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Lactobacillus reuteri compared with placebo as an adjuvant in *Helicobacter pylori* eradication therapy: a meta-analysis of randomized controlled trials

Meng Li, Xiaolei Wang, Xinhong Dong, Guigen Teng, Yun Dai and Weihong Wang

Abstract

Background: Given the growing problem of antibiotic resistance, it is crucial to improve *Helicobacter pylori* (*H. pylori*) treatment interventions or provide adjunctive therapy. The objective of this meta-analysis was to evaluate whether *Lactobacillus reuteri* (*L. reuteri*) could improve *H. pylori* eradication rate, reduce the incidence of adverse events (AEs), and alleviate gastrointestinal symptoms.

Design: A meta-analysis of randomized controlled trials (RCTs) comparing *L. reuteri* supplementation therapy with placebo was conducted.

Sources and methods: We retrieved relevant studies from PubMed, Embase, and the Cochrane Library. The primary outcome was *H. pylori* eradication rate, and the scores on the Gastrointestinal Symptom Rating Scale and AEs were secondary outcomes.

Results: Eight RCTs including 1087 patients were included in this analysis. The *L. reuteri* supplementation group showed significantly higher *H. pylori* eradication rates in both intention-to-treat (ITT) and per-protocol (PP) analysis [ITT: 80.0% *versus* 72.6%; $p = 0.005$, relative risk (RR): 1.10; 95% confidence interval (CI): 1.03–1.17; number needed to treat (NNT) = 14; PP: 81.8% *versus* 75.0%; $p = 0.006$, RR: 1.09; 95% CI: 1.03–1.16; NNT = 15]. Patients treated with *L. reuteri* showed greater improvements in gastrointestinal symptoms (pooled mean difference: −2.43, 95% CI: −4.56 to −0.29, $p = 0.03$). The incidence of AEs was significantly reduced in the *L. reuteri* supplementation group based on ITT and PP analysis (ITT: $p < 0.00001$, RR: 0.72, 95% CI: 0.67–0.78; PP: $p < 0.00001$, RR: 0.70, 95% CI: 0.65–0.77).

Conclusion: The present meta-analysis demonstrated that supplementation with *L. reuteri* was beneficial for improving the eradication rate of *H. pylori*, reducing the overall incidence of side effects, and relieving gastrointestinal symptoms in patients during treatment. The findings provide new insights into clinical decision-making.

Trial registration (PROSPERO): CRD42023424052.

Plain language summary

Lactobacillus reuteri compared with placebo as an adjuvant in *Helicobacter pylori* eradication therapy: a meta-analysis of randomized controlled trials

Given the growing problem of antibiotic resistance, it is crucial to improve Helicobacter pylori (H. pylori) treatment interventions or provide adjunctive therapy. Eight randomized controlled trials (RCTs) including 1087 patients were included in this analysis. The present meta-analysis demonstrated that supplementing with L. reuteri tends to increase the eradication rate of H. pylori, reduce the overall incidence of antibiotic-related side effects, and alleviate gastrointestinal symptoms in patients during treatment, providing new insights for clinical decision-making.

Correspondence to:
Weihong Wang
Department of Gastroenterology, Peking University First Hospital, No. 8 Xishiku Street, Beijing 100034, China
wangweihong2581@163.com
weihongwang03829@pkufh.com

Meng Li
Xiaolei Wang
Xinhong Dong
Guigen Teng
Yun Dai
Department of Gastroenterology, Peking University First Hospital, Beijing, China

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Background

Helicobacter pylori (*H. pylori*), as the main pathogenic bacteria of chronic gastritis, peptic ulcer, mucosa-associated lymphoid tissue (MALT) lymphoma, and gastric adenocarcinoma, has attracted significant attention worldwide since its discovery.[1] The treatment of *H. pylori* is challenged by the increasing prevalence of antibiotic resistance, and the impact of antibiotic therapy on the gut microbiome is an important consideration that must not be overlooked.[2,3] Therefore, it is crucial to improve therapeutic interventions or add adjuvant treatments.

Probiotics are non-pathogenic living bacteria that confer health benefits to the host, including antioxidative and anti-inflammatory effects that may help prevent intestinal infections, cancer, and cardiovascular disease.[4,5] Numerous studies have demonstrated that certain *Lactobacillus* strains, such as *Lactobacillus GG, Lactobacillus acidophilus*, and *Lactobacillus reuteri* (*L. reuteri*), possess anti-*H. pylori* properties. Several clinical trials have integrated specific probiotics into conventional regimens to reduce adverse effects (AEs), improve drug compliance, and increase eradication rates.[6–9] According to a meta-analysis by Yu *et al.*,[10] supplementing *Lactobacillus* during the treatment of *H. pylori* infection can effectively improve the eradication rate and reduce the incidence of therapy-related taste disturbance. Another study compared the effectiveness of various probiotics in *H. pylori* eradication therapy, suggesting that *Lactobacillus* and multiple strains are favorable choices among probiotics. Additionally, subjects in China exhibited higher eradication rate than those in other countries in this study.[11] It is worth mentioning that *L. reuteri* has demonstrated promising results in eradicating *H. pylori* by producing powerful antimicrobial compounds that inhibit the growth of *H. pylori* and strengthen the mucosal barrier against infection by increasing mucin secretion.[12,13]

Despite the promising results observed in clinical trials, there is currently no clear consensus on when to administer probiotics as an adjuvant therapy for *H. pylori* eradication, and the appropriate dosage and duration of treatment continue to be debated. To evaluate the potential benefit of *L. reuteri* supplementation in combination with standard therapy, this meta-analysis was conducted to determine whether it could significantly improve *H. pylori* eradication rate, reduce the incidence of AEs, and alleviate gastrointestinal symptoms.

