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EFFECTIVENESS OF PROBIOTIC SUPPLEMENT ON *HELICOBACTER PYLORI* INFECTION ERADICATION IN GASTRIC ULCERS

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Abstract

Background: *Helicobacter pylori* colonizes the gastric mucosa in 50% of the human population. *H. pylori* infection causes several upper gastrointestinal tract diseases, such as chronic gastritis, peptic ulcer, duodenal ulcer, and gastric cancer. *H. pylori* is also associated with a high risk of developing gastric adenocarcinoma. The World Health Organization classifies *H. pylori* infection as a class 1 carcinogen. Giving probiotics may improve the immune system and suppress the effects of pathogens. However, mixed results were obtained from the use of various kinds of bacteria and fungi as probiotics.

Objective: To determine the effectiveness of probiotic supplementation against the eradication of *Helicobacter pylori* infection in gastric ulcers.

Methods: Article searches were conducted using advanced searching by combining MesH Terms and abstracts/titles in the Pubmed, Cochrane Library, and Scopus databases. The search found two selected literature to further conduct a critical assessment.

Result: From the results of the literature search, it was found that 2 studies that met the criteria were a clinical trial study from Chang et al. which analyzed the effect of probiotic supplementation and broccoli extract on *H. pylori* eradication and a clinical trial study from Oh et al. comparing the combination of antibiotics and probiotics with antibiotics alone in *H. pylori* eradication. The results of these two studies of *H. pylori* eradication with probiotics got a higher eradication rate, but it was not statistically significant. However, the number of these research subjects was not large enough.

Conclusion: The effectiveness uses of probiotics to eradicate *H. pylori* has not been proven. It will take clinical trials with a sufficient number of subjects and certain probiotic strains to be able to determine the type of strain, dosage, duration of use, and side effects that can be caused.

Keywords: Probiotics, *Helicobacter pylori*, *H. pylori*, gastric ulcer

Introduction

Peptic ulcer disease (PUD), including gastric and duodenal ulcers, is a major health burden in China. The prevalence of PUD in Western countries ranges from 0.1% to 4.7%, with an annual incidence of 0.19% to 0.3%.[1] Peptic ulcer disease is strongly related to chronic *Helicobacter pylori* (*H. pylori*) infection. Data from the developed world has shown that in the first decade of the discovery of *H. pylori*, 95% of duodenal ulcers and 85% of gastric ulcers were associated with *H. pylori* infection and that the lifetime risk of developing PUD was 3–10-times higher in *H. pylori*-positive subjects than in their *H. pylori*-negative counterparts.[2]

H. pylori is a gram-negative microaerophilic bacterium that colonizes the gastric mucosa in 50% of the human population.[3] It is estimated that more than 50% of the world population is infected with *H. pylori*, with a remarkable variation in the prevalence among countries and within different regions of the same country. Interest in *H. pylori* resulted from its association with a variety of gastrointestinal conditions,

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ranging from benign to malignant diseases.[2] It causes several upper gastrointestinal tract diseases, such as chronic gastritis, peptic ulcer, duodenal ulcer, and gastric cancer. *H. pylori* is also associated with a high risk of developing gastric adenocarcinoma. The world health organization classifies *H. pylori* infection as a class 1 carcinogen.[3,4]

The success of antimicrobial therapy depends on adherence to medication, dose, formula, duration, and rate of reinfection.[5] During the eradication of *H. pylori*, the most common problems facing gastroenterologists include (1) antibiotic resistance phenomenon, (2) persistence of bacteria in latent status, (3) degradation of antibiotics in acidic gastric conditions, (4) re-infection, especially in regions with high prevalence, (5) adverse side effects of antibiotics such as diarrhea, nausea, vomit, and abdominal pain, (6) rapid metabolization of antibiotics due to CYP2C19 enzyme, (7) poor compliance of multiple antibiotics.[6]

In recent years, antibiotic resistance (with high divergence) has led to increased therapeutic failure in eradicating *H. pylori* with current regimens. There are several recommended regimens for *H. pylori* eradication. One of them was a combination therapy of proton pump inhibitor, amoxicillin, and clarithromycin or metronidazole. This regimen can be used in cases with low clarithromycin resistance.[5] A study by Savoldi et al.,[7] showed an increase in *H. pylori* resistance in both primary and secondary regimens. According to the World Health Organization (WHO) report, the rate of resistance to clarithromycin and metronidazole ranged from 14–34% and 20–38%, respectively. The therapeutic regimens with less than 80% efficacy are considered as treatment failure. Recently, adjuvant therapy with probiotics has received much attention as a new strategy to increase the success of anti-*H. pylori* therapy.[6]

