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Effect of *Saccharomyces boulardii* supplementation to bismuth quadruple therapy on *Helicobacter pylori* eradication

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Abstract

Background *Helicobacter pylori* (*H. pylori*) infection is a common chronic infection, and there are over half of the global population infected with *H. pylori*. It is still controversial whether the supplementation of *Saccharomyces boulardii* (*S. boulardii*) to bismuth quadruple therapy is beneficial for *H. pylori* eradication.

Aim To determine the effects of *S. boulardii* supplementation to bismuth quadruple therapy on *H. pylori* eradication.

Methods We performed a systematic literature search across PubMed, Embase, Web of Science, and China National Knowledge Infrastructure for articles published up to October 2023. We calculated the pooled relative risk (RR) with the 95% confidence interval (CI). Statistical analyses were conducted using Stata/SE 15.1 software.

Results Ten randomized controlled trials were included. Notably, *S. boulardii* supplementation to bismuth quadruple therapy significantly improved *H. pylori* eradication rates (RR = 1.08, 95% CI: 1.04–1.12) and reduced the incidence of total adverse effects (RR = 0.53, 95% CI: 0.45–0.62). Specifically, it reduced the incidence of some gastrointestinal adverse effects and nonspecific adverse effects, including diarrhea (RR = 0.28, 95% CI: 0.22–0.36), constipation (RR = 0.32, 95% CI: 0.18–0.55), abdominal distention (RR = 0.39, 95% CI: 0.26–0.59), nausea (RR = 0.59, 95% CI: 0.36–0.97), and rash (RR = 0.49, 95% CI: 0.28–0.86). In the subgroup analysis, long-term eradication duration (> 10 days; RR = 1.08, 95% CI: 1.04–1.13) and *S. boulardii* supplementation to be started and stopped at the same time as eradication treatment (RR = 1.09, 95% CI: 1.04–1.14) were found to significantly improve the eradication rate regardless of the *S. boulardii* dose (500 mg/day, RR = 1.10, 95% CI: 1.03–1.17; 1000 mg/day, RR = 1.08, 95% CI: 1.03–1.12).

Conclusions The addition of *S. boulardii* to bismuth quadruple therapy significantly increased *H. pylori* eradication rates and decreased the adverse effects. We recommend adding 500 mg/day *S. boulardii* concurrently with bismuth quadruple therapy and continuing this therapy for > 10 days for optimal *H. pylori* eradication efficacy.

Keywords *Saccharomyces boulardii*, Helicobacter pylori, Bismuth quadruple therapy, Meta-analysis

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Introduction

Helicobacter pylori (*H. pylori*) can cause various gastrointestinal diseases, including gastritis and peptic ulcers. It is also associated with an increased risk of developing gastric cancer [1]. According to the Maastricht VI/Florence consensus report, in areas of high (> 15%) or unknown clarithromycin resistance, the first-line recommended treatment is bismuth quadruple therapy [2]. Additionally, the 2022 Chinese national clinical practice guideline on *H. pylori* eradication treatment recommended a 14-day bismuth quadruple therapy as the first-line treatment for *H. pylori* eradication [3]. Nonetheless, the efficacy of bismuth quadruple therapy has diminished because of the increasing prevalence of antimicrobial-resistant strains and the high occurrence of adverse effects [4, 5].

Probiotics are living microorganisms that provide a health benefit to the host when administered in sufficient quantities [6]. They have attracted much attention as an adjunctive therapy for *H. pylori* eradication. *Saccharomyces boulardii* (*S. boulardii*) was originally isolated from the peel of a tropical fruit. Given that it is a type of fungi, it is inherently resistant to antibiotics and remains stable even when exposed to acidic environments, such as gastric acid [7]. Therefore, *S. boulardii* has higher viability than other common probiotics. Also, this yeast contributes to the homeostasis of the normal microbiome and plays a relevant role in modulating immunological function [8].

Previous studies have shown that the addition of *S. boulardii* to *H. pylori* eradication therapy significantly increased the eradication rate and decreased adverse effects [9–11]. However, all studies included in the two meta-analyses by Szajewska et al. [9, 10] focused only on the synergistic effect of *S. boulardii* on triple therapy for eradicating *H. pylori*. In 2019, Zhou et al. [11] conducted a meta-analysis to assess the effects of *S. boulardii* supplementation as an adjunct to standard triple therapy, quadruple therapy, and sequential therapy for eradicating *H. pylori*. Nevertheless, only two trials involving the use of bismuth quadruple therapy with *S. boulardii* supplementation were included in the subgroup analysis, which revealed that supplementing *S. boulardii* to bismuth quadruple therapy did not significantly improve eradication rates. There is a lack of evidence regarding the trials using the current recommended quadruple therapy. Furthermore, earlier meta-analyse lacked some subgroup analysis such as doses of S. boulardii supplementation, timing of S. boulardii administration.

Therefore, this meta-analysis was aimed at evaluating the efficacy and safety of bismuth quadruple therapy with *S. boulardii* supplementation and exploring the optimal timing and dose for adding *S. boulardii*.

