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Probiotics for Treatment of *Helicobacter pylori* Infections and Gastric Cancer Prevention

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ABSTRACT

Helicobacter pylori is a gram-negative, microaerophilic, and curved or spiral bacterium that lives in the stomach of 50% of humans. The bacterium causes various diseases, containing gastritis, stomach ulcer, and gastric cancer. Hence, eradicating the bacterium from the stomach is essential. Using several antibiotics to treat and eliminate *H. pylori* and creating resistant strains cause an imbalance of the normal intestinal flora. Therefore, the use of new therapies, such as the use of probiotics, is of particular importance. Yogurt contains probiotics such as *Lactobacillus* and *Bifidobacterium* that balance the gastrointestinal microflora. Fruit and vegetable extracts are suitable carriers for probiotics. In this research, articles published in various sources were studied, including Web of Sciences databases, PubMed, Scopus, Elsevier, Wiley, Springer, and Google Scholar search engines. The search was conducted using the keywords *H. pylori*, probiotic therapy, gastritis, and stomach cancer. Probiotics produce different types of antibacterial compounds, including lactic acid, short-chain fatty acids, hydrogen peroxide, and bacteriocin. Therefore, they can play an important role in the treatment of *H pylori* infection. Various studies have shown that *Lactobacillus* spp., *Bifidobacterium* spp., *Pediococcus* strains, and *Saccharomyces boulardii* have had inhibitory effects on *H. pylori in vivo* and *in vitro*. A combination of probiotics and antibiotics is more effective in eradicating and treating infections caused by *H. pylori*. Probiotics reduce inflammation by binding to epithelial cells and controlling the excretion of anti-inflammatory cytokines. *Lactobacillus salivarius* inhibits the secretion of pro-inflammatory cytokines interleukin-8 stimulated by *H. pylori* in gastric epithelial cells.

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Introduction

H. pylori strains cause gastritis, duodenal wound, and stomach cancer in humans. (Qureshi *et al*., 2019). In most people, *H. pylori* infection is asymptomatic, however, in sensitive people, it may increase the risk of developing gastritis, gastric atrophy, ulcers, as well as gastric cancer. Also, there is an association between *H. pylori* infections and other diseases, which include Idiopathic Thrombocytopenic Purpura (ITP), unexplained iron deficiency anemia, and vitamin D and B12 deficiency. (Espinoza *et al*., 2018). In developing countries, the outbreak of *H. pylori* infection is between 70 and 90% before the age of 10 while in developed countries, it changes from 25 to 50%. *H. pylori* strains cause over 60% of gastric cancers. If the *H. pylori* infection is not eradicated, it will continue throughout life (Alipour, 2021). To prevent and treat infections and stomach cancers developed by *H. pylori*, the killing of the bacterium is recommended.

Currently, the cure of *H. pylori* infections involves a proton pump suppressor such as omeprazole along with clarithromycin and amoxicillin or clarithromycin and metronidazole for 10 to 14 days (Saleem and Howden, 2020). The triple therapy used to treat *H. pylori* infection has many side effects, e.g., diarrhea, nausea, flatus, and flavor disorder, and can also lead to resistant strains (Patel *et al*., 2014). Clarithromycin-resistant *H. pylori* strains have been reported by the World Health Organization. Metronidazole resistance *H. pylori* strains have been described in the United States and Europe (Goderska *et al*., 2018; Roszczenko-Jasińska *et al*., 2020). A new and ideal plan to treat *H. pylori* infection is that the infection should be treated without antibiotic resistance and side effects (Alvi *et al*., 2017). Because of the high level resistance to clarithromycin, and metronidazole antibiotics, new methods are needed to treat *H. pylori* inflammation. A new strategy in treating *H. pylori* infection is probiotics, which both reduce antibiotic resistance and balance intestinal microbiota. Probiotics are microbes that play a crucial role in host health if used in adequate quantity (Tan *et al*., 2021). Compared to the word antibiotic, which means anti-life, probiotic is formed from the Latin prefix pro, meaning for, and the Greek word biotic, meaning bios or being (Anandharaj *et al*., 2014). The theory of probiotics was first proposed by Eli Metchnikoff in 1908, who argued that longevity was related to the feeding of fermented milk products. Probiotics are stable to bile salts, pancreatic enzymes, and gastric acid. Hence, they can colonize the intestinal tracts (Khoder *et al*., 2016). Probiotics are non-pathogenic and can tolerate adverse gastrointestinal conditions (Khoder *et al*., 2016; Aleta *et al*., 2020). In some studies, probiotics have shown resistance to several antibiotics (Wang *et al*., 2020a). Probiotics produce nutrients such as vitamins, amino acids, oligosaccharides, and chain-short fatty acids (Scott *et al*., 2020). Prebiotics are indigestible carbohydrates for the host that serve as adiet for the probiotic (Indira *et al*., 2019). Cereals, bananas, onions, garlic, honey, and artichokes contain prebiotics (Peng *et al*., 2020). A mixture of probiotics and prebiotics is called synbiotics (Mohanty *et al*., 2018). Table 1 presents the microbes utilized as probiotics. Due to the high prevalence of *H. pylori* infections in humans, the present study aimed to treat infections caused by the bacterium and stomach cancer prevention.

