decoction (Dried rhizome of *Atractylodes lancea* (Thunb.) DC. 10g, Dried blighted caryopsis of *Triticum aestivum* L. 10g, Dried rhizome of *Cyperus rotundus* L. 10g, Dried leaf and young foliferous branch of *Murraya paniculate* (L.) Jack 10g, Dried ripe fruit of *Gardenia jasminoides* J.Ellis 10g, Flower of *Inula japonica* Thunb. 9g, Tuber of *Pinellia ternata* (Thunb.) Makino 9g, Dried rhizome of *Glycyrrhiza uralensis* Fisch. ex DC. 9g, Dried root of *Panax ginseng* C.A.Mey. 6g, *Haematites* 6g, Dried rhizome of *Zingiber officinale* Roscoe 8g, Dried ripe fruit of *Ziziphus jujuba* Mill. 10g)

3.2.1. Participants. The total number of included participants was 3759, all of whom were diagnosed with NERD based on clinical symptoms and endoscopy results.

3.2.2. Intervention. As an intervention in the treatment group, herbal medicine alone was used in 15 articles[25–39] and herbal medicine combined with Western medicine was used in the other 17 articles.[22,23,40–54] Herbal medicine with Western medicine placebo was used in another 2 studies,[21,24] and lifestyle modifications such as limiting alcohol consumption, avoiding smoking and overeating, or wearing loose clothes were recommended to all participants in 7 studies.[30,34,35,37,44,48,52] The treatment period varied from 2 to 12 weeks in all the included studies, and 8-weeks of duration was reported to be the most common.

PPI was used most frequently in Western medicine. Omeprazole, rabeprazole, esomeprazole, pantoprazole, and lansoprazole were used in order of frequency, and the first 2 were used in 8 studies each. Mosapride and domperidone were used as prokinetics in combination with PPIs in all 6 cases.[26,39,43,44,49,50] Flupentixol and melitracen have been used as other Western medicinal interventions. The composition of herbal medicines was reported in 28 articles,[21,22,25–31,33–44,46–50,52–54] and specific herbal materials were added according to the symptoms in 8 studies.[26,31,34,35,37,39,53,54] Studies that reported the exact composition of each herbal medicine are presented in Table 2, while a summary of the added herbs is presented in Table 3.

3.2.3. Adverse events. Adverse effects reported in each study are presented in Table 1. Seventeen studies[21–25,28,30–33,39,45,49–53] reported side effects during or after the intervention. Among them, the results of liver and renal function tests were mentioned in 3 studies.[45,49,52] Participants in the treatment groups in 2 of these studies[45,52] were administered herbal medicine and PPI, and participants in another study[49] were administered herbal medicine and both PPI and prokinetic agents. Results in both groups of all 3 studies revealed no abnormalities after treatment. No severe intervention-related adverse events were observed in the remaining studies.

3.3. Assessment of risk of bias

The total results and summary of the quality assessment for each domain are shown in Figures 2 and 3, respectively.

The overall risk of bias was identified to be some concern in 27 studies,[25–32,34,35,37–48,50–54] low risk in 5 studies,[21–24,33] and high risk in 2 studies.[36,49] The risk of bias in the randomization process was evaluated to be some concerns or high in 10 studies[26,28,30,31,36,37,43,47,52] because the randomization methods were not reported or conducted according to the order of visits. Most of the included studies were rated as having a high risk of bias on deviations from the intended interventions owing to the differences in the properties of the intervention administered. For bias on missing outcome data, all the included studies had a low risk of bias, except for 2 studies[36,49] with missing values. Because there were no sufficient explanations on the appropriate blinding process in the outcome measure, most studies were rated to some concerns and 5 studies[21–24,29] had a low risk of bias. In addition, 3 studies[29,36,49] were evaluated as having a high risk of bias, and the remaining 31 studies had a low risk.

3.4. Primary outcome: total clinical efficacy rate

Twenty-eight studies[26–36,39–49,51–54] among the included studies used TCE as an outcome measure, and a total of 2989 participants were included in the analysis. In these studies, the treatment outcome of each participant was classified as one among "clinically cured," "efficient," "improved," or "invalid," according to the degree of change in symptom scores. Among them, "clinically cured," "efficient," and "improved" were regarded as clinically effective cases, and TCE was defined as ratio of the total number of cases and clinically effective cases. The combination of herbal medicine alone or in combination with Western medicine showed that including herbal medicines for the treatment of NERD was significantly more effective than administering Western medicine alone (RR = 1.21; 95% CI [1.16, 1.27]; $P < .00001$), and the heterogeneity was moderate ($I^2 = 49\%$). Studies using herbal medicine alone or in combination with Western medicine in the treatment group were also analyzed separately. Administering herbal medicine alone was more effective than Western medicine with statistical significance (RR = 1.16; 95% CI [1.08, 1.25]; $P < .0001$). Co-administration of herbal medicine and conventional Western medicine was also found to be significantly more effective in treating NERD compared to the control groups (RR = 1.25; 95% CI [1.19, 1.31]; $P < .00001$). Owing to the high heterogeneity in the former case ($I^2 = 57\%$), a random-effects model was applied (Fig. 4).

Table 3

Summary of added herbs mentioned twice or more in the text according to symptoms.