Probiotics are defined as live microorganisms which, when in adequate amounts, can provide benefits to the host.[8] Probiotics have been used as a preventive and therapeutic agent in several gastrointestinal diseases, such as diarrhea, irritable bowel syndrome, and inflammatory bowel disease. Giving probiotics will improve the immune system and suppress the effects of pathogens. In an in vitro study, we found the inhibitory effect of probiotics on the expression of genes encoding virulence factors. Some probiotics such as *Lactococcus lactis*, *Lactobacillus reuteri*, and *Lactobacillus bulgaricus* produce peptide and nonpeptide antipathogens that suppress the development and adhesion of *H. pylori*.[9,10]

Probiotics have various mechanisms to eradicate or restrict *H. pylori* growth within the stomach of humans, including (1) inhibition of the colonization of *H. pylori* via

conquering gastric epithelial receptors or co-aggregation mechanism, (2) anti-*H. pylori* activity throughout the production of bacteriocins, organic acids, as well as biosurfactants, (3) supportive role in intestinal tissues by promoting mucin synthesis, (4) modulation of immune system response, (5) induction of antigen-specific antibodies, and (6) reduction of stomach inflammation.[6]

Defenses mechanisms against *H. pylori* infection, which are subdivided into two main mechanisms, including physiological barriers and the immune system. Upon entrance of *H. pylori* into the stomach, both innate and specific immunity enter the area of infection (lamina propria). Consumption of probiotics has several advantages in strengthening and stimulating the immune system versus this pathogen. Antibacterial activities of probiotics, direct and indirect, are helpful for human health. Therapeutic effects of these bacteria in the gastric tract include immune modulation via interaction with Toll-Like Receptors (TLRs) and anti-*H. pylori* activity, co-aggregation of invasive bacteria, decrease pH by secretion of short-chain fatty acids, support epithelial barrier integrity, mucin production, as well as promoting immune cells to inhibit gastric inflammatory response, particularly Interleukin-8 production, and induction of immunoglobulin secretions.[6]

Clinical Question

A 40-year-old male patient came to the hospital complaining of nausea, frequent burping, bloating and burning sensation in the epigastric that interrupted activities. The symptoms appear several times and usually get better after eating. But now the complaints persist and feel worsening. He is a field worker who often skips meals and regularly drinks coffee. He often consumes herbal medicine whenever he feels tired after work. The patient's blood pressure was 140/100 mmHg, pulse 80 times per minute, breath 20 times per minute. The body weight was 70 kg, height 154 cm, BMI 29,5 kg/m^2. In addition, the patient was also subjected to a blood examination of Hemoglobin 11 g/dL, leukocytes 15,400/µL and platelets 354,000/µL. There is a history of diabetes mellitus for a couple of years. He was diagnosed with gastric ulcer caused by *Helicobacter pylori* infection and treated with a combination of proton pump inhibitor, amoxicillin and clarithromycin. The patient asked whether probiotic consumption can be beneficial to improve his condition or not.

Methods

The article searches were conducted using basic and advanced searching methods by combining Pubmed, Cochrane Library, and

Scopus databases. The search was carried out on December 19, 2021. Keywords were entered in the MeSH Terms and title/abstract categories. The articles included in the search were systematic reviews, meta-analyses, and randomized controlled trials within the last 5 years. Studies on animals, studies that were not fully available, and studies other than in English were not included in the search. Titles and abstracts were reviewed, articles that did not meet the eligibility criteria and PICO were excluded, and duplication screening was carried out. A critical study was carried out using tools from the Center for Evidence-Based Medicine, Oxford Center for Evidence-Based Medicine.

Research Results

The search results yielded 72 articles from Pubmed database, 7 articles from Cochrane Library, and 46 articles from Scopus. After the search results were obtained, a screening of duplicated articles was conducted using the Mendeley program. A subsequent screening test was carried out by comparing the title and abstract to the suitability of the PICO. Eligibility criteria such as full text and limitations on the publication of articles within the last 5 years were applied before conducting a critical review of the articles obtained. After screening duplication and selecting articles according to eligibility criteria, 2 literature from Chang et al.,[11] and Oh et al.,[12] were found to be relevant and could be analyzed to answer clinical questions **(Figure 1)**.

