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IP International Journal of Medical Microbiology and Tropical Diseases

Journal homepage: <https://www.ijmmttd.org/>

## Review Article

## The prospect of probiotics in *Helicobacter pylori*-induced peptic ulcer disease: A perspective review

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## ARTICLE INFO

## Article history:

Received 26-12-2023

Accepted 01-05-2024

Available online 22-06-2024

## Keywords:

Probiotics

Helicobacter pylori

Peptic ulcer disease

Antibiotics

## ABSTRACT

The relationship between the human host and the intestinal microbiota is dynamic and symbiotic. This review examines whether there is a correlation between a disruption in host-microbial interactions caused by an alternative composition of gut microbiota and an increased susceptibility to peptic ulcer disease, mainly when hazardous bacteria are present in the coexistence. Peptic ulcers frequently arise from infections caused by *Helicobacter pylori* (*H. pylori*), a pathogen that evades the host's immune system and establishes a lifelong colony. This protracted infection gives rise to chronic inflammation, which substantially raises the risk of developing gastric ulcers and gastric cancer. One of the significant obstacles in the treatment of *H. pylori* infection is antibiotic resistance, which develops as a result of improper antibiotic treatment for bacterial infections. Such misuse of antibiotics also results in dysbiosis. In such cases, probiotics become an essential tool that restores the balance of the normal flora in the body and eliminates critical infections. This results in probiotics being utilized extensively for ulcer treatment and potentially serving a dual-purpose in combating *H. pylori* infection; consequently, antibiotic usage will be reduced, and human health will advance.

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### 1. Introduction

*H. pylori* serves as an exceptional model organism for investigating the interplay between hosts and pathogens and the mechanisms underlying bacterial-induced peptic ulcers due to its persistent development of strategies to colonize hosts and deregulate cellular functions.<sup>1</sup> Several environmental, bacterial, and host factors associated with the pattern and severity of gastritis and the degree to

which the inflammation has progressed into a peptic ulcer influence the risk of this development.<sup>2</sup> To treat this form of ulcer, the *H. pylori* bacterium must be eradicated, nonsteroidal anti-inflammatory drugs (NSAIDs) must be reduced, and the ulcer must be allowed to heal. It is established that *H. pylori* colonizes the gastric mucosa, subsequently inducing inflammation, hindering bicarbonate secretion, and promoting acidity. Therefore, long-term *H. pylori* suppression may mitigate the risk of associated diseases, enabling probiotics to bridge this therapeutic gap.<sup>3</sup>

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However, probiotics have been proposed as supplementary interventions to antibiotics and other pharmaceuticals when treating *H. pylori*.<sup>4</sup> The bacteria that produce lactic acid most frequently are *Lactobacillus* isolates, although *Bifidobacterium* spp., *Saccharomyces* spp., and *Bacillus* spp. also produce lactic acid.<sup>5</sup>

## 2. Peptic Ulcer Disease (PUD)

PUD is the most prevalent disease of the gastrointestinal tract (GIT). It manifests as excruciating ulcers accompanied by symptoms of the gastrointestinal tract. Clinically, PUD is challenging to differentiate from other GI diseases. A mucus layer constitutes the normal physiological barrier, which preserves the stomach against its digestive fluids. However, this protective layer can be compromised by various factors, allowing acid and harmful microorganisms to damage the tissue, including duodenal and gastric ulcers.<sup>6</sup>

### 2.1. Pathophysiology of PUD

The mechanism of occurrence results from an imbalance between the destructive and defensive factors. The major underlying causes predisposing to the development of PUD disease are a history of ulcers, some illnesses such as liver, kidney or lung disease, drinking alcohol regularly, physiological stress, smoking, and the intake of iron supplements have been associated with gastric pathology too and other factors which increase the level of acid, so all these factors will attenuate typical mucosal defence and healing mechanisms.<sup>6</sup> But studies have shown two leading causes of ulcers: *H. pylori* bacteria and frequent use of NSAIDs (Aspirin, Naproxen, Ibuprofen).<sup>7</sup> It usually begins with damage to the mucosa, which extends to the muscularis mucosa and the inner layers exposed to acidity result in bleeding or perforation.<sup>8</sup>

