Review Article

What Roles Do Probiotics Play in the Eradication of Helicobacter pylori? Current Knowledge and Ongoing Research

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With the rising global prevalence of antibiotic resistance, the eradication rate of Helicobacter pylori (HP) is continuing to decrease. Probiotics are beneficial to human health and may be an adjunct therapy to increase the eradication rate of HP, lower treatment-associated side effects, and reduce HP-associated gastric inflammation. However, inconsistent test results have prevented conclusions about the therapeutic prowess of probiotics for HP. The mechanisms of actions of probiotics include the production of substances that inhibit or kill HP or compete with HP for the adhesion site on gastric epithelial cells. Probiotics can also reduce the release of inflammatory factors by regulating the local immune response of the host. We searched the available literature for full-length articles focusing on the role of probiotics in HP management. This review presents the latest advances in this area.

1. Introduction

Helicobacter pylori (HP) is the main cause of chronic active gastritis, peptic ulcer, gastric mucosa-associated lymphoid tissue lymphoma, and gastric cancer. Dyspepsia, unexplained anemia, and idiopathic thrombocytopenic purpura are also closely related [1]. Approximately half of all humans harbor HP which is the most common cause of chronic gastritis worldwide. The 2015 Kyoto consensus suggested that HP gastritis is an infectious disease and those who test positive should receive treatment designed to eradicate the infection [2]. At present, no therapy regimen can guarantee 100% eradication of HP. The eradication rate is related to many factors, including therapeutic regimen, patient tolerance to adverse reactions, patient compliance, patient genetic polymorphism, smoking, diabetes, and other factors [3–5]. Among them, antibiotic resistance of HP is the main cause of the failure of HP eradication treatment [6]. The Maastrict V/Florence consensus suggested that in areas where clarithromycin resistance exceeds 15% or in areas with high clarithromycin and metronidazole resistance, a 10–14-day bismuth quadruple therapy is recommended as the first-line eradication regimen [7]. In North America, the average rates of resistance of HP to metronidazole, clarithromycin, and levofloxacin between 2009 and 2011 were 20%, 16%, and 31%, respectively, of isolates [8]. A recent study from China reported average metronidazole, clarithromycin, and levofloxacin resistance rates of HP of 63.8%, 28.9%, and 28%, respectively, of isolates [9]. Although increasing the dose and course of antibiotics can increase the eradication rate of HP, there can be consequences. Severe adverse reactions during antibiotic therapy can include diarrhea, constipation, bloating, nausea, abdominal pain, abdominal discomfort, dysbacteriosis of the intestinal flora, liver function damage, and fungal infection. The reported rate of adverse reactions during the eradication therapy ranges from 5 to 30%, with treatment discontinued in some cases. Furthermore, the increased prevalence of Escherichia coli-resistant strains, methicillin-resistant Staphylococcus aureus, and extended-spectrum beta-lactamase strains isolated from the intestine after HP eradication treatment has been described [10]. In addition, bismuth is neurotoxic, which restricts the use in
children and the elderly. In patients, gastric mucosa is acquired by gastroendoscopy for the culture of HP to determine antibiotic susceptibility. The prudent selection of antibiotics according to the results of drug susceptibility testing can effectively increase the eradication rate of HP. However, the harsh HP growth conditions and long growth cycle do not guarantee the success of HP culture, which has hindered the widespread use of HP culture techniques [11]. Molecular biology techniques, such as polymerase chain reaction (PCR) and fluorescent labeling nucleic acid in situ hybridization (FISH), can be used to detect HP resistance sites in fresh or paraffin-embedded gastric mucosa tissues and feces, but only to clarithromycin and quinolones. Metronidazole resistance sites cannot be determined due to the complex drug resistance mechanisms that are involved [12].

These challenges have spurred exploration of new individualized approaches to treat HP infections. The many adjuvant HP eradication treatments that have emerged include an oral HP vaccine [13], Chinese herbal medicine [14], probiotics and periodontal scaling [15, 16], and gastric mucosal protective agents [17]. Among them, probiotics have received increasing attention in recent years because of their safety. A large number of clinical and basic studies have reported that some specific probiotics can boost the HP eradication rate and significantly reduce the adverse reactions during the eradication treatment, which facilitates improved patient compliance with the therapy [18–20]. These attributes should seemingly make probiotics a promising adjuvant treatment.

However, according to the 2016 Toronto consensus, there is insufficient evidence that the addition of probiotics can increase the HP eradication rates and reduce adverse reactions [21]. The 2017 ACG clinical guideline, which was based on evidence from a meta-analysis, reported that probiotics can indeed increase HP eradication rates and reduce the overall incidence of adverse reactions. However, the studies involved in the meta-analysis were mainly clinical trials conducted in China and were subject to a high risk of bias. Thus, currently, there is no conclusion about the best choice of probiotics as well as the dose and course of treatment [8].

The fifth Chinese HP consensus opinion pointed out that the conclusion that some probiotic strains can alleviate gastrointestinal side effects following HP eradication is widely accepted. Whether the addition of probiotics can increase the HP eradication rate requires confirmation in future well-designed studies. For now, the anti-HP mechanisms of probiotics remain unclear. In the context of the high global prevalence of antibiotic resistance, determination of the roles of probiotics in the eradication of HP is important, as is the feasibility of using bacteria to cure bacteria. Here, we have a review of the latest advances in the role of probiotics in the treatment of HP infections.

2. Definition and Classification of Probiotics

The Food and Agriculture Organization of the United Nations and the World Health Organization define probiotics as living microorganisms that are beneficial to life; can tolerate the effects of stomach acid, bile, and pancreatic juice; can colonize the host’s gastrointestinal tract or reproductive system; induce host reactions; and balance the intestinal flora to improve health [22]. Currently, compound active probiotics composed of various kinds of microorganisms are widely used globally, mainly for the treatment of diarrhea caused by dysbacteriosis of the intestine and to regulate the body’s immune functions.

