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Efficacy of traditional Chinese medicine for chronic gastritis

A meta-analysis of randomized controlled trials

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Abstract

Background: To systematically evaluate efficacy of traditional Chinese medicine (TCM) in treating chronic gastritis (CG).

Methods: Data sources from PubMed, Embase, Springer Link, China National Knowledge Infrastructure, Chinese Scientific Journals Database, Chinese Biomedicine Database, and Wan-fang database were searched up to July 5, 2018. Review Manager software version 5.3, the Cochrane Collaboration's risk of bias tool, and the Grading of Recommendations Assessment, Development, and Evaluation profiler software were conducted for this meta-analysis.

Results: Sixteen studies involving 1673 participants (906 vs 767) were included in this study. Pooled data showed significant statistical differences between TCM groups and current routine pharmacotherapy (RP) groups in overall clinical efficacy (odds ratio [OR] 4.65; 95% confidence interval [CI] 3.29, 6.56; $P < .00001$), efficacy under endoscopy (OR 2.46; 95% CI 1.12, 5.43; $P = .03$), stomach distension (mean difference [MD] −0.37; 95% CI −0.56, −0.19; $P < .0001$), stomachache (standardized MD [SMD] −0.80; 95% CI −1.45, −0.14; $P = .02$), and belching (SMD −2.00; 95% CI −3.80, −0.20; $P = .03$). However, acid regurgitation (SMD −0.71; 95% CI −1.69, 0.28; $P = .16$) and anorexia (SMD −0.75; 95% CI −2.30, 0.80; $P = .35$) showed no significant statistical differences between 2 groups. In addition, incidence of adverse reactions of TCM groups was lower than that of RP groups.

Conclusion: Evidence from this meta-analysis suggests that TCM could be more efficacious than current RP in treating CG. But further standardized research of rigorous design should be needed to further validate its efficacy.

Abbreviations: CAG = chronic atrophic gastritis, CG = chronic gastritis, CIs = confidence intervals, CSG = chronic superficial gastritis, EGFRs = epiderminal growth factor receptors, GC = gastric cancer, GRADE = the Grading of Recommendations Assessment, Development, and Evaluation, Hp = *Helicobacter pylori*, MD = mean difference, NF-κB = nuclear transcription factor kappa B, OR = odds ratio, PGE_2 = prostaglandin E_2, RCTs = randomized clinical trials, RP = routine pharmacotherapies, SMD = standardized mean difference, TCM = traditional Chinese medicine.

Keywords: chronic gastritis, meta-analysis, traditional Chinese medicine

1. Introduction

Chronic gastritis (CG) is defined as an inflammation even atrophy on the gastric mucosa, usually accompanied with gastric mucosal lesions including structural alterations of glandular compartment.[1,2] Based on its different elementary lesions, this condition is classified into 2 different levels: a basic level and a hierarchically higher level.[2] *Helicobacter pylori* (Hp), as a class I carcinogen,[3] is the most common cause of CG around the world. Furthermore, CG is biologically and epidemiologically connected with the development of gastric cancer (GC) in a population.[4–7] With an increasing incidence of CG in China,[8] risk of GC has been growing, thereby seriously affecting people's daily life.[9]

Numerous efforts including histopathologic examination of gastric biopsy specimens have been made to look into pathogenesis of CG, but we lack a straightforward analysis of cancer risk, as well as its treatment.[2] As current routine pharmacotherapies (RPs), Hp eradication agents, antiacid, spasmolytic, and gastric mucosa protectant have been put into clinical practice. However, efficacy of these RP is less than satisfactory.[10] Therefore, many sufferers have turned to traditional Chinese medicine (TCM) for help.[11–15] So far, 4 relevant studies have been published.[16–19] However, 2 conducted meta-analyses of chronic atrophic gastritis (CAG) not

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CG.[16,17] One reported a systematic review of Huangqi Jianzhong Tang for CG.[18] The remaining 1 reported a PRISMA-compliant systematic review and meta-analysis of common mechanism of pathogenesis in gastrointestinal diseases treating in single Chinese medicine formula.[19] Nevertheless, the current state of evidence of TCM for CG remains inadequately explained. Therefore, a meta-analysis of randomized controlled trials was conducted to evaluate its efficacy.

2. Materials and methods

2.1. Searching strategy

The following seven electronic databases were searched up to July 5, 2018: PubMed, Embase, Springer Link, China National Knowledge Infrastructure, Chinese Scientific Journals Database, Chinese Biomedicine Database, and Wan-fang database. No limitation was conducted for language in literature search. Ambiguous or missing information was obtained through combining electronic searches with manual searches. The following medical terms used individually or in combination in literature retrieval were as follows: "traditional Chinese medicine," "TCM," "Chinese medicine," "herbs," "chronic gastritis," "gastritis," and "randomized controlled trial."

2.2. Inclusion and exclusion criteria

Literatures meeting all of the following criteria were included: randomized controlled trials; patients with CG; more than 4 weeks in treatment course; and RP including Hp eradication agents, antiacid, spasmolytic, or gastric mucosa protectant. Literatures meeting the following criteria were excluded: literature reviews; no control group; not TCM but RP in experiment groups; and incomplete or error data in included literatures.

2.3. Literature screening

Literature search, study selection, and data extraction were independently conducted by 2 reviewers. Information of data extraction was as follows: authors, study design (baseline), characteristics of patients, sample size, details of intervention, and outcome measurements (primary outcome, second outcomes, follow-up, withdrawals or dropouts, and side effects). One reviewer extracted the initial data, and the other subsequently reexamined each trial and verified their results.

2.4. Quality assessment

The evaluation of methodologic quality was conducted by 2 independent researchers on the basis of the Cochrane Collaboration's risk of bias tool.[20] The specific details were as follows: random sequence generation; allocation concealment; blinding of participants and personnel; blinding of outcome assessment; incomplete outcome data; and selective reporting. Disagreements were resolved after discussing with a 3rd investigator.

2.5. Data synthesis and analysis

Review Manager 5.3 software was used for statistical analysis from more than 2 separate studies to generate forest plots, 95% confidence intervals (CIs), and odds ratio (OR) or standardized mean difference (SMD) or mean difference (MD). Statistical heterogeneity was statistically computed by using the Chi-squared (χ^2) test and inconsistency index statistic (I^2).[21] A model of fixed effect could be appropriate where statistical heterogeneity exists ($I^2 < 50\%$ or $P > .05$). Otherwise, random effect model was used ($I^2 > 50\%$ or $P < .05$).[22] In addition, potential sources of substantial heterogeneity were evaluated by sensitivity analysis. And publication bias was estimated by funnel plots. Meanwhile, to understand current situation of evidence rating and analyze possible problems, the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) system was performed to grade the evidence quality of published systematic reviews/meta-analyses of CG. GRADE profiler version 3.6 was used for calculating overall quality of grading evaluation for the review of evidence.

3. Results

3.1. Study description

Based on the retrieval strategy and screened records, a total of 1260 full-text articles were initially identified. In accordance with our inclusion and exclusion criteria, 16 randomized clinical trials (RCTs) involving 1673 participants (906 in experiment groups and 767 in control groups) were included in this study.[23–38] All trials were published on Chinese literatures in China mainland. Experiment groups used TCM while control groups used RP. Flow chart of literature search process is shown in Figure 1. Clinical characteristics of included studies are described in Table 1. Meanwhile, to present discrepancies among different TCMs, constituents of herbal formulae are listed in Table 2.

3.2. Risk of bias evaluation

Two researchers independently evaluated methodologic quality of included trials using the Cochrane Collaboration's risk of bias tool.[20] And results of this quality summarized in Table 3 showed that all included studies were biased with high risks and the quality was generally poor. But all of them accounted for baseline comparability. As for generation of random sequence, 4 studies used specific methods including random number table,[24,34] coin flipping,[28] and picking method.[30] However, the remaining eleven only mentioned "randomization" with no explanation of random-allocation process.[23,25–27,29,31–33,35,37,38] Besides, no studies mentioned blinding or allocation concealment.[23–38] Meanwhile, considering the integrity of outcome data, follow-up visit, and intention-to-treat analysis should have been conducted for all included studies. And only 3 trials reported no withdrawals or dropouts in treatment course.[28,30,33] In a word, inadequate reporting may result in possible bias and risk validity of the results (Fig. 2).

