Probiotics as the live microscopic fighters against *Helicobacter pylori* gastric infections

Masoud Keikha\(^1,2\) and Mohsen Karbalaei\(^3^*\)

**Abstract**

**Background:** *Helicobacter pylori* (*H. pylori*) is the causative agent of stomach diseases such as duodenal ulcer and gastric cancer, in this regard incomplete eradication of this bacterium has become to a serious concern. Probiotics are a group of the beneficial bacteria which increase the cure rate of *H. pylori* infections through various mechanisms such as competitive inhibition, co-aggregation ability, enhancing mucus production, production of bacteriocins, and modulating immune response.

**Result:** In this study, according to the received articles, the anti-*H. pylori* activities of probiotics were reviewed. Based on studies, administration of standard antibiotic therapy combined with probiotics plays an important role in the effective treatment of *H. pylori* infection. According to the literature, *Lactobacillus casei*, *Lactobacillus reuteri*, *Lactobacillus rhamnosus GG*, and *Saccharomyces boulardii* can effectively eradicate *H. pylori* infection. Our results showed that in addition to decrease gastrointestinal symptoms, probiotics can reduce the side effects of antibiotics (especially diarrhea) by altering the intestinal microbiome.

**Conclusion:** Nevertheless, antagonist activities of probiotics are *H. pylori* strain-specific. In general, these bacteria can be used for therapeutic purposes such as adjuvant therapy, drug-delivery system, as well as enhancing immune system against *H. pylori* infection.

**Keywords:** Gastric cancer, *Helicobacter pylori*, *Lactobacillus*, Peptic ulcer, Probiotic

**Background**

*Helicobacter pylori* (*H. pylori*) is a gram-negative, motile, helical and microaerophilic microorganism that is considered as one of the most successful pathogens due to persistent infection in human stomach [1]. The global prevalence of this bacterium is high, so that according to the latest statistics *H. pylori* has colonized the stomachs of 4.4 billion people worldwide [2]. There is ample evidence that *H. pylori* is the etiologic agent of both gastric (gastric malignancy, peptic ulcer, chronic gastritis) and extragastric diseases [3–5]. Depending on the geographical area, the rate of infection with this pathogen varies; frequency of infection with this bacterium is associated with several factors such as virulence factors (e.g. CagA and VacA) and socioeconomic status, for example the rate of infection in some parts of Africa is close to 100% [6]. According to the literature, post-treatment re-infection is common in low-income countries with poor public health policy [7]. Basically all patients infected with this bacterium should be treated; complete eradication of *H. pylori* improves peptic ulcer and mucosa-associated lymphoid tissue (MALT) lymphoma, as well as reduces the risk of gastric cancer and autoimmune liver disease [8–10]. The most common problems facing gastroenterologists include, (1) antibiotic-resistance phenomenon, (2) persistence of bacteria in latent status, (3) degradation of antibiotics in acidic gastric conditions, (4) re-infection especially in regions with high prevalence, (5) adverse side effects of antibiotics such as diarrhea, nausea, vomit,
and abdominal pain, (6) rapid metabolism of antibiotics due to CYP2C19 enzyme, (7) poor compliance of multiple antibiotics [11–13]. In recent years, antibiotic resistance (with high divergence) has led to increased therapeutic failure in eradicating H. pylori with current regimens [14, 15]. In the early 1990s, the eradication rate of the standard triple therapy was more than 90%; however, in recent decades, the effectiveness of this regimen has dropped to less than 70% [16–18]. According to the World Health Organization (WHO) report, the rate of resistance to clarithromycin and metronidazole ranged 14–34% and 20–38%, respectively [19]. Graham et al. suggested that the therapeutic regimens with less than 80% efficacy are considered as treatment failure [20]. Recently, adjuvant therapy with probiotics has received much attention as a new strategy to increase the success of anti-H. pylori therapy [15]. Probiotics are a group of bacteria that confer various health benefits to the host [21]. Intestinal colonization with these microorganisms maintains the integrity of the mucosal immune system and inhibits the side effects associated with antibiotic use [21, 22]. Probiotics are used for purposes such as treating diarrhea and preventing allergic reactions [23]. In vitro studies have shown that some probiotics particularly Lactobacillus spp. possess anti-H. pylori activities [24]. García et al. found that co-existence of Lactobacillus and H. pylori in patients with severe gastrointestinal diseases was significantly lower than control subjects (without clinical symptoms); colonization of Lactobacillus spp. in stomach leads to several events such as reducing gastritis, promoting mucin regeneration, as well as downregulating gene expression in cag pathogenicity island [25]. Therefore, probiotic supplementation is considered as one of the promising solutions for the treatment of H. pylori infection in symptomatic patients [15]. Based on studies, the use of probiotics as a supplement in addition to standard antibiotic treatment significantly improves the eradication rate of H. pylori infection compared to the administration of antibiotics alone [26, 27]. The main purpose of this study was to provide an overview of the benefits of using probiotics in the treatment of H. pylori infection.

H. pylori antibiotic resistance and current treatment regimens

First-line therapy

According to European Helicobacter and Microbiota Study Group (EHMSG) guidelines, triple therapy is still recommended as the first-line treatment for H. pylori infection in areas with low clarithromycin rate [28]. Increasing clarithromycin resistance leads to reduce the eradication rate of clarithromycin-containing triple therapy, for example in Argentina cure rate is estimated at 75% [29]. The situation in South Korea is even worse, so that based on the duration of treatment, the cure rate with this regimen has been estimated at 64% and 66% for 7 and 14 days, respectively [30]. According to the literature, clarithromycin resistance rates are 10.6–25%, 16%, and 1.7–23.4% in North America, Japan, and Europe, respectively [30–33]. On the other hand, metronidazole resistance is also increasing, so that the resistance in European and African countries is 17–44% and 100%, respectively [34–36]. Recently, Yao et al. showed that the rate of infection eradication in type 2 diabetic patients is up to 74% [37]. Bismuth quadruple therapy, a complex regimen containing proton pump inhibitors (PPIs), bismuth salt, tetracycline, and metronidazole is also recommended as second-line (or even first-line) in high clarithromycin resistance areas [38]. In accordance with multicenter randomized controlled trials (RCTs), curing rate of bismuth quadruple therapy is significantly higher than the standard triple therapy (90.4% vs. 83.7%) at the same time (for 14 days) [39]. However, in a meta-analysis study, Luther et al. evaluated nine RCTs, and found that the eradication rate of infection in patients receiving bismuth quadruple therapy was the same as those who had received clarithromycin triple therapy (78.3% vs. 77%) [40]. But it should be noted that bismuth citrate is harmful to human health, so this drug (or even tetracycline) is contraindicated in some areas [41]. In a comprehensive meta-analysis on fourteen RCTs studies, it was shown that the eradication rate of infection with both bismuth and non-bismuth quadruple regimens was 6% higher than sequential treatment [42].

Second-line therapy

Levofoxacin triple therapy and bismuth quadruple therapy are considered as two well-known therapeutic strategies against H. pylori infection [43]. Levofoxacin-containing regimen contains a PPIs plus levofoxacin and amoxicillin [44]. According to the literature, eradication rate of infection in levofoxacin triple therapy and bismuth quadruple therapy is 74.5% and 78%, respectively [43, 45]. Increased resistance to quinolones has now become a major concern in reducing the clinical efficacy of levofoxacin-containing therapy; resistance to quinolones in Europe, America, and Asia is 20%, 15%, and 10% respectively [46]. Due to the adverse event rates of levofloxacin in patients, it is recommended that treatment with levofloxacin be prescribed only in cases of treatment failure [47].

Third-line therapy

In general, third-line therapy is prescribed following antibiotic susceptibility testing (AST) and considered as a rescue regimen in case of failure in the first and
second lines of treatment [43]. Nevertheless, due to the impossibility of testing in all areas, therefore therapeutic protocols such as bismuth-based levofloxacin quadruple therapy or rifabutin triple therapy (a PPI, rifabutin, and amoxicillin) are used as alternative empiric treatments [48]. All three treatment lines are summarized in Fig. 1.

Drawbacks of antibiotic therapy against H. pylori
Overall, there are some drawbacks versus successful antibiotic therapy that include, increasing antibiotic resistance (especially against clarithromycin and metronidazole), unfavorable acidic conditions of the stomach (degradation of antibiotics), non-FDA-approved of some antibiotics (e.g. nitazoxanide), side effects of all antibiotics, as well as toxicity and high price of some drugs [47, 49, 50]. Treatment failure may gradually lead to the progression of the primary infection to more severe complications such as peptic ulcer, MALT lymphoma, and gastric cancer [51]. In summary, probiotics help human body against H. pylori through direct or indirect antagonism interactions including secreting antibacterial substances (lactic acid, short-chain fatty acids, hydrogen peroxide, and bacteriocins), inhibiting bacterial colonization, enhancing mucosal barriers, and regulating the immune responses [52].

