Efficacy and Safety of *Saccharomyces Boulardii* with Standard Quadruple Therapy for Eradication of *Helicobacter Pylori* in Adults: Meta-Analysis

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ABSTRACT

Helicobacter pylori is a class I carcinogen, strongly associated with gastric cancer, gastric ulcers, and gastric mucosa-associated lymphoid tissue (MALT) lymphoma. *Helicobacter pylori* (*H. pylori*) infection necessitates effective eradication strategies. This study evaluated *Saccharomyces boulardii (S. boulardii)* as an adjunctive therapy to standard bismuth-containing quadruple therapy for *H. pylori* eradication. Comprehensive searches across PubMed, Embase, Cochrane Library, CNKI, WanFang Data, CBM, and Web of Science identified relevant randomised controlled trials (RCTs). Analysis of 11 RCTs (n = 2,295 patients) demonstrated significantly higher eradication rates (78.6% to 89.2%) with adjunctive *S. boulardii* (n = 2,295; ITT analysis: RR = 1.12; 95% CI: 1.06–1.18; Z = 4.27, p <0.01) *versus* standard therapy alone. Crucially, the probiotic combination also substantially reduced treatment-related adverse events (n = 2,183; RR = 0.46; 95% CI: 0.28–0.74; Z = 3.16; p = 0.002), with pronounced reductions in diarrhoea (n = 2,091; RR = 0.46; 95% CI: 0.22–0.93; Z = 2.15; p = 0.03) and rash occurrence (n = 1,271; RR = 0.33; 95% CI: 0.14–0.77; Z = 2.55; p = 0.01). These findings support *S. boulardii* supplementation as an effective strategy that enhances standard bismuth quadruple therapy efficacy while mitigating gastrointestinal and dermatological complications in *H. pylori* management. Therefore, the combination of *S. boulardii* and bismuth-containing quadruple therapy was effective in the treatment of *H. pylori* infection and has shown significant efficacy and safety as an effective and safe treatment.

Key Words: *Saccharomyces boulardii*, *Helicobacter pylori, Bismuth, Quadruple therapy*.

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INTRODUCTION

Helicobacter pylori (*H. pylori*) is a Class I carcinogen for gastric cancer. According to a national *H. pylori* infection epidemiological survey conducted by the China Early Gastrointestinal Cancer Prevention and Treatment Centre, the infection rate in China stands at 40.66%, with intrafamilial transmission reaching 71.21%.[1] Eradicating *H. pylori* can have significant benefits in preventing gastric cancer, and international consensus dictates that eradication therapy is essential for *H. pylori*-infected individuals without contraindications.[2]

Antibiotic-based eradication regimens have historically constituted the mainstay approach, although divergent protocols yield variable efficacy.[3-7] Initial triple therapy predominated, yet declining eradication rates emerged alongside rising antibiotic resistance.

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Subsequently, bismuth-containing quadruple therapy was introduced, with bismuth supplementation enhancing eradication rates.[8] Recent evidence indicates that dual therapy demonstrates non-inferiority to conventional triple or quadruple regimens while offering improved tolerability and adherence. Nevertheless, quadruple therapy remains predominant, as bismuth inclusion elevates eradication rates for resistant strains by 30-40%, thereby improving overall efficacy. Given its favourable efficacy-safety profile, 14-day bismuth-containing quadruple therapy is recommended as a first-line treatment in numerous countries.[1,2,9]

However, suboptimal eradication rates persist due to antibiotic resistance and poor adherence stemming from adverse drug reactions.[10] Consequently, more effective and safer therapeutic approaches are required. With advances in probiotic research, these agents have been incorporated into *H. pylori* eradication strategies. Studies indicate adjunctive probiotic supplementation to bismuth quadruple therapy enhances eradication rates while significantly reducing treatment-related adverse effects and improving adherence.[11-14] Although probiotics demonstrate efficacy, evidence suggests compound probiotics confer no significant therapeutic or tolerability advantage over single-strain formulations.[15] The selection of optimal probiotic strains is therefore imperative.