Materials and methods

This meta-analysis was registered in PROSPERO (registration no.: CRD42023424052) and conducted following the Preferred Reporting Items for Systematic Review and Meta-analyses guidelines.[14]

Search strategy

To identify relevant literature, we systematically searched the following databases: (1) PubMed, (2) The Cochrane Library, and (3) Embase. The cut-off date for inclusion in our study was 31 December 2023, and only English articles were included across all databases within our scope. Potentially relevant randomized controlled trials (RCTs) were retrieved using the following MeSH terms: '*Helicobacter pylori* or *H. pylori*', 'probiotic or probiotics', and '*Lactobacillus reuteri* or *L. reuteri*'. Furthermore, references from the retrieved articles as well as relevant meta-analyses or reviews were manually screened and incorporated into the eligible literature. The search strategies for each database were presented in Supplemental Table S1.

Selection criteria

All studies included in this meta-analysis were based on the following PICOS principles: (1) P (population): *H. pylori*-infected adult patients; (2) I and C (intervention and comparison): articles evaluating the efficacy and safety of *L. reuteri* as an adjuvant therapy for *H. pylori* eradication compared with placebo; (3) O (outcomes): endpoints included the eradication rate, AEs, and symptom scores before and after treatment; and (4) S (study): RCTs published in English.

The exclusion criteria were as follows: basic studies, conference abstracts, reviews, meta-analyses, case reports, summary-only articles, and literature with insufficient data.

Data extraction

Two investigators independently extracted data from the included studies, and any discrepancies were resolved through discussion until a reasonable solution was reached. Otherwise, the decision was made by a third reviewer. The detailed data were as follows: first author, year of publication, country, numbers of enrolled patients, baseline characteristics (age and previous experience in *H. pylori* eradication), eradication regimen, types and dosage of probiotics, follow-up time, eradication rates (intention-to-treat analysis, ITT; per-protocol analysis, PP), scores of Gastrointestinal Symptom Rating Scale (GSRS), and AEs.

Quality assessment

The Cochrane Risk of Bias Assessment Tool was used to assess the quality of all eligible studies, which included the following main evaluation indicators: random sequence generation, allocation concealment, blinding of patients and personnel, incomplete outcome data, selective reporting, and other bias.[15] Two researchers independently evaluated the quality of each study and reached a consensus. Studies with a score of 3 or higher were considered to be of high quality.

Statistical analysis

This meta-analysis was performed using the following data management software: Review Manager (version 5.3; Copenhagen: The Nordic Cochrane Center, The Cochrane Collaboration, 2014) and STATA (version 14.0; Stata Corp, College Station, Texas, USA). The dichotomous outcomes were expressed as relative risk (RR) with corresponding 95% confidence intervals (CIs). The effect size of the continuous variable was expressed as the mean difference (MD) and 95% CIs. When the p-value was less than 0.05, it was considered as statistically significant. We calculated the number needed to treat (NNT), using the formula NNT = 1/(assumed control risk (ACR) × (RR − 1)). Summary estimates of the eradication rates and AEs were performed on the ITT and PP principles. Subgroup analysis of *H. pylori* eradication rate was performed to determine whether the results were stable according to nations, eradication regimens, treatment lines, and the timing and duration of *L. reuteri* supplementation. In addition, heterogeneity in our study was assessed by the I^2 statistic and χ^2 test with the random-effects or fixed models. Significant heterogeneity was indicated when $p < 0.10$ or $I^2 > 50\%$, then we used a random-effects model. Otherwise, the fixed-effects model was used. We also explored the potential publication bias through the funnel plot and Egger' s linear regression test.[16]

Results

Search results and quality assessment

Through a preliminary literature search, we identified 1826 potentially eligible studies. However, most studies were excluded because they did not meet the inclusion criteria regarding the intervention. Ultimately, only 8 RCTs, consisting of 1087 patients (*L. reuteri* group: 544 patients; placebo group: 543 patients), were included in this analysis[6,17–23] (Figure 1). One of the included articles had a mean age of over 18 years and was also deemed eligible for analysis.[6] Additionally, one of the studies included two comparisons that met our inclusion criteria (7-day and 14-day eradication rates, respectively), and were included in our analysis as independent studies (Poonyam a and Poonyam b).[17] Table 1 summarized the baseline characteristics and main evaluation indicators. Furthermore, all the studies scored 3–5 points on the quality assessment scale, indicating high quality (Supplemental Table S2, Supplemental Figure S1).