Probiotics as anti-H. pylori agents
Comprehensive definition of probiotics
Probiotics are a group of living microorganisms that generally colonize the gastrointestinal tract and have undeniable effects for improving human health [53]. Today, the clinical benefits of probiotics are widely accepted; their therapeutic applications are in disorders such as diarrhea, antibiotic-associated diarrhea, functional digestive involvements, inflammatory bowel disease, cardiovascular diseases, allergic reactions, and cancer [54]. Lactobacillus spp. are one of the most well-known probiotics that their anti-H. pylori properties have been proven [55]. According to the evidence, colonization rate of Lactobacillus spp. in normal human gastric is $0-10^3$ CFU (resistant to acidic conditions of the human stomach for 2 h); some Lactobacillus strains prevent the persistent colonization of H. pylori due to their specific adhesins [56]. According to the European Helicobacter Pylori Study Group (EHPSG), adjuvant therapy with probiotics can be helpful in increasing the cure rate of infections [57]. In addition to Lactobacillus spp., many other bacteria are accounted as bacterial probiotics against H. pylori; characteristics such as names of probiotics, their potential activity, in-vitro or in-vivo examinations, and country of study are listed in Table 1. However, some probiotics such as Lactobacillus spp. and Bifidobacterium spp. have been used more in clinical trials than other probiotics [58]. According to the literature, administration of a dairy

![Fig. 1 Flowchart of the three eradication regimens for the treatment of H. pylori infection](image-url)
product supplemented with *Lactobacillus* spp. and *Bifidobacterium* spp. increases both mucosal and systemic IgA response against gastrointestinal infections [59]. Sheu et al. showed in their study that a yogurt containing these bacteria could improve the eradication rate of *H. pylori* infection, and also restore the depletion of *Bifidobacterium* in stool at the fifth week of treatment [60]. In addition, these bacteria can produce significant amounts of lactic acid in the stomach after successful colonization [61].

**Table 1** List of probiotics with potential activity against *H. pylori* infection by in vitro and in vivo studies

| Probiotic name                  | Potential activity                                      | Human/animal/in-vitro examination | Country       | Ref  |
|--------------------------------|---------------------------------------------------------|-----------------------------------|---------------|-----|
| *L. salivarius* WB1004          | Inhibition of colonization, lactic acid                 | BALB/c mice                       | Japan         | [62]|
| *L. acidophilus* (johnsonii) La1 | Inhibition of colonization, lactic acid, H2O2, bacteriocins | Human                            | Switzerland   | [63]|
| *L. johnsonii* La1              | Inhibition of colonization, lactic acid, H2O2, bacteriocins | Human                            | Switzerland   | [64]|
| *L. acidophilus* CRL 639         | Autolysins, lactic acid                                 | In-vitro                          | Sweden        | [65]|
| *L. gasseri* OLL 2716           | Anti-inflammatory activity, lactic acid                 | Human                            | Japan         | [66]|
| *L. reuteri*                    | Anti-inflammatory activity (inhibition of IL-8 synthesis), lactic acid | In-vitro                          | Canada        | [67]|
| *L. casei* Shiroti              | Biocine, lactic acid, Inhibition of colonization        | Human                            | Netherlands   | [68]|
| *L. casei* Shiroti              | Biocine, lactic acid, Inhibition of colonization        | C57BL/6 mice                     | Greece        | [69]|
| *L. brevis*                     | Arginine deiminase activity, inhibition of colonization | Human                            | Italy         | [70]|
| *L. rhamnosus* R0011 and *L. acidophilus* R0052 | Inhibition of colonization, lactic acid                  | C57BL/6 mice                     | Canada        | [71]|
| *L. salivarius*                 | Lactic acid, bacteriocin                                 | In-vitro                          | Ireland       | [72]|
| *L. bulgaricus* BB18 and *Enterococcus faecium* MH3 | Lactic acid, bulgaricin BB18, enterocin MH3           | In-vitro                          | Bulgaria      | [73]|
| *L. brevis* BK11 and *E. faecalis* BK61 | Lactic acid, bacteriocin                                   | In-vitro                          | Korea         | [74]|
| *L. lactis* A164 and *L. lactis* BH5 | Lactic acid, lactacin A164, lactacin BH5                   | In-vitro                          | Korea         | [75]|
| *Bacillus clausii*              | inhibition of colonization (bacterial cell and spores)  | Human                            | Italy         | [76]|
| *B. subtulis*                   | Amicoumacin A                                           | In-vitro                          | France        | [77]|
| Lactobacilli and Bifidobacteria | Lactic acid                                             | Human                            | Germany       | [78]|
| *Weissella confusa* PL9001      | Bacteriocin, inhibition of colonization                  | In-vitro                          | Korea         | [79]|
| *E. faecium* GM-1               | Lactic acid, bacteriocin                                 | In-vitro                          | South Korea   | [80]|
| *E. faecium* TM39               | Lactic acid, bacteriocin                                 | In-vitro                          | Taiwan        | [81]|
| *Saccharomyces boulardii*       | Anti-inflammatory activity                               | Human                            | Romania       | [82]|
| *L. reuteri* ATCC 55730         | Reuterin                                               | Human                            | Italy         | [83]|
| *L. rhamnosus* JB3              | Antagonist of AI-2                                      | In-vitro                          | Taiwan        | [84]|

Substantial mechanism of probiotics against *H. pylori* infection

Probiotics have various mechanisms to eradicate or restrict *H. pylori* growth within the stomach of humans including, (1) inhibition the colonization of *H. pylori* via conquering gastric epithelial receptors or co-aggregation mechanism, (2) anti-*H. pylori* activity throughout the production of bacteriocins, organic acids, as well as biosurfactants, (3) supportive role in intestinal tissues by promoting mucin synthesis, (4) modulation of immune system response, (5) induction of antigen-specific antibodies, and (6) reduction of stomach inflammation (Fig. 2). The details of each of the hypotheses proposed are discussed below.

**Competition for binding sites**

Like other bacteria, attachment is an important step in the continued colonization of *H. pylori* [85]. According to in vitro studies, *L. reuteri* inhibits the attachment of *H. pylori* via competition binding to asialo-GMI and sulfatide receptors [86]. Sakarya et al. showed that *S. boulardii* blocks the attachment of *H. pylori* to gastric epithelial cells through binding to sialic acid receptors [87]. Moreover, other probiotics such as *L. acidophilus* LB, *L. johnsonii*, *L. salivarius*, and *W. confusa* prevent the colonization of this pathogen through specific adhesion molecules [88–90]. Based on studies in thirty C57BL/6 female mice, Johenson et al. found that pre-treatment with *L. acidophilus* R0052 and *L. rhamnosus* R0011 completely inhibited the colonization of this bacterium compared to control group [71]. In addition, in a study on 13 patients infected with *H. pylori*, Myllyluoma et al. found that consuming a solution containing four probiotics for 56 days reduced the rate of infection by 27% [91].
**Mucosal barrier**

Mucous membranes are one of the first lines of defense to protect humans (or animals) against environmental pathogens; excessive secretion of mucins and large glycoproteins effectively cover the surface of gastrointestinal tracts and prevent the colonization of infectious agents, especially *H. pylori* [92]. Recent studies have shown that this bacterium inhibits the expression of several mucins genes such as MUC1 and MUC5 [93]. In vitro studies show that some probiotics e.g. *L. rhamnosus* and *L. plantarum* induce the expression of MUC2 and MUC3 genes (the most important mucins in gastrointestinal tract), leading to inhibition of *H. pylori* colonization [94]. Interestingly, Pantoflickova et al. showed in their study that consumption of *L. johnsonii* thickens the mucosal layer, which in turn prevents bacterial colonization [95].

**Probiotics as antibiotics**

Scientific studies have shown that probiotics can also act as antibiotic-producing bacteria, and are able to contain the growth of *H. pylori* by producing antimicrobial substances [96]. *Streptomyces* spp. are the largest antibiotic-producing probiotics; these bacteria produce a large number of antibiotics such as streptomycin, chloramphenicol, tetracycline, kanamycin, vancomycin, cycloserine, lincomycin, neomycin, cephalosporins, clavulanic acid [97–99]. Moreover, bacitracin as an effective antibiotic on peptidoglycan of Gram-positive bacteria is produced by *B. licheniformis* and some strains of *B. subtilis* [100].

