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Probiotic Role in Helicobacter Pylori Eradication

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Abstract

In this literature review, we evaluate the effectiveness of Lactobacillus reuteri in the treatment of peptic ulcer disease.Peptic ulcer refers to a group of ulcerative disorders of the upper gastrointestinal tract involving mainly the most proximal portion of the duodenum and the stomach, which have in common the participation of acid-pepsin in its pathogenesis. The most important risk factors are Helicobacter pylori (H. pylori) infection and the use of non-steroidal anti-inflammatory Gastric colonization with Helicobacter pylori has been reported in 90 to 95 percent of patients with duodenal ulcer and 60 to 70 percent of patient with gastric ulcer. Lactobacillus reuteri is considered as new beneficial therapy due to its probiotic effects on gastrointestinal system. The utilization of lactobacillus reuter alone for Helicobacter pylori infection significantly improves gastric mucosal inflammation and decreases the density of H. pylori on the mucosa, although complete eradication of H. pylori has not yet been demonstrated. The use of probiotics alongside of triple drug regimen or quadruple drug regimen , especially when the H. pylori strains are resistant to antimicrobial agents has significantly increased the H pylori eradication rate.

1. INTRODUCTION

Peptic ulcer disease continues to be a source of significant morbidity and mortality worldwide-[1] Considerable number of patients found to have peptic ulcer disease are asymptomatic-[2]. The most common presenting symptoms of peptic ulcer disease is epigastric pain, which may be associated with dyspepsia, bloating, abdominal fullness, nausea, or early satiety, bleeding and perforation with complicated disease. Most cases of peptic ulcer disease are associated with Helicobacter pylori-[3,4] H pylori is a spiral, gram-negative bacillus with multiple flagella with preference for a microaerophilic environment. H. pylori does not invade tissues-[5].

The organism resides in the mucus lining coating the epithelial celis, with a minor proportion of H. pylori directly adherent to the epithelial cells. H pylori being the important and modifiable factor associated with peptic ulcer-[6]. For the last two decades the regimen for H. pylori eradication has changed from triple to quadruple, the course of treatment has been extended, and the type and dose of antibiotics have been adjusted, with limited improvement in efficacy but gradually increasing side effects and repeated treatment failures in an increasing number of patients-[7]. In recent years, probiotics have become one of the most important tools for supporting intestinal health and immunity. The most used probiotic bacteria are Lactobacillus and Bifidobacterium Probiotics could improve H. pylori eradication and reduce side effects during therapy-[8]. Lactobacillus reuteri is able to inhibit the growth of several pathogenic bacteria through different mechanisms In particular, it is able to secrete reutericycline and Reuterin which exhibit antimicrobial properties, among other molecules. Through the secretions and the formation of the biofilm, it has been found to strongly inhibit the growth of Helicobacter pylori and at higher concentrations to kill it-[9] Various H. pylori eradication treatment regimens are used worldwide, with the standard treatment regimen varying with region and country owing to differences in drug availability and antimicrobial

resistance of H. pylori. Further, eradication of H. pylori is becoming increasingly challenging because of new issues including metabolic changes and gut microbiota changes after treatment-[10] Numerous in vitro studies, animal studies, and clinical observations have demonstrated that probiotics have the advantage of reducing side effects and increasing eradication rates in adjuvant anti-H. pylori therapy and are a valuable supplement to conventional therapy. However, many different types of probiotics are used as adjuncts against H. pylori, in various combinations, with different doses and timing, and the quality of clinical studies varies, making it difficult to standardize the results. In this paper, we focus on the risk, status, prevention, control, and treatment of H. pylori infection and review international consensus guidelines. We also summarize the available scientific evidence on using Limosilactobacillusreuteri (L. reuteri) as a critical probiotic for H. pylori treatment and discuss its clinical research and application from an evidence-based perspective.

2. Review

Helicobacterpylori (H. pylori) is a bacterium that infects more than half of the world's population. Moreover, the adequate clinical management by means of proper diagnosis and effective treatment is crucial for reaching success in bacterial eradication. This article aims to provide a broad overview of H. pylori infection, from pathogenesis to clinical management.