S. boulardii, a classical fungal probiotic, inhibits *H. pylori* colonisation and growth through multiple mechanisms, including antimicrobial substance production and immune modulation.[16,17] Its intrinsic antibiotic resistance preserves viability during co-administration with antibiotics, while its adverse effect profile remains favourable. Comparative studies indicate that *S. boulardii* outperforms bacterial probiotics when combined with antibiotic therapy, exhibiting superior capacity to suppress antibiotic resistance and reduce antimicrobial resistance gene (ARG) abundance—particularly for lincosamide, tetracycline, MLS-B, and β-lactam resistance determinants.[18,19] Crucially, bismuth's protective colloidal precipitate formation in acidic environments does not impair S. boulardii viability. These advantages have generated interest in potential synergistic effects between *S. boulardii* and standard bismuth-containing quadruple therapy.

Despite existing applications of *S. boulardii* in adjuvant *H. pylori* eradication, inconsistent findings preclude definitive conclusions regarding its efficacy and safety. Although numerous studies have evaluated its combination with triple therapy, meta-analyses examining its adjunctive use with standard bismuth-containing quadruple therapy remain scarce. Consequently, the therapeutic impact of *S. boulardii* co-administration cannot be adequately assessed despite quadruple therapy's current predominance. This meta-analysis aimed to evaluate the efficacy and safety of *S. boulardii* supplementation in standard bismuth-containing quadruple therapy for *H. pylori* eradication, thereby informing future treatment approaches.

METHODOLOGY

This meta-analysis adhered to predefined protocols to evaluate the efficacy of *S. boulardii* as an adjunct to 14-day bismuth-containing quadruple therapy for *H. pylori* eradication. Eligible studies were restricted to randomised controlled trials (RCTs) involving adult patients with confirmed *H. pylori* infection diagnosed *via* urea breath test, histologic examination, or foecal antigen testing. The experimental intervention comprised standard quadruple therapy (proton pump inhibitor, bismuth agent, and two antibiotics) combined with *S. boulardii*, while the Control group received identical quadruple therapy without the probiotic. Exclusion criteria included paediatric populations, non-bismuth regimens, animal studies, duplicates, and non-RCT designs.

A comprehensive search of PubMed, Embase, Cochrane Library, CNKI, Wanfang Data, CBM, and Web of Science was conducted from database inception to June 2022. Search strategies combined Medical Subject Headings (MeSH) terms and free-text keywords related to *S. boulardii*, *H. pylori*, and quadruple therapy. Two independent reviewers screened titles or abstracts, followed by full-text assessments against inclusion criteria. Data extraction forms captured study characteristics (*e.g.*, sample size and antibiotic combinations), intervention details (dosage or duration of *S. boulardii*), and outcomes (eradication rates and adverse events). Discrepancies were resolved through consensus or consultation with a third reviewer. The risk of bias was evaluated using the Cochrane Collaboration's tool, assessing randomisation, allocation concealment, blinding, and reporting completeness.

Statistical analyses were performed using RevMan 5.4.1. Dichotomous outcomes (eradication success and adverse events) were pooled using relative risk (RR) with 95% confidence intervals (CIs). Heterogeneity was quantified *via* the I^2 statistic, with I^2 >50% indicating substantial heterogeneity and prompting the use of a random-effects model. Sensitivity analyses alternated fixed- and random-effects models to assess robustness. Publication bias was evaluated *via* funnel plots for outcomes involving ≥10 studies.

RESULTS

Initially, 694 papers were identified. After applying the inclusion and exclusion criteria, 11 RCTs meeting the specified criteria were ultimately chosen (Figure 1).[20-30]

These 11 trials collectively involved 2,295 patients. All trials exclusively involved adult participants and incorporated *S. boulardii* as an adjunct to standard quadruple therapy, consisting of two antibiotics: a proton pump inhibitor and bismuth. Although the dosage of *S. boulardii* varied among the studies, the baseline characteristics were generally comparable across all trials (Table I).

