Efficacy of Chinese herbal medicine in functional dyspepsia: A meta-analysis of randomized, double-blind, placebo-controlled trials

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KEYWORDS
Functional dyspepsia; Meta-analysis; Chinese herbal medicine; Placebo

Abstract  Objective: To evaluate the efficacy and safety of Chinese herbal medicine (CHM) for the treatment of functional dyspepsia (FD).
Methods: Web of Science, PubMed, EMBASE, Cochrane Library, and four other Chinese electronic databases, including China National Knowledge Infrastructure (CNKI), Chinese Biological Medical Database (CBM), Chinese Scientific Journals Database (VIP), and WanFang Database were used to search (up to Feb, 2016) for randomized, double-blind, placebo-controlled trials recruiting adults with FD treated with CHM. Study selection, data extraction, quality assessment, and data analyses were conducted based on Cochrane standards using Review Manager software.
Results: Fourteen publications (1424 patients) were included. Evidence revealed that CHM was more efficacious than the placebo in improving global dyspepsia symptoms (RR, 1.45; 95% CI, 1.31–1.60), Chinese medicine syndrome (CMS) (RR, 1.36; 95% CI, 1.23–1.50), and quality of life (SMD, 0.30; 95% CI, 0.15–0.45) in FD patients. Furthermore, the difference in the incidence of adverse events between CHM and placebo groups had no statistical significance (RR, 1.06; 95% CI, 0.66–1.70).

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Introduction

As defined by Rome III criteria, functional dyspepsia (FD) is associated with several upper gastrointestinal symptoms, including postprandial fullness, early satiety, epigastric pain or discomfort lasting for 6 months or longer, without an organic explanation. Based on the dominant symptoms, FD can be separated into two subtypes, postprandial distress syndrome (PDS) and epigastric pain syndrome (EPS). According to Rome III criteria, the estimated prevalence of uninvestigated dyspepsia (UD) and FD is in the range of 9.8%–20.2% in the West and between 5.3% and 12.8% in the East, with a global prevalence between 4.6% and 11.3%. FD is considered a functional gastrointestinal disorder (FGID) and follows a chronic and fluctuating course. Up to 15%–20% of patients claim to have persistent symptoms, and this condition negatively impacts physical and mental health as well as quality of life. Nearly 42% of people with FD consult a physician though many patients do not seek medical advice, resulting in decreased work productivity due to poor health. A burden of illness study found that in 2009 costs associated with FD in the United States were estimated at $18.4 billion. Given the health and economic burdens of FD, its effective management is vitally important. However, because of the nonspecific symptoms and varied pathogenesis of this disease, definitive therapy that is beneficial for all individuals is still lacking. Conventional treatments, including lifestyle adjustments, antacids, prokinetic drugs, psychotropic agents, and even Helicobacter pylori eradication, often remain unsatisfactory. Therefore, up to 50% patients seek other therapies, such as complementary and alternative medicine (CAM).

One such CAM is traditional Chinese medicine (TCM), of which an essential branch is Chinese herbal medicine (CHM). CHM as represented by herbal formulation is an organic combination of Chinese herbs in based on the theories of TCM. CHM appears to have a regulatory effect on the human body and clinical and experimental studies seem to indicate that herbal therapy is an encouraging option for the treatment of FD. Several meta-analyses have been conducted to evaluate the therapeutic benefits of CHM compared with Western medicine, mainly prokinetic drugs. However, evidence from these studies has been weak. Furthermore, these studies have been limited by use of specific herbal formulations, such as Pinellia Decoction to Drain the Epigastrium (Banxia Xiexin Tang) or Modified Rambling Powder (Xiao Yao San Jia Jian). Therefore, the therapeutic value of CHM for FD is unknown. To address this question, we conducted a meta-analysis of clinical trials on the CHM treatment of FD, aiming to determine the efficacy and the safety of CHM and to make recommendations on future investigations of the clinical usage of CHM in treating FD.