Methods

Search strategy

Without any restrictions on regions or languages, we searched the following online databases for relevant clinical trials published from the date of inception to October 2023: PubMed, Web of Science, MEDLINE, Embase, and China National Knowledge Infrastructure (CNKI). The following Medical Subject Headings (MeSH) and free text keywords were used: "Helicobacter pylori," "*H. pylori*," "Saccharomyces boulardii," "boulardii," "probiotic," "bioflor," "randomized controlled trial," and "controlled clinical trial." The complete search strategy is shown in Table S1.

Inclusion and exclusion criteria

Clinical trials meeting the following criteria were included: (1) prospective randomized controlled trials; (2) studies with full-text available; (3) first-line treatment studies for *H. pylori* eradication; (4) studies with acceptable comparisons: conventional bismuth quadruple therapy with vs. without *S. boulardii*; (5) studies wherein *H. pylori* eradication results was confirmed at least four weeks after the completion of eradication therapy; and (6) studies with availability of the necessary data required for analyses.

The following were the exclusion criteria: (1) studies published as letters, case reports, comments, meta-analyses, reviews, and meeting abstracts; (2) studies with incomplete data; (3) studies using probiotics other than *S. boulardii* or using multi-strain probiotics which could confound the specific effects of *S. boulardii*; (4) studies on rescue therapy for *H. pylori* eradication; and (5) studies that were duplication or continuation of previous studies.

Data extraction

Two researchers (Yizhou Jiang and Kai Ma) independently screened the studies and assessed the quality of the included studies. Any disagreements were resolved by involving a third researcher (Xiaoyong Wang). The following data were extracted from each included study: the first author's name, year of publication, number of participants, eradication regimen, *S. boulardii* (dose, duration, and supplementation time), diagnostic methods of *H. pylori* (urea breath test, stool antigen test, rapid urease test, or histology), and the interval for rechecking *H. pylori* infection after the therapy.

Quality assessment

The risk of bias was assessed using the Cochrane Collaboration's tool for RCTs [12], which includes evaluation criteria of random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome

data, selective reporting, and other biases. Discrepancies in risk-of-bias judgments were resolved through discussion between two independent reviewers (Yizhou Jiang and Kai Ma), with unresolved cases arbitrated by a third researcher (Xiaoyong Wang). Review Manager 5.1(The Cochrane Collaboration, 2011) statistical software was used to perform the assessment of these studies. In addition, the quality of evidence for main outcomes was assessed using GRADEpro GDT.

Statistical analysis

We used the metan command in Stata/SE 15.1 (StataCorp, College Station, TX, USA) for the standard meta-analysis. Data on the eradication rate and incidence of total adverse effects were dichotomous outcomes, which were used for assessing the efficacy. We calculated pooled relative risk (RR) with a 95% confidence interval (CI). The heterogeneity across these studies was quantified using the I^2 statistic. An I^2 value of ≤ 50% indicated no heterogeneity between studies, and a fixed-effects model was used for the analysis. An I^2 value of > 50% indicated the presence of heterogeneity, and a random-effects model was used for the analysis. In addition, visual inspection of the funnel plot and Egger's tests were used to detect potential publication bias. We defined a P value of < 0.05 as statistically significant.

Results

Characteristics of the included studies

The selection process is shown in Fig. 1. A total of 1159 articles were retrieved from the database. Among these studies, 373 studies were excluded because of duplication. Then, the titles and abstracts of the remaining 786 publications were reviewed, and 767 studies that did not meet the inclusion criteria were excluded. A more detailed assessment was performed for the remaining 18 studies. Based on the selection criteria, 8 studies were excluded (Table S2). Finally, 10 RCTs enrolling 2307 participants were included in the meta-analysis [13–22]. The main characteristics of the studies are listed in Table 1. Among them, two studies were split into two parts to be included [16, 19], according to their group design. The publication year of the articles included in the analysis ranged from 2013 to 2023. The sample size varied from 82 to 348 participants. In two studies [16, 18], the eradication therapy was given for 10 days. The dose of *S. boulardii* supplementation was 1000 mg/day, except for two studies [15, 22], which used a dose of 500 mg/day.

