Review Article
Role of Gastric Microorganisms Other than Helicobacter pylori in the Development and Treatment of Gastric Diseases

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The microenvironment in the stomach is different from other digestive tracts, mainly because of the secretion of gastric acid and digestive enzymes, bile reflux, special mucus barrier, gastric peristalsis, and so on, which all contribute to the formation of antibacterial environment. Microecological disorders can lead to gastric immune disorders or lead to the decrease of dominant bacteria and the increase of the abundance and virulence of pathogenic microorganisms and then promote the occurrence of diseases. The body performs its immune function through innate and adaptive immunity and maintains microbial balance through the mechanism of immune homeostasis. Microecological imbalance can lead to the invasion of pathogenic microorganisms and damage mucosal barrier and immune system. The coexistence of gastric microorganisms (including viruses and fungi) may play a synergistic or antagonistic role in the pathogenesis of gastric diseases. Probiotics have the ability to compete with intestinal pathogens, increase the secretion of immunoglobulin A (IgA), stimulate the production of mucin, bacteriocin, and lactic acid, regulate the expression and secretion of cytokines, and regulate the growth of microbiota, which all have beneficial effects on the host microbial environment. At present, most studies focused on Helicobacter pylori, ignoring other stomach microbes and the overall stomach microbiology. So, in this article, we reviewed advances in human gastric microbiology, the relationship between gastric microbiology and immunity or gastric diseases, and the treatment of probiotics in gastric diseases, in order to explore new area for further study of gastric microorganisms and treatment of gastric diseases.

1. Introduction

The gastrointestinal tract contains the largest microbiome in the human body, accounting for 80% of the total microbial biomass. For a long time, people believed that the stomach was sterile. By the early 1980s, Marshall and Warren isolated Helicobacter pylori (H. pylori) from gastric biopsies obtained from patients with chronic gastritis and peptic ulceration, for which they won the 2005 Nobel Prize in Physiology or Medicine for their discovery, after that the researchers were interested in the bacterial cause for ulcer disease [1]. With the advent of 16sRNA gene sequencing, next-generation sequencing technology, metagenomics, and other research methods, it is possible to identify gastric microbes and to explore the functional activities and interrelationship of gastric microbial communities. It has been found that in addition to H. pylori, there are other microorganisms in the stomach, which jointly form the microbial environment in the stomach and may be related to the occurrence of many gastrointestinal diseases. The total number of bacteria carried in the intestines of a healthy person is estimated to be 10^{14}, which is constituting a microbiome and an ecosystem in dynamic balance as a whole [2]. In general, the number of bacteria from the stomach to the large intestine is different, and the bacterial concentration presents an increasing state successively. The count of bacteria in oral cavities is higher. There is the least count of bacteria in the stomach. The small intestine has more bacteria, while the colon has the most bacteria, which is nearly 10^{10} times more than the count of bacteria in the stomach [3, 4] (shown in Figure 1).

At present, there are few studies on microbes living in the stomach and duodenum, mainly due to its special...
physiological processes such as gastric acid secretion, bile secretion, and gastrointestinal motility. However, little is known about the relationship between microorganisms and these physiological processes and how they affect health and disease throughout the digestive tract. In this article, we reviewed advances in human gastric microbiology, the relationship between gastric microbiology and immunity or gastric diseases, and the treatment of probiotics in gastric diseases, in order to explore new areas for further study of gastric microorganisms and treatment of gastric diseases.

2. Anatomy and Physiological Mechanism of the Stomach

The stomach accommodates food, secretes gastric juice, digests food, and has a secretory function. Due to its special anatomical structure, the secretion of gastric acid and digestive enzymes, bile reflux, special mucus barrier, and gastric peristalsis all contribute to the formation of an antibacterial environment. This is also different from other digestive tracts. Normal gastric juice has a pH of 0.9-1.5 and its secretion is 1.5-2.5 L/d. During or after eating, the movement of the stomach is enhanced, and the secretion of gastric juice is increased. The stomach can also secrete other mucus, which covers the surface of the gastric mucosa, forming a protective gel-like layer. The mucous layer on the mucosal surface is divided into inner and outer layers, the pH of which gradually increases from the outer layer to the inner layer (shown in Figure 2).

When microecological imbalance in the stomach or other reasons cause damage to the first line of gastric mucosal immunity, which is composed of gastric mucosal epithelial cells and the mucous layer on the surface, the permeability between gastric epithelial cells increases, and pathogens and their metabolites enter the mucosa through the gap, which causes the macrophages to accumulate. Recognition of pattern recognition receptors (PPR) in dendritic cells and other immune cells can lead to direct macrophage phagocytosis and the production of cytokines by the cells mentioned above, which can stimulate T cells and B cells to produce cellular immunity and humoral immunity, and finally, further eliminate microorganisms through the innate immunity and adaptive immunity of the gastric mucosa. However, some microorganisms can achieve immune escape by targeting gene expression. Microecological imbalance can also lead to a decrease in dominant bacteria and an increase in the abundance and virulence of pathogenic microorganisms, thereby leading to the occurrence of diseases. Normal digestive motility is also essential to maintain the balance of microorganisms in the digestive tract. Impaired gastrointestinal motility can hinder the absorption of drugs and nutrients, resulting in immune function and intestinal mucosal integrity impairing, bacterial overgrowth and translocation, and the release of endotoxins into the circulation and activation of immune responses. On the other hand, bacterial overgrowth may also cause gastrointestinal dysfunction, such as gastroparesis and other gastro motility disorders. Due to the special structure and function of the stomach mentioned above, the growth of microorganisms in the stomach is restricted to physiological levels. If the pH, the mucosal barrier, or gastric physiological movement of the stomach are altered, the microecological balance in the stomach may be disturbed, which will affect its normal function and promote the occurrence of gastric diseases [5]. For example, histamine 2 receptor antagonist therapy or atrophic gastritis increases the growth of nitrosating bacteria, which can convert nitrite and other nitrogen compounds in gastric juice to carcinogenic N-nitroso compounds [6]. In healthy conditions, gut flora is involved...
in maintaining the integrity and function of the epithelial mucosal barrier, and gastrointestinal immune cells strengthen the epithelial barrier function by maintaining a healthy microbial community. Once the gastrointestinal immunity is unbalanced, it may lead to gastrointestinal dysfunction and diseases, including inflammatory bowel disease [7], irritable bowel syndrome [8], small intestinal bacterial overgrowth [9], B cell lymphoproliferative diseases [10], and allergic intolerances to foods [11]. Proper gastrointestinal motility allows for a constant flow of luminal materials through the gastrointestinal tract, which prevents bacterial overgrowth in the small intestine. However, patients with gastrointestinal dysmotility have a stagnant flow of luminal materials, leading to the development of small intestinal bacterial overgrowth (SIBO) [12].

