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Review

Are probiotics useful for therapy of *Helicobacter pylori* diseases?

Majid Eslami[a], Bahman Yousefi[b,*], Parviz Kokhaei[b,c], Ali Jazayeri Moghadas[a], Bizhan Sadighi Moghadam[b], Vahid Arabkari[d], Zohreh Niazi[e]

[a] Department of Bacteriology and Virology, Semnan University of Medical Sciences, Semnan, Iran
[b] Department of Immunology, Semnan University of Medical Sciences, Semnan, Iran
[c] Immune and Gene Therapy Lab, Cancer Centre Karolinska, Karolinska University Hospital, Stockholm, Sweden
[d] Discipline of Pathology, Lambe Institute for Translational Research, Clinical Science Institute, School of Medicine, National University of Ireland, Galway, Ireland
[e] Department of Basic Medical Sciences, Neyshabur University of Medical Sciences, Neyshabur, Iran

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ABSTRACT

Chronic infection with *Helicobacter pylori* (*H. pylori*) is a known risk factor for gastric cancer. Eradication rate of *H. pylori* infection by the classic triple treatment of PPIs and antibiotics is low. Therefore, probiotics are a useful tool for improving the rate of eradication and reduction of side effects. Several studies in animal models showed that *Lactobacillus* spp. alone and in combination with other probiotic strains have inhibitory effects on growth and suppression of inflammatory responses in *H. pylori* infections. However, some studies showed significant effects of *Pediococcus* strains on suppression, survival, and eradication of *H. pylori* infections. Therefore, it is suggested that in the treatment of *H. pylori* infections along with the usual probiotic strains, different strains of *Pediococcus* could be used. Recent studies showed that *Lactobacillus reuteri* and *Lactobacillus gasseri* alone with PPIs in human have a high eradication effect on *H. pylori* infections and it is suggested as the probiotic treatment of patient's in future therapeutic protocols. In relation to the probiotic treatment process, it should not be recommended that probiotics could be used as a single treatment for *H. pylori* eradication. However, use of probiotics as a supplement will increase eradication and reduce side effects associated with treatment. It is widely believed that probiotics could improve the eradication of *H. pylori* and reduce side effects during standard treatment, but some probiotic bacterial species could be useful with drug therapy. Generally, probiotic supplements could increase the eradication rate of *H. pylori* infections and reduced the side effects of antibiotics.

1. Context

Helicobacter pylori (*H. pylori*) is a common pathogen, which is present in the human stomach 60,000 years ago. Warren and Marshall in Australia reported H. pylori in 1983 for the first time [1]. *H. pylori* is a gram-negativebacilli in the gastric mucosa that leading to diseases of the upper gastrointestinal tract such as chronic gastritis, peptic ulcer and mucosa-associated lymphoid tissue (MALT lymphoma) and gastric cancer. In addition, the eradication of *H. pylori* can quickly reduce the activity of inflammation in the gastric mucosa and prevent progression towards pre-cancerous ulcers [2]. The epidemiology of *H. pylori* infection is not yet clear. However, infection with this bacterium occurs all over the world and there are geographically different in the prevalence of infection within and between countries (Prevalence: Sweden 11%, Spain 60.3%, China 83.4%, Canada and the United States 30%) [3]. *H. pylori* eradication leads to healing of the gastric and peptic ulcer, prevents gastric ulcers, and reduces the risk of developing gastric cancer [4].

The prevalence of bacterial antibiotic resistance varies regionally and appears to be evolving over time in different countries, and subsequently, the global eradication rate of *H. pylori* is decreasing. The ratio of *H. pylori* anti-microbial eradication has been declining, which may have several reasons. Most likely, the main reasons for this are defective treatment with one or more antibiotics and patient compliance [5]. The widespread use of clarithromycin and other macrolides for respiratory tract infections leads to an antibiotic resistance of *H. pylori* to these antibiotics and reduces its success rate to less than 80%. Particularly in clarithromycin resistance cases, which in the past decade has been increasing rapidly in many countries (Japan and Italy with a resistance of 30%, China 50%, and Turkey 40%, while in some countries including Taiwan and Sweden is almost low, and there is little information available in the United States) [6–8].

Antibiotic resistance in *H. pylori* is one of the effective factors in the therapeutic methods against the infection caused by this organism. The

* Corresponding author.
E-mail address: Yosefi_bahman@semums.ac.ir (B. Yousefi).

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traditional method for testing antibiotic susceptibility is costly and requires a period of 10–14 days [9]. *H. pylori* are known by the International Agency for Research on Cancer and the World Health Organization (WHO/IARC) as a carcinogenic group 1 and are associated with the development of gastric cancer. Eradication of *H. pylori* infection has been reported as an effective strategy for the treatment of peptic ulcers and lymphoma associated with gastric mucus as well as the prevention of gastric cancer [10].

According to the agreement of Maastricht v/Florence, the Kyoto global agreement and the Toronto agreement, which confirmed the importance of *H. pylori* with gastritis, eradication of *H. pylori* was an essential factor to the prevention of gastric cancer [11]. In early 1990, the ratio of eradication success with the combination of three drugs (proton pump inhibitor (PPI), clarithromycin and amoxicillin) was more than 80%. This diet is not currently accepted as the first treatment line for *H. pylori* [12]. Various factors in the failure of *H. pylori* eradication are included poor diet, poor patient compliance, a high bacterial load of the gastric, internalization of bacteria, gastric acidity, gene polymorphisms, antimicrobial washout, and most importantly, antibiotic resistance. In recent years, antibiotic resistance to clarithromycin has been increasing rapidly in many countries [13]. In regions with high resistance to clarithromycin, treatment with four drugs including bismuth subsalicylate, PPI, tetracycline, and metronidazole are recommended as primary therapies [14]. After the failure of this treatment, a triple treatment containing levofloxacin is recommended. Following the failure of the second line of treatment, the next treatment should be done whenever possible to test for antimicrobial susceptibility. The alternative option for the third line treatment is the rifabutin, fluoroquinolones, tetracycline, furazolidone, and high dose PPI/amoxicillin [15].

