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Therapeutic efficacy and safety of Kangfuxin in combination with rabeprazole in the treatment of peptic ulcer

A systematic review and meta-analysis

Meisi Lin, MD[a,b], Siyuan Zhang, BD[a,c], Minyue Zhang, PhD[d], Jinfeng Shi, BD[a], Chen Zhang, PhD[a], Ruifeng Luo, BD[a], Jieshu You, PhD[e], Jiayi Sun, MD[f], Jinming Zhang, PhD[a], Fei Gao, PhD[a,*] iD

Abstract

Background: Kangfuxin (KFX), a well-known Chinese patent medicine which extracted from *Periplaneta americana*, is widely used as an adjuvant in the treatment of peptic ulcers (PUs) with proton pump inhibitors (PPIs) such as rabeprazole, in China. However, no clear consensus has been reached on the efficacy for PU treatment.

Methods: We searched in 7 electronic databases to find randomized controlled trials (RCTs) completed before May 31, 2020 to explore the clinical efficiency of KFX plus rabeprazole in the treatment of PU. Risk ratio (RR) corresponding to 95% confidence interval (CI) was calculated to estimate the outcomes. Publication bias was assessed by both Egger's and Begg's tests. Statistical analyses were performed using RevMan 5.4 and Stata version 10.0.

Results: Twenty-five RCTs, comprising 2555 PU patients, were included in this study. Meta-analysis showed that, when compared with rabeprazole-based treatment alone, KFX plus rabeprazole significantly improved the healing rate (RR = 1.34, 95% CI 1.25–1.44) and overall response rate of ulcers (RR = 1.16, 95% CI 1.13–1.20), alleviated the clinical symptoms of PU (RR = 1.14, 95% CI 1.08–1.21), and reduced the recurrence of PU (RR = 0.38, 95% CI 0.24–0.61) without an increase in the occurrence of adverse events (RR = 0.92, 95% CI 0.66–1.28).

Conclusion: Our study suggests that KFX combined with rabeprazole showed positive therapeutic effects and is safe for treating PU, which may provide more reliable evidence for the clinical use of KFX in the treatment of PU.

Abbreviations: CBM = Chinese Biomedical Database, CFDA = China Food and Drug Administration, CI = confidence interval, CNKI = China National Knowledge Infrastructure, DU = duodenal ulcer, GAP = Good Agricultural Practice, GU = gastric ulcer, *H pylori* = *Helicobacter pylori*, KFX = Kangfuxin, NSAIDs = non-steroidal anti-inflammatory drugs, PA = *Periplaneta americana*, PPIs = proton pump inhibitors, PU = peptic ulcers, RCTs = randomized controlled trials, RR = risk ratios, TCM = traditional Chinese medicine, VMIS = VIP Medicine Information System.

Keywords: peptic ulcer, Kangfuxin, rabeprazole, meta-analysis, combination, Periplaneta Americana

1. Introduction

Peptic ulcer (PU), which usually occurs in the stomach (gastric ulcer [GU])or proximal duodenum (duodenal ulcer [DU]), is one of the most common gastrointestinal diseases worldwide. The lifetime prevalence of PU in the general population is estimated to be 5% to 10%.[1] The infection of *Helicobacter pylori* (*H pylori*) and long-term use of non-steroidal anti-inflammatory drugs (NSAIDs) are regarded as the main risk factors for developing PU.[1] In the past 30 years, the incidence of PU has been rapidly declined due to *H pylori* eradication therapy using proton pump inhibitors (PPIs) and antibiotics.[1,2] PPIs can protect the gastric mucosal barrier by suppressing the secretion of gastric acid. However, in the clinic, the side-effects caused by long-term use of PPIs, including an increased risk of both acute and chronic kidney disease, *C difficile* infection, osteoporotic fractures, as well as other effects, have caused increasing concern among clinicians and patients.[3,4] In addition, some patients, such as those with a history of NSAID-related GU bleeding, have a high risk of recurrence of PU.[5] Therefore, determining how to increase the healing rate, as well as decrease the recurrence of ulcers and PPIs-related side-effects, has become a main concern for clinicians.

Emerging evidence has shown that the integration of traditional Chinese medicine (TCM) and Western Medicine appears to be a favorable option for the treatment of PU.[6–9] Based on the theory of TCM, PU is caused by qi stagnation in the stomach and malnutrition of the arteries and/or veins.[10] Kangfuxin (KFX) is an extract obtained from *Periplaneta americana* (PA) and is a Chinese patent medicine approved by the China Food and Drug Administration (CFDA, Approval #Z51021834).[11] Over \$150 million of KFX are sold every year and it is ranked first among the Chinese herb/animal extract products used for gastrointestinal disease treatment in China. PA, also known as the American Cockroach, was recorded in the ancient medical book Sheng Nong's Herbal Classic over 2000 years ago and has been used as the traditional Chinese herb for the treatment of gastrointestinal disease for many years.[12] PA breeding is performed under the guidelines of Good Agricultural Practice (GAP) approved by China, which guarantees the production of high quality KFX. It has been reported that KFX can promote blood circulation, nourish yin and promote granulation.[13] Moreover, pharmacological studies have demonstrated the gastroprotective effects of KFX through its ability to attenuate oxidative and ER stress, reduce gastric acid secretion, and promote anti-inflammatory and immunomodulatory effects.[14–16] Hence, KFX has been widely applied in the treatment of PU and has shown promising therapeutic efficacy.[17,18]

Recently, a number of studies have reported the clinical efficacy of KFX combined with the PPI rabeprazole in the treatment of PU.[19–22] However, these results were obtained in randomized controlled trials (RCTs) with small sample sizes and little statistical scale. In addition, two relevant meta-analysis have been published.[17,18] One reported KFX in combination with all kinds of PPIs, not specifically rabeprazole in the treatment of PU.[18] Another study evaluated the efficacy of KFX in combination with pantoprazole for treating PU.[17] Nevertheless, the current state of evidence of rabeprazole for PU treatment remains inadequately explained. Therefore, through the use of meta-analysis, we sought to systematically evaluate the clinical efficacy and safety of KFX in combination with rabeprazole for the treatment of PU, which can provide more reliable evidence for the clinical application of KFX.

2. Materials and methods

2.1. Literature research

A literature search of seven electronic databases, including PubMed, Cochrane Library, Embase, the Chinese Biomedical Database (CBM), the China National Knowledge Infrastructure (CNKI), the VIP medicine information system (VMIS), and Wanfang, was performed to identify all studies completed before May 31, 2020 investigating the efficacy of KFX combined with rabeprazole in the treatment of PU. The publication language was limited to Chinese or English. The following search terms were used: ("rabeprazole") AND ("Kangfuxin") AND ("Peptic Ulcer" or "Gastroduodenal Ulcer" or "Stomach Ulcer" or "Gastric Ulcer" or "Duodenal Ulcer" or "Curling Ulcer"). The references of retrieved studies, meeting abstracts and meta-analyses were also screened. In case that a report overlapped with a more detailed publication, only the latter was included.