Table 1. Microorganisms applied as probiotics.

Probiotic Genus	Species	References
Lactobacillus	*L. plantarum*, *L. paracasei*, *L. acidophilus*, *L. casei*, *L. rhamnosus*, *L. crispatus*, *L. gasseri*, *L. reuteri*, *L. bulgaricus*	Zendeboodi *et al*., 2020
Bifidobacterium	*B. adolescentis*, *B. animalis*, *B. bifidum*, *B. infantis*, *B. lactis*, *B. longum*, *B. catenulatum*	Zendeboodi *et al*., 2020
Bacillus	*B. cereus*, *B. clausii*, *B. polyfermenticus*, *B. pumilus*, *B. subtilis*, *B. licheniformis*	Lee *et al*., 2019
Streptococcus	*S. sanguis*, *S. oralis*, *S. mitis*, *S. thermophilus*, *S. salivarius*	Kerry *et al*., 2018
Saccharomyces	*S. cerevisiae* var. boulardii	Pais *et al*., 2021
Enterococcus	*E. faecium* and *E. durans* strains	Yerlikaya and Akbulut, 2020
Pediococcus	*P. acidilactici*, *P. pentosaceus*	Jiang *et al*., 2021; Chanalia *et al*., 2018
Leuconostoc	*Leuconostoc mesenteroides spp. Dextranicum*	Lee *et al*., 2021; Nyanzi *et al*., 2021
Lactococcus	*Lactococcus lactis*	Radaic *et al*., 2020
Propionibacterium	*Propionibacterium freudenreichii*	Nyanzi *et al*., 2021
Weissella	*Weissella cibaria*	Yeu *et al*., 2021

Materials and Methods

Literature searches were performed on international databases, including Medline, Scopus, Web of Science, and Google Scholar. This search included articles published between 2000 and 2021. Only English studies were considered. In addition, a manual review of the sources of the obtained literature was performed. Keywords such as *H. pylori*, probiotic therapy, gastritis, and stomach cancer were used as single words or in combination.