2. Drugs used to treat *H. pylori* and drug resistance

2.1. Clarithromycin

Clarithromycin resistance is reported in pediatric, respiratory and urinary tract infections [16,17]. Clarithromycin resistance rate in the world increased from 9% in 1998 to 17.6 in 2008 in Europe and 7% in 2000 to 27.7% in 2006 in Japan [18]. In patients with *H. pylori* susceptible to clarithromycin, it has been reported that the rate of eradication shown to be significantly reduced by clarithromycin-based regimens, so the selection of this antibiotic has a promising approach after testing the sensitivity of the drug [19]. Macrolides anti-bacterial activity depends on their ability to inhibition of bacterial protein biosynthesis with effect on the 23S of ribosomal RNA [20]. Extensive studies have shown that point mutations in the region of peptidyltransferase in the domain V of 23S rRNA are responsible for creating resistance to macrolides. These mutations lead to inhibition of the binding between clarithromycin and the subunit of the ribosome dedicated to protein synthesis associated with a specific antibiotic. In particular, the major mutations of 23S rRNA are included the conversion of adenine to guanine at 2142 (11.7%) and 2143 (69.8%), and adenine to cytosine conversion at 2142 (2.6%). Another mechanism of resistance to macrolides is related to the efflux pump system, with at least 4 protected families of this system with antibiotic resistance [21] (Fig. 1).

2.2. Fluoroquinolones

The initial resistance of *H. pylori* to fluoroquinolones has been reported in countries and regions of 2–22 percent. Resistance to this drug is easily created and relatively high in countries with high drug intake. Therefore the rapid development of fluroquinolone resistance, levofloxacin-based regimens should be reserved as a second-line treatment option [22]. The antibiotic function of fluoroquinolones is related to the inhibitory function of bacterial gyrase enzyme [23]. The bacterial gyrase enzyme plays a role in maintaining the stability of the helical structure, proliferation, recombination and DNA transcription. A point mutation in the quinolones resistance-determining region (QRDR) inhibits the binding of the antibiotic and enzyme in the gyrase enzyme, resulting in bacterial resistance [24,25].

Levofloxacin is a fluoroquinolones drug that acts as an antibacterial agent by interacting with *gyrA* and *gyrB* [20]. Point mutations in regions that determine the resistance to quinolone *gyrA* may limit the process of contributing to low or high resistance to fluoroquinolones for *H. pylori*. The most common mutation in levofloxacin-resistant strains is *gyrA* at positions 87, 88, 91 and 97 [26]. In addition, Rimbara et al. showed that *gyrB* mutation at position 463 may also be helpful in resistance to fluoroquinolones in *H. pylori* [23] (Fig. 1).

2.3. Metronidazole

The prevalence of Helicobacter pylori resistance to metronidazole has been reported in 8–80% of countries [27]. Resistance to this antibiotic in developing countries is much higher than in developed countries. This regeneration is mediated through the NADPH nitroreductase (RdxA), NADPH-flavin-oxidoreductase (FrxA) and ferredoxin-like enzymes (FrxB) in *H. pylori*. Various mutations in these enzymes have been identified in the recovery of this antibiotic in strains with antibiotic resistance [23,28] (Fig. 1).

2.4. Amoxicillin

Fortunately, amoxicillin resistance prevalence as a beta-lactamase antibiotic has remained low and some studies reported 2% resistance in countries other than Bangladesh, which reaches 6.6% [29].In terms of mechanism, amoxicillin acts through interfering with the synthesis of peptidoglycans, especially by controlling transmitters such as penicillin-binding proteins (PBPs), leads to inhibiting cell wall synthesis and bacterial degradation [30].Several mutations in the PBP1 gene are one of the most important causes of antibiotic resistance to amoxicillin. One of the common mechanisms that result in low to moderate resistance to amoxicillin is the point mutations that occur in the *pbp1A* gene. In addition, mutations occurring in the *pbp2*, *pbp3*, *hefC*, *hopC*, and *hofH* genes can also lead to the resistance of *H. pylori* to this antibiotic [31] (Fig. 1).

2.5. Tetracycline

Fortunately, antibiotic resistance to tetracycline is low, and this resistance is less than 2%in many reports. The tetracycline activity through the effect on the 30S subunit of the ribosome and inhibition of amino acid transferase function, which results in a defect in protein biosynthesis [32]. Antibiotic resistance of *H. pylori* to tetracycline (Tet^r) is due to mutation in 16S rRNA gene, especially at 956–967 positions, which are the most important points for this resistance [33]. The AGA triple mutations (926–928) to TTC are highly related to tetracycline with resistance to *H. pylori*. However, single and double-base-pair mutations only lead to poor resistance to tetracycline by *H. pylori* [34] (Fig. 1).

2.6. Rifabutin

H. pylori resistance to rifabutin is approximately 1.3% [35].This drug is an anti-tuberculosis agent derived from S rifamycin, which is similar in structure compare to rifampicin, which could inhibit the beta subunit of RNA polymerase-dependent DNA polymerase of *H. pylori* that encoded by the *rpoB* gene. Resistant isolates from *H. pylori* exhibit mutations in codons 149 and 525 to 545 or codon 586 [36,37] (Fig. 1).