Symptom	Added-herbs
Obvious acid reflux or regurgitation	*Sepia esculenta* Hoyle, *Arca inflata* Reeve.
Obvious heartburn	Dried root of *Gentiana lutea* L.
Obvious belching	*Haematites*, Flower of *Inula japonica* Thunb., Dried root tuber of *Curcuma aromatica* Salisb.
Chest discomfort or irritability or anxiety	Stem bark of *Magnolia officinalis* Rehder & E.H.Wilson, Dried root of *Dolomiaea costus* (Falc.) Kasana & A.K.Pandey
Obvious epigastric or chest pain	Dried tuber of *Corydalis yanhusuo* (Y.H.Chou & Chun C.Hsu) W.T.Wang ex Z.Y.su & C.Y.Wu, Stem bark of *Melia azedarach* L., Dried root of *Vincetoxicum mukdenense* Kitag.
Decreased appetite	Dried blighted caryopsis of *Triticum aestivum* L.
Depression	Dried blighted caryopsis of *Triticum aestivum* L., Dried ripe fruit of *Ziziphus jujuba* Mill.
Insomnia	Dried lianoid stem of *Reynoutria multiflora* (Thunb.) Moldenke, Dried stem bark of *Albizia julibrissin* Durazz., Dried ripe fruit of *Ziziphus jujuba* Mill.
Fatigue	Dried root of *Astragalus mongholicus* Bunge

3.4.1. Subgroup analysis. To reduce heterogeneity, subgroup analysis was conducted based on the Western medicine method.

3.4.1.1. Herbal medicine versus PPI. The results of 18 studies using PPI as a Western medicine intervention[25,27–36,45,47,48,51–54] with 1936 participants were analyzed. The use of herbal medicine alone or in combination with PPI was significantly effective in treating NERD (RR = 1.23; 95% CI [1.15, 1.33]; $P < .00001$). Heterogeneity was high ($I^2 = 65\%$) when herbal medicines were used alone and low ($I^2 = 0\%$) when herbal medicines were combined with PPI. A random-effects model was used because of high heterogeneity (Fig. 5).

3.4.1.2. Herbal medicine versus PPI + prokinetics. PPI combined with prokinetics was used as a Western medicine intervention in 6 studies[26,32,33,36,39,44,50] and 574 participants were included. The inclusion of herbal medicine in the treatment of NERD was significantly more effective than PPI plus prokinetics without herbal medicine (RR = 1.23; 95% CI [1.14, 1.33]; $P < .00001$), and the heterogeneity was low ($I^2 = 0\%$) in all cases of total, herbal medicine alone, and herbal medicine combined with Western medicine. A fixed-effects model was used for analysis (Fig. 6).

3.5. Secondary outcome

3.5.1. Recurrence rate. In 7 studies[26,32,33,36,39,44,50] NERD recurrence rates were reported after the end of treatment. A total of 643 participants were included, and the results showed that administration of herbal medicines significantly reduced the recurrence rate of NERD (RR = 0.35; 95% CI [0.27, 0.45]; $P < .00001$). Heterogeneity was low ($I^2 = 4\%$) and a fixed-effects model was used (Fig. 7).

3.5.2. Reflux diagnostic questionnaire score. RDQ evaluates the frequency and severity of heartburn, regurgitation, and upper abdominal pain in patients with GERD. Eight studies[29,31,34,39–41,50,51] with 756 participants, measured the total RDQ score. Herbal medicine was significantly effective in improving the RDQ score despite high heterogeneity ($I^2 = 95\%$). A random-effects model was used for the analysis (Fig. 8).

3.5.3. Short-form 36 health survey score. The quality of life of the participants was assessed using the SF-36 tool in 6

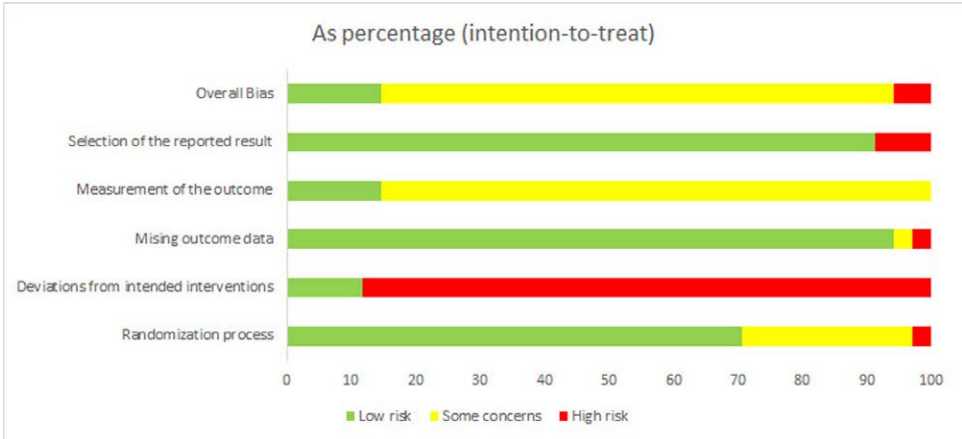

Figure 2. Risk of bias graph.