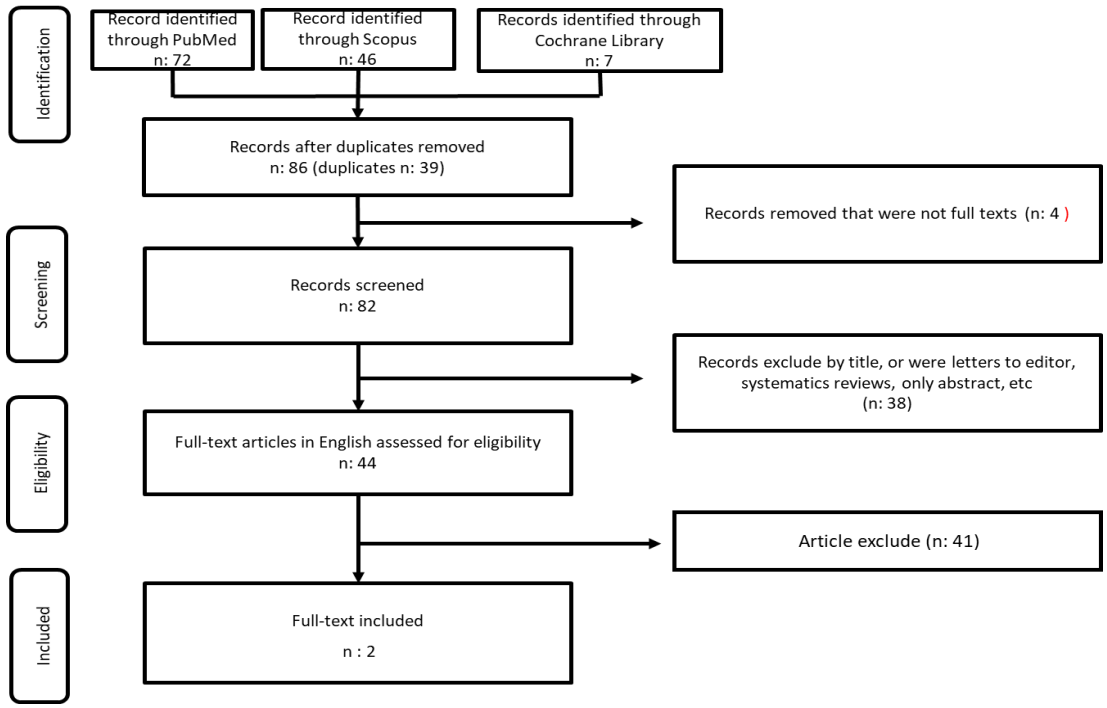

Figure 1. PRISMA's Flow Chart

Discussion

The gastric mucosa is well protected against bacterial infection. Mucous membranes are one of the first lines of defense to protect humans against environmental pathogens; excessive secretion of mucins and large glycoproteins effectively cover the surface of gastrointestinal tracts and prevent the colonization of infectious agents, especially *H. pylori*.[6]

After ingestion, *H. pylori* must survive the bactericidal activity of the gastric lumen and enter the mucus layer. *H. pylori* is highly adapted to special conditions in the stomach. It possesses flagella, which enables colonization of the gastric epithelium. Moreover, the bacteria produce the enzyme urease, which hydrolyzes urea into carbon dioxide and ammonia and elevates the pH in the surroundings of the bacteria. The enzyme activity is highest at low pH. The *H. pylori* bacteria usually causes chronic infection due to a complex balance between host factors and virulence bacterial factors. Among several bacterial factors, one of the main factors, which drive Th17 inflammation, represents the secreted peptidyl-prolyl cis, trans isomerase.[13] Recent studies have shown that this bacterium inhibits the expression of several mucins genes, such as MUC1 and MUC5. In vitro studies show that some probiotics, for example, *L. rhamnosus* and *L. plantarum*, induce the expression of MUC2 and MUC3 genes (the most important mucins in the gastrointestinal tract), leading to inhibition of *H. pylori* colonization. Interestingly, the study showed that consumption of *L. johnsonii* thickens the mucosal layer, which in turn prevents bacterial colonization.[6]