3. Pathogenesis, Clinical Manifestations and Diagnosis of H Pylori

H. pylori successful colonization in gastric habitat requires special mechanisms. Primaryly, after reaching the stomach, H. pylori uses its essential flagellar motility for movement in gastric content, what allows the bacterium to get in the gastric mucus layer. Four to eight sheathed flagella compose the flagellar group situated on a single or on both poles of the bacterium-[11]. The activity of H. pylori urease contributes to the colonization of the microorganism, once this enzyme catalyzes the hydrolysis of urea to carbon dioxide and ammonia, which are buffer substances that attenuate the acidity of the stomach environment In turn, hydrogenase is part of a signaling cascade that induces an alternative airway, allowing H. pylori to use molecular hydrogen as a source of energy for its metabolism-[11] The cell subsequently moves towards the gastric epithelium using its flagella-mediated motility. H. pylori adhesins further interact with the host cell receptors leading to successful colonization and persistent infection. Upon successful colonization, H. pylori produce several effector proteins/toxins responsible for damage to the host tissues. During the infection, the secreted chemokines trigger innate immunity.

There is also the activation of neutrophils and subsequent clinical manifestation-[12]. After H. pylori enters the host stomach, four steps are critical for bacteria to establish successful colonization, persistent infection, and disease pathogenesis: (1) Survival in the acidic stomach; (2) movement toward epithelium cells by flagella-mediated motility; (3) attachment to host cells by adhesions/receptors interaction; (4) causing tissue damage by toxin release-[13]. H pylori virulence factors for successful colonization in gastric mucosa include acid neutralization factors, epithelial cell colonizing factors, epithelial cell pathogenicity factors as shown in the figure [1]

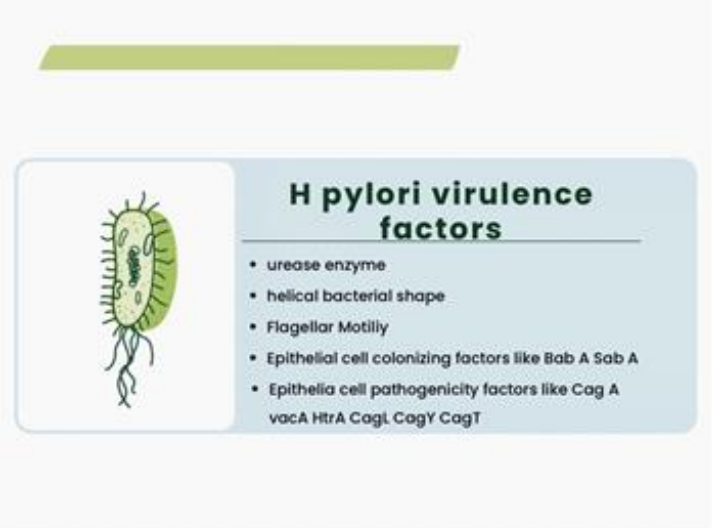

Figure 1. *Helicobacter pylori virulence factors*

The mucus layer that overlies the epithelial cells in the gastrointestinal tract is a physical barrier which acts to prevent pathogens from colonizing and interacting with the underlying epithelium. Pathogens which infect mucosal surfaces share two main goals: (1) to overcome the mucus barrier; and (2) to interact with the underlying epithelial cells which results in disease-[14]

The ability of H. pylori to utilize urea to raise the pH in its microenvironment modifies mucus so that it is less gel-like, enabling the bacterium to move quickly through it, The production of urease in 10% of bacterial proteomes enables it to hydrolyze large amounts of gastric urea to generate ammonia and CO2, causing a sharp increase in the pH around H. pylori, Thus, H. pylori would not survive in the stomach without its potential to escape high acidity which is not observed in any other H. pylori can transiently enter the intracellular space for a short time to reduce exposure duration to antibiotics, acidic conditions and the immune response. Moreover, as H. pylori is optimally evolved to reduce its exposure to acidic gastric conditions, it can localize in mucus close to the epithelial surface where acidity is tolerable for longer survival.

