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Efficacy of Jianpi Liqi therapy for functional dyspepsia

A meta-analysis of randomized, positive medicine-controlled trials

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Abstract

Background: We performed this meta-analysis to assess the efficacy and safety of Jianpi Liqi therapy (JLT), a traditional Chinese medicine therapy, in treating functional dyspepsia (FD).

Methods: We systematically searched 13 databases from their inception to 15th, May 2019. Eligible studies were randomized controlled trials (RCTs) that compared JLT medicine with conventional pharmacotherapy (CP) in treating patients with FD. Cochrane Collaboration tool, Review Manager 5.3 and STATA 11.0, GRADE profiler 3.6 were used for evaluating risk of bias, analyzing, and assessing quality of evidence respectively.

Results: After exclusions, 15 RCTs including a total of 1451 participants were included for analysis. We found evidence that JLT had better efficacy than CP (domperidone, omeprazole, esomeprazole, mosapride, lansoprazole, compound digestive enzymes, lactasin tablets) for FD (OR 0.34; 95% CI 0.26, 0.45; $P < .00001$). Moreover, JLT had more improvement on symptoms including abdominal pain, abdominal distention, early satiety, belching, poor appetite, and fatigue compared with CP. In addition, serious adverse events were not observed in treatment courses.

Conclusion: This meta-analysis suggested that JLT appears to have better efficacy in treating FD compared with CP. It may be an effective and safe therapy option for patients with FD. Though, more large-sample and strictly designed RCTs are needed to confirm our findings.

PROSPERO registration number: CRD42019133241.

Abbreviations: JLT = Jianpi Liqi therapy, FD = functional dyspepsia, RCTs = randomized controlled trials, CP = conventional pharmacotherapy, TCM = traditional Chinese medicine, OR = odds ratio, CI = confidence interval, SMD = standardized mean difference, AChE = acetylcholin esterase, 5-HT_4R = 5-hydroxytryptamine 4 receptor, CaMKII = Ca^{2+}/calmodulin-dependent kinase II, ITT = Intention to treat.

Keywords: Chinese traditional medicine, functional dyspepsia, meta-analysis

1. Introduction

Functional dyspepsia (FD) is a chronic, recurrent, and non-organic disease, which presents with typical gastroduodenal symptoms of epigastric pain or burning, early satiety, postprandial fullness, or a combination of them.[1–3] FD places high healthcare cost and financial burden on families and society.[4–7] It also significantly reduces the quality of life and productivity of individuals suffering from it. Furthermore, the global prevalence of FD ranged from 5% to 11%.[8] However, causes of FD remain to be established and current pharmacological treatments for FD cannot satisfy clinical needs.[9–16]

JLT (Invigorating spleen and regulating qi therapy, named Jianpi Liqi in Chinese pinyin) is a widely used therapeutic method in traditional Chinese medicine (TCM). JLT includes various herbal formulas which have the same aims for invigorating spleen and regulating qi. TCM, as an alternative treatment for FD, has been reported to be effective frequently.[17–24] But evidences of JLT medicine in treating FD were still insufficient. Therefore, to provide solid evidence for its efficacy, we performed this meta-analysis of randomized controlled clinical trials. In this study, our primary objective was to determine whether use of JLT in patients with FD results in better efficacy compared with CP. Our secondary goal was to identify whether use of JLT leads to greater alleviations on individual symptoms of FD.

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J-TY and Y-KD contributed equally to this work.

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2. Methods

2.1. Search strategy

Literature searches was conducted using the following databases: PubMed, Embase, Cochrane Library, Web of Science Core Collection, KCI-Korean Journal Database, MEDLINE, Russian Science Citation Index and SciELO Citation Index, Springer Link, China National Knowledge Infrastructure, Chinese Scientific Journals Database, Wan-fang database, and Chinese Biomedicine Database from their inception to 15th May 2019. RCTs comparing JLT medicine alone with conventional medical treatment were potentially eligible for inclusion. Our search has no language limitation. Key words used for search were "functional dyspepsia", "epigastric pain syndrome", "postprandial discomfort syndrome", "FD", "traditional Chinese medicine", "Jianpi", "Liqi", "herb formula", "randomized controlled trial", "controlled clinical trial" and "clinical trials". These searched words were used separately and collectively. Moreover, manual searches in cited references were performed to prevent missing relevant articles.

2.2. Selection criteria

Studies were chosen for this meta-analysis when they met the following criteria:

1. Randomized controlled trial;
2. Patients were diagnosed with FD by ROME III or IV criteria;
3. The experiment group used JLT medicine alone;
4. The control group used CP.
5. The Jadad score was at least 1.

While major exclusions were:

1. Not clinical trial;
2. Duplicated publication;
3. Patients accompanied by other digestive diseases;
4. Review article, case report or selective reporting.

2.3. Data extraction and quality assessment

Two reviewers independently extracted data from the selected studies. The information consisted of:

1. general information including name of first author, publication year, sex, sample size, age of subjects, intervention, and duration of treatment;
2. methodological information including details of randomization, blinding, allocation concealment, and description of withdrawals;
3. outcome measures, follow-up periods, and adverse events.

Evaluation of methodological quality was also conducted independently by 2 reviewers using the Cochrane Collaboration's risk of bias tool[25] and Jadad scale.[26] Disagreements were resolved by discussion or by consulting a third reviewer.

3. Data analysis

Data analysis was performed by using Review Manager 5.3, STATA 11.0 and GRADE profiler 3.6. Efficacy of JLT compared with CP in treating FD was estimated by odds ratio (OR) and 95% confidence interval (95%CI) for each study. The TCM symptoms score, as continuous data, was estimated by standardized mean difference (SMD) and 95%CI. Heterogeneity was statistically assessed by χ^2 test and I^2 test, and it was presented as significant when I^2 was over 50% or $P < .1$.[27] A random effect model was applied to calculate the pooled statistics when there was significant heterogeneity, or else the fixed effect model was used.[27] Sensitivity analysis was performed to investigate potential study which would obviously influence results. Begg test was used for evaluating publication bias. In addition, GRADE profiler 3.6 was used to assess the quality of outcomes.

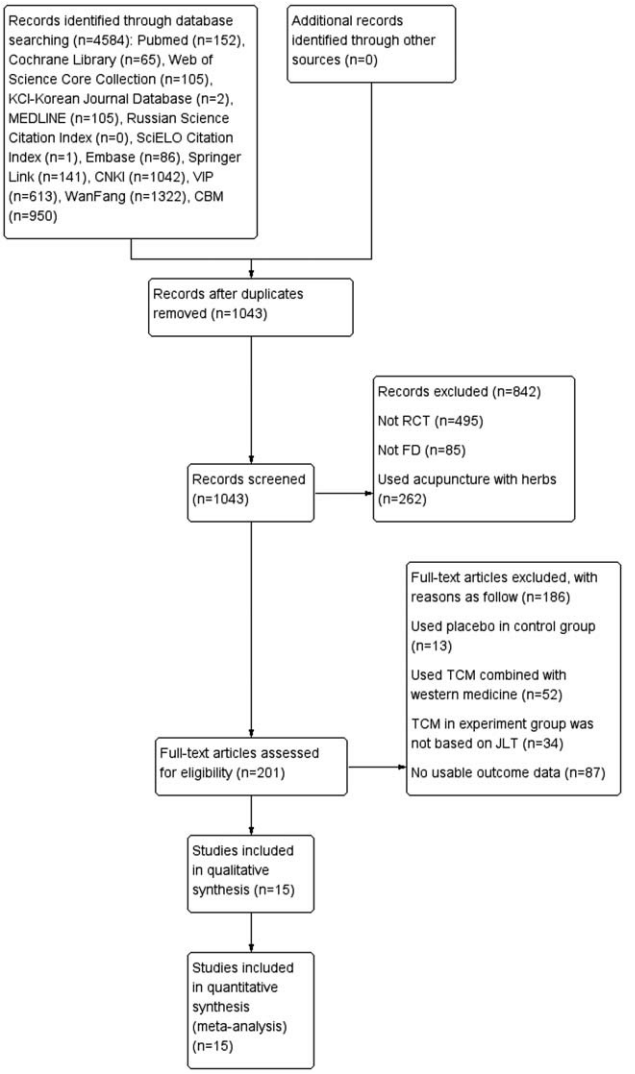

Figure 1. Flow chart of study selection process.