2.2. Study selection

The studies included in the meta-analysis all satisfied the following criteria:

1. The studies were RCTs exploring the effectiveness of KFX in the treatment of PU;
2. the study population consisted of patients diagnosed with PU, including GU and DU. The diagnosis of PU was based on clinical symptoms and upper endoscopy results. The sample size in each arm was ≥25;
3. The patients in experimental group received KFX (30 mL/day) plus rabeprazole-based treatment while the patients in control group received only rabeprazole-based treatment;
4. The therapeutic course lasted over 2 week;
5. The outcomes of included studies included one of the following outcomes: healing rate of the ulcer, overall response rate, alleviation of PU-related clinical symptoms, ulcer recurrence rate and overall occurrence of adverse events.

Exclusion criteria were:

1. patients with complications, such as gastrorrhagia, gastric perforation, dysfunction of liver, kidney, etc;
2. patients taking salicylic acid and other drugs that could affect the stomach during the treatment period.

When the relevant data was not available in paper, we contacted the corresponding author via email to obtain more information. The process of study selection was based on The PRISMA Statement.[23] The result and diagram of study selection was shown in Figure 1.

2.3. Data extraction

Two reviewers (Zhang SY and Lin MS) independently extracted data and assessed the methodological quality of the studies included. The following information from each study was summarized:

1. first author,
2. year of publication,
3. diagnosis,
4. number of cases,
5. treatment regimes,
6. therapeutic courses and
7. outcomes measured.
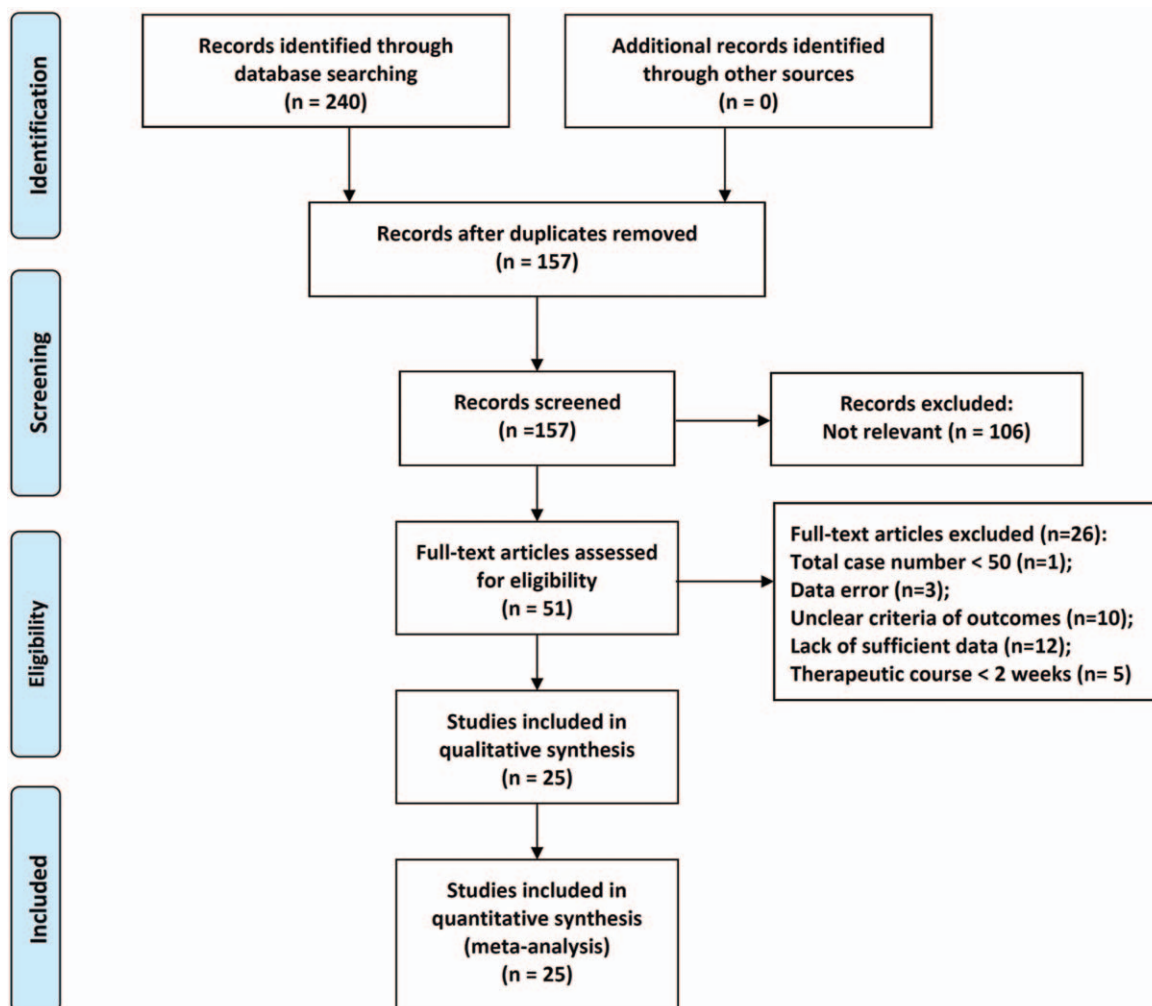
Figure 1. Literature search and selection.

2.4. Outcome measures

The primary outcome was healing rate of ulcer. The secondary outcome measured overall response rate of ulcer, alleviation of PU-related clinical symptoms, recurrence rate of ulcer, and overall incidence of adverse events. Healing of ulcer was defined that the inflammation around the ulcer disappeared and the scar was formed under endoscopy. Overall response of ulcer was defined that ulcer area reduced more than 50% under endoscopy after treatment compared with pretreatment. PU-related clinical symptoms included changes in appetite, nausea, bloody or dark stools, indigestion, vomiting, etc. Adverse events included itchy skin, diarrhea, nausea, constipation, dizziness, etc.

2.5. Risk of bias

The methodological quality of included studies was evaluated using the Revised Cochrane risk-of-bias tool for randomized trials (RoB 2),[24] which consisted of the following five domains: bias arising from the randomization process; bias due to deviations from intended interventions; bias due to missing outcome data; bias in measurement of the outcome; bias in selection of the reported result. Each domain was assessed using three levels: "low," "high," and "some concern." Any discrep-

ancies in opinion between the two reviewers were resolved by a third reviewer, Shi JF.