In 2013, the International Probiotics and Prebiotics Science Association classified probiotics as follows: (1) bacteria in the genus Lactobacillus, including Lactobacillus acidophilus, Clostridium butyricum, L. reuteri, L. bulgaricus, L. casei, L. paracasei L. rhamnosus, L. salivarius, and L. plantarum; (2) bacteria in the genus Bifidobacterium, including Bifidobacterium infantis, B. adolescentis, B. animalis, B. longum, B. breve, and ovary double Bacteroides; (3) Gram-positive cocci, such as Streptococcus thermophilus, S. faecalis, and Lactococcus; and (4) yeast, such as Saccharomyces boulardii. At present, commercially available probiotic products include probiotic amended yogurt, encapsulated live bacteria, bacteria powder, oral liquids, and various preparations of single strains.

3. Theoretical Basis of Microecological Therapy

Human skin and gastrointestinal, respiratory, and urogenital tracts harbor huge numbers of colonized microbes, which are important in regulating the immune function of the human body to resist the colonization of pathogens [23]. These microorganisms include beneficial bacteria, conditional pathogens, and pathogenic bacteria, which have evolved to a normal state of microecological balance in the human body. The gastric environment is particularly harsh and difficult for microbiota to colonize. The common wisdom for a long time was that the stomach was sterile for approximately 80% of microbes are not cultivatable. With the development of high-throughput sequencing technology, this view has been debunked. HP is not the only inhabitant of the gastric mucosa anymore; a non-HP microbial community has been recognized and is called gastric microbiota [24]. HP may be influenced in their pathogenicity by the community they live in [25]. The gastric microbiota belong mainly to the Proteobacteria, Firmicutes, Actinobacteria, and Fusobacterium phyla, the majority of which were Streptococcus and Staphylococcus [26]. HP infection can affect the balance of gastric microbiota, and microbial interactions are a major factor in regulating the indigenous microbiota. Reports showed that the gastric microbiota of HP-negative subjects has a higher diversity than that of HP-positive patients [27].

Adhesion and virulence factors of HP contribute to pathogenicity. Colonization of the stomach by HP affects the distribution and quantity of the original gastric bacteria and upsets the microecological balance, resulting in disease. For example, there are fewer lactobacilli in the HP-infected stomach compared to the stomach not infected with HP [23]. HP leads to a microecological imbalance principally because of its production of an antibacterial peptide called cecropin. This peptide can cause other bacteria to undergo “autogenic autolysis” [28]. The lack of competition from these bacteria allows HP to multiply unimpeded. A series of virulence factors are able to stimulate the gastric epithelial
cells, resulting in apoptosis and inflammation. In the context of the global prevalence of antibiotic resistance, increasing the dose of antibiotics or prolonging the course of antibiotics to increase the eradication rate of HP is not an ideal method, because it can promote the further development of antibiotic resistance.

Microecological therapy has brought new ideas to the treatment of HP. Remodeling the microecological balance in the stomach can reduce HP colonization. Concerning an animal model of HP infection, sterile, immunodeficient, or knockout animals are the easiest to establish. The use of ordinary mice is hampered by the difficulty to establish a chronic HP infection. An analysis of the components of the gastric microbiota in sterile and normal mice revealed that the number of bacteria in the stomach of normal mice reached was up to \(10 \times 10^8\) colony forming units (CFU)/g, with Lactobacillus and Bifidobacterium dominating [29]. In an animal experiment conducted in China, normal mice received HP suspensions for 7 days. The resulting HP infection rate was 30%. If the mice were first fed with a mixture of gentamicin and azithromycin for 3 days to eliminate the original microbiota of the stomach, the 7-day administration of HP produced a 100% HP infection rate. After the gastric microbiota balance was remodeled by feeding the Lactobacillus and Bifidobacterium suspension for 7 days, the HP infection rate was reduced to 30% and HP colonization decreased significantly. Some experiments confirm that some components of the gastric microbiota have been shown to exert antibacterial properties and could drive HP conversing from a spiral to a coccoidal form [30, 31]. The findings support the speculation that the immune system and normal gastric microbiota can effectively antagonize the colonization of HP, while disruption of the gastric microbiota balance increases the susceptibility to HP infection. The data provide a theoretical basis for the clinical use of probiotics to increase the HP eradication rate.

4. Effect of Probiotics on HP Eradication

Many meta-analyses and clinical trials have confirmed that probiotic supplementation can increase the eradication rate of HP and reduce adverse reactions during eradication. It can be concluded from literature analysis that not all probiotics have antagonistic effects on HP and different probiotics have specific effects. The antagonistic effect of mixed strains of probiotics on HP was greater than that of a single strain. Probiotics alone cannot completely eliminate HP but can reduce the amount of HP load in the stomach, reduce the delta value of UBT, and alleviate gastric mucosal inflammation. More details on the role of probiotics on the HP eradication rate can be seen in Tables 1–4.

Some clinical trials proved that probiotics can reduce the DOB values of UBT, despite a complete eradication of HP not being obtained [32–34]. Whether DOB values quantitatively reflect the density of gastric HP is a controversial question. DOB value is affected by many factors, such as the density of HP colonization, urease activity, and gastric emptying. Different probiotics can reduce the DOB value by inhibiting urease activity [35] or decreasing the attachment of HP to the gastric mucosa, suppressing the HP density [36].