Eradication rates

Data on the eradication rates were available from all included studies. No significant heterogeneity was observed between them (ITT: $p = 0.36$, $I^2 = 10\%$; PP: $p = 0.27$, $I^2 = 19\%$). Compared with the placebo group, a significantly increased eradication rate was observed in the *L. reuteri* supplementation group with ITT analysis [$p = 0.005$, RR: 1.10; 95% CI: 1.03–1.17, Figure 2(a)] and an NNT of 14. In PP analysis, compared with the control group, the *L. reuteri* supplementation group also had better eradication rates, with the eradication rates of 75.0% and 81.8%, respectively [$p = 0.06$, RR: 1.09; 95% CI: 1.03–1.16, NNT = 15, Figure 2(b)].

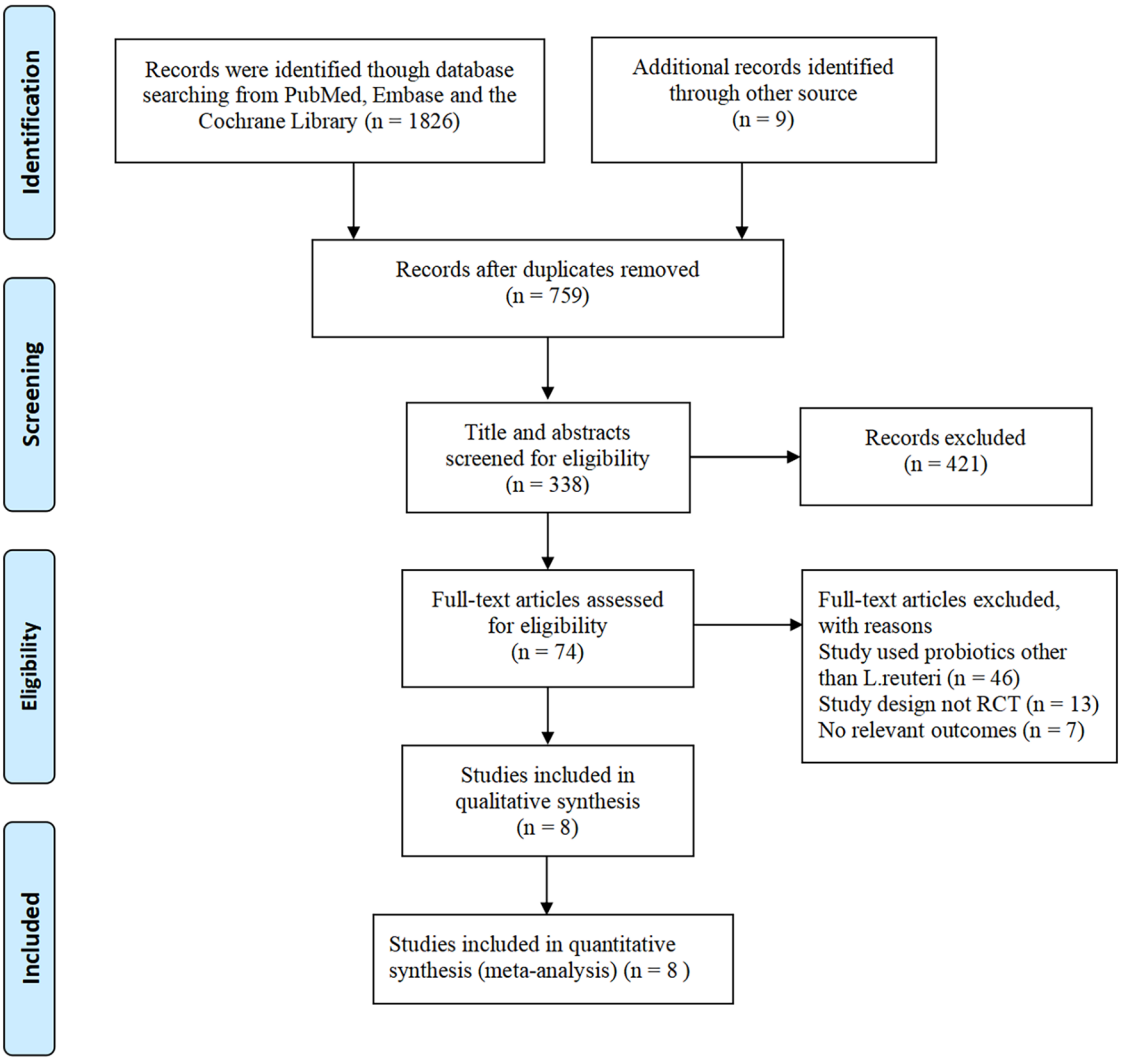

Figure 1. Flow chart of studies included in the meta-analysis.