4. Result

4.1. Description of studies

The search results and the number of studies reviewed, excluded, and included were presented in a flow diagram in Figure 1. The eligible 15 RCTs included 1451participants (727 in experiment group and 724 in control group).[28–42] All included studies were single-center trials and were published in Chinese. Interventions between experiment groups and control groups were all JLT

Table 1

Characteristics of included studies.

First Author	Sample Size (E/C)	Sex		Age (years)	Diagnostic criteria	Intervention		Duration (weeks)	Outcome measures
		Male (E/C)	Female (E/C)			EG	CG		
Zhang et al[29]	30/28	N.R	N.R	N.R	Rome III	Yunpi Xingqi decoction	Domperidone	4	A+B+C+F+G+H
Li et al[28]	30/30	11/12	19/18	E:43.43±11.98 C:42.50±12.22	Rome III	Jianpi Liqi decoction	Domperidone	4	A+B+C+E+F+L
Wang et al[31]	40/38	17/20	23/18	E:31.47±20.86 C:33.88±23.75	Rome III	Jianpi Liqi formula	Domperidone	4	A+B+C+E+F+G+H
Zhu et al[30]	60/57	N.R	N.R	N.R	Rome III	Modified Jianpi Liqi decoction	Omeprazole	4	A+B+C+D+I
Cai et al[32]	31/34	18/15	13/19	E:43.64±11.83 C:46.63±14.03	Rome III	Modified Xiangsha Liujunzi decoction	Esomeprazole/ Domperidone	4	A+J+P+Q
Li et al[35]	55/55	32/29	23/26	E:36.5±18.3 C:33.2±16.7	Rome III	Jianpi Tiaozhong Xiaoshi formula	Mosapride + Lansoprazole	4	A+B+C+E+F
Liao et al[34]	103/103	42/47	61/56	E:38.3±2.9 C:36.8±4.3	Rome III	Jianpi Xiaoshi Liqi formula	Domperidone	4	A+B+C+D
Li et al[37]	60/60	32/26	28/34	E:38.70±12.22 C:38.53±11.36	Rome III	Weiguagnping granules	Domperidone	4	A+B+C+E+F+G
Li et al[36]	70/72	30/30	40/42	E:41.63±8.84 C:43.54±6.47	Rome III	Anwei No.1 granules	Domperidone	4	A+J+K
Xu et al[38]	64/64	N.R	N.R	42.6±16.7	Rome III	Xiangsha Liujunzi granules combined with Zhi zhu granules	Compound digestive enzymes	4	A+B+C+D+I+K
Hu et al[33]	30/30	N.R	N.R	N.R	Rome IV	Jianpi Xiaopi formula	Domperidone	4	A
Wang[40]	30/30	13/14	17/16	E:25-59 C:24-56	Rome III	Zhishi Xiaopi formula combined with Huangqi Jianzhong decoction	Domperidone + Omeprazole	4	A+J+O
Zhang et al[42]	49/49	N.R	N.R	N.R	Rome III	Tiaozhong Jianpi decoction	Domperidone	4	A+C+L+M+N+O
Wang[41]	36/36	15/16	21/20	E:31.5±5.9 C:32.3±5.6	Rome IV	Liqi Xiaozhang oral liquid	Domperidone	2	A+B+C+D+I+G
Hu et al[39]	44/43	21/24	23/19	E:44.12±11.51 C:43.16±13.08	Rome III	Jianpi Liqi formula	Mosapride	4	A+C+E+F+G+H

A = clinical effect rate; B = abdominal pain, C = abdominal distention, D = early satiety, E = belching, F = poor appetite, G = fatigue, H = nausea and vomiting, I = heartburn, J = SF-36, K = gastric emptying rate, L = susceptible sigh, M = loss of appetite, N = SDS scores, O = SAS scores, P = PCS scores, Q = MCS scores, **E** = experiment group, **C** = control group.

versus CP. Eleven studies used TCM decoction in experiment groups,[28–35,39,40,42] 3 used TCM granule[36–38] and the remain used TCM oral liquid.[41] More characteristics of the included studies were described in Table 1. The constituents of herbal formulae were listed in Table 2 and the frequencies of usage were summarized in Table 3. *Atractylodes macrocephala Koidz* (*Bai Zhu*), *Radix Glycyrrhizae preparata* (*Gan Cao*), *Poria cocos (Schw.) Wolf* (*Fu Ling*), and *Amomum villosum Lour* (*Sha Ren*) were the most frequently used among 51 kinds of herbs used in experiment group.

4.2. Methodological quality of included studies

All included studies reported that baselines were comparable among groups. Jadad scores of the included RCTs ranged from 1 to 3 points. Studies got 3 points in Jadad scores were considered as high quality,[28,30–32] and those got 1 or 2 points were considered as low quality.[29,33–42] There are respectively 13,[28,29,32–42] 15,[28–42] and 14[28–30,32–42] trials which did not mention allocation concealment, blinding of participants and personnel, blinding of outcome assessment. Therefore, these studies were considered having high risk of selection bias, performance bias and detection bias respectively. A description of methodological quality of the selected trials were summarized in Table 4. And the risk of bias assessment of selected studies was shown in Figure 2.

4.3. Primary outcomes: clinical efficacy rate

Fifteen comparisons from all included studies were pooled for the primary outcome of clinical efficacy rate, which were calculated according to the standards of the Guiding Principles for the Clinical Research of New TCM.[43] There were 727 patients in experiment groups received JLT, while 724 patients received CP in control groups. Under 90% significance level, heterogeneity analysis indicated that there was no statistical heterogeneity among these studies ($Chi^2 = 7.82$, $P = .90$, $I^2 = 0\%$) (Fig. 3). Therefore, fixed effect model was chosen to perform the trial and the result showed that JLT had significantly better clinical efficacy than CP on treating FD (OR 2.85; 95%CI 2.14, 3.78; $P < .00001$) (Fig. 3). Besides, potential publication bias was identified by funnel plot analysis (Begg test $P = .018$) (Fig. 4).

4.4. Second outcomes: Improvement of TCM symptoms scores

4.4.1. Abdominal pain scores. Among all included trials, 9 trials reported the improvement of abdominal pain,[28–31,34,35,37,38,41] but 4 of them used different scoring criteria.[28,31,35,41] Therefore, only 5 studies were used for analysis.[29,30,34,37,38] The result showed that JLT medicine had better efficacy in relieving abdominal pain (SMD −0.45; 95%CI −0.61, −0.29; $P < .00001$) with no statistical heterogeneity ($Chi^2 = 3.78$, $P = 0.44$, $I^2 = 0\%$) (Fig. 5).