3. Relationship between Gastric Microbe and Gastric Immune Regulation

The human immune system contains PPRs that distinguish harmful pathogenic microorganisms from harmless symbiotic ones. Toll-like receptors (TLRs) are kind of important PRR expressed in the macrophage and dendritic cell membrane, and the other PRR group is the nodal receptors (NLRs). NLRs are associated with a family of innate cytoplasmic receptors that are involved in the detection of intracellular pathogens and endogenous byproducts of tissue injury [13]. Microecological imbalance can contribute to the invasion of pathogenic microorganisms and can damage the mucosal barrier and the immune system. This process results in increased mucosal permeability, inflammation of the digestive tract, and thus, activation of TLR and NLR signals. When the antigen comes into contact with the human body, immune cells in the blood bind to chemokines and induce immune cells to adhere to the cell adhesion factor of endothelial cells by integrin and then migrate through endothelial cells to the stomach [14]. Finally, the body exerts immune function through innate immunity and adaptive immunity [15] and maintains microbial balance through the immune homeostasis mechanism [16] (shown in Figure 2).

Immune-related gastric mucosal cells are composed of gastric mucosal epithelial cells, macrophages, and dendritic cells. Gastric mucosal epithelial cells are located in the gastric mucosal epithelium, which together with mucus layer on the surface constitute the first line of defense for gastric mucosal immunity. Macrophage microaggregates are widely distributed in the gastric mucosa [17]. Cytokines generated after macrophage activation stimulate the occurrence of immune response, play an immunomodulatory role, and promote the occurrence of adaptive immune response [18, 19]. Dendritic cells exist in the human gastric mucosa. Mature dendritic cells are activated as antigen-presenting cells (APCs), which activate effector T and B cells through the TLR signal and induce an adaptive immune response [14, 20–24].

Gastric mucosal adaptive immunity-related cells are composed of T cells, B cells, and other immune lymphocytes. In gastric mucosal cell immunity, CD4+ T cells and regulatory cells play an important role [25, 26]. The humoral immunity of the gastric mucosa mainly involves B cells and immunoglobulin. B cells exert humoral immune function with the joint participation of macrophages, helper T cells, and chemokines [27]. The microbiota can damage host DNA and activate signal transduction, resulting in chromosomal aberrations, microbial translocation, and the activation of myeloid cells that produce interleukin (IL-23) and

Figure 2: Schematic diagram of the cause for gastric mucosal immune disorder caused by microorganisms.
thus promoting tumor growth [28]. Some studies have shown that a high abundance of *Fusobacterium nucleatum* in the gastrointestinal tract can increase plasma proinflammatory cytokine levels and reduce the activity of NK cells [29]. In addition, *Fusobacterium nucleatum* can suppress accumulation of tumor infiltrating T cells and promote tumor growth and metastatic progression [30].

4. Microecological Environment of the Stomach

The fetus is aseptic when it is in the mother’s body. It is in contact with the outside environment after birth, and many bacteria enter the body within a few hours. The presence of bacteria in the stomach may be due to the increasing pH from the gastric cavity (pH 1-2) to the mucosal surface (pH 6-7), while the mucosal surface is covered with mucus secreted by the gastric glands (shown in Figure 2). This pH gradient leads to a different environment in the stomach and allows the growth of microorganisms [31]. Since the proximal end of the stomach is connected to the esophagus and mouth and the distal end is connected to the duodenum, microbes from other parts of the human gastrointestinal tract can also enter the stomach.

*H. pylori* can cause a variety of stomach diseases. As an important pathogenic factor for chronic gastritis and gastric ulcer, *H. pylori* has been widely recognized and is closely related to the occurrence, development, and outcome of gastric cancer. Researchers have performed the first modern high-throughput sequencing study on stomach bacteria [32]. They characterized the gastric microbiota using PCR and 16S rDNA sequence analysis. They found that the human gastric environment contained rDNA from a wealth of bacteria, in addition to *H. pylori*. Of these, some were derived from uncultivated bacteria, and some had been previously described in specimens from the human mouth. Because it was likely that the composition of the gastric community was not only determined by niche-specific factors but also by stochastic colonization from upstream components of the alimentary tract.

Early studies have found microorganisms related to the gastric mucosa, such as *Enterococcus, Pseudomonas, Staphylococcus, and Stomatococcus* [33]. The composition of the gastric microbiota is highly variable between individuals. However, recent studies have identified five major phyla in the stomach, including *Firmicutes, Bacteroidetes, Actinomycetes, Clostridium*, and *Proteobacteria*. The main genera in the stomach include *Prevotella, Streptococcus, Roseburia*, and *Haemophilus* [34–39]. A systematic review of the gastric microbiota recently published also showed that the results of the gastric microbiota composition were highly heterogeneous. A total of 266 bacterial genera were identified, of which 57 were mainly found in normal acidic stomach [40].