Short-chain fatty acids produced by probiotics such as acetic acid, propionic acid, and lactic acid can lower the pH of the environment, leading to unfavorable gastric conditions for *H. pylori* [101]. Bacteriocins (antibacterial peptides) are other properties of probiotics that in turn have antagonistic activity against the survival of *H. pylori* [102]. Coconnier et al. first found that the supernatant fluid from *Lactobacillus acidophilus* LB significantly could reduce the viability of *H. pylori* [24]. In a clinical trial study, Michetti et al. showed that oral administration of culture supernatant fluid of *L. acidophilus* strain La1 had anti-*H. pylori* activity [63]. In later years, discovered that this property was due to antimicrobial nisin A [75]. Bacteriocins are a heterogeneous group of antimicrobial...
proteins that are mostly produced by lactic acid bacteria [103, 104]. Although studies on the effects of bacteriocin-like compounds against *H. pylori* are limited, bacteriocins with anti-*H. pylori* activity are produced by some probiotic genera such as *Pediococcus*, *Lactococcus*, *Bacillus*, *Weissella*, and *Bifidobacterium* [74, 105]. Bacteriocins reduce or inhibit the growth of *H. pylori* by a variety of mechanisms including, inducing pores in membrane, activating of autolytic enzymes, and downregulating expression of vacA, cagA, luxS, and flaA genes [52, 106–108]. In other study, Boyanova et al. introduced seven bacteriocins from *L. bulgaricus* that were able to kill both antibiotic-susceptible and-resistant bacteria [102]. However, although bacteriocins have been proposed as a new alternative to drug-resistant *H. pylori* strains, these antimicrobial peptides (AMPs) are strain-specific and are also sensitive to gastrointestinal enzymes [52, 75].

**Co-aggregation and auto-aggregation (querish)**

Co-aggregation status occurs between different species (or strains) of probiotics and pathogenic strains (heterogeneous bacteria), while in the auto-aggregation status, only species of one genus react with each other [109]. According to in vitro studies, some probiotics such as *L. reuteri* DSM17648, *L. gasseri*, and *L. johnsonni* La1 (NCC533) are able to co-aggregate with *H. pylori* strains [110, 111].

**Immunomodulatory mechanism**

Probiotics also modulate the immune system responses; Blum et al. was first showed the role of probiotics in modulating the immune system responses against *H. pylori* infection [111]. This bacterium increases the inflammatory response by promoting the secretion of TNF-α and IL-8, which in turn lead to the upregulation of gastrin-17, apoptosis, and finally peptic ulcer [91]. Yang et al. found that pre-treatment with *L. salivarius* in animal model reduced chronic gastritis through the inactivation of JAK1/STAT1 and NF-κB pathways [112]. In addition, probiotics through some processes such as upregulating the expression of MUC3, cyclooxygenase-1, and PGE2, facilitate the secretion of mucin and angiotensin, thus preventing the apoptosis of mucosal cells [113, 114].

**Probiotics as delivery system for the treatment of *H. pylori* infection**

Although many people around the world are infected with this bacterium in the first years of life, the search for an effective vaccine began after identification of *H. pylori* by Varan and Marshall; however, the effectiveness of the vaccine is doubtful, because this bacterium suppresses the immune responses [115]. Until recently, the vaccines entered in phase III clinical trials were stopped due to insufficient immunity against this pathogen [116]. At the moment, *Lactobacillus* spp. can be used as promising candidates for oral vaccination; the most important reasons are: (1) safety, (2) being immunogenic, (3) low cost, (4) accessibility, (5) ease of administration [117]. Here are some recombinant probiotics containing *H. pylori* antigens such as *Lactococcus lactis* (UreB), *L. lactis* (NapA), *L. lactis* (CTB-UE), and *B. subtilis* (UreB); oral administration of each of them leads to an increase in serum levels of IgG and IgA [118–121].

**Probiotics and animal models**

According to animal studies, researchers have shown the benefits of probiotics including, (1) elimination of *H. pylori* infection, (2) reduction of gastritis, (3) inhibition of the progression of primary infection to gastric cancer and MALT lymphoma (Table 2). According to animal experiments, probiotic supplementation can reduce the persistent colonization of *H. pylori* as well as gastric inflammation by modulating pro-inflammatory cytokines i.e. IL-8, IL-12, TNF-α, and *H. pylori*-specific IgG titer [69, 122–124]. Chronic infection can stimulate the immune system to create favorable conditions to support the growth of bacteria [125–127]. Bacterial virulence factors can disrupt the signaling pathways and cell junctions, leading to the formation of pre-cancerous lesions as hummingbird phenotype [128, 129]. Curing *H. pylori* infection is considered as the main strategy for preventing gastric MALT lymphoma and can decrease the risk of secondary gastric cancer or relapse of gastric ulcers [130, 131]. Probiotics can reduce the colonization of *H. pylori* by their protective compounds such as bacteriocins, organic acids, and biosurfactants [104]. According to the literature, *H. pylori* infection significantly affects the gastric microenvironment by several changes including DNA instability, disruption of NF-κB signaling pathway, as well as differentiation of autoreactive B cells and subsequent malignant transformation by genomic alternations [132, 133]. In general, the use of probiotics effectively modulates immune responses, reduces gastritis by reducing pro-inflammatory cytokines, and ultimately prevents *H. pylori*-induced gastric malignancies [134–136].

**Probiotics as adjuvant therapy**

*Therapeutic effects of probiotics against *H. pylori* infection in children*

There is ample evidence of the clinical effects of probiotics in treating and reducing bacterial load in children. Cruchet et al. conducted a randomized double-blind trial on children with asymptomatic *H. pylori* infection. In their study, the children were divided into five groups, so that four groups received probiotic *Lactobacillus* strains (live *L. paracasei* ST11 or *L. johnsonii* La1,
and heat-killed *L. paracasei* ST11 or *L. johnsonii* La1) and one group received placebo. They found that the C13UBT value in children receiving live *L. johnsonii* La1 was significantly lower than other groups [151]. In a similar study, asymptomatic children were randomly treated with three regimens containing standard triple therapy (8 days), *L. acidophilus* LB (daily for 8 weeks) and, *Saccharomyces boulardii* plus inulin (daily for 8 weeks). Finally, results showed that the C13UBT value was significantly lower in children receiving triple therapy and *Saccharomyces boulardii* [152]. Based on several clinical trials, it has been concluded that the rate of eradication of *H. pylori* infection increases in children receiving probiotic diets (without antibiotics). Some of these studies that suggested clinical efficacy of probiotic supplementation in the eradication of *H. pylori* infection are listed in Table 3. Based on these studies, probiotics can significantly increase *H. pylori* eradication rate particularly in patients receiving *Lactobacillus* spp. and *Bifidobacterium* spp. supplementation. These probiotics have a high potential against *H. pylori* infection using various mechanisms [55, 153]. In addition, probiotics can alter the gut microbiota to reduce gastrointestinal symptoms and drug side effects [154, 155].

Recently, two meta-analyses have evaluated the clinical effects of probiotics in the treatment of *H. pylori* infection in children. Li et al. evaluated data from 508 sick children; the pooled ORs for *H. pylori* eradication rate by intention-to-treat (ITT) and per-protocol (PP) analysis in children who had received probiotic supplementation and control group was 1.96 (95% CI: 1.28–3.02) and 2.25 (95% CI: 1.41–3.57), respectively [167]. In another study, Fang et al. analyzed the clinical efficacy of *Lactobacillus* supplemented triple therapy in 484 children, and found