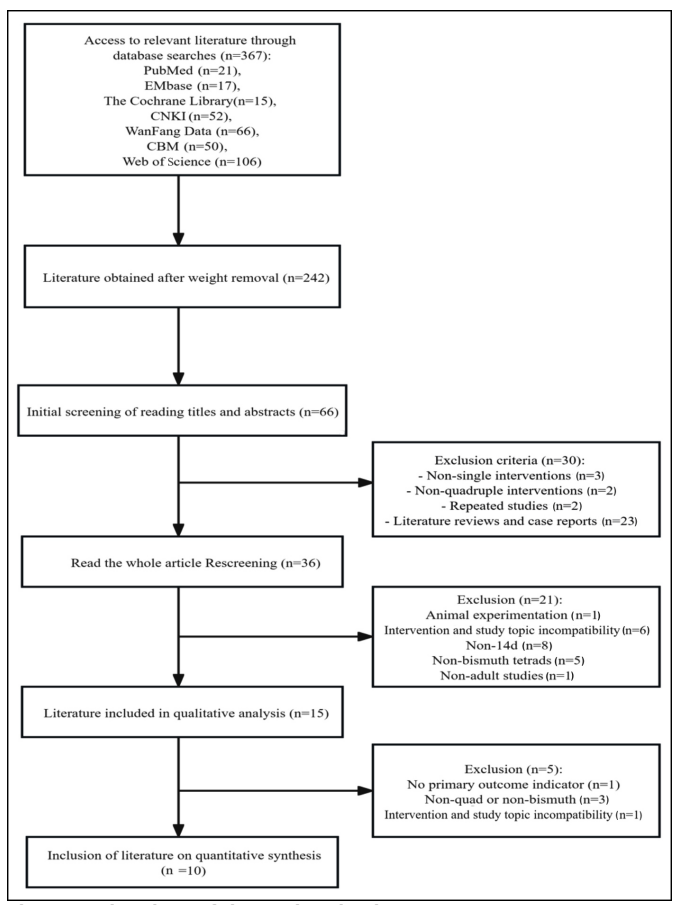

Figure 1: Flowchart of the study selection.

Table I: Characteristics of the included literature (baseline table).

Inclusion of studies	Country	Quadruple programme	Age/Gender		*H. pylori* infection eradication judgment method
			***Boulardii* + quadruple therapy group n = 1143**	**Quadruple therapy group n = 1152**	
Duwenjie 2018	China	A+C+O+CB	37.5 ± 12.3 Male 53.7%	40.3 ± 10.6 Male 55.6%	UBT
Yinjuan 2020	China	A+C+L+B	52.45 ± 4.24 Male 51.7%	53.52 ± 4.42 Male 53.3%	UBT
Dongshanzeng 2017	China	A+F+R+CB	29.6 ± 3.5 Male 51.2%	33.3 ± 5.9 Male 49.2%	UBT
Tianying 2019	China	A+F+E+B	43.52 ± 11.63 Male 59.1%	44.52 ± 10.94 Male 63.6%	UBT
Wanghuixia 2021	China	A+C+R+B	46.80 ± 16.46 Male 58.8%	46.78 ± 14.15 Male 65.9%	UBT
Songjindong 2018	China	A+F+R+B	41.69 ± 13.67 Male 61.4%	41.49 ± 11.69 Male 67.1%	UBT
Hechenxi 2019	China	A+F+P+B	47.0 ± 12.8 Male 61.0%	49.3 ± 12.6 Male 23.0%	UBT
Sunyuhong 2022	China	A+C+R+CB	41.09 ± 4.65 Male 58.7%	43.69 ± 5.29 Male 52.2%	UBT
Songyiwei 2019	China	T+C+P+B	43.76 ± 10.81 Male 61.8%	45.66 ± 12.26 Male 53.9%	UBT
ZhaoYuchong 2021	China	A+C+E+B	45.31 ± 11.46 Male 50.9%	46.68 ± 12.85 Male 54.2%	UBT
Nooshin, Naghibzadeh 2022	Iran	A+C+E/L/P/R+B	49.32 ± 13.42 Male 48.1%	46.57 ± 14.20 Male 34.6%	UBT

A: Amoxicillin; C: Clarithromycin; F: Furazolidone; T: Tinidazole; L: Lansoprazole; R: Rabeprazole; O: Omeprazole; P: Pantoprazole; E: Esomeprazole; B: Bismuth potassium citrate; CB: Colloidal bismuth pectin.