3.3. Effects of the interventions: primary outcome

3.3.1. Comparison of overall clinical efficacy. Based on the TCM Illness Diagnosis Affect Standard and Guiding Principles for Clinical Research of New TCM,[39,40] efficacy assessment is divided into 4 grades: cure, clinical symptoms disappeared; markedly effective, clinical symptoms markedly improved; effective, clinical symptoms improved; ineffective, clinical symptoms did not improve even deteriorate. Specifically, improvement of clinical symptoms is not only evaluated by clinical manifestation, but judged from pathologic changes on

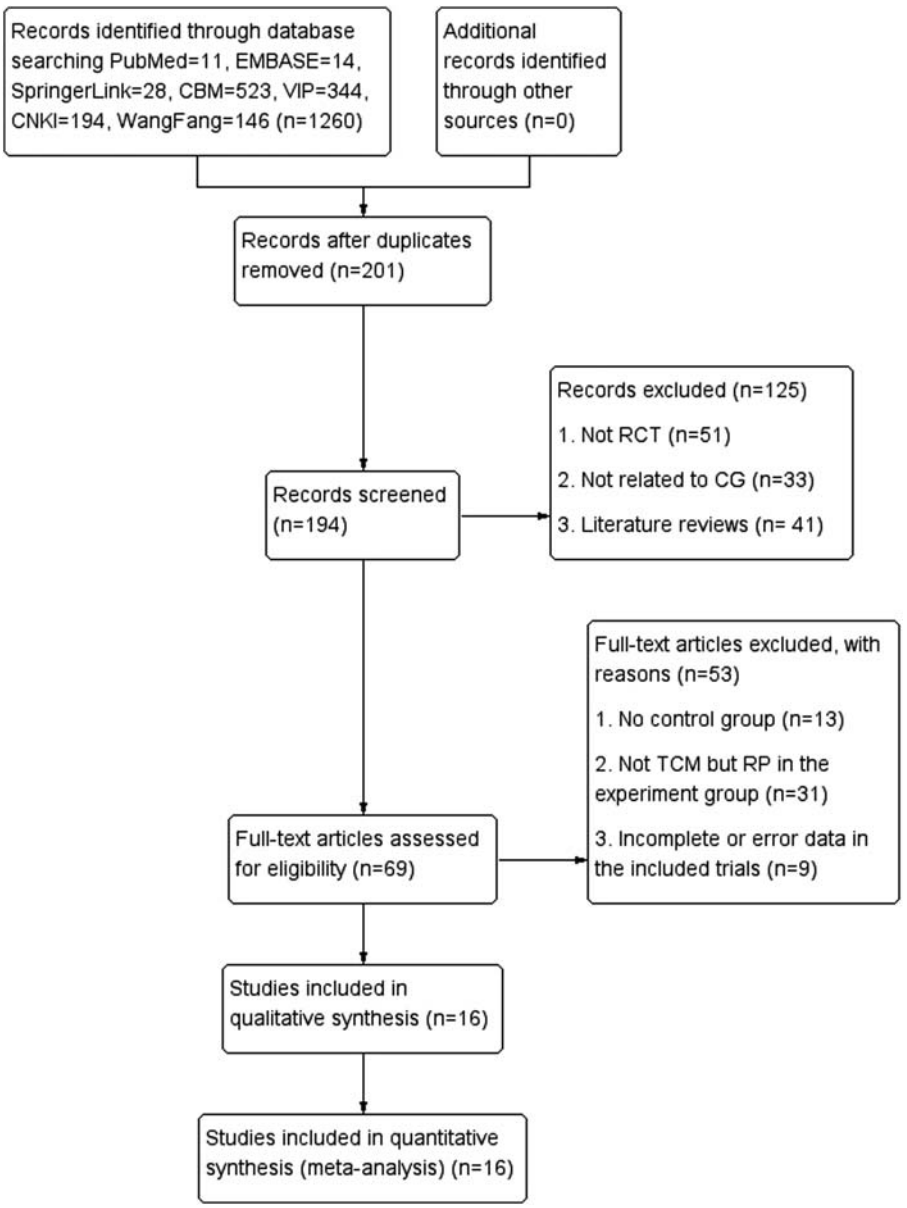


Figure 1. Flow chart of the process for literature retrieval. CG = chronic gastritis, TCM = traditional Chinese medicine.

gastric mucosa by endoscopy. Therefore, both of the 2 items are used for overall clinical efficacy. In addition, symptom scores are analyzed by mean ± standard deviation. Meanwhile, according to the nimodipine method,[40] efficacy index is calculated with a formula [(pretreatment symptom scores − posttreatment symptom scores)/pretreatment symptom scores] × 100%. In addition, we did not conduct a sensitivity analysis because of no substantial heterogeneity in primary outcome.

3.3.2. TCM vs RP. Fifteen studies[23–36,38] with a total of 1547 patients reported overall clinical efficacy. Because of discrepancy in treatment courses, subgroup analysis of durations of 4, 6, and 8 weeks was performed. Meanwhile, with a good homogeneity ($\chi^2 = 5.05$, $P = .99$, $I^2 = 0\%$) for this analysis, a fixed effect model was conducted to estimate pooled effect size. Results of subgroup analysis showed that higher clinical efficacy rate was attributed to TCM groups than RP groups for 4 weeks (OR 4.47; 95% CI 2.71, 7.37; $P < .00001$),[23,24,26,28,32,34,36,38] 6 weeks (OR 9.15; 95% CI 1.91, 43.90; $P = .006$)[30] and 8 weeks (OR 4.45; 95% CI 2.68, 7.37; $P < .00001$).[25,27,29,31,33,35] Meanwhile, the combined OR was 4.65 (95% CI 3.29, 6.56) with significant overall effect ($Z = 8.71$, $P < .00001$) between TCM groups and RP groups (Fig. 3). However, potential publication bias was observed by asymmetrical funnel plot in Figure 4.

3.4. Secondary outcomes

3.4.1. Efficacy under endoscopy. In the period of treatment, 3 trials including 282 participants reported efficacy under endoscopy.[26,33,37] Because of no significant heterogeneity ($\chi^2 = 0.85$, $P = .65$, $I^2 = 0\%$), a fixed effect model was performed (Fig. 5). Meanwhile, higher efficacy under endoscopy was attributed to TCM groups than RP groups on the improvement

Table 1

Characteristics of the studies included in the meta-analysis.

Study ID (author, year)	No. of participants (E/C)	Age (E/C)	Duration	Intervention		Outcome measures
				Experiment group	Control group (RP)	
Zhao et al, 2018[23]	30/30	E: 26–79 C: 24–80	4 wks	TCM	Rabeprazole sodium enteric capsules + itopride tablets + quadruple therapy (Hp positive): amoxicillin potassium clavulanate chewable tablets, clarithromycin sustained release tablets, rabeprazole sodium enteric capsules, colloidal pectin bismuth dry suspension	①
Guo et al, 2017[24]	40/38	E: 21–70 C: 21–68	4 wks	TCM	CSG: omeprazole enteric-coated tablets; CAG: lactobacillin tablets; CG with bleeding or erosion: sucralfate tablets	①④
Xue, 2017[25]	43/43	E: 46–76 C: 47–75	8 wks	TCM	Triple therapy: Lansoprazole tablets + Clarithromycin tablets + Moxapride citrate tablets	①
Zeng et al, 2015[26]	48/48	E: 21–70 C: 23–68	4 wks	TCM	Esomeprazole magnesium enteric-coated tablets + amoxicillin + clarithromycin + hydrotalcite tablets (bile regurgitation) + Hp eradication agents (Hp positive)	①②④
Jin, 2015[27]	43/43	E: 25–78 C: 26–77	8 wks	TCM	Omeprazole + triple therapy (Hp positive): bismuth potassium citrate, tinidazole, tetracycline	①⑩
Yu et al, 2015[28]	40/40	E: 22–76 C: 22–76	4 wks	TCM	Domperidone + omeprazole	①
Yang et al, 2014[29]	100/100	E: 18–65 C: 20–63	8 wks	TCM	Omeprazole tablets + amoxicillin tablets + Clarithromycin tablets + Domperidone	①④⑨⑩⑫
Ye, 2014[30]	40/40	E: 27–78 C: 28–76	6 wks	TCM	Omeprazole + metronidazole	①
Yu, 2013[31]	40/40	E: 38.5 ± 2.3 C: 38.1 ± 2.2	8 wks	TCM	Amoxicillin capsules + clarithromycin tablets + Domperidone tablets + Omeprazole capsules	①④
Li, 2013[32]	64/64	E: 29–68 C: 27–70	4 wks	TCM	Triple therapy: omeprazole + amoxicillin + metronidazole	①
Han, 2013[33]	30/30	E: 32–66 C: 34–67	8 wks	TCM	Omeprazole	①②③④⑤
Zhang et al, 2010[34]	33/32	E: 38.60 ± 8.48 C: 39.95 ± 7.62	4 weeks	TCM	CSG with bile regurgitation: omeprazole + hydrotalcite tablets; CSG with erosion: omeprazole + gefarnate; CAG: gefarnate + folic acid	①④⑦
Chen et al, 2009[35]	61/59	E: 18–77 C: 19–81	8 wks	TCM	Omeprazole + amoxicillin + clarithromycin	①
Lin, 2008[36]	90/58	E: 30–67 C: 28–68	4 wks	TCM	Clarithromycin + amoxicillin + Omeprazole	①②
Gong et al, 2006[37]	84/42	E: 19–65 C: 20–61	17 wks	TCM	Amoxicillin capsules + metronidazole; CG with dyspepsia: bismuth potassium citrate; CG with full belch, nausea and vomiting: domperidone; CG with hyperacidity: sucralfate	②⑥⑧⑪
Guo, 2006[38]	120/60	E: 19–70 C: 18–67	4 wks	TCM	Omeprazole capsules + clarithromycin capsules	①⑪