Fungal flora can also be detected in the gastrointestinal tract, most of which are aerobes or facultative anaerobes, and the number of fungi in the human stomach ranges from 0 to 10^2 cfu/ml [41]. *Candida albicans* can grow well in a highly acidic environment [42], and some genotypes can aggravate the severity of gastric mucosal lesions [43]. A study showed that 66.7% of patients with gastric diseases had colonization of *Candida* and *H. pylori* in the gastric mucosa [44]. Although a causal relationship with secondary colonization was never examined in these studies, the coexistence of *Candida albicans* and *H. pylori* may indicate a synergistic role in the pathogenesis of gastric ulcer, and the mycelium formed by *Candida* may contribute to ulcer perforation. Although fungi play an important role in the study of gastric microbiology, their potential role in the pathogenesis of diseases needs to be further studied with more modern techniques. At the same time, the composition of the gastric microbiota is affected by factors such as *H. pylori*, health status, diet habits, drug use, age, surgical intervention, and inflammation [45, 46].

5. Interactions between Microbes in the Stomach

The gastrointestinal microecosystem is a unity formed by the interaction and influence of the gastrointestinal flora, its host, and its external environment. The gastrointestinal flora maintains the stability and balance of the gastrointestinal microecosystem through a variety of regulatory systems and pathways. Once the balance is destroy, there will be a microecological imbalance, which will lead to the generation of diseases. At present, many studies have found that non-*H. pylori* gastric microorganisms are related to gastric diseases, and *H. pylori*, which has been much more studied, also interacts with other gastric microorganisms.

The colonization of *H. pylori* in the gastric mucosa changes the gastric environment by decomposing the mucosal layer and alkalizing gastric juice [47]. Some studies have confirmed that non-*H. pylori* gastric microorganisms are related to the development of gastric cancer. In this study, transgenic Ins-GAS mice with gastrin overexpression were used. Ins-GAS mice treated with antibiotics developed gastric cancer later than control mice without antibiotic treatment for *H. pylori* [48], suggesting that gastric microorganisms may enhance the role of *H. pylori* in gastric cancer. Changes in gastric microbial ecology after *H. pylori* eradication indicate that *H. pylori* affects the interaction of other microorganisms in the stomach, possibly promoting the development of inflammation and cancer in patients [49]. Eradication of *H. pylori* can prevent the progression of gastric mucosal lesions [50, 51], but some patients continue to progress to precancerous lesions, including gastric atrophy (GA) and intestinal metaplasia (IM), after radical treatment with *H. pylori* [36]. Less than 3% of patients infected with *H. pylori* develop gastric cancer [52], and about 20% of patients with chronic gastritis are negative for *H. pylori*, suggesting that other microorganisms may induce gastritis and even gastric cancer [53]. Although *H. pylori* initiates the gastric inflammation process, other gastric microorganisms with proinflammatory potential may play an important role in maintaining the progression of inflammation and abnormal hyperplasia, which then leads to the development of gastric cancer.

The effect of *Lactobacillus salivarius* supplementation has been demonstrated in mouse models, and its effectiveness is related to the large amount of lactic acid produced by the bacteria that interferes with the urease activity of
the pathogen [54]. Furthermore, in vitro, L. salivarius can reduce gastric inflammation by regulating local cytokine secretion, especially IL-8, which is directly related to neutrophil recruitment and mucosal inflammation, possibly in response to inhibiting the secretion of cytotoxin-associated protein virulence factor (Cag A) [55]. Multiple studies have found the presence of Epstein-Barr virus (EBV) and H. pylori in gastric cancer specimens (ranging from 6% to 12%). Meta-analysis has also evaluated the importance of co-infection of these two pathogens in gastric cancer [56–59]. Currently, different studies [56, 57, 60] have explored the possible roles of combined infection by H. pylori and EBV in the development of gastritis, peptic ulcer, dyspepsia, and gastro esophageal reflux disease (GERD). In the coinfection process of H. pylori and EBV, the recruitment of immune cells at the infected site significantly increase, thus aggravating gastric inflammation and tissue damage [61]. For example, monochloramine is an oxidant produced in the stomach during H. pylori infection, which can induce the transition of EBV from the latent phase to the cleavage phase [62], and H. pylori induces the secretion of interferon γ (IFN-γ), which promotes the inflammatory environment and exacerbates the severity of the disease [61]. The intestinal microbiota can regulate H. pylori infection, and vice versa, this bacterium can alter the composition of the stomach microbiota [63–65]. On the other hand, the microbiota in several human niches have a direct or indirect influence on viral infection, such as EBV and human papillomavirus [66].

Daily changes in intestinal flora composition have been observed after the administration of a drug used to eliminate H. pylori to rats, and it has been found that the number of obligate anaerobes is significantly reduced, the number of short-chain fatty acids (SCFAs) is reduced, and the stall is slightly abnormal [67]. Clostridium difficile has been reported to grow particularly well when strong and/or broad-spectrum antibiotics are used [68]. Administration of CBM588 probiotics at the same time as eradication of H. pylori can inhibit the production of Clostridium difficile toxin A, thus reducing the risk of diarrhea and soft stool in these patients [67]. The stomach microecology of healthy people is balanced, and a stable microenvironment is formed between microorganisms due to long-term symbiosis. The change in any kind of microorganism may have an impact on other microorganisms and microecology.

6. The Microecology of the Stomach Is Involved in the Occurrence of Gastric Diseases

H. pylori can hydrolyze urea to produce ammonia through urease, which in turn increases the local pH value and is conducive to the colonization of other microorganisms. Furthermore, both epigenetic and direct inheritance of H. pylori can directly lead to gene instability, including double-stranded DNA breakage [69, 70].