| First author          | Year   | Probiotic strain name                                      | Dosage /duration | Animal model       | Conclusion remarks                                      | Ref  |
|-----------------------|--------|------------------------------------------------------------|------------------|--------------------|--------------------------------------------------------|------|
| Ushiyama et al        | 2003   | *L. gasseri* OLL2716                                       | 10⁸ CFU/mL       | BALB/c mice        | Anti-*H. pylori* effects                                | [122]|
| Sgouras et al         | 2004   | *L. casei* Shirota                                         | 10⁸ CFU/mL       | C57BL/6 mice       | Reducing *H. pylori* colonization                        | [69] |
| Henry et al           | 2004   | *L. rhamnosus* R0011, *L. acidophilus* R0052              | 10⁸ CFU/mL, 9 months | C57BL/6 mice       | Anti-*H. pylori* effects                                | [71] |
| Pena et al            | 2005   | *L. reuteri* 1602, *L. paracasei* 6798                    | 10⁸ CFU/mL, 12 weeks | C57BL/6 mice       | Reducing the TNF-α and IL-12 levels                     | [123]|
| Sgouras et al         | 2005   | *L. johnsonii* La1, *L. amylovorus* CDE471, *L. acidophilus* IBB 801 | 1.5–4 × 10⁸ CFU/mL, 3 months | C57BL/6 mice       | Reducing *H. pylori* colonization and decrease gastric inflammation | [137]|
| Brzozowski et al      | 2006   | *L. acidophilus* R0052, *L. rhamnosus* R0011              | 2 × 10⁸ CFU/mL, 2 weeks | Mongolian gerbil   | Reduction gastrin and gastric inflammation             | [138]|
| Chenoll et al         | 2011   | *B. bifidum* CECT 7366                                     | 10⁷ CFU/mL       | C57BL/6 mice       | Blocking colonization of *H. pylori*                   | [139]|
| Kuo et al             | 2013   | *L. acidophilus*, *B. lactis*                              | 5 × 10⁸ CFU/mL   | C57BL/6 mice       | Reduction of gastric inflammation                      | [140]|
| Kaur et al            | 2014   | *P. acidilactici* BA28                                     | 10⁷ CFU/mL, 24 weeks | C57BL/6 mice       | Anti-*H. pylori*                                        | [141]|
| Kim et al             | 2014   | *P. pentosaceus* (SL4)                                     | 10⁷ CFU/mL, 6 weeks | C57BL/6 mice       | Anti-*H. pylori*                                        | [142]|
| Zaman et al           | 2014   | *L. reuteri*, *L. johnsonii*, *L. munnus*                 | 10⁷ CFU/mL       | Mongolian gerbil   | Anti-*H. pylori*                                        | [143]|
| Matsui et al          | 2015   | *L. gasseri* SBT2055                                       | 10⁷ CFU/mL       | C57BL/6 mice       | Production of specific IgA, Blocking progression of MALT infection | [144]|
| Yu et al              | 2015   | *E. faecalis*, *B. longum*, *L. acidophilus*               | 10⁷ CFU/mL       | C57BL/6 mice       | Reducing gastric inflammation                           | [145]|
| Pan et al             | 2016   | *L. plantarum* ZDY 2013                                    | 10⁷ CFU/mL       | C57BL/6 mice       | Reducing gastric inflammation                           | [146]|
| Afsahi et al          | 2018   | *L. plantarum* ATCC8014                                    | 10⁷ CFU/mL, 2 weeks | C57BL/6 mice       | Anti-*H. pylori*                                        | [147]|
| Chen et al            | 2018   | *L. rhamnosus* JB3                                         | 5 × 10⁷ CFU/mL   | C57BL/6 mice       | Anti-*H. pylori*                                        | [148]|
| Merino et al          | 2018   | *L. fermentum* UCO-977C                                    | 10⁷ CFU/mL       | Mongolian gerbil   | Inhibited *H. pylori* SS1                               | [149]|
| Lin et al             | 2020   | *L. fermentum* P2 (P2), *L. casei* L21 (L21), *L. rhamnosus* JB3 (JB3) | 10⁷ CFU/mL       | C57BL/6 mice       | Reduction of gastric inflammation                      | [150]|

**Table 2** Clinical advantages of probiotics in animal studies
| First author         | Year   | Type of study          | Eradication therapy | Probiotic regimen                                      | Duration | Cure rate          | Statistical significance | Ref  |
|---------------------|--------|------------------------|---------------------|--------------------------------------------------------|----------|--------------------|--------------------------|------|
| Gotteland et al     | 2005   | Open randomized        | NA                  | Saccharomyces boulardii, L. acidophilus                 | 8 weeks  | 12%, 6.5%          | p < 0.000                | [152]|
| Sykora et al        | 2005   | Double blind randomized| Omeprazole, amoxicillin, clarithromycin for 7 days | L. casei DN-114 001                                     | 2 weeks  | 84.6%              | p = 0.0019               | [156]|
| Goldman et al       | 2006   | Double blind randomized| Omeprazole, amoxicillin, clarithromycin for 7 days | B. animalis + L. casei                                   | 3 months | 45.4%              | p < 0.01                | [157]|
| Lionetti et al      | 2006   | Double blind randomized| Omeprazole, amoxicillin, clarithromycin, tinidazole (sequential therapy) | L. reuteri ATCC 55,730                                   | 20 days  | 85%                | p < 0.009                | [158]|
| Gotteland et al     | 2008   | Double blind randomized| NA                  | L. janssonii La1 plus cranberry, L. janssonii La1, cranberry plus heat-killed L. janssonii La1 | 3 weeks  | 22.9%, 14.9%, 16.9%, 1.5% | p = 0.542               | [159]|
| Hurdac et al        | 2009   | Open randomized        | Omeprazole, amoxicillin, clarithromycin for 7 days | Saccharomyces boulardii                                 | 4 weeks  | 93.7%              | p < 0.002                | [82] |
| Szajewska et al     | 2009   | Double blind randomized| Omeprazole, amoxicillin, clarithromycin for 7 days | L. rhamnosus GG                                         | 1 weeks  | 67.6%              | Not significant          | [160]|
| Boonyaricaikij et al| 2009   | Single blind           | NA                  | L. gasseri OLL2716                                      | 1 years  | 29.3%              | p = 0.03                 | [161]|
| Tolone et al        | 2012   | NA                     | Omeprazole, amoxicillin, clarithromycin for 7 days | Probinul-Cadigroup                                      | NA       | 88.2%              | p < 0.05                 | [162]|
| Zhao et al          | 2014   | prospective randomized controlled study | Omeprazole, amoxicillin, clarithromycin for 7 days | Saccharomyces boulardii                                 | 7 days   | 85%                | p < 0.05                 | [163]|
| Wang et al          | 2014   | NA                     | Omeprazole, amoxicillin, clarithromycin for 7 days | L. acidophilus, B. bifidum                              | 2 weeks  | 83.7%              | p < 0.05                 | [164]|
| Akcam et al         | 2015   | Open randomized        | triple therapy (lansoprazole, amoxicillin, clarithromycin for 14 days) | L. casei, L. acidophilus, B. lactis                     | 2 weeks  | 66.6%              | p = 0.78                 | [165]|
| Zhu et al           | 2017   | Double blind randomized| Sequential, Triple therapy | Sequential-Lactobacillus, triple-Lactobacillus therapy | NA       | Sequential-Lactobacillus and triple-Lactobacillus better than any of them alone (P < 0.05) | p < 0.01 | [166]|

Table 3: Available clinical trials of probiotics in the treatment of *H. pylori* infection in children.
that the relative risk (RR) of curing rate in the Lactobacillus-treated group was significantly higher than control group (RR: 1.19; 95% CI: 1.07–1.33); diarrhea was also significantly reduced (RR: 0.3; 95% CI: 0.10–0.85) in this group [168].

**Therapeutic effects of probiotics against H. pylori infection in adults**

In the present study we evaluated all studies conducted on the effect of probiotics against *H. pylori* infection in human (Table 4).

According to the literature, probiotic supplementation increases the rate of infection eradication during first- and second-line treatment (Table 4). However, according to some studies, probiotic supplementation was significantly ineffective in improving the eradication rate of infection; in their network meta-analysis, Wang et al. found that probiotics in combination with triple therapy could not increase the eradication rate of infection [186].

In addition, most studies have shown that adverse events were significantly lower in the group receiving probiotics plus antibiotic than in the control group, but this was not the case in a number of other studies [178, 181, 185]. It is important to note that probiotics alone are not effective, but can only be prescribed as adjunctive therapy in clinical improvement [174]. In recent, using data of 467 patients with treatment failure, we showed that Lactobacillus-containing bismuth quadruple therapy for 10 days, significantly increases the cure rate of *H. pylori* infection in patients with previous treatment failure (RR: 1.77; 95% CI: 1.11–2.83; p value: 0.01. (Among all probiotics, the clinical effects of Lactobacillus spp. and *S. boulardii* have been further studied; *S. boulardii* and *Lactobacillus* species such as *L. casei*, *L. reuteri*, and *L. rhamnosus* GG are all safe and improve the quality of treatment [172, 183, 185]. It seems that multi-strain probiotics supplementation has a significant effect on the treatment of infection [173, 181, 182]. In accordance with this theory, Lu et al. showed that multi-strain probiotics (*Bacillus*, *Saccharomyces*, *Streptococcus*, *Bifidobacterium*, and *Lactococcus*) significantly increased the eradication rate of infection (RR: 1.12; 95% CI: 1.07–1.18; *p* value: 0.00001); however, heterogeneity was significant in their study [179]. In general, according to various studies, probiotic supplements are considered as a reliable strategy to increase the quality of treatment in individuals with treatment-naive or treatment-failure.

**Use of probiotics in the prevention of H. pylori infection**

Vaccine prophylaxis as a suitable strategy has become a big challenge for this bacterium, because in many people it is colonized in childhood, the rate of infection is high, as well as the immunology of the stomach is unclear [187]. According to the results of a cohort study on 308 *H. pylori*-negative children, it was defined that the infection rate in groups receiving *L. gasseri* OLL2716 (LG21) was less than control group (4.1% vs 8.1%, respectively); nevertheless; the results was not significant [161].