4.4.2. Abdominal distention scores. Although 11 studies reported abdominal distention,[28–31,34,35,37–39,41,42] 6 trials used different scoring criteria.[28,30,31,35,41,42] Thus, only 5 trials were included in analysis.[29,34,37–39] The fixed effect model was used as there was no apparently statistical heterogeneity ($Chi^2 = 2.63$, $P = .62$, $I^2 = 0\%$). The result indicated that JLT medicine had

Table 2

The ingredients of each formula.

Authors	Ingredients of each formula			
Zhang et a[29]	*Astragalus membranaceus* (Huang Qi) 60 g	*Codonopsis pilosula (Franch.) Nannf* (Dang Shen) 30 g	*Ziziphus jujuba Mill.* (Da Zao) 10 g	*Poria cocos (Schw.)Wolf.* (Fu Ling) 10 g
	Radix Glycyrrhizae preparata (Zhi Gan Cao) 10 g	*Citrus aurantium L* (Zhi Qiao) 15 g	*Pinellia ternata(Thunb) Breit* (Ban Xia) 15 g	*Zingiber officinale Rosc.* (Gan Jiang) 10 g
	Cinnamomum cassia Presl. (Gui Zhi) 15 g	*Magnolia officinalis Rehd.et Wils.* (Hou Po) 15 g	*Atractylodes macrocephala Koidz* (Bai Zhu) 20 g	*Perilla frutescens(L.)Britt.* (Zi Su Geng) 15 g
Li et al[28]	*Atractylodes macrocephala Koidz* (Bai Zhu) 15 g	*Peseudostellaria heterophylla (Miq.)Paxex pax et Hoffm.* (Tai Zi Shen) 15 g	*Aucklandia lappa Decne* (Mu Xiang) 9 g	*Amomum villosum Lour* (Sha Ren) 3 g
	Poria cocos (Schw.)Wolf. (Fu Ling) 10 g	*Radix Glycyrrhizae preparata* (Zhi Gan Cao) 9 g	*Citrus aurantium L*, (Zhi Shi) 10 g	
Wang et al[31]	*Poria cocos (Schw.)Wolf.* (Fu Ling) 10 g	*Atractylodes macrocephala Koidz* (Bai Zhu) 10 g	*Citrus aurantium L*, (Zhi Shi) 10 g	*Aucklandia lappa Decne* (Mu Xiang) 10 g
	Pinellia ternata(Thunb) Breit (Ban Xia) 10 g	*Codonopsis pilosula (Franch.) Nannf* (Dang Shen) 15 g	*Amomum villosum Lour* (Sha Ren) 6 g	*Radix Glycyrrhizae preparata* (Zhi Gan Cao) 5 g
	Magnolia officinalis Rehd.et Wils. (Hou Po) 10 g	*Citrus reticulata Blanco* (Chen Pi) 10 g		
Zhu et al[30]	*Atractylodes macrocephala Koidz* (Bai Zhu) 10 g	*Codonopsis pilosula (Franch.) Nannf* (Dang Shen) 10 g	*Amomum villosum Lour* (Sha Ren) 6 g	*Aucklandia lappa Decne* (Mu Xiang) 10 g
	Poria cocos (Schw.)Wolf. (Fu Ling) 15 g	*Radix Glycyrrhizae preparata* (Zhi Gan Cao) 10 g	*Citrus aurantium L*, (Zhi Shi) 10 g	*Citrus reticulata Blanco* (Chen Pi) 10 g
	Corydalis yanhusuo W.T.Wang (Yan Hu Suo) 10 g			
Cai et al[32]	*Panax ginseng C.A.Mey.* (Ren Shen) 10 g	*Atractylodes macrocephala Koidz* (Bai Zhu) 15 g	*Poria cocos (Schw.)Wolf.* (Fu Ling) 18 g	*Radix Glycyrrhizae preparata* (Zhi Gan Cao) 5 g
	Citrus reticulata Blanco (Chen Pi) 12 g	*Pinellia ternata(Thunb) Breit* (Ban Xia) 12 g	*Cyperus rotundus L.* (Xiang Fu)15 g	*Amomum villosum Lour* (Sha Ren) 9 g
	Aucklandia lappa Decne (Mu Xiang) 10 g	*Corydalis yanhusuo W.T.Wang* (Yan Hu Suo) 12 g	*Ziziphus jujuba Mill. var. spinosa (Bunge)Hu ex H. F. Chou* (Suan Zao Ren) 15 g	*Raeonia lactiflora pall*, (Bai Zhu) 10 g
Li et al[35]	*Panax ginseng C.A.Mey.* (Ren Shen) 15 g	*Raeonia lactiflora pall*, (Bai Zhu) 15 g	*Poria cocos (Schw.)Wolf.* (Fu Ling) 15 g	*DioscoreaoppositaThunb.* (Shan Yao) 15 g
	Platycodon grandiflorus (Jacq.) A. DC. (Jie Geng) 8 g	*Aucklandia lappa Decne* (Mu Xiang) 12 g	*Nelumbo nucifera Gaertn.* (Lian Zi) 15 g	*Coix lacryma-jobi L.var.ma-yuen (Roman.) Stapf* (Yi Yi Ren) 15 g
	Magnolia officinalis Rehd.et Wils. (Hou Po) 15 g	*Citrus aurantium L*, (Zhi Shi) 15 g	*Citrus reticulata Blanco* (Qing Pi) 15 g	*Areca catechu L.* (Bing Lang) 15 g
	Dolichos lablab L. (Bai Bian Dou) 10 g	*Amomum villosum Lour* (Sha Ren) 10 g	*Radix Glycyrrhizae preparata* (Zhi Gan Cao) 5 g	
Liao et al[34]	*Peseudostellaria heterophylla (Miq.)*	*Raeonia lactiflora pall*, (Bai Zhu) 15 g	*Citrus reticulata Blanco* (Chen Pi) 10 g	*Citrus aurantium L*, (Zhi Shi) 10 g
	Paxex pax et Hoffm. (Tai Zi Shen) 15 g			
	Aucklandia lappa Decne (Mu Xiang) 7 g	*Amomum villosum Lour* (Sha Ren) 5 g	*Hordeum vulgare L.* (Mai Ya) 15 g	*C.pinnatifidaBge* (Shan Zha) 10 g
	Areca catechu L. (Bing Lang) 10 g	*Poria cocos (Schw.)Wolf.* (Fu Ling) 10 g		