Methods

Data sources and search strategy

Articles published up to February 11, 2016 were retrieved from 8 electronic databases: Web of Science, PubMed, EMBASE (Excerpt Medica Database), Cochran Library, and 4 Chinese electronic databases, including China National Knowledge Infrastructure (CNKI), WanFang Database, Chinese Biological Medical Database (CBM), and Chinese Scientific Journals Database (VIP). CNKI and WanFang databases were used to search for conference proceedings and dissertations from unpublished clinical trials. Studies were identified using the following search terms were as in this PubMed example: "randomized"[Title/Abstract] AND "placebo"[Title/Abstract] AND ("blind"[Title/Abstract] OR "blinded"[Title/Abstract]) AND ("Traditional Chinese Medicine"[Title/Abstract] OR "Chinese Medicine, Traditional"[Title/Abstract] OR "Medicine, Chinese Traditional"[Title/Abstract] OR "Chinese Traditional Medicine"[Title/Abstract] OR "herb"[Title/Abstract] OR "Medicine, Herbal"[Title/Abstract] OR "TCM"[Title/Abstract] OR "herbal"[Title/Abstract] OR "formula"[Title/Abstract] OR "Octopus"[Title/Abstract] OR "kampo"[Title/Abstract]).

Inclusion/exclusion criteria

Randomized, double-blind, and placebo-controlled clinical trials that compared CHM with a placebo were included. The full-text articles had to be published in English or Chinese.

Participants (not limited to specific groups of the population) who were diagnosed with FD based on Rome criteria, including Rome I, II, and III, were included. All participants were aged 18 years or older.

The treatment groups only received CHM by oral administration in any form of preparation, including decoctions, extracted granules, capsules, tablets, powders, and liquids. Placebos, which were identical in appearance, taste, and smell, were compared to the herbal medicines and used alone in the controlled group. The minimum duration of therapy and follow-up was 7 days.

In terms of outcome measures, studies were included if dichotomous assessment of responses to therapy based on the effect of CHM or the placebo on global dyspepsia symptoms was used as a measurement for the primary outcome, with a preference for patient-reported assessment if the

Conclusion: This meta-analysis demonstrates that CHM has a therapeutic potential in treating FD with a certain safety. However, due to the restricted number of trials included, well-planned, long-term studies are necessary to provide credible evidence.

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study involved both investigator-reported and patient-reported results, and secondary outcomes were measured using Chinese medicine syndrome (CMS) improvement, quality of life, and adverse events. However, clinical trials without dichotomous outcomes in global dyspepsia symptoms, but with information on CMS improvement or quality of life, were also included. Studies, based on one clinical trial but published as separate articles with varied outcome measures, were merged as a single study.

Data extraction

All data were extracted separately by two investigators (Y G and JJ Z), where disagreements were determined by consensus with the corresponding author (W W). Extracted information included country of origin of the study, diagnostic criteria and subtypes, TCM syndrome differentiation, population and baseline characteristics, interventions, duration of therapy, follow-ups, outcome measurements, and adverse events.

Assessment of quality

Two investigators (Y G and JJ Z) used the Cochrane risk of bias tool to evaluate methodological quality, and disagreements were resolved by discussion and consensus with the corresponding author. Quality of included trials was evaluated for generation of randomization, concealment of allocation, blinding method, incomplete outcome data, selective reporting, and other bias.

Data analysis

Data processing and analysis were performed using Review Manager version 5.2.7 (Cochrane Collaboration, Oxford, UK). Dichotomous data were represented as relative risk (RR) and continuous variables were compared using mean difference (MD), both with 95% confidence interval (CI). In cases where different measurement scales were used, standardized mean difference (SMD) was chosen instead of MD. The number needed to treat (NNT), with 95% CI, was computed based on the formula $NNT = \frac{1}{control\ event\ rate \times (1 - RR)}$. Heterogeneity, which represents the variation between individual study results, was evaluated by the $\chi^2$ test and the $I^2$ statistic. When the $P > .10$ of $\chi^2$ test with $I^2 < 50\%$, the heterogeneity was considered acceptable, and the fixed effects model was adopted. Otherwise, the data were pooled by using the random effects model. Z (u) test was used for the hypothesis test in order to evaluate the overall impact of CHM. Differences between CHM and placebo groups were considered statistically significant when $P \leq .05$, as represented in forest plots.