### 2.2. *Helicobacter pylori* (*H. pylori*) bacteria

Gastric ulcers have been associated with *H. pylori*, a gram-negative *bacillus* belonging to the Epsilon proteobacteria class.<sup>9</sup> They induce inflammation and chronic gastritis in the upper gastrointestinal tract by employing a spiral motion of their flagella to traverse the mucus and adhere to the epithelial cells. This condition compromises the integrity of the protective lining by elevating gastric pH via the secretion of urease, which hydrolyses urea (a byproduct of protein catabolism by cellular organisms). Consequently, an alkaline environment is produced to shield the bacteria from acid, diminishing the acidic environment they inhabit.<sup>10</sup> Numerous *H. pylori* strains generate proteins such as VacA, which functions on mucosal cells to enhance urea movement in the stomach, and CagA, which induces alterations in the morphology and surface elements of the cells.<sup>10</sup> Furthermore, *H. pylori* fosters the production of reactive oxygen species (ROS),

induces oxidative DNA damage in the gastric mucosa of infected humans, and induces apoptosis of gastric epithelial cells.<sup>11</sup> The colonisation of the gastric epithelium can be attributed to its ability to navigate through secretions and its predilection for areas of stomach injury.<sup>12</sup> It frequently infects the stomach, and approximately fifty percent of the population is asymptomatic with an *H. pylori* infection. This is owing to its capacity to endure short-lived pH levels below 4, although growth is inhibited at such levels; infection exclusively transpires within a restricted pH spectrum of 5.5 to 8.0.<sup>13</sup> Individuals aged fifty and above have a higher susceptibility to contracting the infection.

### 2.3. Several conditions are associated with reduced gastric acid secretion and help in *H. pylori* infection

Chronic gastritis is the first symptom that occurs after *H. pylori* colonization. The severity of the chronic inflammatory process depends on several factors: host genetics, immune system response, diet regimen, characteristics of the colonizing strain and acid production level.<sup>2</sup> Acid makes the luminal content of the stomach and small intestine relatively sterile by killing swallowed microorganisms, including *H. pylori*. The average stomach is rich in microbiota but is lower than other gastrointestinal parts because of the high acid level.<sup>14</sup> Although an acute infection with *H. pylori* decreases acid secretion, chronic infection may increase or decrease acid secretion. Anyway, the presence of *H. pylori* changes the composition of the gastric microbiota.<sup>15</sup> There are many other factors which increase the probability of infection like age (people over 65 years have low levels of hydrochloric acid, so the infection of *H. pylori* increases with age),<sup>16</sup> psychosocial factors (stress, depression and anxiety), surgery (Bariatric surgery reduce the secrete of hydrochloric acid),<sup>17</sup> vitamins deficiency (Vitamin B12, Vitamin C, Vitamin D, folic acid and calcium), chronic atrophic gastritis and malnutrition cause gastric hypoacidity, fever may inhibit gastric acid secretion in humans and medication.<sup>18</sup> The effective treatment with one or more antibiotics, like prolonged use of clarithromycin and other macrolides in respiratory infections, reduces the success of antibiotic treatment to less than 80 % because of their resistance to *H. pylori*.<sup>19</sup> In addition, antibiotics have adverse effects on the microflora of GIT because they don't kill only the pathogens but also the normal microflora responsible for maintaining the stomach's acid environment.<sup>20</sup> Taking antacids or other medications to treat ulcer or acid reflux for a long time, such as proton pump inhibitors (PPIs) and H<sub>2</sub>-antagonists, may lead to hypochlorhydria and could inhibit normal gastric acid secretion by up to 99 % and affect the composition of the gastric microbiota.<sup>21</sup> Furthermore, the composition of the gastric microbiota changes in the setting of *H. pylori* by inducing the host to secrete antimicrobial peptides that indirectly kill the other bacteria.<sup>22</sup>

#### 2.4. Treatment of peptic ulcer

Treatment depends on the case. Usually, this includes the eradication of *H. pylori*, minimizing the use of NSAIDs, and providing elements that help heal.