Advert effects

There were only two studies comparing the overall AEs.[6,19] The incidence of total AEs in the placebo group was significantly higher than that in the *L. reuteri* supplementation group, and the difference was statistically significant by both ITT and PP analyses [ITT: $p < 0.00001$, RR: 0.72; 95% CI: 0.66–0.78, Figure 3(a); PP: $p < 0.00001$, RR: 0.70; 95% CI: 0.64–0.77, Figure 3(b)]. Furthermore, we performed a subgroup analysis of the top 10 AEs (nausea/vomiting, loss of appetite, taste disturbance, abdominal pain, heartburn, flatulence, diarrhea, headache, dizziness, cramp). Compared with the placebo group, the *L. reuteri* supplementation group showed superiority in reducing AEs in all outcomes except for dizziness (Table 2).

Symptom assessment

Gastrointestinal symptoms before and after treatment were assessed and scored according to the 15-item GSRS in 5 studies.[18–20,22,23] Results were expressed as mean ± standard deviation (SD) in four studies[18,20,22,23] and as median ± SD in one study.[19] Therefore, we performed a meta-analysis of the score changes from baseline in the first four studies. By comparison, patients treated with *L. reuteri* showed greater improvements in gastrointestinal symptoms (pooled MD: −2.43, 95% CI: −4.56 to −0.29, $p = 0.03$, Figure 4).

Subgroup analysis

To validate the consistency of the results, we conducted subgroup analyses on the eradication rates

Table 1. Characteristics of the studies included in this meta-analysis.

First authors	Year	Country	Treatment line	Patients (exp/cont)	Follow-up time	Treatment regimes		Eradication rate (exp/cont)%	
						Eradication regimen (dose/duration)	*L. reuteri* regimen	ITT	PP
Ismail	2023	Malaysia	Unclear	45/45	8 wek	AMO 1000 mg BID + CLA 500 mg BID/MET 400 mg BID + ESO 40 mg BID, 14 days	*L. reuteri* DSM 17648 (200 mg/day, 30 days)	91.1/68.9	93.2/68.9
Mohtasham	2023	Iran	1	225/225	8 wek	AMO 1000 mg BID + CLA 500 mg BID + PAN 40 mg BID + BIS 240 mg BID, 14 days	*L. reuteri* (200 mg/day, 14 days)	78.7/72.0	80.1/75.2
Yang	2021	China	1	100/100	8 wek	AMO 1000 mg BID + CLA 500 mg BID + ESO 20 mg BID, 14 days	*L. reuteri* DSM 17648 (4×10^{10} CFU/day, 14 days)	81.8/83.7	86.2/87.2
Poonyam	2019	Thailand	1	50/50	4 wek	MET 400 mg BID + TET 500 mg BID + BIS 1048 mg BID + dexLAN 60 mg BID, 7/14 days	*L. reuteri* DSM 17938 *and L. reuteri* ATCC PTA *6475* (75 mg/day, 7/14 days)	7 days: 68.0/72.0 14 days: 96.0/88.0	7 days: 68.0/72.0 14 days: 96.0/88.0
Francavilla	2014	Italy	1	25/25	96 days	AMO + CLA + PPI (dosage unclear), 7 days	*L. reuteri* DSM 17938 and *L. reuteri* ATCC PTA 6475 (2×10^8 CFU/day, 14 days)	75.0/65.9	76.7/67.4
Emara	2014	Egypt	Unclear	35/35	8 wek	AMO 1000 mg BID + CLA 500 mg BID + OME 20 mg BID, 14 days	*L. reuteri* DSM 17938 and *L. reuteri* ATCC PTA 6475 (2×10^8 CFU/day, 28 days)	74.3/65.7	74.3/65.7
Ojetti	2012	Italy	2 and more	45/45	6 wek	AMO 1000 mg BID + LEV 500 mg BID + ESO 20 mg BID, 7 days	*L. reuteri* (3×10^8 CFU/day, 14 days)	80.0/60.0	80.0/80.0
Francavilla	2008	Italy	1	20/20	38 days	(RAB 20 mg BID + AMP 1000 mg BID), 5 days + (RAB 20 mg BID + CLA 500 mg BID + TIN 500 mg BID, 5 days	*L. reuteri* ATCC 55730 (1×10^8 CFU/day, 28 days)	70.0/70.0	87.5/82.4

AMO, amoxicillin; BID, two times a day; BIS, bismuth; CFU, colony-forming units; CLA, clarithromycin; cont, control group; dexLAN, dexlansoprazole; ESO, esomeprazole; exp, experimental group; LAN, lansoprazole; LEV, levofloxacin; *L. reuteri, Lactobacillus reuteri*; MET, metronidazole; OME, omeprazole; PAN, pantoprazole; PPI, proton-pump inhibitor; RAB, rabeprazole; TET, tetracycline; TIN, tinidazole; wek, week.

of *H. pylori* based on several categories of variables in our meta-analysis, including nations, eradication regimens, treatment lines, and the timing and duration of *L. reuteri* supplementation. As shown in Table 3, we performed subgroup analysis by nation and found that in the PP analysis, the *L. reuteri* supplementation group had higher eradication rates in both Europe and Asia. In the ITT analysis, there was no statistical significance in Europe. We observed that the eradication rate of *H. pylori* in the *L. reuteri* supplementation group was significantly higher than that in the