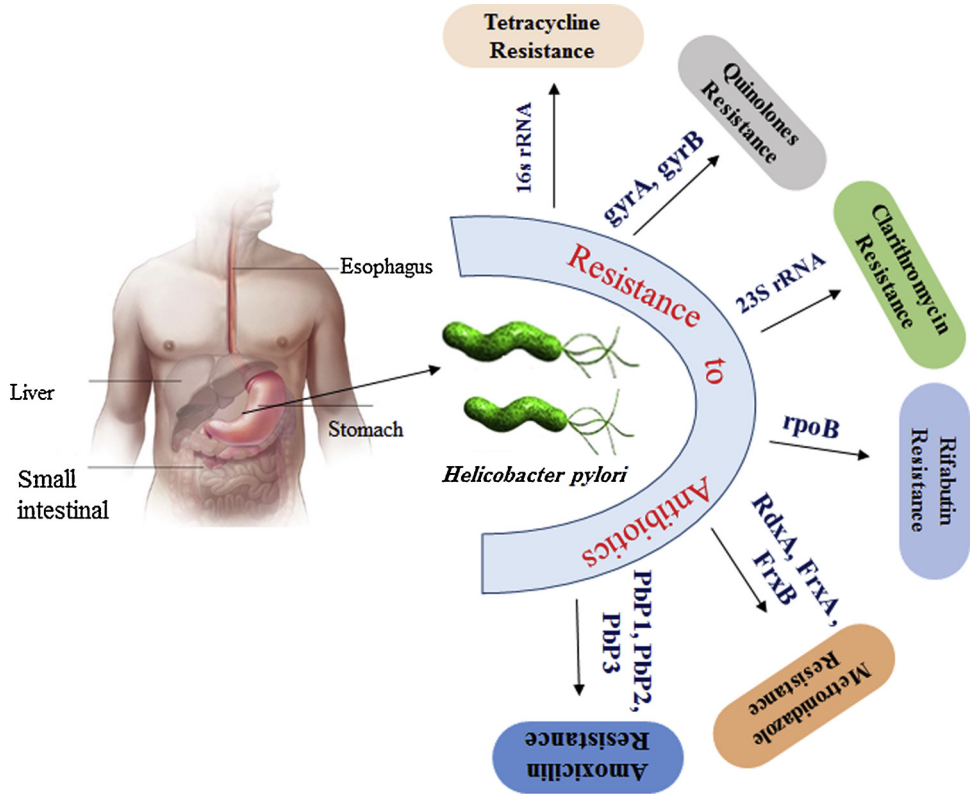

Fig. 1. Mutations and mechanisms involved in *H. pylori* antibiotic resistance.

2.7. Proton pump inhibitors (PPIs)

PPI drugs include Omeprazole, Lansoprazole, Esomeprazole, Pantoprazole, and Rabeprazole, which are widely used in combination with 2 or 3 types of antibiotics to treat *H. pylori* infection. PPIs are pre-drugs which, require gastric acid secretion to convert sulfonamide or activated sulfanilic acid to block gastric acid secretion [38]. Most studies conducted using standard doses do not show a significant difference between PPIs for the improvement of esophageal reflux and duodenal ulcer. These drugs are successfully used in three-drug regimens with clarithromycin and amoxicillin to eradicate *H. pylori* [39]. PPIs have a weak antibacterial effect against *H. pylori* in laboratory conditions, and clinical trials have shown that PPIs have a weak eradication effect and there is no significant difference in PPI-based regimens. Proton pump inhibitors irreversibly block the enzymatic system of hydrogen/potassium adenosine triphosphatase (H^+/K^+ ATPase or gastric proton pump) in the gastric parietal cell. The proton pump is the last step in the secretion of gastric acid, which is directly responsible for secreting H^+ ions to the stomach lumen, and this is an ideal target for inhibiting acid secretion. Targeting the final stage in acid production could decrease the irreversible nature of the inhibition of gastric acid secretion by up to 99% [40].

All PPIs except tenatoprazole have a half-life of about 1 h and good bio-nutritional status. Most PPI drugs are metabolized by CYP2C19 and 3A4 [41]. Liver dysfunctions and aging could decrease the PPIs clearance due to mutations in CYP2C19.It is demonstrated that acid inhibitors comparing drugs such as omeprazole, lansoprazole, rabeprazole, and pantoprazole have similar efficacy. Esomeprazole and tenatoprazole are potent inhibitors of the acid with a longer duration [42].

3. Probiotics

Probiotics are known as strains of living microorganisms that may have a positive effect on intestinal micro-ecology and improved health conditions [43]. Most of the investigated probiotics are bacteria that producing lactic acid, especially *Lactobacillus* strains [44].However, recently different species of bacteria belonging to the *Bifidobacterium* spp., *Saccharomyces* spp. and *Bacillus* spp. are also used as probiotics. *Lactobacillus* species are resistant to acid and commensalism, and their concentration in the normal human gastric is 0 to 10^3 ml *Lactobacillus* spp. are able to survive in the stomach for 2 h and some strains are attached to stomach epithelial cells in the in vitro possibly via lipoteichoic acid [45]. Probiotics have been shown to be useful in the treatment of many gastrointestinal diseases such as acute diarrhea, antibiotic-associated diarrhea, functional digestive disorders, and inflammatory bowel disease [46]. Their use for various reasons can also be beneficial for people infected with *H. pylori* depending on the type and varies the dose of bacteria [47].

Given that the rate of infection with *H. pylori* is still high in developing countries, and carcinoma of the esophagus is constantly increasing [18]. Therefore, at least in some patients, dietary approaches could maintain *H. pylori* congestion and chronic inflammation of the infection at a low level. This approach could be preferred for substitute treatment for *H. pylori*. As a result, permanent or long-term suppression of *H. pylori* could reduce the risk of *H. pylori*-related diseases, including gastric ulcers and gastric cancer. In this way, there is a significant interest in launching low-cost alternative solutions on a large scale to prevent or reduce *H. pylori* colonization. In this regard, probiotics may eliminate this therapeutic gap [48,49].