1. Different medications treat *H. pylori*.<sup>23</sup> For example, clarithromycin exhibits antibacterial properties by inhibiting bacterial protein biosynthesis; fluoroquinolones impede the operation of the bacterial gyrase enzyme, which regulates DNA transcription, recombination, proliferation, and structural stability.<sup>24</sup> Levofloxacin, a fluoroquinolone medication, is employed as a second-line treatment due to the expeditious development of resistance.<sup>25</sup> *H. pylori* contains ferredoxin-like enzymes, NADPH nitro reductase, and NADPH-flavin oxidoreductase, all utilized by metronidazole. By interfering with peptidoglycan synthesis, amoxicillin prevents the synthesis of bacterial cell walls and degradation.<sup>26</sup> Anti-tuberculosis agent rifabutin can inhibit the *H. pylori* reverse transcriptase (RT) beta subunit. Tetracycline disrupts protein biosynthesis by inhibiting amino acid transferase activity and exerts an influence on the 30S subunit of the ribosome.<sup>27</sup>
2. (Proton pump inhibitors (PPIs): a drug used to treat *H. pylori* infection with antibiotics like Omeprazole, Esomeprazole, Pantoprazole and Lansoprazole. Those block H<sup>+</sup>/K<sup>+</sup> ATPase or gastric proton pump irreversibly in the partial gastric cell, the last step in gastric acid secretion.<sup>28</sup> However, PPI has been reported with severe side effects in long-term use, such as a higher risk for infection (enteric or pneumonia), chronic renal disease, bone fracture and symptomatic hypomagnesemia.<sup>29</sup>
3. Medications to reduce acid production: histamine (H<sub>2</sub>) blockers or acid blockers; these medications relieve the pain of ulcers by reducing the amount of acid in the stomach but, in general, are not used alone to heal the ulcer. Acid blockers include Famotidine, Cimetidine and Nizatidine.<sup>29</sup>
4. Bismuth quadruple therapy: This treatment lasts fourteen days and includes two antibiotics, like Tetracycline and Metronidazole, with Bismuth and PPI. It is used as a first-line treatment when the resistance of clarithromycin is high or as a second-line treatment when the triple therapy fails.<sup>30</sup>
5. Probiotics: Probiotics are live microorganisms promoted with claims that they provide health benefits when consumed, generally by improving or restoring the gut microbiota;<sup>31</sup> it was proposed by Russian Nobel Laureate Elie Metchnikoff in 1908 due to its effect on preventing the overgrowth of harmful bacteria, improving the function of the epithelial barrier and enhancing the resistance of the gut.<sup>32</sup> Probiotics are used more as preventive medicine

than therapeutics.<sup>33</sup> Previous studies have shown that probiotics are helpful in the treatment of many gastrointestinal diseases (GIT) like inflammatory bowel disease, functional digestive disorders, acute diarrhoea and antibiotic-associated diarrhoea; in addition, they can reduce the consumption and side effects of antibiotics and improve health conditions for that probiotics can be beneficial for infection with *H. pylori* in several mechanisms depending on their ability to survive the acidity of the stomach, bile and hydrolytic enzymes.<sup>34</sup>

#### 2.5. Mechanism of action of probiotics against *H. pylori*

There are two functional mechanisms by which probiotics can treat and eliminate the infection of *H. pylori*:

1. Physiological or non-immunological mechanisms like (a) production of antimicrobial peptides and other substances which are the end products of lactic acid fermentation like lactic, acetic acid and hydrogen peroxidase by stimulated gastric epithelial cells.<sup>35</sup> (b) Reduction of the pH in the gastric by secreting SCAFs that can inhibit *H. pylori* growth.<sup>22</sup> (c) Increase mucin production to improve epithelial barrier function and inhibit bacterial adhesion to the mucosal layer by creating competitive conditions (competitive with *H. pylori* for adhesion in the gastric mucosa, which is essential to determine the result in *H. pylori* disease).<sup>36</sup>
2. Immunological mechanisms such as inhibiting the production of IL-8, stimulating anti-inflammatory cytokines, suppressing the inflammatory function of lymphocytes and their cytokines via probiotics and their products through activating dendritic cells, and increasing the production of IgA by B cells due to changes in cytokines profiles through effects on dendritic cells.<sup>37</sup> Some studies showed that linoleic acid and linolenic acid can inhibit the effect of *H. pylori*.<sup>38</sup>

First-line treatment for *H. pylori* infection includes proton pump inhibitors and antibiotics, especially (Amoxicillin and Clarithromycin).<sup>38</sup> Still, due to the high resistance and percentage of side effects of antibiotic therapy, recent studies have shown they proposed using probiotics as an auxiliary or supplementation during the treatment. This is useful because it decreases the undesirable effects of antibiotics, improves the eradication rates, and improves compliance.<sup>39</sup>