Gastric microorganisms can aggravate the histological changes caused by H. pylori infection. After H. pylori eradication, the atrophy score of 20.8% for subjects decreased [50]. Coinfection of H. pylori and Neisseria subflava has been reported to be associated with the formation of lymphatic follicles in the human stomach [71]. Neisseria subflava can induce IL-8 production by gastric epithelial cells and promote the progression of hypochloric-induced gastric function lesions. The occurrence of GA and IM leads to a reduction in gastric acid-secreting wall cells [72], which may be conducive to the proliferation of gastric microorganisms or the colonization of oral microorganisms in the stomach [73]. In the absence of H. pylori infection, the presence of atrophy or IM was associated with an increased abundance of Granulicatella, Actinomyces, Rothia, Peptostreptococcus, Streptococcus, Abiotrophia, and Parvimonas [49]. A previously published study by Parsons et al. focused on evaluating the diversity of stomach microbes in various hydrochloric acid states, including H. pylori-induced atrophic gastritis and autoimmune atrophic gastritis (AIG). This study showed that the microbial diversity and bacterial abundance of AIG patients were higher than those of normal stomachs, and Streptococcus accounted for the largest proportion in the investigated group [74]. Currently, the study on the gastric microbiota of patients with AIG is still in an early stage. In subjects with gastric mucosal atrophy after removal of H. pylori, the number of Faecalibacterium, Kais- tobacter, and Rahmella decreased [49]. Sjöstedt et al. studied microbial colonization in the oropharynx, esophagus, and stomach of 60 patients and found that patients with a history of gastritis, gastric cancer, and gastrectomy had more gastric microbes than patients with gastric or duodenal ulcers. Gastric cancer patients have the largest number of different microbial colonization [75].

Currently, there are many studies on the effects of viruses on the intestinal nervous system, and it is found that the effects of viruses on the intestinal nervous system can lead to gastrointestinal motor disorders. EBV infection is closely related to gastritis and gastric cancer [20, 57]. EBV can inhibit the proliferation of T cells and the toxicity of natural killer cells and maintain the activity of the virus in host cells, resulting in sustained damage to the gastric mucosa [76]. EBV can keep the virus at a very low expression level by targeting the gene expression of the virus and avoid the attack of the human immune response [76, 77]. Recently, some authors reviewed the changes of some microorganisms in gastric diseases [78] (shown in Table 1).

7. Microorganism and the Treatment of Gastric Disease

The modern history of probiotics begins at the beginning of the 1900s, Nobel Prize winner Elie Metchnikoff found that when yoghurt or fermented milk containing Lactobacillus bulgaricus was consumed, the gastrointestinal condition improved significantly, and hence, the practice of using probiotics has arisen [89, 90].

According to the Food and Agriculture Organization/World Health Organization [91, 92], probiotics are living microbial agents that, when given in sufficient quantities, have a beneficial effect on the host. Many strains of lactic
acid bacteria benefit the host by inhibiting the growth of pathogens and inhibiting inflammation, tumor, and allergic modification [93–96]. The beneficial effects of probiotic bacteria on host microbial environment may be due to their potential impact on the digestive tract microbial community and the intestinal immune system, including their ability to compete with intestinal pathogens, increase the secretion of Immunoglobin A (IgA), regulate the expression and secretion of cytokine, stimulate mucin, bacteriocins, and lactic acid production, and adjust the microbiota growth [97–99]. Some probiotics have not only preventive effects but also therapeutic effects by promoting epithelial cell growth [100] and angiogenesis [101] and upregulating the expression of anti-inflammatory cytokines [102]. Therefore, the addition of probiotics to patients undergoing radical treatment for H. pylori can prevent gastritis caused by other microorganisms [49]. Probiotics have a potential role in alleviating gastritis after radical treatment for H. pylori [103, 104]. Lactobacillus given to rats as a single probiotic strain, such as Lactobacillus gasseri OLL2716 [105, 106], Lactobacillus acidophilus [100, 107], Lactobacillus rhamnosus GG [108], or in the form of probiotic mixtures, has been reported to promote ulcer healing. Lactobacillus rhamnosus GG improves the ratio of proliferation to apoptosis of host cells and causes continuous regeneration of epithelial cells, especially around the edge of ulcers [108, 109]. Saccharomyces boulardii has a good therapeutic effect on ibuprofen-induced gastric ulcer in rats [110]. The neuraminidase activity of the Saccharomyces boulardii can remove surface α (2-3)-linked sialic acid from apical cells of the gastric epithelium. Thus, by eliminating sialic acid, H. pylori mucin-mediated adhesion to gastric epithelial cells is prevented [111].

Acetic acid, propionic acid, and butyric acid are all SCFAs that are important energy sources in the body and are produced primarily in the colon as a result of the metabolism of indigestible carbohydrates by microorganisms [112], which can regulate energy balance through the brain-gut axis. Excess alcohol consumption damages the gastric mucosal barrier, leading to extensive hemorrhagic damage, accumulating oxidative stress, and increasing the inflammatory response through the production of cytokines such as interleukin-1α, TNF-α, β, interleukin-6 (IL-6), and tumor necrosis factor-α (TNF-α) [113]. Butyrate pre-treatment can negatively regulate the proinflammatory cytokines IL-1β, TNF-α, and IL-6, enhance the function of gastric wall mucus [114], and has a protective effect on ethanol-induced gastric ulcer formation. Lactobacilli and Bifidobacteria, as the main genera of probiotics, have been shown to produce acetic acid in vitro, but cannot produce propionic acid and butyric acid as the main metabolites. However, these common probiotics can stimulate the production of SCFAs by other colonic bacteria, producing pyruvate and lactic acid from dietary carbohydrates [115]. Nagaoka et al. reported that Bifidobacterium bifidum YIT 4007 improved acute gastric injury induced by ethanol and acetic acid in rats [116]. In addition, probiotics, prebiotics, and/or symbiotics can regulate the gut microbiome, thereby inhibiting pathogens and promoting the growth of SCFA-producing bacteria [117].