Mechanism of antibacterial activity of probiotics

Probiotics have antagonistic effects on various microorganisms by different mechanisms. Gastrointestinal mucosa is vital for maintaining good health (Paone and Cani, 2020). The gastric mucosa comprises columnar epithelium, lamina propria containing leukocytes, and mucosal muscle. The surface of the mucosa is masked with mucus (Martens *et al*., 2018). Probiotics can stimulate the production of mucus, which contains high-weight glycoproteins. Therefore, this layer is a physical barrier to the attachment of microorganisms to the epithelial layer (Bravo Santano *et al*., 2020). Lactic acid bacteria adhere to the epithelial cells of gastric mucosal and prevent *H. pylori* colonization. (Wang *et al*., 2020b). Bacterial motility is necessary to cross the gastric mucus and attachment to the gastric epithelial cells. *Lactobacillus agilis* strains are absorbed into the mucosa and can penetrate the mucosal layer (Kajikawa *et al*., 2018). *L. agilis* and *L. ruminis* are the solely motile lactobacilli found in the intestines of animals and humans (Suzuki *et al*., 2020). Dincer and Kivanc (2019) illustrated that all strains of *L. plantarum* showed resistance to acid and stomach environment. Probiotics can discharge antibacterial factors, including lactic acid, short-chain fatty acids, hydrogen peroxide, and bacteriocin. Due to the incomplete ionization of lactic acid and short-chain fatty acids, they usually have greater antibacterial activity than the potent acids. The undigested form of these organic acids acts as proton carriers that can disrupt *H. pylori* via acidifying the cytoplasm and accumulating toxic anions. Hydrogen peroxide created by probiotics gives rise to oxidative destruction of pathogenic proteins, membrane lipids, and DNA (Ji and Yang, 2020). Franco-Robles *et al*. (2020) showed that *Lactobacilli* and *Bifidobacteria* could inhibit *H. pylori* through competition for host cell surface receptors. Probiotics secrete a wide range of bacteriocins, such as nisin, lactulin, acidophiline, lactosidine, acidoline, bifidin and bifidosin. Bacteriocins are small peptides with antibacterial properties (Zimina *et al*., 2020). Nisin is the unique bacteriocin approved as a foodstuff maintainer (Singh *et al*., 2021). *L. planatarum* produces lactulin. There are reports that *L. acidophilus* produces acidophiline, lactosidine, and acidoline (Bajaj *et al*., 2021). Touré et al. (2003) reported that the bacteriocins bifidin and bifidosin B are produced by *Bifidobacterium bifidum*. Anti-pathogenic compounds such as bacteriocin and peptides increase the permeability of target cells, which causes depolarization of the cell membrane and eventually leads to the cell death (Santacroce *et al*., 2019). Bacteriocins are synthesized on the ribosome and kill related or unrelated bacterial strains while bacteriocin-producing bacteria are not damaged by the production of specific immune proteins (Yang *et al*., 2014). The mechanisms of the antibacterial activity of the probiotics are shown in Fig. 1.

Eradication of *H. pylori* infection by probiotics

The standard therapy for *H. pylori* infections is suggested for communities where resistance to the antibiotic clarithromycin is less than 15% or in patients who have not recently been prescribed a macrolide. Bismuth quadruple therapy is prescribed for regions with high macrolide resistance or in patients who have been treated with macrolides. (Spiteri *et al*., 2021). The bismuth quadruple treatment includes a proton pump inhibitor, bismuth, metronidazole, and tetracycline, which is suggested as the second plan of cure (Shin *et al*., 2021). Bismuth has a direct effect on H. pylori by inhibiting various enzymes, ATP synthesis, and adhesion to the gastric mucosa (Alkim *et al*., 2017). Proton pump inhibitors are irreversible suppressors of the $H^+ K^+$ pump in gastric parietal cells that secrete acid (Fossmark *et al*., 2019). However, the resistance of H. pylori to antibiotics reduced the effectiveness of treatment. Another challenge to the cure of *H. pylori* infections is the side effects of antibiotics. A compound of two antibiotics leads to over-destruction of the host's gastrointestinal microbiome, imbalance of the microbial population, and proliferation of pathogenic microbes. Alternative strategies are required to treat infections caused by antibiotic-resistant *H. pylori* strains. One of these treatment regimens is using probiotics, which increase the ability of eradication regimens and reduce the side effects of antibiotics (Tang *et al*., 2021). Treatment with *L. reuteri* ATCC 55730 for 4 weeks reduced the number of H. pylori in the stomach (Abdelhamid, 2020).