① = overall clinical efficacy, ② = gastroscope curative effect, ③ = gastroscope scores, ④ = clinical symptom scores, ⑤ = clinical symptom efficacy, ⑥= clinical symptom improvement rate, ⑦ = the ratio of clinical symptom scores, ⑧ = Hp negative rate, ⑨ = pathologic scores, ⑩ = the rate of side effects, ⑪ = recurrence rate, ⑫ = the serum gastrin levels, E = experiment group, C = control group, Hp = Helicobacter pylori, TCM = traditional Chinese medicine, RP = routine pharmacotherapies.

of pathologic changes of gastric mucosa (OR 2.46; 95% CI 1.12, 5.43; $P = .03$) (Fig. 5).

3.4.2. Stomach distension. In the included trials, TCM-treated 221 patients and RP-treated 218 patients were included in 4 trials of stomach distension improvement.[24,26,29,34] As shown in Figure 6, pooled estimates were conducted by using a model of random effect for significant heterogeneity ($\chi^2 = 12.96$, $P = 0.005$, $I^2 = 77\%$). The combined MD was −0.37 (95% CI −0.56, −0.19) with significant overall effect ($Z = 3.92$, $P < .0001$), indicating that TCM groups had potentially superior to RP groups on the improvement of stomach distension.

3.4.3. Stomachache. Four trials of 221 patients in TCM group and 218 in RP group were qualified with description of stomachache alleviation.[24,26,29,34] Considering significant heterogeneity ($\chi^2 = 29.53$, $P < .00001$, $I^2 = 90\%$) between 2 groups in Figure 7, random-effects model was used for statistical analysis. Meanwhile, results of this analysis favored TCM group by pooled data (SMD −0.80; 95% CI −1.45, −0.14) and test for overall effect ($Z = 2.39$, $P = .02$).

3.4.4. Acid regurgitation and belching. Four studies of acid regurgitation and belching involving 439 patients were identified for the comparison between TCM groups and RP groups.[24,26,29,34] As shown in Figures 8 and 9, significant heterogeneity can be perceived both acid regurgitation ($\chi^2 = 66.02$, $P < .00001$, $I^2 = 95\%$) (Fig. 8) and belching ($\chi^2 = 150.29$, $P < .00001$, $I^2 = 98\%$) (Fig. 9). Therefore, random effect models were conducted. However, compared with RP groups, TCM

Table 2

The ingredients of each formula.