**Table 1:** Clinical/preclinical effect of some probiotic strains in treating peptic ulcers

S. No.	Probiotics strain	Study design (Dose/Duration/Route)	Clinical/Preclinical model	Effect on Peptic ulcer	
1	Lactobacillus gasseri OLL2716	Dose: 109 CFU (Per Unit Of Yogurt. Duration: 16 Weeks Route: Orally Dose: 107CFU/MI	Human (20-64 Years) BALB/C Mice (5-Week-Old)	Blocking the production of the Proinflammatory Cytokines IL-6 and TNF → Suppress The Reduction of <i>H. pylori</i> In Gastric Mucosal Inflammation.	40
2	<i>Lactobacillus</i> Rhamnosus GMNL-74 And <i>Lactobacillus</i> <i>Acidophilus</i> Termed GMNL-185	Dose: 5×10 <sup>8</sup> CFU Duration: 7 Days Route: Orally	BALB/C Mice	Inhibit <i>H. Pylori</i> Adhesion to Gastric Epithelial Cells Which Weakened NF-Kb Activation And IL-8	41
3	<i>Lactobacillus</i> Gasseri OLL2716, <i>Lactobacillus</i> Rhamnosus GMNL-74, And <i>Lactobacillus</i> <i>Acidophilus</i> Termed GMNL-185	Dose: 109 CFU/MI Duration: 7 Days Before 49 Days After <i>H.</i> <i>pylori</i> Infection. Route: Orally	C57BL/6 Mice	Produce Lactic Acid → Suppress the Colonization of <i>H. pylori</i> Strain SS1 → ↓ <i>H.</i> <i>Pylori</i> Growth → ↓ Gastric Inflammation.	42
4	<i>Lactobacillus</i> Gasseri OLL2716, <i>Lactobacillus</i> Rhamnosus GMNL-74, And <i>Lactobacillus</i> <i>Acidophilus</i> Termed GMNL-185 <i>Lactobacillus</i> Bulgaricus	Dose: 109 CFU/MI Duration: 1st Week 3 Times, Then Once Per Week For 3 Weeks Route: Orally	Gnotobiotic BALB/C Mice	Producing high Lactic Acid → Inhibits the Colonization of <i>H. pylori</i> and Inflammatory Responses (IL-8) → ↓ <i>H. pylori</i> Growth.	43
5	<i>Lactobacillus</i> <i>Acidophilus</i> <i>Lactobacillus</i> <i>Bulgaricus</i>	Dose: 108 CFU/Day Duration: 4 Weeks Route: Orally	Human	Increasing Eradication Rate and Decreasing Percentage of Side Effects Associated With Antibiotics Therapy	42
6	<i>Lactobacillus</i> gasseri <i>Lactobacillus</i> acidophilus <i>Lactobacillus</i> bulgaricus	Dose: Tablets Reutertina Duration: 8 Weeks Route: Orally	Human (Adults)	Suppression of Urease Activity and <i>H.</i> <i>pylori</i> Density	44
7	<i>Lactobacillus</i> gasseri <i>Lactobacillus</i> acidophilus <i>Lactobacillus</i> bulgaricus	Dose: 2×10 <sup>8</sup> CFU/MI Duration: 7 Days Route: Orally	Human (Adults)	Reduce activity of Urease and Side Effects While Eradication Therapy	42
8	<i>Lactobacillus</i> reuteri <i>Lactobacillus</i> gasseri	Dose: 109CFU Duration: 81 Days Route: Orally	C57BL/6 Mice (6–13-Week-Old)	Modulation of mucosal inflammatory responses	45
9	<i>Lactobacillus</i> reuteri <i>Lactobacillus</i> gasseri, <i>Bifidobacterium</i> species	Dose: 109 CFU/MI Duration: 1-6 Days Route: Orally	BALB/C Mice (7-Week-Old) Rat	Inhibition of <i>H. pylori</i> adhesion to Mucus by Site Competition	(48)

Table 1 continued

10	<i>Lactobacillus reuteri</i> <i>Lactobacillus gasseri</i> And Other <i>Lactobacillus</i> Species	Dose: 5×10 <sup>9</sup> CFU/MI Duration: 4-17 Weeks Route: Orally	Gerbil (8 Weeks Old)	Increase expression of IL-10 and decrease TNF- $\alpha$ → ↑Eradication Rate, ↓Side Effects	46
11	<i>Lactobacillus casei</i> , <i>Lactobacillus acidophilus</i> , And <i>Bifidobacterium lactis</i>	Dose: Capsules Containing 7×10 <sup>9</sup> CFU Twice Daily Duration: 14 Days Route: Orally	Children	↑eradication rate of <i>H. pylori</i>	47
12	<i>Lactobacillus reuteri</i> <i>Lactobacillus gasseri</i>	Dose: 10 <sup>9</sup> CFU Duration: 24 Weeks Route: Orally	C57BL/6 Mice (6–8-Week-Old)	Producing bacteria delays growth and gastric colonization by <i>H. pylori</i> → eliminates <i>H. pylori</i> infection.	47
13	<i>Lactobacillus reuteri</i> <i>Lactobacillus gasseri</i>	Dose: 10 <sup>8</sup> CFU Duration: 6 Weeks Route: Orally	C57BL/6 Mice (5-Week-Old)	Inhibiting the binding of <i>H. pylori</i> and suppressing <i>H. pylori</i> induce IL-8 production → Suppress <i>H. pylori</i> viability.	47
14	<i>Lactobacillus gasseri</i>	Dose: 5×10 <sup>8</sup> CFU/G Cheese Duration: 1 Year Route: Orally Dose: 5×10 <sup>8</sup> CFU/G Duration: 2 Weeks Before Infection And Continuing For 1 Year After Infection Route: Orally	Human (Asymptomatic 5-7 Years Old) C57BL/6J Mice	Enhance a specific IgA production, suppress the progression of gastric MALT lymphoma, → Prevent and eradicate <i>H.</i> <i>pylori</i> .	47
91 15	<i>Lactobacillus plantarum</i>	Dose: 10 <sup>9</sup> CFU/MI Duration: 3 Weeks Route: Orally	Mice	Prevent the increase of inflammatory cytokines (IL-1 $\beta$ and IFN- $\gamma$ ) preventing gastric mucosal inflammation and gastric microbiota alteration	48
16	<i>Lactobacillus reuteri</i> <i>Lactobacillus gasseri</i>	Dose: 10 <sup>6</sup> CFU/MI Duration: 2 Weeks Route: Orally	C57BL/6 Mice (6–8-Week-Old)	Preventing and treating <i>H. pylori</i> Infection	26