This strategy adopted by the microbe further highlights the importance of research in finding effective antibiotics to treat this organism-[15]. Clinical manifestations include, dyspepsia and peptic ulcer disease are frequently observed in clinical practice, symptoms of symptomatic PUD includes epigastric pain, bloating, nausea abdominal fullness, early satiety-[16]. recent studies have associated H. pylori infection with a wide range of diseases. The infection was linked with the pathophysiology of neurological, dermatological, hematologic, cardiovascular, ocular, metabolic, hepatobiliary and allergic diseases-[17]. There are several invasive and non-invasive diagnostic tests to detect H. pylori infection. Invasive tests include endoscopic biopsy specimen for histology, culture and rapid urease test (RUT) and polymerase chain reaction (PCR). Non-invasive tests consist of urea breath test (UBT), serum antibody test, stool antigen test, saliva antibody test and urinary antibody test the choice of diagnostic tests is based on the prevalence of H. pylori infection, the availability and cost of the diagnostic tests, and patient-related characteristics. Various diagnostic tests, with their specific advantages and disadvantages, are offered for H. pylori detection. Histology is the precursor method for H. pylori infection diagnosis, which, in such a technique, consists in the observation of typical bacteria associated with inflammatory reactions in the tissue slides. This method includes the use of several stains, such as Giemsa staining, and immunostaining to allow pathogen detection-[18]. Another important H. pylori diagnostic method, the rapid urease test (RUT), The RUT is an indirect test of the presence of H. pylori based on the presence of urease in or on the gastric mucosa It detects an increase in reagent pH after the addition of a biopsy specimen containing H. pylori to the reagent. Such pH variation is caused by the conversion of the urea test reagent into ammonia-[19]. RUT is a relatively cheap, quick, easy, specific and widely available test. The RUT is based on detecting urea produced by H. pylori, and results are obtained within minutes to hours-[20]. Polymerase chain reaction (PCR) has also been applied for H. pylori detection. H. pylori DNA present in clinical biopsy samples and to develop a specific and sensitive PCR by use of primers based on the sequences of the H. pylori urease genes. PCR amplification of H. pylori DNA sequences has the potential to be a rapid and highly sensitive and specific method for the laboratory diagnosis of H. pylori infection. The technique could be used to quickly predict a relapse of infection-[21].However, the necessity of endoscopy is an important limitation of the three methods mentioned above, and the advances in non-invasive diagnostic techniques have strengthened the idea of prioritizing the use of diagnostic alternatives for which endoscopy is dispensable. The urea breath test (UBT) is now the main non-invasive method for such a diagnosis, gradually taking the place of RUT as the most suitable method for H. pylori detection. This test is based on the mechanism of bacterium degradation of 13C or 14C-labeled urea into CO2, which can be measured in the exhaled air using a mass or infrared spectrometer-[22]. A less expensive option for UBT, stool antigen tests (SATs), are good alternatives for H. pylori diagnosis. SATs can be made by means of enzyme immunoassay or immuno-chromatography. H. pylori antigen in stool specimens has been detected successfully for the first time in 1997. Using polyclonal antibodies, the sensitivity and specificity have been found to be 88.8% and 94.5% respectively. The advantage of antigen detection test is to evaluate the eradication of H. pylori infection. However, if concentration of antigen becomes low, false negativity may also be reported. Perri et al compared the performance of antigen detection vs UBT in 458 dyspeptic patient and reported discrepancy in 8% of the case. They suggested that antigen detection was less accurate than UBT