Author	Ingredients of each formula				
Zhao et al, 2018[23]	*Bupleurum chinense* DC (Chai Hu) 10 g	*Lilium longiflorum* Thunb. (Bai He) 15 g	*Perilla frutescens* (L.) Britt. (Su Ye) 5 g	*Coptis chinensis* Franch. (Huang Lian) 5 g	*Euodia ruticarpa* (Juss.) Benth (Wu Zhu Yu) 3 g
	Amomum kravanh Pierre ex Gagnep. (Bai Kou Ren) 5 g				
Guo et al, 2017[24]	*B chinense* DC (Chai Hu) 10 g	*Cinnamomum cassia* Presl (Gui Zhi) 10 g	OsDraconis (FossiliaOssiaMastodi) (Long Gu) 18 g	*Ostrea gigas* Thunberg (Mu Li) 18 g	*Pseudostellaria heterophylla* (Miq.) Pax (Tai Zi Shen) 10 g
	Pinellia ternata (Thunb.) Breit. (Ban Xia) 10 g	*Paeonia lactiflora* Pall. (Bai Shao) 20 g	*Scutellaria baicalensis* Georgi (Huang Qin) 10 g	*C chinensis* Franch. (Huang Lian) 10 g	*Rheum palmatum* L. (Da Huang) 6 g
Xue, 2017[25]	*Citrus aurantium* L. (Zhi Qiao) 15 g	*Codonopsis pilosula* (Franch.) Nannf. (Dang Shen) 15 g	*P ternata* (Thunb.) Breit. (Ban Xia) 12 g	*Aucklandia lappa* Decne. (Mu Xiang) 10 g	*S baicalensis* Georgi (Huang Qin) 10 g
	Bletilla striata (Thunb.) Reichb.f. (Bai ji) 10 g	*C aurantium* L. (Zhi Shi) 10 g	*Bambusa tuldoides* Munro (Zhu Ru) 8 g	*Glycyrrhiza uralensis* Fisch (Gan Cao) 6 g	*Ziziphus jujuba* Mill. (Da Zao) 4 pieces
	Zingiber officinale Rosc. (Gan Jiang) 4 g	*C chinensis* Franch. (Huang Lian) 3 g			
Zeng et al, 2015[26]	*Amomum villosum* Lour. (Sha Ren)	*Areca catechu* L. (Bing Lang)	*Corydalis yanhusuo* W. T. Wang (Xuan Hu Suo)	*P ternata* (Thunb.) Breit. (Ban Xia)	*P frutescens* (L.) Britt. (Su Geng)
	Cannabis sativa L. (Huo Ma Ren)	*C aurantium* L. (Zhi Shi)	*Glehnia littoralis* Fr. Schmidt ex Miq.(Bei Sha Shen)	*B striata* (Thunb.) Reichb. f. (Bai ji)	
Jin, 2015 [27]	*Atractylodes macrocephala* Koidz. (Bai Zhu) 15 g	*C pilosula* (Franch.) Nannf. (Dang Shen) 20 g	*A lappa* Decne. (Mu Xiang) 10 g	*C aurantium* L. (Zhi Qiao) 10 g	*P lactiflora* Pall. (Bai Shao) 15 g
	G uralensis Fisch (Zhi Gan Cao) 5 g	*Carthamus tinctorius* L. (Hong Hua) 10 g	*Cyperus rotundus* L. (Xiang Fu Zi) 15 g	*Panax notoginseng* (Burk.) F.H. Chen (San Qi) 5 g	
Yu et al, 2015[28]	*G uralensis* Fisch (Gan Cao) 9 g	*Lycium barbarum* L. (Gou Qi) 14 g	*Polygonatum odoratum* (Mill.) Druce (Yu Zhu) 10 g	*C chinensis* Franch. (Huang Lian) 9 g	*P lactiflora* Pall. (Bai Shao) 12 g
	E ruticarpa (Juss.) Benth (Wu Zhu Yu) 11 g	*Rehmannia glutinosa* Libosch. (Sheng Di Huang) 14 g	*Ophiopogon japonicus* (L.f.) Ker-Gawl. (Mai Dong) 14 g	*A macrocephala* Koidz. (Bai Zhu) 13 g	*P lactiflora* PallChi Shao) 10 g
	Typha angustifolia L. (Pu Huang) 10 g	*B chinense* DC (Chai Hu) 12 g	*Salvia miltiorrhiza* bge (Dan Shen) 12 g	*Angelica sinensis* (Oliv.) Diels (Dang Gui) 10 g	*C rotundus* L. (Xiang Fu) 7 g
	C yanhusuo W.T. Wang (Yuan Hu) 9 g	*Scutellaria barbata* D. Don (Ban Zhi Lian) 9 g	*Oldenlandia diffusa* (Willd.) Roxb. (Bai Hua She She Cao) 9 g	*Astragalus membranaceus* (Fisch.) Bge var. Mongholicus (Bge.) Hsiao (Huang Qi) 14 g	*C pilosula* (Franch.) Nannf. (Dang Shen) 14 g
	Poria cocos (Schw.) Wolf (Fu Ling) 14 g	*Aitrus reticulata* Blanco (Chen Pi) 8 g	*C rotundus* L. (Xiang Fu) 5 g	*Dioscotea opposita* Thunb. (Shan Yao) 5 g	*Z jujuba* Mill. (Da Zao) 5 g
	P ternata (Thunb.) Breit. (Ban Xia) 13 g	*Alpinia officinarum* Hance (Liang Jiang) 9 g	*Atractylodes lancea* (Thunb.) DC (Cang Zhu) 16 g	*P cocos* (Schw.) Wolf (Hou Po) 16 g	*S baicalensis* Georgi (Huang Qin) 11 g
	Pogostemon cablin (Blanco) Benth (Huo Xiang) 9 g	*Taraxacum mongolicum* Hand.-Mazz. (Pu Gong Ying) 9 g	*Forsythia suspensa* (Thunb.) Vahl (Lian Qiao) 9 g	*C aurantium* L. (Zhi Qiao) 11 g	*Lindera aggregata* (Sims) Kosterm. (Wu Yao) 11 g
	C yanhusuo W.T. Wang (Yuan Hu) 9 g	*Citrus medica* L. var. *sarcodactylis* Swingle (Fo Shou) 9 g			
Yang et al, 2014[29]	*P cocos* (Schw.) Wolf (Hou Po) 15 g	*C pilosula* (Franch.) Nannf. (Dang Shen) 15 g	*S miltiorrhiza* bge (Dan Shen) 20 g	*A membranaceus* (Fisch.) Bge var. Mongholicus (Bge.) Hsiao (Huang Qi) 20 g	*P lactiflora* Pall. (Bai Shao) 15 g
	A macrocephala Koidz. (Bai Zhu) 10 g	*G uralensis* Fisch (Zhi Gan Cao) 10 g	*P cocos* (Schw.) Wolf (Fu Ling) 10 g	*Z officinale* Rosc. (Sheng Jiang) 5 g	*Z jujuba* Mill. (Da Zao) 3 pieces
Ye, 2014[30]	*C pilosula* (Franch.) Nannf. (Dang Shen) 25 g	*P lactiflora* Pall. (Bai Shao) 16 g	*A villosum* Lour. (Sha Ren) 11 g	*G uralensis* Fisch (Gan Cao) 10 g	*P cocos* (Schw.) Wolf (Fu Ling) 11 g
	A macrocephala Koidz. (Bai Zhu) 11 g	*C cassia* Presl (Gui Zhi) 10 g	*R glutinosa* Libosch. (Sheng Di Huang) 20 g	*G littoralis* Fr. Schmidt ex Miq. (Bei Sha Shen) 20 g	*O japonicus* (L.f.) Ker-Gawl. (Mai Dong) 15 g
	A sinensis (Oliv.) Diels (Dang Gui) 13 g	*L barbarum* L. (Gou Qi) 15 g	*Dendrobium nobile* Lindl. (Shi Hu)15 g	*Melia toosendan* Sieb.et Zucc (Chuan Lian Zi) 10 g	*R palmatum* L. (Sheng Da Huang) 15 g
	A membranaceus (Fisch.) Bge var. Mongholicus (Bge.) Hsiao (Huang Qi) 15 g	*E ruticarpa* (Juss.) Benth (Wu Zhu Yu) 13 g	*Lysimachia christinae* Hance (Jin Qian Cao) 15 g	*B chinense* DC (Chai Hu) 13 g	*C chinensis* Franch. (Huang Lian) 10 g
	Gardenia jasminoides Ellis (Zhi Zi) 10 g	*C aurantium* L. (Zhi Shi) 10 g	*S miltiorrhiza* bge (Dan Shen) 30 g	*T mongolicum* Hand.-Mazz. (Pu Gong Ying) 30 g	*O diffusa* (Willd.) Roxb.(Bai Hua She She Cao) 20 g
	S barbata D. Don (Ban Zhi Lian) 20 g	*C yanhusuo* W. T. Wang (Yuan Hu) 12g	*C rotundus* L. (Xiang Fu) 12 g	*Trogopterus xanthipes* Milne-Edwards (Wu Ling Zhi) 10 g	*T angustifolia* L. (Pu Huang) 10 g
	Curcuma phaeocaulis Val. (E Zhu) 10 g	*Sparganium stoloniferum* Buch.-Ham. (San Leng) 10 g	*L aggregata* (Sims) Kosterm. (Wu Yao) 10 g	*P frutescens* (L.) Britt.(Su Geng)10 g	*C aurantium* L. (Zhi Qiao) 10 g
	C medica L. var. *sarcodactylis* Swingle (Fo Shou) 10 g				
Yu, 2013[31]	*P cocos* (Schw.) Wolf (Hou Po) 15 g	*C pilosula* (Franch.) Nannf. (Dang Shen) 15 g	*S miltiorrhiza* bge (Dan Shen) 20 g	*A membranaceus* (Fisch.) Bge var. Mongholicus (Bge.) Hsiao (Huang Qi) 20 g	*P lactiflora* Pall. (Bai Shao) 15 g
	A macrocephala Koidz. (Bai Zhu) 10 g	*G uralensis* Fisch (Zhi Gan Cao) 10 g	*P cocos* (Schw.) Wolf (Fu Ling) 10 g	*Z officinale* Rosc. (Sheng Jiang) 5 g	*Z jujuba* Mill. (Da Zao) 3 pieces
Li, 2013[32]	*P ternata* (Thunb.) Breit. (Jiang Ban Xia) 10 g	*C pilosula* (Franch.) Nannf. (Dang Shen) 10g	*S baicalensis* Georgi (Huang Qin) 10g	*Z officinale* Rosc. (Gan Jiang) 3 g	*G uralensis* Fisch (Gan Cao) 6g

(*continued*)

Table 2

(continued).