Li et al[37]	*Astragalus membranaceus* (Huang Qi) 10 g	*Codonopsis pilosula (Franch.) Nannf* (Dang Shen) 10 g	*Raeonia lactiflora pall*, (Bai Zhu) 10 g	*Amomum villosum Lour* (Sha Ren) 10 g
	Magnolia officinalis Rehd.et Wils. (Hou Po) 10 g	*Evodia rutaecarpa (Juss.) Benth.* (Wu Zhu Yu) 10 g	*Alpiniakatsumadai Hayata* (Cao Dou Kou) 10 g	*Citrus aurantium L* (Zhi Qiao) 10 g
	Corydalis yanhusuo W.T.Wang (Yan Hu Suo) 10 g	*1satis indigotica Fort.* (Ban Lan Gen) 10 g		
Li et al[36]	*Raeonia lactiflora pall*, (Bai Zhu)	*Codonopsis pilosula (Franch.) Nannf* (Dang Shen)	*Poria cocos (Schw.)Wolf.* (Fu Ling)	*Radix Glycyrrhizae preparata* (Zhi Gan Cao)
	Pinellia ternata(Thunb) Breit (Ban Xia)	*Citrus reticulata Blanco* (Chen Pi)	*Aucklandia lappa Decne* (Mu Xiang)	*Amomum villosum Lour* (Sha Ren)
	Eupatorium fortunei Turcz. (Pei Lan)	*Gallus gallus domesticus Brisson.* (Ji Nei Jin)	*Melia toosendan Sieb. et Zucc.* (Chuan Lian Zi)	
Xu et al[38]	*Poria cocos (Schw.)Wolf.* (Fu Ling) 15 g	*Codonopsis pilosula (Franch.) Nannf* (Dang Shen) 15 g	*Raeonia lactiflora pall.* (Bai Zhu) 15 g	*Citrus reticulata Blanco* (Chen Pi) 12 g
	Pinellia ternata(Thunb) Breit (Ban Xia) 10 g	*Citrus aurantium L* (Zhi Qiao) 15 g	*Amomum villosum Lour* (Sha Ren) 6 g	*Aucklandia lappa Decne* (Mu Xiang) 10 g
	Radix Glycyrrhizae preparata (Zhi Gan Cao) 6 g			
Hu et al[33]	*Poria cocos (Schw.)Wolf.* (Fu Ling) 15 g	*Codonopsis pilosula (Franch.) Nannf* (Dang Shen) 15 g	*Raeonia lactiflora pall*, (Bai Zhu) 15 g	*Citrus reticulata Blanco* (Chen Pi) 10 g
	Aucklandia lappa Decne (Mu Xiang) 10 g	*Cyperus rotundus L.* (Xiang Fu)10 g	*Pinellia ternata(Thunb) Breit* (Ban Xia) 10 g	*Amomum villosum Lour* (Sha Ren) 6 g
	ArecacatechuL. (Da Fu Pi) 10 g	*Pogostemoncablin (Blanco) Benth* (Huo Xiang) 10 g	*Setaria italica (L.) Beauv.* (Gu Ya) 20 g	*Hordeum vulgare L.* (Mai Ya) 20 g
	Radix Glycyrrhizae preparata (Zhi Gan Cao) 6 g	*Curcuma wenyujin Y.H.Chen et C.Ling* (Yu Jin) 10 g		
Wang[40]	*Citrus aurantium L* (Zhi Qiao) 20 g	*Codonopsis pilosula (Franch.) Nannf* (Dang Shen) 20 g	*Raeonia lactiflora pall*, (Bai Zhu) 20 g	*Areca catechu L.* (Bing Lang) 15 g
	Perilla frutescens(L.)Britt. (Zi Su Ye) 15 g	*Bupleurum chinensis DC.* (Chai Hu) 20 g	*Astragalus membranaceus* (Huang Qi) 30 g	*Cinnamomum cassia Presl.* (Gui Zhi) 15 g
	Raeonia lactiflora pall. (Bai Shao) 15 g	*Zingiber officinale Rosc.* (Gan Jiang) 10 g	*Ziziphus jujuba Mill.* (Da Zao) 30 g	*Radix Glycyrrhizae preparata* (Zhi Gan Cao) 10 g
Zhang et al[42]	*Bupleurum chinensis DC.* (Chai Hu) 10 g	*Raeonia lactiflora pall.* (Bai Shao)15 g	*Citrus reticulata Blanco* (Chen Pi) 15 g	*Pinellia ternata(Thunb) Breit* (Ban Xia) 15 g
	Gallus gallus domesticus Brisson. (Ji Nei Jin) 15 g	*Codonopsis pilosula (Franch.) Nannf* (Dang Shen) 15 g	*Medicated Leaven* (Shen qu) 15 g	*Raeonia lactiflora pall*, (Bai Zhu) 15 g
	Citrus medica L.Var.Sarcodactylis Swingle (Fo Shou) 15 g	*Salvia miltiorrhiza Bge.* (Dan Shen) 15 g	*Citrus aurantium L* (Zhi Qiao) 30 g	*Radix Glycyrrhizae preparata* (Zhi Gan Cao) 6 g
Wang[41]	*Raeonia lactiflora pall*, (Bai Zhu)	*Salvia miltiorrhiza Bge.* (Dan Shen)	*Poria cocos (Schw.)Wolf.* (Fu Ling)	*Citrus aurantium L* (Zhi Qiao)
	Aucklandia lappa Decne (Mu Xiang)	*Magnolia officinalis Rehd.et Wils.* (Hou Po)	*Hordeum vulgare L.* (Mai Ya)	*RaphanussativusL.* (Lai Fu Zi)
	Prunus persica(L.)Batsch (Tao Ren)	*Rheum palmatum L.* (Da Huang)	*Zingiber officinale Rosc.* (Gan Jiang)	*Radix Glycyrrhizae preparata* (Zhi Gan Cao)
Hu et al[39]	*Raeonia lactiflora pall*, (Bai Zhu) 15 g	*Codonopsis pilosula (Franch.) Nannf* (Dang Shen) 15 g	*Poria cocos (Schw.)Wolf.* (Fu Ling) 15 g	*Radix Glycyrrhizae preparata* (Zhi Gan Cao) 5 g
	Amomum villosum Lour (Sha Ren) 10 g	*Aucklandia lappa Decne* (Mu Xiang) 10 g	*Pinellia ternata(Thunb) Breit* (Ban Xia) 15 g	*Citrus reticulata Blanco* (Chen Pi) 10 g
	Corydalis yanhusuo W.T.Wang (Yan Hu Suo) 15 g	*Curcuma wenyujin Y.H.Chen et C.Ling* (Yu Jin) 15 g	*Sepiella maindroni de Rochebrune* (Hai Piao Xiao) 15 g	*AlbiziajulibrissinDurazz.* (He Huan Pi) 15 g

