VOLUME - 10, ISSUE - 08, AUGUST- 2021 • PRINT ISSN No. 2277 - 8160 • DOI : 10.36106/gjra

Original Research Paper

Medical Science

EFFICACY OF PROBIOTICS IN *HELICOBACTER PYLORI* ERADICATION THERAPY: A SYSTEMATIC REVIEW

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ABSTRACT *Helicobacter pylori is a Gram-negative bacillus that selectively colonizes the gastric epithelium. In most people, the infection is asymptomatic. However, it is considered the main cause of active chronic gastritis and plays an important role in peptic ulcer, as well as in the genesis of gastric adenocarcinoma and Mucosa-Associated Lymphoid Tissue (MALT) lymphoma.* The aim of this systematic review study is to check the efficacy of probiotics in the *H. pylori* eradication therapy and a decrease in the treatment adverse effects. The most relevant studies in the MedLine databases via PubMed were reviewed, and only clinical trials in English were considered. The search strategy used the following combinations of keywords: *("Helicobacter pylori" OR "H. pylori") AND probiotics*. The following terms were used to identify the study designs: *Clinical Trial, English*. Ten articles were included in the scope of this review, showing controversies in the outcomes regarding the use of probiotics in the *H. pylori* eradication therapy, but with good efficacy in decreasing adverse symptoms. It can be concluded that there is still a lack of consistent scientific evidence for the use of probiotics in the *H. pylori* eradication therapy. However, the reviewed studies showed an improvement in the eradication rate when probiotics were combined with the therapy and a decrease in the treatment adverse effects.

KEYWORDS : Helicobacter pylori, probiotics, therapy, eradication.

INTRODUCTION

Helicobacter pylori is a Gram-negative bacillus that selectively colonizes the gastric epithelium,[1] and which was first identified in 1983 by Marshall & Warren.[2] *In most people, the infection is asymptomatic.*[2,3] *However, it is considered the main cause of active chronic gastritis and plays an important role in peptic ulcer, as well as in the genesis of gastric adenocarcinoma and Mucosa-Associated Lymphoid Tissue (MALT) lymphoma.*[2,3] In 1994, it was classified as a Class I carcinogen for gastric adenocarcinoma by the International Agency for Research on Cancer (IARC) and also by the World Health Organization (WHO).[4-6]

In most cases, *H. pylori* is acquired in the family environment by the oral-oral and fecal-oral route during the first five years of life.[1] The prevalence of *H. pylori* varies widely among countries, and it is estimated that 50% of the world's population is infected with this microorganism. In developing countries, the prevalence of this infection in the general population ranges between 60-90%, while in developed countries it ranges between 25-50%, confirming that socioeconomic status and sanitation are risk factors for *H. pylori*.[1] In Brazil, the prevalence of the *H. pylori* infection can be as high as 90% in poorer areas.[5]

The detection of *H. pylori* includes invasive tests (gastroscopy by collecting gastric fragments for histology, culture, urease test, or molecular tests) and non-invasive tests (serological tests, stool antigen, and urea breath test). The urea breath test is the gold standard method for the diagnosis of *H. pylori*, with a >95% sensitivity and specificity.

Currently, the recommended treatment scheme for *H. pylori* eradication worldwide includes a proton pump inhibitor (PPI) and two types of antimicrobials. For a first-line treatment, amoxicillin and clarithromycin are used more frequently, while amoxicillin and levofloxacin are used as a second-line scheme.[1] However, the efficacy of this therapy has dramatically decreased in the last decade, mainly due to the increased rates of clarithromycin resistance worldwide, decreased affinity of the macrolide with the 50S subunit of the bacterial ribosome due to point mutations in the nucleotides adjacent to the V-domain of the 23S rRNA[1,4] gene, and low treatment compliance.

In this context, probiotics have gained a scientific interest in recent years as an adjuvant in *H. pylori* eradication therapy.[7] Probiotics are living microorganisms that have a beneficial effect on the host[8]. Multiple benefits have been described for probiotics, including the synthesis of antimicrobial substances (fatty acids, ammonia, hydrogen peroxide, and bacteriocins), a competitive interaction with pathogens for adhesion receptors and immunomodulation (microbiota modulation).[6-8] In addition, probiotics stabilize the gut

microbiota, reducing the frequency of adverse effects of antibiotics and, consequently, increasing patient compliance, and decreasing the risk of resistant strains.[9] The most commonly used and most widely studied probiotics in the clinical practice are *Lactobacillus* spp, *Biffidobacterium* spp., and *Saccharomyces boulardii*.[6,8]

In view of the above, the purpose of this study was to use a systematic review to check whether there is any improvement in the *H. pylori* eradication rate with the adjuvant use of probiotics, either by direct action or by minimizing the adverse effects of antibiotics, which would lead to less treatment discontinuation and less risk of antibiotic-resistant strains.