5. Action Mechanism of Probiotics

5.1. Production of Substances That Inhibit or Kill HP. The antagonistic mechanism of probiotics to HP is unclear. Probiotic microorganisms can produce a variety of substances that inhibit HP and induce the secretion of antibodies by the host. A partial list of the antibacterial compounds includes bacteriocins, lactic acid, acetic acid, and hydrogen peroxide (\(\text{H}_2\text{O}_2\)). Different probiotic strains produce different antibacterial substances. Strep. lactis can produce nisin. This positively charged molecule can combine with cell membranes by electrostatic and hydrophobic interactions followed by membrane insertion to form a permeable channel that precludes cell autolysis and death [56]. Bacillus subtilis produces the antibiotic amicoumacin A and similar isocoumarins, and L. roche produces a variety of reoterms that all inhibit the growth and activity of HP. One of the characteristics of HP is the secretion of urease, which breaks down urea in the stomach to produce ammonia and which neutralizes gastric acid to protect the bacteria from gastric acid damage. Most lactobacilli produce lactic acid, which can inhibit the activity of urease. Lactic acid is deleterious to HP. The morphological alteration that occurs is independent of pH [57]. Fujinura et al. cocultured an HP standard strain and L. gasser OLL2716 on agar for 24 h. Electron microscopy examination revealed a spherical shape of HP. The bacteria had also lost their growth ability [58]. Another characteristic of HP is catalase activity. Probiotics can produce \(\text{H}_2\text{O}_2\). Catalase action results in the production of many oxygen radicals, which are antibacterial due to their interference with HP enzyme activity. Live probiotics antagonize HP, but bacterial viability may not be a prerequisite for the deleterious activity. Heat-inactivated L. johnsonii No. 1088 (HK-LJ88) can kill HP in vitro and, when cocultured with HP for 24 h, can lead to altered HP morphology and lysis. Orally administered HK-LJ88 can reduce HP colonization in the mouse stomach. The anti-HP effect of HK-LJ88 does not involve coagglutination of the bacteria. Rather, some surface molecules of HK-LJ88 are not inactivated by the heat [59]. In another study on the coculture of HP with L. acidophilus CRL 639 for 24 hours, the latter appeared to be lysed and the released protein compounds deformed or killed HP [60].

5.2. Effect on HP Colonization in the Stomach. The colonization of HP in the gastric epithelium is a prerequisite for the disease. HP has multiple flagella at one end, which provide the mechanical for a bacterium to penetrate the thick layer of the mucus and colonize the surface of gastric epithelial cells rather than being excreted with the peristalsis of the stomach. The HP surface contains adhesions, such as neutrophil activator protein, fibrillar N-acetyleneuraminyl lactose-binding hemagglutinin (NLBH), Bab A, Lewis antigen, heat shock protein, Alp A, and Alp B. The gastric epithelial cells contain mucin receptors, mucopolysaccharide receptors, Lewis blood group substances, glycolipid receptors, and other corresponding receptors. The binding of the HP adhesins to the receptors mediates the colonization of HP in the gastric mucosa. Identifying the ability of probiotic bacteria to colonize the gastric mucosa is the first step in
develop when the HP density of the gastric antrum is to the virulence and quantity of HP. Peptic ulcers do not infection does not necessarily lead to disease, which is related in the stomach, the amount of HP will be reduced [63]. HP the stomach is antagonistic to each other. If Lactobacilli exist demonstrated that the growth of Lactobacillus and HP in reduce the adhesion of HP to gastric mucosa [62]. Others can downregulate the expression of HP adhesin sabA and

fatide [61].

screening probiotics that can antagonize HP adhesion and colonization. Such probiotics can compete with HP for the adhesion site of gastric epithelial cells to reduce the colonization of HP in the stomach. Mukai et al. found that L. reuteri affects the colonization of HP by the secretion of sialic acid gangliosides and thiolas that inhibit HP's glycolipid linkage with gastric epithelial cells, as well as competing with HP for the adhesion of asialo-ganglio-N-tetraosylceramide and sul-

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5.3. Inhibition of Inflammation after HP Infection. HP infection leads to gastric mucosal inflammation. This can begin a pathway, which is termed the Correa cascade, from chronic gastritis to atrophic gastritis to intestinal metaplasia to atypical hyperplasia, culminating in gastric cancer. This is the most common pattern of evolution after gastric mucosal infection with HP. Urease, cytotoxin-associated gene A (CagA), vacuolating cytotoxin A (VacA), and neutrophil-activating protein (NAP) are common virulence factors of HP. As its name implies, NAP activates neutrophils. It also activating protein (NAP) are common virulence factors of (CagA), vacuolating cytotoxin A (VacA), and neutrophil-infection with HP. Urease, cytotoxin-associated gene A (CagA), vacuolating cytotoxin A (VacA), and neutrophil-activating protein (NAP) are common virulence factors of HP. As its name implies, NAP activates neutrophils. It also

In vitro experiments confirmed that Lactobacillus can downregulate the expression of HP adhesion sabA and reduce the adhesion of HP to gastric mucosa [62]. Others demonstrated that the growth of Lactobacillus and HP in the stomach is antagonistic to each other. If Lactobacilli exist in the stomach, the amount of HP will be reduced [63]. HP infection does not necessarily lead to disease, which is related to the virulence and quantity of HP. Peptic ulcers do not develop when the HP density of the gastric antrum is <10^9 CFU/g [64]. The foregoing support the view that, while the oral administration of probiotics may well not completely eliminate HP, adhesion of HP can be reduced and gastric mucosal inflammation can be lessened. For children and elderly people who do not have digestive symptoms, oral administration of probiotics to reduce HP colonization is superior to traditional treatment.