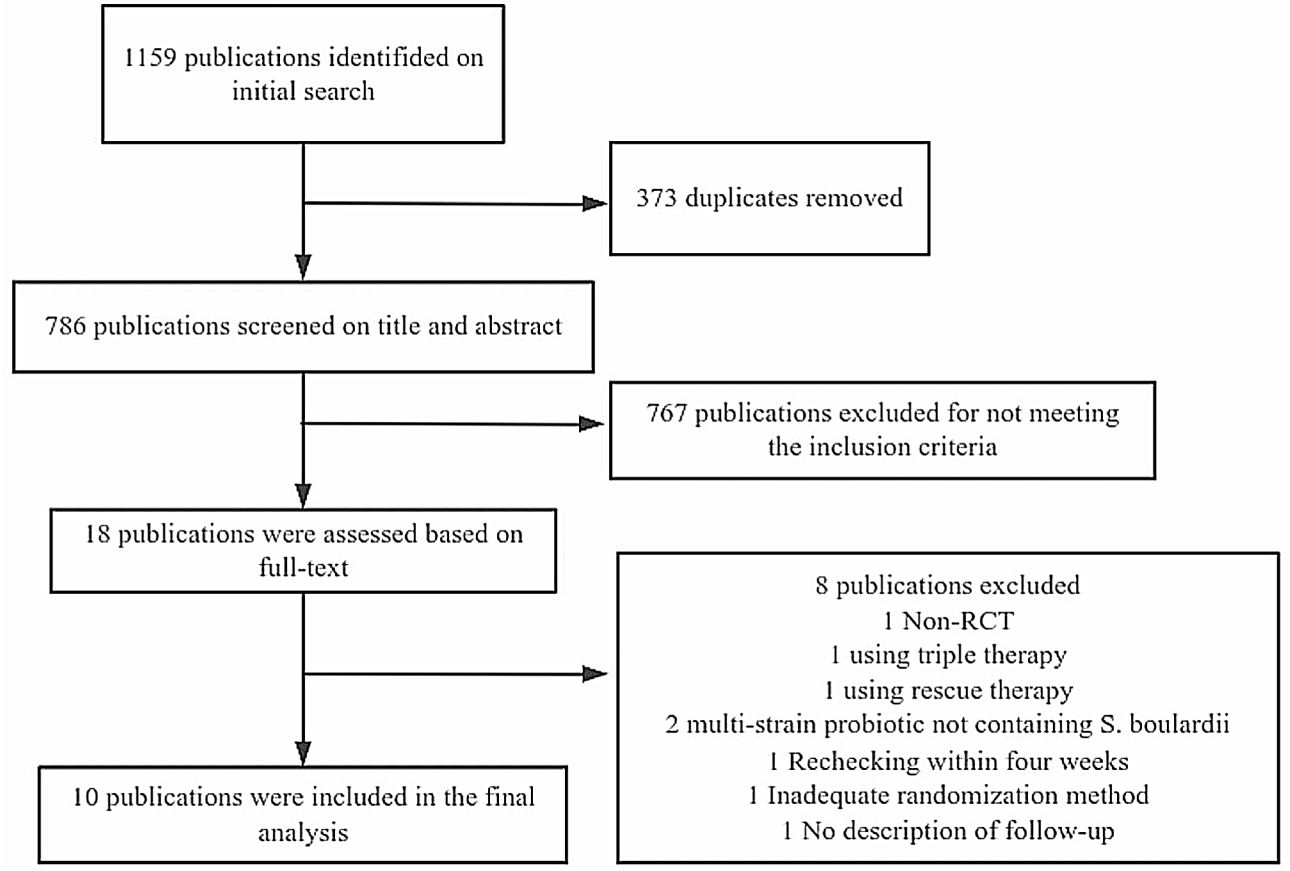

Fig. 1 Flow chart depicting screening and selection procedures

Table 1 Baseline characteristics of the included studies

First author and year	Total cases (Exp/Con)	Eradication regimen	Saccharomyces boulardii regimen (form, dose, duration)	Supplementation time	H. pylori assessment Initial/Rechecking		Follow-up time
Zhao 2021	348 (169/179)	E 20 mg bid, AMO 1000 mg bid, C 500 mg bid, B 600 mg bid, 14 d	Sachets, 1000 mg, 14 d	Same	UBT	UBT	4 w
He 2022	180 (90/90)	P 40 mg bid, AMO 1000 mg bid, C 500 mg bid, B 200 mg bid, 14 d	Sachets, 1000 mg, 14 d	Same	UBT/RUT	UBT	4 w
Dong 2017	249 (125/124)	R 20 mg qd, AMO 1000 mg bid, F 100 mg bid, B 100 mg bid, 14 d	Sachets, 500 mg, 14 d	Same	UBT	UBT	4–6 w
Zhu 2017(1)	160 (80/80)	R 10 mg bid, AMO 1000 mg bid, F 100 mg bid, B 220 mg bid, 10 d	Sachets, 1000 mg, 14 d	Different	UBT	UBT	4 w
Zhu 2017(2)	160 (80/80)	R 10 mg bid, AMO 1000 mg bid, F 100 mg bid, B 220 mg bid, 10 d	Sachets, 1000 mg, 28 d	Different	UBT	UBT	4 w
Du 2018	108 (54/54)	O 20 mg bid, AMO 1000 mg bid, C 500 mg bid, B 300 mg bid, 14 d	Sachets, 1000 mg, 14 d	Same	Histology /UBT	UBT	4 w
Zhu 2018	240 (120/120)	E 20 mg bid, AMO 1000 mg bid, F 100 mg bid, B 220 mg bid, 10 d	Sachets, 1000 mg, 14 d	Different	UBT	UBT	4 w
He 2019(1)	200 (100/100)	P 40 mg bid, AMO 1000 mg bid, F 100 mg bid, B 220 mg bid, 14 d	Sachets, 1000 mg, 14 d	Same	UBT/RUT	UBT	4 w
He 2019(2)	200 (100/100)	P 40 mg bid, AMO 1000 mg bid, F 100 mg bid, B 220 mg bid, 14 d	Sachets, 1000 mg, 14 d	Different	UBT/RUT	UBT	4 w
Zhao 2013	208 (104/104)	L 30 mg bid, AMO1000 mg bid, C 500 mg bid, B 150 mg tid, 14 d	Unspecified, 1000 mg, 14 d	Same	UBT	UBT	4 w
He 2023	172 (86/86)	E 20 mg bid, AMO 1000 mg bid, AN 500 mg bid, B 200 mg tid, 14 d	Sachets, 1000 mg, 14 d	Same	Histology /UBT	UBT	4 w
Chen 2023	82 (41/41)	E 20 mg bid, AMO 1000 mg bid, D 100 mg bid, B 600 mg bid, 12-14d	Sachets, 500 mg, 12–14 d	Same	UBT/RUT/Histology	UBT	4 w