Increased attention has been paid to the use of probiotics as an auxiliary treatment in the standard triplet's therapy. The failure rate in the eradication of more than 20% and the high percentage of undesirable effects of antibiotic therapy are major problems in the standard treatment protocols for *H. pylori* eradication. In addition, low compliance due to side effects increases antibiotic resistance to bacterial strains. Published studies to date indicate that probiotics can play a double role in the fight against *H. pylori* infection. They reduce the

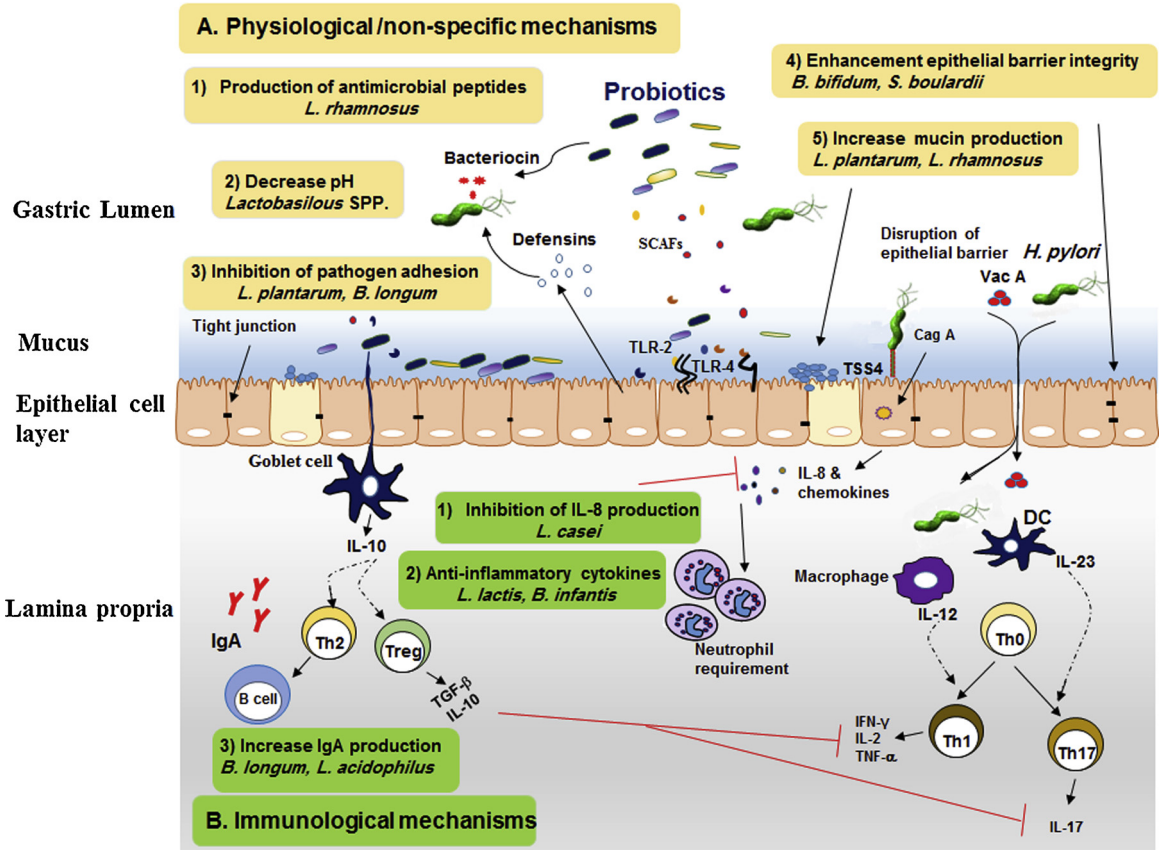

Fig. 2. Possible functional mechanisms whereby probiotic bacteria might impact treatment and elimination of *H. pylori* infection. These mechanisms generally divided in two groups of mechanisms of physiological/non-specific and immunological mechanisms. A. physiological/non-specific mechanisms include: 1) Production of antimicrobial peptides: Including bacteriocin produced directly by certain probiotics and antimicrobial peptides produced through stimulated gastric epithelial cells with probiotics and their products, 2) Decrease pH: Probiotics can inhibit *H. pylori* growth by secreting SCAFs which results in lowering the pH in gastric lumen, 3) Inhibition of pathogen adhesion: Probiotics create competitive conditions and inhibit bacterial adherence to mucosal layer, 4) Enhancement epithelial barrier integrity: Improved barrier function by 5) Increase mucin production: Mucus production can also be increased by probiotics that stimulate goblet cells leading to activation of mucin gene expression and therefore altering colonization and persistence condition. B. Immunological mechanisms: 1) Inhibition of IL-8 production: Probiotics directly and indirectly affect the epithelial cells and modulate signaling pathways that leads to a reduction expression of IL-8. 2) Anti-inflammatory cytokines: Probiotics with their products stimulate dendritic cells might be leading to anti-inflammatory pathways by witch inhabit inflammatory function of lymphocyte subtype (Th1 and Th17) and their cytokines, 3) Increase IgA production: Probiotics changes the cytokine profiles through effects on dendritic cells and so as increase the production secretory IgA by B cells.

SCAFs, Short Chain Fatty Acids; **TLR**, Toll-like receptor; **TNF-α**, Tumor Necrosis Factor α; **IFN-γ**, Interferon γ; **TGF-β**, Transforming Growth Factor β; **IL-10**, Interleukin 10; **IL-23**, Interleukin 23; **IL-17**, Interleukin 17; **IL-8**, Interleukin 8; **IL-2**, Interleukin 2; **CagA**, Cytotoxin-associated gene A; **VacA**, Vacuolating cytotoxin A; **Treg**, Regulatory T cell; **Th**, T cell helper; **DC**, Dendritic Cell; **TSS4**, Type IV Secretion System.

digestive side effects of antibiotic therapy and increase the rate of eradication [50]. Recently, it is accept that most commercial probiotic products are safe and can be able to prevention and treatment of cancer [51].The available studies in the literature indicate that probiotics can accelerate the healing of gastric ulcers via multiple mechanisms that involve both damaging and defensive factors [52].

4. Possible functional mechanisms of probiotic for the treatment and eradication of *H. pylori* infection

Probiotics have been used in vitro as a single treatment in eradicating protocols or as complementary agents to standard eradication treatments [14]. Several mechanisms are performed in *in vitro* and *in vivo* in the host intestinal and animal models or cellular immune responses to probiotics. In this context, probiotic bacteria appear to inhibit *H. pylori* by using immunological or physiological/non-specific mechanisms [53] (Fig. 2).