| Author                  | Trials                        | Probiotic                                        | Result                                      |
|-------------------------|-------------------------------|--------------------------------------------------|---------------------------------------------|
| Jian et al. [37]         | 8 RCT (n = 1372)              | Lactobacilli + triple therapy                     | Pooled eradication rate                     |
|                         |                               |                                                  | Probiotic: 82.26% (95% CI = 78.01–86.51%)   |
|                         |                               |                                                  | No probiotic: 76.97% (95% CI = 73.11–80.83%)|
|                         |                               |                                                  | OR = 1.78 (95% CI = 1.21–2.62)             |
| Sachdeva and Nagpal [38]| 10 RCT (n = 963)              | Multistrain (fermented milk) + triple or quadruple therapy | Eradication rates were improved by approximately 5–15% |
|                         |                               |                                                  | OR = 1.91 (95% CI: 1.38–2.67)              |
| Dang et al.[39]         | 33 RCT (n = 4459), 9 RCT for children, 24 RCT for adults | Probiotics + triple therapy or sequential therapy or quadruple therapy | The pooled eradication rate in probiotic supplementation groups was significantly higher than that in controls (RR = 1.122, 95% CI = 1.086–1.159) |
|                         |                               |                                                  | Eradication rate (adult)                    |
|                         |                               |                                                  | Probiotic: 80.0% (95% CI = 77–82)           |
|                         |                               |                                                  | No probiotic: 71.0% (95% CI = 68–74)        |
|                         |                               |                                                  | RR = 1.11, 95% CI = 1.06–1.17               |
| Szajewska et al.[40]    | 9 RCT (adult, n = 1708) 2 RCT (children, n = 330) | Saccharomyces boulardii + triple therapy | Eradication rate (children)                |
|                         |                               |                                                  | Probiotic: 87.5%                           |
|                         |                               |                                                  | No probiotic: 77.2%                         |
|                         |                               |                                                  | RR = 1.13, 95% CI = 1.03–1.25               |
| Zhang et al. [41]       | 45 RCT (n = 6997)             | Probiotics + standard therapy                     | Eradication rate                           |
|                         |                               |                                                  | Probiotic: 82.31%                           |
| Wen et al. [42]         | 17 RCT in Asian pediatric patients (n = 1932) | Multistrain probiotics + 14-day triple therapy | Probiotics + standard therapy              |
|                         |                               |                                                  | Side effects (RR = 0.59; 95% CI = 0.48–0.71) |
|                         |                               |                                                  | Probiotic: 21.44%                          |
|                         |                               |                                                  | No probiotic: 36.27%                        |
| Losurdo et al. [43]     | 7 RCT (n = 517)               | Probiotic strain alone                           | Lactobacillus infantis + Clostridium butyricum was most beneficial for eradication rates (RR: 1.16, 95% CI: 1.07–1.26) |
|                         |                               |                                                  | Bifidobacterium infantis + Clostridium butyricum was most beneficial for eradication rates (RR: 1.16, 95% CI: 1.07–1.26) |
|                         |                               |                                                  | The mean weighted eradication rate was 14% (95% CI = 2%–25%) |
|                         |                               |                                                  | Lactobacilli: 16% (95% CI: 1%–31%)          |
|                         |                               |                                                  | Saccharomyces boulardii: 12% (95% CI: 0%–29%) |
|                         |                               |                                                  | Multistrain: 14% (95% CI: 0%–43%)           |
mucosa cells, and also stimulate mucosal monocytes and dendritic cells to produce tumor necrosis factor, IL-1, and IL-6. The dendritic cell activity produces an inflammatory cascade. These responses are insufficient to clear HP infection but cause chronic inflammation [65]. Virulence and inflammatory factors are now being used to prepare HP-associated vaccines. Animal studies have demonstrated the considerable (80%) effectiveness of oral vaccines based on NAP [66]. Some probiotic strains can also reduce the release of inflammatory factors by regulating the local immune response of the host and relieving the inflammatory response of the gastric mucosa. An in vitro study confirmed that HP-induced secretion of IL-8 in gastric epithelial cells can be reduced by *L. salivarius* [67]. Another study showed that the exopolysaccharide of *Streptococcus thermophilus* CRL1190 reduces the colonization of HP to AGS cells and also relieves the inflammatory response of AGS cells caused by HP [68]. The mechanism by which probiotics regulate mucosal immune responses is unclear. *L. reuteri* can inhibit the activation of nuclear factor-kappa B (NF-kB) and downstream factors by blocking the release of the tumor necrosis factor from macrophages. *L. acidophilus* can inhibit the expression of Smad7, inactivate the transduction of the NF-kB pathway, and weaken the HP-induced gastric mucosal inflammatory response [69]. *L. plantarum* and *L. acidophilus* applied prior to HP infection reduce the degree of gastritis. Phosphorylation of Janus kinase 2 and the expression of the cytokine factor suppressors of cytokine signaling-2 and -3 are increased in the JAK-STAT pathway. SOCS-2 and SOCS-3 can inhibit a variety of signal transduction pathways, which reduces the release of inflammatory factors [70]. Probiotics can reduce the release of IL-8, interferon gamma, and other inflammatory factors by inhibiting the Toll-like receptor 4-NF-kB signaling pathway [71]. *L. salivarius* UCC118 and UCC119 can reduce the secretion of IL-8 by the gastric mucosa after HP infection. This effect has

