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 < .0001). 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-HT4R = 5-hydroxytryptamine 4 receptor, CaMKII = Ca2+/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.
2. Methods

2.1. Search strategy

Literature searches were 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 $\chi^2$ 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.

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 1451 participants (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.
1. 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,[28,33,34,37] and those got 1 or 2 points were considered as low quality.[29,34,35] There are respectively 13,11,12 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.

2.6. 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.[28,31,34,41] 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 < .0001) with no statistical heterogeneity (Chi² = 3.78, I² = 0%) (Fig. 5). The result indicated that JLT medicine had better efficacy in relieving abdominal pain (SMD = -0.45; 95% CI [-0.61, -0.29]; P < .0001) with no statistical heterogeneity (Chi² = 3.78, I² = 0%) (Fig. 5). The result indicated that JLT medicine had better efficacy in relieving abdominal pain (SMD = -0.45; 95% CI [-0.61, -0.29]; P < .0001) with no statistical heterogeneity (Chi² = 3.78, I² = 0%) (Fig. 5).

3.3. 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 (Chi² = 7.82, P = .90, I² = 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 < .0001) (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.[28,31,34,41] 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 < .0001) with no statistical heterogeneity (Chi² = 3.78, I² = 0%) (Fig. 5). The result indicated that JLT medicine had better efficacy in relieving abdominal pain (SMD = -0.45; 95% CI [-0.61, -0.29]; P < .0001) with no statistical heterogeneity (Chi² = 3.78, I² = 0%) (Fig. 5). The result indicated that JLT medicine had better efficacy in relieving abdominal pain (SMD = -0.45; 95% CI [-0.61, -0.29]; P < .0001) with no statistical heterogeneity (Chi² = 3.78, I² = 0%) (Fig. 5). The result indicated that JLT medicine had better efficacy in relieving abdominal pain (SMD = -0.45; 95% CI [-0.61, -0.29]; P < .0001) with no statistical heterogeneity (Chi² = 3.78, I² = 0%) (Fig. 5). The result indicated that JLT medicine had better efficacy in relieving abdominal pain (SMD = -0.45; 95% CI [-0.61, -0.29]; P < .0001) with no statistical heterogeneity (Chi² = 3.78, I² = 0%) (Fig. 5). The result indicated that JLT medicine had better efficacy in relieving abdominal pain (SMD = -0.45; 95% CI [-0.61, -0.29]; P < .0001) with no statistical heterogeneity (Chi² = 3.78, I² = 0%) (Fig. 5). The result indicated that JLT medicine had better efficacy in relieving abdominal pain (SMD = -0.45; 95% CI [-0.61, -0.29]; P < .0001) with no statistical heterogeneity (Chi² = 3.78, I² = 0%) (Fig. 5). The result indicated that JLT medicine had better efficacy in relieving abdominal pain (SMD = -0.45; 95% CI [-0.61, -0.29]; P < .0001) with no statistical heterogeneity (Chi² = 3.78, I² = 0%) (Fig. 5).
The ingredients of each formula.
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.\cite{10,34,38,41} One trial was excluded from analysis because of significant heterogeneity.\cite{41} No apparently heterogeneity was found among the other 3 trials (Chi2 = 0.27, I^2 = 0%). The result showed that JLT groups was superior to control groups in relieving early satiety (SMD = -0.34; 95% CI = -0.56, -0.19; P < .0001) (Fig. 7).

4.4.4. Belching scores. Three trials were included in analysis\cite{31,37,39} and fixed model was used because of no apparently 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\cite{29,31,17} which were included in analysis (Chi^2 = 0.90, P = .64, I^2 = 0%).

