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The impact of probiotics on gut microbiota in the eradication of *Helicobacter pylori* infection: a systematic review

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Abstract. – OBJECTIVE: The effect of probiotics supplementation on the gut microbiota in *Helicobacter pylori* (*H. pylori*) eradication therapy is controversial. Therefore, this review aimed to illustrate changes in the gut microbiota after standard eradication therapy with probiotics supplements.

MATERIALS AND METHODS: A computerized literature search in PubMed, Cochrane Library, Web of Science, and Embase database was performed up to February 1st, 2022, with English language restriction. The extracted outcomes were analyzed, including gut microbiota, adverse effects, and eradication rate.

RESULTS: 13 studies reported data on 777 participants who were finally eligible for this systematic review. All of them are randomized controlled trials investigating the effect of *H. pylori* eradication with probiotics supplementation therapy on gut microbiota. Probiotics supplementation seems to play a positive role in restoring the gut microbiota during *H. pylori* eradication therapy. However, the changes in the gut microbiota are still controversial. The included studies had significant heterogeneity in the study population, diagnostic methods of *H. pylori* infection, and detection techniques of the gut microbiota and probiotics species.

CONCLUSIONS: The results provided a basis for the rational selection of probiotics in the *H. pylori* eradication process. Probiotic supplementation might keep the balance of gut microbiota and reduce the gastrointestinal adverse effects of antibiotics, but whether it could improve the eradication rate or not is a debatable point. Therefore, more research is needed to provide evidence.

Key Words:
Gut microbiota, *Helicobacter pylori*, Probiotics, Eradication therapy.

Introduction

Helicobacter pylori (*H. pylori*) is a Gram-negative, microaerophilic, spiral-shaped, and flagellated bacterium that infected approximately half of the human population worldwide. The infection rate reached more than 70% in developing countries[1,2]. Reports of infection prevalence rates range widely among geographic regions, achieving the highest levels in developing countries and showing a well-established relationship with socioeconomic status and hygiene conditions[3,4]. *H. pylori* infection is related to developing diverse gastrointestinal diseases such as peptic ulcers, gastric adenocarcinomas, and mucosa-associated lymphoid tissue lymphomas, resulting in multiple extra-gastrointestinal diseases, including idiopathic thrombocytopenic purpura, idiopathic iron deficiency anemia, neurological, cardiovascular and metabolic diseases[5-8]. *H. pylori* gastritis should be considered an infectious disease and need to eradicate regardless of patients' symptoms, complications, or subsequent diseases[9,10]. Nevertheless, there is no generally accepted treatment for *H. pylori* infection. Generally, the standard triple therapy, which combines two antibiotics with a proton pump inhibitor (PPI), has been widely used as a first-line regimen to eradicate *H. pylori* in most countries[9]. However, the effect of standard triple therapy was unsatisfactory due to the increase in antibiotic resistance and the decrease in compliance with therapeutic regimens. In most World Health Organization (WHO) regions, a study showed that the pooled prevalence of primary and secondary resistance of *H. pylori* to clarithromycin, metronidazole, and levofloxacin was more than 15%, which was the standard threshold for choosing alternative empiric regimens[11]. The eradication rate of traditional triple therapy, which included metronidazole and clarithromycin, was less than 80%[12]. Therefore, supplementary treatments have been proposed for *H. pylori* eradication.

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Many clinical trials[13-15] recently reported that specific probiotic therapy not only improved the eradication rate but also reduced the side effects caused by antibiotic therapy. A meta-analysis[16] of 19 randomized controlled trials found that different strains of probiotics could prevent side effects from treatment and improve the success rate of *H. pylori* eradication. Animal model experiments and clinical trials showed that probiotics positively impact the host gastrointestinal microbiota by keeping the balance of gastric microbiota during *H. pylori* infection and eradication therapy[17,18]. According to Liou et al[19], α-diversity was significantly decreased compared with baseline, and β-diversity was altered considerably at the end of triple therapy, concomitant therapy, and bismuth quadruple therapy. Wu et al[20] found that gut microbiota diversity was remarkably reduced when *H. pylori*-positive subjects were treated with triple therapy alone. At the same time, supplementation with *Bacillus subtilis* and *E. faecalis* could inhibit the reduction. However, a study concluded that probiotics supplementation could not improve the efficacy or tolerability of *H. pylori* eradication treatment regardless of the species of microorganism used[21]. Myllyluoma et al[22] found standard triple therapy with probiotics only exerts a minor influence on the intestinal microbiota. The results of different experiments[20,22] were inconsistent; thus, we performed this systematic review to summarize the evidence concerning the impact of probiotics on gut microbiota in *H. pylori* eradication.