AMO: amoxicillin; AN: antofloxacin; B: bismuth; C: clarithromycin; Con: control group; D: doxycycline; E: esomeprazole; Exp: experimental group (*S. boulardii* supplementation group); F: furazolidone; L: lansoprazole; O: omeprazole; P: pantoprazole; R: rabeprazole; RUT: rapid urease test; UBT: urea breath test

bid: twice daily; tid: three times daily; d: days; w: weeks

Same: the *S. boulardii* supplementation was started and ended at the same time as the eradication treatment

Different: the *S. boulardii* supplementation was not started and/or ended at the same time as the eradication treatment

Quality of the included studies

Among the 10 included studies, 9 studies [13–19, 21, 22] described the randomization processes used by them, and 2 studies [13, 21] provided adequate data regarding allocation concealment and described the blinding method. The remaining studies were judged as having unclear risk of bias due to insufficient information. The whole risk of bias is shown in Figure S1, and Figure S2. Moreover, the GRADEpro GDT tool was used to assess the quality of evidence for main outcomes; the quality of evidence for the *H. pylori* eradication rate and total adverse effects were assessed as moderate due to methodological shortcomings of some included studies (e.g., unclear random sequence generation, unclear allocation concealment, unclear or no blinding). Figure S3 shows the GRADE quality of findings in detail.

H. pylori eradication rates and incidence of adverse effects

Overall results

Among the included studies, there were 1173 patients in the *S. boulardii* supplementation group and 1181 patients in the control group. The eradication rate in the former was 87.3%, compared to 80.8% in the latter. In addition, the pooled RR was 1.08 (95% CI: 1.04–1.12, $P<0.0001$), suggesting that the addition of *S. boulardii* to bismuth quadruple therapy significantly improved the *H. pylori* eradication rate. Given the lack of any significant heterogeneity, these findings were analyzed with a fixed-effects model ($I^2=0\%$, $P=0.688$; Fig. 2).

Subgroup analysis

As the included studies differed in terms of eradication durations, doses of *S. boulardii* supplementation, timing of *S. boulardii* administration, and types of antibiotics, we conducted analyses on the following subgroups—the eradication duration: short-term (10 days) and long-term (>10 days); *S. boulardii* dose: low-dose (500 mg/day) and high-dose (1000 mg/day); *S. boulardii* supplementation time: *same* (*S. boulardii* supplementation was started and stopped at the same time as eradication treatment) and *different* (*S. boulardii* supplementation was not started and/or ended at the same time as eradication treatment); and type of antibiotics: amoxicillin + clarithromycin (AMO + C) and amoxicillin + furazolidone