| Author            | Study size | Probiotic                         | Study type                          | Result                                                                 |
|-------------------|------------|-----------------------------------|-------------------------------------|------------------------------------------------------------------------|
| Zhao et al. [44]  | 240        | Saccharomyces boulardii           | A prospective, randomized, controlled study | Eradication rate Probiotic: 85.0% No probiotic: 75.8% Adverse reaction decreases |
| Dore et al. [45]  | 45         | Lactobacillus reuteri (DSM 17938) | A case report series                | Eradication rate Probiotic: 93.3%                                      |
| Cekin et al. [18] | 159        | Bifidobacterium animalis subsp. lactis B94 | Randomized, placebo-controlled study | Saccharomyces boulardii reduced the overall side effect rate, and there was no difference observed in efficacy on the eradication rate No significant difference in eradication rates was observed. Supplementation of probiotics led to improvement of gastrointestinal symptoms |
| Zhu et al. [46]  | 240        | Saccharomyces boulardii           | Randomized clinical trial           |                                                                              |
| Chen et al. [47]  | 105        | Clostridium butyricum             | Open-label, randomized clinical trial |                                                                              |

| Author            | Study size | Probiotics                              | Study type                          | Result                                                                 |
|-------------------|------------|-----------------------------------------|-------------------------------------|------------------------------------------------------------------------|
| Du et al. [48]    | 228        | L. acidophilus + S. faecalis + B. subtilis | Randomized Prospective Open         | Eradication rate Probiotic: 79.5% No probiotics: 60.8% Adverse reaction decreases |
| Wang and Huang [49]| 100        | L. acidophilus + B. bifidum             | Randomized Prospective Open         | Probiotic: 83.7% No probiotics: 64.4%                                   |
| Tongtawee et al. [50]| 200    | Lactobacillus delbrueckii + Streptococcus thermophilus | Double-blind Placebo-controlled Randomized | Probiotic: 90.8% No probiotics: 84.3%                                   |
| Haghdoost et al. [51]| 176       | Lactobacillus + Bifidobacterium         | Randomized Placebo-controlled study | Probiotic: 78.4% No probiotics: 64.8%                                   |
nothing to do with the life or death of *L. salivarius, but the probiotic body must be complete. *L. salivarius UCC118 and UCC119 can destroy the type IV secretion system encoded by the cagPAI of the HP toxin-related gene and block the entry of the effector molecule cagA into host epithelial cells [72]. A probiotic mixture of *Enterococcus faecalis, B. longum, and L. acidophilus reportedly tolerated the acidic environment in the stomach and survived for 8 hours. These three probiotics could not reduce the colonization of HP in the stomach but could reduce the release of inflammatory factors such as tumor necrosis factor-alpha, IL-1β, IL-10, IL-6, granulocyte colony-stimulating factor, and macrophage inflammatory protein 2 by inhibiting the NF-κB and mitogen-activated protein kinase signal transduction pathways [73]. Arginine is a substrate for the synthesis of nitric oxide, one of the strongest mediators of inflammation. The arginine deiminase activity following L. brevis administration causes arginine deficiency and prevents polyamine generation from proliferating cells [52].

### 6. Conclusion

With the deepening of the research on the intestinal microflora, microecological therapy is attracting increasing attention. Probiotics can help improve the eradication rate of HP and reduce the adverse reactions. However, not all probiotics but only some specific probiotic strains have such effects. Here are several research hurdles still to be surmounted. First, the gut microflora of humans is affected by various factors, such as the environment, diet, genetics, and lifestyle, and it is difficult to directly study the effects of probiotics on the human body. Second, due to the synergistic or antagonistic effect between bacteria, it is difficult to generalize the effects of certain probiotic strains in the different probiotic combinations. Third, due to the specificity of the strains and the inconsistent results of the research, the results to date can be questioned.

The results to date consistently support the prowess of probiotics in alleviating adverse reactions in the eradication of HP. However, questions remain. Can probiotics increase the eradication rate of HP? If so, what is the mechanism? Which probiotic strain has the best anti-HP effect? What is the best dose and the timing of medication (i.e., before or after eradication)? Is there a difference in efficacy between single strains and mixed strains? Are there side effects of supplemental exogenous probiotics? The answers await future basic and clinical studies.

### Conflicts of Interest

The authors declare no competing interests.

### Authors’ Contributions

Han-Yi Song did the literature search, the design, and the writing. Long Zhou did the analysis and interpretation. Dong-yan Liu did the critical reviews. Xin-Jie Yao did the data collection and processing. Yan Li did the concept and supervision.
References

[1] P. Malfertheiner, F. Megraud, C. A. O’Morain et al., “Management of Helicobacter pylori infection—the Maastricht IV/Florence consensus report,” *Gut*, vol. 61, no. 5, pp. 646–664, 2012.

[2] K. Sugano, J. Tack, E. J. Kuipers et al., “Kyoto global consensus report on Helicobacter pylori gastritis,” *Gut*, vol. 64, no. 9, pp. 1353–1367, 2015.

[3] Y. A. Lin, H. Wang, Z. J. Gu et al., “Effect of CYP2C19 gene polymorphisms on proton pump inhibitor, amoxicillin, and levofloxacin triple therapy for eradication of Helicobacter pylori,” *Medical Science Monitor*, vol. 23, pp. 2701–2707, 2017.

[4] D. Itskoviz, D. Boltin, H. Leibovitz et al., “Smoking increases the likelihood of Helicobacter pylori treatment failure,” *Dietary and Liver Disease*, vol. 49, no. 7, pp. 764–768, 2017.

[5] C. Horikawa, S. Kodama, K. Fujihara et al., “High risk of failing eradication of Helicobacter pylori in patients with diabetes: a meta-analysis,” *Diabetes Research and Clinical Practice*, vol. 106, no. 1, pp. 81–87, 2014.

[6] D. Y. Graham, Y.–. C. Lee, and M.–. S. Wu, “Rational Helicobacter pylori therapy: evidence-based medicine rather than medicine-based evidence,” *Clinical Gastroenterology and Hepatology*, vol. 12, no. 2, pp. 177–186.e3, 2014.