Results

Description of included studies

A total of 140 citations were identified from the 8 electronic databases. Of these 140 citations, 34 published articles appeared to be relevant and were evaluated in full-text, of which 20 articles were excluded for various reasons (Fig. 1). Fourteen studies are deemed eligible for inclusion in the meta-analysis, including 11 journal articles and 3 theses. Among these 14 articles, 25–28,34,36–38 were merged into 4 studies, 34,36–38 as varied results were reported in these different articles but all results were derived from a single clinical trial. Finally, 10 studies were included, 29–38 of which were completed in China31,32,34–38 with 3 published in English, 36–38 2 were completed in Korea, 29,30 and 1 was completed in Japan (Table 1).33

There were a total of 1424 patients in the 10 studies, and the total participants in each study ranged from 46 to 273. The proportion of male patients recruited by the trials ranged from 30.4% to 47.0%; the proportion of male patients in one study was unknown. Seven studies were multicenter trials with the total number of centers involved ranging between 2 and 31.30,33–38 Outcomes of global symptom improvement were not provided as dichotomous data in 3 of the trials. 29,30,32 Seven trials completed in China elaborated TCM syndrome differentiation, with 6 reporting CMS improvements in their results, 31,32,34–37 while studies completed in Japan and Korea did not include this information. Moreover, 7 studies adopted quality of life as one of the outcome measures in 3 of the trials. 29,30,33,34 Specific details of each study are presented in Table 1, as well as the composition of CHM used in each eligible study is provided in Table S1 of the Supplementary Information.

Methodological quality

Most of the included studies elaborated on the specific methods used in random sequence generation and allocation concealment. Among the 10 studies, 9 articles stated blinding methods of participants and investigators, 29,30,32–38 while in 7 articles there was indication of outcome assessments being conducted by a third party. 29,30,33,34,36–38 Furthermore, 9 of the 10 studies reported dropouts 29,30,32–38 and most studies adopted intention-to-treat (ITT) analyses. 29–31,33,34,36–38 However, only 3 studies were registered as clinical trials online 29,33 or had published a protocol, 30,39 while such information for the 7 other studies were unavailable. Baseline characteristics in all studies were comparable between the treatment and control groups, but the exact figures were not provided in 2 of the studies. 24,35 Moreover, 5 investigations had clear statements about competing interests. 28,30,33,36–38 Methodological assessment of included studies was represented as a graph of From our analyses, we performed risk bias (Fig. 2A) and a risk bias summary (Fig. 2B).

Global symptom improvement

Dichotomous data on responses to therapy with respect to its effect on global symptoms were extracted from 7 of the 10 included trials. 31,33–38 In total, there were 624 participants who received CHM therapy and 450 participants who received placebos. Overall, 468 (75.0%) of 624 patients assigned to the CHM group reported improved global dyspepsia symptoms, compared to 217 (48.2%) of 450...
patients who were part of the placebo group. There was a therapeutic gain of 26.8% in the CHM group in comparison with the placebo group, and the NNT value was up to 4 in the range of 3–7 (Table 2). The results of the heterogeneity tests ($\chi^2 = 6.50, P = .37, I^2 = 8\%$) revealed that the studies selected were clinically and statistically homogeneous. Hence, the fixed effects model was applied in the meta-analysis. Based on the outcome of the hypothesis test ($Z = 7.29, P < .00001$), the difference in the results between the CHM and control groups was statistically significant, which indicated that CHM was more efficacious in improving global symptoms than the placebo (pooled RR, $1.45; 95\%$ CI, $1.31$–$1.60$) (Fig. 3).