2.6. Statistical analysis

The methods for meta-analysis and publication biases tests have been described in our previous publications.[25–27] Briefly, risk ratios (RR) corresponding to 95% confidence interval (CI) were calculated to estimate outcomes. The statistical work for the meta-analysis was performed using Review-Manager 5.4 software (The Cochrane Collaboration, Oxford, UK). I-square (I^2) statistic was used to evaluate heterogeneity. I^2 is a quantity describing approximately the proportion of variation in point estimates that is due to heterogeneity of a sample rather than error in sampling of the population. A value of $I^2 \geq 50\%$ indicated significant heterogeneity.[28] Based on the I^2 value, the fixed-effects model ($I^2 < 50\%$) or random-effects model ($I^2 \geq 50\%$) was used to describe the combined RR. When unexpected heterogeneity was detected, sensitivity analysis was performed to check the origin of the heterogeneity by a sequential exclusion of individual studies. Specific sensitivity of the findings and joint P-values were checked and re-calculated after excluding studies. Publication biases were assessed using Begg's and Egger's tests

Table 1

Characteristic of the included studies.

Author [Ref]	Year	Diagnosis	No. case Exp	No. case Con	Treatment Exp	Treatment Con	Therapeutic course (day)	Outcome measure*
Chen J[29]	2012	GU, DU	26	27	Rabe + KFX	Rabe	28	1, 2, 3
Cheng JY[30]	2015	GU, DU	49	49	Rabe + KFX	Rabe	28	1, 2, 3, 5
Diao PY[31]	2015	GU, DU	42	42	Rabe+ Amox+ Metr+ KFX	Rabe+ Amox+ Metr	28	1, 2, 3, 4, 5
Feng JD[32]	2011	GU, DU	45	45	Rabe+ KFX	Rabe	28	1, 2, 5
Huai HY[33]	2013	GU, DU	54	54	Rabe+ Amox+ Clar+ KFX	Rabe+ Amox+ Clar	28–42	1, 2, 3, 4, 5,
Jiang ZY[34]	2014	GU, DU	39	39	Rabe+ Amox+ Clar+ KFX	Rabe+ Amox+ Clar	28–42	1, 2
Li DF[35]	2014	GU, DU	60	60	Rabe+ Amox+ Levo+ KFX	Rabe+ Amox+ Levo	28	1, 2, 5
Li R[48]	2019	GU, DU	40	40	Rabe+ KFX	Rabe	14	1, 2, 5
Liu J[45]	2009	GU, DU	47	45	Rabe+ Amox+ Clar+ KFX	Rabe+ Amox+ Clar	28	1, 2, 4, 5
Ou J[36]	2014	GU, DU	25	25	Rabe+ KFX	Rabe	35	1, 2, 3
Su CZ[50]	2020	GU, DU	30	30	Rabe+ Amox+ Clar+ KFX	Rabe+ Amox+ Clar	30	1, 2, 4
Sun Y[37]	2013	GU, DU	47	47	Rabe+ KFX	Rabe	28	1, 2, 5
Tang M[38]	2017	GU, DU	50	50	Rabe+ Levo+ Clar+ KFX	Rabe+ Levo+ Clar	28	1, 2, 5
Tu XH[39]	2017	GU, DU	54	54	Rabe+ Amox+ Metr+ KFX	Rabe+ Amox+ Metr	28	1, 2, 5
Wang BX[40]	2017	PU	40	40	Rabe+ Amox+ Levo+ KFX	Rabe+ Amox+ Levo	14	1, 2, 5
Wang J[41]	2017	PU	38	38	Rabe+ KFX	Rabe	30	1, 2, 5
Wang K[19]	2018	GU, DU	50	50	Rabe+ KFX	Rabe	21	1, 2
Wang K[49]	2020	GU, DU	60	60	Rabe+ KFX	Rabe	28	1, 2, 5
Wang L[42]	2017	GU	60	60	Rabe+ KFX	Rabe	60	1, 2, 4
Wang WS[46]	2018	GU, DU	200	200	Rabe+ KFX	Rabe	21	1, 2
Yang SL[47]	2015	GU, DU	40	40	Rabe+ KFX	Rabe	28	1, 2
Yang Y[22]	2018	GU	32	32	Rabe+ KFX	Rabe	90	1, 2, 4, 5
Yu W[51]	2016	GU, DU	60	60	Rabe+ Metr+ Amox/Clar+ KFX	Rabe+ Metr+ Amox/Clar	14	1, 2
Yu ZG[43]	2013	GU, DU	45	45	Rabe+ Amox+ Levo+ KFX	Rabe+ Amox+ Levo	28	1, 2, 3, 5
Zhou C[44]	2016	GU, DU	48	42	Rabe+ KFX	Rabe	28	1, 2, 3, 5

Amox = amoxicillin, Clar = clarithromycin, Con = control group, DU = duodenal ulcer, Exp = experimental group, GU = gastric ulcer, KFX = Kangfuxin, Levo = levofloxacin, Metr = metronidazole, PU = peptic ulcer, Rabe = rabeprazole.
* Outcomes measures included: (1) Healing rate of ulcer; (2) overall response rate of ulcer; (3) alleviation rate of clinical symptoms; (4) recurrence rate of ulcer; (5) overall incidence of adverse events.

(Stata version 10, Stata Corp, College Station, TX). Subgroup analysis was conducted according to the treatment regimes in the control group. All P-values were two-tailed and a P-value of <.05 was considered significant.

3. Results

3.1. Characteristics of the included trials

Through our systematic search, a total of 240 potentially relevant articles were initially identified. Based on the inclusion and exclusion criteria outlined above, 201 studies were excluded. Ultimately, 25 studies[19,22,29–51] with a total of 2555 PU patients, including 1281 patient receiving KFX plus rabeprazole-based treatment and 1274 patients receiving rabeprazole-based treatment alone, were included in the meta-analysis (Fig. 1). Sample size ranged from 50 to 400 patients. Patients in 11 of the 25 trials received rabeprazole triple therapy ±KFX while patients in other trials received rabeprazole monotherapy ±KFX. The dose of KFX was 30 mL/day in all studies included. The therapeutic courses ranged from 14 to 90 days. Detailed characteristics of the included studies can be found in Table 1.