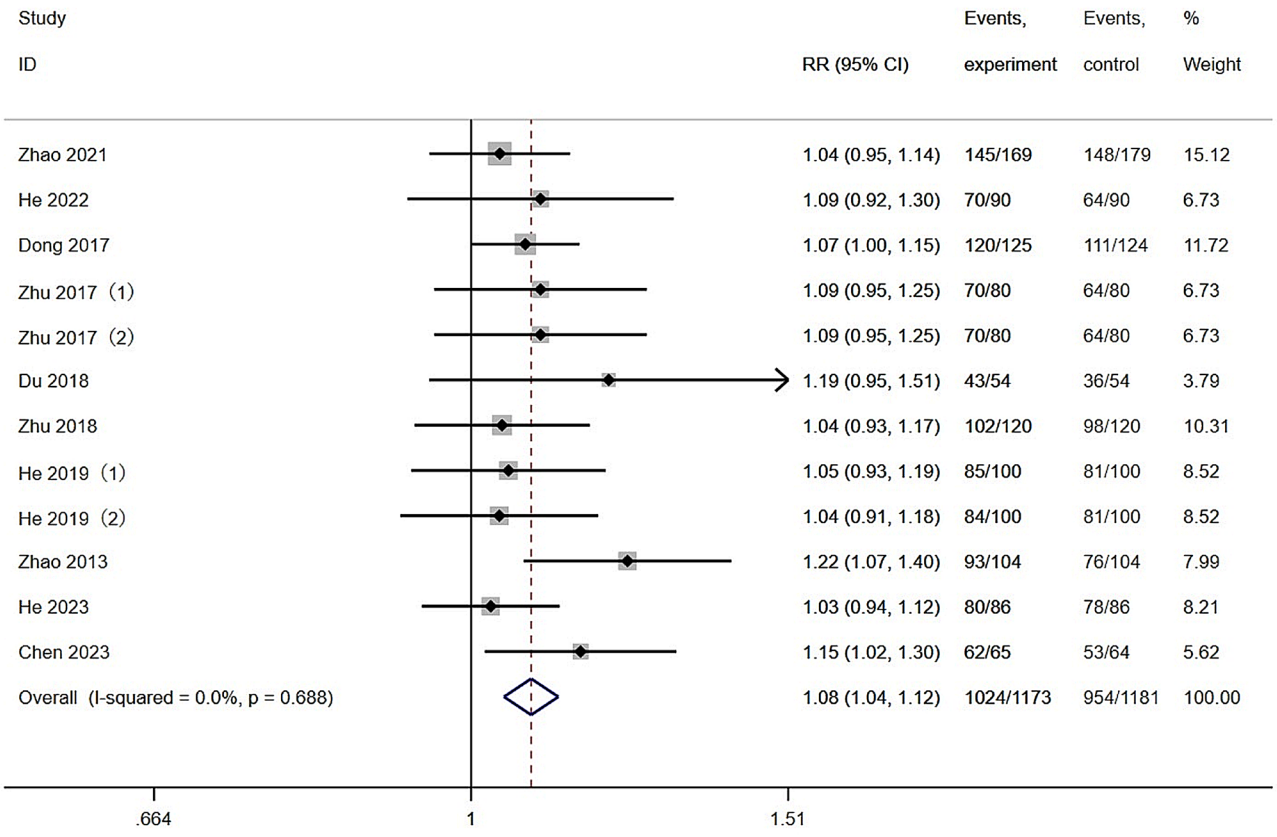

Fig. 2 Forest plot of *H. pylori* eradication rates for effects of *S. boulardii* supplementation

Table 2 Results of subgroup analyses for *H. pylori* eradication rates

Variable	Number of studies	RR (95% CI)	P_{effect}	I^2 (%)	$P_{heterogeneity}$
Eradication duration					
Short-term (10 days)	3	1.07 (0.99, 1.15)	0.069	0.0	0.809
Long-term (> 10days)	9	1.08 (1.04, 1.13)	< 0.0001	0.0	0.443
Saccharomyces boulardii dose					
Low-dose (500 mg/day)	2	1.10 (1.03, 1.17)	0.003	1.0	0.315
High-dose (1000 mg/day)	10	1.08 (1.03, 1.12)	< 0.0001	0.0	0.635
S. boulardii supplementation time					
Same[a]	8	1.09 (1.04, 1.14)	< 0.0001	8.8	0.362
Different[b]	4	1.06 (1.00, 1.13)	0.065	0.0	0.895
Type of antibiotics					
AMO + C	4	1.11 (1.04, 1.19)	0.002	34.3	0.207
AMO + F	6	1.06 (1.01, 1.11)	0.012	0.0	0.982

a: The *S. boulardii* supplementation was started and ended at the same time as the eradication treatment

b: The *S. boulardii* supplementation time was not started and/or ended at the same time as the eradication treatment

AMO: amoxicillin; C: clarithromycin; F: furazolidone

(AMO + F; Table 2). The subgroup analysis showed that *S. boulardii* supplementation caused a significant improvement in eradication rates (RR = 1.08, 95% CI: 1.04–1.13, $P < 0.0001$) in the long-term subgroup, whereas no significant statistical difference was observed (RR = 1.07, 95% CI: 0.99–1.15, $P = 0.069$) in the short-term subgroup. Subgroup analysis based on the *S. boulardii* dose showed that the pooled RRs in the low-dose and high-dose subgroups were 1.10 (95% CI: 1.03–1.17, $P = 0.003$) and 1.08 (95% CI: 1.03–1.12, $P < 0.0001$), respectively. In the subgroup analysis based on the *S. boulardii* supplementation time, *S. boulardii* supplementation was found to significantly improve the eradication rates in the *same* subgroup (RR = 1.09, 95% CI: 1.04–1.14, $P < 0.0001$) but

not in the *different* subgroup (RR = 1.06, 95% CI: 1.00–1.13, $P = 0.065$). Moreover, subgroup analysis based on the type of antibiotics showed that the pooled RRs in the AMO + C and AMO + F subgroups were 1.11 (95% CI: 1.04–1.19, $P = 0.002$) and 1.06 (95% CI: 1.01–1.11, $P = 0.012$). No significant heterogeneity was found in the subgroup analysis.

Incidence of adverse effects

A total of seven RCTs involving 1725 patients reported the incidence of adverse effects. Among them, two studies were split into two parts to be included. The overall incidence of adverse effects was significantly lower in the *S. boulardii* supplementation group than in the control group (18.5% vs. 35.2%, RR = 0.53, 95% CI: 0.45–0.62, $P < 0.0001$). There was no significant statistical heterogeneity between trials ($I^2 = 35.3\%$, $P = 0.135$; Fig. 3).

In terms of gastrointestinal adverse effects, the incidence of diarrhea (RR = 0.28, 95% CI: 0.22–0.26, $P < 0.0001$), nausea (RR = 0.59, 95% CI: 0.36–0.97, $P = 0.039$), constipation (RR = 0.32, 95% CI: 0.18–0.55, $P < 0.0001$), and abdominal distention (RR = 0.39, 95% CI: 0.26–0.59, $P < 0.0001$) were significantly lower in the *S. boulardii* supplementation group. However, *S. boulardii* supplementation could not lower the incidence of vomiting (RR = 0.82, 95% CI: 0.59–1.14, $P = 0.238$) and abdominal pain (RR = 0.64, 95% CI: 0.42–1.00, $P = 0.051$; Table 3). Besides, regarding other nonspecific adverse effects, the *S. boulardii* supplementation group showed significantly decreased incidence of the development of a rash in comparison to the control group (RR = 0.49, 95% CI: 0.28–0.86, $P = 0.013$; Table 3). Conversely, the incidence of dizziness did not significantly differ between the two groups (RR = 1.03, 95% CI: 0.62–1.72, $P = 0.898$; Table 3). Owing to the limitation of the obtained data, the incidence of other adverse effects, such as palpitations and blurred vision, could not be comparatively analyzed in this study.