Later a new generation of stool antigen kits has been developed using monoclonal antibodies giving comparable accuracy as that of UBT-[23]. There is no gold standard for diagnosis of H pylori infection and the diagnosis is made by a combination of tests following endoscopic biopsy. Endoscopic biopsy followed by rapid urease testing has poor sensitivity following treatment with proton pump inhibitors. Endoscopic biopsy with culture has high specificity but poor sensitivity. We therefore considered only endoscopic biopsy followed by histology (using haemotoxylin and eosin (H & E) stain, special histological stains such as Giemsa stain and Warthin-Starry stain, or immunohistochemical stain) as the reference standard in this review. We considered endoscopic biopsy with histology using immunohistochemical stain as the best reference standard, and endoscopic biopsy with histology using H & E stain as the worst reference standard-[24]

4. Treatment Modalities for H pylori Eradication

First- line treatment -Increasing clarithromycin resistance leads to reduce the eradication rate of clarithromycin-containing triple therapy, which contains amoxicillin, clarithromycin, PPI. 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. Second-line therapy-Levofloxacin triple therapy and bismuth quadruple therapy are considered as two well-known therapeutic strategies against H. pylori infection. Levofloxacin-containing regimen contains a PPIs plus levofloxacin and amoxicillin.

Third line treatment-Bismuth based levofloxacin quadruple therapy or rifabutin triple therapy (a PPI, rifabutin, and amoxicillin) are used as alternative empiric treatments, Depending on the mode of administration-[25].

Bismuth-Quadruple therapy -The classic bismuth quadruple regimen, which dates back to 1995 and consists of PPI, bismuth, tetracycline, and metronidazole, was established before the clarithromycin triple regimen. As clarithromycin triplet was the first-line regimen at that time, bismuth quadruplet was used only as a remedial treatment. As the rate of H. pylori resistance to clarithromycin increased, the efficacy of the clarithromycin triplet regimen declined, and bismuth quadruple therapy was relegated to first-line treatment. Bismuth increases the eradication rate of H. pylori resistant strains by 30% to 40%. Despite the high resistance rates of clarithromycin, metronidazole, and levofloxacin, adding bismuth to triple regimens containing these agents has resulted in Non-Bismuth Quadruple regimen-Non-Bismuth Quadruple regimen can be divided into sequential therapy (PPI + amoxicillin for the first 5 or 7 days and PPI + clarithromycin + metronidazole for the second 5 or 7 days), concomitant therapy (4 drugs for 10 or 14 days), and mixed therapy (same as sequential therapy for the first 5 or 7 days and concomitant therapy for the second 5 or 7 days). Of these regimens, concomitant therapy with 3 antibiotics is the most effective in overcoming antibiotic resistance and therefore has the best relative efficacy but also has a correspondingly higher side effect profile. Because sequential therapies are vulnerable to single resistance to clarithromycin or metronidazole, when both clarithromycin and metronidazole become resistant, non-bismuth quadruple therapy effectively becomes PPI plus amoxicillin two-component therapy, and eradication rates for sequential, mixed, and concomitant therapy are all reduced-[26] figure 2 demonstrates the treatment modalities in H pylori eradication.