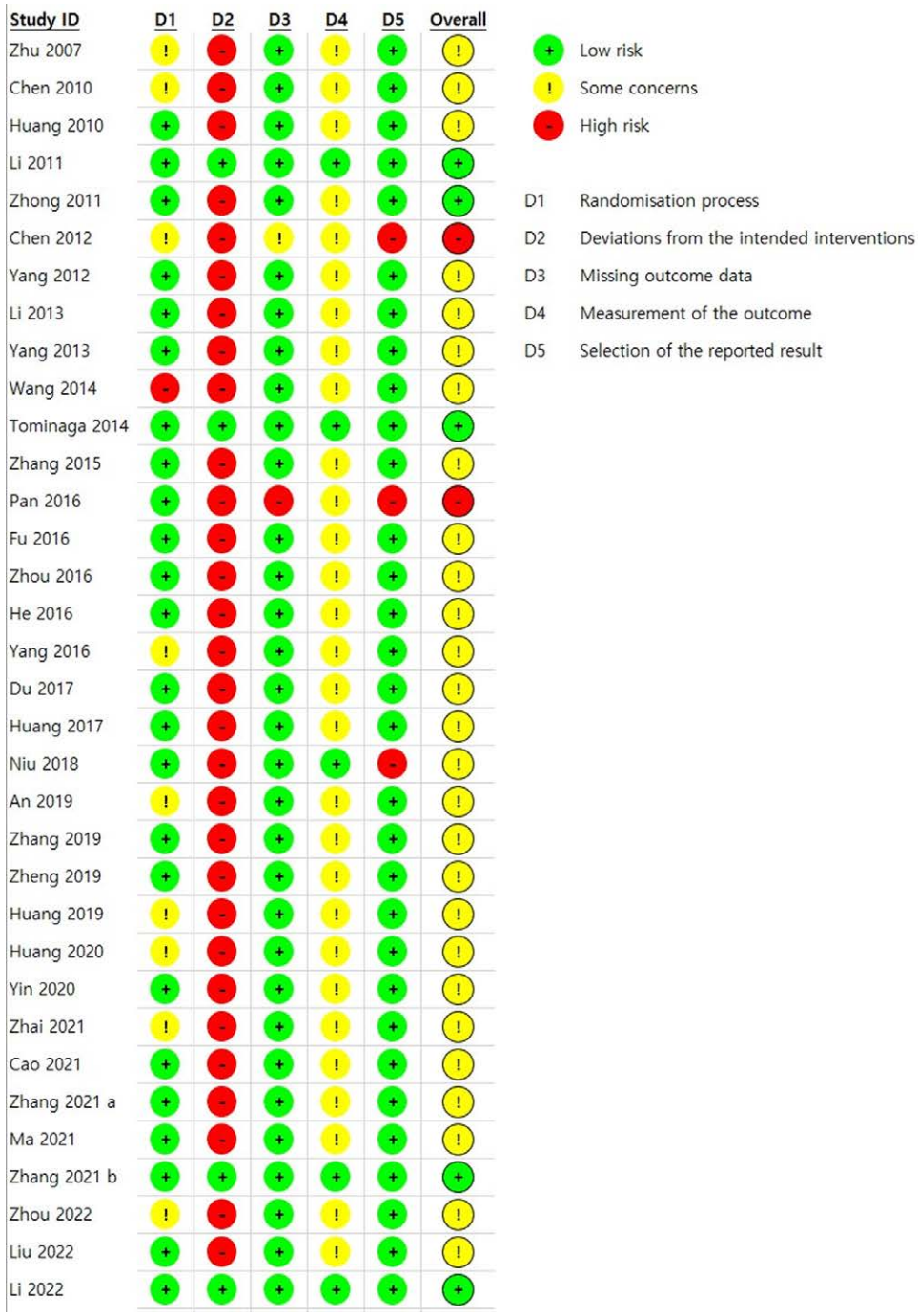

Figure 3. Risk of bias summary.

studies.[21,25,30,37,39,53] This tool evaluates 8 domains: physiological function, physical function, body pain, general health, vitality, social functioning, emotional functioning, and mental health. One study reported the results of 7 domains, excluding general health.

Administering herbal medicine significantly improved the 4 domains of physical function (MD: 9.70; 95% CI [0.96, 18.43]; $P = .03$), body pain (MD: 6.23; 95% CI [1.83, 10.63]; $P = .006$), vitality (MD: 7.46; 95% CI [1.96, 12.95]; $P = .008$), and social functioning (MD: 13.12; 95% CI [1.20, 25.05]; $P = .03$). In the remaining 4 domains (physiological function, general health, emotional functioning, and mental health), the differences between the 2 groups were not significant. Heterogeneity was severe in all domains and a random-effects model was used in the analysis (Fig. 9).

3.5.4. Serum motilin level. In 3 studies,[44,52,53] serum motilin levels (pg/mL) were measured before and after treatment. Herbal medicine was significantly effective in increasing serum motilin levels in participants with NERD (MD: 48.50; 95% CI [38.07, 58.93]; $P < .00001$). Heterogeneity was high ($I^2 = 61\%$) and a random-effects model was used (Fig. 10).

3.6. Publication bias

Figure 11 shows a funnel plot of TCE comparing herbal medicine to Western medicine, and co-administration of herbal medicine and Western medicine to the Western medicine alone group. Studies with smaller sample sizes tend to have larger effect sizes;

