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META ANALYSIS AND SYSTEMATIC REVIEW

Effects of the herbal medicine Rikkunshito, for functional dyspepsia: A systematic review and meta-analysis

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Author contribution: The protocol was conceptualized by Seok-Jae Ko. The study was drafted by Seok-Jae Ko and Jae-Woo Park. The search strategy was developed by Jiseon Park and Min-ji Kim. Jiseon Park and Min-ji Kim participated in screening potential studies, data extraction, and assessment of risk of bias. Data synthesis and analysis were performed by Jinsung Kim. Seok-Jae Ko was the arbiter who would intervene and resolve any disagreements, so as to make no errors in this review. All authors have read and approved the final manuscript.
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Abstract

Background and Aim: Functional dyspepsia (FD) is characterized by chronic and unexplained indigestion at upper abdomen. Because of unsatisfactory effect of conventional treatments, demand is growing for complementary and alternative medicine. Rikkunshito (RKT) is a herbal medicine, which has been widely used for FD in Asia; however, the evidence is lacking. We carried out systematic review and meta-analysis to evaluate the effect and safety of RKT in the treatment of FD.
Methods: Electronic databases were searched in April 2019, including PUBMED, EMBASE, and Cochrane Library. All eligible studies should be randomized controlled trials (RCTs) comparing RKT or combination therapy (RKT and western medicine) group to western medicine group. The primary outcome measure was the total clinical efficacy rate (TCE). The secondary outcomes were total dyspepsia symptom scale, gastric emptying rate, gastrin, motilin, recurrence 6 months after treatment, and Hamilton depression rating scale.
Results: Fifty-two RCTs with 5475 patients were involved in this systematic review and meta-analysis. Compared with western medicine, RKT showed significant better result, with higher TCE (relative risk = 1.21, 95% confidence interval 1.17 to 1.25, $P < 0.001$). RKT presented higher reduction of total dyspepsia symptom scale, more improved gastric emptying rate, and lower recurrence 6 months after treatment compared with western medicine. However, there was no significant difference in Hamilton depression rating scale between RKT and western medicine group. Combination therapy brought significant symptom improvement with TCE compared with western medicine alone.
Conclusions: Rikkunshito and combination therapy might be considered an effective alternative treatment for FD. Further rigorously designed and high-quality RCTs are needed.

Introduction

Functional dyspepsia (FD) is a common disease defined by bothersome dyspeptic symptoms such as early satiation, postprandial fullness, epigastric pain, and epigastric burning without structural diseases (including esophagogastroduodenoscopy) that explain the symptoms.[1] Globally, the prevalence of FD varies between 11% and 29.2%, and the direct and indirect costs of FD are substantial because of its chronic and recurrent characteristics.[2,3] Conventional treatments for FD include *Helicobacter pylori* eradication, prokinetics (PK), proton pump inhibitors (PPIs), and antidepressants (AD).[3] The pathophysiology of FD remains unclear and is associated with multiple mechanisms.[4] Thus, a single drug cannot manage all dyspeptic symptoms.[5] Because of

insufficient efficacy of conventional treatments, demand is growing for complementary and alternative treatments, such as herbal medicine.[4]

Rikkunshito (RKT; 六君子湯; Liu Jun Zi Tang in Traditional Chinese Medicine) is an herbal medicine composed of eight constituents: *Atractylodes japonica*, *Panax ginseng*, *Pinellia ternata*, *Poria cocos*, *Zingiber officinale*, *Ziziphus jujuba*, *Citrus unshiu*, and *Glycyrrhiza uralensis*. RKT has been widely prescribed in Asia to treat upper gastrointestinal symptoms, such as FD.[6,7] According to previous studies, RKT improves FD patients' symptoms by facilitating gastric emptying and increasing plasma ghrelin levels.[8]

Several systematic reviews and meta-analyses for the efficacy of RKT were published.[7,9–12] However, some reviews included studies on gastrointestinal symptoms or anorexia induced by drugs, gastritis, or cancer.[9,10] Other reviews did not compare RKT with placebo, or combination therapy (RKT and western medicine) with western medicine alone.[7,11,12] Further, the selection of patients used the Rome criteria (I, II, III, or IV depending on the date of the study) and criteria similar to Rome (requiring that dyspeptic symptoms should last at least 4 weeks).[7,12] As a result, there is still limited evidence supporting a recommendation of RKT for treating FD. Therefore, this review aimed to systematically examine the efficacy and safety of RKT on FD by comparing RKT with placebo or western medicine. This study also evaluated the clinical efficacy and safety of combination therapy (RKT and western medicine) compared with western medicine alone.

Methods

Protocol and registration. The protocol for this systematic review was registered in the International Prospective Register of Systematic Reviews (PROSPERO) with registration number CRD42018090139.[13] This study was performed according to the Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) guidelines.[14]

Inclusion and exclusion criteria

Types of studies. Randomized controlled trials (RCTs) and quasi-RCT were included, and animal studies, case reports, reviews, and commentaries were excluded.

Types of participants. Patients diagnosed with FD according to the Rome criteria (I, II, III, or IV depending on the date of diagnosis), without limitations of age, gender, or race, were included. For studies before 1994 when Rome I was published, patients diagnosed with FD based on criteria compatible with the Rome criteria were included by two reviewers (J. P. and M. K.) consensus.

We excluded dyspepsia induced by drugs or caused by secondary pathologies (e.g. gastroesophageal reflux diseases, ulcer, and irritable bowel syndrome).