3.2. Methodological quality of included trials

As shown in Supplemental Table 1 (http://links.lww.com/MD/F218), the methodological quality of the 25 included trials was generally low assessed by ROB 2.0. Although all trials mentioned

randomized allocation of participants, 4 of them described improper randomization, such as that ordered by admission to hospital, that organized by odd–even judgement or ambiguous demonstration.[19,31,35,45] No eligible trials mentioned allocation concealment, blinding of participants for the intervention or blinding of outcome assessment, causing the evaluation of low quality featured by "some concerns" and "high risk" in "Bias arising from the randomization process," "Bias due to missing outcome data," and "Bias in measurement of the outcome." Undecided and inconsistant interventions occurred in two trials, resulting in bias from deviations of intended intervention, which was evaluated in "high risk."[38,51] On the whole, based on the aforementioned assessment proportions, 8 of the chosen trials were with "some concern" evidence,[30,36,39–42,44,47] 17 were of "high risk" while no "low risk" evidence was reported.[19,22,29,31–35,37,38,43,45,48–51]

3.3. Healing rate of ulcer

A total of 25 studies[19,22,29–51] were examined to assess the healing rate of ulcer. Overall, 1281 patients received KFX plus rabeprazole-based treatment and 1274 received rabeprazole-based treatment alone. As no significant heterogeneity was observed (P = .89, $I^2 = 0\%$), the fixed-effect model was used to analyze the healing rate. Our meta-analysis revealed that the ulcer healing rate in the KFX+rabeprazole treatment group was significantly higher than that in the rabeprazole-only treatment group (RR = 1.34, 95% CI 1.25–1.44, P < .00001, Fig. 2).
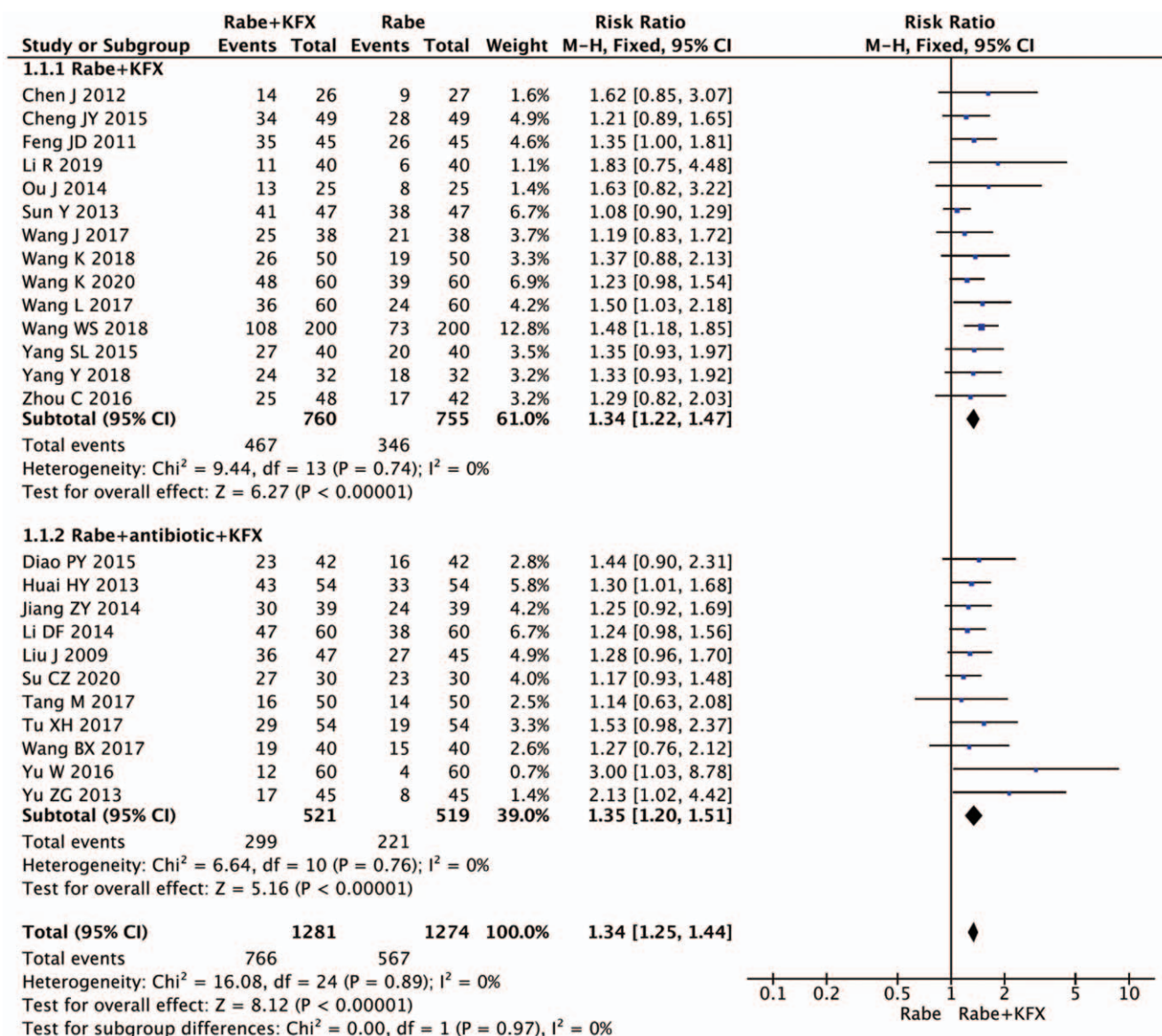
Figure 2. Forrest plot of the healing rate of ulcer.

3.4. Overall response rate

Overall ulcer response rate was evaluated in 25 trials,[19,22,29–51] and so we were able to include them in our meta-analysis. The fixed-effect model was applied to analyze the result since there was no significant heterogeneity ($P = .01$, $I^2 = 42\%$). As shown in Figure 3, KFX combined with rabeprazole significantly improved the overall response rate compared to rabeprazole-based treatment alone (RR = 1.16, 95% CI 1.13–1.20, $P < .00001$; Fig. 3).

3.5. Alleviation of clinical symptoms

Seven[29–31,33,36,43,44] of 25 RCTs, consisting of 289 patients that received KFX plus rabeprazole-based treatment and 284 that received rabeprazole-based treatment alone, assessed the alleviation of clinical symptoms. As there was no significant heterogeneity ($P = .37$, $I^2 = 8\%$), the fixed-effect model was used

to analyze the data. The results showed that KFX plus rabeprazole significantly alleviated the clinical symptoms of PU compared with rabeprazole-based treatment alone (RR = 1.14, 95% CI 1.08–1.21, $P < .00001$; Fig. 4).

3.6. Recurrence rate of ulcer

Six of the 25 studies,[22,31,33,42,45,50] totaling 246 patients receiving KFX plus rabeprazole-based treatment and 231 received rabeprazole-based treatment alone, assessed the recurrence rate of rate. The fixed-effect model was used since no significant heterogeneity existed between the studies ($P = .44$, $I^2 = 0\%$). The results indicated that combination treatment with KFX and rabeprazole could significantly decrease the recurrence of PU compared to rabeprazole-based treatment alone (RR = 0.38, 95% CI 0.24–0.61, $P < .0001$; Fig. 5).