Table 3

Frequencies of usage and distribution in TCM.

Chinese herbs	Frequency	Rate (%)	Chinese herbs	Frequency	Rate (%)
Atractylodes macrocephala Koidz (Bai Zhu)	15	9.4	*Prunus persica(L.)Batsch* (Tao Ren)	1	0.6
Radix Glycyrrhizae preparata (Gan Cao)	12	7.5	*Citrus medica L.Var.Sarcodactylis Swingle* (Fo Shou)	1	0.6
Poria cocos (Schw.)Wolf (Fu Ling)	11	6.9	*Medicated Leaven* (Shen qu)	1	0.6
Amomum villosum Lour (Sha Ren)	11	6.9	*Perilla frutescens(L.)Britt.* (Zi Su Ye)	1	0.6
Aucklandia lappa Decne(Mu Xiang)	10	6.3	*Setaria italica (L.) Beauv.* (Gu Ya)	1	0.6
Codonopsis pilosula (Franch)Nannf (Dang Shen)	9	5.7	*ArecacatechuL.* (Da Fu Pi)	1	0.6
Pinellia ternata(Thunb) Breit.(Ban Xia)	8	5.0	*AlbiziajulibrissinDurazz.* (He Huan Hua)	1	0.6
Citrus reticulata Blanco (Chen Pi)	8	5.0	Sepiella maindroni de Rochebrune (Hai Piao Xiao)	1	0.6
Citrus aurantium L (Zhi Qiao)	6	3.8	*Pogostemoncablin (Blanco) Benth* (Huo Xiang)	1	0.6
Magnolia officinalis Rehd.et Wils. (Hou Po)	5	3.1	*Rheum palmatum L.* (Da Huang)	1	0.6
Corydalis yanhusuo W.T.Wang (Yan Hu Suo)	4	2.5	*Alpiniakatsumadai Hayata* (Cao Dou Kou)	1	0.6
Citrus aurantium L. (Zhi Shi)	4	2.5	Dolichos lablab L. (Bai Bian Dou)	1	0.6
Areca catechu L. (Bing Lang)	3	1.9	*Platycodon grandiflorus (Jacq.) A. DC.* (Jie Geng)	1	0.6
Zingiber officinale Rosc. (Gan Jiang)	3	1.9	*DioscoreaoppositaThunb.* (Shan Yao)	1	0.6
Hordeum vulgare L. (Mai Ya)	3	1.9	*Panax ginseng C.A.Mey.* (Ren Shen)	1	0.6
Astragalus membranaceus (Huang Qi)	3	1.9	*Citrus reticulata Blanco* (Qing Pi)	1	0.6
Ziziphus jujuba Mill. (Da Zao)	2	1.3	*Coix lacryma-jobi L.var.ma-yuen (Roman.) Stapf* (Yi Yi Ren)	1	0.6
Cyperus rotundus L. (Xiang Fu)	2	1.3	*Nelumbo nucifera Gaertn.* (Lian Zi)	1	0.6
Raeonia lactiflora pall. (Bai Shao)	2	1.3	*Perilla frutescens(L.)Britt.* (Zi Su Geng)	1	0.6
Cinnamomum cassia Presl. (Gui Zhi)	2	1.3	*C.pinnatifidaBge* (Shan Zha)	1	0.6
Gallus gallus domesticus Brisson. (Ji Nei Jin)	2	1.3	*Evodia rutaecarpa (Juss.) Benth.* (Wu Zhu Yu)	1	0.6
Salvia miltiorrhiza Bge. (Dan Shen)	2	1.3	*1satis indigotica Fort.* (Ban Lan Gen)	1	0.6
Bupleurum chinensis DC. (Chai Hu)	2	1.3	*Eupatorium fortunei Turcz.* (Pei Lan)	1	0.6
Peseudostellaria heterophylla (Miq.) Paxex pax et Hoffm. (Tai Zi Shen)	2	1.3	*Ziziphus jujuba Mill. var. spinosa (Bunge)Hu ex H. F. Chou* (Suan Zao Ren)	1	0.6
Curcuma wenyujin Y.H.Chen et C.Ling (Yu Jin)	2	1.3	*Melia toosendan Sieb. et Zucc.* (Chuan Lian Zi)	1	0.6
RaphanussativusL. (Lai Fu Zi)	1	0.6			

greater abdominal distention alleviation compared to control groups (SMD −0.34; 95%CI −0.50, −0.18; $P < .0001$) (Fig. 6).

4.4.3. Early satiety scores. In the included studies, 4 studies reported early satiety.[30,34,38,41] One trial was excluded from analysis because of significant heterogeneity.[41] No apparently heterogeneity was found among the other 3 trials ($Chi^2 = 0.27$, $P = .88$, $I^2 = 0\%$). The result showed that JTL groups was superior to control groups in relieving early satiety (SMD −0.37; 95%CI −0.56, −0.19; $P < .0001$) (Fig. 7).

4.4.4. Belching scores. Three trials were included in analysis[31,37,39] and fixed model was used because of no apparently statistical heterogeneity ($Chi^2 = 1.71$, $P = .42$, $I^2 = 0\%$). The result indicated that JLT groups had more significant improvement on belching than control groups (SMD −0.50; 95%CI −0.74, −0.27; $P < .0001$) (Fig. 8).

4.4.5. Poor appetite scores. Fixed model was conducted as no apparently heterogeneity was found among the 3 trials[29,31,37] which were included in analysis ($Chi^2 = 0.90$, $P = .64$, $I^2 = 0\%$).

Table 4

Evaluation of methodological quality of included studies.

Study ID	Baseline	Randomization	Double Blinding	Withdrawal or dropout	Allocation concealment	Follow-up	Side effects	Jadad scores
Zhang et al[29]	Comparability	Mentioned not described	N.R	N.R	N.R	N.R	No	1
Li et al[28]	Comparability	Random number table	N.R	No	N.R	N.R	E: 2 C: 3	3
Wang et al[31]	Comparability	Random number table	Single-blind	C: 2 cases	Sealed envelop	1 month	No	3
Zhu et al[30]	Comparability	Random number table	N.R	C: 3 cases	Sealed envelop	1 month	N.R	3
Cai et al[32]	Comparability	Random number table	N.R	E: 4 cases C: 3 cases	N.R	N.R	No	3
Li et al[35]	Comparability	Random number table	N.R	N.R	N.R	6 months	No	2
Liao et al[34]	Comparability	Random number table	N.R	N.R	N.R	N.R	N.R	2
Li et al[36]	Comparability	Random number table	N.R	N.R	N.R	N.R	No	2
Li et al[37]	Comparability	Mentioned not described	N.R	N.R	N.R	6 months	No	1
Xu et al[38]	Comparability	Mentioned not described	N.R	N.R	N.R	N.R	E: 2 C: 1	1
Hu et al[33]	Comparability	Random number table	N.R	N.R	N.R	N.R	N.R	2
Wang[41]	Comparability	Mentioned not described	N.R	N.R	N.R	N.R	N.R	1
Zhang et al[42]	Comparability	Mentioned not described	N.R	N.R	N.R	N.R	N.R	1
Wang[40]	Comparability	Random number table	N.R	N.R	N.R	N.R	No	2
Hu et al[39]	Comparability	Mentioned not described	N.R	E: 1 cases C: 2 cases	N.R	N.R	No	1

N.R = not reported, **E** = experiment group, **C** = control group.