Types of interventions. This systematic review includes RKT, modified RKT, and combination therapy (RKT and western medicine). Modified RKT is a RKT decoction with additional medicinal herbs, such as Xiangsha Rikkunshito (XSRKT; 香砂六君子湯; RKT added to *Cyperus rotundus*, *Amomum villosum*, and *Costus root*), Chaishao Rikkunshito (CSRKT; 柴芍六君子湯; RKT added to *Bupleurum falcatum* and *Paeonia japonica*), Guishao Rikkunshito (GSRKT; 歸芍六君子湯; RKT added to *Angelica gigas* and *P. japonica*) and Jiawei Rikkunshito (JWRKT; 加味六君子湯, RKT added to other herbs excluding XSRKT, CSRKT, and GSRKT). The intervention involving a combination of RKT and other alternative treatments such as moxibustion, acupuncture, or thread embedding acupuncture were excluded. Comparisons included in this review are as follows:

1. Rikkunshito, modified RKT group *versus* the placebo group (similar color, taste, and odor to RKT), no treatment group, and conventional western medicine group such as PK, PPI, and AD.
2. Combination therapy (RKT and western medicine) group *versus* western medicine alone group.

Types of outcome measures. The primary outcome measure was the total clinical efficacy rate (TCE). The secondary outcomes were total dyspepsia symptom scale (TDS), gastric emptying rate (GE), gastrin, motilin, recurrence 6 months after treatment (R6MAT), Hamilton depression rating scale (HAMD), and adverse events.

Search strategy. A search of the literature was conducted using the following sources on April 03, 2019: Medline (via PubMed), EMBASE, the Cochrane Central Register of Controlled Trials, and Allied and Complementary Medicine Database. We also searched Korean Medical Databases such as KoreaMed, National Digital Science Library, Korean medical Database, Oriental Medicine Advanced Searching Integrated System, and Korean Studies Information Service System. Other Asian databases, including the China National Knowledge Infrastructure Database in Chinese and Citation Information by Nii in Japanese, were also searched.

The search terms consisted of combining disease terms (e.g. intestine, digest, dyspepsia, disturbance, and dysfunction) and intervention terms (e.g. Yukgunja in Korean, Liu Jun Zi in Chinese, and Rikkunshito in Japanese). The search strategy of Medline (via PubMed) is described in Table 1. Modified search strategies were used in other databases. No language or publication date restrictions were applied.

Selection and data extraction. Two review authors (J. P. and M. K.) independently screened the titles, abstracts, and full text of the studies to assess their eligibility for inclusion. Endnote X9 (Clarivate Analytics, Philadelphia, PA, USA) was used for managing the electronic and manual searches for the studies. Data extraction was independently conducted also by two reviewers (J. P. and M. K.) for accuracy. All discrepancies during the selection and extraction were resolved by discussion and consensus between the same two reviewers (J. P. and M. K.). If the discrepancies were not resolved, an arbiter (S. K.) intervened and resolved the disagreement. Extracted data include study information such as the first author, year of publication, written language,

Table 1 Search strategy of PubMed

No.	
#1	indigestion*
#2	Intestin* OR Digest* OR Gastr* OR gut OR epigastr* OR stomach*
#3	#1 AND #2
#4	dyspepsia*
#5	epigastric [tiab] AND pain [tiab]
#6	epigastric [tiab] AND burn* [tiab]
#7	Rome* AND criteria*
#8	(disturbance* OR disorder* OR difficult* OR dysfunction* OR disease* OR impair* OR condition* OR abnormal* OR illness* OR patholog* OR discomfort* OR hazard* OR damage* OR injur* OR irritab* OR pain* OR distress* OR burning) AND postprandial*
#9	#3 OR #4 OR #5 OR #6 OR #7 OR #8
#10	Herbal medicine [MeSH Terms]
#11	Plants, medicinal [MeSH Terms]
#12	Medicine, traditional [MeSH Terms]
#13	Drugs, Chinese herbal [MeSH Terms]
#14	Herb* [tiab]
#15	Plant [tiab] OR plants [tiab]
#16	Phytomedicine [tiab]
#17	Botanical [tiab]
#18	Weed* [tiab]
#19	Algae [tiab]
#20	Fungi [tiab] OR fungus [tiab]
#21	(Traditional [tiab] OR Chinese [tiab] OR herbal [tiab]) AND medicine [tiab]
#22	(Oriental [tiab] OR Chinese [tiab]) AND tradition* [tiab]
#23	#10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22
#24	Yukgunja* OR Liujunzi* OR Rikkunshito* OR Rikkunshi-to*
#25	Randomized controlled trial [pt]
#26	Controlled clinical trial [pt]
#27	Randomized [tiab]
#28	Randomly [tiab]
#29	Trial [ti]
#30	#25 OR #26 OR #27 OR #28 OR #29
#31	#9 AND #23 AND #24 AND #30

study design, interventions, duration of treatment, outcome measures, and main results.

Quality assessment. Two reviewers (J. P. and M. K.) independently assessed the risk of bias using the Cochrane Collaboration's Tool. The following were evaluated: (i) random sequence generation (selection bias); (ii) allocation concealment (selection bias); (iii) blinding of participants and personnel (performance bias); (iv) blinding of outcome assessment (detection bias); (v) incomplete outcome data (attrition bias); (vi) selective reporting (reporting bias); (vii) other bias. All research result was evaluated by three categories such as low, unclear, and high. A consensus was reached (for any dispute) by a discussion between two evaluators (J. P. and M. K.), and if necessary, an arbiter (S. K.) was consulted.