METHODS

The most relevant studies originally published in English were reviewed using the *National Library of Medicine* and *National Institutes of Health* (MedLine via PubMed) databases as references. Only clinical trials were considered in order to select studies with greater scientific evidence.

The search strategy used the following keywords: "*Helicobacter pylori*"; "*probiotics*". The following terms were used to identify the study designs: *clinical trial, English*. The inclusion and exclusion criteria were applied based on the types of studies, language, type of therapy, and patient age considering the points in each of the foregoing items (Chart 1). The inclusion and exclusion criteria shown in Chart 1 were applied in selecting the studies.

Chart 1.Inclusion and exclusion criteria applied in the selection of studies

Inclusion criteria	
Design	• Clinical trials
Patients	• *H. pylori* positive • Adults
Intervention	• *H. pylori* eradication therapy with the use of probiotics
Language	• English
Exclusion criteria	
Design	• Case reports and case series
Intervention	• Unclear, poorly described, or inadequate interventions
Form of publication	• In abstract only
Main clinical outcomes	
• Effects of probiotics on the eradication of *H. pylori* (increase in eradication rate and decrease in adverse effects)	

RESULTS

Eighty studies were initially identified involving the use of probiotics in the treatment of *H. pylori*. Next, sixteen articles were identified by applying the "*clinical trial*" and "*English*" criteria. After reviewing the studies and excluding by their abstracts, ten articles were selected involving the subject of analysis and included in the scope of this review (Fig. 1).

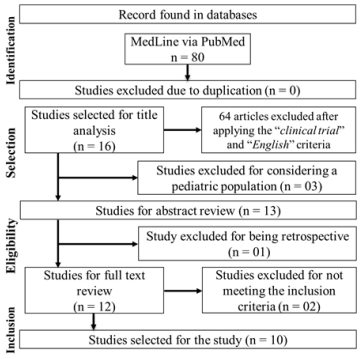

Figure 1. Study Selection Process Flowchart

Table 1 shows a summary of the studies selected and reviewed for this study. Table 2 shows the eradication rates and the treatment adverse effects.

Table 1. Synthesis of studies involving the use of probiotics in the treatment of H. *pylori*.

Author/year	Sample	Method/Intervention	Results
Hauser et al.[9]	n = 804 Age >18	Multicenter, prospective, randomized, placebo-controlled and double-blind. PbG (n = 333): TT + Pb; PcG (n =3 17): TT + placebo	Eradication rate: PbG (87.38%) > PcG (72.55%). The addition of Pb to TT has significantly contributed to the efficacy of the treatment and has distinctly decreased the adverse effects of the therapy and the symptoms of the underlying disease. Symptoms related to antibiotic therapy: PcG (0.76) > PbG (0.55); p < 0.001.
Oh et al.[10]	n = 23. With gastric or duodenal ulcers. Mean age: AtbG = 49.3 ± 3.56 years; PbG = 51.7 ± 4.79 years	AtbG (n = 10): TT PbG (n = 10): TT + Pb	Resistant bacteria AtbG > PbG. The use of Pb can restrict the growth of antibiotic-resistant bacteria in the intestine and improve the success rate of *H. Pylori* eradication.
Du et al.[11]	n = 234 Age 18-65	G1 (n = 78): TT p/day; G2 (n = 76): Pre-treatment with probiotics + TT; G3 (n = 74): Post-treatment with Pb + TT	Eradication rate: G1 (60.8%) < G2 (79.5%) and G3 (79.2%). The administration of Pb before or after the standard TT can improve *H. pylori* eradication rates.
Manfredi et al.[12]	n = 238; Mean age: GA = 50.6 years (18-75 years); GB = 48.2 years (18-84 years); GC = 46.4 (18-75 years)	GA (n = 76): TT + placebo; GB (n = 78): ST + LF + Pb; GC (n = 73): ST + Pb	Eradication rate: GA = GB = GC. Adverse symptoms: GA > GB and GC. There was no statistically significant difference in treatment compliance between GB and CG.
Yasar et al.[13]	n = 76; Exclusion criteria: Age < 18	GA (n = 38): TT + Pb GB (n = 38): TT	*H. pylori* eradication GA = 66% and GB = 53%; non-significant difference (p = 0.350). The addition of Pb to TT significantly reduced the frequency of stomatitis and constipation (p = 0.037 and p = 0.046, respectively).
Kim et al.[14]	n = 347; 03/2006-02/2007; Exclusion criteria: Age < 18 and > 85	G1 (n = 168): TT + yogurt; G2 (n = 179): TT	Eradication rates (ITT): G1 (79.2%) = G2 (72.1%); p = 0.124 Eradication rates (PP): G1 (87.5%) > G2 (78.7%); p = 0.037. Adverse effects: G1 (41.1%) > G2 (26.3%); p = 0.003. The addition of yogurt did not reduce the side effects of TT.