Author	Ingredients of each formula				
	C chinensis Franch. (Huang Lian) 5 g				
Han, 2013[33]	*C pilosula* (Franch.) Nannf. (Dang Shen) 30 g	*P cocos* (Schw.) Wolf (Fu Ling) 25 g	*A reticulata* Blanco (Chen Pi) 15 g	*P ternata* (Thunb.) Breit. (Ban Xia) 15 g	*C chinensis* Franch. (Huang Lian) 6 g
	S baicalensis Georgi (Huang Qin) 15 g	*A lancea* (Thunb.) DC (Cang Zhu) 15 g	*P cocos* (Schw.) Wolf (Hou Po) 15 g	*G uralensis* Fisch (Zhi Gan Cao) 10 g	*Z jujuba* Mill. (Da Zao) 5 pieces
Zhang et al, 2010[34]	*A reticulata* Blanco (Chen Pi) 5 g	*B chinense* DC (Chai Hu) 6 g	*Ligusticum chuanxiong* Hort. (Chuan Xiong) 9 g	*C rotundus* L. (Xiang Fu) 9 g	*C aurantium* L. (Zhi Qiao) 9 g
	P lactiflora Pall. (Shao Yao) 9 g	*G uralensis* Fisch (Gan Cao) 4 g	*A membranaceus* (Fisch.) Bge var. Mongholicus (Bge.) Hsiao (Huang Qi) 18 g	*Panax ginseng* C.A. Mey. (Ren Shen) 6 g	*A sinensis* (Oliv.) Diels (Dang Gui) 3 g
	Cimicifuga heracleifolia Kom. (Sheng Ma) 6 g	*A macrocephala* Koidz. (Bai Zhu) 8 g	*P cocos* (Schw.) Wolf (Hou Po) 6 g	*C chinensis* Franch. (Huang Lian) 3 g	*Acorus tatarinowii* Schott. (Shi Chang Pu) 3 g
	P ternata (Thunb.) Breit. (Ban Xia) 5g	*Glycine max* (L.) Merr. (Dan Dou Chi) 9 g	*G jasminoides* Ellis (Zhi Zi) 9 g	*G littoralis* Fr. Schmidt ex Miq. (Bei Sha Shen) 9 g	*P odoratum* (Mill.) Druce (Yu Zhu) 6 g
	Morus alba L. (Sang Ye) 5 g	*O japonicus* (L.f.) Ker-Gawl. (Mai Dong) 9 g	*Dolichos lablab* L. (Bai Bian Dou) 5 g	*Trichosanthes kirilowii* Maxim (Tian Hua Feng) 5 g	*S miltiorrhiza* bge (Dan Shen) 30 g
	Santalum album L. (Tan Xiang) 6 g	*A villosum* Lour. (Sha Ren) 4 g	*P cocos* (Schw.) Wolf (Fu Ling) 6 g	*A lappa* Decne. (Mu Xiang) 2 g	
Chen et al, 2009[35]	*C pilosula* (Franch.) Nannf. (Dang Shen) 30 g	*A membranaceus* (Fisch.) Bge var. Mongholicus (Bge.) Hsiao (Huang Qi) 30 g	*Coix lacryma-jobi* L. var. *mayuen* (Roman.) Stapf (Yi Yi Ren) 30 g	*P cocos* (Schw.) Wolf (Fu Ling) 20 g	*A macrocepha*la Koidz. (Bai Shu) 10 g
	P ternata (Thunb.) Breit. (Jiang Ban Xia) 10 g	*P cocos* (Schw.) Wolf (Hou Po) 10 g	*Z officinale* Rosc. (Gan Jiang) 10 g	*A reticulata* Blanco (Chen Pi) 10 g	*G uralensis* Fisch (Zhi Gan Cao) 6g
Lin, 2008[36]	*P cocos* (Schw.) Wolf (Fu Ling) 10 g	*P lactiflora* Pall. (Bai Shao) 10 g	*A lappa* Decne. (Mu Xiang) 10 g	*A villosum* Lour. (Sha Ren) 6 g	*C chinensis* Franch. (Huang Lian) 6 g
	T mongolicum Hand.-Mazz. (Pu Gong Ying) 15 g	*B chinense* DC (Chai Hu) 15 g	*Curcuma wenyujin* Y. H. Chen et C. Ling (Yu Jin) 15 g	*Zanthoxylum nitidum* (Roxb.) DC. (Liang Mian Zhen) 15 g	
Gong et al, 2006[37]	*A membranaceus* (Fisch.) Bge var. Mongholicus (Bge.) Hsiao (Sheng Huang Qi) 30 g	*C pilosula* (Franch.) Nannf. (Dang Shen) 25 g	*P lactiflora* Pall. (Bai Shao) 30 g	*P cocos* (Schw.) Wolf (Hou Po) 10 g	*C rotundus* L. (Xiang Fu) 12 g
	C medica L. var. *sarcodactylis* Swingle (Fo Shou) 15 g	Human placenta (Zi He Che) 30 g	*A macrocephala* Koidz. (Bai Zhu) 12 g	*T mongolicum* Hand.-Mazz. (Pu Gong Ying) 15 g	*C chinensis* Franch. (Huang Lian) 9 g
	Z jujuba Mill. (Da Zao) 10 g	*G uralensis* Fisch (Gan Cao) 6g	*A villosum* Lour. (Sha Ren) 12 g		
Guo, 2006[38]	*P heterophylla* (Miq.) Pax (Tai Zi Shen) 15 g	*A macrocephala* Koidz. (Bai Zhu) 10 g	*A membranaceus* (Fisch.) Bge var. *mongholicus* (Bge.) Hsiao (Huang Qi) 15 g	*A reticulata* Blanco (Chen Pi) 10 g	*P ternata* (Thunb.) Breit. (Ban Xia) 10 g
	A villosum Lour. (Sha Ren) 6 g	*C aurantium* L. (Zhi Shi) 10 g	*C phaeocaulis* Val. (E Zhu) 10 g	*P lactiflora* Pall. (Bai Shao) 15 g	*T mongolicum* Hand.-Mazz. (Pu Gong Ying) 30 g
	G uralensis Fisch (Gan Cao) 5 g				

groups had significant statistical difference in belching (SMD −2.00; 95% CI −3.80, −0.20; $P = .03$) (Fig. 9), while no significant statistical difference in acid regurgitation (SMD −0.71; 95% CI −1.69, 0.28; $P = .16$) (Fig. 8).

3.4.5. Anorexia. Three trials with description of anorexia improvement were included involving 239 participants (121 in TCM groups and 118 in RP groups).[24,26,34] As shown in Figure 10, results of comparison with significant heterogeneity ($\chi^2 = 59.40$, $P < .00001$, $I^2 = 97\%$) in 2 groups suggested a model of random effect should be an appropriate method. However, no significant statistical difference can be observed between TCM groups and RP groups in the improvement of anorexia (SMD −0.75; 95% CI −2.30, 0.80; $P = .35$).

3.4.6. Other secondary outcomes. As for other secondary outcomes, Han study[33] reported endoscopy scores and clinical symptom efficacy. Gong et al study[37] reported clinical symptom improvement rate and Hp negative rate. Zhang and Zhang study[34] reported the ratio of clinical symptom scores. Yang et al study[29] reported pathologic scores and the serum gastrin levels. Jin study[27] and Yang et al study[29] reported the rate of side effects. Gong and Gong study[37] and Guo study[38] reported recurrence rate. Because these outcomes were reported by only 1 or 2 studies, they were only qualitatively analyzed. However, with the evaluation of efficacy in treating CG, results implied that TCM groups were more positive effects than RP groups.

3.5. Safety evaluation

Meta-analysis of 6 trials evaluated safety of TCM in the course of treatment.[25,27–30,32] Two had no adverse reactions during TCM treatment.[28,30] Four reported adverse reactions[25,27,29,32] which included nausea, vomiting, abdominal pain, dizziness, diarrhea, constipation, anorexia, rash, waist and leg pain, sexual dysfunction, weak, abnormal weight loss. However, these adverse events did not have impact on experimental process.

3.6. GRADE evidence of quality

To grade evidence quality of this meta-analysis of CG and understand current situation of evidence rating thereby analyzing possible problems, GRADE profiler software was performed. The GRADE system, which classified the strength of recommenda-

Table 3

Evaluation of methodologic quality of the included studies based on the Cochrane Handbook.

Study ID	Baseline	Randomization	Blinding	Allocation concealment	Follow-up	Withdrawals or dropouts	Jadad score
Zhao et al, 2018[23]	Comparability	Mention not described	NR	NR	NR	NR	1
Guo et al, 2017[24]	Comparability	Random number table	NR	NR	NR	NR	2
Xue, 2017[25]	Comparability	Mention not described	NR	NR	NR	NR	1
Zeng et al, 2015[26]	Comparability	Mention not described	NR	NR	NR	NR	1
Jin, 2015[27]	Comparability	Mention not described	NR	NR	NR	NR	1
Yu et al, 2015[28]	Comparability	Coin flipping	NR	NR	NR	No	3
Yang et al, 2014[29]	Comparability	Mention not described	NR	NR	NR	NR	1
Ye, 2014[30]	Comparability	Picking method	NR	NR	NR	No	3
Yu, 2013[31]	Comparability	Mention not described	NR	NR	NR	NR	1
Li, 2013[32]	Comparability	Mention not described	NR	NR	NR	NR	1
Han, 2013[33]	Comparability	Mention not described	NR	NR	NR	No	2
Zhang et al, 2010[34]	Comparability	Random number table	NR	NR	NR	NR	2
Chen et al, 2009[35]	Comparability	Mention not described	NR	NR	NR	NR	1
Lin, 2008[36]	Comparability	Random sampling	NR	NR	NR	NR	1
Gong et al, 2006[37]	Comparability	Mention not described	NR	NR	NR	NR	1
Guo, 2006[38]	Comparability	Mention not described	NR	NR	NR	NR	1

NR = not reported.

