Research Article

The Probiotic Role of Lactic Acid Bacteria (LAB) in Helicobacter Pylori Gastritis

Arif Sabta Aji ^{1,2*}, Ranne Balqis ²

¹ Department of Nutrition, Universitas Alma Ata Yogyakarta 55183, Indonesia

² Postgraduate Biomedical Science Department, Andalas University Padang 25127, Indonesia

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**Corresponding author:*

E-mail: sabtaaji@almaata.ac.id

ABSTRACT

Gastrointestinal tract infections are still common in developing countries such as Indonesia. Gastritis as a gastric health problem has a risk factor for developing into a peptic ulcer or stomach cancer. This literature review aims to discuss the role of probiotics against the incidence of gastritis caused by Helicobacter pylori infection. This article based on a literature review of the role of lactic acid bacteria probiotics in the treatment of Helicobacter Pylori infection. It was found that the probiotic role of Lactobacillus and Bifidobacterium was non-pathogenic and they were often used as probiotic mediators for H. Pylori eradication. Probiotics affect the gastrointestinal tract through immunologic and non-immunological responses. Utilization of probiotic intake as one of adjuvant therapy in the treatment of gastritis disease

Keywords: Probiotic, gastritis, Lactic Acid Bacteria, helicobacter pylori

Introduction

Prevalence of gastrointestinal tract infections is still quite high in developing countries such as in Indonesia [1]. The prevalence of gastritis as one of the gastric health problems has decreased significantly in the population of developed countries over the last few decades. Although chronic gastritis is still one of the pandemic infections that often, occur with the greatest risk of becoming a peptic ulcer or gastric cancer [2]. Globally, more than 50% of people have a chronic gastritis

According to WHO the incidence of gastritis in the world is around 1.8-2.1 million of the population every year, in the UK (22%), China (31%), Japan (14.5%), Canada (35%), and France (29.5%). In Southeast Asia, around 583,635 of the total population each year, gastritis considered a trivial thing, but gastritis is the beginning of a disease that can cause a person's pain. The percentage of the incidence of gastritis in Indonesia, according to WHO is 40.8%, and the incidence of gastritis in several

regions in Indonesia is quite high with a prevalence of 274,396 cases from 238,452,952 inhabitants. Based on Indonesia's health profile in 2011, gastritis was one of the top 10 diseases in hospitalized patients in Indonesia with 30,154 cases (4.9%) [3].

H. Pylori infection known as one of the chronic bacterial infections that are common in humans and is associated with peptic ulcer disease, gastric cancer, and primary B cell lymphoma in the stomach [4]. The presence of *H. Pylori* in saliva, dental plaque, and feces indicates that the transmission mode of this bacterial transmission spread from person to person, which is assumed the same as a mechanism for transmitting *H. Pylori* bacteria. A study found that low hygiene standards, densely populated settlements and low sanitation are ways of spreading *H. Pylori* in children and spreading the disease [5].

H. Pylori infection control carried out with antibiotic therapy as a vaccine approach. A large-scale study identifying at how preclinical

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efficacy of a number of vaccine candidates to inhibit the development of *H. Pylori* has published, although there are still very few randomized controlled trials and most of these studies have not been successful. Until now, there has not been officially an anti-*H. Pylori* vaccine. Probiotics are an alternative in preventing the spread of *H. Pylori* in the body because they contain many microorganisms, especially *Lactobacillus* or *Bifidobacterium*, which grouped based on the ability of the microorganisms to live. Later in a certain amount, they can help to control infections that used for other health benefits [6].

The benefits of probiotics in gastrointestinal disease as antibiotics had found. *H. Pylori* colonization in the stomach and its relationship with gastric disease make many studies that study the effects of probiotics on *H. Pylori*. In vitro research shows that the ability of probiotics to inhibit or kill bacteria followed by pre-clinical and clinical research. Research is only one part of the efficacy of probiotics against *H. Pylori* when given alone, but it increases its ability when given along with other *H. Pylori* eradication treatment [7].

This current literature review aims to determine the role of probiotics on health and treatment applications caused by *H. Pylori* infection.

Material and Methods

The writing of this article based on a literature study that related to the role of probiotics in human health, especially in the application of medication caused by *H. Pylori* infection.