### Table 3

| Chinese herbs | Frequency | Rate (%) | Chinese herbs | Frequency | Rate (%) |
|---------------|-----------|----------|---------------|-----------|----------|
| Atractylodes macrocephala Koiz (Bai Zhu) | 15 | 9.4 | Prunus persica(L.)Batsch (Tao Ren) | 1 | 0.6 |
| Radix Glycyrrhizae preparata (San Qiao) | 12 | 7.5 | Citrus medica L.Var.Sarcodactylis Swingle (Fo Shou) | 1 | 0.6 |
| Poria cocos (Scheele)Wolf (Fu Ling) | 11 | 6.9 | Perilla frutescens(L.)Britt. (Zi Su Ye) | 1 | 0.6 |
| Amomum volkameri Lour (Sha Ren) | 11 | 6.0 | Medicated Leaven (Shen qi) | 1 | 0.6 |
| Aucklandia lappa Decne(Mu Xiang) | 10 | 6.3 | Sutaria indica (L.)Beauv. (Yu Ya) | 1 | 0.6 |
| Codonopsis pilosula (Franch)Willd (Dang Shen) | 9 | 5.7 | Dipsaci minor f (Da Fu Pi) | 1 | 0.6 |
| Pinellia ternata(Thunb) Breit(Ban Xia) | 8 | 5.0 | Albizia julibrissin Durazz. (He Huang Hu) | 1 | 0.6 |
| Citrus reticulata Blanco | 8 | 5.0 | Pogostemon cablin (Blanco) Benth (Xu Huang) | 1 | 0.6 |
| Citrus aurantium L. | 8 | 5.0 | Rheum palmatum L. (Da Huang) | 1 | 0.6 |
| Hordeum vulgare L. (Mai Ya) | 6 | 3.8 | Alpinia officinarum Rehder et Wils. (Hou Po) | 5 | 3.1 |
| Magnolia officinalis Rehder et Wils. (Hou Po) | 6 | 3.8 | Rhaponticum carthamoides Hayata (Yan Hu Suo) | 4 | 2.5 |
| Corydalis yanhusuo W.T.Wang (Yan Hu Suo) | 6 | 3.8 | Aconitum carmichaelii De Candolle (Aconitum carmichaelii) | 4 | 2.5 |
| Citrus aurantium L. | 4 | 2.5 | Dolichos lablab L. (Bai Bian Dou) | 1 | 0.6 |
| Areca catechu L. | 4 | 2.5 | Platycodon grandiflorus (Jacq.) A. DC. | 1 | 0.6 |
| Zinger officinalis Rosc. (Gan Jiang) | 3 | 1.9 | Dioscorea opposita Thunb. (Shan Yao) | 1 | 0.6 |
| Hordeum vulgare L. (Mai Ya) | 3 | 1.9 | Panax ginseng C.A.Mey. | 1 | 0.6 |
| Astragalus membranaceus (Huang Qi) | 3 | 1.9 | Citrus reticulata Blanco (Bing Pi) | 1 | 0.6 |
| Ziziphus jujuba Mill. var. spinosa (Bunge)Hu | 3 | 1.9 | Coix lacryma-jobi L.var.ma-yuen (Roman.) Stapf (Yi Yi Ren) | 1 | 0.6 |
| Ophiopogon planus (Zhang Fu) | 2 | 1.3 | Neomucuna pruriens Gaetn. | 2 | 1.3 |
| Aronia lactiflora pall. (Bai Shaoren) | 2 | 1.3 | Perilla frutescens(L.)Britt. (Zi Su Geng) | 1 | 0.6 |
| Cinnamomum cassia Presl. (Gui Zhi) | 2 | 1.3 | Cinnamomum zeylanicum | 1 | 0.6 |
| Galus galus domesticus Brisson. (Ji Nei Jin) | 2 | 1.3 | Evodia rutaecarpus (Juss.) Berth. (Wu Zhu Yu) | 1 | 0.6 |
| Salvia miltiorrhiza Bge. (Dan Shen) | 2 | 1.3 | Isatis indigotica Fort. (Ban Lan Gen) | 1 | 0.6 |
| Paeonlaurus lactiflorus DC. (Chai Hu) | 2 | 1.3 | Eupatorium fortunei Turcz. (Pai Lan) | 1 | 0.6 |
| Paeonlaurus lactiflorus DC. (Chai Hu) | 2 | 1.3 | Ziziphus jujuba Mill. var. spinosa (Bunge) | 1 | 0.6 |
| Parex par et Hoffm. (Tai Zi Shen) | 2 | 1.3 | Ex H. F. Chou (Shan Zhuo) | 1 | 0.6 |
| Curcumae longae J. H. Chens et C.Ling (Yin Jin) | 2 | 1.3 | Mela toosendan sieb. | 1 | 0.6 |
| Raphanus sativus(L.) (Lai Fu Zi) | 1 | 0.6 | Sunna lutea Klink. et Zucc. (Chuan Lian Zi) | 1 | 0.6 |