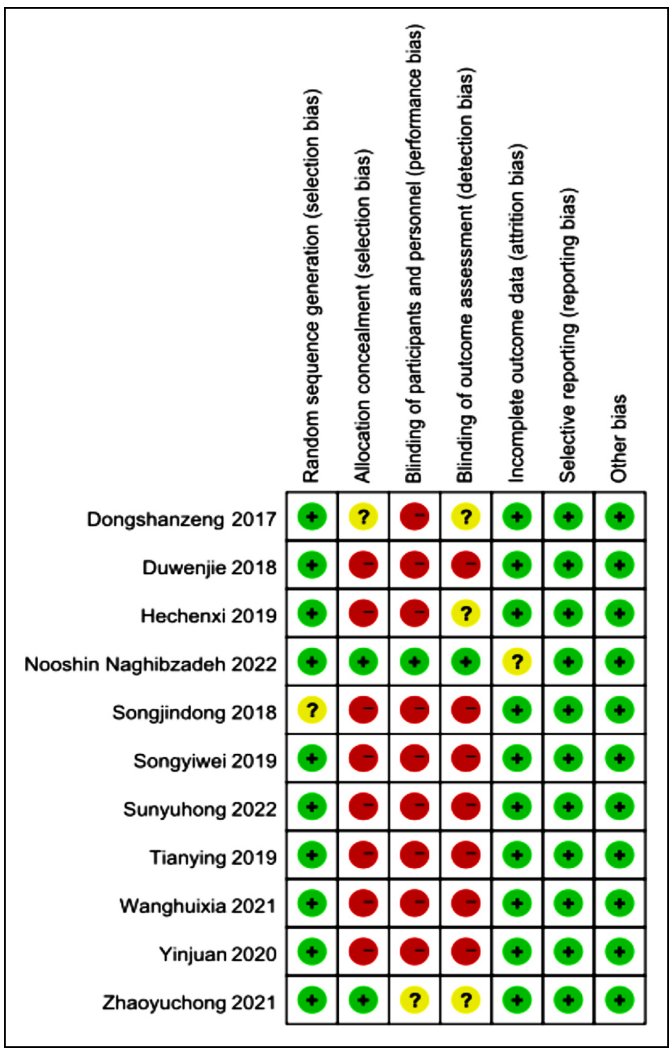

Figure 2: Risk of bias summary: Review authors' judgments for each risk-of-bias item in each included study.

All the included studies reported the application of a randomised controlled methodology, with ten studies providing detailed descriptions of the randomisation process and one study mentioning blinding. While outcome data completeness was confirmed in all studies, ten of them were categorised as unclear in terms of allocation concealment and other biases. Overall, the studies had issues with inadequately described blinding and allocation concealment, resulting in a moderate overall study quality (Figure 2).

The analysis of *H. pylori* eradication outcomes demonstrated statistically and clinically superior efficacy with *S. boulardii* supplementation. The probiotic adjunct group achieved an 89.2% eradication rate (1019/1143) compared to 78.6% (906/1152) in the Control group, yielding a robust relative risk of 1.12 (95% CI: 1.06-1.18; p <0.001). This represents an absolute risk difference of 10.6% (95% CI: 8.1-13.1%). Heterogeneity remained low (I^2 = 12%), confirming consistent effects across studies (Figure 3).

All of the included studies reported data regarding adverse reactions during *H. pylori* eradication with *S. boulardii* therapy. Of these, 10 studies provided information on the overall incidence of adverse reactions.[21-24,26,27,29,31] There was significant heterogeneity among the included studies (p <0.001, I^2 = 78%). This meta-analysis used the intention-to-treat (ITT) data with a random effects model (REM). The findings indicated a significantly reduced overall incidence of adverse reactions in the group receiving *S. boulardii* combination therapy compared to the Control group. (RR = 0.46; 95% CI: 0.28-0.74; Z = 3.16; p = 0.002; Figure 4).

Regarding specific adverse reaction rates, the combination therapy with *S. boulardii* demonstrated reduced rates of diarrhoea (n = 2,091; ITT analysis: RR = 0.46; 95% CI: 0.22-0.93; p = 0.03) and rash (n = 1,271; ITT analysis: RR = 0.33; 95% CI: 0.14-0.77; p = 0.01) incidence (Figure 5A and 5B). However, no statistically significant differences were observed in the incidence of adverse reactions, such as bloating, abdominal pain, nausea, dizziness, constipation, and abnormal taste (Figure 6).