**Chinese medicine syndrome improvement**

Six studies (787 participants) reported results of CMS improvement both in the CHM therapy group and the placebo group. The pooled RR of CMS improvement after
<table>
<thead>
<tr>
<th>First author, year</th>
<th>Country (study centers)</th>
<th>Sample sizes (% male)</th>
<th>Diagnostic criteria (subtypes)</th>
<th>Syndrome differentiation</th>
<th>Intervention Durations</th>
<th>Follow-up</th>
<th>Primary outcomes</th>
<th>Secondary outcomes</th>
<th>Adverse events (T:C)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Suzuki et al, 2009</td>
<td>Japan (31)</td>
<td>247 (36.8)</td>
<td>Rome III (EPS, PDS, mixed type)</td>
<td>NR</td>
<td>Rikkunshito; powder, 2.5 g, 3 times/day</td>
<td>8 weeks</td>
<td>30 days</td>
<td>GPA score</td>
<td>1. Single symptom improvement (Likert scale)</td>
</tr>
<tr>
<td>Wang et al, 2011; Zhao et al, 2011</td>
<td>China (5)</td>
<td>104 (NR)</td>
<td>Rome III (NR)</td>
<td>Spleen-stomach damp-heat</td>
<td>Gastrostosis No.3 compound; granule, 150 mL, 2 times/day</td>
<td>4 weeks</td>
<td>4 weeks</td>
<td>1. TDS (investigator and patient)</td>
<td>SF-36</td>
</tr>
<tr>
<td>Che, 2011</td>
<td>China (1)</td>
<td>46 (30.4)</td>
<td>Rome III (NR)</td>
<td>Exclusion of yin deficiency syndrome and blood stasis</td>
<td>Tablets for Clearing and Resolving and Harmonizing the Stomach (Qing Hua He Wei Pian); 4 tablets, 1.2 g, 3 times/day</td>
<td>4 weeks</td>
<td>4 weeks</td>
<td>1. TDS (investigator and patient)</td>
<td>SF-36</td>
</tr>
<tr>
<td>Zhang et al, 2013; Wu et al, 2011</td>
<td>China (5)</td>
<td>162 (34.0)</td>
<td>Rome III (NR)</td>
<td>Spleen and stomach deficiency-cold</td>
<td>Gastrostosis No.1 compound; granules, 150 mL, 2 times/day</td>
<td>4 weeks</td>
<td>4 weeks</td>
<td>1. SDS scale</td>
<td>SF-36</td>
</tr>
<tr>
<td>Zhao et al, 2013; Zhao et al, 2013</td>
<td>China (5)</td>
<td>101 (33.7)</td>
<td>Rome III (NR)</td>
<td>Cold-heat complex</td>
<td>Modified Pinellia Decoction to Drain the Epigastrum (Ban Xia Xie Xin Tang); granules, 150 mL, 2 times/day</td>
<td>4 weeks</td>
<td>4 weeks</td>
<td>1. TDS scale</td>
<td>SF-36</td>
</tr>
<tr>
<td>Zhang et al, 2013; Zhao et al, 2013</td>
<td>China (5)</td>
<td>160 (31.3)</td>
<td>Rome III (NR)</td>
<td>Spleen deficiency and qi stagnation</td>
<td>Modified Six Gentlemen Decoction (Li Juan Zi Tang); granules, 150 mL, 2 times/day</td>
<td>4 weeks</td>
<td>4 weeks</td>
<td>1. TDS scale</td>
<td>SF-36</td>
</tr>
<tr>
<td>Xu, 2013</td>
<td>China (3)</td>
<td>273 (34.1)</td>
<td>Rome III (NR)</td>
<td>1. Damp-heat stasis; 2. Spleen deficiency and qi stagnation; 3. Constrained liver qi; 4. Liver-stomach heat stasis</td>
<td>No.1—No.4 compound; granules, 2 times/day</td>
<td>4 weeks</td>
<td>5 months</td>
<td>1. CMS improvement</td>
<td>1. Gastric emptying using radiopaque barium markers</td>
</tr>
<tr>
<td>Park et al, 2013</td>
<td>Korea (2)</td>
<td>100 (47.0)</td>
<td>Rome III (EPS, PDS, mixed type)</td>
<td>NR</td>
<td>Banha-sasim-tang; granules, 3 g, 3 times/day</td>
<td>6 weeks</td>
<td>2 months</td>
<td>GIS scale</td>
<td>1. Gastric emptying using radionuclide (partially)</td>
</tr>
<tr>
<td>Kim et al, 2014</td>
<td>Korea (1)</td>
<td>170 (23.5)</td>
<td>Rome III (EPS, PDS)</td>
<td>NR</td>
<td>Hyangsa-Pyeongwi san; powder, 9.68 g, 3 times/day</td>
<td>4 weeks</td>
<td>4 weeks</td>
<td>ND</td>
<td>1 (10)</td>
</tr>
<tr>
<td>Lü, 2014</td>
<td>China (1)</td>
<td>61 (42.6)</td>
<td>Rome III (PDS, mixed type)</td>
<td>1. Spleen deficiency and qi stagnation syndrome; 2. Spleen deficiency and damp stagnation syndrome; 3. Spleen yang deficiency syndrome</td>
<td>No.1—No.3 compound; granules, 1 package, 3 times/day</td>
<td>4 weeks</td>
<td>4 weeks</td>
<td>1. SF-36</td>
<td>2. HAMA &amp; HAMD</td>
</tr>
</tbody>
</table>