### Table 4

| Study ID | Baseline | Randomization | Double Blinding | Withdrawal or dropout | Allocation concealment | Follow-up | Side effects | Jadad scores |
|----------|----------|---------------|-----------------|----------------------|------------------------|-----------|--------------|--------------|
| Zhang et al\cite{29} | Comparability | Mentioned not described | N.R | N.R | N.R | N.R | No | 1 |
| Li et al\cite{30} | Comparability | Random number table | N.R | No | N.R | N.R | E: 2 C: 3 | 3 |
| Wang et al\cite{31} | Comparability | Random number table | Single-blind | C: 2 cases | Sealed envelop | 1 month | No | 3 |
| Zhu et al\cite{32} | Comparability | Random number table | N.R | C: 3 cases | Sealed envelop | 1 month | N.R | 3 |
| Cai et al\cite{33} | Comparability | Random number table | N.R | E: 4 cases C: 3 cases | N.R | N.R | No | 3 |
| Li et al\cite{34} | Comparability | Random number table | N.R | N.R | N.R | 6 months | No | 2 |
| Liao et al\cite{35} | Comparability | Random number table | N.R | N.R | N.R | N.R | 6 months | No | 2 |
| Li et al\cite{36} | Comparability | Random number table | N.R | N.R | N.R | N.R | 6 months | No | 1 |
| Li et al\cite{37} | Comparability | Mentioned not described | N.R | N.R | N.R | N.R | E: 2 C: 1 | 1 |
| Xu et al\cite{38} | Comparability | Random number table | N.R | N.R | N.R | N.R | N.R | 2 |
| Hu et al\cite{39} | Comparability | Random number table | N.R | N.R | N.R | N.R | N.R | 1 |
| Wang\cite{40} | Comparability | Mentioned not described | N.R | N.R | N.R | N.R | N.R | 1 |
| Zhang et al\cite{41} | Comparability | Mentioned not described | N.R | N.R | N.R | N.R | N.R | 1 |
| Wang\cite{42} | Comparability | Random number table | N.R | N.R | N.R | No | 2 |
| Hu et al\cite{43} | 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).
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 (Chi² = 1.53, P = .47, I² = 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 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).

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%) | OR 2.85 (2.14 to 3.78) | 154 more per 1000 (from 122 more to 180 more) | @@@@ 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) | @@@@ 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) | @@@@ 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) | @@@@ LOW | IMPORTANT |
| belching scores (Better indicated by lower values) | 3 | randomised trials | serious | no serious inconsistency | no serious indirectness | no serious imprecision | serious | none | 144 | 141 | – | SMD 0.5 lower (0.74 to 0.27 lower) | @@@@ LOW | IMPORTANT |
| poor appetite scores (Better indicated by lower values) | 3 | randomised trials | serious | no serious inconsistency | no serious indirectness | no serious imprecision | serious | none | 130 | 126 | – | SMD 0.52 lower (0.77 to 0.27 lower) | @@@@ LOW | IMPORTANT |
| fatigue scores (Better indicated by lower values) | 3 | randomised trials | serious | no serious inconsistency | no serious indirectness | no serious imprecision | serious | none | 134 | 131 | – | SMD 0.76 lower (1.01 to 0.51 lower) | @@@@ 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). 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. 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. 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. 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. Meanwhile, the study of Pan 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-HT4R (5-hydroxytryptamine 4 receptor) mRNA and 5-HT4R protein.

There was also experiment showed that JLT medicine can raise the level of ghrelin, cholecystokinin, and vasoactive intestinal polypeptide in rats to alleviate the symptoms of FD. Study of Xiaona Wang showed that JLT medicine can increase the expression level of CaMKII (Ca2+/calmodulin-dependent kinase II) to promote gastric motility in rats. Experiment of Yuhong Ge proved that Sijun Zi Decoction can lower visceral hypersensitivity by decreasing the expression level of phospholipase C-γ and transient receptor potential vanilloid 1 mRNA in rats.

We also summarized the frequency of each single herb used in included trials. 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 (Shou 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 various pharmacological effects, including anti-tumor, anti-inflammatory, anti-aging activity, immunomodulatory, and improving gastrointestinal function. 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. 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. 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.

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 JLT for FD can be consider as encouraging but not convincing, the low-quality evidence is insufficient to recommend the use of JLT. 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

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