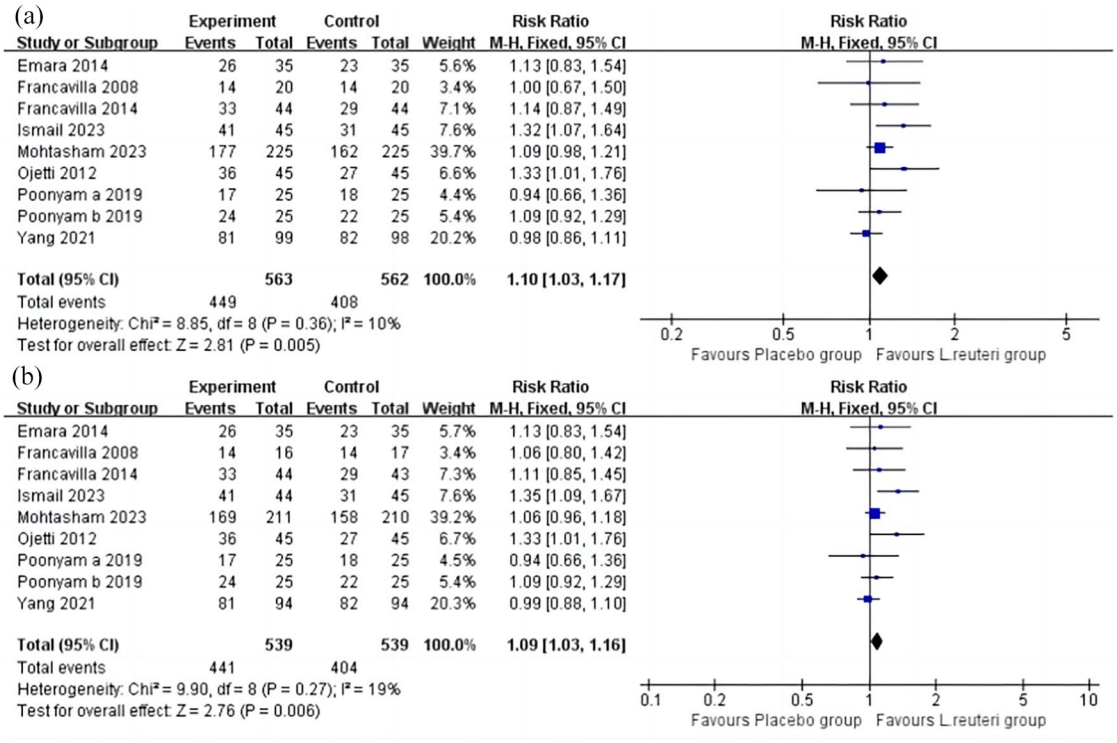

Figure 2. Forest plots of the pooled *H. pylori* eradication rates with ITT (a) and PP (b) analysis for the comparison of *L. reuteri* supplementation group *versus* placebo group.
ITT, intention-to-treat; PP, per-protocol.

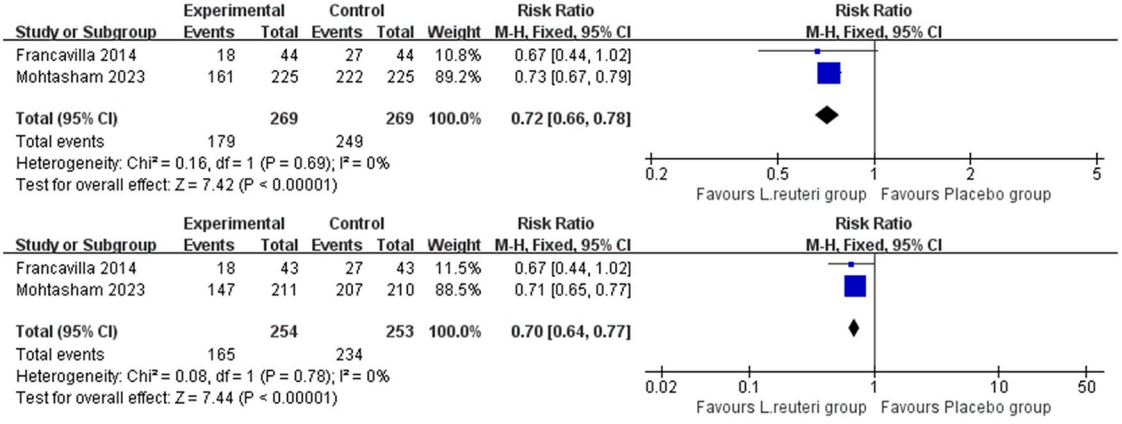

Figure 3. Forest plots of the total adverse events with ITT (a) and PP (b) analysis for the comparison of *L. reuteri* supplementation group *versus* placebo group.
ITT, intention-to-treat; PP, per-protocol.

placebo group when the supplementation was extended to a period after conventional eradication therapy. Both ITT and PP analyses displayed statistically significant differences (ITT: $p = 0.03$, RR: 1.20; 95% CI: 1.02–1.42; PP: $p = 0.04$, RR: 1.19; 95% CI: 1.01–1.41; Table 3). When patients received *L. reuteri* as a pretreatment or in combination with standard treatment, there was no significant difference in the eradication rates between the two groups (Table 3). Additionally,

Table 2. Comparison of top 10 adverse effects between the *L. reuteri* group and the placebo group.