**Diversity of gut microbiota during H. pylori treatment with probiotic supplementation**

In total, about 100 trillion bacteria have been colonized in the human body. Gastrointestinal microflora is one of the most complex microbial ecosystem, and protects host against colonization of pathogenic microorganisms [188, 189]. Imbalance in this ecosystem due to the excessive use of antibiotics leads to several disorders such as inflammatory bowel disease (IBD), metabolic syndrome and even colon cancer [190–192]. According to the literature, *H. pylori* infection can cause dysbiosis in the intestinal microbiota, but short- and long-term changes in human gut microbiome after *H. pylori* infection are controversial [193, 194]. In their meta-analysis, Ye et al. showed that the during long-term follow-up the frequency of *Actinobacteria* and *Bacteroidetes* was reduced; they also found that the frequency of *Enterococcus* and *Enterobacteriaceae* was increased, while *Proteobacteria* after a short-term increase, again returned to their normal amounts during long-term follow-up [194]. There is limit information about the effects of probiotics on gut microbiota during the *H. pylori* infection. In their study, Oh et al. evaluated functional changes in intestinal microbiota using the Illumina MiSeq system after standard anti-*H. pylori* treatment and probiotic supplementation. They found that the expression of genes involved in selenocompound metabolism pathway was significantly reduced in patients receiving probiotic; this phenomenon can be led to a reduction in side effects such as intestinal irritation as well as antibiotic resistance [195]. Wang et al., recently explored the effect of anti-*H. pylori* concomitant therapy vs. concomitant therapy plus probiotic supplementation (with *S. boulardii*) on the alternation of gut and throat microbiota in human subjects. They showed that there was significant quantitative and qualitative alternations in microbiota composition in both concomitant anti-*H. pylori* therapy and concomitant therapy plus probiotic supplementation groups. Nevertheless, in probiotic supplementation group most changes in gut microbiota reverted after 71 days (except for *Bacteroides* spp. and yeast counts), whereas changes in the throat microbiota were persistent. In addition, antibiotic resistance rate of bacteria such as *Enterobacteriaceae*, *Enterococcus* spp., and *Bacteroides* spp. was significantly higher in patients receiving concomitant therapy than patients receiving concomitant therapy plus probiotic supplementation. Moreover, their
Table 4  Recent meta-analysis studies on the effect of probiotics in the treatment of *H. pylori* infection

| First author   | Year | Sample size | Eradication regimen                                      | Probiotics                                         | Conclusion remarks                                                                 | Significance | Ref   |
|----------------|------|-------------|----------------------------------------------------------|----------------------------------------------------|-----------------------------------------------------------------------------------|--------------|-------|
| Tong et al     | 2007 | 1671        | First-line and second-line therapy (triple and bismuth containing quadruple therapy) | *B. clausii*, *Lactobacillus*, *Saccharomyces*    | ER: RR: 1.84; 95% CI: 1.34–2.54 AE: OR: 0.44; 95% CI: 0.03–06 Both significant AE was adverse event ER was eradication rate | [169]        |       |
| Sachdeva et al | 2009 | 963         | First-line therapy (Triple and Quadruple)               | *Lactobacillus*, *Bifidobacterium*                | ER: 1.91; 95% CI: 1.3–2.6 AE: OR: 0.51; 95% CI: 0.01–2.5 but AE was not significant Reduction of adverse event rate was not significant | [170]        |       |
| Zou et al      | 2009 | 1372        | First-line therapy (Triple)                             | *Lactobacillus*                                    | ER: 1.78; 95% CI: 1.21–2.62 AE: OR: 0.49 (95% CI: 0.24–1.02) Both significant | [171]        |       |
| Zou et al      | 2010 | 1307        | First-line therapy (Triple)                             | *S. boulardii*                                     | ER: 1.13, 95% CI: 1.05–1.21 AE: RR 0.46, 95% CI: 0.3–0.7 Both significant | [172]        |       |
| Zheng et al    | 2013 | 1163        | First-line therapy (Triple)                             | *Lactobacillus*                                    | RR: 1.14; 95% CI: 1.06–1.22 (significant increase of eradication rate) but no significant reduction of overall adverse event | [173]        |       |
| Wang et al     | 2013 | 1469        | First-line and second-line therapy (triple and bismuth containing quadruple therapy) | *Bifidobacterium*, *Lactobacillus*               | ER: 2.066 (95% CI: 1.398–3.055 AE: 0.305; 95% CI: 0.117–0.793) Both significant | [174]        |       |
| Zhu et al      | 2014 | 2259        | Standard triple *H. pylori*                             | *Lactobacillus*, *Bifidobacterium*, *Saccharomyces* | ER: 1.67 (95% CI: 1.38–2.02 AE: (OR = 0.49, 95% CI: 0.26–0.94 Both significant | [175]        |       |
| Dang et al     | 2014 | 4459        | First-line therapy (Triple)                             | *L. acidophilus*, *L. casei* DN-114001, *L. gasseri*, *Bifidobacterium infantis* | Curing rate was significantly increase in probiotics (RR: 1.11; 95% CI: 0.5–0.9) as well as reduce of adverse event (RR: 0.73, 95% CI: 0.05–1.0) Both significant | [176]        |       |
| Zhang et al    | 2015 | 6997        | First-line and second-line therapy (triple and bismuth containing quadruple therapy) | *Lactobacillus*, *Bifidobacterium*, *Streptococcus*, *Saccharomyces*, *Enterococcus*, *Bacillus* | ER: RR = 1.13, 95% CI: 1.10–1.16 AE: RR = 0.59; 95% CI: 0.48–0.71 Both significant | [177]        |       |
| Lu et al       | 2016 | 3349        | First-line therapy (triple)                             | *Lactobacilli*, *Bifidobacteria*, *Bacillus clausii*, *E. faecium* | ER: OR 1.44, 95% CI: 0.87, 2.39 but not significant AE probiotics did improve the adverse effects OR 0.56, 95% CI: 0.31, 1.01 Both not significant | [178]        |       |
| Lu et al       | 2016 | 2306        | First-line therapy (Triple)                             | *Lactobacillus*, *Bifidobacterium*                | Eradication rate in probiotic supplementation group was significantly higher than control (RR: 1.15; 95% CI: 1.1–1.12) and reducing adverse event (RR: 0.71; 0.05–0.9) probiotic supplementation increased eradication of triple therapy in both 7 and 14-days Both significant | [179]        |       |
| First author  | Year | Sample size | Eradication regimen                                      | Probiotics | Conclusion remarks                                                                 | Significance | Ref  |
|--------------|------|-------------|----------------------------------------------------------|------------|-----------------------------------------------------------------------------------|--------------|------|
| Si et al     | 2017 | 2466        | First-line therapy (bismuth containing quadruple therapy) | Lactobacillus | Eradication rate was significant increase in probiotics (89% vs. 84.7% for first-line) (91% vs. 73.8% for second-line) | significant  | [180]|
| Losurdo et al| 2018 | NA          | NA                                                       | Lactobacillus | ER: UBT value: 8.61% vs. 0.19% AE: 1, 95%CI: 0.06–18.08 not significant for AE | Reduction of adverse event rate was not significant | [181]|
| Shi et al    | 2019 | 8924        | First-line therapy (Triple and Quadruple)                | Lactobacillus | RR: 1.14; 95%CI: 1.10–1.18 (significant increase of eradication rate) and reduced side effects | Both significant | [182]|
| Yu et al     | 2019 | 724         | First-line therapy (Triple)                              | Lactobacillus | Eradication rate was significantly increase in Lactobacillus supplement group (RR: 1.1; 95%CI: 1–1.2) and decrease significantly adverse event (RR: 0.36; 95%CI: 0.1–0.7) | Both significant | [183]|
| Pourmasoumi et al | 2019 | 525        | First-line therapy (Triple and Quadruple)                | Lactobacillus, Bifidobacterium Saccharomyces | Eradication: RR: 1.28; 95% CI: 1.15–1.43 Adverse: RR: 0.90; 95% CI: 0.69–1.16 | Both significant | [184]|
| Zhou et al   | 2019 | 3592        | First-line therapy (Triple)                              | S. boulardii | ER: 1.09, 95% CI: 0.5–1.13 AE: RR= 0.33, 95%CI:0.16–0.69 | Both significant | [185]|
Table 5  Clinical trials on the role of probiotics in treating H. pylori infections (https://clinicaltrials.gov/)