Study or Subgroup	Rabe+KFX Events	Total	Rabe Events	Total	Weight	Risk Ratio M–H, Fixed, 95% CI	Risk Ratio M–H, Fixed, 95% CI
1.3.1 Rabe+KFX							
Chen J 2012	25	26	23	27	2.2%	1.13 [0.95, 1.34]	
Cheng JY 2015	48	49	38	49	3.6%	1.26 [1.08, 1.48]	
Feng JD 2011	44	45	41	45	3.9%	1.07 [0.97, 1.19]	
Li R 2019	27	40	13	40	1.2%	2.08 [1.27, 3.41]	
Ou J 2014	25	25	20	25	2.0%	1.24 [1.01, 1.53]	
Sun Y 2013	47	47	42	47	4.1%	1.12 [1.01, 1.24]	
Wang J 2017	36	38	28	38	2.7%	1.29 [1.05, 1.58]	
Wang K 2018	48	50	42	50	4.0%	1.14 [1.00, 1.31]	
Wang K 2020	56	60	47	60	4.5%	1.19 [1.03, 1.38]	
Wang L 2017	54	60	41	60	3.9%	1.32 [1.09, 1.60]	
Wang WS 2018	195	200	166	200	15.8%	1.17 [1.10, 1.26]	
Yang SL 2015	38	40	33	40	3.1%	1.15 [0.98, 1.35]	
Yang Y 2018	31	32	24	32	2.3%	1.29 [1.05, 1.59]	
Zhou C 2016	47	48	38	42	3.9%	1.08 [0.97, 1.20]	
Subtotal (95% CI)		760		755	57.1%	1.20 [1.15, 1.25]	
Total events	721		596				

Heterogeneity: Chi^2 = 18.84, df = 13 (P = 0.13); I^2 = 31%
Test for overall effect: Z = 9.18 (P < 0.00001)

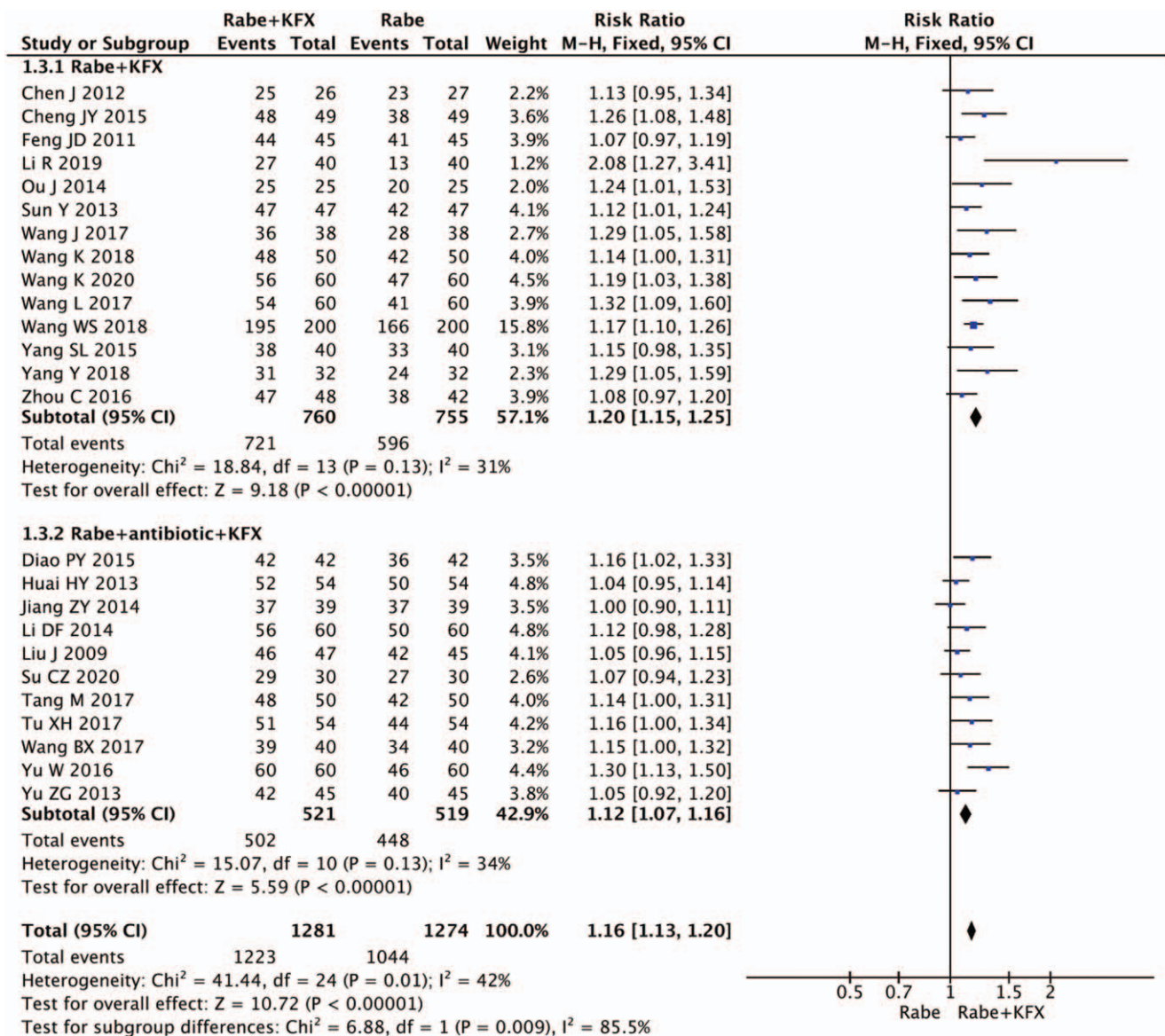| Study or Subgroup	Rabe+KFX Events	Total	Rabe Events	Total	Weight	Risk Ratio M–H, Fixed, 95% CI	Risk Ratio M–H, Fixed, 95% CI
1.3.2 Rabe+antibiotic+KFX							
Diao PY 2015	42	42	36	42	3.5%	1.16 [1.02, 1.33]	
Huai HY 2013	52	54	50	54	4.8%	1.04 [0.95, 1.14]	
Jiang ZY 2014	37	39	37	39	3.5%	1.00 [0.90, 1.11]	
Li DF 2014	56	60	50	60	4.8%	1.12 [0.98, 1.28]	
Liu J 2009	46	47	42	45	4.1%	1.05 [0.96, 1.15]	
Su CZ 2020	29	30	27	30	2.6%	1.07 [0.94, 1.23]	
Tang M 2017	48	50	42	50	4.0%	1.14 [1.00, 1.31]	
Tu XH 2017	51	54	44	54	4.2%	1.16 [1.00, 1.34]	
Wang BX 2017	39	40	34	40	3.2%	1.15 [1.00, 1.32]	
Yu W 2016	60	60	46	60	4.4%	1.30 [1.13, 1.50]	
Yu ZG 2013	42	45	40	45	3.8%	1.05 [0.92, 1.20]	
Subtotal (95% CI)		521		519	42.9%	1.12 [1.07, 1.16]	
Total events	502		448				

Heterogeneity: Chi^2 = 15.07, df = 10 (P = 0.13); I^2 = 34%
Test for overall effect: Z = 5.59 (P < 0.00001)

Total (95% CI)		1281		1274	100.0%	1.16 [1.13, 1.20]	
Total events	1223		1044				

Heterogeneity: Chi^2 = 41.44, df = 24 (P = 0.01); I^2 = 42%
Test for overall effect: Z = 10.72 (P < 0.00001)
Test for subgroup differences: Chi^2 = 6.88, df = 1 (P = 0.009), I^2 = 85.5%

Figure 3. Forrest plot of the overall response rate.