Adverse effects	*L. reuteri* group (event/total)	Placebo group (event/total)	Total incidence (%)	RR (95% CI)	*p* Value
Nausea/vomiting	79/429	271/428	40.84	0.29 (0.24–0.36)	<0.00001
Loss of appetite	61/300	161/298	37.10	0.38 (0.29–0.48)	<0.00001
Taste disturbance	74/528	283/526	33.90	0.26 (0.21–0.33)	<0.00001
Abdominal pain	62/300	130/298	32.10	0.47 (0.37–0.61)	<0.00001
Heartburn	35/255	113/253	29.10	0.31 (0.22–0.43)	<0.00001
Flatulence	53/335	125/333	26.60	0.42 (0.32–0.56)	<0.00001
Diarrhea	20/404	111/403	16.23	0.18 (0.11–0.28)	<0.00001
Headache	10/255	69/255	15.50	0.14 (0.08–0.27)	<0.00001
Dizziness	6/50	8/50	14.00%	0.75 (0.28–2.00)	=0.57
Cramp	13/211	44/210	13.54%	0.29 (0.16–0.53)	<0.00001

CI, confidence interval; *L. reuteri, Lactobacillus reuteri*; RR, relative risk.

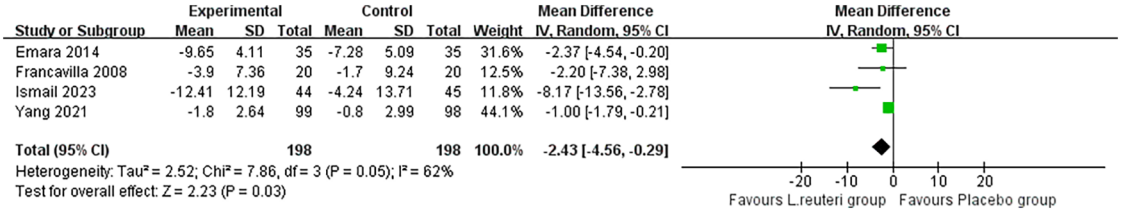

Figure 4. Forest plots of the score changes from the baseline of Gastrointestinal Symptom Rating Scale with or without *L. reuteri* supplementation.

we found that the treatment duration of *L. reuteri* for 4 weeks or longer showed a significant advantage in improving the eradication rate compared with the placebo group (ITT: $p = 0.02$, RR: 1.18; 95% CI: 1.02–1.35; PP: $p = 0.01$, RR: 1.19; 95% CI: 1.04–1.36). This superiority was also significant in first-line treatment (ITT: $p = 0.03$, RR: 1.08; 95% CI: 1.01–1.16; PP: $p = 0.04$, RR: 1.07; 95% CI: 1.00–1.14). Although some subgroup analysis results indicated a favorable trend in the *L. reuteri* supplementation group, there was no statistical difference due to the limited number of articles included.

Sensitivity analysis

By conducting a one-study-removed sensitivity analysis, we found that none of the studies had a substantial impact on the pooled risk of *H. pylori* eradication rates, indicating the reliability of our results (Supplemental Figure S2).

Publication bias

The funnel plot obtained by ITT and PP analyses of the eradication rates showed a roughly symmetrical distribution (Supplemental Figure S3). We found no significant publication bias in the pooled eradication rates as determined by Egger's test. However, it should be noted that the number of studies included in the analysis was relatively small (Supplemental Figure S4).

Discussion

The management of *H. pylori* infection is becoming increasingly critical, particularly in countries

Table 3. Subgroup analysis for the eradication rate of *H. pylori*.