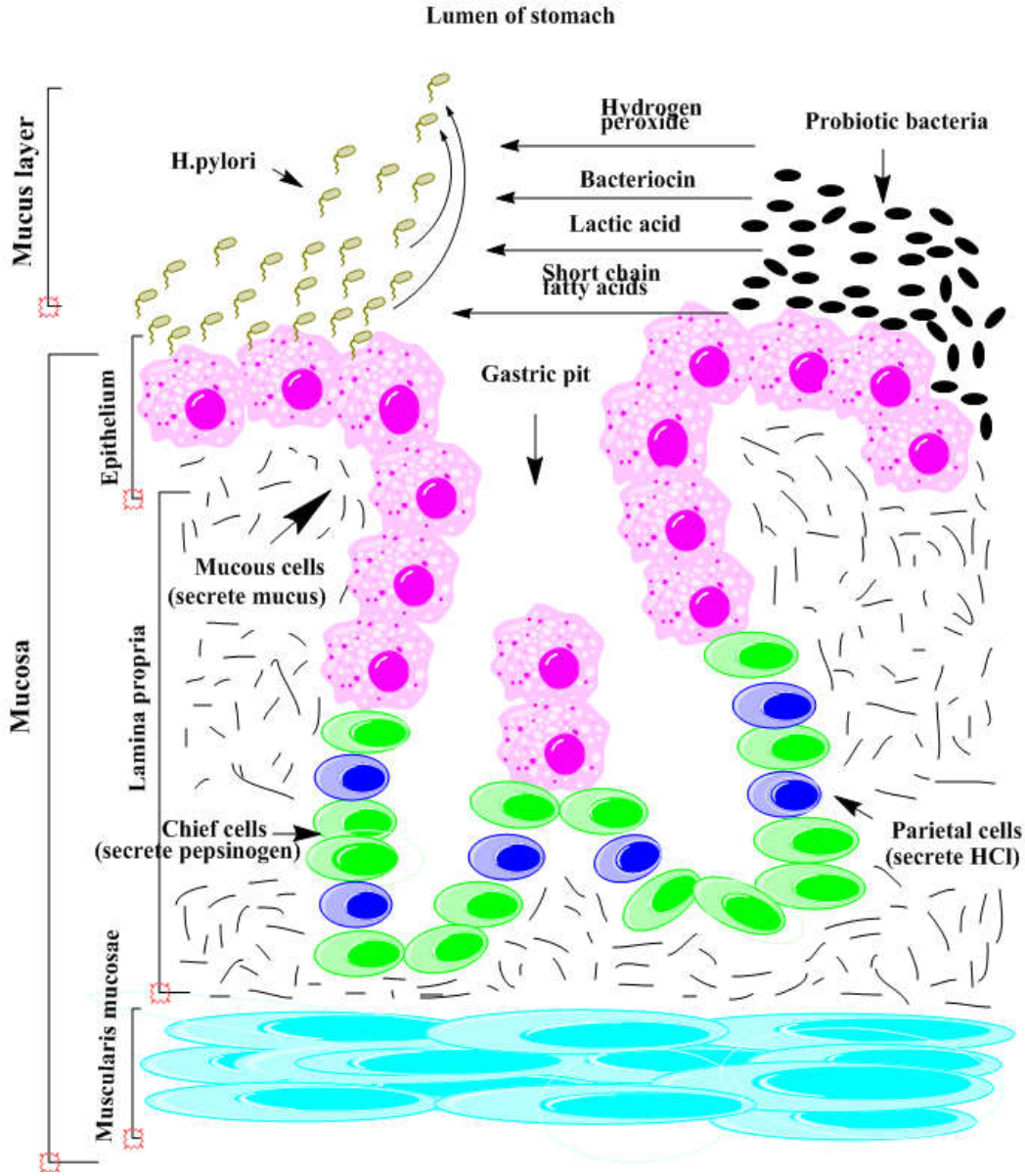

Fig. 1. Mechanisms of probiotics antibacterial activity: The inner layer of the stomach called mucosa is histologically divided into three layers: the epithelial, the lamina propria, and the mucosal muscle layer. Probiotics inhibit H. pylori by colonizing the epithelial layer of the stomach and producing various antimicrobial compounds such as hydrogen peroxide, bacteriocin, lactic acid, and short-chain fatty acid. The figure was prepared by Chem Bio Office Software.

In another study, Zhu and Liu (2017) reported that *L. reuteri* had a helpful impact on *H. pylori* eradication and cure-dependent side effects. It was shown that the supernatant prepared from L. acidophilus La1 culture prevents the sticking of H. pylori to gastric epithelial cells in laboratory conditions (Lin *et al*., 2020). *L. paracasei* HP7 obtained from kimchi, a fermented vegetable in Korea, has suppressive outcomes on *H. pylori in vitro* and *in vivo* (Lee *et al*., 2020). Sun *et al*. (2018) expressed that *L. sake*, *L. plantarum*, *L. rhamnosus,* and *L. brevis* separated from fermented foodstuffs in Northeast China, could inhibit *H. pylori* growth to varying degrees. *L. gasseri* ameliorates inflammation developed by *H. pylori* and therefore can be prescribed as an augment to the common treatment for *H. pylori* infections (Yarmohammadi *et al*., 2021). L.