3.7. Overall occurrence of adverse events

Among the 25 RCTs analyzed, 16 reported adverse events during treatment.[22,30–33,35,37–41,43–45,48,49] No significant heterogeneity of the included studies was observed (P = .60, I^2 = 0%). As shown in Figure 6, the overall occurrence of adverse events calculated by the fixed-effect model was comparable between patients receiving KFX plus rabeprazole-based treatment and rabeprazole-based treatment alone (RR = 0.92, 95% CI 0.66–1.28, P = .63).

3.8. Subgroup analysis

Although we compared the therapeutic effects of treatment with rabeprazole alone and in combination with KFX, other drugs were involved. Therefore, subgroup analysis was conducted according to the treatment regimes in the control group. The results showed that compared with rabeprazole monotherapy or

rabeprazole-based triple therapy, the addition of KFX could significantly improve ulcer healing and overall response rate, alleviate clinical symptoms and reduce ulcer recurrence rate without increasing the overall occurrence of adverse events (Figs. 2–6).

3.9. Publication bias

Publication bias was investigated by Begg's and Egger's tests. The results were shown in Table 2, which indicated no publication bias for all the outcomes.

4. Discussion

KFX is a well-known Chinese patent medicine extracted from PA. It has been demonstrated to have gastroprotective effects and can promote ulcer healing, reduce inflammation, relieve pain, and
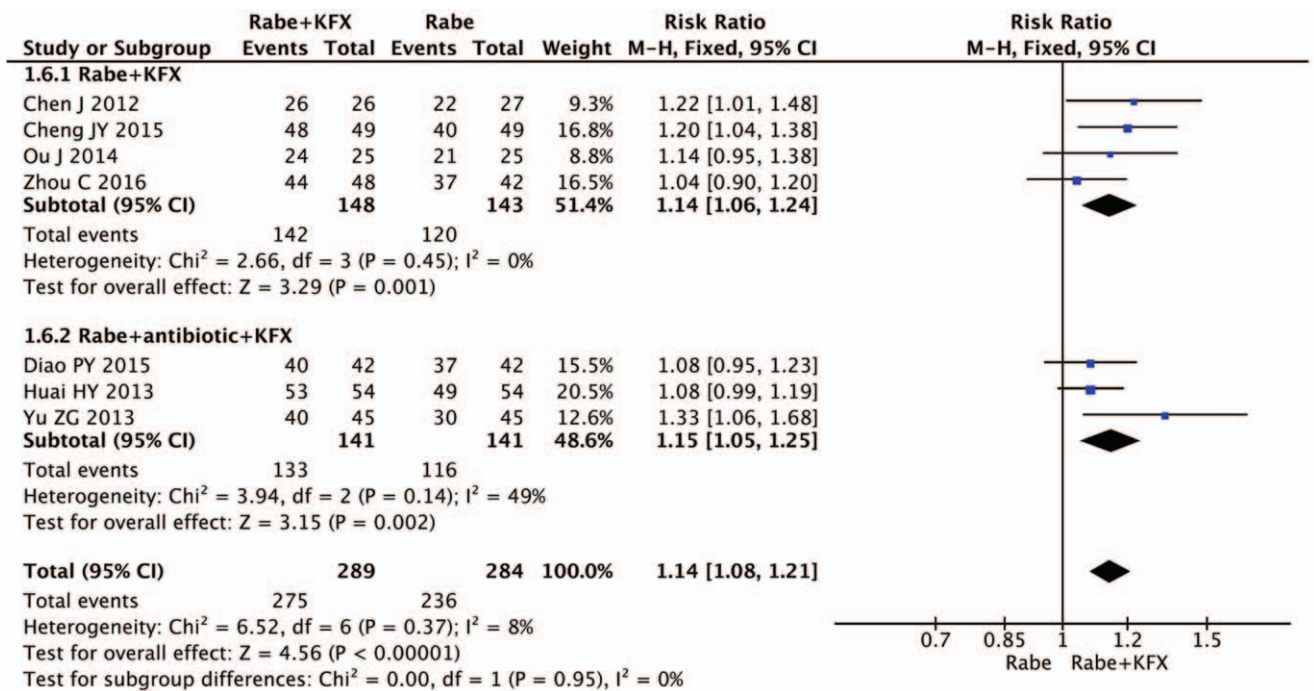
Study or Subgroup	Rabe+KFX		Rabe			Risk Ratio	Risk Ratio
	Events	Total	Events	Total	Weight	M–H, Fixed, 95% CI	M–H, Fixed, 95% CI
1.6.1 Rabe+KFX							
Chen J 2012	26	26	22	27	9.3%	1.22 [1.01, 1.48]	
Cheng JY 2015	48	49	40	49	16.8%	1.20 [1.04, 1.38]	
Ou J 2014	24	25	21	25	8.8%	1.14 [0.95, 1.38]	
Zhou C 2016	44	48	37	42	16.5%	1.04 [0.90, 1.20]	
Subtotal (95% CI)		148		143	51.4%	1.14 [1.06, 1.24]	
Total events	142		120				
Heterogeneity: Chi² = 2.66, df = 3 (P = 0.45); I² = 0%							
Test for overall effect: Z = 3.29 (P = 0.001)							
1.6.2 Rabe+antibiotic+KFX							
Diao PY 2015	40	42	37	42	15.5%	1.08 [0.95, 1.23]	
Huai HY 2013	53	54	49	54	20.5%	1.08 [0.99, 1.19]	
Yu ZG 2013	40	45	30	45	12.6%	1.33 [1.06, 1.68]	
Subtotal (95% CI)		141		141	48.6%	1.15 [1.05, 1.25]	
Total events	133		116				
Heterogeneity: Chi² = 3.94, df = 2 (P = 0.14); I² = 49%							
Test for overall effect: Z = 3.15 (P = 0.002)							
Total (95% CI)		289		284	100.0%	1.14 [1.08, 1.21]	
Total events	275		236				
Heterogeneity: Chi² = 6.52, df = 6 (P = 0.37); I² = 8%							
Test for overall effect: Z = 4.56 (P < 0.00001)							
Test for subgroup differences: Chi² = 0.00, df = 1 (P = 0.95), I² = 0%							

Figure 4. Forrest plot of alleviation of clinical symptoms of peptic ulcer.