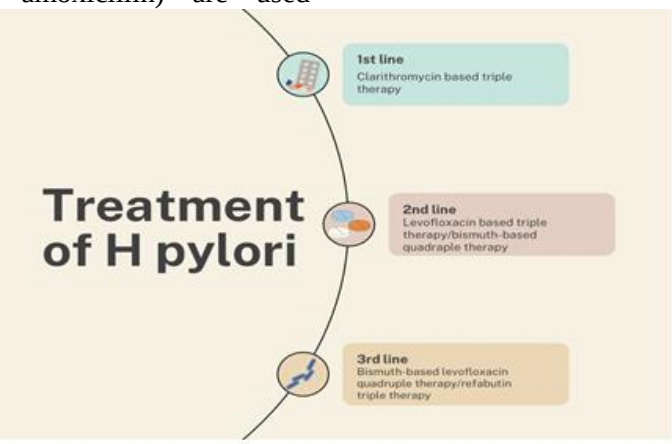

Figure 2. *Management options for H pylori*

5. PROBIOTICS INTERVENTION IN H PYLORI ERADICATION

Probiotic bacteria have positive effect on host when given in appropriate proportion and effective when given through antibiotic based therapy-[27]. Lactobacillus reuteri is a well-studied probiotic which produce lactic acid with known cholesterol-lowering effects and anti-inflammatory properties-[28] With Recent advances in treatment modalities probiotics are widely used to prevent and treat numerous gastrointestinal disorders. Among many probiotics available in the market Lactobacillus reuteri meets all the criteria to be considered well-tolerated, safe and efficacious probiotic that is able to contribute to the beneficial effects on gut health, preventing and treating many gastrointestinal symptoms, and speeding up the recovery-[29] In this literature there are reports of efficacy of probiotics in H pylori eradication there are also reports providing evidence on how probiotic can over all be Benificial for gut health-[30]. Probiotics, particularly Lactobacillus reuteri DSM 17938 (LR), have been shown to exhibit anti-inflammatory properties, as demonstrated in a study by Yuying Liu and colleagues. In their research, LR was administered to healthy breastfed mice, promoting intestinal immune tolerance and fostering the proliferation of beneficial gut microbiota. This probiotic strain up regulates plasma metabolites involved in the TCA cycle methionine methylation, the urea cycle, and the polyamine pathway. Notably, Lactobacillus reuteri administration in newborn mice specifically increases levels of tryptophan metabolites and the purine nucleoside adenosine, which are known to enhance tolerance to inflammatory stimuli-[31]. various properties of probiotics shown in figure 3.

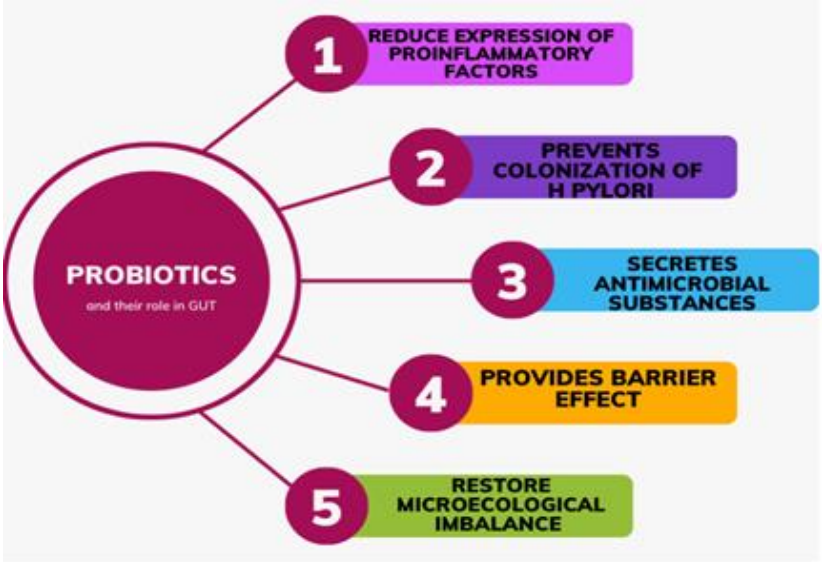

Figure 3. *Properties of probiotics*

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-[32] In addition to its anti-inflammatory properties, Lactobacillus reuteri has been shown to possess antioxidant properties. Studies on piglets have demonstrated that strain-specific L. reuteri administered to these animals colonizes the intestinal mucosa and enhances the cecal microbiota profile. This supplementation improves the whole-body antioxidant and immune status, resulting in better growth, and reduced morbidity and mortality rates. L. reuteri supplementation also enhances body antioxidant status and immune function compared to control animals-[33].Lactobacillus reuteri also improves the barrier function of the gut by enhancing the intestinal microbial community in pigs. A study investigating the expression of tight junction (TJ) genes using q-PCR revealed that the mRNA levels of occludin and zonulaoccludens (ZO-1) were significantly increased in the antibiotic group (AO) at 14 days compared with other groups ($p < 0.05$). At 164 days, the expression of ZO-1 and occludin was significantly higher in the Lactobacillus reuteri (LR) group compared to the AO group ($p < 0.05$).