Materials and Methods

Data Sources, Search Strategies, and Data Collection

The systematic review was conducted following the PRISMA guidelines[23]. A literature search in PubMed, Cochrane Library, Web of Science, and Embase database was performed in December 2021, with English language restriction. Both medical subject headings and free-language terms were used as search terms. The MeSH database was used as a terminology search filter. From the combination of terminology (MeSH terms) and methodological search filters, relevant journal articles were retrieved[24,25]. The search terms were probiotics, gastrointestinal microbiota, and *H. pylori* infections/therapy. **Appendix I** presented the query formula. The first time we conducted the literature search in the databases was in December 2021. We also conducted the second search in February 2022 and the results of searching were the same as the previous (last update 1 February 2022).

All the abstracts were screened, and all the studies examining gastrointestinal microbiota before and after treatment as an outcome were considered to meet the inclusion criteria. Then, the full articles were retrieved. All the eligible abstracts and articles were assessed for inclusion in this systematic review. Contact was made with the authors of the pieces when further information was required. Using a standardized approach, two reviewers (X.-F. Bai and M.-J. Zhu) independently assessed the extracted data, including titles, abstracts, references, and full-text articles. Each data set was reviewed by a third reviewer (D. Tian), and any disagreements were solved by discussion.

The following data were extracted from each study: (1) author and published year; (2) country; (3) study design; (4) number of enrolled patients; (5) mean age and sex of enrolled patients; (6) study period; (7) abdominal symptoms; (8) test used to diagnose *H. pylori* infection; (9) medication of *H. pylori* eradication therapy; (10) probiotics strains and method of administration; (11) eradication rates; (12) sample and collection time; (13) the technique of testing gastrointestinal microbiota and (14) outcomes assessed.

Selection Criteria

Inclusion criteria

A study was eligible for inclusion in our systematic review if the following criteria were met: (1) the study was a randomized controlled trial; (2) enrolled patients with *H. pylori* infection underwent probiotics as adjuvant therapy in combination with standard eradication therapy, including triple therapy and quadruple therapy; (3) the control group and the probiotics group were treated with the same standard eradication therapy; (4) the trial outcome contained at least one of the following: the diversification or the abundance of the gastrointestinal microbiota.

Exclusion criteria

The exclusion criteria were as follows: (1) studies were reviews, case reports, nonhuman studies, letters to editors, or editorials; (2) the enrolled patients had received *H. pylori* eradication therapy before; (3) the enrolled patients who had *H. pylori* infection underwent probiotics treatment but without standard eradication therapy;

(4) the enrolled patients underwent proton-pump inhibitors (PPI) or H2 receptor antagonists in the past two weeks; (5) studies reported overlapping data and previously published; (6) studies spanned greater over 15 years; (7) total enrolled patients were minor than ten; (8) the enrolled patients' ratio between the two groups was more significant than 10:1.

Quality Assessment

Two review authors (X.-F. Bai and M.-J. Zhu) independently assessed the quality of trials according to the recommendations of the Cochrane Collaboration 26, including random sequence generation (selection bias), allocation concealment (selection bias), blinding of participants and personnel (performance bias), blinding of outcome assessment (detection bias), incomplete outcome data (attrition bias), selective reporting (reporting bias) and other bias. For each study, the response options for an overall risk-of-bias judgment were "low risk of bias", "unclear", and "high risk of bias". Application of the Cochrane criteria guidelines was used to judge the presence of methodological biases. Any discrepancy was adjudicated by a third reviewer (D. Tian).