casei, L. paracasei, and L. acidophilus inhibited 100% of H. pylori strains (Saracino *et al*., 2020). Studies in gerbils have shown that the genera Lactobacillus and Bifidobacterium had high suppressive effects on *H. pylori* (Eslami *et al*., 2019). A combination of probiotics and antibiotics is suitable for maintaining the balance of the gastrointestinal microbiome and for better therapeutic results. (Ji and Yang, 2020). The triple treatment with *Saccharomyces boulardii* significantly increases *H. pylori* eradication and reduces its side effects compared to triple treatment alone (Hu et al., 2020). Eslami et al. (2019) illustrated that the genus *Pediococcus* showed significant effects on inhibiting and eradicating *H. pylori* infection. Table 2 shows the antagonistic consequences of probiotics on *H. pylori*.

Table 2. Antagonistic results of probiotics on *H. pylori*

Probiotics	Model	Consequence	References
L. reuteri	Human	Positive effect on *H. pylori* eradication	Zhu and Liu, 2017
The supernatant of *L. acidophilus*	Gastric epithelial cells in laboratory condition	Inhibition of sticking *H. pylori*	Lin *et al*., 2020
L. paracasei HP7	*In vitro* and *in vivo*	Inhibitory effects on *H. pylori*	Lee *et al*., 2019; 2021)
L. gasseri	Human	Amelioration of inflammation	Yarmohammadi *et al*., 2021
L. casei, *L. paracasei*, and *L. acidophilus*	*In vitro*	Bactericidal on *H. pylori*	Saracino *et al*., 2020
Lactobacillus and *Bifidobacterium*	Gerbil	Inhibition of *H. pylori* and reduction of inflammatory	Eslami *et al*., 2019
Triple treatment with *Saccharomyces boulardii*	Human	Enhancement destruction of *H. pylori*	Hu *et al*., 2020
Pediococcus strains	Human	Elimination of *H. pylori* infections	Eslami *et al*., 2019

Prevention of gastric cancer by probiotics

Extirpation of *H. pylori* from gastritis is a critical factor in preventing gastric cancer. At present, probiotics are considered an element in the prevention and remedy of cancer, mainly through the stimulation of programmed cell death. L. rhamnosus supernatant has a high potential in preventing the reproduction of human colorectal cancer cell lines (HT-29). The HT-29 is widely used in biological and cancer investigations (Eslami *et* al., 2019; Dehghani *et al*., 2021). It has been shown that the genera Lactobacillus and Bifidobacterium and their products have an influential function in the reduction of stomach cancer. In addition, the anti-reproduction and anti-tumor processes of these bacteria against cancer cells play a critical role in human well-being (Rasouli *et al*., 2017). Cancer involves the rapid and uncontrolled multiplication of cells and the spread of cancer cells to other organs of the body as metastases (Meng *et al*., 2021). Probiotic bacteria, especially *Lactobacillus* spp. and *Bifidobacterium* spp., stimulate anti-cancer properties through programmed cell death (Badgeley *et al*., 2021). Bifidobacterium adolescentis SPM0212 and L. rhamnosus GG have antiproliferative properties on HT-29 and gastric cancer cells (Arian *et al*., 2019; Bahmani *et al*., 2019). Research by Sener et al. has shown that L. rhamnosus GG has an anti-proliferative role in gastric cancer and colon cancer cells (Şener *et al*., 2021). Shamakhi et al. showed that S. cerevisiae had anti-proliferative and anti-tumor roles in vivo and *in vitro*. (Shamekhi *et al*., 2020). S. boulardii supernatant has anti-reproductive and apoptotic features in gastric adenocarcinoma (Pakbin *et al*., 2021). The anti-multiplicative and anti-tumor features of the probiotics are presented in Table 3.

Studies of laboratory systems and animal models have shown that probiotics, prebiotics, and synbiotics have anti-neoplastic properties. Probiotics may help prevent the onset of cancer and the treatment of existing tumors. However, most probiotic anti-cancer therapies are in the preclinical stages (Fotiadis *et al*., 2008).

Table 3. The anti-proliferative and anti-tumor effects of probiotics.