Group	No. of studies	ITT				PP			
		Pooled estimate		Test of heterogeneity		Pooled estimate		Test of heterogeneity	
		RR (95% CI)	*p*	I^2 (%)	*p* Value	RR (95% CI)	*p*	I^2 (%)	*p* Value
Total	8	1.10 (1.03–1.17)	0.005	10	0.36	1.09 (1.03–1.16)	0.006	19	0.27
Nation									
Asia	5	1.08 (1.01–1.16)	0.03	21	0.27	1.07 (1.00–1.15)	0.04	32	0.20
Europe	3	1.19 (0.99–1.41)	0.06	0	0.49	1.19 (1.01–1.40)	0.04	0	0.48
Eradication therapy									
Triple therapy	5	1.15 (0.99–1.33)	0.06	51	0.08	1.16 (0.99–1.35)	0.07	59	0.05
BQT	2	1.08 (0.98–1.18)	0.11	0	0.75	1.06 (0.97–1.16)	0.23	0	0.77
Sequential therapy	1	1.00 (0.67–1.50)	–	–	–	1.06 (0.80–1.42)	–	–	–
Duration of *L.reuteri*									
1-week	1	0.94 (0.66–1.36)	–	–	–	0.94 (0.66–1.36)	–	–	–
2-week	4	1.08 (1.00–1.17)	0.04	35	0.2	1.07 (1.00–1.15)	0.06	32	0.22
4-week and more	4	1.18 (1.02–1.35)	0.02	0	0.60	1.19 (1.04–1.36)	0.01	0	0.50
Supplement time for *L.reuteri*									
Pre-treatment	3	1.09 (0.88–1.36)	0.43	65	0.06	1.11 (0.90–1.37)	0.32	71	0.03
Concurrent with treatment	2	1.08 (0.98–1.18)	0.11	0	0.75	1.06 (0.97–1.16)	0.23	0	0.77
Continued after treatment	3	1.20 (1.02–1.42)	0.03	0	0.66	1.19 (1.01–1.41)	0.04	0	0.61
Treatment lines									
First	6	1.08 (1.01–1.16)	0.03	8	0.36	1.07 (1.00–1.14)	0.04	17	0.30
Second and more	1	1.33 (1.01–1.76)	–	–	–	1.33 (1.01–1.76)	–	–	–
Unclear	1	1.13 (0.83–1.54)	–	–	–	1.13 (0.83–1.54)	–	–	–

BQT, bismuth quadruple therapy; CI, confidence interval; ITT, intention-to-treat; *L. reuteri, Lactobacillus reuteri*; –, not available; PP, per-protocol; RR, relative risk.

with high antibiotic resistance. Despite the availability of different treatment approaches, concerns over treatment failure and side effects continue to grow in routine clinical practice.[2] Many researchers have explored whether probiotic supplementation can benefit *H. pylori* treatment, but the results are contradictory. Several studies showed that probiotics helped improve the eradication rate of *H. pylori*, but this benefit was only applicable to specific strains, including different strains of *Lactobacillus* spp., *Bifidobacteria* spp., and *Saccharomyces boulardii*.[3] In the absence of sufficient evidence, recent guidelines were conservative on the recommendation of probiotics in *H. pylori* eradication therapy and only suggested that supplementation with probiotics may reduce

the incidence of side effects associated with eradication therapy.[3,24] In our meta-analysis, we included eight RCTs comparing supplementation with *L. reuteri versus* placebo in the treatment with *H. pylori* and observed positive findings across several outcome measures, including an increased eradication rate of *H. pylori*, a reduced overall incidence of antibiotic-related side effects, and alleviation of gastrointestinal symptoms in patients during treatment. Notably, the probiotic group exhibited a significantly higher eradication rate than the placebo group, with a 7.4% improvement in the ITT analysis (80.0% *versus* 72.6%, $p=0.005$) and a 6.8% improvement in the PP analysis (81.8% *versus* 75.0%; $p=0.006$).

Probiotics may exert direct inhibition on *H. pylori* in a variety of ways. Primarily, the synthesis of antimicrobial peptides or organic acids may be one of the mechanisms through which specific probiotics, such as *Lactobacillus* and *Bifidobacterial*, combat *H. pylori* infections.[25,26] Second, probiotics such as *Lactobacillus* spp. can exert anti-inflammatory effects by activating suppressor of cytokine signaling expression in patients with *H. pylori* infection.[27] Furthermore, some studies have demonstrated that *L. reuteri* can significantly reduce the bacterial load,[28] inhibit the colonization of *H. pylori* in the gastric mucosa, and eliminate the bacteria without the need for antibiotics, thus minimizing the damage to the human body.[29]

A number of meta-analyses of RCTs have assessed the efficacy and side effects of probiotics in *H. pylori* eradication therapy and have shown that certain probiotics (certain strains of *Lactobacillus, Bifidobacterium*, and *S. boulardii*) can be effective in increasing the eradication rate and mitigating AEs associated with *H. pylori* eradication therapy.[30–33] However, pooling data from studies of different probiotic strains may lead to bias. In the present study, we focused on the effects of *L. reuteri* on *H. pylori* therapy; however, there is a lack of studies that directly compare the efficacy of different probiotic strains in the adjuvant treatment of *H. pylori*. Therefore, more studies are needed to explore the impact of different probiotic strains on *H. pylori* eradication to provide new insights into clinical treatment.

Some previously published studies on the efficacy of probiotics for treating *H. pylori* have not yielded conclusions consistent with ours. For example, in the retrospective study of Zagari *et al.*,[34] there was no difference in eradication rates in patients with and without probiotic supplementation. However, although various probiotics were used and evaluated in the study, only three patients used *L. reuteri* as the probiotic supplementation; the cure rate achieved with the bismuth quadruple therapy regimen was so high that any potential benefits of probiotic supplementation were not evident. In addition, the convenience of the three-in-one pill increased patient compliance, thus reducing the likelihood that probiotics enhanced eradication rate by improving patient adherence. In contrast, probiotics demonstrate a clear advantage in triple therapy with lower *H. pylori* eradication rate.[10]