enhancement of immunity through various mechanisms.[52] For instance, treatment with KFX led to the attenuation of ethanol-induced GU by reducing both oxidative and ER stress in mice models, as shown by an increase of plasma and gastric SOD activity and reduction of ER stress markers (CHOP, GRP78, and caspase 12), respectively. In addition, treatment with KFX could also promote the recovery of GU lesions in mice by inhibiting apoptosis, as illustrated by the decreased expression of the pro-apoptotic protein BAX and increased expression of Bcl-2, an anti-apoptotic protein.[14] Furthermore, KFX has been shown to have anti-inflammatory effects. It is able to repress the release of the inflammatory cytokines TNF-α and IL-1β, and prevent the activation of the NF-κB signaling pathway via the inhibition of IκB phosphorylation and subsequent reduction of nuclear NF-κB

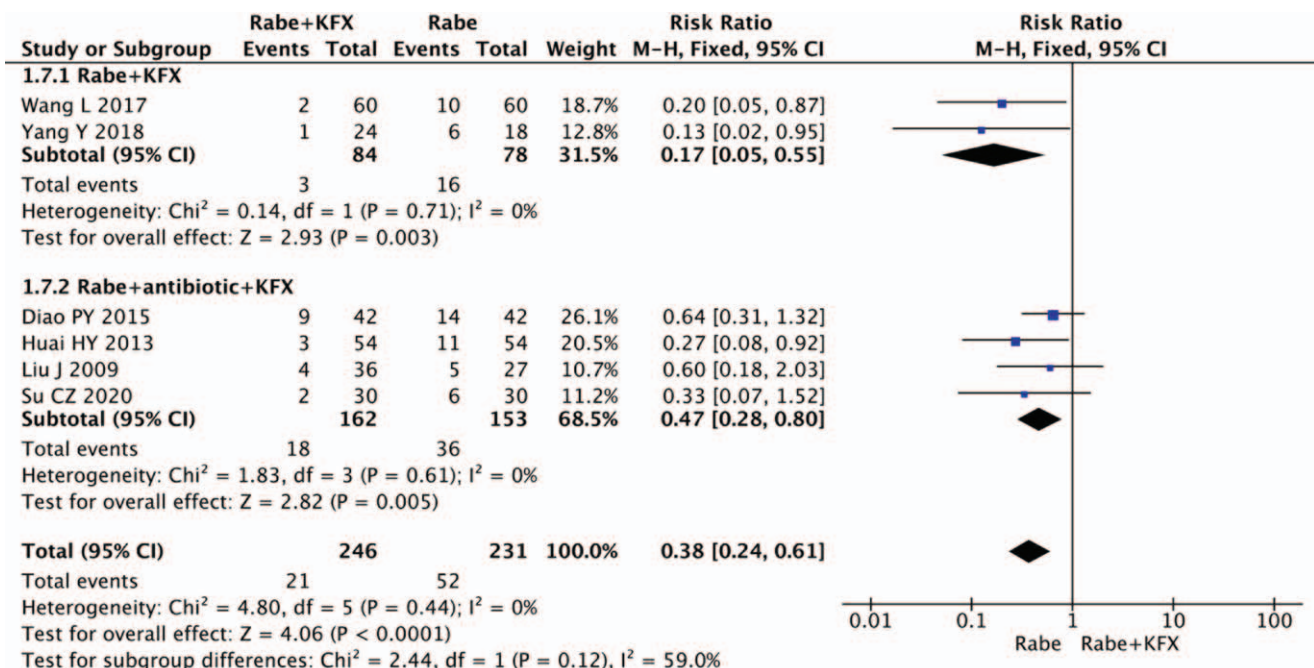| Study or Subgroup	Rabe+KFX		Rabe			Risk Ratio	Risk Ratio
	Events	Total	Events	Total	Weight	M–H, Fixed, 95% CI	M–H, Fixed, 95% CI
1.7.1 Rabe+KFX							
Wang L 2017	2	60	10	60	18.7%	0.20 [0.05, 0.87]	
Yang Y 2018	1	24	6	18	12.8%	0.13 [0.02, 0.95]	
Subtotal (95% CI)		84		78	31.5%	0.17 [0.05, 0.55]	
Total events	3		16				
Heterogeneity: Chi² = 0.14, df = 1 (P = 0.71); I² = 0%							
Test for overall effect: Z = 2.93 (P = 0.003)							
1.7.2 Rabe+antibiotic+KFX							
Diao PY 2015	9	42	14	42	26.1%	0.64 [0.31, 1.32]	
Huai HY 2013	3	54	11	54	20.5%	0.27 [0.08, 0.92]	
Liu J 2009	4	36	5	27	10.7%	0.60 [0.18, 2.03]	
Su CZ 2020	2	30	6	30	11.2%	0.33 [0.07, 1.52]	
Subtotal (95% CI)		162		153	68.5%	0.47 [0.28, 0.80]	
Total events	18		36				
Heterogeneity: Chi² = 1.83, df = 3 (P = 0.61); I² = 0%							
Test for overall effect: Z = 2.82 (P = 0.005)							
Total (95% CI)		246		231	100.0%	0.38 [0.24, 0.61]	
Total events	21		52				
Heterogeneity: Chi² = 4.80, df = 5 (P = 0.44); I² = 0%							
Test for overall effect: Z = 4.06 (P < 0.0001)							
Test for subgroup differences: Chi² = 2.44, df = 1 (P = 0.12), I² = 59.0%							