Data analysis and synthesis. Data analyses were performed by the Review Manager program (V.5.3 Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014). Continuous data were assessed as the mean difference (MD) with a 95% confidence interval (CI), while dichotomous data were evaluated as relative risk (RR) with a 95% CI. A random-effects model was applied for meta-analysis. The heterogeneity of selected studies was evaluated by evaluating the χ^2, and *I*-squared (I^2) statistics. $P < 0.1$ indicated statistical significance, and $I^2 \geq 50\%$ represented substantial heterogeneity. Subgroup analyses were conducted to remedy heterogeneity. The subgroups were analyzed by classifying the species of added herbs and the type of western medicine. We performed funnel plots to assess the presence of publication bias and small-study effects.

Results

Selection of study. The primary search identified a total of 436 studies. After 33 duplicates were removed, 280 of the remaining studies were discarded after screening the titles and abstracts. Of these, 14 articles were not available, and the full texts of 50 were excluded because they did not meet the inclusion criteria. Finally, 59 articles were included, and 52 studies were selected for meta-analysis as shown in Figure 1.

Characteristics of included studies. The 59 included articles were published between 2005 and 2018, and all RCTs were parallel design studies. Six studies were written in English, and 53 in Chinese. One trial was conducted in Korea, 3 in Japan, and 55 in China. RKT in 44 studies[15–58] was compared with western medicine. RKT was compared with a placebo in five of the studies, and combination therapy (RKT and western medicine) was compared with western medicine only, in 10 studies. The number of patients in each study included in the meta-analysis varied from 27 to 418, and there was a total of 5475.

Risk of bias assessment

Random sequence generation. The 26 studies that used a random number table or a computer random number generator were assessed as a low risk of bias. Four studies generated numbers at the time of the patient's visit or used the patient registration number, and those studies were evaluated as a high risk of bias. The 29 studies that did not refer to methods of random sequence generation were rated as unclear risk of bias.

Allocation concealment. Six trials concealed allocation by using a center-controlled method or opaque envelope, while the other 53 trials did not mention allocation concealment.

Blinding of participants and personnel. Five RCT comparing RKT with placebo used blinding of participants and study personnel and were assessed as a low risk of bias. On the other hand, 54 RCTs did not report whether blinding was used, and these studies were appraised as a high risk of bias.

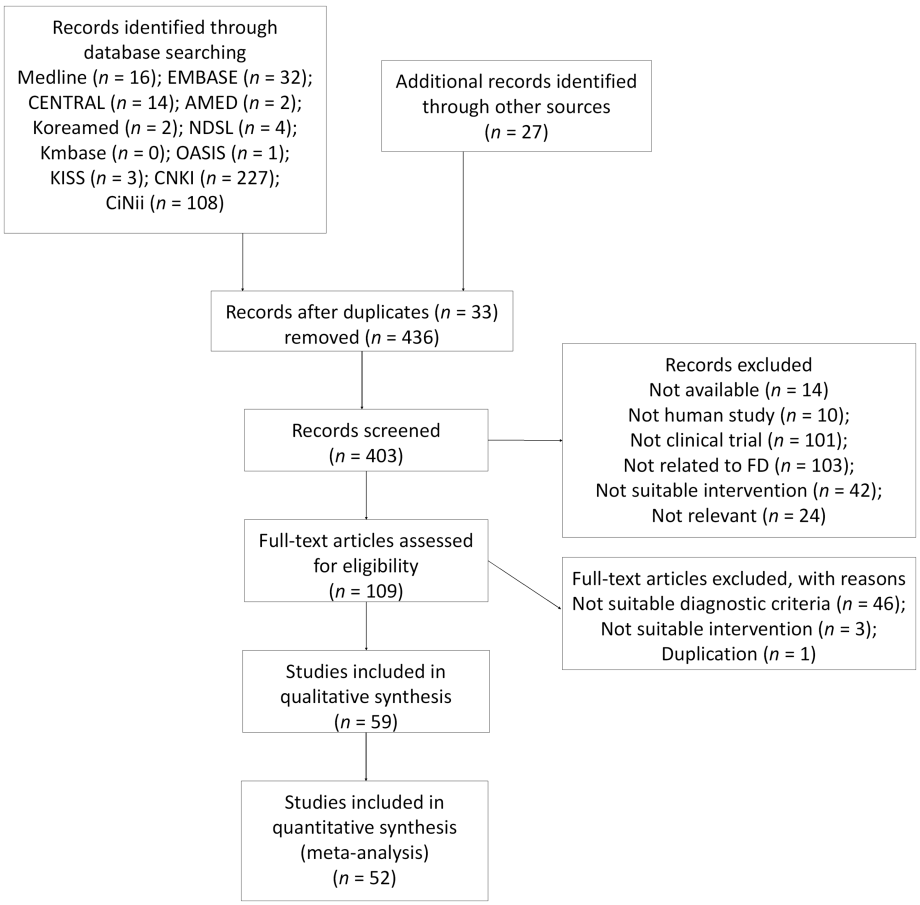

FIGURE 1 Preferred reporting items for systematic reviews and meta-analyses chart of the selection process. CNKI, China National Knowledge Infrastructure Database; CiNii, Citation Information by National Institute of Informatics; AMED, Allied and Complementary Medicine Database; KISS, Korean Studies Information Service System; NDSL, National Digital Science Library; OASIS, Oriental Medicine Advanced Searching Integrated System.

Blinding of outcome assessment. Three studies mentioned blinding the statistical analyses, while 56 studies did not mention blinding the statistical assessment.