Abbreviations: C, control group; CHM, Chinese herbal medicine; CMS, Chinese medicine symptom; EPS, epigastric pain syndrome; FD, functional dyspepsia; FD-QoL, FD-related quality of life; GIS, gastrointestinal symptom scale; GMA, gastric myoelectric activity; GPA, global patient assessment; GSRS, Japanese version of the Gastrointestinal Symptom Rating Scale; HAMA, Hamilton Anxiety Scale; HAMD, Hamilton Depression Scale; NDI, Nepean Dyspepsia Index; NR, not reported; PDS, postprandial distress syndrome; SDS, single symptom scale; SF-36, the MOS 36-item short-form health survey; T, treatment group; TDS, total symptom scale; VAS, visual analogue scale.
treatment with CHM versus the placebo was 1.41 (95% CI, 1.28–1.56), with significant heterogeneity detected among studies ($\chi^2 = 13.60, P = .02, I^2 = 63\%$) (Fig. 4A). The sensitivity analysis was conducted and indicated using the Che’s study, which might have been the main contributor towards the heterogeneity. As a result, Che’s study was excluded and the remaining 5 articles had no significant heterogeneity ($\chi^2 = 5.84, P = .21, I^2 = 31\%$). Based on the fixed effects model, the overall effect test ($Z = 6.17, P < .00001$) performed found a significant difference in CMS improvement between the CHM group and the placebo group (pooled RR, 1.36; 95% CI, 1.23–1.50) (Fig. 4B).

Quality of life improvement

Among the 10 included studies, 7 trials stated that there was an improvement in quality of life with CHM therapy and placebo while Che’s study provided incomplete data that could not be further extracted. Of these 6 studies (698 participants, 29,30,32,34,37,38) 4 studies completed in China applied the Medical Outcomes Study (MOS) 36-item short-form health survey (SF-36) as an evaluation tool, while the 2 trials completed in Korea adopted the functional dyspepsia-related quality of life (FD-QoL) questionnaire. Additionally, in this meta-analysis, the sum of the physical component summary (PCS) score and the mental component summary (MCS) score was calculated as the result of SF-36. Since statistical heterogeneity was not detected among these studies ($\chi^2 = 3.84, P = .57, I^2 = 0\%$), the fixed effects model was applied. According to the outcome of the hypothesis test ($Z = 3.80, P = .0001$), CHM resulted in a better improvement in quality of life in comparison with the placebo (pooled SMD, 0.30; 95% CI, 0.15–0.45) (Fig. 5).