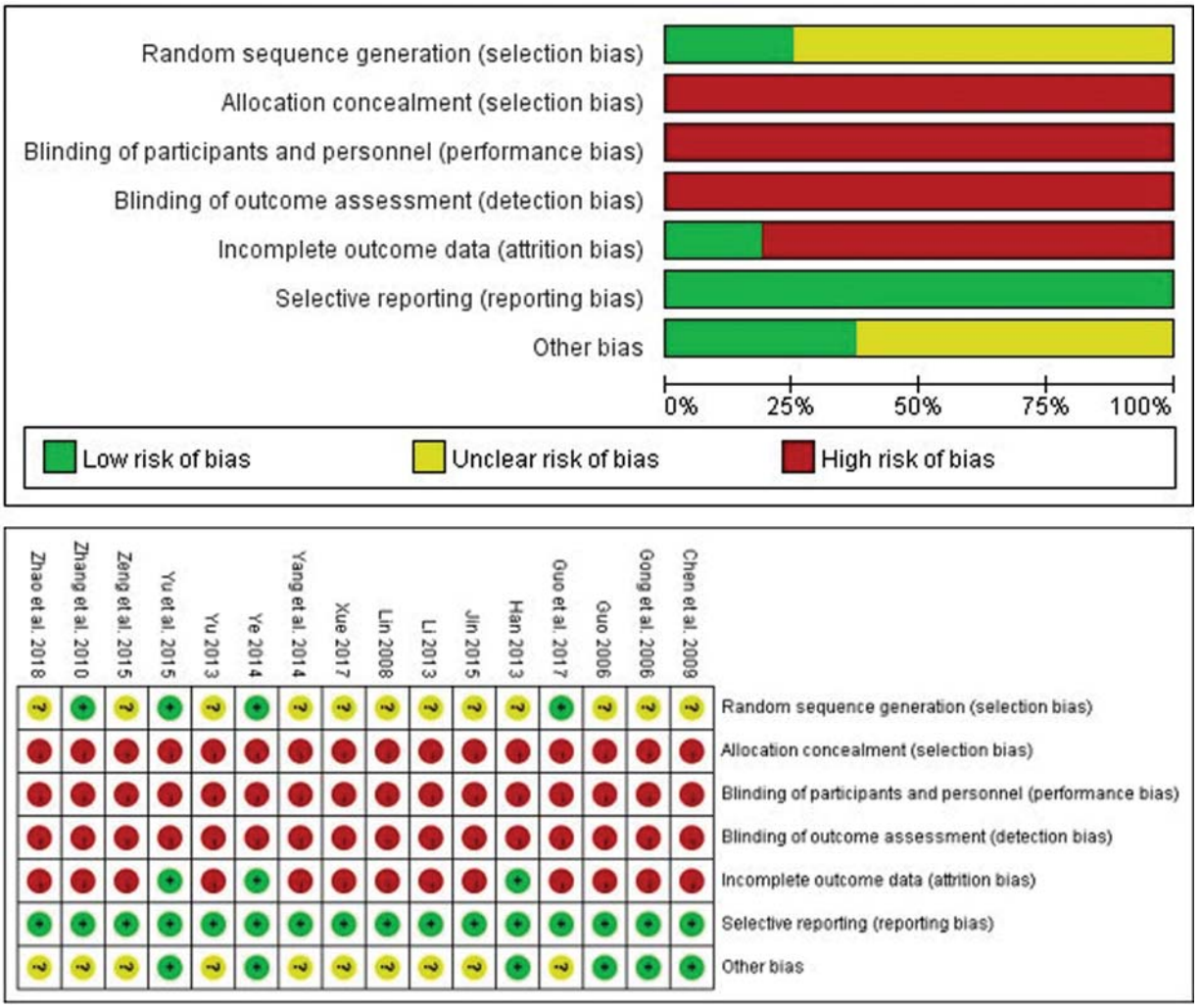


Figure 2. Risk of bias graph and summary.

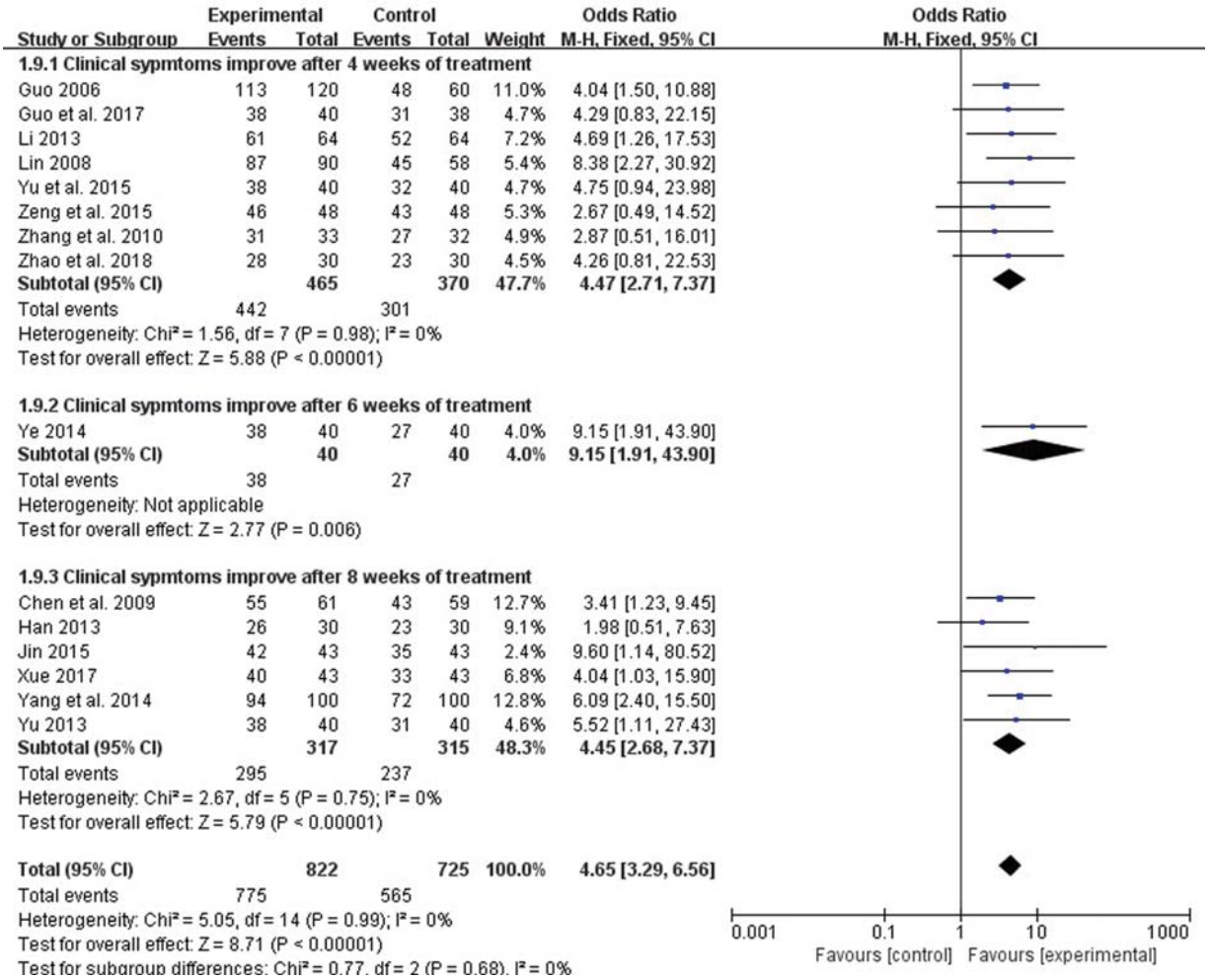


Figure 3. Forest plot of overall clinical efficacy.

tions as strong or weak, evaluates the quality of a body of evidence as high, moderate, low, and very low.[41,42] Moreover, these levels were based on 5 downgrade factors: limitations, inconsistency, indirectness, imprecision, and publication bias.[43–47] As shown in Figure 11, results of GRADE for this meta-analysis suggested that evidence quality was "very low."

4. Discussion

Results of this meta-analysis show that TCM is superior to RP in the treatment of CG. Meanwhile, adverse events (namely safety evaluation) in TCM groups were significantly lower than that in RP groups, indicating that TCM can improve CG to a certain degree. Based on these, it possibly suggests that TCM is a promising therapy in treating CG and provides practitioners with important reference value on clinical syndrome differentiations. However, high risk of bias was identified in all included studies using the Cochrane Collaboration's risk of bias tool. Moreover, results of GRADE evidence classification for the quality level indicated "very low," which could imply that this meta-analysis did not include complete original data and some included trials contained a few methodologic defects.