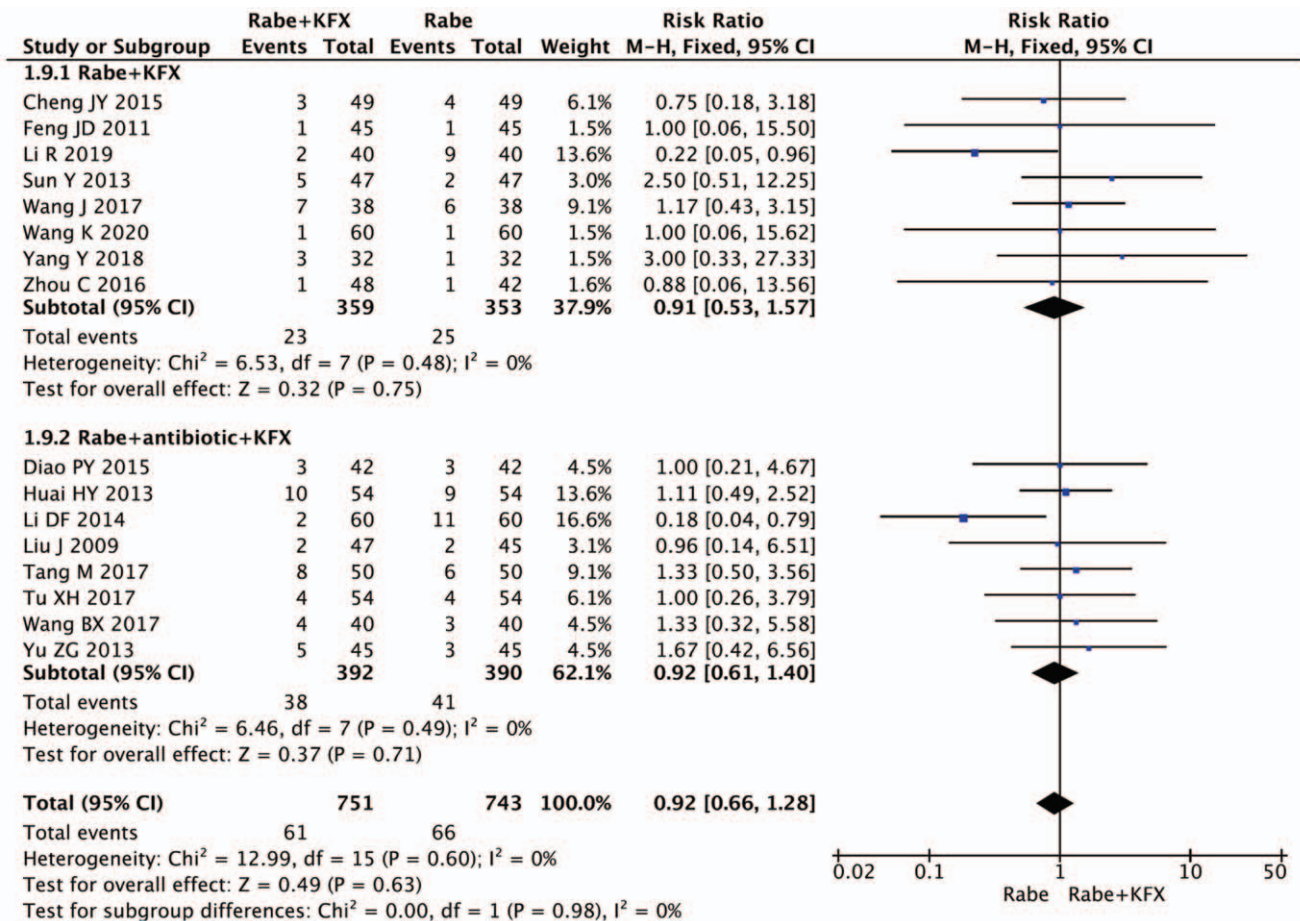**Figure 5.** Forrest plot of recurrence rate of ulcer.

Figure 6. Forrest plot of overall occurrence of adverse events.

p65.[53] Taken together, KFX can promote a protective effect on GU through multiple pharmacological mechanisms, which provide compelling evidence to support its clinical application in the treatment of PU. Although the main etiology and therapeutic course of DU and GU are different, KFX serves as an adjuvant therapy in the treatment of both DU and GU, based on its anti-inflammatory, immunomodulatory and wound healing effects. Therefore, it is important to evaluate the therapeutic effect of KFX in PU patents, which consist of both DU and GU patients.

To our best knowledge, this is the first large-scale review to systematically and comprehensively investigate the clinical efficacy of KFX combined with rabeprazole in the treatment of PU. The results of this meta-analysis showed that in comparison to rabeprazole-based treatment alone, KFX plus rabeprazole-based treatment could significantly improve the healing rate and overall response rate of PU, alleviate clinical symptoms and reduce recurrence of ulcer without increasing the occurrence of adverse events. This is similar to the results obtained in other meta-analysis studies assessing the efficacy of KFX in combination with other PPIs for the treatment of PU.[17,18] Recently a meta-analysis of 9 RCTs comprising 913 participants also showed that KFX combined with pantoprazole treatment significantly improved healing rate and overall response rate of PU and was associated with a reduction of the rate of recurrence.[17] Therefore, together with our data presented here, KFX has been shown to be a promising therapeutic additive for PU.

There were, however, several limitations in this study. First, there was some risk of biases among the included studies. When performing our literature search in the seven electronic databases, the publication language was restricted to Chinese or English. Ultimately, the relevant data about KFX in PU treatment mainly came from Chinese patients, which may not reflect the clinical efficacy of KFX in other ethnicity. Secondly, the methodological quality of the included studies, as evaluated by Cochrane Collaboration's risk of bias tool, was generally low and many items showed an unclear risk. In several RCTs included here, the methods for randomization, allocation concealment and blinding were not clearly described, which might produce the negative influences on researchers in getting the accurate clinical efficacy

Table 2

Results of Begg's test and Egger's test.

Outcome	Begg's test	Egger's test
Healing rate of ulcer	0.118	0.425
Overall response rate of ulcer	0.717	0.707
Alleviation of clinical symptoms	0.382	0.707
Recurrence rate of ulcer	0.133	0.053
Overall incidence of adverse events	0.392	0.872

of KFX to some degree. Furthermore, long-term follow-up was lacking in a majority of the included studies. Therefore, long-term recurrence of PU treated by combination of KFX and rabeprazole were unclear. Finally, there are six different kinds of PPIs, including omeprazole, lansoprazole, pantoprazole, ilaprazole, and esomeprazole, in addition to rabeprazole. The therapeutic efficacy of KFX combined with these different types of PPIs will be further evaluated by network meta-analysis in the future. Because of these limitations, caution should be practiced when interpreting the conclusions presented here. A well-designed and high-quality RCT in different ethnicity is needed to further testify the clinical effectiveness of KFX.

5. Conclusion

In this systematic review, the addition of KFX to rabeprazole-based treatment showed promising therapeutic effects, as it was able to improve ulcer healing, alleviate clinical symptoms and reduce recurrence of ulcer without obvious side-effects in PU patients. Due to some limitations, such as potential publication bias and low methodological quality of the included studies, additional large-scale, rigorously designed RCTs with long-term follow-up are needed.

Author contributions

Conceptualization: Meisi Lin.
Data curation: Meisi Lin, Siyuan Zhang, FEI GAO.
Formal analysis: Meisi Lin, Siyuan Zhang.
Investigation: Minyue Zhang, FEI GAO.
Methodology: Meisi Lin, Chen Zhang, Jiayi Sun, FEI GAO.
Project administration: FEI GAO.
Resources: Meisi Lin, Siyuan Zhang, Minyue Zhang, Ruifeng Luo, Jieshu You, Jiayi Sun, Jinming Zhang, FEI GAO.
Software: Meisi Lin, Siyuan Zhang, Jinfeng Shi, Chen Zhang, FEI GAO.
Supervision: FEI GAO.
Writing – original draft: Meisi Lin, Minyue Zhang, FEI GAO.
Writing – review & editing: Meisi Lin, Minyue Zhang, FEI GAO.

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