<table>
<thead>
<tr>
<th>First author, year</th>
<th>No. of participants</th>
<th>Response rate, % (response/N)</th>
<th>Therapeutic gain, %</th>
<th>NNT (95%, CI)</th>
<th>RR of global symptoms improving (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Suzuki et al, 2009</td>
<td>247</td>
<td>33.6 (42/125)</td>
<td>23.8 (29/122)</td>
<td>9.8</td>
<td>10 (4, 84)</td>
</tr>
<tr>
<td>Wang et al, 2011; Zhao et al, 2011</td>
<td>104</td>
<td>78.6 (55/70)</td>
<td>55.9 (19/34)</td>
<td>22.7</td>
<td>4 (2, 89)</td>
</tr>
<tr>
<td>Che, 2011</td>
<td>46</td>
<td>91.3 (21/23)</td>
<td>30.4 (7/23)</td>
<td>60.9</td>
<td>2 (1, 5)</td>
</tr>
<tr>
<td>Zhang et al, 2013; Wu et al, 2011</td>
<td>162</td>
<td>91.7 (99/108)</td>
<td>68.5 (37/54)</td>
<td>23.2</td>
<td>4 (2, 13)</td>
</tr>
<tr>
<td>Zhao et al, 2013; Zhao et al, 2012</td>
<td>160</td>
<td>92.5 (98/106)</td>
<td>63.0 (34/54)</td>
<td>29.5</td>
<td>3 (2, 8)</td>
</tr>
<tr>
<td>Zhang et al, 2013; Zhao et al, 2013</td>
<td>101</td>
<td>86.6 (58/67)</td>
<td>55.9 (19/34)</td>
<td>30.7</td>
<td>3 (2, 14)</td>
</tr>
<tr>
<td>Xu, 2013</td>
<td>273</td>
<td>76.0 (95/125)</td>
<td>55.8 (72/129)</td>
<td>20.2</td>
<td>5 (3, 14)</td>
</tr>
<tr>
<td>Total</td>
<td>1093</td>
<td>75.0 (466/624)</td>
<td>48.2 (217/450)</td>
<td>26.8</td>
<td>4 (3, 7)</td>
</tr>
</tbody>
</table>

Abbreviations: CI: confidence interval; CHM: Chinese herbal medicine; N: numbers of participants; NNT: number needed to treat; RR: relative risk.
Figure 3  Forest plot of the global symptom improvement of the Chinese herbal medicine (CHM) group versus the placebo group in functional dyspepsia.

Figure 4  (A) Forest plot of Chinese medicine syndrome in the Chinese herbal medicine (CHM) group versus the placebo group in functional dyspepsia patients; (B) forest plot of sensitivity analysis by the exclusion of one study.

Figure 5  Forest plot of quality of life improvement in the Chinese herbal medicine (CHM) group versus the placebo group in functional dyspepsia patients.
Adverse events

All included studies mentioned adverse events, but only 4 studies reported the details.29,30,33,35 Thirty (7.8%) of the 386 participants reported adverse events in the CHM group compared to 28 (7.3%) of 385 participants assigned to the placebo group. Under the fixed effects model, there was no significant difference between the CHM group and the placebo group in the incidence of adverse events (pooled RR, 1.06; 95% CI, 0.66–1.70) according to the result of the overall effect test (Z = 0.23, P = .82), with no heterogeneity between results (χ² = 2.97, P = .40, I² = 0%) (Fig. 6).

Discussion

Our meta-analysis appears to show that CHM is effective for FD, with an NNT value of 4 when data of global dyspepsia symptoms were pooled from all included studies. Furthermore, the differences in both CMS and quality of life between the CHM therapy and placebo groups were statistically significant (P ≤ .05), which indicates that CHM has a greater impact on the improvement of CMS and quality of life compared with placebo. Meanwhile, there was no statistically significant difference between CHM and placebo groups in the incidence of adverse events, which illustrates that CHM may be used as an effective and safe treatment for FD.