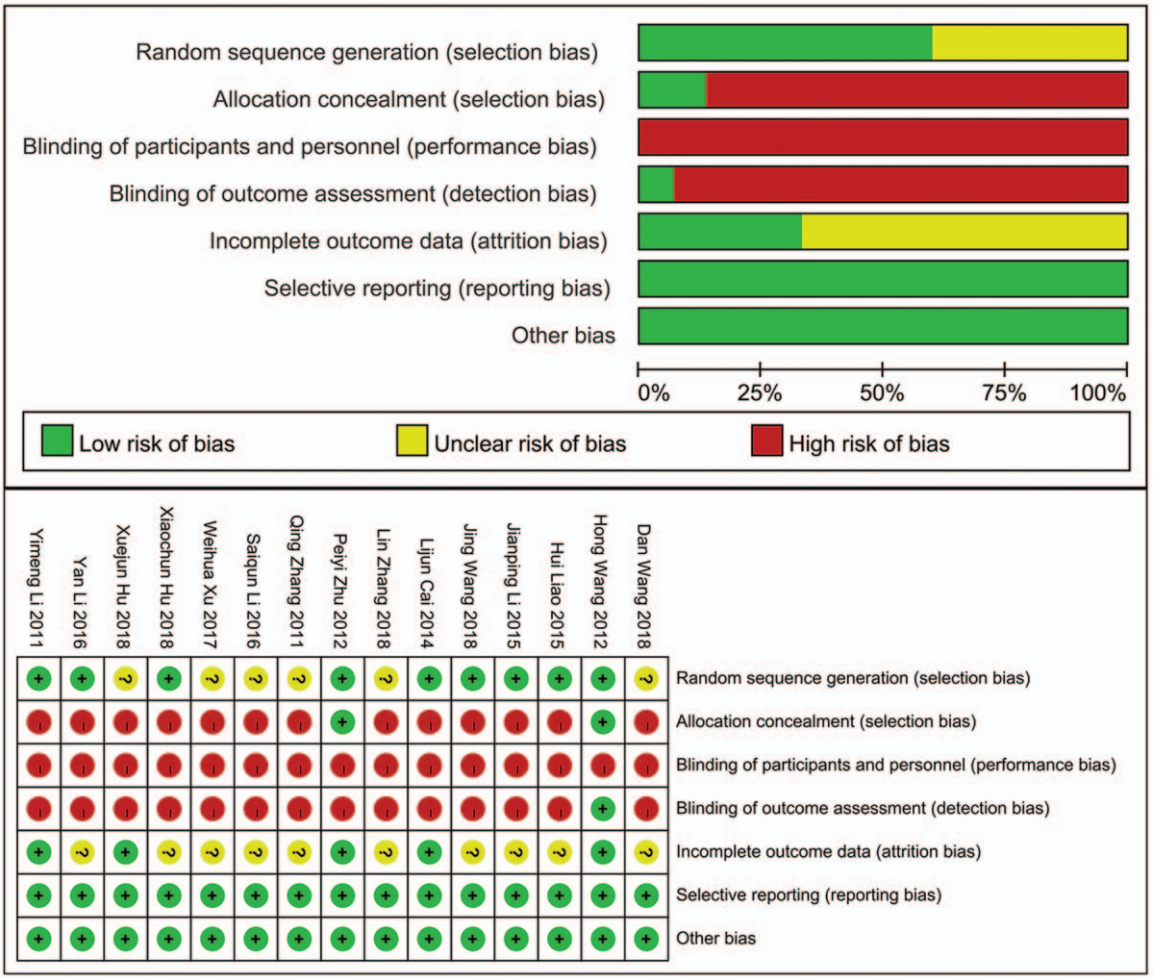

Figure 2. Risk of bias summary and graph.

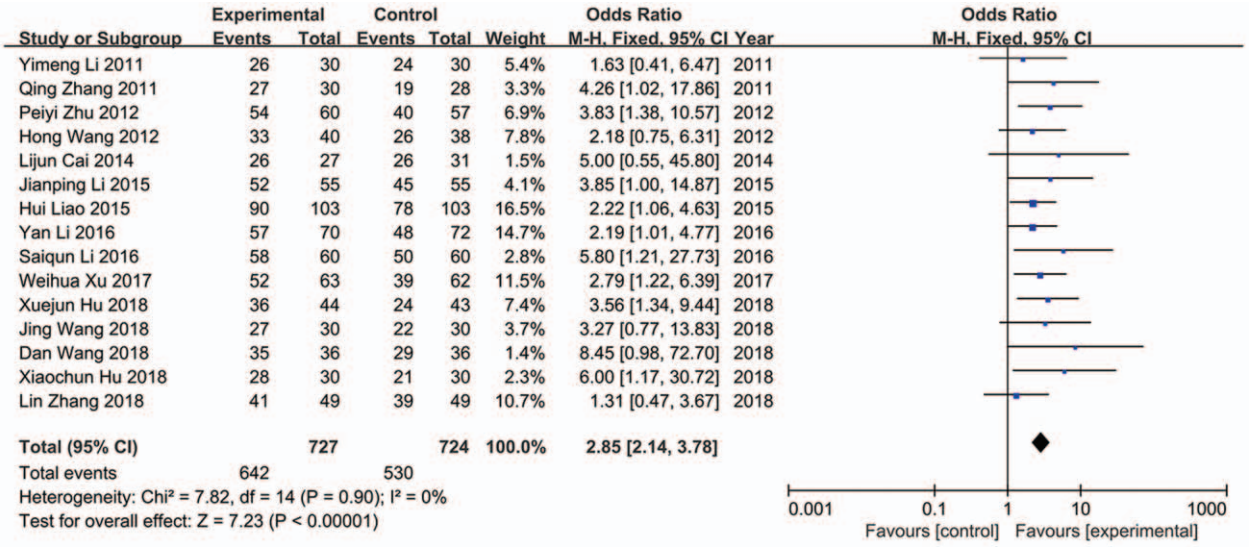

Figure 3. Forest plot of effective rate (fixed effect model).

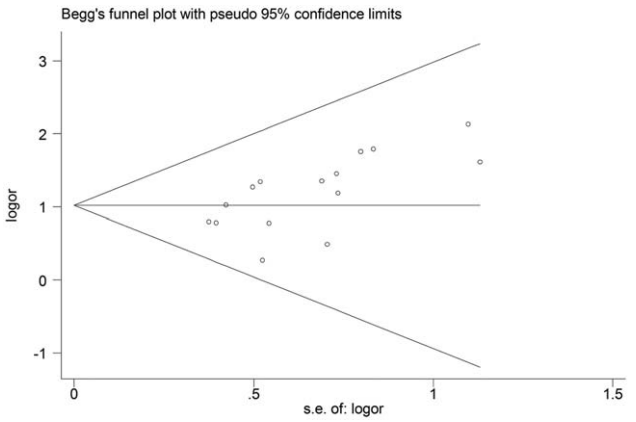

Figure 4. Funnel plot of effective rate.

The result showed that JLT had better efficacy in alleviating poor appetite (SMD −0.52; 95%CI −0.77, −0.27; $P < .0001$) (Fig. 9).

4.4.6. Fatigue scores. Three trials were included in analysis,[29,37,39] and there was no significant heterogeneity among them ($Chi^2 = 1.53$, $P = .47$, $I^2 = 0\%$). The result showed greater improvement in fatigue for JLT groups compared with control groups (SMD −0.76; 95%CI −1.01, −0.51; $P < .00001$) (Fig. 10).

4.5. GRADE evidence of quality

In order to assess the quality of evidences and reliability of this meta-analysis, we performed an evaluation by using GRADE profiler software. The results showed that the evidence quality was "low". Detailed information of assessment and basis of classification were showed in Figure 11 and Table 5.

4.6. Adverse events

Ten studies reported adverse events.[28,29,31,32,35–40] Among them, 8 trials mentioned no adverse event.[29,31,32,35–37,39,40] One study reported that 2 patients in experiment group had loose stool for 2 days, 3 patients in control group appeared mild diarrhea for 3 days[28]. These discomforts disappeared without any intervention. Another study reported that 2 patients in experiment group experienced mild diarrhea and 1 patient appeared rash.[38] All discomforts disappeared after drug withdrawal and no further measure was needed.

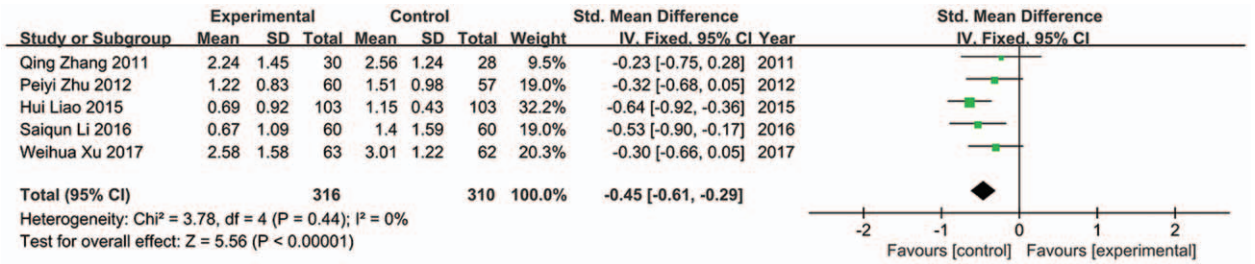

Figure 5. Forest plot of abdominal pain (fixed effect model).