| Row | Identifier       | Start year | Participants | Allocation          | Intervention model                                                                 | Masking                      | Primary Purpose                  | Status                  | Country            |
|-----|------------------|------------|--------------|--------------------|-------------------------------------------------------------------------------------|------------------------------|----------------------------------|-------------------------|--------------------|
| 1   | NCT04319991      | 2019       | 100          | Randomized         | Parallel assignment                                                                 | Single (Participant)         | Supportive Care                  | Recruiting             | Taiwan            |
| 2   | NCT01115296      | 2010       | 100          | Randomized         | Parallel assignment                                                                 | Quadruple (Participant, Care Provider, Investigator, Outcomes Assessor) | Treatment               | Unknown                | Italy              |
| 3   | NCT03150394      | 2017       | 80           | Randomized         | Parallel assignment                                                                 | Double (Participant, Investigator) | Treatment                   | Unknown                | Spain              |
| 4   | NCT04178187      | 2019       | 800          | Randomized         | Parallel assignment                                                                 | Single (Participant)         | Treatment                       | Recruiting             | Greece             |
| 5   | NCT01969331      | 2008       | 804          | Randomized         | Parallel assignment                                                                 | Triple (Participant, Care Provider, Investigator) | Treatment | Completed           | Croatia            |
| 6   | NCT02645201      | 2016       | 0            | Randomized         | Parallel assignment                                                                 | Triple (Participant, Care Provider, Investigator) | Treatment | Withdrawn            | Belgium, Croatia, Germany, Israel, Slovenia |
| 7   | NCT03220542      | 2016       | 360          | Randomized         | Factorial assignment                                                               | Single (Participant)         | Treatment                       | Unknown                | Korea              |
| 8   | NCT03722433      | 2018       | 200          | Randomized         | Parallel assignment                                                                 | Double (Participant, Care Provider) | Treatment | Unknown                | Taiwan             |
| 9   | NCT03997279      | 2019       | 200          | Randomized         | Parallel assignment                                                                 | Triple (Participant, Care Provider, Investigator) | Treatment | Unknown                | Sebia              |
| 10  | NCT03377933      | 2019       | 40           | N/A                | Single group assignment                                                             | None (Open Label)            | Treatment                       | Unknown                | China              |
| 11  | NCT04473079      | 2020       | 100          | Randomized         | Parallel assignment                                                                 | Quadruple (Participant, Care Provider, Investigator, Outcomes Assessor) | Supportive Care | Recruiting           | Thailand           |
| 12  | NCT04527055      | 2020       | 252          | Randomized         | Parallel Assignment                                                               | Single (Outcomes Assessor)   | Treatment                       | Enrolling by invitation | Taiwan            |
| 13  | NCT03297242      | 2017       | 30           | N/A                | N/A                                                                                | N/A                          | N/A                             | Unknown                | China              |
| 14  | NCT04786938      | 2016       | 63           | Randomized         | Parallel assignment                                                                 | Single (Participant)         | Treatment                       | Completed              | Ecuador            |
| 15  | NCT02689583      | 2016       | 3000         | Randomized         | Parallel assignment                                                                 | Single (Participant)         | Treatment                       | Unknown                | China              |
| 16  | NCT03688828      | 2018       | 776          | Randomized         | Parallel assignment                                                                 | Triple (Participant, Investigator, Outcomes Assessor) | Treatment | Recruiting           | China              |
| 17  | NCT03404440      | 2016       | 56           | Randomized         | Parallel assignment                                                               | Double (Participant, Investigator) | Treatment | Completed              | Italy              |
| 18  | NCT01456728      | 2011       | 56           | Randomized         | Parallel assignment                                                               | Double (Participant, Investigator) | Treatment | Completed              | Bulgaria            |
| 19  | NCT02051348      | 2014       | 24           | Non-Randomized     | Crossover assignment                                                              | Single (Participant)         | Treatment                       | Completed              | Ireland            |
study revealed that co-administration of probiotics in the treatment of \textit{H. pylori} infection could be more effective than post-antibiotic supplementation \cite{196}. In a recent study by Cárdenas et al. the clinical effects of \textit{S. boulardii} CNCM I-745 on gut microbiota of patients receiving standard anti-\textit{H. pylori} therapy was evaluated. According to their results, supplementation with this probiotic significantly reduced gastrointestinal symptoms ($p=0.028$); alterations in gut microbiota was also seen with higher abundance of Enterobacteria and lower abundance of Bacteroides and Clostridia upon treatment completion ($p=0.0156$) \cite{197}. In general, the antimicrobial activity of probiotics kills or inhibits the growth of resistant bacteria and ultimately reduces antibiotic resistance \cite{195, 196}. According to information at https://clinicaltrials.gov/, all clinical trial studies on the effects of probiotic supplements on the eradication of \textit{H. pylori} by August 2021 are listed in Table 5.

**Disadvantages and limitations**

Despite extensive research on the effectiveness of probiotics in eradicating \textit{H. pylori} infection, there are many challenges in this filed. Due to differences in study design, duration of treatment, and variety of probiotics between clinical trial studies, there is no a reliable homogeneity between them, which in turn affects the interpretation of results. In addition, due to the small sample size of studies, more research needs to be done with larger populations. Unfortunately, in some studies, there is no significant difference between the probiotic supplement group and the control group. Finally, although the exact role of probiotics in the prevention or treatment of \textit{H. pylori} is unknown, consumption of probiotics may be associated with side effects such as increasing in serum histamine and also digestive disorders \cite{198}.

**Conclusions and future perspectives**

\textit{H. pylori} is one of the most successful pathogens in the gastrointestinal tract, which through its virulence factors creates a complex interaction with the human host. Chronic infection caused by this bacterium leads to severe clinical outcomes. The frequency with this bacterium is high in developing countries and poor socioeconomic conditions, so that people living in these conditions are generally at high risk for re-infection. Moreover, self-medication with antibiotics on the one hand, and the spread of resistant strains on the other hand, all are considered as a serious threat for the successful eradication of this bacterium. Over the decades, the controversial results of all conducted studies about the treatment of \textit{H. pylori} infection have been led to the failure to the eradication of this pathogen. Hence, probiotics have been considered by many researchers around the world. In the present study, based on in vitro, animal studies, and human clinical trials, we demonstrated the beneficial effects of probiotics against \textit{H. pylori} infection. However, those alone are not effective in treating the bacterial infection. In addition, the anti-\textit{H. pylori} activity of probiotics is strain-specific and remains as a mysterious phenomenon. To date, the therapeutic effects of probiotics against resistant strains of the bacterium have not been evaluated, and whole genome sequencing may solve the existing puzzles. It seems that to decrease the heterogeneity of results and make better decisions, future studies should focus on items such as genus/species, dosage, formulation, and treatment course.

**Acknowledgements**

We appreciate from both Mashhad University of Medical Sciences and Jiroft University of Medical Sciences.

**Authors’ contributions**

1. MK1 have contributed to design of the work. 2. MK2 have drafted the work and substantively revised it. All authors read and approved the final manuscript.

**Funding**

We have not received any funding for this research.

**Availability of data and materials**

All data generated or analyzed during this study are included in this published article.

**Declarations**

**Ethics approval and consent to participate**

Not applicable (this paper was provided based on researching in global databases).

**Consent for publication**

Not applicable.

**Competing interests**

There is no any conflict of interest among the all authors.

**Author details**

1. Department of Microbiology and Virology, Faculty of Medicine, Mashhad University of Medical Sciences, Mashhad, Iran. 2. Student Research Committee, Mashhad University of Medical Sciences, Mashhad, Iran. 3. Department of Microbiology and Virology, School of Medicine, Jiroft University of Medical Sciences, Jiroft, Iran.

**Received**: 6 July 2021  **Accepted**: 15 October 2021

**Published online**: 20 October 2021

**References**

1. Karbalaei M, Khorshidi M, Sisakht-pour B, Ghazvini K, Farsiani H, Youssefi M, et al. What are the effects of IL-1β (rs1143634), IL-17A promoter (rs2275913) and TLR4 (rs4986790) gene polymorphism on the outcomes of infection with \textit{H. pylori} within an Iranian population; A systematic review and meta-analysis. Gene Rep. 2020;20:100735.

2. Hooi JK, Lai WY, Ng WK, Suen MM, Underwood FE, Tanyingoh D, et al. Global prevalence of Helicobacter pylori infection: systematic review and meta-analysis. Gastroenterology. 2017;153(2):430–9.

3. Keikha M. Is there a relationship between Helicobacter pylori vacA i1 or i2 alleles and development into peptic ulcer and gastric cancer?
4. Youssefi M, Tafaghodi M, Farsiani H, Ghazvini K, Keikha M. Helicobacter pylori infection and autoimmune diseases: Is there an association with systemic lupus erythematosus, rheumatoid arthritis, autoimmune atrophy gastritis and autoimmune pancreatitis? A systematic review and meta-analysis study. J Microbiol Immunol Infect. 2021;54(3):359–69.