Probiotics group (PbG); Placebo group (PcG); Antibiotics group (AtbG); Group 1 (G1); Group 2 (G2); Group 3 (G3); Group A (GA); Group B (GB); Group C (GC); Triple therapy (TT); Probiotics (Pb); Sequential therapy (ST); Lactoferrin (LF); intention-to-treat (ITT) analysis; Per-protocol (PP) analysis; percentage (%); greater than (>); equal to (=); less than (<); standard deviation ( ); plus (+).

Table 1. Synthesis of studies involving the use of probiotics in the treatment of H. *pylori*.

Author/year	Sample	Method/Intervention	Results
de Bortoli et al.[15]	n = 206; 10/2003-11/2005; Mean age: GA = 50.1 ± 15.2 years; GB = 51.5 ± 13.7 years	GA (n = 96): TT; GB (n = 101): TT + Pb + LF	Eradication rate (ITT): GA (72.3%) < GB (88.6%); p = 0.005. Eradication rate (PP): GA (76%) < GB (92.1%); p = 0.004. Adverse effects: GA (40.6%) > GB (9.5%); p < 0.005. LF + Pb could improve the standard for *H. pylori* eradication therapy; LF increasing the eradication rate and Pb reducing the side effects of antibiotic therapy.
Grgov et al.[16]	n = 167; Mean age: G1 = 56.2 ± 14.8 (21-80 years) G2 = 56.3 ± 14.8 (20-82 years)	G1 (n = 77): TT; G2 (n = 90): TT + Pb	Eradication rate: G1 (81.8%) < G2 (93.3%); p < 0.05. Adverse effects: G1 (28.6%) > G2 (17.7%); non-significant difference.
Scaccianoce et al.[17]	n = 65; 19-71 years Mean age: G1 = 48 years; G2 = 51 years; G3 = 50 years; G4 = 52 years	G1 (n = 15): TT/7 days; G2 (n = 17): TT/7 days + *L. reuteri*; G3 (n = 15): TT/7 days + Pb mixture; G4 (n = 15): TT/14 days + Pb	No therapy scheme has reached an eradication rate > 80%. Eradication rate (ITT): G2 (53%) = G3 (53%) < G1 (62%) < G4 (71%). Eradication rate (PP): G2 (53%) = G3 (53%) < G1 (67%) < G4 (80%). G4 > eradication rate (non-significant difference). G2 < adverse effects (non-significant difference).
Park et al.[18]	n = 352	G1: TT + Pb; G2: TT	Eradication rate: G1 (83.5%) > G2 (73.3%); p = 0.027. Adverse effects: G2 > G1; p < 0.05.

Group 1 (G1); Group 2 (G2); Group 3 (G3); Group 4 (G4); Group A (GA); Group B (GB); Group C (GC); Triple therapy (TT); Probiotics (Pb); Lactoferrin (LF); Intention-to-treat (ITT) analysis; Per-protocol (PP) analysis; percentage (%); greater than (>); equal to (=); less than (<); standard deviation ( ); plus (+).

Table 2. Eradication rates and treatment adverse effects

Article	Eradication rate	Significance	Adverse effects of antibiotics	Significance
Hauser et al.[9]	PbG (87.38%) > PcG (72.55%)	p < 0.001	PcG (0.76) > PbG (0.55)	p < 0.001
Oh et al.[10]	PbG (100%) > AtbG (90%)	p > 0.05	PbG (50%) > AtbG (40%)	p > 0.05
Du et al.[11]	G2 (79.5%) = G3 (79.2%) > G1 (60.8%)	p < 0.05	G3 (89.2%) = G1 (87.2%) = G2 (85.5%)	p > 0.05
Manfredi et al.[12]	GA = GC = GB	p > 0.05	GA > GC and GB	p < 0.001
Yasar et al.[13]	GA (66%) > GB (53%)	p = 0.350	GA < GB	p < 0.05
Kim et al.[14]	G1 (79.2%) = G2 (72.1%)	p = 0.124	G1 (41.1%) > G2 (26.3%)	p = 0.003
de Bortoli et al.[15]	GA (72.3%) < GB (88.6%)	p = 0.005	GA (40.6%) > GB (9.5%)	p < 0.005
Grgov et al.[16]	G2 (93.3%) > G1 (81.8%)	p < 0.05	G2 (17.7%) < G1 (28.6%)	p > 0.05
Scaccianoce et al.[17]	G4 (71%) > G1 (62%) > G2 (53%) = G3 (53%)	p > 0.05	G2 (5.9%) < G3 (20%) < G1 (26.7%) < G4 (33.3%)	p > 0.05
Park et al.[18]	G1 (83.5%) > G2 (73.3%)	p = 0.027	G2 > G1	p < 0.05