Sensitivity analyses were conducted for both *H. pylori* eradication rates and the overall incidence of adverse effects. The alternated between utilising a fixed-effects model (FEM) and a REM for the meta-analysis, comparing their respective outcomes. The results from the two models were found to be highly consistent. Additionally, item-by-item exclusion was used to evaluate the influence of each study on the meta-analysis outcomes, with no significant alterations. Publication bias analysis was conducted using funnel plots. The outcomes revealed that the funnel plots for each outcome exhibited a symmetrical shape. However, a potential publication bias was detected for adverse reactions such as diarrhoea, nausea, and constipation. Further assessment through Egger's test was pending in the subsequent step.

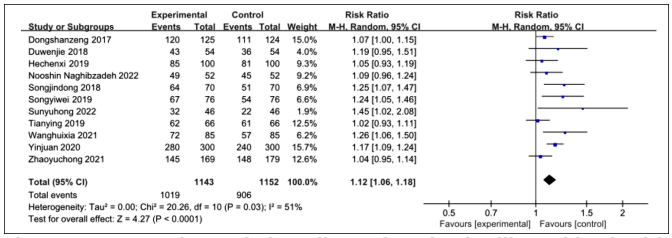

Figure 3: Comparison of the effect of *S. boulardii* combined with bismuth quadruple therapy and the Control group on *H. pylori* eradication rates.

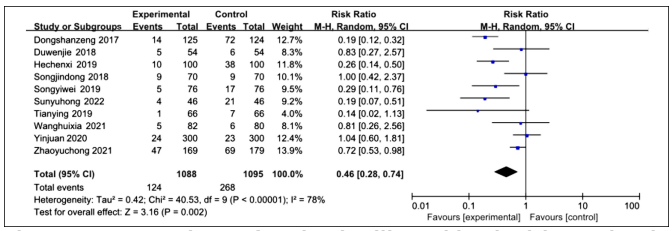

Figure 4: Comparison of *S. boulardii* combined with quadruple therapy and the Control group in terms of overall adverse reaction rate associated with *H. pylori* eradication.

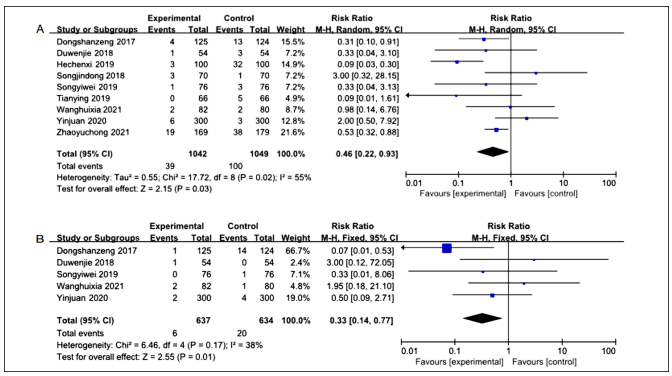

Figure 5: (A) Forest plot of the meta-analysis assessing the effect of *S. boulardii* on diarrhoea. (B) Forest plot of the meta-analysis assessing the effect of *S. boulardii* on rash.

DISCUSSION

This study encompassed 11 published RCTs involving 2,295 patients. The meta-analysis results indicated that a 14-day standard therapy incorporating *S. boulardii* in conjunction with bismuth-containing agents had a positive impact on *H. pylori* eradication rates and effectively reduced the overall incidence of adverse events, as per the ITT analysis. The pooled eradication rate for *H. pylori* was 85.2% (973/1143) in the *S. boulardii* group compared to 76.8% (884/1152) in the Control group, yielding an absolute improvement of 8.4% (95% CI:5.2–11.6%). This outcome aligns with the existing literature focusing on the overall efficacy of *S. boulardii* when combined with triple, quadruple, or sequential therapies.[31] Moreover, several studies have emphasised that probiotic supplementation, whether administered before, during, or after *H. pylori* eradication treatment, can enhance eradication rates and decrease the occurrence of side effects.[32] However, there have been conflicting reports suggesting that *S. boulardii* may not effectively enhance *H. pylori* infection eradication rates. One study indicated that neither *S. boulardii* nor broccoli sprout extract radish sulfide supplementation, when combined with standard triple therapy, improved *H. pylori* eradication rates or reduced adverse events.[33] Additionally, it has been reported that *S. boulardii* does not influence the *H. pylori* infection eradication rate when combined with quadruple therapy,[21] which contrasts with the findings of this meta-analysis. The discrepancies in results may be attributed, firstly, to the variations in the types of antibiotics utilised in the different study protocols. For instance, amoxicillin and furazolidone exhibit low resistance rates, while medicines such as clarithromycin and tinidazole exhibit high resistance rates. Consequently, disparities in the eradication rates of quadruple therapy may lead to divergent conclusions. Secondly, some studies had limited sample sizes, which may not have been sufficient to demonstrate statistically significant differences. Additionally, the effectiveness of *S. boulardii* in specific patient populations or geographic regions remains unclear.