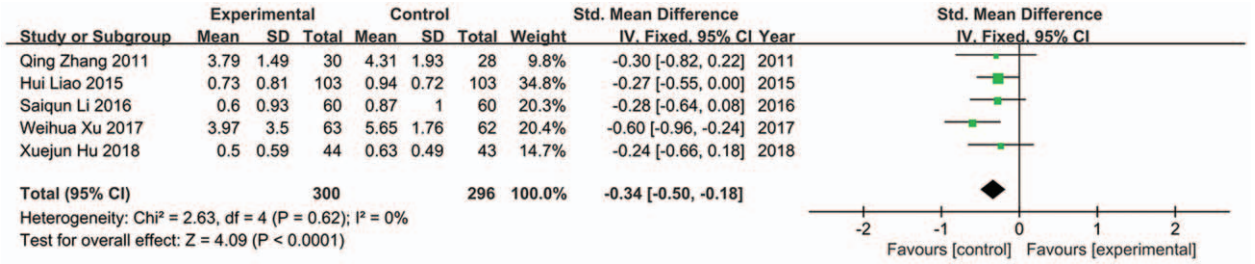

Figure 6. Forest plot of abdominal distention (fixed effect model).

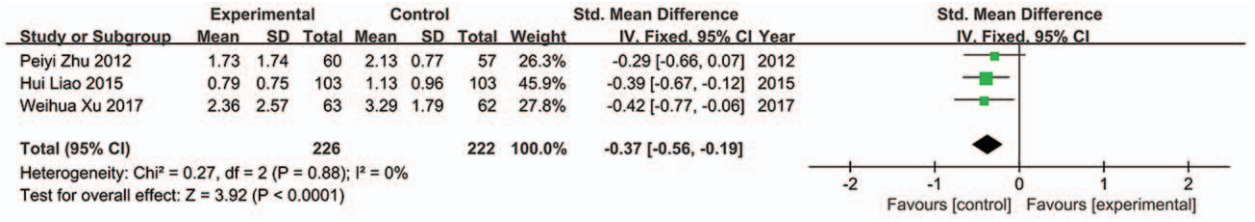

Figure 7. Forest plot of early satiety (fixed effect model).

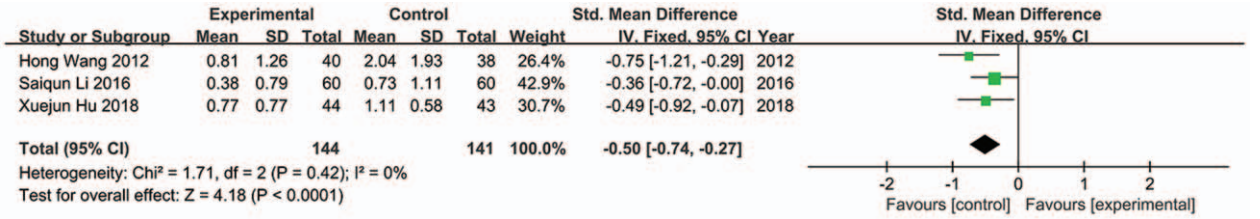

Figure 8. Forest plot of belching (fixed effect model).

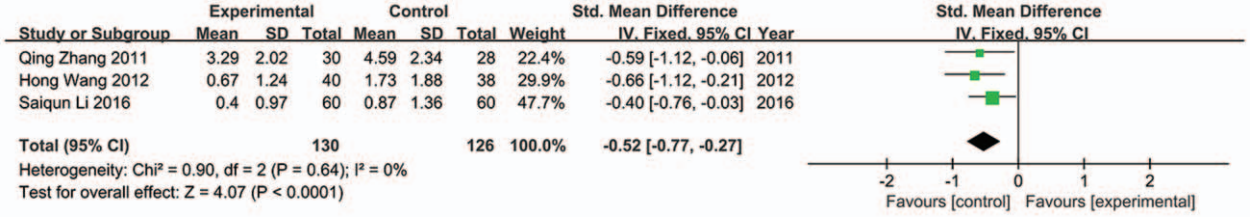

Figure 9. Forest plot of poor appetite (fixed effect model).

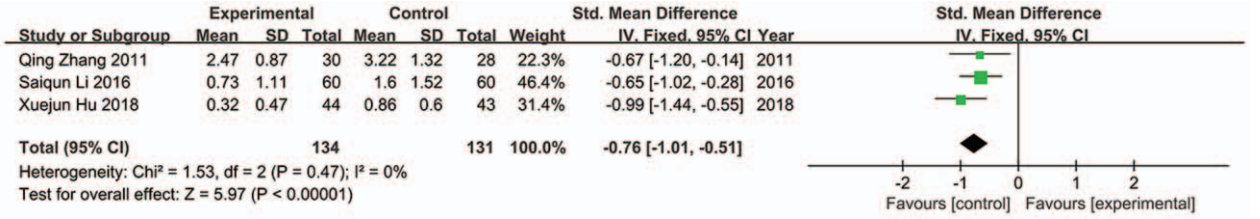

Figure 10. Forest plot of fatigue (fixed effect model).

JLT medicine for FD

Patient or population: patients with FD
Settings:
Intervention: JLT medicine

Outcomes	Illustrative comparative risks* (95% CI) Assumed risk Control	Corresponding risk JLT medicine	Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
clinical efficacy rate	Study population		OR 2.85 (2.14 to 3.78)	1451 (15 studies)	⊕⊕⊕⊕ low	
	732 per 1000	886 per 1000 (854 to 912)				
	Moderate					
	900 per 1000	962 per 1000 (951 to 971)				
abdominal pain scores		The mean abdominal pain scores in the intervention groups was **0.45 standard deviations lower** (0.61 to 0.29 lower)		626 (5 studies)	⊕⊕⊕⊕ low	SMD 0.45 (0.29 to 0.61)
abdominal distention scores		The mean abdominal distention scores in the intervention groups was **0.34 standard deviations lower** (0.50 to 0.18 lower)		596 (5 studies)	⊕⊕⊕⊕ low	SMD 0.34 (0.18 to 0.5)
early satiety scores		The mean early satiety scores in the intervention groups was **0.37 standard deviations lower** (0.56 to 0.19 lower)		448 (3 studies)	⊕⊕⊕⊕ low	SMD 0.37 (0.19 to 0.56)
belching scores		The mean belching scores in the intervention groups was **0.5 standard deviations lower** (0.74 to 0.27 lower)		285 (3 studies)	⊕⊕⊕⊕ low	SMD 0.5 (0.27 to 0.74)
poor appetite scores		The mean poor appetite scores in the intervention groups was **0.52 standard deviations lower** (0.77 to 0.27 lower)		256 (3 studies)	⊕⊕⊕⊕ low	SMD 0.52 (0.27 to 0.77)
fatigue scores		The mean fatigue scores in the intervention groups was **0.76 standard deviations lower** (1.01 to 0.51 lower)		265 (3 studies)	⊕⊕⊕⊕ low	SMD 0.76 (0.51 to 1.01)

*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.

Figure 11. GRADE quality grading evaluation.

Table 5

GRADE quality grading evaluation.