Probiotics can inhibit *H. pylori* by several immunological and non-immunological mechanisms. Probiotics are capable of modifying the immunologic response of the host. Neutrophils, lymphocytes, plasma cells, and macrophages are involved in the inflammatory response to *H. pylori*. The consequences are increased levels of pro-inflammatory cytokines, such as IL-1β, IL-2, IL-6, IL-8 and tumor necrosis factor α in the gastric mucosa. Probiotics like *L. salivarius* WB 1004 have *in vitro* reduced IL-8 secretion by gastric epithelial cells. It looks like that, at least in vitro, *L. acidophilus* can improve *H. pylori*-induced gastric inflammation by inactivating the Smad7 and NFκB pathways.[13]

Furthermore, the study demonstrated that *L. bulgaricus* inhibited the activation of the TLR4 signaling pathway and IL-8 production induced by *H. pylori* lipopolysaccharide in SGC-7901 cells. Gastric inflammation can be controlled to

some level by different strains of *Lactobacilli* through inactivating JAK2 through JAK–STAT pathways and through the higher expression of the SOCS protein family. *H. pylori* also induce humoral response of gastric mucosa, which may contribute to gastric mucosal damage. *Lactobacilli* were able to increase the local IgA concentration and decrease specific anti-*H. pylori* IgG antibodies in animal models. [13]

Among non-immunological mechanisms, probiotics are capable of influencing bacterial growth by secreting antibacterial substances such as lactic acid, short-chain fatty acids, hydrogen peroxide and bacteriocins. The metabolites can diminish the number of spiral bacteria. Lactic acid has probably an additional effect on *H. pylori* by lowering the pH and inhibiting the urease. *L. acidophilus* CRL 639 secret an autolysin, a proteinaceous compound released after cell lysis, which has some antibacterial activity. Substances similar to isocoumarin antibiotics are produced by *B. subtilis,* and those can also kill *H. pylori* bacteria. *L. reuteri* ATCC 55730 produces a unique substance called reuterina, which suppresses the growth of spiral bacteria. [13]

Chang et al. [11] conducted a study on 183 patients with *H. pylori* infection who received the conventional eradication regimen compared with additional probiotics and sulforaphane supplementation of broccoli extract. The results measured the rate of eradication and side effects of treatment. A population study was randomly divided into 3 groups, namely the group that received conventional therapy only, conventional therapy with additional probiotics, and with sulforaphane addition. The results showed a similar eradication rate in each group, namely group A = 89.2%, B = 86.8% and C = 96.3%). The frequency of occurrence of side effects was also not significantly different (A vs B p = 0.574; A vs C; p = 1.00). There were no statistically significant results in this study.[11]

There are several limitations; first, the small number of subjects in each group, conducted in one study center, and limitations in taking subjects during the study period. In this study, supplementation of probiotics and sulforaphane did not significantly increase the rate of eradication or side effects. Further studies with a large number of subjects and the selection of other probiotic strains are needed to study the effect of probiotics on the eradication of *H. pylori*.[11]

In Oh et al. study,[12] 23 subjects with *H. pylori* infection were randomly divided into two groups, the antibiotic group and the probiotic group. The intervention was carried out for two weeks, and then a stool examination was carried out to obtain the *H. pylori* eradication rate from each group. It was found that the eradication rate in the probiotic group was higher than the antibiotic group,

namely 100% and 90%, respectively. However, this result is not statistically significant because the number of research subjects is small.[12]

This study also did not get a sufficient number of subjects to get meaningful results. In addition, the lifestyle of the subjects, such as alcohol consumption and smoking, changes in gut microbiota before and after the intervention were also different. Nutrient intake factors also play an important role in changes in the gut microbiota. In previous studies, it was reported that the positive effect of probiotics in the eradication of *H. pylori* was quite high using several strains such as *Lactobacillus acidophilus*, *Lactobacillus casei DN-114001*, *Lactobacillus gasseri*, and *Bifidobacterium infantis 2036*.[12]

Conclusions

Based on the result of the critical review, the effectiveness of using probiotics for eradication of *H. Pylori* has not been proven. So, probiotics cannot be recommended as *H. Pylori* eradication regimen. Further studies are needed to obtain better results. The research duration should be longer with a sufficient number of subjects using certain probiotic strains to determine the strains type, dosage, duration of use, and side effects that can be caused.

Competing Interest

The authors have no conflict of interest in this study.

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