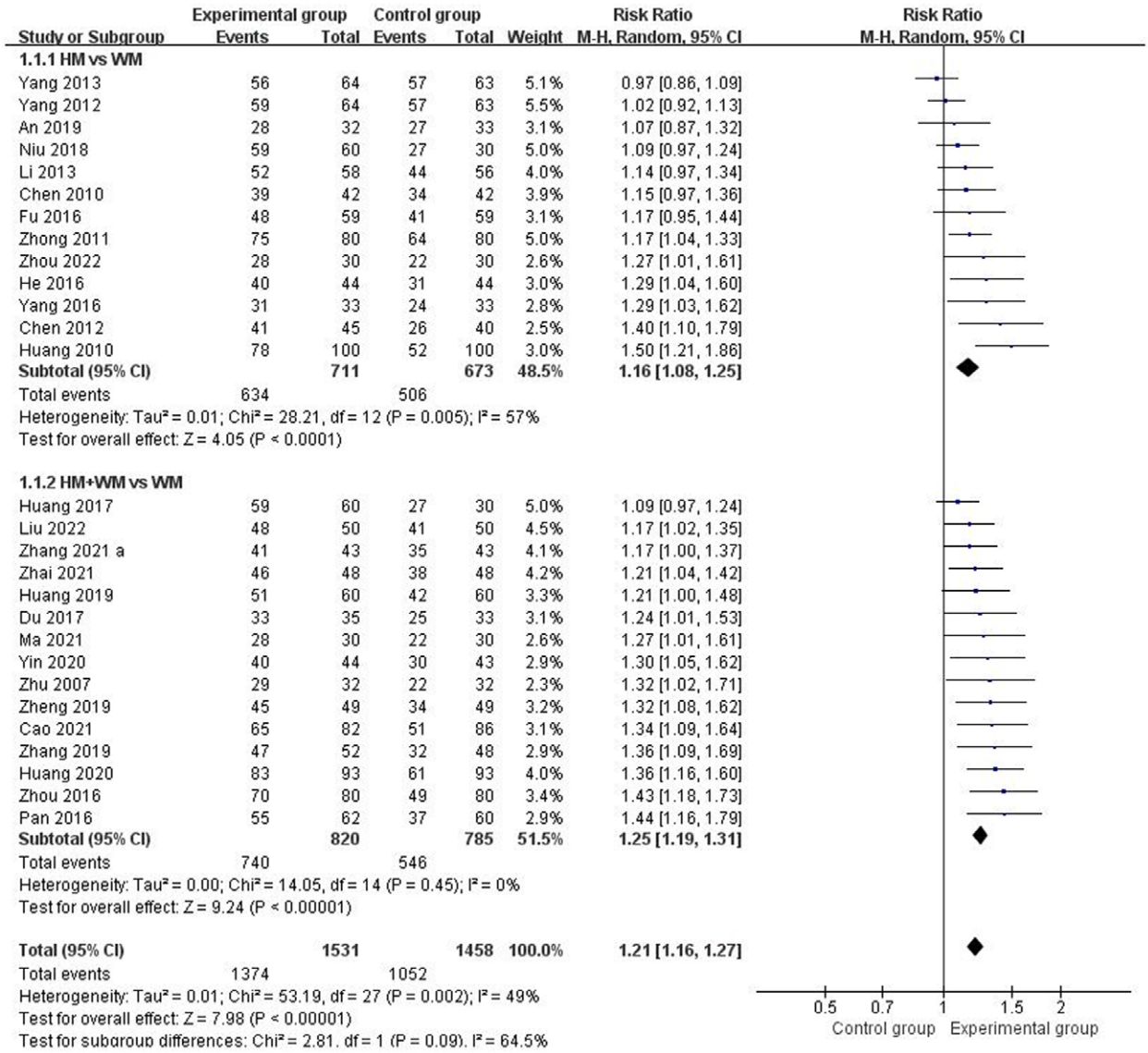

Figure 4. Forest plot comparing TCE of HM alone and combination of HM and WM groups with WM only groups. HM = herbal medicine, TCE = total clinical efficacy rate, WM = Western medicine.

however, it cannot be concluded that there is a publication bias due to the low methodological quality and heterogeneity among the studies.[55]

3.7. Level of evidence

Table 4 shows the quality of evidence for each outcome. For TCE, the primary outcome, the level of evidence was moderate in both cases of using herbal medicine alone or in combination with Western medicine. Owing to the high risk of performance bias in most studies, the level of evidence was low. Regarding secondary outcomes, the level of evidence was moderate for recurrence rate and serum motilin level. For RDQ scores, the level of evidence was low. Among the 8 domains of the SF-36 questionnaire, 4 domains – physiological function, general health, emotional functioning, and mental health – were found to have very low levels of evidence. The remaining 4 domains – physical function, body pain, vitality, and social functioning – were found to have a low level of evidence. Although all included studies were RCTs, in most cases of outcomes, the high heterogeneity and high risk of bias among the studies were factors that lowered the level of evidence.

4. Discussion

Because of the many PPI-resistant cases and various relevant factors other than regurgitation, NERD is thought to be a difficult-to-treat acid reflux disorder, even with PPI compared to reflux esophagitis, and the optimal treatment method has not yet been established.[56] However, the symptoms of NERD experienced by patients are no less severe than those of erosive esophagitis, and largely reduce their quality of life. This study aimed to reveal the effectiveness of herbal medicine as an alternative method for the treatment of NERD with less clinical risk, based on recent evidence.

4.1. Review of the main results

In this study, we systematically reviewed the details of herbal formulations administered in trials conducted in patients with NERD. More recent studies have tended to measure the effect of herbal medicine combined with Western medicine rather than administering herbal medicine alone as an intervention.[40–46,52–54] The formulations of herbal medicine used were variously presented as decoction, capsule, granule, and