5. Gravina AG, Zagari RM, De Musis C, Romano L, Loguercio C, Romano M. O’connor A, O’morain CA, Ford AC. Population screening and treatment of Helicobacter pylori infection. Nat Rev Gastroenterol Hepatol. 2018;14(4):320.

6. 0’Connor A, Do, A. Comparing, A. 0, with, A. 10-year, a. follow-up, period. Surg Endosc. 2012;26(1):72–8.

7. Hildebrandt P, Bardhan P, Rossi L, Parvin S, Rahman A, Arefin MS, et al. Recrudescence and reinfection with Helicobacter pylori after eradication therapy in Bangladesh adults. Gastroenterology. 2001;121(4):792–8.

8. Keikha M. The association between Helicobacter pylori eradication in peptic ulcer patients and gastric cancer? Investigation in an East-Asian population. Trends Pharm Sci. 2020;64(4):279–82.

9. Lee Y-C, Chiang T-H, Chou C-K, Tu Y-K, Liao W-C, Wu M-S, et al. Association between Helicobacter pylori eradication and gastric cancer incidence: a systematic review and meta-analysis. Gastroenterology. 2016;150(3):1113–24.

10. Georgopoulos S, Papastephanou V. An update on current and advancing pharmacotherapy options for the treatment of H. pylori infection. Expert Opin Pharmacother. 2020;22(6):1–13.

11. Savoldi A, Camara E, Graham DY, Conti M, Tacconelli E. Prevalence of antibiotic resistance in Helicobacter pylori: a systematic review and meta-analysis in World Health Organization regions. Gastroenterology. 2018;155(5):1372–82, e1.

12. Graham DY, Lu H, Shiotani A. Failure of optimized dual proton pump inhibitor amoxicillin therapy: what now? Saudi J Gastroenterol. 2017;23(5):265.

13. Thung J, Aramini H, Vavinjvaksya V, Gupta S, Park J, Crover S, et al. The global emergence of Helicobacter pylori antibiotic resistance. Aliment Pharmacol Ther. 2016;43(4):514–33.

14. Hu Y, Zhang M, Lu B, Dai J. Helicobacter pylori and antibiotic resistance, a continuing and intractable problem. Helicobacter. 2016;21(5):349–63.

15. Goderska K, Pena SA, Alarcón T. Helicobacter pylori treatment: antibiotics or probiotics. Appl Microbiol Biotechnol. 2018;102(1):1–7.

16. Malferttheiner P, Megraud F, O’Morain C, Bazzoli F, El-Omar E, Graham D, et al. Current concepts in the management of Helicobacter pylori infection: the Maastricht III Consensus Report. Gut. 2007;56(6):772–81.

17. De Francesco V, Zullo A, Ierardi E, Vaira D. Minimal inhibitory concentration (MIC) values and different point mutations in the 23S rRNA gene for clarithromycin resistance in Helicobacter pylori. Dig Liver Dis. 2009;41(8):610–1.

18. Guerra V, Cordell AG. Helicobacter pylori: a review of current diagnostic and management strategies. Dig Dis Sci. 2020;65(7):1917–31.

19. Graham DY, Lu H, Yamaoka Y. A report card to grade Helicobacter pylori infection therapy. Wiley Online Library, 2007.

20. Gong EI, Yun S-C, Jang H-Y, Lim H, Choi K-S, Ahn JY, et al. Meta-analysis study on an Iranian population. New Microbes New Infect. 2020;36:100726.

21. Eslami M, Bahar A, Keikha M, Karbalaei M, Kobyliak N, Yousefi B. Probiotics or probiotics. J Nutr. 2007;137(3):812S–818.

22. Eslami M, Yousef B, Kohkhaip, Moghadam AJ, Moghadam BS, Arabkari V, et al. Are probiotics useful for therapy of Helicobacter pylori diseases? Comp Immunol Microbiol Infect Dis. 2019;64:99–108.

23. Lesbos-Pantofflickova D, Corhesive-Thelau I, Blum A. Helicobacter pylori and probiotics. J Nutr. 2007;137(3):812S–818.

24. Malfertheiner P, Megraud F, O’Morain C, Gisbert J, Kupers E, Axon A, et al. Management of Helicobacter pylori infection—the Maastricht V/Florence consensus report. Gut. 2017;66(1):6–30.

25. Matsuzaka T, Nishikawa T, Ueda T. The association between Helicobacter pylori eradication and autoimmune diseases; Is there an association with Helicobacter pylori and extragastric diseases: a review. World J Gastroenterol. 2017;14(4):230–40.

26. Liou J-M, Fang Y-J, Chen C-C, Bair M-J, Chang C-Y, Lee Y-C, et al. Current concepts in the management of Helicobacter pylori infection—the Maastricht 2-2000 Consensus Report. Aliment Pharmacol Ther. 2002;16:167–80.

27. Malfertheiner P, MeÁGRAUD F, O’morain C, Hungin A, Jones R, Axon A. Current concepts in the management of Helicobacter pylori infection: The Maastricht 2-2000 Consensus Report. Aliment Pharmacol Ther. 2018;48(8):1387–9.

28. Yao C-C, Kuo C-M, Hsu C-N, Yang S-C, Wu C-K, Tai W-C, et al. First-line Helicobacter pylori eradication rates are significantly lower in patients with than without those type 2 diabetes mellitus. Infect Drug Resist. 2019;12:1425.

29. Falsafi T, Mobashseri F, Parvin S, Rahman A, Arefin MS, et al. Are probiotics useful for therapy of Helicobacter pylori diseases? A meta-analysis study. J Microbiol Immunol Infect. 2021;54(3):359–69.
Lee Y-H. Weissella confusa strain PL9001 inhibits growth and adherence of genitourinary pathogen. J Microbiol Biotechnol. 2004;14(4):680–5.

Kankan E, et al. Probiotic intervention decreases serum gastrin-17 in Helicobacter pylori infection. Dig Liver Dis. 2007;39(6):S16–23.

Khan S, Moore RJ, Stanley D, Chousalkar KK. The gut microbiota and colorectal cancer. Gastro Rev. 2012;17(6):466–77.

Mack DR, Michail S, Wei S, McDougall L, Hollingsworth MA. Probiotics and immune response. Clin Microbiol Rev. 2013;10(18):899–9.

Norris SE, Bennick AL, Bartoloni A, Johnston DA. Efficacy of probiotic supplementation in preventing Helicobacter pylori recurrence in gastric ulcer patients. Gut. 2000;46(S5):601–7.

O’Brien RN, Ferril S, Verbeke F, Parida P, Sheahan NF, Beatty A. Association of Helicobacter pylori infection with inflammatory bowel disease. Scand J Gastroenterol. 2007;42(9):903–8.

Peña JA, Rogers AB, Ge Z, Ng V, Li SY, Fox JG, et al. Probiotics and anti-infective activities of Bifidobacterium lactis against Helicobacter pylori. PLoS ONE. 2016;11(3):e0150061.

Sgouras DN, Panayotopoulos P, Martinez-Gonzalez B, Petraki K, Michopoulos S, Mentis A. Lactobacillus johnsonii La1 attenuates Helicobacter pylori infection in mice. Int J Antimicrob Agents. 2015;13(10):889–99.

Shi Y, Sun Y, Wang Y, Peng X, Cao D, et al. Probiotic Lactobacillus johnsonii MH-68 and L. salivarius ssp. salicinius AP-32. Helicobacter. 2012;17(6):466–77.

Watanabe H, Miyagawa S, Seki M, Nakamura T, et al. Significant improvement of dyspeptic symptoms associated with Helicobacter pylori infection in Japanese women treated with probiotics: a randomized, double-blind and placebo-controlled study. World J Gastroenterol WJG. 2014;20(19):5583.

Xiao W, Zhao Y, Liao C, et al. Probiotics and Helicobacter pylori infection: a systematic review and meta-analysis. J Gastroenterol. 2017;52(2):175–94.

Yang Q, Zhang J, Xing J, et al. Probiotics and Helicobacter pylori infection: a systematic review and meta-analysis. J Gastroenterol. 2017;52(2):175–94.
134. Ailioaie LM, Litscher G. Probiotics, photobiomodulation, and disease management: controversies and challenges. Int J Mol Sci. 2021;22(9):4942.

135. Fujimura S, Watanabe A, Kimura K, Kaji M. Probiotic mechanism of Lactobacillus gasseri OLL2716 strain against Helicobacter pylori. J Clin Microbiol. 2012;50(3):1134–6.