Our subgroup analysis based on different regimens found that *L. reuteri* supplementation had no statistically significant effect on the eradication rates in triple, quadruple, or sequential therapy, and high eradication rates (>90%) were not achieved in any of these regimens. However, the results of our subgroup analysis supported that supplementation with *L. reuteri* in first-line treatment regimen improved *H. pylori* eradication rates by 5.8% (80.1% *versus* 74.3%, $p=0.03$) in ITT analysis and 5.5% (82.6% *versus* 77.1%, $p=0.04$) in PP analysis. We also examined the effect of the timing and duration of *L. reuteri* supplementation on the eradication rates. In our meta-analysis, we found that treatment with *L. reuteri* for 4 weeks or longer had a significant advantage compared to the placebo group. Therefore, we supposed that appropriately extending the probiotic treatment course may be beneficial for improving the eradication rate. When considering the timing of *L. reuteri* supplementation, it would be advantageous to use it with an eradication regimen and to continue its use for a period of time after the withdrawal of treatment. These conclusions were consistent with some published studies,[10,35] which reported higher eradication rates with *Lactobacillus*-supplemented triple therapy and indicated that a longer duration of *Lactobacillus* supplementation may improve the eradication efficacy. Furthermore, variations in the duration and species of supplementation with *Lactobacillus* and other factors, as well as the large sample size and multi-center nature of these studies, may have contributed to the different results observed.

When we assessed gastrointestinal symptoms using a self-assessment questionnaire, we observed significant improvements in both the

frequency and severity of symptoms in patients who received *L. reuteri* supplementation. Similarly, several studies have explicitly reported the effectiveness of *L. reuteri* in improving symptoms such as functional constipation, abdominal distension, and diarrhea.[36,37] The gut microbiota is in a delicate balance and can easily be disrupted by antibiotics, leading to a series of imbalances. We also investigated whether *L. reuteri* can reduce the incidence of antibiotic-related side effects and found that the group supplemented with probiotics had a lower incidence of AEs. In our meta-analysis, it was found that the three most common AEs were nausea or vomiting, loss of appetite, and taste disturbance. However, due to the chronic nature of *H. pylori* infection and the fact that *L. reuteri* may not be able to colonize sustainably in the human gut after stopping supplementation, we cannot afford the possibility that these benefits are temporary. There is evidence that patient compliance is a crucial factor in *H. pylori* eradication, which is significantly impacted by AEs of treatment.[38,39] Therefore, our conclusions tend to favor supplementation with *L. reuteri* to improve the eradication rate by improving patient compliance. Nevertheless, the eradication rate of *H. pylori* was slightly improved, with an NNT of 14 in the ITT analysis and 15 in the PP analysis. Clinical supplementation of *L. reuteri* as an adjuvant for *H. pylori* eradication still requires individualized consideration and comprehensive evaluation.

Our meta-analysis had two main advantages. First, this was the first meta-analysis to evaluate the efficacy and safety of supplementing *L. reuteri* with standard *H. pylori* eradication therapy, providing a basis for its future clinical application. Second, all studies included were high quality RCTs, ensuring the reliability and validity of the overall results. However, there were also some limitations in our review. First, the sample size of our study was limited, especially in subgroup analyses; therefore, no conclusion can be drawn on the timing of *L. reuteri* supplementation. Second, we used GSRS to assess patients' symptoms, which have strong individual perceptual differences and may increase the risk of information bias. Finally, studies that were published in languages other than English or did not mention relevant keywords in the title or abstract may have been missed.

Conclusion

In summary, this meta-analysis demonstrated that supplementation with *L. reuteri* was beneficial for improving the eradication rate of *H. pylori*, reducing the overall incidence of antibiotic-related side effects, and relieving gastrointestinal symptoms in patients during treatment. The findings provide new insights into clinical decision-making. Further larger-scale trials are necessary to verify our results.

Declarations

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Author contributions

Meng Li: Data curation; Formal analysis; Investigation; Writing – original draft; Writing – review & editing.

Xiaolei Wang: Conceptualization; Resources; Writing – original draft.

Xinhong Dong: Formal analysis; Resources; Software; Supervision; Writing – review & editing.

Guigen Teng: Data curation; Formal analysis; Methodology; Project administration; Writing – review & editing.

Yun Dai: Data curation; Investigation; Validation; Visualization; Writing – review & editing.

Weihong Wang: Methodology; Project administration; Supervision; Writing – original draft; Writing – review & editing.

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Competing interests

The authors declare that there is no conflict of interest.

Availability of data and materials

All data and materials involved in this article are available from the author.

ORCID iDs

Meng Li https://orcid.org/0009-0001-0280-0111

Weihong Wang https://orcid.org/0000-0003-4740-7388

Supplemental material

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Appendix

Abbreviations

ACR	assumed control risk
AEs	adverse events
BQT	bismuth quadruple therapy
CIs	confidence intervals
GSRS	Gastrointestinal Symptom Rating Scale
H. pylori	*Helicobacter pylori*
ITT	intention-to-treat
L. reuteri	*Lactobacillus reuteri*
MDs	mean differences
NNT	number needed to treat
PP	per-protocol
RCTs	randomized controlled trials
RRs	risk ratios