Additionally, the expression levels of mRNA for mucin1 (MUC1) and mucin2 (MUC2) were significantly increased in the LR group on day 164 compared to other groups ($p < 0.05$). Furthermore, the mRNA levels of protegrin (PG1-5) and porcine antibacterial peptide β-Defensin-2 (pBD2) were significantly increased

in the AO group ($p < 0.05$). However, the levels of PG1-5 and pBD2 were even more significantly increased in the LR group compared to the AO group ($p < 0.05$) - [34]. Lactobacillus reuteri* demonstrates several notable capabilities. It can hydrolyze urea and survive in the acidic pH of the stomach. The presence of L. reuteriinhibits the survival of other pathogenic bacteria such as *E. coli*. Rodent strains of L. reuteri have the capacity to adhere to and proliferate on the epithelial surface of the fore stomach, forming an epithelium-associated biofilm. This biofilm formation is also observed in the anterior digestive tract of birds-[35].Lactobacillus reuteri LB1-7, a strain isolated from raw bovine milk, produces hydroxypropionaldehyde (HPA), an antimicrobial compound, during the anaerobic reduction of glycerol under strict anaerobic conditions. This compound exhibits antimicrobial activity against the enterohemorrhagicEscherichia coli (EHEC) strain FCH6, with the activity of EHEC being completely suppressed when inoculated with

L. reuteri LB1-7-[36].Adhesion plays a crucial role in the outcome of H. pylori associated diseases, occurring through multiple bacterial surfaces interacting with the epithelial surface of the host. Among nine *Lactobacillus reuteri* strains, two—JCM 1081 and TM 105—were able to bind to asialo-GM1 and sulphatide. These strains also inhibited the binding of *H. pylori* to both glycolipids, as observed in animal models-[37].Probiotics are beneficial non-pathogenic living bacteria that provide health advantages to the host, such as anti-oxidative and anti-inflammatory effects, which may help prevent intestinal infections, cancer, and cardiovascular disease. Numerous studies have shown that specific Lactobacillus strains, including Lactobacillus GG, Lactobacillus acidophilus, and Lactobacillus reuteri (L. reuteri), have properties that combat H. pylori. Several clinical trials have incorporated these probiotics into standard treatments to reduce adverse effects, enhance drug compliance, and improve eradication rates-[38]. L. reuteri supplementation could reduce the frequency and intensity of antibiotic-associated side effects. In a study, H. pylori infection was diagnosed in 90 adult dyspeptic patients, 83 of whom completed the study. The sequential treatment regimen achieved a significantly higher eradication rate of H. pylori compared to the standard 7-day triple therapy, which includes a proton pump inhibitor (PPI) plus clarithromycin and amoxicillin or metronidazole. There was a low incidence of adverse effects in all groups receiving sequential therapy, which consisted of a 5-day PPI plus amoxicillin regimen followed by a 5-day regimen of PPI, clarithromycin, and tinidazole, supplemented with L. reuteri during antibiotic treatment. This reduced incidence of adverse effects is likely due to the L. reuteri supplementation-[39]. There are numerous treatment options for curing H. pylori infection and many are still under investigation. The eradication rate of H. pylori following 7-d triple treatment [proton pump inhibitor (PPI) plus clarithromycin and amoxicillin or metronidazole] is decreasing due to an increasing prevalence of bacterial resistance, poor patient compliance and the occurrence of antibiotic adverse effects-[40]. The eradication of H. pylori infection using PPIs in combination with various antibiotics involves high risks of side effects and poor patient adherence. Therefore, probiotics have been proposed as a treatment option for H. pylori infection. They have been proven effective in reducing antibiotic side effects and improving patient compliance. Strains of Lactobacillus reuteri (L. reuteri) have demonstrated an inhibitory effect on the colonization of human gastric mucosa by H. pylori. L. reuteri can produce reuterin, a broad-spectrum antibiotic active against H. pylori. The L. reuteri strain DSMZ 17648 was tested for antibiotic resistance, and no resistance was found-[41].The efficacy of probiotics in the prevention and treatment of gastrointestinal diseases has garnered considerable attention in recent years. In Western countries, there has been an increase in gut-related health issues, such as autoimmune and inflammatory diseases. Changes in gut flora have emerged as a significant factor in the rising prevalence of certain gastrointestinal diseases. Due to improved hygiene and nutrition, the Western diet contains far fewer bacteria than pre-industrial diets. This reduction is partly due to the consumption of processed and sterile foods with preservatives, rather than fresh fruits, vegetables, or foods containing important microbes for anti-inflammatory processes. Probiotics—products or preparations containing sufficient amounts of viable microorganisms to alter a host's gut microbiota—are believed to exert beneficial effects by providing protective barriers, enhancing immune responses, and clearing pathogens from the gastrointestinal tract-[42]. Currently, probiotics are widely utilized to prevent and treat numerous gastrointestinal disorders. Among the various probiotics available, L. reuteri stands out as well-tolerated,