A Physiological/non-specific mechanisms

The first line of defense against this pathogenic bacterium (*H. pylori)* is gastric acidity. It was suggested that using probiotics could increase producing antimicrobial agents competing with *H. pylori* for adhesion receptors, stimulating the production of mucin and stabilizing the intestinal mucous membrane as the first defensive line [54]. Probiotics could inhibit *H. pylori* growth by secreting short-chain fatty acids and antibacterial agents. Short chain fatty acids such as acetic acid, propionic acid, and lactic acid are produced during probiotic carbohydrate metabolism, which results in lowering the pH [55]. In 1989, Bhatia et al. were the first group to show the antagonistic effect of a *Lactobacillus* suspension against *H. pylori* associated with short-chain fatty acids [56]. In addition, antimicrobial activity *lactobacillus* may be due to the inhibitory activity of *H. pylori* urease, including the study of Sgouras et al 2004, which represents this activity [57].Some *Lactobacillus* species produce antimicrobial compounds associated with bacteriocin classes. Bacteriocins are a protein toxin with potential antibacterial activity [58]. They have small peptide structures that could be digested, which have antimicrobial activity. The bacteriocin types are produced by probiotics, and the antimicrobial activity of bacteriocins is variable among different strains of *H. pylori*. Some bacteriocins show

Table 1
Probiotic strains treatment in animal models.

Ref.	Year	Country	Results	Effects	Dose, Time	Probiotic Strain	Model
[80]	2003	Japan	Inhibited the growth of *H. pylori*	suppressed *H. pylori*-associated IL-8 production	$1 \cdot 10^7$ CFU/mL	*L. gasseri* OLL2716	BALB/c mice 5 week old
[78]	2004	Canada	Reduced *H. pylori* infection	Probiotics reduce *H. pylori*-induced gastric inflammation	10^9 CFU/ml 9weeks	*L. rhamnosus* R0011 *L. acidophilus* R0052	C57BL/6 mice 6 week old
[79]	2005	USA	Direct modulation of mucosal inflammatory responses	TNF-α and IL-12 levels were lowered in *Lactobacillus*-treated animals	10^9 CFU of lactobacilli 81 days	*L. reuteri* 1602 *L. paracasei* 6798	C57BL/6 mice 6-13 week old
[82]	2011	Spain	Inhibitory effect ↑	Inhibition of *H. pylori* adhesion to intestinal mucus by site competition	10^9 CFU per 100 µl 1-6 days	*B. bifidum* CECT 7366	BALB/c mice 7 week old
[81]	2013	Taiwan	Lower inflammatory score	increase expression of IL-10 and decrease of TNF- α	5×10^9CFU 4-17 weeks	*L. acidophilus* *B. lactis*	Gerbil 8 week old
[83]	2014	India	Eliminate *H. pylori* infection	pediocin-producing of bacteria retards growth as well as gastric colonization by the *H. pylori*	10^9 CFU 24weeks	*P. acidilactici* BA28	C57BL/6 mice 6-8 week old
[84]	2014	Republic of Korea	Effectively suppressed *H. pylori* viability	inhibiting the binding of *H. pylori* and suppressing *H. pylori*-induced IL-8 production	10^8 CFU 6 weeks	*P. pentosaseus (SL4)* *B. longum(BG7)* *L. lactis (SL3)* *E.faecalis(SL5)*	C57BL/6 mice 5 week old
[85]	2014	Japan	Inhibitory effect ↑ anti-infective effect ↑	Anti-*H. pylori* colonization and suppressive effect on the growth of *H. pylori*	$1{\cdot}10^9$ CFU 28 days	*L. reuteri* *L. johnsonii* *L. murinus*	Gerbil 5 week old
[86]	2015	Japan	Effective for suppressing the progression of gastric MALT lymphoma	enhancement of *H. suis*-specific IgA production	10^8–10^9 CFU 3-12 months	*L. gasseri* SBT2055	C57BL/6 mice 6 week old
[88]	2015	China	Inhibiting the inflammatory response in gastric epithelial cells	inhibiting the inflammatory response in gastric epithelial cells	10^7 CFU 3-5 weeks	*E. faecalis* *B. longum* *L. acidophilus*	C57BL/6 mice 6-8 week old
[87]	2016	Hong Kong	Preventing gastric mucosal inflammation	Preventive effect of bacteria might occur through selective modulation of specific bacterial taxa in gastric microbiota by changing the overall gastric microbiota.	10^9 CFU/mL 3 weeks	*L. plantarum* ZDY 2013	C57BL/6 mice 6 week old
[13]	2018	Iran	Preventing and treating *H. pylori* infection	Average number of leukocytes in depth or middle of the mucus and neutrophils in the glands and mild inflammation in the mucosa	10^6 CFU/mL 2 weeks	*L. plantarum* ATCC8014	C57BL/6 mice 6-8 week old

L; *Lactobacillus*, **B**; *Bifidobacterium*, **P**; *Pediococcus*, **E;** Enterococcus, **IL-8**; Interleukin 8, **IL-12**; Interleukin 12, **TNF-α**; Tumor Necrosis Factor, **IgA**; Immunoglobulin A.

stronger antibacterial activity against *H. pylori* strains than other strains [59]. *E. faecium* TM39 produced bacteriocin-like substance with antagonistic activity against *H. pylori*. The bacteriocin secreted by *W. confusa* PL9001 was the main substance that reduced the growth of *H. pylori* [60]. Bulgaricin BB18 secreted by *L. bulgaricus* BB18 shows an inhibitory effect on *H. pylori*. [61]. *L. brevis* BK11 and *E. faecalis* BK61 bacteriocin is produced that has a strong inhibitory effect on *H. pylori* growth. [62]. Of the tested bacteriocins (nisin A; lacticins A164, BH5, JW3, and NK24; pediocin PO2; and leucocin K), lacticins A164 and BH5 produced by *L. lactis* A164 and *L. lactis* BH5 showed the strongest inhibitory effect on H. pylori growth. [63].