Probiotic	Model	Effects	References
Bifidobacterium adolescentis SPM0212	*In vitro*	Anti-proliferative	Arian *et al*., 2019; Bahmani *et al*., 2019
Lactobacillus rhamnosus GG	*In vitro*	Anti-proliferative	Şener *et al*., 2021
L. rhamnosus supernatant	*In vitro*	Anti-proliferative	Eslami *et al*., 2019; Dehghani *et al*., 2021
Lactobacillus spp. and *Bifidobacterium* spp.	*In vitro*	Apoptosis of cancer cells	Badgeley *et al*., 2021
S. boulardii	*In vivo* and *in vitro*	Anti-proliferative and apoptosis	Pakbin *et al*., 2021

Immunomodulation of *H. pylori* infection by probiotics

The first stage in colonization is the junction of *H. pylori* to the stomach epithelium (Park *et al*., 2016). *H. pylori* serotypes can form biofilms resistant to antimicrobial therapy (Yonezawa *et al*., 2019). The bacterium neutralizes the stomach's acidic environment by the production of the urease enzyme and then colonizes the gastric mucosa (Salman *et al*., 2021). In the gastric lamina propria, neutrophils and eosinophils are not usually found, and under normal conditions, lymphocytes and plasma cells are scarce. However, they increase sharply in infections (Zevering *et al*., 1999). *H. pylori* components bind to Toll-Like Receptors (TLRs) and Nucleotide-binding Oligomerization Domain (NOD)-like receptors in gastric epithelial cells and induce the expression of inflammatory genes. *H.* pylori strains induce gastric epithelial cells to produce cytokines and chemokines, containing Inter-Leukin (IL) -6, IL-8, IL-12, IL-1β, and Tumor Necrosis Factor α (TNFα) (Robinson and Atherton, 2021). The secreted cytokines and chemokines attract neutrophils, macrophages, Dendritic Cells (DC), Natural Killer cells (NK), and lymphocytes to the lamina propria. These stimulated cells release Reactive Oxygen Species (ROS) and Reactive Nitrogen Species (RNS). T-Helper 1 (Th1) cells release the interferon-γ (IFN-γ) and TNFα, which drive macrophages to excretion of other inflammatory elements. Reactive oxygen species released cause intensive destruction of the stomach mucosa. Sticking of *H. pylori* to stomach epithelial cells reduces the transcription and translation of anti-inflammatory cytokines such as IL-10. (White *et al*., 2015). Moreover, dendritic cells stimulated by *H. pylori* and *its* components secrete IL-12 stimulating T-Helper type 1 (Guiney *et al*., 2003). This immune response cannot eliminate *H. pylori in vivo* (Ren *et al*., 2019). *H. pylori* strains secrete particular proteases, Vacuolating cytotoxin A (VacA) and certain phospholipases, which damage gastric epithelial cells and destroy tight junctions (Ito *et al*., 2020). *H. pylori* infection induces the secretion of local and systemic IgA and IgG antibodies, although the effects of antibodies on the colonization of this bacterium are still arguable (Srivastava *et al*., 2013). IgA antibodies produced versus *H. pylori* urease can neutralize the activity of this enzyme (Morrow *et al*., 2000). Treatment using Lactobacillus strains has shown that the attachment and invasion of *H. pylori* to gastric epithelial cells as well as the production of interleukin 8 has been significantly reduced (Chen *et al*., 2019). Gebremariam *et al*. (2019) presented that *Lactobacillus gasseri* inhibits the excretion of pro-inflammatory cytokines TNF and IL-6 in macrophages. Probiotics play a critical role in inhibiting pathogens by increasing IgA and strengthening the mucosal barrier (Zhang *et al*., 2020). In the gastric mucosa, the pro- and anti-inflammatory reactions caused by *H. pylori* are presented in Fig. 2.