safe, and effective. It contributes to gut health, helps prevent and treat various gastrointestinal symptoms, and accelerates recovery-[43]. The inhibition of H. pylori by the two L. reuteri strains is likely due to their production of reuterin, a powerful antimicrobial agent effective against both Gram-positive and Gram-negative bacteria. L. reuteri also produces other strong antimicrobial compounds, such as reutericin 6 and reutericyclin, though these do not impact Gram-negative bacteria. Regardless of the exact source of this inhibitory activity, using these human stomach-derived L. reuteri strains as probiotics to protect against H. pylori infection should be considered. While L. gasseri is more common in the gastric ecosystem than L. reuteri, the latter strains show more probiotic-relevant properties and higher activity levels. The antimicrobial, especially anti-H. pylori, activity of L. reuteri strains, along with their antioxidative effects, may help protect the gastric mucosa from infection and damage. These L. reuteri strains also exhibit technological traits that make them suitable for inclusion in fermented dairy products- [44]. Between 1950 and 1960, L. reuteri was frequently identified in studies as part of the human gut microbiota, but its presence has significantly diminished in modern times. This decline suggests that environmental changes linked to contemporary lifestyles—such as antibiotic use, hygiene practices, and dietary shifts—may have displaced L. reuteri from its previous role as a predominant gut microbe, a phenomenon noted for other microbiota members as well. Recent research has underscored this notion, highlighting L. reuteri as a dominant component of the microbiota in rural Papua New Guineans, contrasting with its reduced prevalence in modern human populations. In contrast, L. reuteri remains a crucial and abundant Lactobacillus species within the gut microbiota of pigs, indicating its symbiotic relationship in this species-[45]. However, there remains ambiguity regarding the clinical application of L. reuteri, underscoring the importance of understanding its underlying mechanisms in promoting gut health. The effects of L. reuteri on gastrointestinal (GI) diseases may involve maintaining gut barrier function, suppressing pro-inflammatory substances, modulating the gut microbiota, and producing metabolites. This review explores the potential application of L. reuteri in digestive system diseases and outlines its mechanisms. L. reuteri has been shown to inhibit the early colonization stages of H. pylori in the human GI tract by suppressing the binding of H. pylori to glycolipid receptor molecules. Additionally, L. reuteri produces reuterin, an antibiotic that targets H. pylori, thereby reducing H. pylori load. Moreover, recent research has demonstrated that L. reuteri 2892 attenuates H. pylori-induced gastritis through its anti-inflammatory and antioxidative stress properties, as well as by suppressing the gene expression of the virulence factor CagA-[46].SCFAs synthesized by L. reuteri demonstrate direct anti-tumor properties-[47]. L reuteri DSMZ17648 specifically forms aggregates with H. pylori in vitro and in artificial gastric juice, without affecting other bacteria in the normal intestinal flora. This binding process potentially masks surface structures of H. pylori and disrupts its motility. As a result, the aggregated pathogens may lose their ability to adhere to the gastric mucosa and are subsequently cleared from the stomach. An additional mode of action of L reuteri may be competition for specific binding-[48] In a study, oral administration of Lactobacillus reuteri strain DSM17938, in combination with pantoprazole twice daily for 8 weeks, significantly reduced the urease breath test-[49] it is suggested that Lactobacillus reuteri DSM17648 disrupts the mobility of H. pylori and its adherence to the gastric mucosa by forming cell aggregates that mask the surface sites normally used for binding to human epithelium. Once bound, these co-aggregates are expelled from the stomach through natural bowel movements. Additionally, Lactobacillus reuteri strain ATCC55730 has been shown to inhibit H. pylori-associated urease activity-[50].Table 1 demonstrates the various experimental studies and the conclusions