H. pylori adhesion to epithelial cells is important in determining the outcome of *H. pylori*-related diseases. There are various mechanisms that probiotic bacteria could inhibit *H. pylori* adhesion. Mucosal surfaces have protective strategies against the risk factors and pathogens in the lumen of the intestine. Some strategies such as mucins are large and complex glycoprotein of the intestinal mucosal surfaces that protect these cells from microbial pathogen damages by restricting the access of environmental materials to epithelial cells [64]. *H. pylori* could suppress the expression of *MUCI* and *MUC5* in human gastric cell lines. In vitro studies showed that probiotics such as *L. plantarum* strains and *L. rhamnosus* strains increase the expression of *MUC2* and *MUC3* genes, and thus secretion of extracellular mucin by colon culture cells could inhibit the binding of pathogenic bacteria. Adherence ability of probiotic strains with to cell lines induces upregulation of mucin gene expression there was a direct relation between upregulation of MUC3 mucin mRNA expression and extracellular secretion of MUC3 mucin. These strains that increased extracellular secretion of MUC3 mucin led to reduced adherence of enteropathogenic bacteria during coincubation experiments. These strains of probiotics are able to repair gastric mucosal permeability and prevent the binding of bacterial pathogens such as *H. pylori* [65,66].

In general, probiotics such as lactic acid bacteria (LAB) and *Bifidobacterium* could inhibit other pathogens by producing organic acids, hydrogen peroxide, carbon dioxide, and some other antimicrobial compounds [67]. In addition, some *Bifidobacterium* species could produce heat-resistant antimicrobial compounds against *H. pylori* in vitro [68].

- Immunological mechanisms

According to Haller et al., study, probiotic strains may develop distinct immune responses depending on the host's immune status. Animal investigations have shown that immune system modifying effects of probiotic bacteria may be mediated through regulation of immune system in particular by controlling the cytokines balance and inflammatory/anti-inflammatory chemokines, which in turn reduces gastric activity and inflammation [69]. Probiotic bacteria could be bonded to related cognitive receptors such as TLRs that are expressed on the surface of the epithelial cells, and thus trigger a cascade of immune defense mechanisms.TLR4 could detect gram-negative bacteria lipopolysaccharide, while TLR2 could detect various types of microbial components, such as peptidoglycan and teichoic acid, in gram-positive bacteria [70].The cytokine response initially appears through the release of IL-8, which results in the migration of neutrophils and monocytes to the mucus. These activated monocytes and dendritic cells

Table 2
Probiotic strains as an adjuvant therapy in patients.

Patient group	Study design	Eradication therapy	Probiotic strain	Product, dose, time	Effects	Results	Country	Year	Ref.
65 consecutive dyspeptic patient > 18 years	PO	Group 1: AC + Lansoprazole + P Group 2: AC + Lansoprazole + Probinol	Group 1: *L. reuteri* (ATCC 55730) Group 2: Probinol	10^8 CFU, 7 days 5 g/dose b.i.d, 14 days	Triple therapy with or without probiotic supplementation failed to achieved acceptable *H. pylori* eradication rates	*H. pylori* eradication rate↔ side effects ↓	Italy	2008	[94]
90 symptomatic children (3-18 years)	RPC	AC + Omeprazole/Esomeprazole	*S. boulardii*	250 mg b.i.d, 28 days	Positive impact on *H. pylori* therapy-related side effects.	*H. pylori* eradication rate ↑ side effects↓	Romania	2008	[93]
83 children patients	PRPD	AC + Omeprazole + P	*L. GG*	10^9 CFU, 7 days	no effect on eradication rates and therapy-related side effects	*H. pylori* eradication rate ↔ side effects↓	Poland	2009	[95]
132 asymptomatic 5-7 years' children	RPC	P	*L.gasseri* OLL2716 (LG21)	5×10^8 CFU/g cheese 1 year	Prevention as well as eradication of *H. pylori* in asymptomatic pre-school children	*H. pylori* eradication rate ↑ side effects↓	Thailand	2009	[92]
61 symptomatic children (7-18 years)	PO	Group 1; AC + Lansoprazole Group 2: AC + Lansoprazole + P	*L. casei* 2401 *L. acidophilus* 2027 *B. lactis* 2211	7×10^9 CFU, 14 days	No evidence in terms of eradication of *H. pylori*, or impact on adverse effects obtained after the addition of probiotics to standard treatment	*H. pylori* eradication↔	Turkey	2012	[96]
90 > 18 years patients	RPC	CAM + P	*L. reuteri* ATCC 5573	10^8 CFU, 7 days	L. reuteri could reduce the frequency and the intensity of antibiotic-associated side-effects	*H. pylori* eradication rate ↔ side effects↔	United states	2012	[97]
227 patients	RPC	AC + Esomeprazole + Tinidazole + Lactoferrin + P	*Lactobacilli, Bifidobacteria*	Selective b.i.d, 10 days	Adjuvant to therapy for *H. pylori* infection	*H. pylori* eradication rate ↔ side effects↔	Italy	2012	[98]
40 patients	RPC	AC + Omeprazole ALe + Omeprazole	*Streptococcus thermophiles* *L. acidophilus* *B. longum* *L. plantarum* *B. brevis* *L. paracasei* *B. infantis,* *L. delbrueckii*	1×10^8CFU, 10 days	Reducing bacterial intra-gastric load, despite this effect did not impact the efficacy of the successive conventional triple therapy.	*H. pylori* eradication rate ↔ side effects↓	Italy	2012	[99]
160 Patients	RPC	Group 1:AC + Omeprazole + P Group 2: AC + Omeprazole	*S. boulardii*	250 mg, b.i.d, 14 days	Decreased the adverse effects associated with *H.pylori* therapy but did not significantly decrease the eradication rate of *H.pylori*	*H. pylori* eradication rate↔ side effects↓	Iran	2013	[103]
107 functional dyspepsia and peptic ulcer patients	PRPD	T + F + Lansoprazole	*L. acidophilus, L. rhamnosus, B. bifidum, Streptococcus faecium*	1.25×10^9 CFU/strain 30 days	did not show an increase in bacterial eradication effectiveness or decrease in adverse effects of *H. pylori* eradication treatment	*H. pylori* eradication rate ↔ side effects↔	Brazil	2013	[101]
22 asymptomatic adults	PRPs	P	*L. reuteri* DSMZ 17648 (pylopass™)	5×10^9 CFU/ solid tablet, 14 days	Reduce *H. pylori* load in high prevalence populations or be used as short-term prophylaxis during high stress periods	*H. pylori* eradication rate ↑ side effects↓	Germany	2013	[100]
180 patients	RPT	AC + Omeprazole + SB + P	*L. casei,* *L. rhamnosus, L. acidophilus,* *L.bulgaricus, B. breve,*	1×10^8CFU/capsule, 14 days	Not beneficial effects in the treatment of *H. pylori* infection	*H. pylori* eradication rate↔ side effects↓	Iran	2013	[102]