Results and Discussion

Helicobacter Pylori and Gastritis

Helicobacter Pylori (*H. Pylori*) is a gram-negative bacterium that can survive in the stomach acid environment, compared to other pathogenic bacteria, inhibits the body's immune system of stomach inflammation to an advanced stage, and can cause gastric cancer. One of the bacteria that can neutralize or inactivate *H. Pylori* is *Bifidobacterium* and *L. acidophilus*. Both bacteria are natural microflora in the human digestive tract and can produce lactic acid as the main product of carbohydrate

fermentation. Besides, they are able to stimulate the formation of antibodies through consumption of food sources of probiotics so that it can support the health of the digestive tract through the balance of intestinal microbiota [8].

H. Pylori has more than 20 species that have been formally established [9]. The gastric mucosa is well protected from bacterial infections. After entering the gastrointestinal tract, *H. Pylori* must survive bactericidal activity from the gastric lumen and into the mucous layer. *H. Pylori* is highly adapted to special conditions in the stomach. In its body, it has flagella, which allows it to form gastric epithelial colonization. In addition, these bacteria produce the urease enzyme and hydrolyses the urea to carbon dioxide and ammonia, and increase the pH around the bacteria. Enzyme activity is highest at low pH. *H. Pylori* bacteria usually cause chronic infections because of a complex balance between host factors and bacterial virulence factors. Among the several bacterial factors, one of the main factors is encouraging inflammation of Th-17, representing Peptidylprolyl cis-trans isomerase [10].

H. Pylori infection is very common in Eastern Europe, Africa and most Asian countries. In developed countries, the prevalence has been reduced and is below 10% in children and under 30% in adults. Twenty percent of infected individuals develop symptomatic gastritis, peptic ulcer or duodenum, gastric adenocarcinoma, and non-Hodgkin's stomach lymphoma. *H. Pylori* is also associated with iron deficiency anemia, idiopathic thrombocytopenic purpura and vitamin B12 deficiency. Several bacterial, host and environmental factors have been studied to determine the clinical outcome of *H. Pylori* infection. Among the bacterial factors, the most important virulence genes and the severity of *H. Pylori*-related diseases correlate with the presence of *cagA*, *vacA*, *s1m1*, and *babA2* genotypes [11]. Recent research results support the positive effects of eradicating *H. Pylori* bacteria to prevent the occurrence of gastric cancer and regression of mucosal atrophy and intestinal metaplasia in the gastric mucosa. Precancerous detection of lesions in the stom-

ach is recommended to be done as early as possible by detecting and eradicating *H. Pylori* bacteria [12].

Probiotics

The definition of probiotics according to the FAO/WHO is a living microorganism which if given in sufficient quantities provides health benefits to its host. Probiotics most commonly used in humans are microorganisms belonging to the genus *Bifidobacterium*, *Lactobacillus*, *Saccharomyces*, and *Bacillus* [13]. Intestinal microbiota includes ~30 species of *Bifidobacterium*, 52 species of *Lactobacillus*, and others, such as *Streptococcus* and *Enterococcus* [14]. The most widely studied to treat and / or prevent gastrointestinal diseases are lactic acid bacteria, namely *Lactobacillus* and *Bifidobacterium*. While these species are not pathogenic, they can withstand the rough luminal environment of the gastrointestinal tract [15].

The beneficial effects of probiotics depend on the specific strain and dosage. Clinical studies of probiotics in humans develop rapidly. The beneficial effects of probiotics have been confirmed in diseases such as acute diarrhea, antibiotic-related diarrhea, gastrointestinal functional disorders, inflammatory bowel disease, etc. *H. Pylori* infection is also a very popular area in using probiotics as an alternative therapy to prevent the use of antibiotics that can increase the risk of antibiotic resistance [16].

The *Lactobacillus* species have acid-resistant abilities and are indeed present in healthy gastric microbiota. Several studies have revealed a number of beneficial effects of certain lactobacilli, such as suppression of pathogenic bacteria in the intestine and inhibition of allergic, inflammatory and neoplastic changes [14]. Some strains can even stick to gastric epithelial cells so they can stay longer

than other bacteria in the stomach. This has been confirmed in a study in which there was a possibility of detecting *L. reuteri* strain 55730 following the gastric epithelial host cell several hours after oral administration [17]. Elliott et al., Had observed in rats with active gastric ulcer making the local microbiota altered into gram-negative bacteria including *E.Coli* while the *Lactobacillus* species experienced a significant decrease. Processed gastric mucosa *Lactobacillus* improves its colonization and this process is accelerated by oral lactulose administration. This study shows that normal gastric microbiota helps maintain mucosal health. In addition, oral intake of probiotics can strengthen the protective function in the gastrointestinal tract [18]. *Lactobacillus* is very useful in promoting gastric ulcer healing in mice, when given as an individual probiotic strain, such as *Lactobacillus rhamnosus* GG. increase cell proliferation to apoptotic ratio and increase epithelial cell regeneration, especially at the ulcer margins [19].