| Gastro-Related Diseases | Control Group                  | Changes in Gastric Microorganisms                                                                 | Reference |
|-------------------------|--------------------------------|-------------------------------------------------------------------------------------------------|-----------|
| Atrophic Gastritis      | Healthy Subjects               | Streptococcus, Prevotella                                                                     | Enstrand L, et al. [79] |
| Gastric Cancer          | Normal Mucosa                  | Microorganisms, Anaerobic Bacteria (eg Clostridium and Bacteroides species)†                    | Dicksved J, et al. [80] |
| Chronic Gastritis       | Normal Control Group           | Prevotella, Streptococcus, Neisseria, Porphyromonas, Haemophilus                               | Nardone G, et al. [81] |
| H. Pylori-Infected Gastritis | H. Pylori-Negative Individuals | Proteobacteria, Firmicutes                                                                     | Li XX, et al. [82] |
| Atrophic Gastritis      | Healthy Controls               | Streptococcus, Prevotella                                                                     | Ozbey G, et al. [83] |
| H. Pylori-Infected Antral Gastritis | Without H. Pylori Infection | Proteobacteria, Firmicutes, Streptococcus                                                     | Liu J, et al. [84] |
| H. Pylori-Infected Peptic Ulcer | /                             | Streptococcus, Neisseria, Rothia, Staphylococcus                                               | Bilello J, et al. [78] |
| Invasive Gastric Cancer | Without Cancer                 | Porphyromonas, Neisseria, Streptococcus Sinensis, Lactobacillus Coleohomonis ↑, Lachnospiraceae↑, Pseudomonas↑ | Zhang S, et al. [85] |
| Gastric Cancer          |                                  | Nitrate-reducing bacterial species reducing nitrate (including Neisseria, Clostridium, Staphylococcus, and Clostridium Colicani)↑ | Hsieh YY, et al. [86] |
| Gastric Cardia Adenocarcinoma | /                             | Firmicutes, Bacteroidetes and Proteobacteria at the phylum level                               | Shao D, et al. [87] |
| Gastric Cancer          | Chronic Gastritis              | Achromobacter, Citrobacter, Phyllobacterium, Clostridium, Rhodococcus, Lactobacillus ↑, Prevotella↑, Streptococcus↑, Veillonella↑, Haemophilus↑, Neisseria↑ | Ferreira RM, et al. [88] |
| Gastric Cancer          | Non-Tumor Tissues              |                                                                                                | Shao D, et al. [87] |
8. Conclusions
In recent years, with changes in diet and increased work pressure, the incidence of H. pylori infection and gastric ulcer is very high, and H. pylori infection is considered a primary risk factor for gastric cancer, and gastric ulcer also has a certain rate of malignant change, so it is particularly important to treat H. pylori infection and gastric ulcer. Most of the previous studies focused on H. pylori and relatively ignored other microorganisms in the stomach and the overall microecology of the stomach. At present, research on the correlation between gastric microorganisms is mostly limited to the relationship between H. pylori and non-H. pylori microorganisms. There is a lack of in-depth understanding for the improving effect of probiotics on gastric ulcers. We should consider microecology as a whole when we study microbes in the stomach in the future. In the treatment of microbial infection, blind sterilization is not recommended, leading to ignore the overall relationship between the stomach microbes. We should also consider the variety of factors that may affect the stomach microbiota, such as drugs, diet, smoking, and drinking habits. The ecological characteristics of different areas in the stomach are different, so the biome may be different. The stomach is not a single ecological environment, and different anatomical parts may have different microbial colonization. In general, these need to be further studied. At present, there is little direct evidence on the non-H. pylori microbiome in gastric ulcers, precancerous lesions, and gastric cancer. Future gastric microbiome research will include transcriptomics, metabolomics, and proteomics, which will provide more opportunities for functional studies of gastric microorganisms.

Conflicts of Interest
The authors have no conflicts of interest to declare.

Authors’ Contributions
Xiaoyan Duan contributed to the writing and the preparation of the manuscript. Ping Chen contributed to the concept of the study. Xiaoxia Xu and Meiling Han participated in a literature search on fungi and viruses in the stomach. Jianbo Li contributed to the design, editing, and review of the manuscript.