[7] P. Malfertheiner, F. Megraud, C. A. O’Morain et al., “Management of Helicobacter pylori infection—the Maastricht V/Florence Consensus Report,” *Gut*, vol. 66, no. 1, pp. 6–30, 2016.

[8] W. D. Chey, G. I. Leontiadis, C. W. Howden, and S. F. Moss, “ACG clinical guideline: treatment of Helicobacter pylori infection,” *The American Journal of Gastroenterology*, vol. 112, no. 2, pp. 212–239, 2017.

[9] Y. Hu, Y. Zhu, and N. H. Lu, “Primary antibiotic resistance of Helicobacter pylori in China,” *Digestive Diseases and Sciences*, vol. 62, no. 5, pp. 1146–1154, 2017.

[10] I. Adamsson, C. Edlund, and C. E. Nord, “Impact of treatment of Helicobacter pylori on the normal gastrointestinal microflora,” *Clinical Microbiology and Infection*, vol. 6, no. 4, pp. 175–177, 2000.

[11] N. Arslan, O. Yılmaz, and E. Demiray-Gurbuz, “Importance of antimicrobial susceptibility testing for the management of eradication in Helicobacter pylori infection,” *World Journal of Gastroenterology*, vol. 23, no. 16, pp. 2854–2869, 2017.

[12] T. Nishizawa and H. Suzuki, “Mechanisms of Helicobacter pylori antibiotic resistance and molecular testing,” *Frontiers in Molecular Biosciences*, vol. 1, no. 19, 2014.

[13] A. T. B. Abadi, “Vaccine against Helicobacter pylori: inevitable approach,” *World Journal of Gastroenterology*, vol. 22, no. 11, pp. 3150–3157, 2016.

[14] F. Ma, Y. Chen, J. Li et al., “Screening test for anti-Helicobacter pylori activity of traditional Chinese herbal medicines,” *World Journal of Gastroenterology*, vol. 16, no. 44, pp. 5629–5634, 2010.

[15] H. Y. Song and Y. Li, “Can eradication rate of gastric Helicobacter pylori be improved by killing oral Helicobacter pylori?,” *World Journal of Gastroenterology*, vol. 19, no. 39, pp. 6645–6650, 2013.

[16] J. K. C. Yee, “Are the view of Helicobacter pylori colonized in the oral cavity an illusion?,” *Experimental & Molecular Medicine*, vol. 49, no. 11, article e397, 2017.

[17] Y. Wang, B. Wang, Z. F. Lv et al., “Efficacy and safety of ecabet sodium as an adjuvant therapy for Helicobacter pylori eradication: a systematic review and meta-analysis,” *Helicobacter*, vol. 19, no. 5, pp. 372–381, 2014.

[18] A. H. Cekin, Y. Sahinturk, F. Akbay Harmandar, S. Uyar, B. Oğuz Yolcular, and Y. Cekin, “Use of probiotics as an adjuvant to sequential *H. pylori* eradication therapy: impact on eradication rates, treatment resistance, treatment-related side effects, and patient compliance,” *The Turkish Journal of Gastroenterology*, vol. 28, no. 1, pp. 3–11, 2017.

[19] T. Kafshdooz, A. Akbarzadeh, A. Majdi Seghinsara, M. Pourhassan, H. T. Nasrabadi, and M. Milani, “Role of probiotics in managing of Helicobacter pylori infection: a review,” *Drug Research*, vol. 67, no. 2, pp. 88–93, 2017.

[20] L. V. McFarland, Y. Huang, L. Wang, and P. Malfertheiner, “Systematic review and meta-analysis: multi-strain probiotics as adjunct therapy for Helicobacter pylori eradication and prevention of adverse events,” *United European Gastroenterology Journal*, vol. 4, no. 4, pp. 546–561, 2016.

[21] C. A. Fallone, N. Chiba, S. V. van Zanten et al., “The Toronto consensus for the treatment of Helicobacter pylori infection in adults,” *Gastroenterology*, vol. 151, no. 1, pp. 51–69.e14, 2016.

[22] C. Hill, F. Guarner, G. Reid et al., “Expert consensus document. The International Scientific Association for Probiotics and Prebiotics consensus statement on the scope and appropriate use of the term probiotic,” *Nature Reviews Gastroenterology & Hepatology*, vol. 11, no. 8, pp. 506–514, 2014.

[23] R. L. Brown and T. B. Clarke, “The regulation of host defences to infection by the microbiota,” *Immunology*, vol. 150, no. 1, pp. 1–6, 2017.

[24] G. Janio, J. Molina-Infante, and A. Gasbarrini, “Gastric microbiota,” *Helicobacter*, vol. 20, pp. 68–71, 2015.

[25] V. Pereira, P. Abraham, S. Nallapeta, and A. Shetty, “Gastric bacterial flora in patients harbouring Helicobacter pylori with or without chronic dyspepsia: analysis with matrix-assisted laser desorption ionization time-of-flight mass spectroscopy,” *BMC Gastroenterology*, vol. 18, no. 1, p. 20, 2018.

[26] I. Yang, S. Nell, and S. Suerbaum, “Survival in hostile territory: the microbiota of the stomach,” *FEMS Microbiology Reviews*, vol. 37, no. 5, pp. 736–761, 2013.

[27] A. F. Andersson, M. Lindberg, H. Jakobsson, F. Bäckhed, P. Nyren, and L. Engstrand, “Comparative analysis of human gut microbiota by barcoded pyrosequencing,” *PLoS One*, vol. 3, no. 7, article e2836, 2008.

[28] J. Bylund, T. Christophe, F. Boulay, T. Nystrom, A. Karlsson, and C. Dahlgren, “Proinflammatory activity of a cecropin-like antibacterial peptide from Helicobacter pylori,” *Antimicrobial Agents and Chemotherapy*, vol. 45, no. 6, pp. 1700–1704, 2001.