Results

Literature Search and Quality Assessment

Based on the literature search strategy, 607 citations were found. After study selection, 13 studies[20,22,26-37] fulfilled the criteria to be included in the final systematic review. A flow chart summarizing search results and identifying eligible studies is provided in Figure 1.

Each study chosen for this review was carefully assessed according to the Cochrane Collaboration. The quality of these 13 studies is shown in Figure 2. All the included studies showed moderate attributes, and most lacked randomization, allocation, and blinding details.

Study Characteristics

In a total of 13 retrospective studies, and 777 *H. pylori*-positive patients were included in this systematic review, reporting on 381 patients with standard triple/quadruple treatment therapy alone and 396 patients with the complement of probiotics. Two studies[31,34] were conducted on the pediatric population. In all included studies except 2 of them[30,32], the initial diagnosis was established by combining more than one test, including urea breath test (UBT), endoscopy with histological examination or rapid urease test (RUT), serology or fecal antigen test. The eradication assessment was determined by a urea breath test in 8 of 13 studies. Stool samples were collected from all patients at baseline, during, and after treatment. The analysis of gastrointestinal flora was determined by 16S rRNA sequencing, bacterial culture, fluorescence in situ hybridization (FISH), and real-time quantitative polymerase chain reaction (PCR). **Supplementary Table I** presents a summary of the main characteristics of the included studies.

In all studies except Kakiuchi et al[34], the therapy of a proton pump inhibitor and two antibiotics was administered, and bismuth potassium citrate was added in two of them[35,36]. Kakiuchi et al[34] used vonoprazan to replace proton pump inhibitor, a novel oral potassium-competitive acid blocker (P-CAB). Only 1 study used compound preparations which consisted of four different strains, *Lactobacillus rhamnosus* GG, *L. rhamnosus* LC705, and *Propionibacterium freudenreichii ssp. shermanii* JS and *Bifidobacterium breve* Bb99[22]. Five studies[27,28,31,32,35] administered two probiotics, three studies[27,28,31] applied *Lactobacillus acidophilus* and *Bifidobacterium bifidum*, whereas the other two studies combined *Bacillus subtilis* with *Enterococcus faecium* or *Streptococcus faecium*[32,35]. The rest of the included studies used one probiotic alone[20,29,30,33,34,36,37]. Only in one study were probiotics given before eradication[29]. The duration of probiotic supplementation varies from 1 week to 6 weeks.

Changes in Gut Microbiota after Eradication

In a study by Madden et al[27], the count of Total anaerobes increased in the control group, while no significant alterations were observed in the probiotic group throughout the study. Nevertheless, one study[22] reviewed that the count of Total anaerobes decreased in both groups, whereas another study[37] reported it remained stable during the study period.

In contrast to the significantly increased in the control group, the numbers of Facultative anaerobic decreased or remained stable after treatment in the probiotic group in two studies[27,28]. However, according to Myllyluoma et al[22], compared with baseline, an apparent decrease was also observed in the number of Facultative anaerobic in the control group. Another two studies[29,30] reviewed showed no significant difference between the two groups. In two studies[29,30], Obligate anaerobes decreased significantly in the control group but remained stable in the probiotic group.