Based on the literature review conducted by Aaragon et al as much as > 13,438 research articles on probiotics found in Pubmed and ~ 1,422 - 2015. Many reports that the effects of probiotics on the GIT are found in in vitro research study designs, experimental animal models, and healthy respondents / not healthy. The majority found was probiotic research on Irritable Bowel Syndrome. But research that looks at the relationship between probiotics and gastric ulcers is still limited. Losses that will be caused by the host that makes this study collide with physiological conditions such as acidic environment, digestive enzymes, bile acids, and mechanical stresses that reduce the survival and growth of certain probiotics. To overcome this, high doses of probiotics have been performed. Various kinds of effects caused by probiotics on the physiological condition of the body are summarized in Figure 1 below [20].

Figure 1. Summary of Gastrointestinal (red), Non-Gastrointestinal (blue) and Neoplastic (green) Disorders Known as Probiotic Response

Effects of Probiotics on *H. Pylori*

Stomach ulcers can occur due to stress, a bad diet, and the use of NSAIDs. The discovery of *H. Pylori* infection and its relationship with peptic ulcers is new to the practice of world gastroenterology. Typically, these bacteria are able to survive and thrive in an acidic environment so that they can cause inflammation, ulcerative, and progressive neoplastic disorders. As much as 10-20% of patients with *H. Pylori* infection can eventually cause ulcers. The regressions of recent ulcer events are highly dependent on eradicating *H. Pylori* [5].

Eradication of *H. Pylori* and changes in gastric mucosa remain a challenge for gastroenterologists. This is caused by infection with *H. Pylori* which can occur early where the development of the gastric glands is characterized by prominent dividing stem cells. No antibiotic is effective enough to get rid of *H. Pylori* when given monotherapy. Triple therapy regimens (clarithromycin and amoxicillin / metronidazole combined with proton pump inhibitors) as

one of the protocols in the world used in eradicating *H. Pylori*. Studies using this standard therapy have shown eradication rates to reach 90%. However, none of the studies has reported being able to eradicate *H. Pylori* as much as 100% [21].

Increased resistance to clarithromycin has caused a decrease in the efficiency of the triple standard therapy. To overcome this problem, new tools including quadruple, sequential, concurrent, dual and rescue therapies have been introduced. However, the development of antibiotic resistance and its side effects has caused poor patient adherence thereby limiting its application [22]. Over the past few decades, many studies have examined the possibility of using probiotics to improve *H. Pylori* eradication protocols and to prevent their side effects. The use of probiotics has also been tested in asymptomatic *H. pylori*-infected patients and has been shown to reduce the risk of developing gastric ulcer. Kabir et al were one of the first groups that report a strain of the probiotic Lactobacil-

lus salivarius could prevent and eliminate *H. Pylori* colonization in the stomachs of Gnotobiotic leprosy rats [23].

Based on in vitro studies using gastric epithelial cells and different probiotic strains, several effects of probiotics on *H. Pylori* infection have been identified. Probiotics can inhibit *H. Pylori* infection by non-immunological and immunological mechanisms. Non-immunological effects of probiotics include: i) Production of antimicrobials and antioxidants that can inhibit the growth activity or *H. Pylori* urease, ii) compete with *H. Pylori* to bind the surface of gastric epithelial cells and block their specific membrane receptors, and iii) stabilize the mucosal barrier the stomach by stimulating mucus production by surface epithelial cells [24].

Probiotic immunological effects include: i) Maintaining a balance between pro and anti-inflammatory cytokines, which causes recovery from gastritis, ii) decreasing IL-8 and TNF- α production by producing conjugated linoleic acid that targets the nuclear- κ B pathway, iii) regulating regression anti-inflammatory cytokine signaling through signal transducer activation and transcription factor activator (STAT) -1 / STAT-3, and iv) increases gastric mucosal barrier by stimulating IgA secretion and transport [25].