The analysis revealed zero significantly higher incidence of adverse reactions in the *S. boulardii* group *versus* the Control group during *H. pylori* eradication therapy. These findings suggest that *S. boulardii* may be safely administered as an adjunctive treatment without elevating the risk of adverse effects. Subgroup analysis demonstrated the efficacy of *S. boulardii* in reducing the incidence of diarrhoea and rash. However, no statistically significant differences were observed for bloating, abdominal pain, nausea, dizziness, constipation, or abnormal taste. The addition of *S. boulardii* increased the *H. pylori* eradication rate from 78.6% to 89.2% (NNT = 9) and significantly reduced the risk of diarrhoea and rash. These findings do not entirely align with the results of previous meta-analyses, which have suggested that *S. boulardii* in combination with standard therapy can reduce the incidence of diarrhoea, bloating, nausea, vomiting, and taste disturbances. However, no statistically significant difference was observed in the incidence of abdominal pain between the two groups.[34] The reasons for these discrepancies may be attributed to the inclusion of populations with different ethnicities in previous studies, whereas the present trial primarily involved Asian populations, especially Chinese. This variation in population demographics could result in differences in baseline characteristics across the studies. Future studies ought to standardise probiotic dosages and treatment durations while ensuring greater inclusion of non-Asian populations. Additionally, variations in the definition of adverse reaction occurrence were noted across the studies, particularly in the reporting of rash as a complication, which was not consistently mentioned in many studies. Therefore, further research is warranted to explore the specific impact of *S. boulardii* use on treatment.

As a mucosal protective agent, bismuth plays a distinct role in *H. pylori* eradication therapy. Research has indicated that bismuth-containing quadruple therapy exhibits superior efficacy in refractory cases, such as drug-resistant or recurrent *H. pylori* infections, achieving higher eradication rates compared to conventional triple therapy.[35]