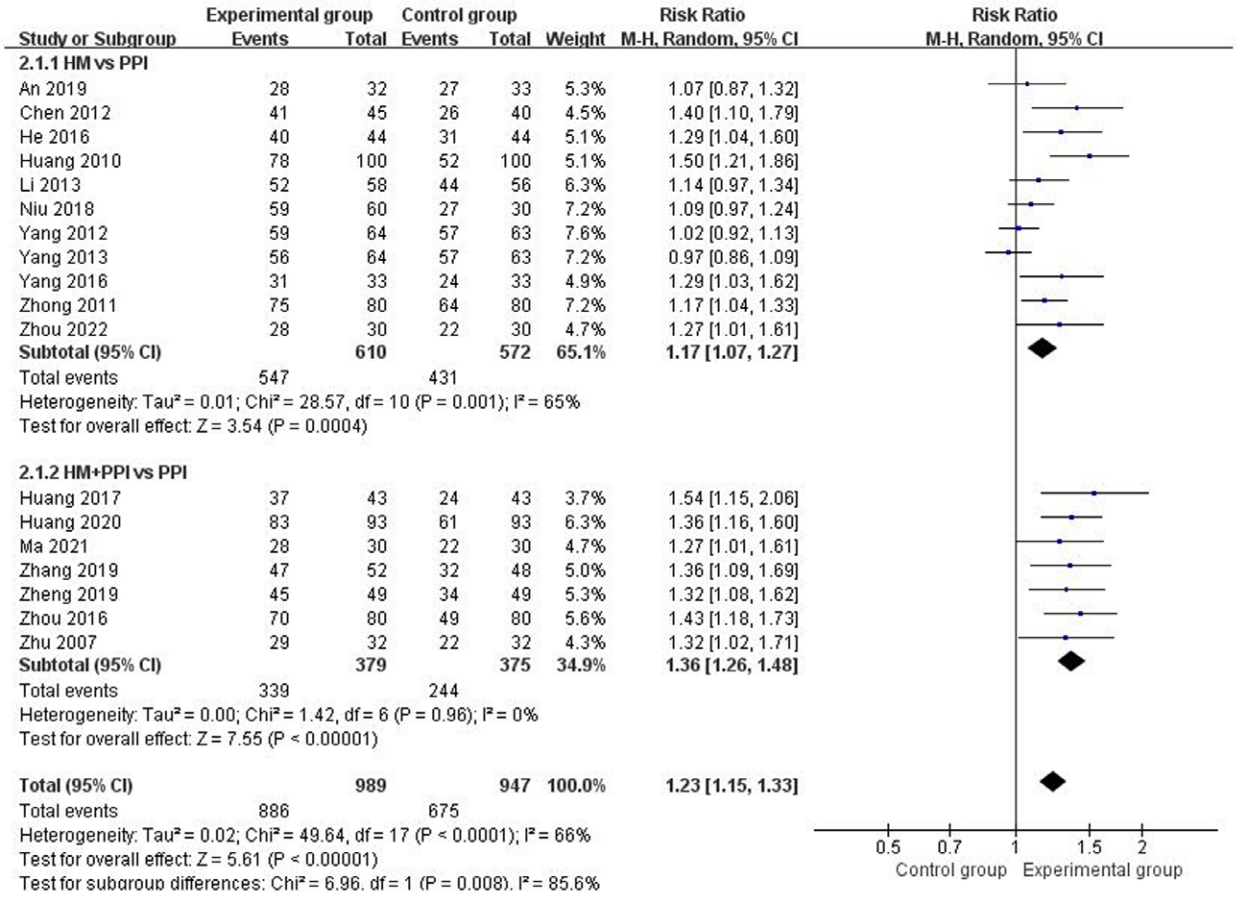

Figure 5. Forest plot comparing TCE of HM alone and combination of HM and PPI groups with PPI only groups. HM = herbal medicine, PPI = proton pump inhibitor, TCE = total clinical efficacy rate.

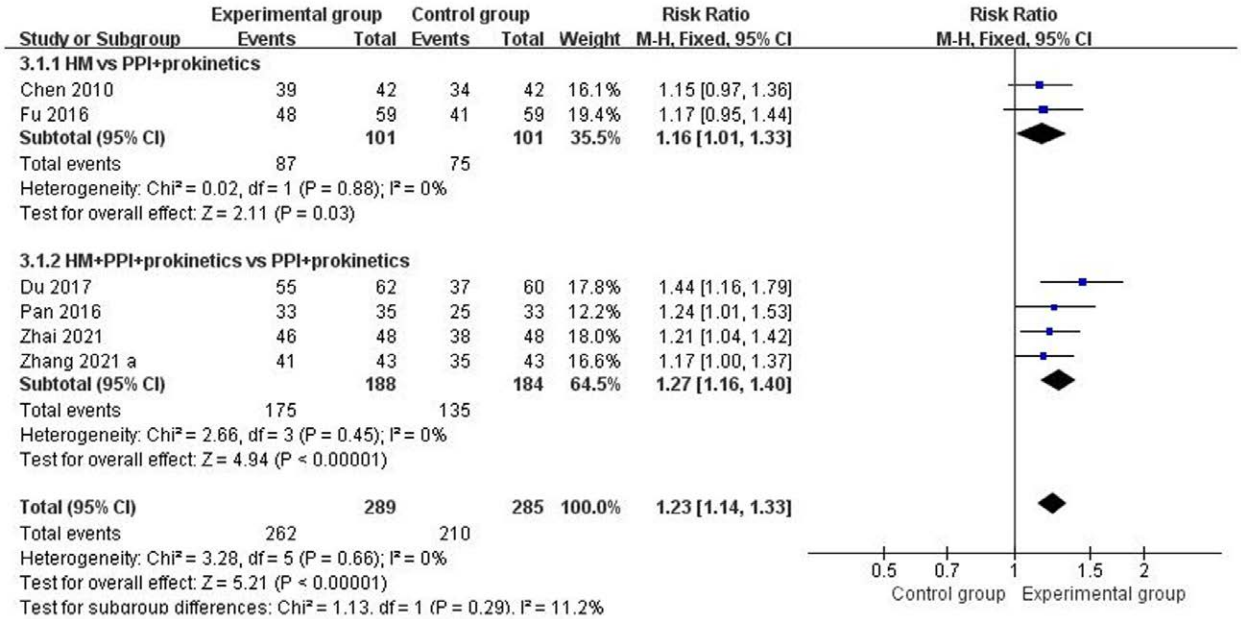

Figure 6. Forest plot comparing TCE of HM alone and combination of HM and PPI plus prokinetics groups with PPI plus prokinetics only groups. HM = herbal medicine, PPI = proton pump inhibitor, TCE = total clinical efficacy rate.

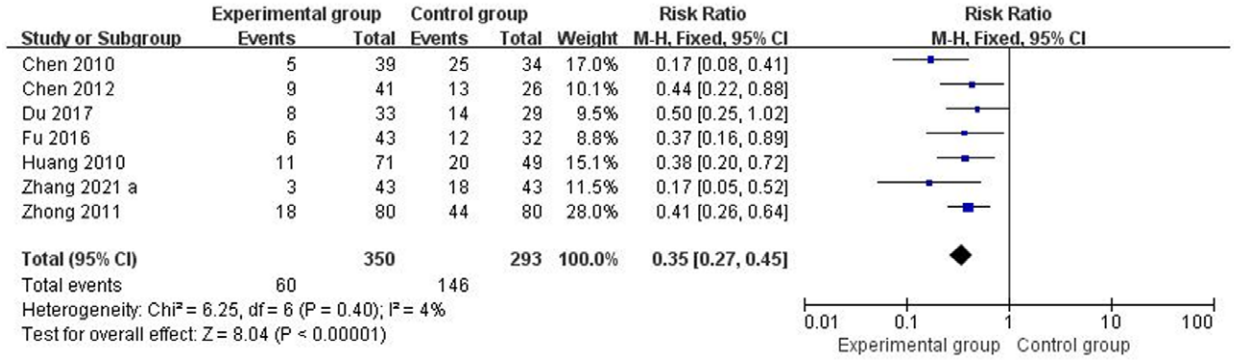

Figure 7. Forest plot comparing recurrence rate of HM alone and combination of HM and WM groups with WM only groups. HM = herbal medicine, WM = Western medicine.