Incomplete outcome data. The number of missing patients was few and not different between the intervention and control groups in seven studies. Five studies conducted intention-to-treat analysis, and the other 47 studies had no missing participants. Thus, all studies were judged as a low risk of bias.

Selective reporting. Seven articles that reported results incompletely or did not report pre-specified outcomes were appraised as a high risk of bias. In 52 articles, the outcomes described in the

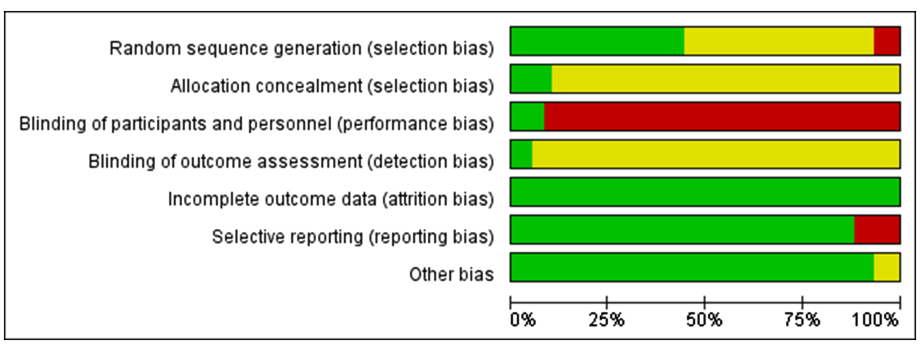

FIGURE 2 Risk of bias assessment graph. , Low risk of bias; , Unclear risk of bias; , High risk of bias. [Color figure can be viewed at wileyonlinelibrary.com]

methods were all reported in the results. These studies were evaluated as a low risk of bias.

Other bias. Four studies did not mention the baseline balance of patients and were assessed as unclear risk of bias. The other 54 studies reported that the baseline of patients was balanced among groups and thus, were judged as low risk of bias.

Overall risk of bias. A summary of the risk of bias is described in Figure 2.

Primary outcome: Total clinical efficacy rate

Rikkunshito versus western medicine. This review investigated the efficacy of RKT on FD using TCE defined as the

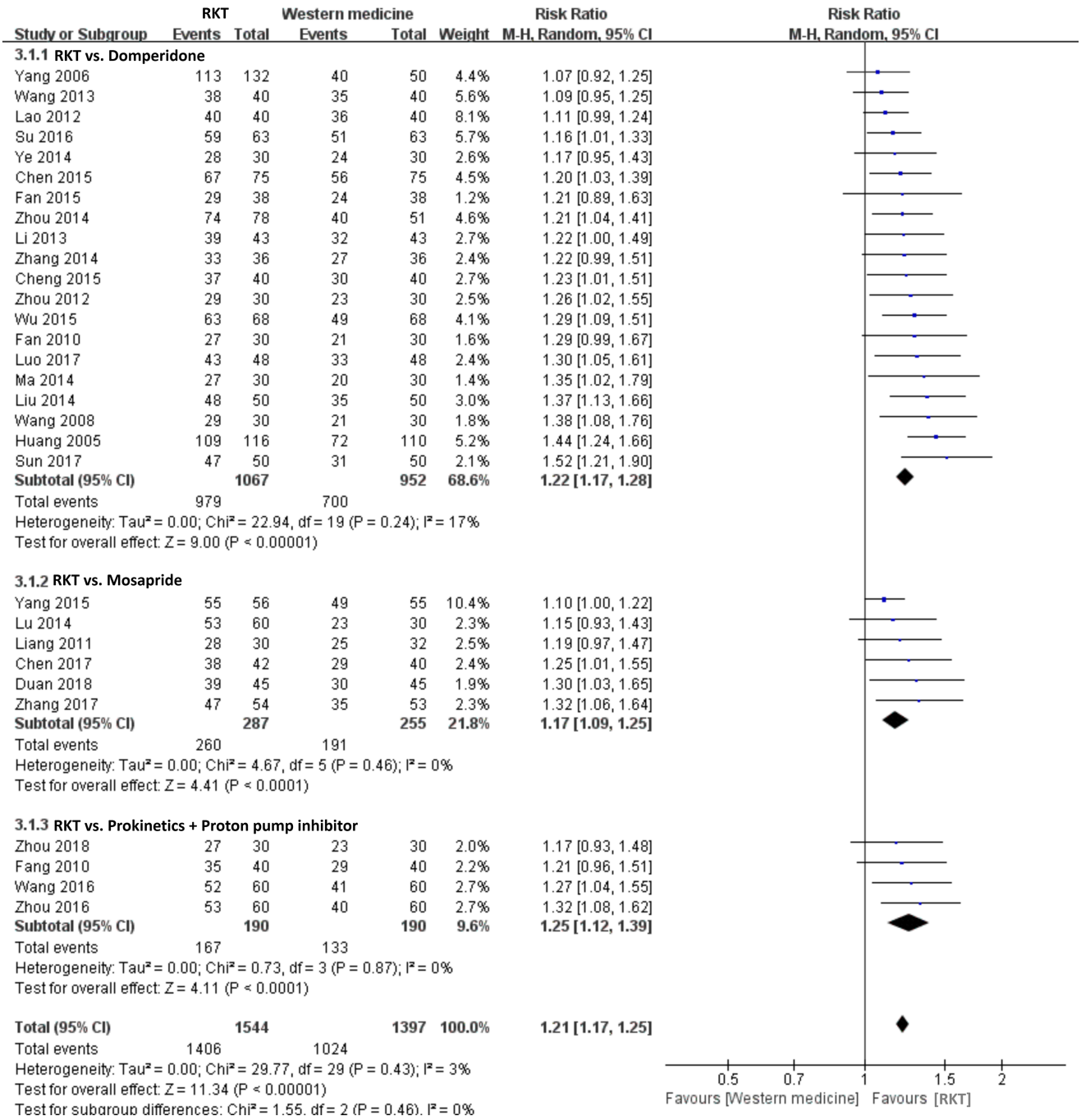

FIGURE 3 Forest plot of TCE between RKT and western medicine group. TCE, Total clinical efficacy rate; RKT, Rikkunshito. [Color figure can be viewed at wileyonlinelibrary.com]