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References
[1] C. P. Pattison, M. J. Combs, and B. J. Marshall, "Helicobacter pylori and peptic ulcer disease: evolution to revolution to resolution," AJR. American Journal of Roentgenology, vol. 168, no. 6, pp. 1415–1420, 1997.
[2] K. Honda and D. R. Littman, “The microbiome in infectious disease and inflammation,” Annual Review of Immunology, vol. 30, no. 1, pp. 759–795, 2012.
[3] M. Hattori and T. D. Taylor, “The human intestinal microbiome: a new frontier of human biology,” DNA Research, vol. 16, no. 1, pp. 1–12, 2009.
[4] N. B. Arweiler and L. Netuschil, “The oral microbiota,” Advances in Experimental Medicine and Biology, vol. 902, pp. 45–60, 2016.
[5] B. Jiang, Gastroenterology, People’s Medical Publishing House, Beijing, China, 2015.
[6] P. Correa, “Human gastric carcinogenesis: a multistep and multifactorial process—First American Cancer Society Award Lecture on Cancer Epidemiol Prevention,” Cancer Research, vol. 52, no. 24, pp. 6757–6740, 1992.
[7] Z. Liu, B. S. Feng, X. Chen, J. Su, and P. C. Yang, “Interleukin (IL)-23 suppresses IL-10 in inflammatory bowel disease,” The Journal of Biological Chemistry, vol. 287, no. 5, pp. 3591–3597, 2012.
[8] E. K. Brint, J. Mac Sharry, A. Fanning, F. Shanahan, and E. M. Quigley, “Differential expression of toll-like receptors in patients with irritable bowel syndrome,” The American Journal of Gastroenterology, vol. 106, no. 2, pp. 329–336, 2011.
[9] C. Chojnacki, P. Mikulska, A. Knopik-Dąbrowicz, A. Kaczka, J. Chojnacki, and P. Konrad, “The role of intraepithelial lymphocytes in pathogenesis of small intestinal bacterial overgrowth syndrome,” Polski Merkuriusz Lekarski: Organ Polskiego Towarzystwa Lekarskiego, vol. 49, no. 289, pp. 23–27, 2021.
[10] F. Liao, Y. C. Hsu, S. H. Kuo et al., “Genetic polymorphisms and tissue expression of interleukin-22 associated with risk and therapeutic response of gastric mucosa-associated lymphoid tissue lymphoma,” Blood Cancer Journal, vol. 4, no. 10, p. XX, 2014.
[11] F. De Filippis, L. Paparo, R. Nocerino et al., “Specific gut microbiome signatures and the associated pro-inflammatory functions are linked to pediatric allergy and acquisition of immune tolerance,” Nature Communications, vol. 12, no. 1, p. 5958, 2021.
[12] U. C. Ghoshal, U. Ghoshal, A. Ayagari et al., “Tropical sprue is associated with contamination of small bowel with aerobic bacteria and reversible prolongation of oroceleal transit time,” Journal of Gastroenterology and Hepatology, vol. 18, no. 5, pp. 540–547, 2003.
[13] R. Nasr, A. Shamseddine, D. Mukherji, F. Nassar, and S. Temraz, “The crosstalk between microbiome and immune response in gastric cancer,” International Journal of Molecular Sciences, vol. 21, no. 18, p. 6586, 2020.
[14] A. Ieni, V. Barresi, L. Rigoli, F. Fedele, G. Tuccari, and R. A. Caruso, “Morphological and cellular features of innate immune reaction in Helicobacter pylori gastritis: a brief review,” International Journal of Molecular Sciences, vol. 17, no. 1, p. 109, 2016.
[15] B. Zhang and J.-L. Ren, “Research progress of gastric mucosal immune mechanism,” World Chinese Journal of Digestology, vol. 13, no. 21, pp. 2605–2609, 2005.
[16] D. Bimczok, J. Y. Kao, M. Zhang et al., “Human gastric epithelial cells contribute to gastric immune regulation by providing retinoic acid to dendritic cells,” Mucosal Immunology, vol. 8, no. 3, pp. 533–544, 2015.
[17] M. H. Magalhães-Costa, B. R. Reis, V. L. Chagas, T. Nunes, H. S. Souza, and C. Zaltman, "Focal enhanced gastritis and macrophage microaggregates in the gastric mucosa: potential role in the differential diagnosis between Crohn’s disease and ulcerative colitis," *Arquivos de Gastroenterologia*, vol. 51, no. 4, pp. 276–282, 2014.

[18] M. Kaparakis, A. K. Walduck, J. D. Price et al., "Macrophages are mediators of gastritis in acute Helicobacter pylori infection in C57BL/6 mice," *Infection and Immunity*, vol. 76, no. 5, pp. 2235–2239, 2008.

[19] S. Gordon, "Alternative activation of macrophages," *Nature Reviews. Immunology*, vol. 3, no. 1, pp. 23–35, 2003.

[20] S. Nie and Y. Yuan, "The role of gastric mucosal immunity in gastric diseases," *Journal of Immunology Research*, vol. 2020, Article ID 7927054, 8 pages, 2020.

[21] J. Shiu and T. G. Blanchard, "Dendritic cell function in the host response to Helicobacter pylori infection of the gastric mucosa," *Pathogens and Disease*, vol. 67, no. 1, pp. 46–53, 2013.

[22] M. Hansson, M. Sundquist, S. Hering, B. S. Lundin, M. Hermansson, and M. Quiding-Järbrink, "DC-LAMP+ dendritic cells are recruited to gastric lymphoid follicles in Helicobacter pylori-infected individuals," *Infection and Immunity*, vol. 81, no. 10, pp. 3684–3692, 2013.

[23] R. M. Steinman, "Decisions about dendritic cells: past, present, and future," *Annual Review of Immunology*, vol. 30, pp. 1–22, 2012.

[24] K. Kranzer, L. Sollner, M. Aigner et al., "Impact of Helicobacter pylori virulence factors and compounds on activation and maturation of human dendritic cells," *Infection and Immunity*, vol. 73, no. 7, pp. 4180–4189, 2005.

[25] M. Michetti, C. P. Kelly, J. P. Kraehenbühl, H. Bouzourene, and P. Michetti, "Gastric mucosal alpha (4) beta (7)-integrin-positive CD4 T lymphocytes and immune protection against helicobacter infection in mice," *Gastroenterology*, vol. 119, no. 1, pp. 109–118, 2000.

[26] A. Carbo, J. Bassaganya-Riera, M. Pedragosa et al., "Predictive computational modeling of the mucosal immune responses during Helicobacter pylori infection," *PLoS One*, vol. 8, no. 9, article e73365, 2013.

[27] C. F. Flach, M. Mozer, M. Sundquist, J. Holmgren, and S. Raghavan, "Mucosal vaccination increases local chemokine production attracting immune cells to the stomach mucosa of Helicobacter pylori infected mice," *Vaccine*, vol. 30, no. 9, pp. 1636–1643, 2012.

[28] P. J. Parekh, L. A. Balart, and D. A. Johnson, "The influence of the gut microbiome on obesity, metabolic syndrome and gastrointestinal disease," *Clinical and Translational Gastroenterology*, vol. 6, no. 6, p. e91, 2015.

[29] Y. J. Kim, B. K. Kim, S. J. Park, and J. H. Kim, "Impact of Fusobacterium nucleatum in the gastrointestinal tract on natural killer cells," *World Journal of Gastroenterology*, vol. 27, no. 29, pp. 4879–4889, 2021.