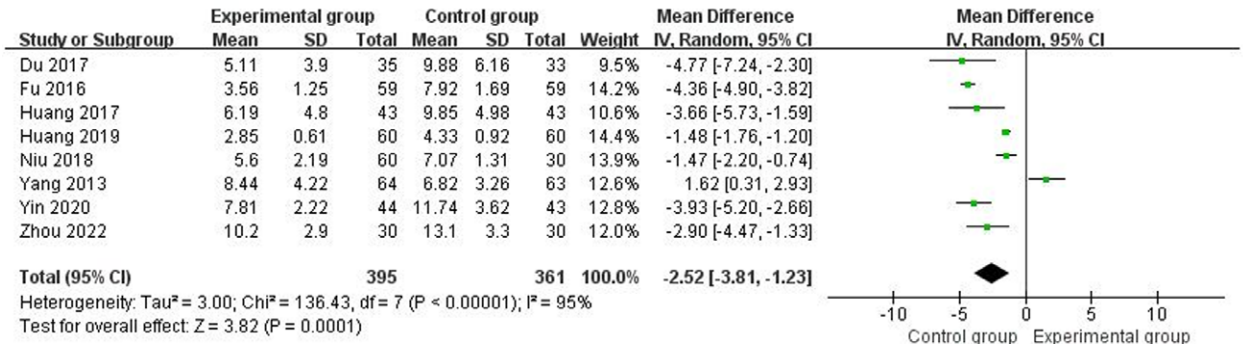

Figure 8. Forest plot comparing RDQ score of HM alone and combination of HM and WM groups with WM only groups. HM = herbal medicine, RDQ = reflux diagnostic questionnaire, WM = Western medicine.

powder, with decoction accounting for the largest proportion at approximately 65%. Different ingredients were added to the basic prescription according to the symptoms of regurgitation, heartburn, belching, chest discomfort, pain, decreased appetite, depression, insomnia, and fatigue. The measures used to investigate the effect of herbal medicine on the improvement of NERD symptoms were TCE, recurrence rate, RDQ score, SF-36 score, and serum motilin levels. Regarding TCE, recurrence rate, RDQ score, 4 domains in SF-36 score, and serum motilin level, using herbal medicine alone or co-administration with conventional Western medicine was significantly more effective than control groups. As a serological indicator, motilin is a gastrointestinal polypeptide that stimulates contraction of smooth muscles of the gastrointestinal tract under physiological conditions. It accelerates gastric emptying in normal subjects and increases lower esophageal sphincter pressure by acting on preganglionic cholinergic neurons to release acetylcholine.[57,58] Several trials included in this study compared serum motilin levels as outcome measures. Although these studies are not the same as those that directly measured the lower esophageal sphincter pressure, it is important because increasing the pressure of the lower esophageal sphincter is meaningful in the treatment of NERD. According to the results of studies that reported adverse events, herbal medicines did not cause severe or meaningful adverse reactions and were found to be safe for use in the treatment of NERD. The main results of this study were summarized in the supplemental content in the form of a graphical abstract, http://links.lww.com/MD/N807.

4.2. Herbs in prescriptions

Among the herbs used in these formulations, components of *Pinellia ternata* (Thunb.) Makino and *Citrus aurantium* L. are phytochemically associated with mechanisms of relieving the symptoms of NERD, according to previous in vivo studies. These were used in 16 and 13 studies, respectively. *Pinellia ternata* contains alkaloids and polysaccharides as its main active components and has medicinal effects in the treatment of cough, vomiting, infection, and inflammatory diseases have been demonstrated.[59] Animal studies have revealed that alkaloids and polysaccharides derived from *Pinellia ternata* induce antiemetic effects and promote gastric emptying.[60] Prescriptions containing *Pinellia ternata* as the main ingredient have been widely used for the treatment of gastrointestinal disorders, and in particular, the promising efficacy of "*Banxia xiexin* decoction" in the treatment of reflux disease has been revealed through systematic reviews and meta-analyses.[7,11] The prescription increases the pressure of the esophageal sphincter and inhibits gastric acid, which are relevant to relieving symptoms of NERD.[7] It is a commonly used herb in traditional herbal medicine with efficacy in treating dampness-phlegm pattern and upward counterflow of qi. These efficacies make the ingredient representative in the treatment considering that the main TCM syndrome types among patients with NERD are qi-deficiency pattern and damp-phlegm pattern, which are characterized by a sensation of fullness in the chest, vomiting, stuffy chest, and epigastrium.[61–64]

Citrus aurantium L. promotes intestinal transit rate and gastric emptying. The extracts of isonaringin, narigin, hesperidin, and neohesperidin are thought to be associated with such efficacy.[65] It demonstrates the same effect as a gastrointestinal prokinetic agent in the treatment of reflux disease and is expected to improve gastrointestinal motility in patients with NERD.