percentage of patients with valid responses to the interventions. Additionally, we analyzed the effectiveness of combination therapy (RKT and western medicine) on FD.

Western medicine groups were subdivided into a domperidone group, mosapride group, and combinations of PK and PPI groups. RKT had better effects than domperidone (RR = 1.22, 95% CI 1.17 to 1.28, $P < 0.001$), mosapride (RR = 1.17, 95% CI 1.09 to 1.25, $P < 0.001$) and combinations of PK and PPI (RR = 1.25, 95% CI 1.12 to 1.39, $P < 0.001$). Heterogeneities were not significant in the domperidone ($P = 0.24$, $I^2 = 17\%$), mosapride ($P = 0.46$, $I^2 = 0\%$), and combinations of PK and PPI ($P = 0.87$, $I^2 = 0\%$) groups.

In the combined analysis of the three groups, 30 RCTs with a total of 2941 patients showed a significant improvement of symptoms in RKT *versus* the western medicine group (RR = 1.21, 95% CI 1.17 to 1.25, $P < 0.001$) and heterogeneity was low ($P = 0.43$, $I^2 = 3\%$) (Fig. 3).

Combination therapy (Rikkunshito and western medicine) versus western medicine alone. A total of 1246 patients in 10 studies were analyzed. Combination therapy (RKT and western medicine) brought significant symptom improvement compared with western medicine alone (RR = 1.19, 95% CI 1.14 to 1.24, $P < 0.001$), with low heterogeneity ($P = 0.94$, $I^2 = 0\%$) (Fig. 4).

Secondary outcomes

Total dyspepsia symptom scale. Two RCTs that compared RKT with placebo used TDS. RKT significantly relieved dyspeptic symptoms compared with placebo (MD = −1.68, 95% CI −2.32 to −1.03, $P < 0.001$), and no evidence of heterogeneity was found ($P = 0.38$, $I^2 = 0\%$).

Gastric emptying rate. Gastric emptying rate was used to assess gastrointestinal motility in four RCTs. Wang[17] did not mention a method of measurement, and Wang[46] measured GE by Doppler while Guo,[38] and Liang[40] used a radiopaque barium marker test. Only two RCTs comparing RKT to mosapride were meta-analyzed because of the inconsistency of the measurement methods. A total of 122 patients were found to have a significant increase of gastric motility in RKT compared with the western medicine group (mosapride) (MD = 16.51, 95% CI 7.36 to 25.67, $P < 0.001$).

Motilin. Among six studies that investigated the efficacy of RKT through motilin, Zhou[45] was excluded in the meta-analysis because the study only reported data from the experimental group. Five studies with 410 participants showed that RKT significantly increased the level of motilin compared with western medicine such as domperidone,[17] mosapride,[38] combinations of PK and PPI,[44,46] and a combination of domperidone and itopride hydrochloride[52] (MD = 27.57, 95% CI 20.08 to 35.06, $P < 0.001$).

Gastrin. Except for Zhou,[45] which reported only gastrin of the RKT group, the analysis of 356 patients in four RCTs showed that RKT promoted significantly more secretion of gastrin than western medicine (MD = 23.28, 95% CI 19.30 to 27.26, $P < 0.001$). The western medicine groups included domperidone,[17] mosapride,[38] a combination of mosapride, pantoprazole and tandospirone citrate,[49] and a combination of domperidone and itopride hydrochloride.[52]

Recurrence 6 months after treatment. Five studies followed up with patients 6 months later to confirm recurrence rates, and R6MAT was compared between the RKT and domperidone group. Of 398 participants, the R6MAT was significantly lower in the RKT than the domperidone group (RR = 0.52, 95% CI 0.35 to 0.76, $P < 0.001$). There was evidence of low heterogeneity ($P = 0.59$, $I^2 = 0\%$).

Hamilton depression rating scale. Three studies evaluated psychological symptoms using HAMD. The groups were domperidone,[17] a combination of mosapride, pantoprazole, and tandospirone citrate,[49] and a combination of domperidone and deanxit.[50] These three studies included a total of 244 patients, and there were no significant differences between the RKT and western medicine groups (MD = −4.55, 95% CI −9.13 to 0.03, $P = 0.05$). Heterogeneity was high ($P < 0.001$, $I^2 = 95\%$). In the combined analysis of two studies, which used AD as a combination therapy with western digestive medicine, two RCTs with a