[30] L. Parhi, T. Alon-Maimon, A. Sol et al., "Breast cancer colonization by Fusobacterium nucleatum accelerates tumor growth and metastatic progression," *Nature Communications*, vol. 11, no. 1, p. 3259, 2020.

[31] R. H. Hunt, M. Camilleri, S. E. Crowe et al., "The stomach in health and disease," *Gut*, vol. 64, no. 10, pp. 1650–1668, 2015.

[32] E. M. Bik, P. B. Eckburg, S. R. Gill et al., "Molecular analysis of the bacterial microbiota in the human stomach," *Proceedings of the National Academy of Sciences of the United States of America*, vol. 103, no. 3, pp. 732–737, 2006.

[33] H. J. Monstein, A. Tiveljung, C. H. Kraft, K. Borch, and J. Jonasson, "Profiling of bacterial flora in gastric biopsies from patients with Helicobacter pylori-associated gastritis and histologically normal control individuals by temperature gradient gel electrophoresis and 16S rDNA sequence analysis," *Journal of Medical Microbiology*, vol. 49, no. 9, pp. 817–822, 2000.

[34] T. H. Li, Y. Qin, P. C. Sham, K. S. Lau, K. M. Chu, and W. K. Leung, "Alterations in Gastric Microbiota After H. Pylori Eradication and in Different Histological Stages of Gastric Carcinogenesis," *Scientific Reports*, vol. 7, no. 1, article 44935, 2017.

[35] K. Ramaswamy, M. Correa, and A. Koshy, "Non-healing gastric ulcer associated with Candida infection," *Indian Journal of Medical Microbiology*, vol. 25, no. 1, pp. 57–58, 2007.

[36] N. Soeta, M. Terashima, M. Gotoh et al., "An improved rapid quantitative detection and identification method for a wide range of fungi," *Journal of Medical Microbiology*, vol. 58, no. 8, pp. 1037–1044, 2009.

[37] S. Rickes, U. Schultze, K. Mönkemüller, and P. Malfertheiner, "Walter Krienzit - Sein Leben und seine intuitive Beschreibung von Bakterien im Magen," *Deutsche Medizinische Wochenschrift*, vol. 131, no. 23, pp. 1341–1343, 2006.

[38] E. Dias-Jácome, D. Libânio, M. Borges-Cança, A. Galagar, and P. Pimentel-Nunes, "Gastric microbiota and carcinogenesis: the role of non-Helicobacter pylori bacteria - a systematic review," *Revista Española de Enfermedades Digestivas*, vol. 108, no. 9, pp. 530–540, 2016.

[39] A. M. Stringer, R. J. Gibson, J. M. Bowen, and D. M. Keefe, "Chemotherapy-induced modifications to gastrointestinal microflora: evidence and implications of change," *Current Drug Metabolism*, vol. 10, no. 1, pp. 79–83, 2009.

[40] M. Rajilic-Stojanovic, C. Figueiredo, A. Smet et al., "Systematic review: gastric microbiota in health and disease," *Alimentary Pharmacology & Therapeutics*, vol. 51, no. 6, pp. 582–602, 2020.

[41] J. Schulze and U. Sonnenborn, "Yeasts in the gut: from commensals to infectious agents," *Deutsches Ärzteblatt International*, vol. 106, no. 51–52, pp. 837–842, 2009.

[42] M. Zwolinska-Wcisło, A. Budak, J. Bogdął, T. Trojanowska, and J. Stachura, "Fungal colonization of gastric mucosa and its clinical relevance," *Medical Science Monitor*, vol. 7, no. 5, pp. 982–988, 2001.

[43] Y. B. Gong, J. L. Zheng, B. Jin et al., "Particular Candida albicans strains in the digestive tract of dyspeptic patients, identified by multilocus sequence typing," *PLoS One*, vol. 7, no. 4, article e35311, 2012.

[44] E. Karczewska, I. Wojtas, E. Sito et al., "Assessment of coexistence of Helicobacter pylori and Candida fungi in diseases of the upper gastrointestinal tract," *Journal of Physiology and Pharmacology*, vol. 60, Supplement 6, pp. 33–39, 2009.

[45] E. C. Von Rosenvinge, Y. Song, J. R. White, C. Maddox, T. Blanchard, and W. F. Fricke, "Immune status, antibiotic medication and pH are associated with changes in the stomach fluid microbiota," *The ISME Journal*, vol. 7, no. 7, pp. 1354–1366, 2013.

[46] J. M. Noto and R. M. Peek Jr., "The gastric microbiome, its interaction with Helicobacter pylori, and its potential role
in the progression to stomach cancer,” *PLoS Pathogens*, vol. 13, no. 10, article e1006573, 2017.

[47] S. M. Kelly, J. R. Crampton, and J. O. Hunter, “Helicobacter pylori increases gastric antral juxtamucosal pH,” *Digestive Diseases and Sciences*, vol. 38, no. 1, pp. 129–131, 1993.

[48] J. L. Lofgren, M. T. Whary, Z. Ge et al., “Lack of commensal flora in Helicobacter pylori-infected INS-GAS mice reduces gastritis and delays intraepithelial neoplasia,” *Gastroenterology*, vol. 140, no. 1, pp. 210–220, 2011.

[49] J. J. Lofgren, M. T. Whary, Z. Ge et al., “Helicobacter pylori infection in gastric carcinogenesis, cytokine expression associated with Helicobacter pylori and intestinal metaplasia 1 year after Helicobacter pylori eradication,” *Gut*, vol. 69, no. 9, pp. 1572–1580, 2020.

[50] J. J. Sung, S. R. Lin, J. Y. Ching et al., “Atrophy and intestinal metaplasia one year after cure of H. pylori infection: a prospective, randomized study,” *Gastroenterology*, vol. 119, no. 1, pp. 7–14, 2000.