Probiotics as Alternative Therapies

H. Pylori invasion has been considered an infection that is difficult to treat, mainly because of its resistance to commonly used antibiotics, there is a tendency for increased use of probiotics together with antibiotic regimens to eradicate *H. Pylori*. Probiotics have been shown to be beneficial in the treatment of several intestinal diseases such as diarrhea, besides the benefits of probiotic bacteria in the intestine; several beneficial effects on the stomach have been reported. Among them, anti-*Helicobacter Pylori* activity has been studied. Many therapeutic models to overcome the problem of *H. Pylori* infection in human gastrointestinal health cases ranging from allopathic therapeutic approaches which include the use of probiotics, fungi, vaccines, propolis, polysaccharides, phototherapy, microorganisms, etc [26].

The benefits of probiotic therapy in the case of *H. Pylori* are increased tolerability by preventing treatment and associated side effects. In addition, probiotics can help to correct diseases caused by *H. Pylori*. The clinical outcome of *H. Pylori* infection is determined by several factors, including the type of *H. Pylori* strain, degree of inflammation, and density of *H. Pylori* colonization. It has been reported that the risk of developing peptic ulcer disease and gastric cancer increases with an increased infection rate. Therefore, permanent or long-term suppression of *H. Pylori* can reduce the risk of *H. Pylori* disease [27]. Several studies have been conducted to show the beneficial effects of using probiotics against *H. Pylori* and have clarified the mechanism of action of probiotics against *H. Pylori*, including its strength in mucosal inhibitors, competition for adhesion, and immunomodulatory mechanisms [28].

Probiotics as a single therapy in the treatment of *H. pylori*

Positive results were obtained from the first in vitro study published in 1989. Bhatia et al found that the growth of *H. Pylori* in vitro was inhibited, if *L. acidophilus* appeared in culture. Michetti et al reported for the first time the effects of probiotics [*L. acidophilus* (La1)] in *H. Pylori* colonization in humans. The study showed that the bacterial load density was reduced in the probiotic group of asymptomatic patients, whereas complete eradication of *H. Pylori* was unsuccessful. Likewise, Wang et al revealed that after intake of *B. lactis* Bb12 and *L. acidophilus* La5 in infected *H. Pylori* adults, there was a decrease in urea breath test values. Bacterial load was evaluated by the 13C-urea semi-quantitative breath test in subjects treated with *L. johnsonii* La1, lyophilized bacteria *L. brevis* CD2, *B. bifidum* BF-1, *L. reuteri* ATCC 55730, *L. gasseri* OLL 2716, and with probiotic multispecies such as a combination of *L. reuteri* DSM 17938 and *L. reuteri* ATCC PTA 6457 or a combination of *L. rhamnosus* GG, *L. rhamnosus* LC705, *P. Freudenreichii* JS and *B. lactis* Bb12. Regardless of the probiotics used, the authors report a significant decrease in the breath test value of 13C-urea in the probiotic

group of patients studied [10,29]. In conclusion, there are only a few studies that can examine the effects of probiotics as monotherapy on the level of *H. eradication. pylori*. The results showed that specific probiotics, such as *S. boulardii* and *L. johnsonii* La1 might reduce the bacterial burden, but did not completely eradicate *H. Pylori* bacteria.

Probiotics as H. Pylori adjuvant therapy

Several systematic reviews and Meta-analyses of the effects of probiotics as adjuvant therapy on standard treatment of *H. Pylori* infection have been published [30]. Probiotic supplementation in general might increase the rate of eradication and reduce the frequency of side effects due to dual antibiotic therapy. However, the beneficial effects of probiotics seem to be strain specific, therefore, gathering data on different strains in a meta-analysis can lead to misleading conclusions. In this connection, a better approach is to collect data on a single probiotic strain and conduct a meta-analysis.

Szajewska et al. conducted a systematic literature review to evaluate the effect of supplementation with *S. boulardii* on a standard triple therapy rule at the level of *H. Pylori* eradication. Five randomized controlled trials with good methodological quality involving 1307 patients were identified. Among them, only 90 children entered. The daily dose of *S. boulardii* ranges from 500 mg to 1000 mg and the duration of therapy is 2-4 weeks. Of the four trials, complete data on eradication rates are available. In 80% of patients treated with *S. boulardii* together with triple therapy, eradication is confirmed by standard diagnostic tools [31].