Sensitivity analyses

By removing one study at a time, it was observed that the included studies retained statistical significance even after exclusion of any individual study, confirming the robustness of the results. The pooled RR was 1.07–1.08 for the eradication rate and 0.49–0.58 for the incidence of total adverse effects.

Publication bias

Publication bias was tested using a funnel plot. The distribution of *H. pylori* eradication rates and the incidence of total adverse effects showed a slight asymmetry (Fig. 4). Nevertheless, we performed the Egger's test to quantitatively assess publication bias, and no evidence of bias relating to eradication rates was identified (P_{Egger}

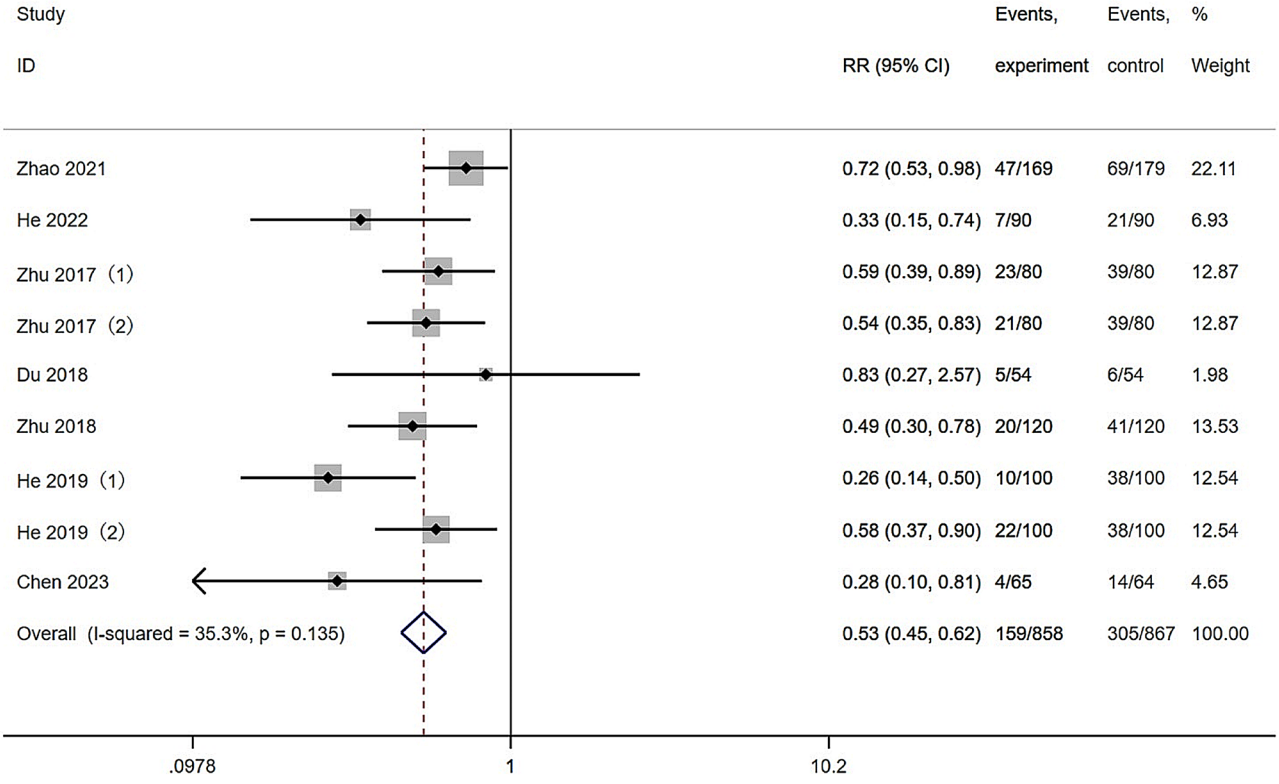

Fig. 3 Forest plot for the effects of *S. boulardii* supplementation on total adverse effects

Table 3 Effects of *S. boulardii* supplementation on adverse effects

Adverse effects	Number of studies	RR (95% CI)	P_{effect}	I^2 (%)	$P_{heterogeneity}$
Total adverse effects	9	0.53 (0.45, 0.62)	< 0.0001	35.3	0.135
Gastrointestinal adverse effects					
Diarrhea	12	0.28 (0.22, 0.36)	< 0.0001	43.7	0.052
Nausea	7	0.59 (0.36, 0.97)	0.039	61.4	0.016
Vomiting	7	0.82 (0.59, 1.14)	0.238	16.1	0.307
Abdominal pain	7	0.64 (0.42, 1.00)	0.051	0.0	0.441
Constipation	6	0.32 (0.18, 0.55)	< 0.0001	0.1	0.415
Abdominal distention	7	0.39 (0.26, 0.59)	< 0.0001	0.0	0.488
Other nonspecific adverse effects					
Rash	7	0.49 (0.28, 0.86)	0.013	12.3	0.336
Dizziness	7	1.03 (0.62, 1.72)	0.898	21.0	0.269