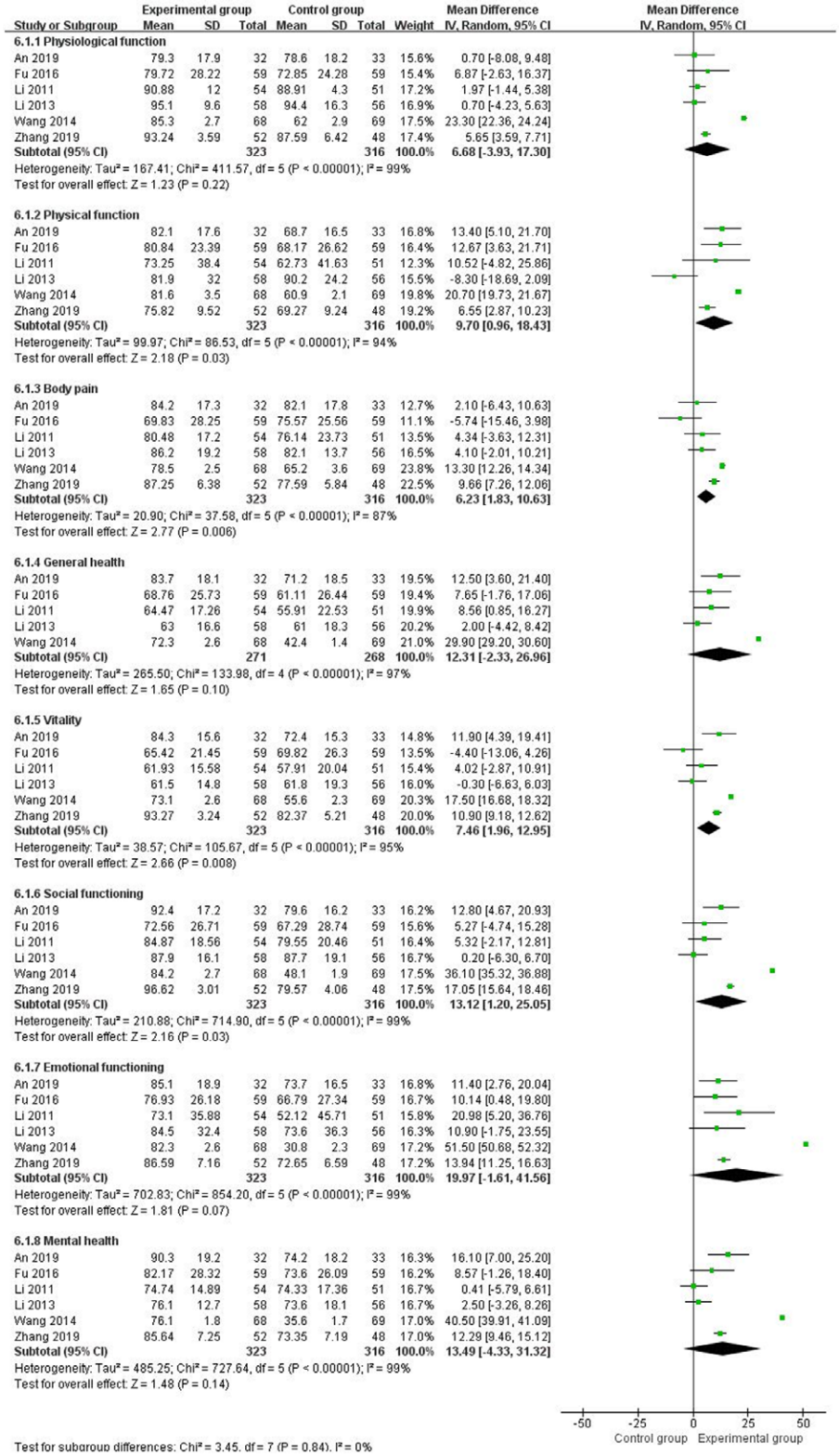

Figure 9. Forest plot comparing SF-36 score of HM alone and combination of HM and WM groups with WM only groups. HM = herbal medicine, SF-36 = short-form 36 health survey, WM = Western medicine.

4.3. Strengths and limitations of the study

When looking at the trends of the included studies, the more recent the studies were conducted, the higher the proportion of cases that used herbal medicine in combination with Western medicine in the treatment group. Therefore, including such cases in the analysis was meaningful for revealing recent evidence from the results. Cases using herbal medicine alone and in combination with Western medicine were compared separately, and a subgroup analysis was performed according to the type of Western medicine used in the intervention. In herbal medicine,

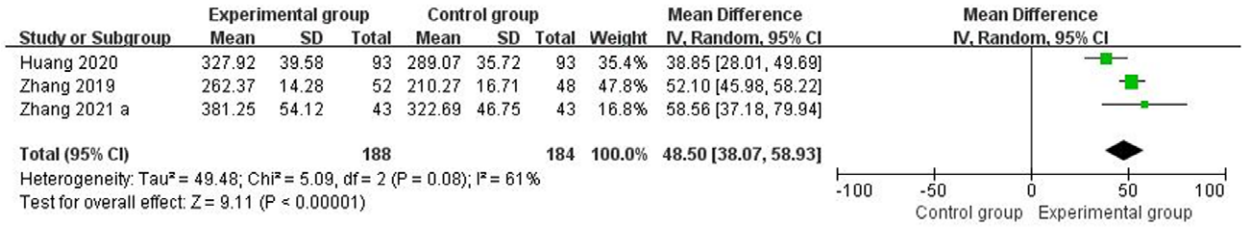

Figure 10. Forest plot comparing serum motilin level (pg/mL) of HM alone and combination of HM and WM groups with WM only groups. HM = herbal medicine, WM = Western medicine.

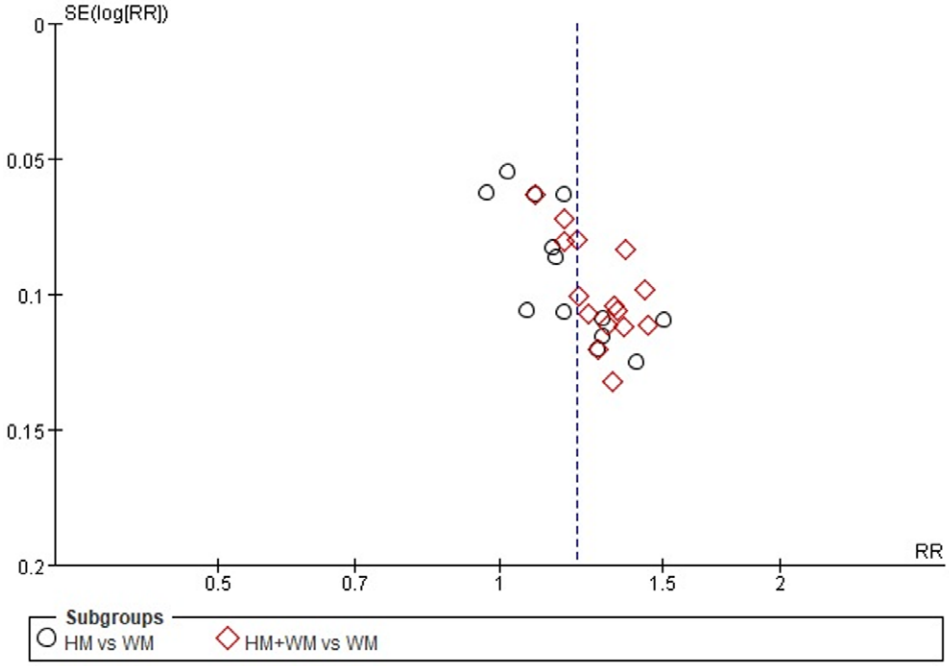

Figure 11. Funnel plot of TCE between HM alone or combination of HM and WM groups and WM only groups. HM = herbal medicine, WM = Western medicine, RR = risk ratio, TCE = total clinical efficacy rate, SE = standard error.