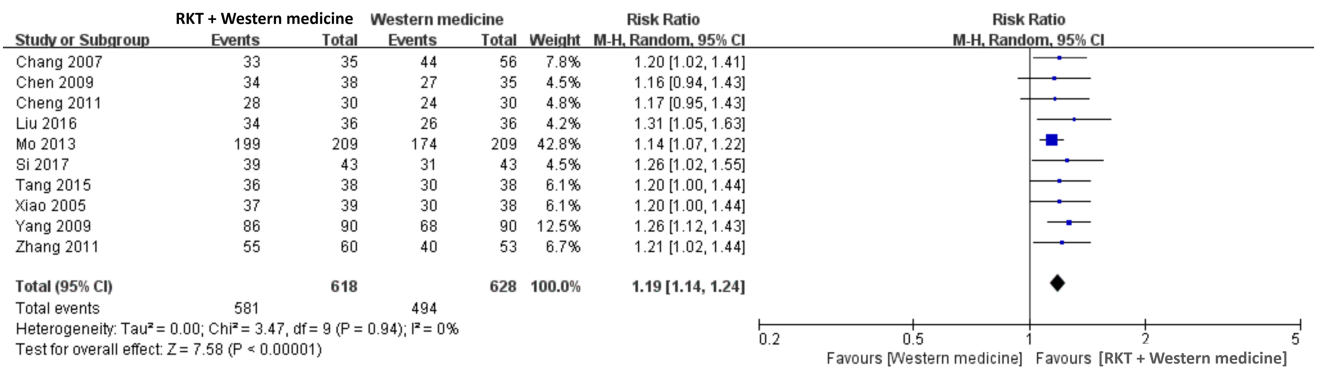

FIGURE 4 Forest plot of TCE between combination therapy (RKT and western medicine) and western medicine alone group. TCE, Total clinical efficacy rate; RKT, Rikkunshito. [Color figure can be viewed at wileyonlinelibrary.com]

total of 164 patients showed a significant improvement of symptoms in RKT *versus* the western medicine group (MD = −6.36, 95% CI −9.94 to −2.79, $P < 0.001$) and heterogeneity was high ($P = 0.07$, $I^2 = 69\%$).

Subgroup analysis. In the meta-analysis of this review, XSRKT, CSRKT, GSRKT, and JWRKT were integrated into the RKT group. A western medicine control group was also composed of PK (e.g. domperidone, mosapride, and cisapride), PPI (e.g. lansoprazole and omeprazole), and AD (e.g. tandospirone citrate and deanxit). Both experimental and control groups might have had a possibility of heterogeneity. Thus, subgroup analyses were conducted to minimize heterogeneity.

XSRKT versus domperidone. A total of 1199 patients in 13 RCTs were included in the meta-analysis. TCE was significantly more ameliorated in the XSRKT than domperidone group (RR = 1.23, 95% CI 1.16 to 1.30, $P < 0.001$) (Fig. 5).

Combination therapy (Xiangsha Rikkunshito and domperidone) versus domperidone alone. Five trials with a total of 511 patients showed that combination therapy (XSRKT and domperidone) improved TCE significantly more than domperidone alone (RR = 1.24, 95% CI 1.15 to 1.34, $P < 0.001$) (Fig. 5).

Adverse events. Among 59 RCT, 33 RCT did not mention the occurrence of an adverse event. Of 26 RCT, 12 trials reported no adverse events, 9 trials reported only the number of occurrences, and 5 studies reported mild adverse events. Liu[21] reported nausea and abdominal discomfort ($n = 1$) in the CSRKT group and mouth dryness ($n = 2$) in the domperidone group. Xu[55] reported diarrhea ($n = 2$) in the XSRKT group, and rash ($n = 1$) in the compound digestive enzyme capsule group. Su[18] reported nausea ($n = 3$), diarrhea ($n = 1$), and dizziness ($n = 1$) in the domperidone group. Ma[30] reported diarrhea ($n = 3$) and nausea ($n = 2$) in the domperidone group. Liu[59] reported mouth dryness (n = 1) and hypnolepsy ($n = 1$) in the domperidone group. A total of 26 studies were meta-analyzed, and the number of adverse events was not significantly different between the experimental groups and control groups (RR = 0.69, 95% CI 0.37 to 1.29, $P = 0.25$).

Publication bias. Funnel plots identified publication bias. Figure 6 shows a funnel plot of TCE comparing RKT with western medicine. Because the funnel plot appears symmetrically distributed by visual inspection, there is no evidence of publication bias.