Quality assessment							No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	JLT medicine	Control	Relative (95% CI)	Absolute	Quality	Importance
clinical efficacy rate												
15	randomised trials	serious	no serious inconsistency	no serious indirectness	no serious imprecision	reporting bias	642/727 (88.3%)	530/724 (73.2%) 90%	OR 2.85 (2.14 to 3.78)	154 more per 1000 (from 122 more to 180 more) 62 more per 1000 (from 51 more to 71 more)	⊕⊕OO LOW	CRITICAL
abdominal pain scores (Better indicated by lower values)												
5	randomised trials	serious	no serious inconsistency	no serious indirectness	no serious imprecision	reporting bias	316	310	–	SMD 0.45 lower (0.61 to 0.29 lower)	⊕⊕OO LOW	IMPORTANT
abdominal distention scores (Better indicated by lower values)												
5	randomised trials	serious	no serious inconsistency	no serious indirectness	no serious imprecision	reporting bias	300	296	–	SMD 0.34 lower (0.5 to 0.18 lower)	⊕⊕OO LOW	IMPORTANT
early satiety scores (Better indicated by lower values)												
3	randomised trials	serious	no serious inconsistency	no serious indirectness	no serious imprecision	reporting bias	226	222	–	SMD 0.37 lower (0.56 to 0.19 lower)	⊕⊕OO LOW	IMPORTANT
belching scores (Better indicated by lower values)												
3	randomised trials	serious	no serious inconsistency	no serious indirectness	serious	none	144	141	–	SMD 0.5 lower (0.74 to 0.27 lower)	⊕⊕OO LOW	IMPORTANT
poor appetite scores (Better indicated by lower values)												
3	randomised trials	serious	no serious inconsistency	no serious indirectness	serious	none	130	126	–	SMD 0.52 lower (0.77 to 0.27 lower)	⊕⊕OO LOW	IMPORTANT
fatigue scores (Better indicated by lower values)												
3	randomised trials	serious	no serious inconsistency	no serious indirectness	serious	none	134	131	–	SMD 0.76 lower (1.01 to 0.51 lower)	⊕⊕OO LOW	IMPORTANT

5. Discussion

In the meta-analysis of RCTs comparing JLT with CP in participants with FD, use of JLT resulted in better efficacy and greater alleviations on individual symptoms (including abdominal pain, abdominal distention, early satiety, belching, poor appetite, and fatigue). However, because of the usage of different scoring criteria or measures in the second outcome, not all studies reporting these symptoms were included in analyses. That could lead to small sample size and bias in the second outcome.

Current study has not fully understood the pathogenesis of FD. It is generally believed that various factors can lead to FD, including gastric motility and compliance, altered gut microbiome, psychological distress (particularly anxiety), visceral hypersensitivity and infection (specially *Helicobacter pylori*).[1,44–47] Present treatments for FD are mostly based on individual symptoms and experience, including *H. pylori* eradication therapy, acid-suppression therapy, prokinetic agents, antidepressants, and psychological therapy.[9–15] On the other hand, FD belongs to the category of Wei Tong (stomachache) or Wei Pi (stomach distention and fullness) in TCM, and the basic pathogenesis is widely considered as Pi deficiency and Qi stagnation.[2,48] The representative formula of JLT is Xiangsha Liujunzi Tang. JLT medicine has been reported to have better clinical efficacy than CP (such as domperidone, mosapride, lansoprazole) in treating patients with FD.[19,49–51] Moreover, numerous studies have found modern pharmacology evidences for JLT medicine's efficacy in treating FD. According to clinical trials, JLT medicine could raise the level of Ghrelin to ameliorate gastric empty rate and consequently relieve symptoms of FD.[52,53] Meanwhile, the study of Pan[54] indicated that JLT medicine can also raise the level of acetylcholin esterase (AChE) to ameliorate gastric emptying rate. Besides, animal experiment proved that JLT medicine can enhance rats' gastric emptying by increasing the content of motilin, gastrin, ghrelin, 5-hydroxytryptamine, decreasing the content of calcitonin gene related peptide and up-regulating the expressions of 5-HT_4R (5-hydroxytryptamine 4 receptor) mRNA and 5-HT_4R protein.[55] There was also experiment showed that JLT medicine can raise the levels of ghrelin, cholecystokinin, and vasoactive intestinal polypeptide in rats to alleviate the symptoms of FD.[56] Study of Xiaona Wang showed that JLT medicine can increase the expression level of CaMKII ($Ca^{[2+]}$/calmodulin-dependent kinase II) to promote gastric motility in rats.[57] Experiment of Yuhong Ge proved that Sijun Zi Decoction can lower visceral hypersensibility by decreasing the expression level of phospholipase C-γ and transient receptor potential vanilloid 1 mRNA in rats.[58]

We also summarized the frequency of each single herb used in included trails. The most frequently used herbs were *Atractylodes macrocephala Koidz* (*Bai Zhu*), *Radix Glycyrrhizae preparata* (*Gan Cao*), *Poria cocos(Schw.)Wolf* (*Fu Ling*), and *Amomum villosum Lour* (*Sha Ren*). There were plenty of ingredients in *Bai Zhu*, including sesquiterpenoids, phenylpropanoids, polyacetylenes, coumarins, triterpenoids, flavonoids, and flavonoid glycosides, steroids, benzoquinones, and polysaccharides. *Bai Zhu* was also proved to have varied pharmacological effects, including anti-tumor, anti-inflammatory, anti-aging activity, immunomodulatory, and improving gastrointestinal function.[59–65]*Gan Cao* was found to mainly contain flavonoid and triterpenoid, and have the effects of anti-inflammatory, analgesia as well as reducing intestinal motility, according to studies.[66–69] Experiments revealed that triterpenoid and pachymaran were the main components of *Fu Ling* and anti-tumor effect, hepatoprotective effect, immunization as well as anti-inflammatory effect were pharmacological actions of *Fu Ling*.[70–73] Sha Ren mainly contains volatile oil and polysaccharide. It has effects of protecting gastric mucosa, anti-inflammatory, facilitating gastric emptying as well as intestine peristalsis, according to researches.[74–78]

Several potential limitations of this study should be noted. First, allocation concealment and blinding were not conducted adequately in most of the included studies (only 2 studies reported detailed description of allocation concealment and only 1 reported blind method). It led to high risk of biases of these trials and consequently resulted in low quality evidence of this meta-analysis. Second, meta-analysis of recurrence rate was not performed, due to the insufficiency of follow-up period in most included trials (only 4 studies reported 1-month or 6-months follow-up period).

In this study the limited evidence available suggests that JLT was superior to CP on treating FD patients. However, the reported effectiveness of JTL for FD can be consider as encouraging but not convincing, the low-quality evidence is insufficient to recommend the use of JTL. But it is sufficient to support the necessity of further study. This study indicated that the assessment of recurrence rate should be performed in further study to evaluate the long-term effect of JLT. The problem that how to perform adequate allocation concealment and blinding should be emphatically solved in future RCTs for TCM versus CP.

6. Conclusions

In summary, this meta-analysis could provide a degree of evidence for the efficacy and safety of JLT medicine in treating patients with FD. However, further standardized, rigorously designed, and large-scale RCTs are required to provide more convincing and solid evidence.

Author contributions

Conceptualization: Jin-Tong Ye, Ling Hu.
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Funding acquisition: Ling Hu.
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Project administration: Ru-Liu Li, Ling Hu.
Resources: Ru-Liu Li, Dan-yan Li.
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Validation: Ru-Liu Li, Ling Hu.
Visualization: Jin-tong Ye, Yun-zhan Zhang, Dan-yan Li, Meng-Xin Huang.
Writing – original draft: Jin-tong Ye.
Writing – review & editing: Jin-tong Ye, Yun-zhan Zhang, Dan-yan Li, Yun-kai Dai.
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