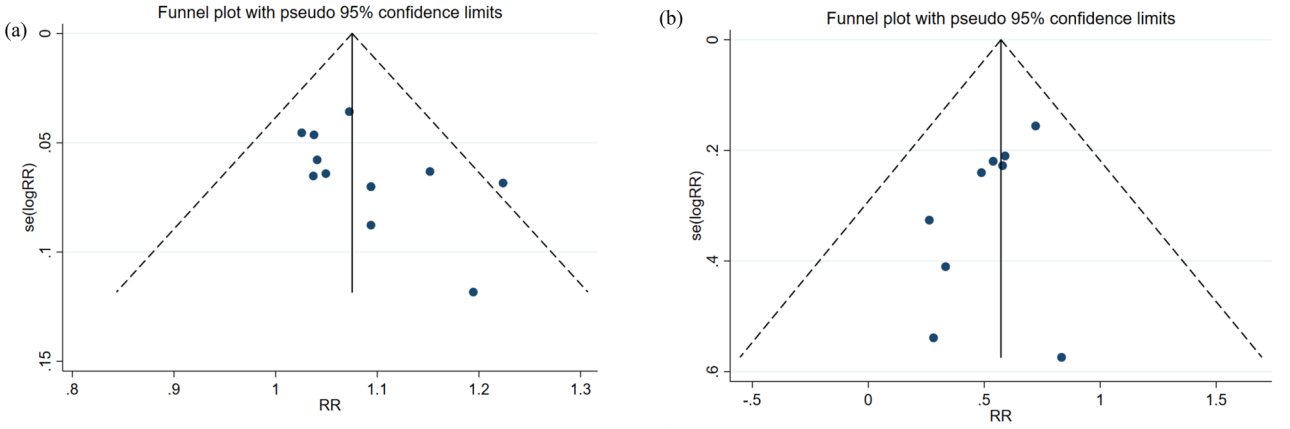

Fig. 4 Funnel plot of the included studies. (**a**) Funnel plot of the eradication rates. (**b**) Funnel plot of the incidence of total adverse effects

= 0.103). Similarly, no substantial evidence of publication bias was identified regarding the overall incidence of adverse effects (P_{Egger} = 0.076).

Discussion

To our knowledge, this meta-analysis is the most comprehensive assessment of the use of *S. boulardii* supplementation as an adjuvant for bismuth quadruple therapy to date. Our meta-analysis revealed that *S. boulardii* supplementation regardless of high-dose or low-dose to bismuth quadruple therapy significantly improved the *H. pylori* eradication rate. Furthermore, a higher eradication rate was closely associated with long-term eradication duration (> 10 days) and the supplementation time of *S. boulardii* being the same as the time of starting and stopping bismuth quadruple therapy. In addition, *S. boulardii* supplementation could reduce the overall incidence of adverse effects. The incidence of diarrhea, constipation, nausea, abdominal distention, and rash was also found to be significantly reduced by *S. boulardii* supplementation.

Considering the conceivable efficacy of *S. boulardii* supplementation in terms of its effects of increasing the eradication rate of *H. pylori* and reducing the occurrence of adverse effects, the addition of *S. boulardii* to *H. pylori* eradication therapy is currently considered a novel clinical treatment option. The potential mechanisms underlying the effect of *S. boulardii* against *H. pylori* can be summarized as follows: (1) *S. boulardii* has a neuraminidase activity that is selective for α(2–3)-linked sialic acid. This activity removes surface α(2–3)-linked sialic acid, which consequently inhibits the adherence of *H. pylori* to duodenal epithelial cells [23]. (2) *S. boulardii* works with the epithelial cells of the digestive tract mucosa to enhance the regeneration of injured gastrointestinal epithelial cells and maintain the integrity of the gastrointestinal epithelial mucus layer [24]. (3) *S. boulardii* can inhibit the synthesis of inflammatory mediators, such as IL-8 and TNF-α, through its ability to suppress the activation of mitogen-activated protein kinase and NF-κB DNA-binding activity. This effect may alleviate the inflammation caused by *H. pylori* infection [25]. (4) *S. boulardii* has a larger surface area than other probiotics, and thus, it can better adhere to the gastric mucosa, preventing the colonization and adhesion of *H. pylori* [26]. (5) *S. boulardii* can produce substances like short-chain fatty acids which can inhibit the growth of *H. pylori* [27]. (6) S. boulardii contributes to the homeostasis of the normal microbiome and plays a relevant role in modulating

immunological functions [8]. (7) S. boulardii reduces H. pylori eradication adverse effects, and subsequently improve patient compliance, which may improve the H. pylori eradication rates.

A previously published meta-analysis [11] by Zhou et al. revealed that bismuth quadruple therapy with *S. boulardii* supplementation did not significantly improve *H. pylori* eradication rates, and this finding is not consistent with the present results. One possible explanation is that their meta-analysis included only two trials, which may affect the reliability of their conclusion. Also, the two trials utilized a furazolidone-containing bismuth quadruple therapy regimen. Since this regimen already achieves high eradication rates, the addition of S. boulardii may haves a less pronounced improvement in eradication efficacy.

In terms of therapy-related adverse effects, we observed that *S. boulardii* supplementation significantly decreased the incidence of adverse effects, which was consistent with the findings of Zhou et al. Furthermore, we had a larger sample size than Zhou et al. [11] We could conduct subgroup analysis, which revealed that long-term eradication duration (> 10 days) and the supplementation time of *S. boulardii* being the same as the time of starting and stopping bismuth quadruple therapy could improve the eradication rate regardless of the *S. boulardii* dose. Considering the cost-effectiveness ratio, we recommend 500 mg/day *S. boulardii* supplementation alongside bismuth quadruple therapy for *H. pylori* eradication.