Table 1. *Experimental studies showing L. reuteri application for H pylori eradication*

Author of Study	Year of Publication	No of Subjects Involved	Focused Sub-Topc	Study Results
Mohammed H Emara-et al-[39]	2014	70	Lactobacillus reuteri in management of Helicobacter pylori infection in dyspeptic patients: a double-blind	Supplementing H. pylori triple therapy with Lactobacillus reuteri increased the eradication rate by 8.6%, improved the Gastrointestinal Symptom Rating Scale (GSRS) score, reduced reported side

			placebo-controlled randomized clinical trial	effects, and enhanced the histological features of H. pylori infection compared to triple therapy with a placebo.
HeidrenMehling-et al[48]	2013	22	Non-Viable Lactobacillus reuteri DSMZ 17648 (Pylopass™) as a New Approach to Helicobacter pylori Control in Humans	Lactobacillus reuteri DSMZ17648 may also be beneficial in populations with high H. pylori prevalence where compliance with antibiotic therapy is low due to cost. Compared to living probiotic cells, dead cells offer advantages such as easier storage and delivery, prolonged shelf life, and reduced production costs. These characteristics suggest that using dead cells could be a practical new approach to controlling H. pylori.
Angela savlano et al-[43]	2021	86	Lactobacillus Reuteri DSM 17938 *(Limosilactobacillusreuteri)* in Diarrhea and Constipation:	Lactobacillus reuteri meets all the necessary criteria to provide beneficial effects on human gut health, even in emergency settings.
Iulia Antonia Pop Muresan et al -[41]	2019	46	46 study subject assigned to test theefficacy of *Lactobacillus reuteri* plus Pantoprazole compared to a triple regimen based on Pantoprazole plus Amoxicillin plus Clarithromycin in patients with *H. pylori* infection and functional dyspepsia	Lactobacillus reuteri is a viable alternative for patients with chronic dyspepsia in eradicating H. pylori infection, offering efficacy comparable to triple therapy.
Cesare Efrati et al [40]	2012	90	Experimental study conducted on 90 patients with H pylori to compare between sequential and standard regimen.	The sequential treatment regimen achieved a significantly higher H. pylori eradication rate compared to the standard 7-day regimen. Lactobacillus reuteri supplementation can reduce the frequency and severity of antibiotic-associated side effects. The eradication rate was significantly higher in the sequential group compared with the 7-d triple regimen (88% vs 63%, P = 0.01)

6. Conclusion

The standard triple regimens containing two antimicrobial agents have seen a decrease in efficacy due to rising macrolide resistance, particularly to clarithromycin. Given the resistance issues, alternative therapies are being explored, including - Bismuth quadruple therapy, Sequential therapy, Hybrid therapy. Levofloxacin-based Regimens should be considered as a second-line treatment option due to the rapid development of quinolone resistance. While probiotics alone are not recommended for eradication therapy, their use alongside standard treatment can enhance eradication rates and reduce treatment-related side effects. This shift in treatment strategies reflects the need to adapt to evolving resistance patterns and optimize therapeutic outcomes for H. pylori infection. The microbiota and their metabolites play pivotal roles in H pylori eradication by affecting intestinal permeability and the immune response.

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