136. Espinoza JL, Matsumoto A, Tanaka H, Matsumura I. Gastric microbiota: an emerging player in Helicobacter pylori-induced gastric malignancies. Cancer Lett. 2018;414:147–52.

137. Sgouras DN, Panayotopoulos EG, Martinez-Gonzalez B, Petraki K, Michopoulos S, Mentis A. Lactobacillus johnsonii La1 attenuates Helicobacter pylori-associated gastritis and reduces levels of proinflammatory chemokines in C57BL/6 mice. Clin Diagn Lab Immunol. 2005;12(12):1378–86.

138. Brzozowski T, Konturek PC, Mierzwa M, Drozdowicz D, Bielanski W, Chenoll E, Casinos B, Bataller E, Astals P, Echevarría J, Iglesias JR, et al. Novel probiotic Bifidobacterium bifidum CECT 7366 strain active on the cyclooxygenase (COX)-2 expression, apoptosis, and functional gastric mucosal impairment in Helicobacter pylori-infected Mongolian gerbils. Helicobacter. 2006;11(1):10–20.

139. Chenell E, Casinos B, Bataller E, Astals P, Echevarría J, Iglesias JR, et al. Novel probiotic Bifidobacterium bifidum CECT 7366 strain active against the pathogenic bacterium Helicobacter pylori. Appl Environ Microbiol. 2011;77(4):1335–43.

140. Kuo C-H, Wang S-S, Lu C-Y, Hu H-M, Kuo F-C, Weng B-C, et al. Long-term use of probiotic-containing yogurts is a safe way to prevent Helicobacter pylori colonization on a Mongolian gerbil's model. Biochem Res Int. 2013;2013:1–8.

141. Kaur B, Garg N, Sachdev A, Kumar B. Effect of the oral intake of probiotic Pediococcus acidilactici BA28 in Helicobacter pylori-causing peptic ulcer in C57BL/6 mice models. Appl Biochem Biotechnol. 2014;172(2):973–83.

142. Kim J-E, Kim M-S, Yoon Y-S, Chung M-J, Yum D-Y. Use of selected lactic acid bacteria in the eradication of Helicobacter pylori infection. J Microbiol. 2014;52(11):955–62.

143. Zaman C, Osaki T, Hanawa T, Yonezawa H, Kurata S, Kamiya S. Analysis of the microbial ecology between Helicobacter pylori and the gastric microbiota of Mongolian gerbils. J Med Microbiol. 2014;63(1):129–37.

144. Matsui H, Takahashi T, Øverby A, Murayama SY, Yoshida H, Yamamoto Y, Afsahi A, Mahmoudi H, Ebrahimi A, Aeini Z, Esmaeili D. Evaluation of the use of probiotic-containing yogurts is a safe way to prevent Helicobacter pylori infection in children. Zhongguo dang wu zhi. 2007;25(2):155–68.

145. Patel A, Shah N, Prajapati J. Clinical application of probiotics in the treatment of Helicobacter pylori infection—a brief review. J Microbiol Immunol Infect. 2014;47(5):429–37.

146. Goldman CG, Barrado DA, Balcarce N, Rua EC, Oshiro M, Calcagno S, Scapinelli E, Calcagno S, et al. Meta-analysis of randomized controlled trials on the efficacy of probiotics in Helicobacter pylori eradication therapy—a brief review. J Microbiol Immunol Infect. 2019;53(1):66–73.

147. Bagarolli RA, Tobar N, Oliveira AG, Araujo TG, Carvalho BM, Rocha GZ, et al. Probiotics modulate gut microbiota and improve insulin sensitiv- ity in DIO mice. J Nutr Biochem. 2017;50:16–25.

148. Li S, Huang X-l, Sui J-z, Chen S-y, Xie Y-t, Deng Y, et al. Meta-analysis: the effect of supple- mentation with probiotics on eradication rates and adverse events during Helicobacter pylori eradication therapy. Aliment Pharmacol Ther. 2015;27(25):155–68.

149. Sachdeva A, Nagpal J. Effect of fermented milk-based probiotic preparations on Helicobacter pylori eradication: a systematic review and meta-analysis of randomized-controlled trials. Eur J Gastroenterol Hepatol. 2009;21(1):145–53.
171. Zou J, Dong J, Yu X. Meta-analysis: Lactobacillus containing quadruple therapy versus standard triple first-line therapy for Helicobacter pylori eradication. Helicobacter. 2009;14(5):449–59.

172. Szajewska H, Horvath A, Pivowarczyk A. Meta-analysis: the effects of Saccharomyces boulardii supplementation on Helicobacter pylori eradication rates and side effects during treatment. Aliment Pharmacol Ther. 2010;32(9):1069–79.

173. Zheng X, Lyu L, Mei Z. Lactobacillus-containing probiotic supplementation increases Helicobacter pylori eradication rate: evidence from a meta-analysis. Rev Esp Enferm Dig. 2013;105(8):445–53.

174. Wang Z-H, Gao Q-Y, Fang J-Y. Meta-analysis of the efficacy and safety of Lactobacillus-containing and Bifidobacterium-containing probiotic compound preparation in Helicobacter pylori eradication therapy. J Clin Gastroenterol. 2013;47(1):25–32.

175. Zhu R, Chen K, Zheng Y-Y, Zhang H-W, Wang J-S, Xia Y-J, et al. Meta-analysis of the efficacy of probiotics in Helicobacter pylori eradication therapy. World J Gastroenterol. 2014;20(7):18013.

176. Dang Y, Reinhardt JD, Zhou X, Zhang G. The effect of probiotics supplementation on Helicobacter pylori eradication rates and side effects during eradication therapy: a meta-analysis. PLoS ONE. 2014;9(11):e111030.

177. Zhang M-M, Qian W, Qin Y-Y, He J, Zhou Y-H. Probiotics in Helicobacter pylori eradication therapy: a systematic review and meta-analysis. Clin Res Hepatol Gastroenterol. 2017;41(4):466–75.

178. Abadi ATB. Vaccine against Helicobacter pylori: Inevitable approach. World J Gastroenterol. 2016;22(11):3150.

179. Savage DC. Microbial ecology of the gastrointestinal tract. Annu Rev Microbiol. 1977;31(1):107–33.

180. Ley RE, Hamady M, Lozupone C, Turnbaugh PJ, Ramey RR, Bircher JS, et al. Evolution of mammals and their gut microbes. Science. 2008;320(5888):1647–51.

181. Weingarden AR, Vaughn BP. Intestinal microbiota, fecal microbiota transplantation, and inflammatory bowel disease. Gut Microbes. 2017;8(3):238–52.

182. Zeng Y, Luo M, Pan L, Chen Y, Guo S, Luo D, et al. Vitamin D signaling maintains intestinal innate immunity and gut microbiota potential intervention for metabolic syndrome and NAFLD. American Journal of Physiology-Gastrointestinal and Liver Physiology. 2020;318(3):GS42-G53.

183. Hold GL. Gastrointestinal microbiota and colon cancer. Dig Dis. 2016;34(3):244–50.

184. Myllyluoma E, Ahlroos T, Veijola L, Rautelin H, Tynkkynen S, Korpela R. Effects of anti-Helicobacter pylori pylor treatment and probiotic supplementation on intestinal microbiota. Int J Antimicrob Agents. 2007;29(1):66–72.

185. Ye Q, Shao X, Shen R, Chen D, Shen J. Changes in the human gut microbiota composition caused by Helicobacter pylori eradication therapy: A systematic review and meta-analysis. Helicobacter. 2020;25(4):e12713.

186. Oh B, Kim JW, Kim BS. Changes in the functional potential of the gut microbiome following probiotic supplementation during Helicobacter pylori pylor treatment. Helicobacter. 2016;21(6):493–503.

187. Wang Z-J, Chen X-F, Zhang Z-X, Li Y-C, Deng J, Tu J, et al. Effects of anti-Helicobacter pylori concomitant therapy and probiotic supplementation on the throat and gut microbiota in humans. Microb Pathog. 2017;109:156–61.

188. Garcia-Dominguez PA, Garcés D, Prado-Vilvar B, Flores N, Fornasini M, Cohen H, et al. Effect of Saccharomyces boulardii CNCM I-745 as complementary treatment of Helicobacter pylori infection on gut microbiome. Eur J Clin Microbiol Infect Dis. 2020;39(7):1365–72.

189. Gao C, Major A, Rendon D, Lugo M, Jackson V, Shi Z, et al. Histamine H2 receptor-mediated suppression of intestinal inflammation by probiotic Lactobacillus reuteri. MBio. 2015;6(6):e01359–15.

Publisher’s Note
Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.