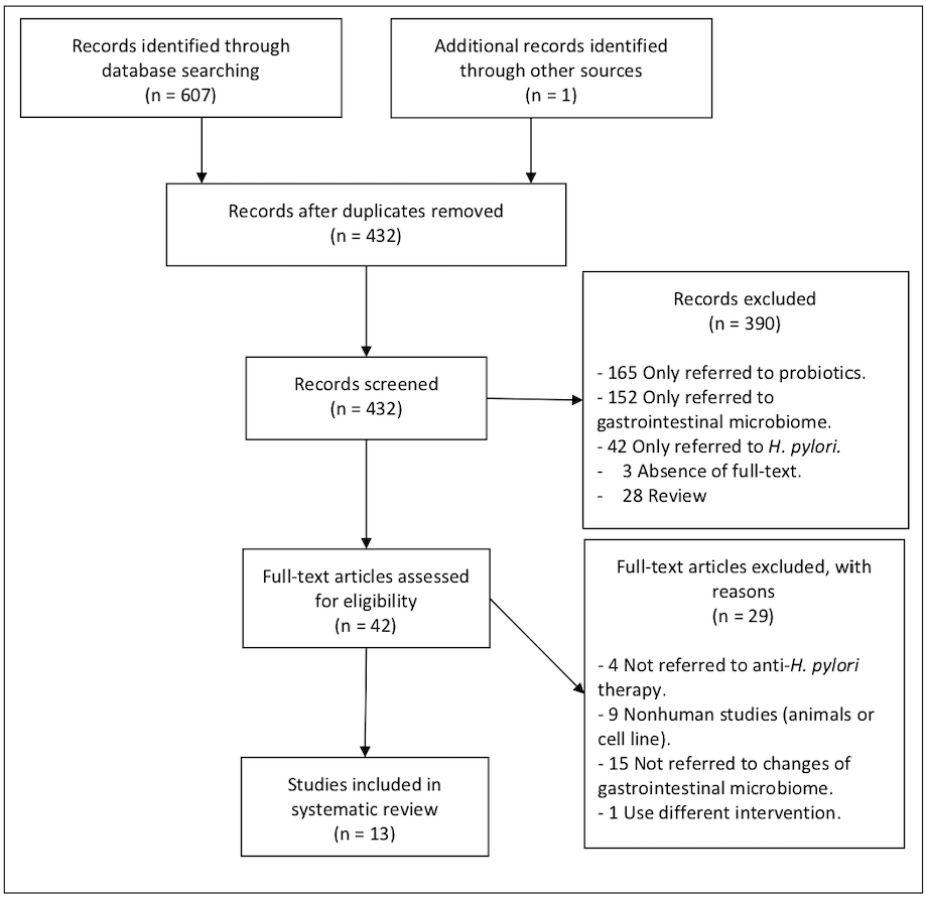

Figure 1. Flow chart of literature search.

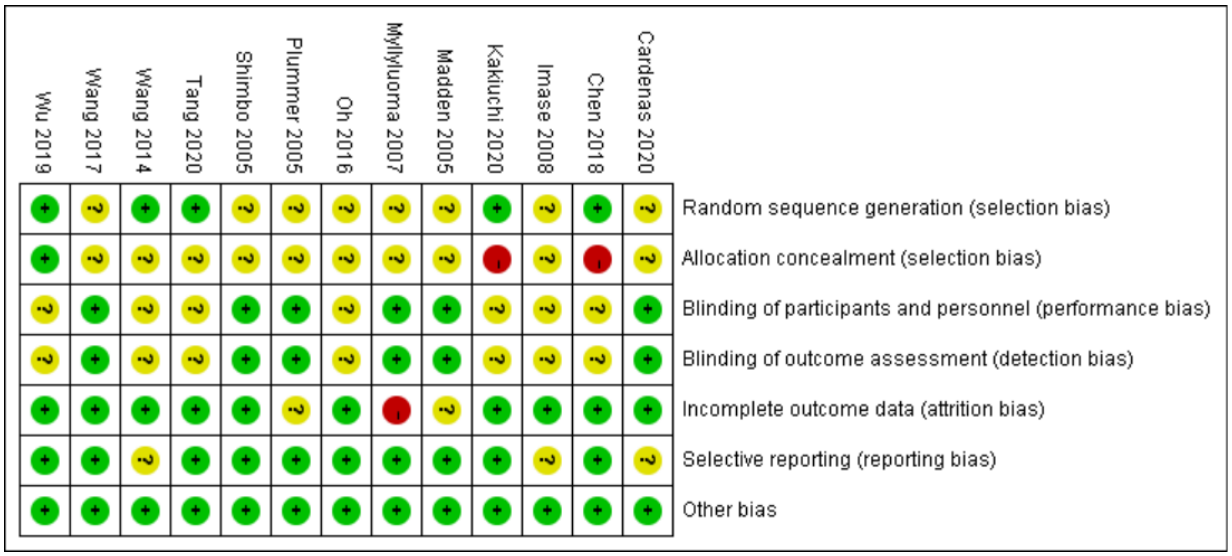

Figure 2. Risk of bias summary across the clinical trials. Low risk of bias: green "+"; Some concerns of bias: yellow "?"; High risk of bias: red "-".