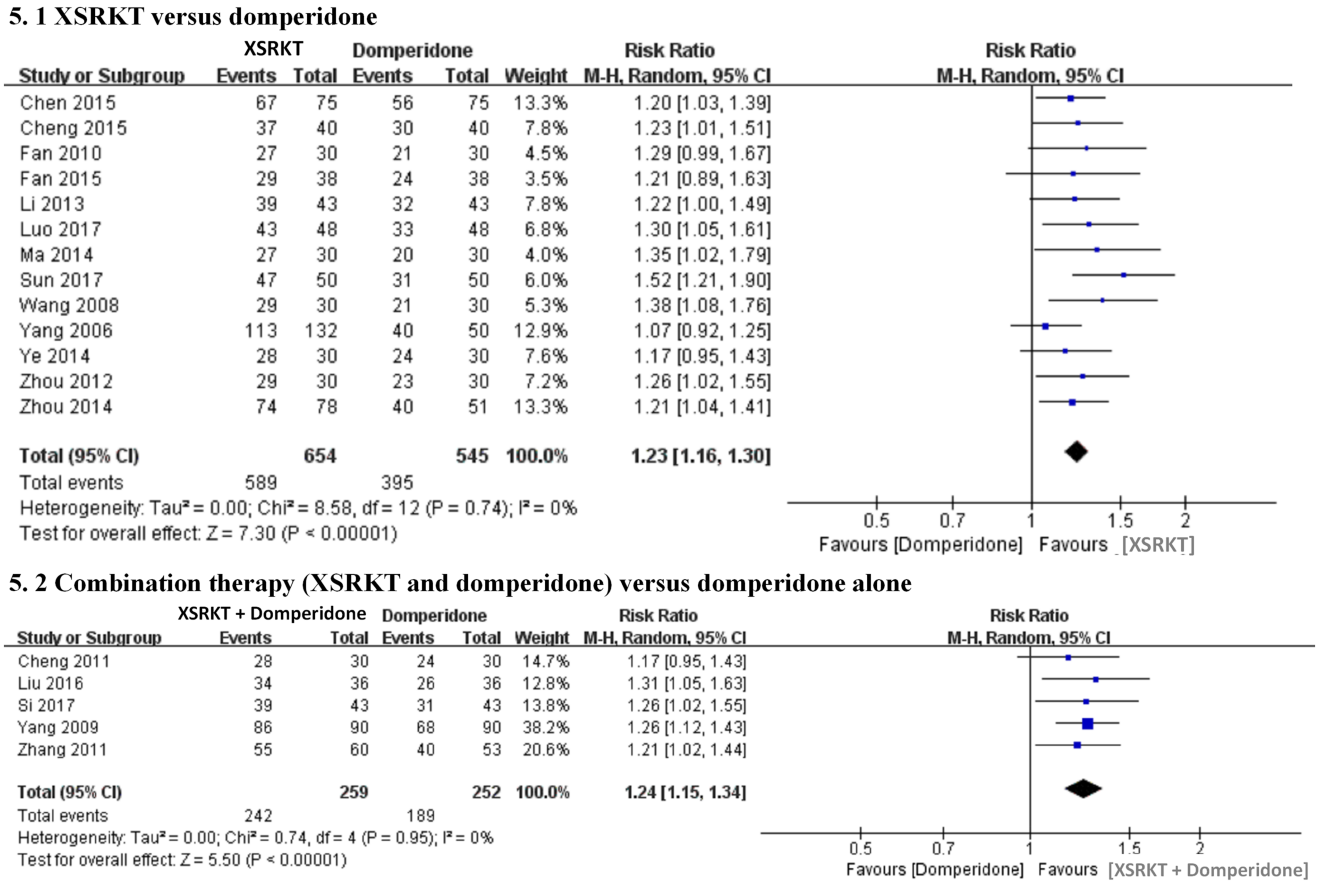

FIGURE 5 Forest plot of TCE between XSRKT and domperidone, and TCE between combination therapy (XSRKT and domperidone) and domperidone alone group. XSRKT, Xiangsha Rikkunshito; TCE, Total clinical efficacy rate. [Color figure can be viewed at wileyonlinelibrary.com]

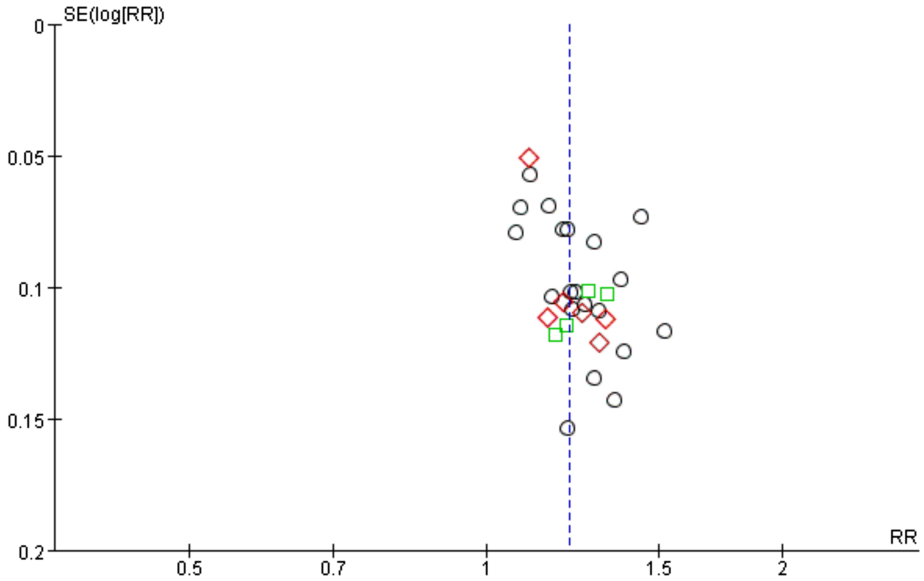

FIGURE 6 Funnel plot of TCE between RKT and western medicine group. TCE, Total clinical efficacy rate; RKT, Rikkunshito. ○, RKT *vs* Domperidone; ◇, RKT *vs* Mosapride; □, RKT *vs* Prokinetics + Proton pump inhibitor. [Color figure can be viewed at wileyonlinelibrary.com]

Discussion

The purpose of this review was to investigate the efficacy and safety of RKT and combination therapy (RKT and western medicine) on FD. The results of TCE as a primary outcome show the superior effects of RKT and combination therapy (RKT and western medicine) to western medicine alone. The results of GE, gastrin, motilin, and R6MAT show that RKT is more effective than western medicine alone. RKT had more clinical benefits based on TDS than the placebo group. The subgroup analyses of XSRKT and combination therapy (XSRKT and domperidone) show superior effects, based on TCE, to the domperidone alone group. The result of HAMD was not different between RKT and the western medicine group. When RKT was compared with western medicine with AD, RKT showed superior effect over western medicine. None of the included studies reported severe adverse reactions, and there was no significant difference in the number of adverse events between the groups.