[29] M. Karita, Q. Li, D. Cantero, and K. Okita, “Establishment of a small animal model for human Helicobacter pylori infection using germ-free mouse,” *The American Journal of Gastroenterology*, vol. 89, no. 2, pp. 208–213, 1994.

[30] C. Zaman, T. Osaki, T. Hanawa, H. Yonezawa, S. Kurata, and S. Kamiya, “Analysis of the microbial ecology between *Helicobacter pylori* and the gastric microbiota of Mongolian gerbils,” *Journal of Medical Microbiology*, vol. 63, pp. 129–137, 2014.

[31] Y. Khosravi, Y. Dieye, M. F. Loke, K. L. Goh, and J. Vadivelu, “*Streptococcus mitis* induces conversion of Helicobacter pylori to coccoid cells during co-culture in vitro,” *PLoS One*, vol. 9, no. 11, article e112214, 2014.
[32] P. Michetti, G. Dorta, P. H. Wiesel et al., “Effect of whey-based culture supernatant of Lactobacillus acidophilus (johnsonii) L1 on Helicobacter pylori infection in humans,” Digestion, vol. 60, no. 3, pp. 203–209, 1999.

[33] I. Sakamoto, M. Igarashi, K. Kimura, A. Takagi, T. Miwa, and Y. Koga, “Suppressive effect of Lactobacillus gasseri OLL 2716 (LG21) on Helicobacter pylori infection in humans,” The Journal of Antimicrobial Chemotherapy, vol. 47, no. 5, pp. 709–710, 2001.

[34] S. Cruchet, M. C. Obregon, G. Salazar, E. Diaz, and M. Gotteland, “Effect of the ingestion of a dietary product containing Lactobacillus johnsonii L1 on Helicobacter pylori colonization in children,” Nutrition, vol. 19, no. 9, pp. 716–721, 2003.

[35] M. J. Salas-Jara, E. A. Sanhueza, A. Retamal-Diaz, C. Gonzalez, H. Urrutia, and A. Garcia, “Probiotic Lactobacillus fermentum UCO-979C biofilm formation on AGS and Caco-2 cells and Helicobacter pylori inhibition,” Biofouling, vol. 32, no. 10, pp. 1245–1257, 2016.

[36] K. Imase, A. Tanaka, K. Tokunaga, H. Sugano, H. Ishida, and S. Takahashi, “Lactobacillus reuteri tablets suppress Helicobacter pylori infection—a double-blind randomised placebo-controlled cross-over clinical study,” Journal of the Japanese Association for Infectious Diseases, vol. 81, no. 4, pp. 387–393, 2007.

[37] J. Zou, J. Dong, and X. Yu, “Meta-analysis: Lactobacillus containing quadruple therapy versus standard triple first-line therapy for Helicobacter pylori eradication,” Helicobacter, vol. 14, no. 5, pp. 97–107, 2009.

[38] A. Sachdeva and J. Nagpal, “Effect of fermented milk-based probiotic preparations on Helicobacter pylori eradication: a systematic review and meta-analysis of randomized-controlled trials,” European Journal of Gastroenterology & Hepatology, vol. 21, no. 1, pp. 45–53, 2009.

[39] Y. Dang, J. D. Reinhardt, X. Zhou, and G. Zhang, “The effect of probiotics supplementation on Helicobacter pylori eradication rates and side effects during eradication therapy: a meta-analysis,” PLoS One, vol. 9, no. 11, article e110330, 2014.

[40] H. Szajewska, A. Horvath, and M. Kolodziej, “Y. Dang, J. D. Reinhardt, X. Zhou, and G. Zhang, “The impact of Helicobacter pylori infection, eradication therapy and probiotic supplementation on gut microenvironment homeostasis: an open-label, randomized clinical trial,” eBioMedicine, vol. 55, pp. 87–96, 2018.

[41] Y.-Q. Du, T. Su, J.-G. Fan et al., “Adjuvant probiotics improve the eradication effect of triple therapy for Helicobacter pylori infection,” World Journal of Gastroenterology, vol. 18, no. 43, pp. 6302–6307, 2012.

[42] Y. H. Wang and Y. Huang, “Effect of Lactobacillus acidophilus and Bifidobacterium bifidum supplementation to standard triple therapy on Helicobacter pylori eradication and dynamic changes in intestinal flora,” World Journal of Microbiology and Biotechnology, vol. 30, no. 3, pp. 847–853, 2014.

[43] T. Tongtawee, C. Dechsukhum, W. Leeannaksiri et al., “Effect of pretreatment with Lactobacillus delbrueckii and Streptococcus thermophilus on tailored triple therapy for Helicobacter pylori eradication: a prospective randomized controlled clinical trial,” Asian Pacific Journal of Cancer Prevention, vol. 16, no. 12, pp. 4885–4890, 2015.

[44] M. Haghdoost, S. Taghizadeh, M. Montazer, P. Poorshahverdi, A. Ramouz, and S. Fakour, “Double strain probiotic effect on Helicobacter pylori infection treatment: a double-blinded randomized controlled trial,” Caspian Journal of Internal Medicine, vol. 8, no. 3, pp. 165–171, 2017.

[45] M. Linsalata, F. Russo, P. Berloco et al., “The influence of lactobacillus brevis on ornithine decarboxylase activity and polyamine profiles in Helicobacter pylori-infected gastric mucosa,” Helicobacter, vol. 9, no. 2, pp. 165–172, 2004.