The present study has several strengths. To our knowledge, this is the first meta-analysis to explore the effects of *S. boulardii* supplementation alongside bismuth quadruple therapy. In addition, the studies included in our analysis were all RCTs, which minimizes the influence of confounding factors. Finally, we identified the ideal dose (500 mg/day), eradication duration (> 10 days), and the time for *S. boulardii* supplementation (the same time as bismuth quadruple therapy).

However, our meta-analysis has several potential limitations. First, all studies included were performed in China, where bismuth quadruple therapy is widely used for *H. pylori* eradication, resulting in potential bias in terms of patient selection. More high-quality studies from different regions are needed to investigate and verify whether these findings can also be applied to regions outside of China. Second, most of the included studies did not report antimicrobial susceptibility testing, which may have some influence on *H. pylori* eradication rates. Third, because the drugs used in the bismuth quadruple therapy are diverse, bismuth quadruple therapy varied among studies, and we did not explore which therapy with the addition of *S. boulardii* shows enhanced efficacy in eradicating *H. pylori*. Fourth, the unclear risk of bias in some included studies, particularly regarding allocation concealment and blinding might influence the results. However, the stability of findings in sensitivity analyses confirm the robustness of our results. Large-scale, high-quality randomized controlled trials are needed to confirm our results in future. Finally, we did not assess the severity of adverse effects in this study because of the lack of relevant data in the included studies. Therefore, more high-quality trials from different regions are needed for further analysis.

Conclusion

Our meta-analysis indicated that *S. boulardii* supplementation significantly increased *H. pylori* eradication rates and reduced the incidence of adverse effects. We recommend 500 mg/d *S. boulardii* supplementation to be started and stopped at the same time as bismuth quadruple therapy and be continued for > 10 days for optimal *H. pylori* eradication effect.

Article highlights

Research background

A 14-day bismuth quadruple therapy was recommended as the first-line treatment for *Helicobacter pylori* (*H. pylori*) eradication. Nonetheless, the efficacy of bismuth quadruple therapy has diminished because of the increasing prevalence of antimicrobial-resistant strains and the high occurrence of adverse effects.

Research motivation

Probiotics are living microorganisms that provide a health benefit to the host when administered in sufficient quantities. They have attracted much attention as an adjunctive therapy for *H. pylori* eradication. It is still controversial whether the supplementation of *Saccharomyces boulardii* (*S. boulardii*) to bismuth quadruple therapy is beneficial for *H. pylori* eradication.

Research objectives

This meta-analysis aimed to determine the effects of *S. boulardii* supplementation to bismuth quadruple therapy on *H. pylori* eradication.

Research methods

We performed a systematic literature search across PubMed, Embase, Web of Science, and China National Knowledge Infrastructure for articles published up to October 2023. We calculated the pooled relative risk (RR) with the 95% confidence interval (CI). Statistical analyses were conducted using Stata/SE 15.1 software.

Research results

Ten randomized controlled trials were included. Notably, *S. boulardii* supplementation to bismuth quadruple therapy significantly improved *H. pylori* eradication rates

(RR = 1.08, 95% CI: 1.04–1.12, $P < 0.0001$) and reduced the incidence of total adverse effects (RR = 0.53, 95% CI: 0.45–0.62, $P < 0.0001$). In the subgroup analysis, long-term eradication duration (> 10 days; RR = 1.08, 95% CI: 1.04–1.13, $P < 0.0001$) and S. boulardii supplementation to be started and stopped at the same time as bismuth quadruple therapy (RR = 1.09, 95% CI: 1.04–1.14, $P < 0.0001$) were found to significantly improve the eradication rate regardless of the S. boulardii dose (500 mg/day, RR = 1.10, 95% CI: 1.03–1.17, $P = 0.003$; 1000 mg/day, RR = 1.08, 95% CI: 1.03–1.12, $P < 0.0001$).

Research conclusions

The addition of *S. boulardii* to bismuth quadruple therapy significantly increased *H. pylori* eradication rates and decreased the adverse effects. We recommend adding 500 mg/day *S. boulardii* concurrently with bismuth quadruple therapy and continuing this therapy for > 10 days for optimal *H. pylori* eradication efficacy.

Research perspectives

More high-quality trials from different regions are needed to confirm our results.

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12876-025-03879-y.

Supplementary Material 1

Supplementary Material 2

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Not Applicable.

Author contributions

Xiaoyong Wang was involved in the conception and design of the study, critical revision, acquisition of data, analysis and interpretation of data, drafting the article, and final approval. Yizhou Jiang and Kai Ma were involved in the acquisition of data, analysis and interpretation of data, drafting the article, and final approval. Cheng Cui was involved in the interpretation of data, revising the article, and final approval. Zhuoya Li involved in the interpretation of data, revising the article, and final approval.

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Data availability

No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate

Not Applicable.

Consent for publication

Not Applicable.

Competing interests

The authors declare no competing interests.

PRISMA 2009 checklist statement

The authors have read the PRISMA 2009 Checklist, and the manuscript was prepared and revised according to the PRISMA 2009 Checklist.

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