## 2.6. Clinical/preclinical effect of probiotics in treating peptic ulcers caused by *H. pylori*

Probiotics are live microorganisms that confer a health benefit on the host when administered in adequate amounts. While they are commonly associated with promoting gut health and aiding digestion, their role in managing peptic ulcers has recently gained attention.<sup>49</sup> Probiotics have been investigated for their potential role in managing peptic ulcers through several mechanisms.

Various clinical and preclinical studies have recently been performed to establish the efficacy and safety of probiotics therapy in managing *H.pylori*-induced peptic ulcer; a few examples are cited in Table 1. One of the randomized clinical studies was performed in Xijing Hospital of Digestive Diseases, where triple therapy comprising *Clostridium butyricum* and *Bacillus coagulans*, esomeprazole, clarithromycin and amoxicillin, shows eradications of *H.pylori* in the peptic ulcer patients after six weeks.<sup>50</sup> Similarly, the efficacy of the combination of probiotics is comprised of *Lactobacillus rhamnosus* GG, *L. rhamnosus* LC705, and *Propionibacterium freudenreichii* ssp. *shermanii* JS and *Bifidobacterium breve* Bb99 against 39 *H.pylori*-infected patients, showing slight alteration of infection after nine weeks of treatment.<sup>51</sup>

As summarised in Table 1, Probiotics can be used as adjunct antibiotic therapy to treat *H. pylori*-induced ulcerations. They can manage the dysbiosis caused by antibiotic treatment and help reduce the side effects caused by it. Probiotic strains like *Bifidobacterium* and *Lactobacillus* improved antibiotic tolerability during *H. pylori* treatment and enabling the replenishment of normal flora post-treatment. Probiotics can also modulate the host's immune response by producing anti-inflammatory cytokines and promoting conditions that reduce inflammation, promote mucosal integrity and alleviate ulcer-related symptoms.

## 3. Conclusion

Although it is frequently asymptomatic, *H. pylori* is the most common bacterial infection in the modern world. Probiotics have been shown to reduce the frequency of *H. pylori* infections and inflammation in several investigations on animals and humans. It is essential to keep in mind that probiotics are still being investigated to see whether they can affect the treatment of *H. pylori*, and the findings of clinical research have been encouraging. It has been discovered in several studies that it is beneficial because it reduces the adverse effects of antibiotics or increases the rate at which they are removed. Regarding the treatment of *H. pylori*, it is essential to determine the types of probiotic supplements, the amounts that should be used, and the duration of the treatment. Therefore, probiotics could be recommended as a regular therapy plan because this supplement will increase the eradication rates and lessen the adverse effects of other

treatments.

## 4. Conflict of Interest

The authors declare there are no conflicts of interest.

## 5. Source of Funding

No financial support was received.

## 6. Acknowledgement

The authors are thankful to the authority of Siksha O Anusandhan, Deemed to be University, Bhubaneswar, for providing the necessary support and facilities for writing this article.

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**Cite this article:** Kar B, Biswaroy P, Dubey D, Rath G, Mishra D, Ghosh G, Rath S. The prospect of probiotics in *Helicobacter pylori*-induced peptic ulcer disease: A perspective review. *IP Int J Med Microbiol Trop Dis* 2024;10(2):87-94.