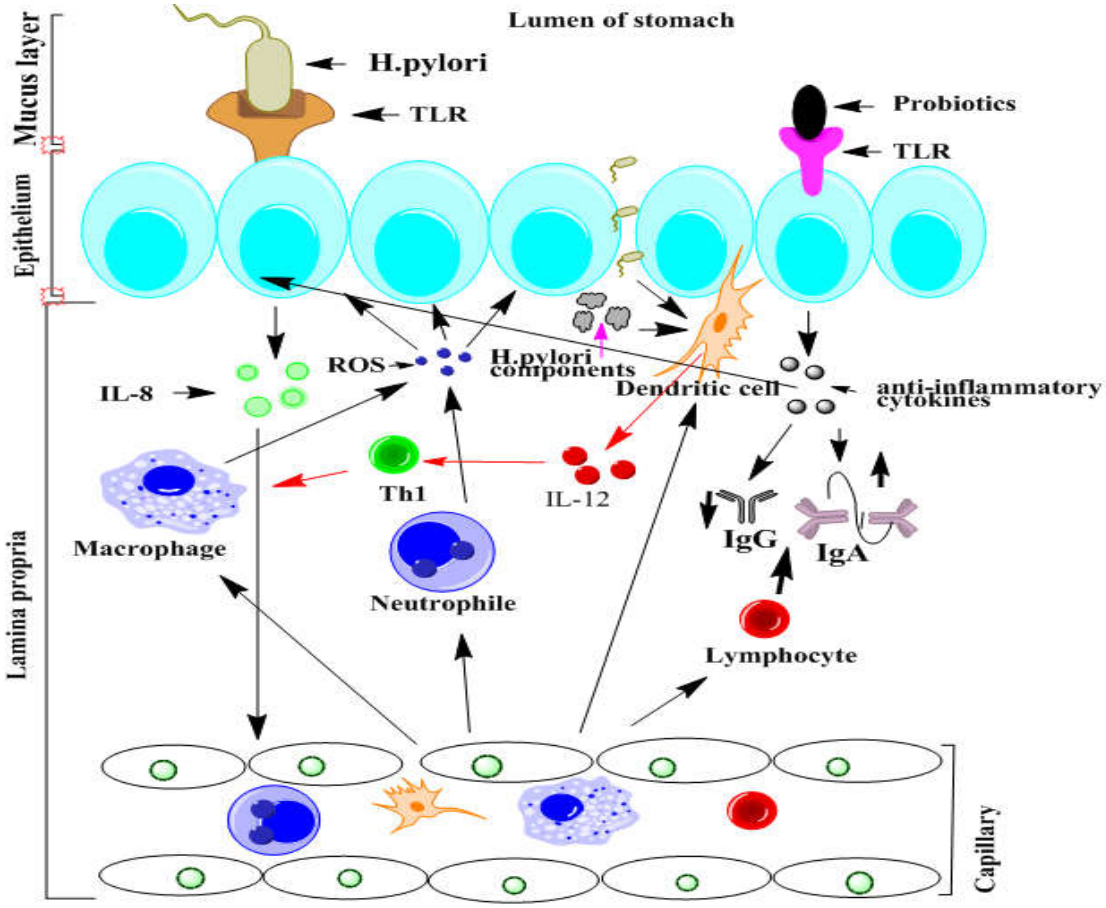

Fig. 2. Pro- and anti-inflammatory reactions to *H. pylori* in the gastric mucosa: In the stomach, *H. pylori* infection leads to the release of various inflammatory mediators, including chemokines and cytokines. Cytokines and chemokines secreted from gastric epithelial cells such as IL-8 cause the migration of neutrophils and monocytes to the gastric mucosa. The triggered macrophages and neutrophils release reactive oxygen species and reactive nitrogen species. By the interaction of probiotics with epithelial cells, the release of anti-inflammatory cytokines modulated, leading to the decrease of stomach inflammation. Lactobacilli can increase local IgA concentration and decrease anti- *H. pylori* IgG antibodies. This schematic was prepared by Chem Bio Office Software.

Conclusion

Resistance to antibiotics has been reported from around the world to be destroying the normal intestinal flora. Thus, alternative therapies with probiotics that increase the effectiveness of antibiotics, protect the microflora of the host's digestive system, and reduce the complications caused by antibiotics are required. The different probiotics can kill and control *H. pylori*. Therefore, the use of probiotic bacteria solely or along with antibiotics recommended to infections treatment. Probiotics with anti-proliferative and anti-apoptotic properties can play an important role in reducing stomach cancer. Thus, the administration of these microorganisms is recommended for the prevention and treatment of stomach cancer. In addition, probiotics can replace harmful bacteria in the gastrointestinal tract, including Bacteroides, which contribute to type 1 diabetes, Alzheimer's, and obesity.

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Conflicts of interest

Authors declared no conflict of interest.

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