[46] R. Rosania, M. Filomena Minenna, F. Giorgio et al., “Probiotic multistrain treatment may eradicate Helicobacter pylori from the stomach of dyspeptics: a placebo-controlled pilot study,” Inflammation & Allergy Drug Targets, vol. 11, no. 3, pp. 244–249, 2012.

[47] R. Francavilla, L. Polimeni, A. Demichina et al., “Lactobacillus reuteri strain combination in Helicobacter pylori infection: a randomized, double-blind, placebo-controlled study,” Journal of Clinical Gastroenterology, vol. 48, no. 5, pp. 407–413, 2014.

[48] C. Holz, A. Busjahn, H. Mehling et al., “Significant reduction in Helicobacter pylori load in humans with non-viable Lactobacillus reuteri DSM17648: a pilot study,” Probiotics and Antimicrobial Proteins, vol. 7, no. 2, pp. 91–100, 2015.

[49] E. H. Lee, I. Khan, and D. H. Oh, “Evaluation of the efficacy of nisin-loaded chitosan nanoparticles against foodborne pathogens in orange juice,” Journal of Food Science and Technology, vol. 55, no. 3, pp. 1127–1133, 2018.

[50] P. S. Hsieh, Y. C. Tsai, Y. C. Chen, S. F. Teh, C. M. Ou, and V. A. E. King, “Eradication of Helicobacter pylori infection by the probiotic strains Lactobacillus johnsonii MH-68 and L. salivarius ssp. salicinus AP-32,” Helicobacter, vol. 17, no. 6, pp. 466–477, 2012.

[51] S. Fujimura, A. Watanabe, K. Kimura, and M. Kaji, “Probiotic mechanism of Lactobacillus gasseri OLL2716 strain against Helicobacter pylori,” Journal of Clinical Microbiology, vol. 50, no. 3, pp. 1134–1136, 2012.
[59] Y. Aiba, H. Ishikawa, M. Tokunaga, and Y. Komatsu, “Anti-Helicobacter pylori activity of non-living, heat-killed form of lactobacilli including Lactobacillus johnsonii no.1088,” FEMS Microbiology Letters, vol. 364, no. 11, 2017.

[60] G. L. Lorca, T. Wadström, G. Font de Valdez, and Å. Ljungh, “Lactobacillus acidophilus autolysins inhibit Helicobacter pylori in vitro,” Current Microbiology, vol. 42, no. 1, pp. 39–44, 2001.

[61] T. Mukai, T. Asasaka, E. Sato, K. Mori, M. Matsumoto, and H. Ohori, “Inhibition of binding of Helicobacter pylori to the glycolipid receptors by probiotic Lactobacillus reuteri,” FEMS Immunology and Medical Microbiology, vol. 32, no. 2, pp. 105–110, 2002.

[62] N. de Klerk, L. Maudsdotter, H. Gebreegziabher et al., “Lactobacilli reduce Helicobacter pylori attachment to host gastric epithelial cells by inhibiting adhesion gene expression,” Infection and Immunity, vol. 84, no. 5, pp. 1526–1535, 2016.

[63] A. García, K. Sáez, C. Delgado, and C. L. González, “Low co-existence rates of Lactobacillus spp. and Helicobacter pylori detected in gastric biopsies from patients with gastrointestinal symptoms,” Revista Española de Enfermedades Digestivas, vol. 104, no. 9, pp. 473–478, 2012.

[64] S. Khulusi, M. A. Mendall, P. Patel, J. Levy, S. Badve, and T. C. Northfield, “Helicobacter pylori infection density and gastric inflammation in duodenal ulcer and non-ulcer subjects,” Gut, vol. 37, no. 3, pp. 319–324, 1995.

[65] H. W. Fu, “Helicobacter pylori neutrophil-activating protein: from molecular pathogenesis to clinical applications,” World Journal of Gastroenterology, vol. 20, no. 18, pp. 5294–5301, 2014.

[66] B. Satin, G. del Giudice, V. Della Bianca et al., “The neutrophil-activating protein (HP-NAP) of Helicobacter pylori is a protective antigen and a major virulence factor,” The Journal of Experimental Medicine, vol. 191, no. 9, pp. 1467–1476, 2000.

[67] A. M. Kabir, Y. Aiba, A. Takagi, S. Kamiya, T. Miwa, and Y. Koga, “Prevention of Helicobacter pylori infection by Lactobacilli in a gnotobiotic murine model,” Gut, vol. 41, no. 1, pp. 49–55, 1997.

[68] G. Marcial, J. Villena, G. Faller, A. Hensel, and G. F. de Valdés, “Exopolysaccharide-producing Streptococcus thermophilus CRL1190 reduces the inflammatory response caused by Helicobacter pylori,” Beneficial Microbes, vol. 8, no. 3, pp. 451–461, 2017.

[69] Y.-J. Yang, C. C. Chuang, H. B. Yang, C. C. Lu, and B. S. Sheu, “Lactobacillus acidophilus ameliorates H. pylori-induced gastric inflammation by inactivating the Smad7 and NFkB pathways,” BMC Microbiology, vol. 12, no. 1, p. 38, 2012.

[70] J. S. Lee, N. S. Paek, O. S. Kwon, and K. B. Hahm, “Anti-inflammatory actions of probiotics through activating suppressor of cytokine signaling (SOCS) expression and signaling in Helicobacter pylori infection: a novel mechanism,” Journal of Gastroenterology and Hepatology, vol. 25, no. 1, pp. 194–202, 2010.

[71] C. Zhou, F. Z. Ma, X. J. Deng, H. Yuan, and H. S. Ma, “Lactobacilli inhibit interleukin-8 production induced by Helicobacter pylori lipopolysaccharide-activated Toll-like receptor 4,” World Journal of Gastroenterology, vol. 14, no. 32, pp. 5090–5095, 2008.