Probiotics group (PbG); Placebo group (PcG); Antibiotics group (AtbG); Group 1 (G1); Group 2 (G2); Group 3 (G3); Group A (GA); Group B (GB); Group C (GC); percentage (%); greater than (>); equal to (=); less than (<).

DISCUSSION

The purpose of this study is to carry out a systematic review of the literature to analyze the effects of probiotics on *H. pylori* eradication. Most of the articles found showed improvement in the *H. pylori* eradication rate with the concomitant use of probiotics. In addition to improving these rates, probiotics also helped to reduce the side effects of antibiotics, improving treatment compliance and, consequently, increasing therapeutic success. The articles under review used different strains of probiotics.

There has been a significant decrease in the *H. pylori* eradication rate recently with the standard triple therapy scheme. Thus, a need to find an alternative treatment was seen. The adjuvant use of probiotics was then proposed, and new studies showed important improvement outcomes in treatment compliance, since probiotics significantly reduce the side effects of antibiotics[12].

The type of underlying disease influences the *H. pylori* eradication rate. Patients with non-ulcer dyspepsia were found to have a significantly lower eradication rate than patients with peptic ulcer. These outcomes are thought to be from a higher proportion of patients with non-ulcer dyspepsia. However, it was suggested that *H. pylori* strains in patients with peptic ulcer are associated with different levels of inflammation, which may allow antibiotics to penetrate the gastric lumen better, and the increase in vascular and epithelial permeability may allow a better systemic distribution of the drug. Such factors may be related to a higher probability of *H. pylori* eradication in patients with peptic ulcer disease.[14]

Pre- or post-administration of probiotics can also improve the *H. pylori* eradication effect of standard triple therapy, the post-treatment being more effective than the pre-treatment. Pre-treatment with *Lactobacillus acidophilus*, *Streptococcus fecalis* and *Bacillus subtilis* for two weeks prior to the triple therapy was found to considerably improve the rate of *H. pylori* eradication and reduced the occurrence of dyspeptic

symptoms, while post-treatment with probiotics significantly increased the *H. pylori* eradication rate from 60.8% to 79.2% compared to the eradication therapy alone, in addition to improving the side effects of antibiotics.[11]

In addition, several species of probiotics showed a direct inhibition activity on *H. pylori*, although in clinical trials, the probiotic treatment alone was not able to completely eradicate the bacterium.[9] Therefore, probiotics should not be considered alone as an alternative to standard treatment, but may definitely be a low-cost, large-scale solution when used as adjunctive agents to prevent or decrease *H. pylori* colonization.[19]

The concomitant use of probiotics in the bismuth quadruple therapy for the treatment of *H. pylori* infection showed no improvement in treatment compliance and no difference in the eradication rates, nor in the frequency of adverse events among patients who received probiotics supplementation and those who did not.[20]

The administration of antibiotics in *H. pylori* eradication therapy was found to cause a dysbiosis, i.e., a change in the enteric microbiota, and that the adjunct use of probiotics can reduce this imbalance in the intestinal flora.[10] Probiotics stabilize the microbiota and also improve bowel inflammation, reducing the frequency of adverse effects from antimicrobial therapy, increasing patient compliance and eliminating the need for additional antibiotics, which greatly reduces the possibility of antibiotic resistance.[9]

However, the wide variety of probiotics used generates conflicting results in the evaluation of their use in the *H. pylori* eradication therapy.[9,20] More studies are needed in this area to determine the best strain, amount, time, and supplementation period.[21]

CONCLUSION

There is still a lack of consistent scientific evidence for the use of probiotics in the *H. pylori* eradication therapy. However, the reviewed studies showed an improvement in the eradication rate when probiotics were associated with the standard eradication therapy. Its efficacy was also observed in reducing the adverse effects of antibiotics and the symptoms of the underlying disease.

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