Several studies have reported the beneficial effects of RKT. Previous reviews suggested that the efficacy of RKT and XSRKT might be superior to PK on FD without adverse events,[7] and XSRKT was more effective than western medicine for treating FD.[11,12] Another review indicated that RKT had ameliorative effects on adverse reactions induced by western medications and could have a synergy with western medicine in FD patients.[10] Moreover, evidence-based clinical practice guidelines for FD in Japan recommend some herbal medicines, including RKT as a second-line treatment (evidence Level A).[60] According to previous studies, RKT has been considered a prospective treatment for FD. The evidence of RKT as a treatment for FD and the underlying mechanism is continually being updated.

Gastric dysmotility is thought to be the cause of FD symptoms, and there is a report that gastric emptying was delayed in FD patients.[61,62] This review showed RKT ameliorated gastric emptying rate measured by radiopaque barium marker test. Also, RKT promoted the secretion of gastrin and motilin which stimulate motility of the gastrointestinal tract more than the western medicine group.[63] Those results suggest that RKT might affect FD via gastrointestinal motility. Measurements of gastric emptying among previous studies include radiopaque markers, scintigraphy, breath tests, and wireless motility capsules. The radiopaque barium marker test has been one of the standard methods to evaluation gastric motility, but when determining extremely delayed gastric motility, it might show poor sensitivity.[64,65] Further studies using other sensitive measurements are needed for association of RKT and gastric motility.

The HAMD scale is widely used for measuring the severity of depression.[66] According to a recent meta-analysis, which investigated a total of 59 029 patients, FD had a positive relationship with depression.[67] Studies using HAMD scale reported that RKT and XSRKT improved both gastrointestinal and psychological symptoms in FD patients compared with placebo.[68,69] Other studies showed synergetic effect of RKT and AD to FD patients with depression and anxiety.[70,71] Our studies showed RKT was not inferior to western medicine in FD patients with depression, and when studies were confined to FD patients using AD, RKT was reported even better effect on psychological symptoms compared to western medicine. However, further research is needed to confirm the correlation between RKT and the psychological symptoms in FD patients because of high heterogeneity and small sample size of the included studies.

There are strengths of this review. First, this study updated the results of the latest RCT on FD patients, diagnosed with Rome criteria. Some previous reviews were focused on gastrointestinal symptoms,[9,10] and other reviews included patients diagnosed based on criteria similar to the Rome criteria.[7,12] Second, to our knowledge, this is the first meta-analysis to confirm the efficacy of combination therapy (RKT and western medicine) for FD patients. In the previous review showing the synergistic efficacy of the combination therapy (RKT and western medicine), significant

effects were limited to gastrointestinal symptoms[10]; this review included the effects of combination therapy (RKT and western medicine) on FD. Also, there are no meta-analyses that compare combination therapy (RKT and western medicine) with western medicine only for FD patients. In this review, we found that combination therapy (RKT and western medicine) has an ameliorative effect on FD *versus* western medicine alone. Third, subgroup analyses revealed that XSRKT and combination therapy (XSRKT and domperidone) were more effective than domperidone alone. This review categorized western medicine as domperidone, mosapride, and combinations of PK and PPI, and subdivided RKT into XSRKT, GSRKT, CSRKT, and JWRKT to reducing heterogeneity. Of these, we compared XSRKT or combination therapy (HYSGT and domperidone) with domperidone alone. Fourth, this systematic review is useful for developing clinical guidelines for FD. The clinical guidelines for FD in the United States and Canada suggest *H. pylori* eradication as a first treatment. If patients are *H. pylori* negative or unresponsive to eradication, PPI, TCA, and PK are recommended as a secondary treatment.[72] Korean clinical guidelines for FD recommend PK or PPI or combinations of PK and PPI as an initial strategy for FD rather than *H. pylori* eradication. Notably, PK is selected as a first treatment, while TCA is used as a secondary treatment in Korea.[73] In this review, the comparison groups were mostly PK, and RKT was more effective than western medicine such as PK (e.g. domperidone and mosapride) and combinations of PK and PPI. Finally, we could infer the non-inferior phycological effect of RKT on FD with depression compared with western medicine. If RKT was compared with AD, it might have better effect in FD patients.

This systematic review has several limitations. First, the overall methodological quality of the included studies was low because of selection bias, performance bias, and detection bias. Most of the studies did not report allocation concealment and blinding assessment. Especially, only 5 of 59 RCT were double-blinded, which leads to poor methodological quality. Second, there might be clinical heterogeneity in the intervention and experimental groups. Modified RKT varies by the species and number of herbs that are added, and several types of western medicine were included in the meta-analysis. Third, the included studies were all from Asia, and majority of them were from China. Finally, pattern identification might influence the effects of RKT. In traditional Chinese medicine, FD is differentiated into various patterns on a basis of clinical signs and symptoms. Most of FD patterns are considered as "Spleen-deficiency and Qi-stagnation."[74] Because RKT has been regarded as a herbal formula for invigorating the spleen and regulating Qi,[75] it may have no effect on FD pattern differentiation other than "Spleen-deficiency and Qi-stagnation." Therefore, further well-designed, randomized, double-blinded RCTs are required.

Conclusions

RKT and combination therapy (RKT and western medicine) might be considered an effective and safe alternative treatment of FD. However, the evidence remains uncertain because the overall quality of the included studies was low. Further rigorously designed high-quality RCTs are needed for more convincing evidence.

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