It is well-established that Hp infection is the most common etiology associated with CG.[48] This pathogenesis is related to inflammation cells (mononuclear cells, plasma cells, predominantly lymphocytes, and macrophages) infiltration,[49–51] thereby resulting in gastric mucosal injury. Another pathogenesis of CG is associated with immune dysfunction that a complex interaction of autoantibodies against the parietal cell proton pump and sensitized T cells progressively destroy the parietal cells.[52] So far, numerous modern pharmacologic researches have verified efficacy of TCM for CG. On one hand, an experimental datum has suggested that Wei-Wei-Kang-Granule could treat CAG in rats by regulating the expression of epiderminal growth factor receptors (EGFRs) and nuclear transcription factor kappa B (NF-κB), whose mechanisms are possibly related with reduction in expression of EGFR and NF-κB in gastric mucosa.[53] Other animal experiment has showed that licoflavone could significantly ameliorate gastric pathology and increase serum prostaglandin E_2 (PGE_2) level, enhance acidic mucin secretion by epithelial cells, and improve gastric microcirculation in rat with chronic superficial gastritis (CSG). These effects were associated with the up-regulation of serum PGE_2 level.[54] On the other hand, a clinical research have also indicated that Yiweikang capsule have the effects of activating the flow of *qi* to check pain and removing blood stasis for gastritis patients, possibly by inhibiting secretion of gastric acid, decreasing activity of pepsase, and regulating the serum gastrin.[55] Meanwhile, other clinical research has

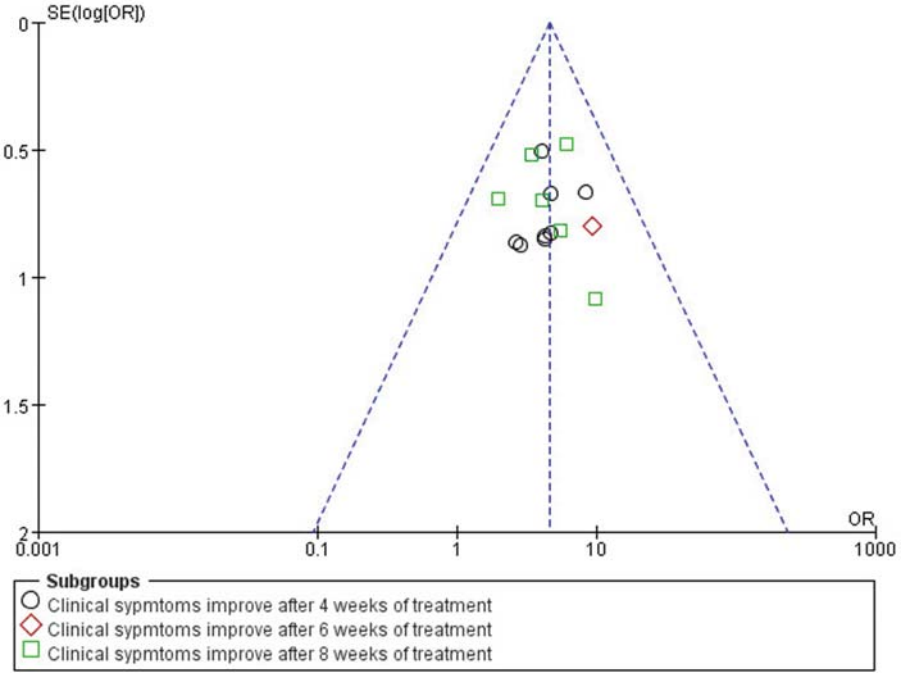


Figure 4. Funnel plot of overall clinical efficacy. OR = odds ratio.

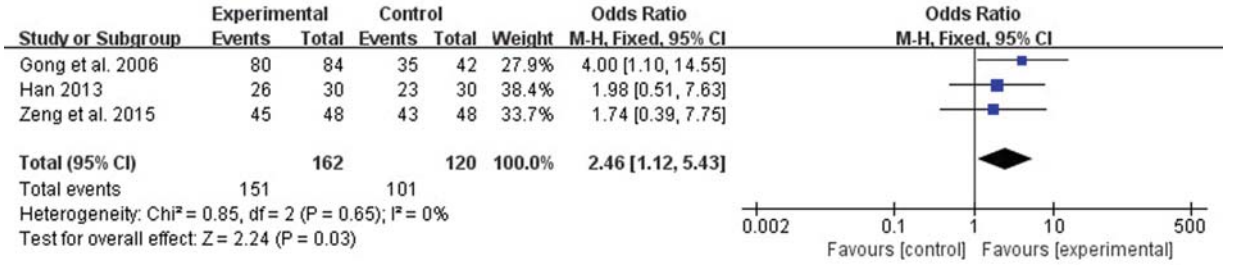


Figure 5. Forest plot of gastroscope curative effect.

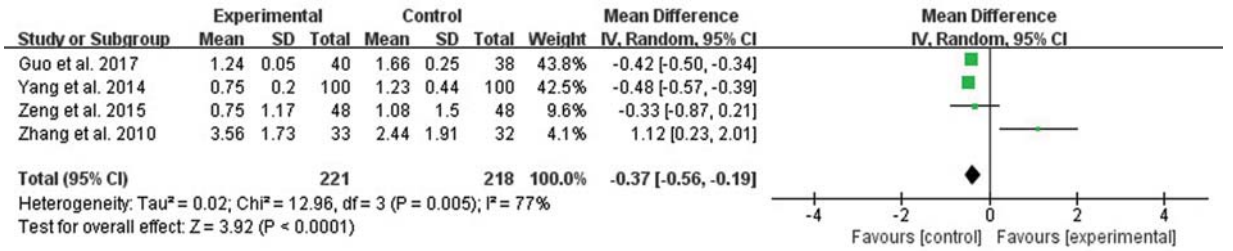


Figure 6. Forest plot of stomach distension.

suggested that Weikangfu Granule can reverse intestinal metaplasia and atypical hyperplasia in patients of CG with Pi-deficiency syndrome, and the effect may be way of increasing the level of Zn, Cu, cyclic adenosine monophosphate, and superoxide dismutase in gastric mucosa, promoting cell differentiation, enhancing cellular immunity, and reducing oxygen free radicals and lipid peroxidation.[56]

Nevertheless, a fact that potential limitations preclude us from drawing definite conclusions should be recognized.

First, low methodologic quality of this meta-analysis must be acknowledged. Without the implementation of blinding and allocation concealment, this study may potentially exist in some subjective bias including selection bias, detection bias, and performance bias. Moreover, only 2 trials used a method of

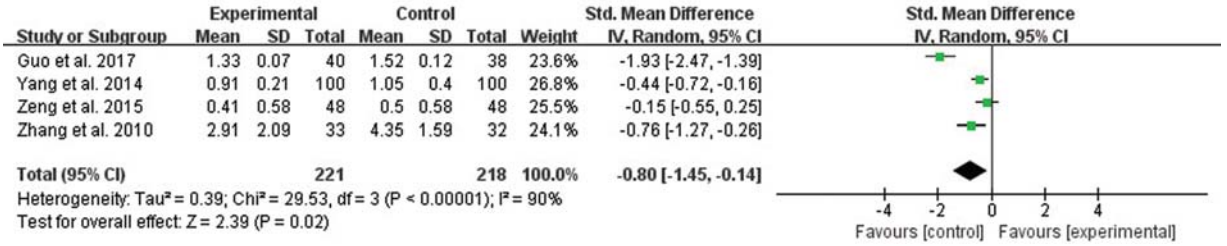


Figure 7. Forest plot of stomachache.

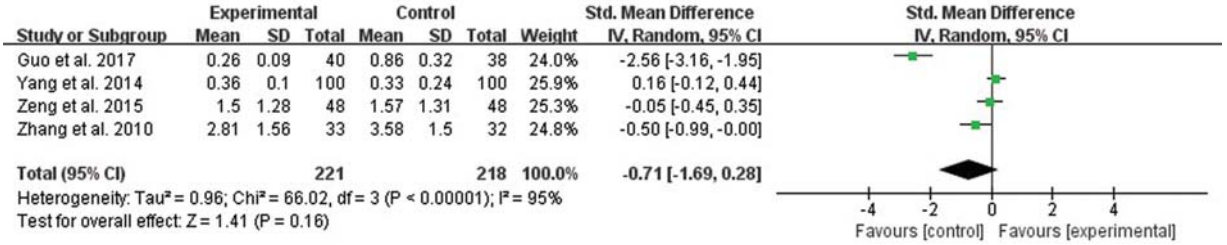


Figure 8. Forest plot of acid regurgitation.

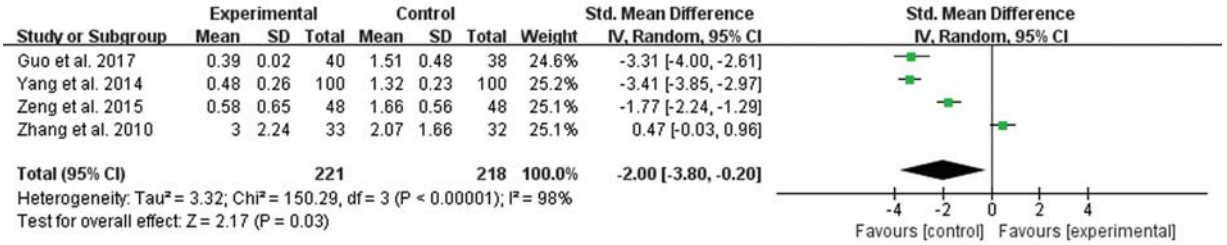


Figure 9. Forest plot of belching.