prescriptions involve the addition or subtraction of different herbs depending on the symptoms. Therefore, we summarized the herbs added according to the symptoms of NERD reported in the included studies. The effect of herbal medicine on improving each aspect of quality of life in patients with NERD was also confirmed.

There are some limitations in this study: First, it seems the heterogeneity of several measures came out to be high due to the basic characteristic of herbal medicine that the composition of each herbal medicine prescription is not the same. In addition, the intervention blinding and practitioner blinding processes were not mentioned in most of the studies, which led to a high risk of performance and detection bias. As a result, a high risk of bias and heterogeneity led to low levels of evidence. For other limitations, the population of the participants was limited to Chinese individuals.

Based on these limitations, we suggest that trials with methodologically high-quality and large-sized samples from a broader population must be conducted in future studies. Approaches to lower the risk of bias, such as administering placebo medicine and blinding the outcome assessment process, are needed. Since TCE, which is used as the main assessment tool in most studies, has different definitions for each study, it is necessary to use a standardized questionnaire tool that can consistently compare results between studies as the main outcome measure.

5. Conclusion

In this systematic review and meta-analysis, we summarized the details of the use of herbal medicine for the treatment of NERD and compared its effects with those of Western medicine. Including herbal medicine in the treatment of NERD has a significantly better effect than using conventional medicine alone in terms of improving the total clinical efficacy rate. Herbal medicine therapy can be effective in lowering the recurrence rate of NERD, relieving the symptoms felt by patients, and improving the quality of life. It also increased the serum motilin levels and did not induce severe intervention-related adverse effects. However, as the evidence is based on low-to-moderate certainty, clinical trials with methodologically improved quality must be conducted.

Author contributions

Conceptualization: Minjeong Kim, Jae-Woo Park.
Data curation: Minjeong Kim, Chaehyun Park, Seok-Jae Ko.
Formal analysis: Minjeong Kim, Chaehyun Park, Jinsung Kim.
Investigation: Jae-Woo Park, Jinsung Kim, Seok-Jae Ko.
Methodology: Jae-Woo Park, Jinsung Kim, Seok-Jae Ko.
Resources: Jae-Woo Park, Seok-Jae Ko.
Writing – original draft: Minjeong Kim.
Writing – review & editing: Jae-Woo Park, Seok-Jae Ko.

Table 4

Level of evidence.

	Certainty assessment					Effect		
	Number of studies	Risk of bias	Inconsistency	Indirectness	Imprecision	Relative (95% CI)	Absolute (95% CI)	Certainty
TCE	28	Serious*	Not serious	Not serious	Not serious	RR 1.21 (1.16–1.27)	152 more per 1000 (from 115 more to 195 more)	Moderate
HM included versus WM								
HM versus WM	13	Serious*	Not serious	Not serious	Not serious	RR 1.16 (1.08–1.25)	120 more per 1000 (from 60 more to 188 more)	Moderate
HM + WM versus WM	15	Serious*	Not serious	Not serious	Not serious	RR 1.25 (1.19–1.31)	174 more per 1000 (from 132 more to 216 more)	Moderate
Recurrence rate	7	Serious*	Not serious	Not serious	Not serious	RR 0.35 (0.27–0.45)	324 fewer per 1000 (from 364 fewer to 274 fewer)	Moderate
RDQ	8	Serious*	Serious†	Not serious	Not serious		MD 2.52 lower (3.81 lower to 1.23 lower)	Low
SF-36								
Physiological function	6	Serious*	Serious†	Not serious	Serious‡		MD 18.45 higher (17.64 higher to 19.26 higher)	Very low
Physical function	6	Serious*	Serious†	Not serious	Not serious		MD 19.38 higher (18.46 higher to 20.3 higher)	Low
Body pain	6	Serious*	Serious†	Not serious	Not serious		MD 12.12 higher (11.2 higher to 13.05 higher)	Low
General health	5	Serious*	Serious†	Not serious	Serious‡		MD 29.18 higher (28.49 higher to 29.87 higher)	Very low
Vitality	6	Serious*	Serious†	Not serious	Not serious		MD 15.73 higher (15 higher to 16.45 higher)	Low
Social functioning	6	Serious*	Serious†	Not serious	Not serious		MD 30.81 higher (30.14 higher to 31.49 higher)	Low
Emotional functioning	6	Serious*	Serious†	Not serious	Serious‡		MD 47.54 higher (46.77 higher to 48.32 higher)	Very low
Mental health	6	Serious*	Serious†	Not serious	Serious‡		MD 38.46 higher (37.9 higher to 39.03 higher)	Very low
Serum motilin level	3	Serious*	Not serious	Not serious	Not serious		MD 48.5 higher (38.07 higher to 58.93 higher)	Moderate

CI = confidence interval, GERDQ = gastroesophageal reflux disease questionnaire, HM = herbal medicine, MD = mean difference, RDQ = reflux diagnostic questionnaire, SF-36 = short-form 36 health survey, TCE = total clinical efficacy, WM = western medicine.

*Most of the studies have high risk of bias.

†The heterogeneity is high.

‡The funnel plot is shown asymmetry.

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