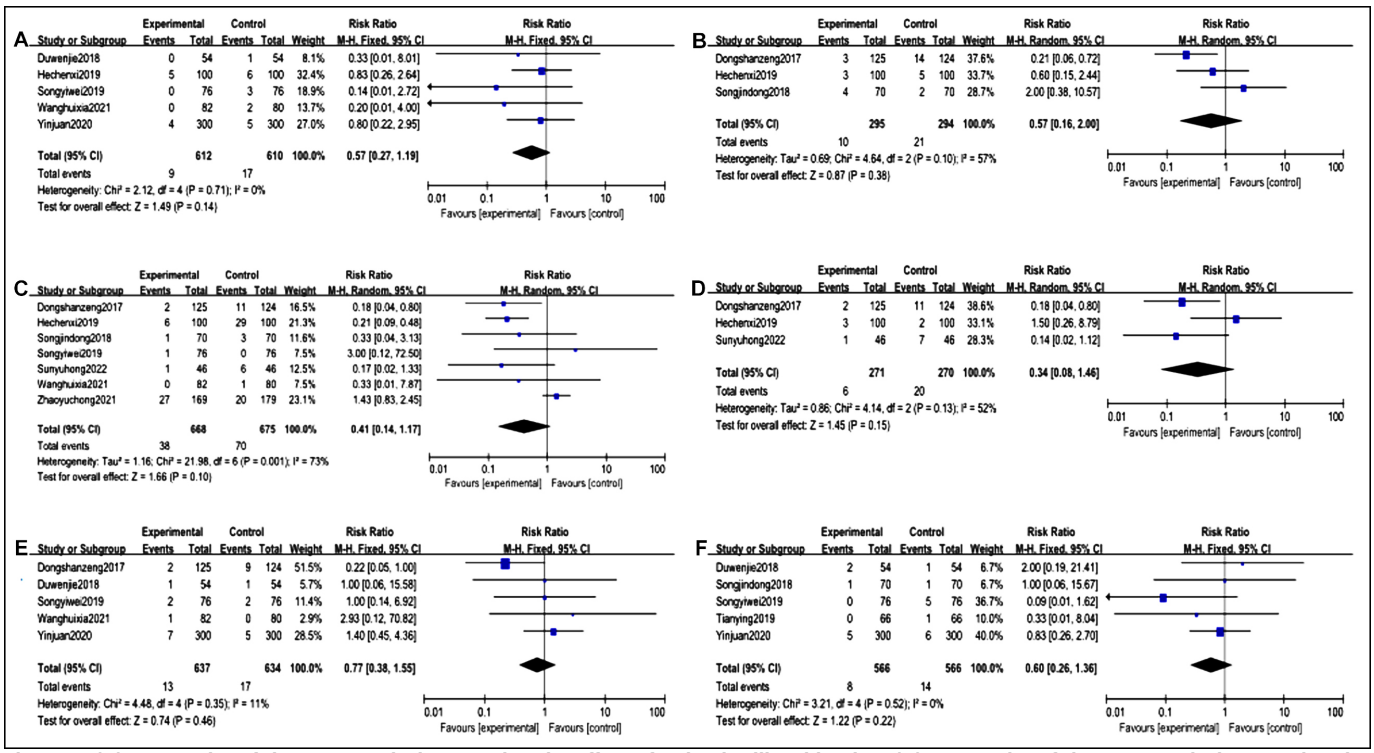

Figure 6: (A) Forest plot of the meta-analysis assessing the effect of *S. boulardii* on bloating. (B) Forest plot of the meta-analysis assessing the effect of *S. boulardii* on abdominal pain. (C) Forest plot of the meta-analysis assessing the effect of *S. boulardii* on nausea. (D) Forest plot of the meta-analysis assessing the effect of *S. boulardii* on dizziness. (E) Forest plot of the meta-analysis assessing the effect of *S. boulardii* on constipation. (F) Forest plot of meta-analysis assessing the effect of *S. boulardii* on taste abnormalities.

Importantly, no resistance to bismuth has been reported, and there is a synergistic effect between bismuth salts and antibiotics.[36,37] It should be noted that not all mucosal protectants enhance *H. pylori* eradication rates, as significant effects on *H. pylori* eradication rates have been observed with probiotics and triple therapy combined with the mucosal protector DA-9601.[38] This suggests variations in the effects and mechanisms of action among different mucosal protectants in *H. pylori* eradication, as well as the fact that these protectants target different aspects of the process.

This study has certain limitations. The study did not provide clear descriptions of the randomisation method, allocation concealment, and blinding. The sample size calculation was only reported in one of the included studies; the remaining studies did not specify how the sample size was determined. The study population primarily consisted of Chinese patients, and differences in antibiotic and bismuth usage patterns between China and Europe or the United States may limit the generalisability of the results to other regions. Adverse reactions are often subjective outcomes, and there may be inconsistencies in the definitions of adverse reactions across studies, which could potentially affect the accuracy of the analysed results. As additional related studies are conducted and updated, more objective conclusions may be drawn, and meta-analysis methods can be further refined to address the aforementioned limitations.

CONCLUSION

Significant efficacy in eradicating *H. pylori* infections and reducing the incidence of overall associated adverse effects, particularly diarrhoea and rash, was demonstrated for *S. boulardii* when used in combination with bismuth-containing agents.

COMPETING INTEREST:

The authors declared no conflict of interest.

AUTHORS' CONTRIBUTION:

FM: Data curation, formal analysis, writing, and original draft preparation.
HH: Original draft preparation.
KT: Data acquisition and analysis.
WW: Interpretation of the data.
All authors approved the final version of the manuscript to be published.

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