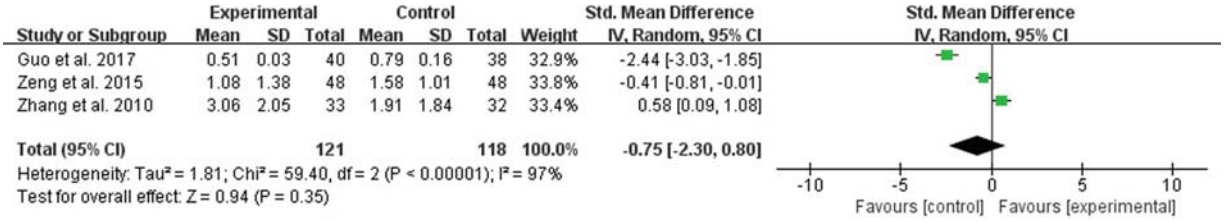
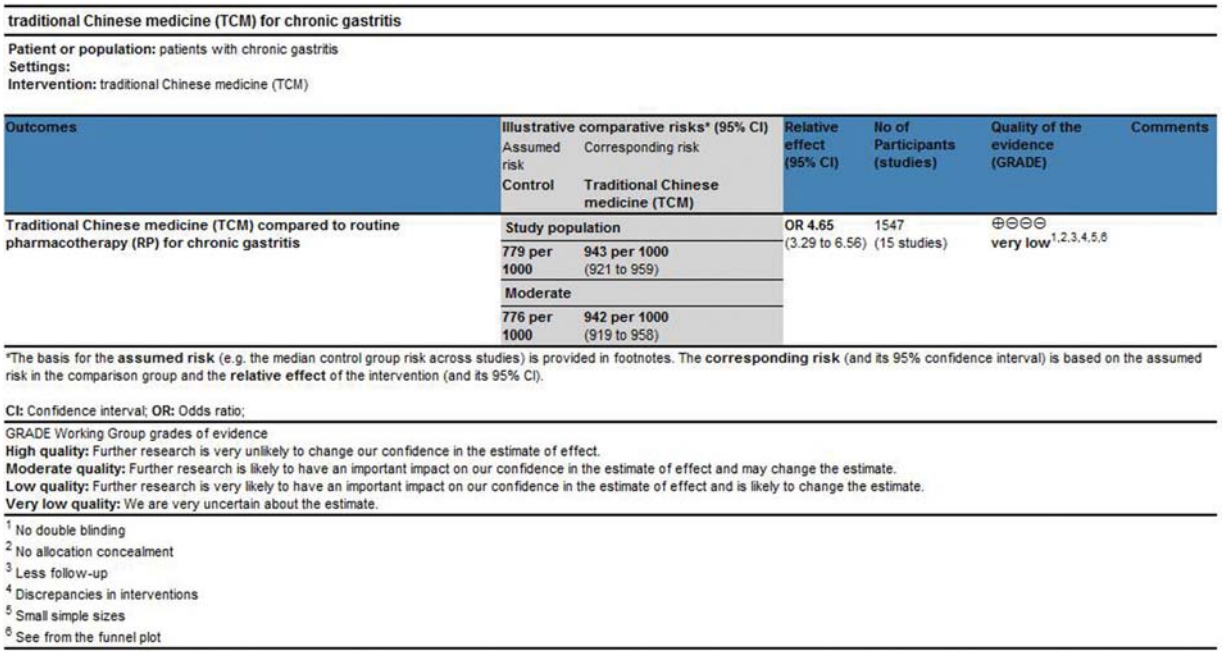


Figure 10. Forest plot of anorexia.

random number table,[24,34] 1 used coin flipping method,[28] 1 used a picking method.[30] The remaining 11 trials reported no detailed randomization method.[23,25–27,29,31–33,35,37,38] Therefore, little or no description in the generation of random sequences could potentially result in high risk of selection bias. Furthermore, no trial reported follow-up visit, which possibly led to attrition bias. In addition, evaluation of overall clinical efficacy was mainly based on compound outcomes. Besides, degrees of clinical efficacy improvement were divided into 4 levels (namely cure, markedly effective, effective, and ineffective) was based on multiple clinical manifestation and pathologic changes on gastric mucosa by endoscopy. These inconsistent judging criteria could lead to misclassification bias. In addition, no calculation method of sample size was mentioned in included trials. To acquire additional methodologic information or statistical data, we had tried our best to contact the original authors by telephone or e-mail. But unfortunately, either their receive responses did not meet our requirements or no response had been returned.

Second, existence of potential publication bias may influence quality of this meta-analysis. In this study, all of included trials were conducted in China and published in Chinese. This geographically limited distribution, to some extent, was identified



traditional Chinese medicine (TCM) for chronic gastritis

Patient or population: patients with chronic gastritis
Settings:
Intervention: traditional Chinese medicine (TCM)

Outcomes	Illustrative comparative risks* (95% CI) Assumed risk / Control	Corresponding risk / Traditional Chinese medicine (TCM)	Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
Traditional Chinese medicine (TCM) compared to routine pharmacotherapy (RP) for chronic gastritis	Study population		OR 4.65 (3.29 to 6.56)	1547 (15 studies)	⊕⊖⊖⊖ very low[1,2,3,4,5,6]	
	779 per 1000	943 per 1000 (921 to 959)				
	Moderate					
	776 per 1000	942 per 1000 (919 to 958)				

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: Confidence interval; **OR:** Odds ratio;

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

[1] No double blinding
[2] No allocation concealment
[3] Less follow-up
[4] Discrepancies in interventions
[5] Small simple sizes
[6] See from the funnel plot

Figure 11. GRADE quality grading evaluation.

as low quality of reporting. Besides, studies with negative efficacy could be ignored, which may further lead to publication bias. In addition, some efforts to acquire additional unpublished data or documents were made through contacting corresponding authors. But no useful data or documents were obtained. Furthermore, although a rigorous and comprehensive searching strategy was performed by 2 independent investigators who strictly followed the selection criteria, the possibility of some potential missing literatures cannot be ruled out.

Third, discrepancies in interventions should be taken into consideration. For TCM groups, although TCM were orally administered for patients, different dose and frequency of taking medication existed. As for RP groups, although RP belongs to conventional western medicine in the treatment of CG, treatments of dual or triple therapy were not separately analyzed, as well as discrepancies in administration. Taken together, these limitations could contribute to the heterogeneity in this meta-analysis.

Finally, quality of evidence in this paper should be noticeable. There were small sample sizes of the included studies (shown in Table 1) and a high risk of bias within RCTs (shown in Table 3). Meanwhile, this meta-analysis of GRADE indicated that evidence quality was "very low" (shown in Fig. 11). Therefore, rigorously designed, large-scale, multi-center RCTs are warranted to evaluate efficacy of TCM for CG and draw more reliable conclusions. Despite above limitations in our study, this meta-analysis demonstrated that TCM could be a promising alternative therapy in treating CG compared with RP.

5. Conclusion

Results of this meta-analysis indicate that TCM could offer certain advantages in the treatment of CG. However, because of weakness in sample sizes and evidence of this methodologic quality, further standardized researches including well-designed and strictly implemented trials should be required.

Author contributions

Conceived and designed the experiments: ZWL. Performed the article search: ZXY, YKD, TM. Analyzed the data: ZXY, YKD, TM, XYL, WHC, YML. Contributed reagents/materials/analysis tools: RZZ, XBZ, PJ, JHY, SL. Wrote the paper: ZXY. Read and approved the final manuscript: ZXY, YKD, TM, XYL, WHC, YML, RZZ, XBZ, PJ, JHY, SL, LSZ, ZWL. Study supervision: ZWL, LSZ.

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Visualization: Yun-kai Dai, Teng Ma, Li-sheng Zheng, Zhen-wen Lin.
Writing – original draft: Zi-xing Yan.
Writing – review & editing: Yun-kai Dai, Teng Ma.
Zhen-wen Lin orcid: 0000-0003-2895-8491.

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