(*continued on next page*)

Table 2 (*continued*)

Patient group	Study design	Eradication therapy	Probiotic strain	Product, dose, time	Effects	Results	Country	Year	Ref.
			B. longum, streptococcus thermophiles						
100 patients > 18 years	PRPs	AC + Lansoprazole + SB + P	*L. acidophilus, L. paracasei, B. lactis*	≥10^9 CFU, 14 days	Reduced the side effects related to the medications during treatment and improved eradication rate	*H. pylori* eradication rate ↑ side effects↓	Thailand	2014	[108]
100 patients	PRPD	AC + PPI	*L. reuteri* DSM 17938, *L. reuteri* ATCC PTA 6475	2 × 10^8CFU, 7 days	potential role in *H. pylori* eradication therapy if the cure rate can be improved by changes in dose, dosing interval, or duration of therapy	*H. pylori* eradication rate ↔ side effects↓	Italy	2014	[107]
29 patients	RPC	Pantoprazole + P	*L. rhamnosus* LR 06, *L.pentosus* LPS 01, *L. plantarum* LP01, *L. delbrueckii* subsp. *delbrueckii* LDD01	10 × 10^9CFU,chewable tablet, 15 days	Significantly reduce bacterial overgrowth in the stomach, rapidly improving the gastric microbiota composition and restoring a protective barrier against harmful bacteria	*H. pylori* eradication rate ↔ side effects↓	Italy	2014	[105]
22 patients	PRPS	Omeprazole + P	*L. reuteri (*DSM 17938*)*	10^8 CFU, 56 days	Decrease serum G17 levels	*H. pylori* eradication rate ↑ side effects↓	Italy	2014	[106]
650 > 18 years patients	PRPD	AC/M + Omeprazole/Pantoprazole + p	*L. rhamnosus GG (*LGG*)* BB-12	10^8-10^{10} CFU, 14 days	significantly contributes to treatment efficacy and distinctly decreases the adverse effects of therapy and the symptoms of the underlying disease	*H. pylori* eradication rate↑ side effects↓	Croatia	2015	[110]
128 patients	RPC	P	*L. reuteri* DSM 17648	3 × 10^7 CFU, 14 days	Reducing the amount of *H. pylori* by selective bacterial–bacterial cell interaction	*H. pylori* eradication rate ↑ side effects↓	Germany	2015	[111]
200 patients	PRPs	Group 1:C/A + M+ Esomeprazole Group 2: C/A + M+ Esomeprazole + P	*L. delbrueckii* subp. *bullgaricus, streptococcus thermophiles*	> 10^5 CFU, 28 days > 10^8 CFU, 28 days	improve the eradication rate of *H. pylori* and associated gastritis in patients both by PP and ITT analysis	*H. pylori* eradication rate ↑ side effects↓	Thailand	2015	[114]
142	RPC	D + L+ Esomeprazole	*L. casei DG.*	24 billion, 7 days	Therapy was well tolerated, and side effects were generally mild	*H. pylori* eradication rate ↑ side effects↓	Italy	2015	[113]
167 Dyspeptic and chronic gastritis Patients	RPC	Group 1: AC + Lansoprazole Group 2: AC + Lansoprazole + P	L. Rosell-52, L. Rosell-11, B. Rosell-1755, *Saccharomyces boulardii*	5 billion live, probiotic lyophilized/capsule 28 days	positive effect on reducing of dyspeptic symptoms, while causing dyspeptic symptoms by probiotics would be less likely	*H. pylori* eradication rate ↑ side effects↓	Serbia	2016	[109]
50 patients	PRPD	P	*L. acidophilus, L. rhamnosus, L. sporogenes*	1 × 10^9 CFU/capsule, 4 × 10^9 CFU/capsule, 2 × 10^8 CFU/capsule 28 days	probiotics is likely to be important as adjuvant to the triple or quadruple therapy for *H. pylori*, especially in resistance cases	*H. pylori* eradication rate ↔ side effects↔	Taiwan	2017	[112]

A (Amoxicillin), **b.i.d** (*Bis in die*: twice a day), **C** (Clarithromycin), **D** (Doxycycline), **Le** (Levofloxacin), **M** (Metronidazole), **P** (Probiotic), **PO** (Prospective Open study), **PPI** (Proton Pump Inhibitors), **PRPD** (Prospective Randomized Placebo-controlledDouble-blind study), **PRPS** (Prospective Randomized Placebo-controlledSingle-blind study), **RPC** (Randomized Placebo-Controlled study), **RPT** (Randomized Placebo-controlled Triple-blind study), **SB** (Sub citrate Bismuth), **CFU** (Colony forming unit). **S** (*Saccharomyces*), **L** (*Lactobacillus*), **B** (*Bifidobacterium*).

stimulate the production of various IL-4, IL-5, IL-6, and INF-γ cytokines [71].A study by Gill et al. indicated that probiotics could alter host immunologic responses by interacting with epithelial cells and modulating the secretion of anti-inflammatory cytokines, thereby could reducing the activity of the stomach and inflammation [72]. Kabir et al., for the first studies in this area showed that *Lactobacillus salivarius* inhibits the secretion of IL-8 by *H. pylori* stimulated stomach epithelial cells. During numerous animal studies, after the administration of probiotics, a decrease in specific IgG against *H. pylori* infection was observed parallel to the reduction of gastric inflammation. Increasing the production of sIgA in the intestinal epithelium may play a central role in defense against the pathogen by enhancing the mucous membrane [73]. It was also found that *H. pylori* infection induced the production of Smad7, IL-8, TNF, and NF-kβ nuclear factor. Recent research by Yang et al. found that pre-treatment with *Lactobacillus acidophilus* at higher doses could reduce inflammation induced by *H. pylori* through inhibiting *H. pylori*-induced transduction of Smad7 by the inactivation of Jak1 and Stat1 pathways, followed by decrease production of NF-kB [74].