The numbers of *Enterobacteriaceae* increased in 3 studies[27-29], while Myllyluoma et al[22] reported a significant decrease in the numbers of *Enterobacteriaceae* in both groups following antimicrobial treatment. In Imase et al[30], *Enterobacteriaceae* was also analyzed, but no significant difference was observed.

In 2 studies[28,30], the numbers of *Enterococci* in both groups had no change, and Madden et al[27] discovered that the *Enterococci* population climbed up and then declined. However, a different opinion came from Myllyluoma et al[22], which found that the *Enterococci* population decreased after eradication.

In most of the included studies, the *Bifidobacterium* population in the control group decreased in response to antibiotic therapy[22,27-31,34,35]. Only one study[28] reported the *Bifidobacterium* population also decreased both in two groups. In addition, two studies[27,30] presented that the *Bifidobacterium* population remained stable after probiotics supplementation with eradication therapy. In comparison, another study[31] found that the number of *Bifidobacterium* was significantly higher in the probiotic group than in the control group.

In the study by Madden et al[27], the *Lactobacilli* population remained unchanged in the two groups. However, five studies[22,28-31] found the numbers of *Lactobacilli* significantly decreased after eradication, while three studies discovered that probiotics supplementation could rapidly restore the levels[28,31,35].

Firmicutes, Bacteroidetes, and *Proteobacteria* were predominant in the gut microbiota of all subjects[20,32,35,36]. Three studies[32,35,36] retrieved the relative abundances of *Firmicutes* were reduced, whereas the relative abundances of *Proteobacteria* were increased in both groups. However, four studies found that the quantity of *Bacteroidetes* was significantly decreased after treatment in the control group[22,35-37]. In the probiotic group, three studies[27,33,35] found that the abundance of *Bacteroidetes* was also decreased, but two studies[20,28] held the opposite opinion.

Discussion

Many studies[38,39] have shown that probiotics supplementation improved the eradication rate and reduced antibiotic-caused side effects. Antibiotic-induced changes in the microbiota could lead to diarrhea and other side effects, which could be avoided by probiotics supplementation and prevent antibiotic-related adverse events. Some researchers[40-42] studied the changes in gut microbiota after *H. pylori* eradication, but the results were inconsistent, and the conclusion was unclear. This systematic review highlighted the studies about the changes in the gut microbiota caused by probiotics in *H. pylori* eradication.

Standard triple therapy was recommended for *H. pylori* eradication therapy which contained two types of antibiotics and one type of PPI12. Studies[42,43] showed that eradication treatment of *H. pylori* could lead to dysbiosis of gut microbiota, which resulted in short-term complications and induced long-term health risks[9,42]. The changes in gut microbiota after antibiotic treatment, including the reduction of microbial taxonomic richness, diversity, and evenness in the gastrointestinal tract[39,44], resulted in a decrease of normal gut bacterial residents and provided opportunities for pathogens colonization such as *Clostridium difficile*[45]. Opportunistic pathogens, like *Shigella*, *Klebsiella*, and *Streptococcus*, would increase and lead to antibiotics-associated diarrhea (AAD)[46]. Moreover, a study by Sung et al[47] found gastric microbiota after *H. pylori* eradication contributed to the progression of gastric carcinogenesis.