The methodological assessment was conducted based on the Cochrane collaboration’s tool for assessing risk of bias. We chose the fixed effects model to establish the hypothesis test in cases where there was an acceptable level of heterogeneity. However, statistical heterogeneity was found among the 6 studies that reported CMS improvement.31,32,34–37 Based on the results of the sensitivity analysis, we speculated that Che’s study31 might be the main cause of heterogeneity, due to the different diagnostic criteria of syndrome differentiation. Syndrome differentiation has a crucial influence on the assessment of CMS improvement and the standard of diagnosis of CMS in Che’s study was inconsistent with the determinative diagnoses used in other studies.32,34–37 The diagnostic criterion of CMS in Che’s study was reported in accordance with a draft of a scheme published in 2003,30 while 4 of the remaining 5 studies used the Guiding Principle for Clinical Research on New Drugs of Traditional Chinese Medicine as the diagnostic criteria32,34,36,37,41 and the final study adopted a consensus published in 2010.35,42 Both of these tools have been widely recognized in the field of TCM and are more highly regarded than the draft used in Che’s study.

There are several limitations of this research, some of which relate to the nature of the included studies. Two articles31,35 did not mention the methods used to generate randomization, one31 of which did not report the method of allocation concealment, which may have resulted in selection biases. There were also potential performance biases due to blinding methods and incomplete information in 3 studies.31,32,35 Considering the use of ITT analyses and publication of research programs, potential attrition and reporting biases cannot be neglected. In addition, it should be noted that the longest duration of therapy in these 10 studies was 8 weeks, indicating that the long-term efficacy of CHM in FD needs to be observed in future studies.

Although, conventional treatments are efficacious for FD to a certain degree,21,43–45 there is still a considerable proportion of patients who do not experience relief of persistent symptoms,6 thus there is a pressing need for more effective therapies in FD. Several meta-analyses confirmed that CHM appears to be an effective alternative for FD therapy but with poor-quality evidence, limited by the particular herbal formulations used.16–18 This underlines the importance of the current meta-analysis, which focuses on randomized, double-blind, placebo-controlled clinical trials without the limitation of herbal formulations and highlights that CHM appear to be more efficacious than placebos for FD.

The mechanism of action of CHMs in FD may be related to gastric motility, receptive relaxation, visceral hypersensitivity, and the neuroendocrine system. Three studies showed that CHM improved gastric motility through gastric emptying tests based on various techniques, including radiopaque barium markers,36 radionuclide,35 and ultrasound.42 Park’s study also showed Banha-sasim-tang (Pine- lilia Decoction to Drain the Epigastrium in TCM) regulated gastric motility, as determined by electrogastrography (EGG).30 Many experimental and clinical studies have demonstrated that Rikkunshito (Six Gentlemen Decoction; Liu Jun Zi Tang in pinyin) may be beneficial for dyspepsia symptoms by altering the gastric accommodation reflex, increasing gastric motility, improving delayed gastric emptying, and regulating gastrointestinal hormones, suggesting that Rikkunshito has prokinetic effects on gastrointestinal disorders.46–50

Figure 6 Forest plot of adverse events in the Chinese herbal medicine (CHM) group versus the placebo group in functional dyspepsia patients.
Additionally, there were regional differences in the evaluation methods of the articles included. CHM is widely accepted in Asia, especially in China, Japan, and Korea, and various clinical trials and mechanistic investigations have been performed in these countries. However, in this study, we observed that evaluation methods varied among studies. SF-36 is widely used in China to measure changes in quality of life, while the FD-QOL questionnaire is popular in clinical trials conducted in Korea. Moreover, the methods adopted to estimate improvement of global symptoms and gastric motility varied in studies, and even the diagnostic criteria of syndrome differentiation were diverse, which might lead to increased difficulties in evaluating the work of systematic reviews. Therefore, there is a need for unified evaluation of protocols using internationally accepted standards in clinical trials for FD.

Conclusions

In conclusion, this meta-analysis demonstrates CHM appears to be more efficacious than placebo in the treatment of FD, as evidenced by improvements seen in the CHM group in global dyspepsia symptoms, CMS, quality of life, and the safety of the drug. However, considering the limited quantity of the literature included, well-planned, long-term, and transnational cooperative studies are necessary to provide credible evidence.

Conflicts of interest

The authors declare no competing financial interests.

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Appendix A. Supplementary information

Supplementary information related to this article can be found at http://dx.doi.org/10.1016/j.jtcms.2016.09.006.

References