5. Probiotics and clinical studies by using animal models

In this regards, the first laboratory results were published in 1989 by Bhatia et al., which inhibits the growth of *H. pylori* in vitro in the presence of *L. acidophilus* in culture [75]. Michetti et al. for the first time demonstrated the effect of probiotic *L. acidophilus* on *H. pylori* colonization in humans. This study showed that bacterial load in the probiotic group of asymptomatic patients was reduced, while complete eradication of *H. pylori* was not achieved. As a result, only a few types of research on probiotic effects have been evaluated as a single treatment for *H. pylori* eradication [76]. The results of these studies indicate that certain probiotics, such as *S. boulardii* and *L. johnsonni La1* probably reduce the bacterial load, but not completely eradicate *H. pylori* [77].In the selected studies from 2000 to 2010, *Lactobacillus* probiotics were more closely studied in the mouse model, and the results showed that these bacteria modulate the mucosal inflammatory responses and inhibited the growth of *H. pylori* [78–80].In studies conducted between 2010 and 2014 on the gerbil models, *Lactobacillus* and *Bifidobacterium* species had a high inhibitory effect on *H. pylori* and reduced inflammatory responses. But in the mouse models, the *Bifidobacterium* has a high inhibitory effect along with *Lactococcus*, *Enterococcus*, and *Pediococcus*, that could inhibit the growth of *H. pylori*, and the use of *Pediococcus* alone has led to the elimination of *H. pylori* infection [81–85]. In studies conducted after 2014, all of them were performed on the C57Bl/6 mouse model, mainly from *Lactobacillus* and *Bifidobacterium* spp. All of the investigated probiotics had an inhibitory effect on the growth of *H. pylori* and inhibited inflammatory responses in epithelial cells [13,86–88].The results of animal model studies are shown in Table 1.

5.1. Probiotics and adjuvant therapy in patients

Researchers examined the combined effect of treatment with probiotics, with or without a placebo, without standard treatment [89]. This data shows that the use of probiotics in addition to standard treatment reduces *H. pylori* infection rates compared with placebo. However, probiotics improve diarrhea and nausea. Some meta-analyses have reported that probiotic supplements can improve the recovery rate of *H. pylori* compared with single treatment [90]. The consumption of fermented products in the diet (for example, 250 g of fermented milk product) can improve the digestive system with good microorganisms in the digestive tract. These data suggest that the use of probiotics with standard therapy reduces *H. pylori* infection rates compared with placebo [91].

The results of the 24 studies reviewed from 2008 to 2017 are as follows: From 2008 to 2010, studies mainly focused on the effects of *Lactobacillus* and the efficacy of this probiotic with drug therapy on *H. pylori* that was not significant and only in one study on *Saccharomyces* showed relative efficacy to *Lactobacilli* [92–95].In studies conducted in 2012 along with *Lactobacillus*, *Bifidobacterium* was also added to the treatment process. In all studies, no effect on the treatment of *H. pylori* was observed with antibiotic therapy and proton pump inhibitors [96–99].In 2013, probiotics used only *Lactobacillus reuteri* plus pantoprazole have a significant effect on the eradication of *H. pylori*. Antibiotics were not used along with this therapeutic process [100–103].In 2014, various studies have been carried out on the use of *Lactobacillus reuteri* with a proton pump inhibitor that has a high eradication effect and low side effect [104–108].In the year 2015, studies have been done on *Lactobacillus* spp. showed that *Lactobacillus reuteri* has the best results in eradicating *H. pylori* and also *Lactobacillus rhamnosus* with proton pump inhibitors plus antibiotic treatment has a high eradication effect in patients with *H. pylori*. From 2015, *Lactobacillus gasseri* with pantoprazole had the best effect in eradicating *H. pylori* [109–114].The results of clinical studies on patients are shown in Table 2.

6. Conclusion

Studies in animal models showed that *Lactobacillus* spp. alone and in combination with other probiotic strains have inhibitory effects on growth of *H. pylori* and suppression of inflammatory responses. However, some studies using *Pediococcus* strains showed a significant elimination of *H. pylori* infection. Therefore, it is suggested that in the treatment of *H. pylori* infection, along with the usual probiotic strains, different species of *Pediococcus* can also to be used. In human studies, *Lactobacillus reuteri* and *Lactobacillus gasseri* alone with proton pump inhibitors have a high eradication effect on *H. pylori* infections, which it is suggested the use of probiotics as the future therapeutic protocols in patients. In relation to the probiotic treatment process, it should not be recommended that probiotics be used as a single treatment for the eradication of *H. pylori*. However, their use in standard treatment as a supplement will increase eradication and reduce side effects associated with treatment. Perhaps it is widely believed that probiotics can improve the eradication of *H. pylori* and reduce side effects during standard treatment, but some probiotic bacterial species could help with drug therapy. In general, probiotic supplements increase the rate of eradication of *H. pylori* infection and could reduce the side effects of antibiotics.

Conflict of interest

All authors declare that there are no conflicts of interest. All source of support by Semnan University of Medical Sciences, Semnan, Iran.

Acknowledgments

I. Department of Bacteriology and Virology, Semnan University of Medical Sciences, Semnan, Iran.

II. Department of Immunology, Semnan University of Medical Sciences, Semnan, Iran.

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