Probiotics are conducive to reducing the rate of antibiotics-associated adverse events *via* regulating intestinal microflora, changing nutritional metabolism in the gut, regulating secretion and absorption of solutes, and improving intestinal barrier and immune function[48-51]. In this article, all the included studies showed that probiotics supplementation had different positive effects degrees on flora disequilibrium caused by *H. pylori* eradication treatment. The most common organisms in human gut microbiota are members of the gram-positive *Firmicutes* and the Gram-negative *Bacteroidetes* species, with several other phyla, including the *Actinobacteria*, *Fusobacteria*, and *Verrucomicrobia*, that are present at subdominant levels[52]. Three Randomized Clinical Trials (RCTs) included in this review showed that the relative abundance of *Firmicutes* and *Bacteroidetes* decreased and that of *Proteobacteria* increased after standard triple therapy[32,35,36]. The *Bacteroidetes*/*Firmicutes* (B/F) ratio is widely accepted to have an important influence in maintaining normal intestinal homeostasis. Increased or decreased B:F ratio was regarded as dysbiosis[53]. B:F ratio first went down and then up in both groups. Compared with the control group, B:F ratio was significantly higher in the probiotics group after eradication therapy[35,36]. Probiotics supplementation could help the gut microbiota return to baseline levels faster. In the included studies, obligate anaerobes decreased significantly in the control group. Still, they remained stable in the probiotic group, whereas debatable conclusions were drawn on the trend of Facultative anaerobes and Total anaerobes. Most of the included studies[27,28,30,31,35] reviewed the numbers of *Bifidobacterium* and *Lactobacilli* decreased throughout the standard treat-

ment, but they increased significantly or remained stable with the complementary therapy of probiotics. *Bifidobacterium* and *Lactobacilli* increased after probiotics supplementation, which may be related to the probiotic strains. Only one RCT in this article showed that during *H. pylori* eradication treatment, *Clostridium difficile* toxin A, one of the primary virulence (disease-causing) factors of *Clostridium difficile*, was detected both in the control group and the regular dose probiotic group, but no finding in the double dose of probiotic group[30,54]. Many clinical studies[15,40,41] and meta-analyses indicated probiotics supplementation improved the *H. pylori* eradication rate, which is usually related to the therapeutic regimen. However, in our article, only one study included proved the eradication rate could be improved by probiotics supplements, and no data is available for analysis.

In our study, although the incidence rate of abdominal symptoms in the probiotic group was lower than in the control group, changes in gut microbiota after probiotic supplementation were still undefined.

Limitations

The limitations of this systematic review are as follows: firstly, methods of *H. pylori*-positive diagnosis and gut microbiota detection in included RCTs are different; secondly, all of the included articles only assessed the short-term effects (within three months); thirdly, most of the included studies were from Asia, and the included population was dominated by Asians; fourthly, inclusion and exclusion criteria were different in the included RCTs. For example, some articles regarded patients with a peptic ulcer as participations, while others excluded them; finally, the eradication therapy, the strains and regimens of probiotics, and the collection time of stool samples differed. Although enough articles were included, few data were available for analysis, and subgroup and bias analyses could not be performed. All these limitations would affect the reliability of the results.

Conclusions

Probiotics supplementation may not have statistical significance in the change of eradication rate, but it reduces abdominal symptoms. Probiotic supplementation could keep the balance of gut microbiota and reduce the gastrointestinal adverse effects of antibiotics during *H. pylori* eradication treatment, such as gastrointestinal side effects, superinfection, and potential hazards of other systems. However, considering the economic reasons and the slight influence on the eradication rate, many guidelines did not recommend adding probiotics supplementation in standard triple/quadruple eradication therapy. To confirm the species of probiotics and duration of probiotics supplementation and draw reliable conclusions, more randomized controlled trials are needed to enlarge the sample size and make quantitative analyses.

Conflict of Interest

The Authors declare that they have no conflict of interest.

Authors' Contributions

Study conception and design (X.-F. BAI); Acquisition of data (M.-J. ZHU, D. TIAN); Analysis and interpretation of data (X.-F. BAI, M.-J. ZHU); Writing, review, and/or revision of the manuscript (X.-F. BAI, M.-J. ZHU, J.-C. SHU, T.-Y. WANG, Y.-J. HE); Study supervision (Y.-J. HE).

Ethics Approval and Informed Consent

Not applicable.

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