Probiotic Mechanism in *H. Pylori*

Probiotic strains, especially Lactobacilli, have shown the opposite of being in one place with the culture of *H. Pylori* bacteria in vitro studies. Several possible mechanisms for the effects of probiotics on *H. Pylori* are being considered. The concentration of *Lactobacilli* species, as colonization of commensal bacteria in the human digestive tract reaches 0-103 / mL in normal stomach fluid. They have a longer viability in the stomach because of their resistance to acidic conditions. The possible role of normal microbiota playing in protection

against gastric lesions. The total level of microorganisms in the stomach tissue of healthy mice ranged from 10³ to 10⁴ CFU / g, with gram-negative bacteria representing 5% of the total population. However, they showed that a few days after treatment of gastric ulcers in healthy mice, the total bacterial count peaked at 10⁹-10¹⁰ CFU / g and maintained this status for about 7 days. At present, gram-negative microorganisms comprise the majority of the total number of bacteria present compared to the population of lactobacilli, a reduction in colonization of gram-negative bacteria occurring everywhere in the lumen, but this event occurs at a higher rate to the ulcer side. This finding concludes that the intestinal microbiota might be the first line of defense against pathogenic bacteria. Therefore, consuming exogenous lactic acid bacteria with probiotic properties can increase this protective effect in the stomach maintaining native microbiological homeostasis, damaging the stability of *H. Pylori* and decreasing the inflammatory response. This situation is certainly present in populations infected with *H. Pylori* and results in a reduction in the bacterial inflammatory response [32].

Two main types of substances including short chain fatty acids (SCFAs) and bacteriocin have been involved in the inhibition of *H. pylori*. During carbohydrate metabolism, SCFAs such as aspartic, propionic, butyric, and lactic acid are secreted by probiotic organisms, and have an important role in reducing pH. Observation of the antagonistic effect of the lactobacillus strain on *H. Pylori* involves SCFA in this effect. SCFA is believed to be an agent that mediates the effects of the antagonists. The antimicrobial effect of lactic acid has an impact on decreasing pH, it can inhibit *H. Pylori* urease, although the reciprocal mechanism of lactobacillus against *H. Pylori* differs from strain to strain. Furthermore, certain genera of lactobacilli produce antimicrobial metabolites that are similar to those produced by the bacteriocin family. They are compounds with anti-bacterial potential of *H. Pylori* and *bacteriocin* which have a heat-resistant peptide structure with antimicrobial properties [33]. *H. Pylori* adhesion inhibition is another important mechanism that protects the gastroduodenal lumen from inflammation as well as atrophic gastritis.

H. Pylori adhesion in host cells is important in determining disease outcome. Some Lactobacilli strains can exert their anti-adhesive activity to secrete antimicrobial substances. Therefore, *Lactobacillus reuteri* (L. reuteri) can inhibit the growth of *H. Pylori* by competing adhesion receptors. An important mechanism of probiotic agents is to modulate and mediate immune responses to pathogens. The presence of *H. Pylori* inflammatory response by the release of inflammatory mediators such as cytokines and chemokines can be prevented by probiotics that modulate the host immune response through interactions with epithelial cells. Reduction in gastric inflammatory activity occurs after changes in the release of anti-inflammatory effectors [34]. However, the effects of probiotics on immune responses are difficult to simplify because certain probiotic strains can produce diverse immunity, which varies depending on the host's immune status and indeed the genetic variation of us might have influenced in a certain phenotypic outcomes[35-38].

Conclusion

Probiotics in general have an important role in preventing *H. Pylori* infection through the action of lactic acid bacteria. In addition, this type of probiotics can be an alternative therapy to reduce the risk of antibiotic resistance in the treatment of gastritis. Although, it still requires a lot of in-depth research and is still a debate among experts to find out the complete mechanism and the proper dosage of use. Lactic Acid Bacteria (LAB) *Lactobacillus* and *Bifidobacterium* are non-pathogenic species and are the most often used as probiotic mediators for eradication of *H. Pylori* bacteria. Probiotics work and affect the health of the digestive tract through immunological and non-immunological responses. Utilization of probiotic intake is an adjuvant therapy in the treatment of gastritis to help the effectiveness of antibiotic drugs.

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