[51] E. Doorakkers, J. Lagergren, L. Engstrand, and N. Brusselaers, “Helicobacter pylori eradication treatment and the risk of gastric adenocarcinoma in a Western population,” *Gut*, vol. 67, no. 12, pp. 2092–2096, 2018.

[52] J. K. Y. Hooi, W. Y. Lai, W. K. Ng et al., “Global prevalence of Helicobacter pylori infection: systematic review and meta-analysis,” *Gastroenterology*, vol. 153, no. 2, pp. 420–429, 2017.

[53] Y. Zavros, G. Rieder, A. Ferguson, and J. L. Merchant, “Gastritis and hypergastrinemia due to *Acinetobacter baumannii* in mice,” *Infection and Immunity*, vol. 70, no. 5, pp. 2630–2639, 2002.

[54] Y. Aiba, N. Suzuki, A. M. Kabir, A. Takagi, and Y. Koga, “Lactic acid-mediated suppression of Helicobacter pylori by the oral administration of Lactobacillus salivarius as a probiotic in a gnotobiotic murine model,” *The American Journal of Gastroenterology*, vol. 93, no. 11, pp. 2097–2101, 1998.

[55] K. A. Ryan, A. M. O’Hara, J. P. Van Pijkeren, F. P. Douillard, and O’Toole PW, “Lactobacillus salivarius modulates cytokine induction and virulence factor gene expression in Helicobacter pylori,” *Journal of Medical Microbiology*, vol. 58, no. 8, pp. 996–1005, 2009.

[56] M. G. Cárdenas-Mondragón, R. Carreón-Talavera, M. Camorlina-Ponce, A. Gomez-Delgado, J. Torres, and E. M. Fuentes-Panana, “*Epstein-Barr virus and Helicobacter pylori co-infection are positively associated with severe gastric atrophy in pediatric patients*,” *PLoS One*, vol. 8, no. 4, article e62850, 2013.

[57] J. L. Martinez-López, J. Torres, M. Camorlina-Ponce, A. Mantilla, Y. A. Leal, and E. M. Fuentes-Panana, “Evidence of *Epstein-Barr virus association with gastric cancer and non-atrophic gastritis*,” *Viruses*, vol. 6, no. 1, pp. 301–318, 2014.

[58] L. Zong and Y. Seto, “CpG island methylator phenotype, Helicobacter pylori, *Epstein-Barr virus, and microsatellite instability and prognosis in gastric cancer: a systematic review and meta-analysis*,” *PLoS One*, vol. 9, no. 1, article e86097, 2014.

[59] J. Y. Kim, B. N. Bae, G. Kang, H. J. Kim, and K. Park, “Cytokine expression associated with Helicobacter pylori and *Epstein-Barr virus infection in gastric carcinogenesis*,” *Apnmis*, vol. 125, no. 9, pp. 808–815, 2017.

[60] O. Del Moral-Hernández, C. A. Castañón-Sánchez, S. Reyes-Navarrete et al., “Multiple infections by EBV, HCMV and Helicobacter pylori are highly frequent in patients with chronic gastritis and gastric cancer from Southwest Mexico: an observational study,” *Medicine*, vol. 98, no. 3, article e14124, 2019.

[61] R. Dávila-Collado, O. Jarquin-Durán, L. T. Dong, and J. L. Espinoza, “*Epstein-Barr virus and Helicobacter pylori coinfection in non-malignant gastroduodenal disorders*,” *Pathogens*, vol. 9, no. 2, p. 104, 2020.

[62] J. Minoura-Etoh, K. Gotoh, R. Sato et al., “Helicobacter pylori-associated oxidant monochloramine induces reactivation of *Epstein-Barr virus* (EBV) in gastric epithelial cells latently infected with EBV,” *Journal of Medical Microbiology*, vol. 55, no. 7, pp. 905–911, 2006.

[63] J. L. Espinoza, A. Matsumoto, H. Tanaka, and I. Matsumura, “*Gastric microbiota: an emerging player in Helicobacter pylori-induced gastric malignancies*,” *Cancer Letters*, vol. 414, pp. 147–152, 2018.

[64] O. O. Coker, Z. Dai, Y. Nie et al., “*Mucosal microbiome dysbiosis in gastric carcinogenesis*,” *Gut*, vol. 67, no. 6, pp. 1024–1032, 2018.

[65] T. Alarcón, L. Llorca, and G. Perez-Perez, “Impact of the microbiota and gastric disease development by Helicobacter pylori,” *Current Topics in Microbiology and Immunology*, vol. 400, pp. 253–275, 2017.

[66] R. Wakabayashi, Y. Nakahama, V. Nguyen, and J. L. Espinoza, “The host-microbe interplay in human papillomavirus-induced carcinogenesis,” *Microorganisms*, vol. 7, no. 7, p. 199, 2019.

[67] K. Imase, M. Takahashi, A. Tanaka et al., “Efficacy of *Clostridium butyricum* preparation concomitantly with Helicobacter pylori eradication therapy in relation to changes in the intestinal microbiota,” *Microbiology and Immunology*, vol. 52, no. 3, pp. 156–161, 2008.

[68] C. D. Settle and M. H. Wilcox, “Review article: antibiotic-induced *Clostridium difficile* infection,” *Alimentary Pharmacology & Therapeutics*, vol. 10, no. 6, pp. 835–841, 1996.

[69] K. Hanada and D. Y. Graham, “*Helicobacter pylori and the molecular pathogenesis of intestinal-type gastric carcinoma*,” *Expert Review of Anticancer Therapy*, vol. 14, no. 8, pp. 947–954, 2014.

[70] D. Kidane, “Molecular mechanisms of *H. pylori*-induced DNA double-strand breaks,” *International Journal of Molecular Sciences*, vol. 19, no. 10, p. 2891, 2018.

[71] M. Nakamura, H. Matsu, H. Serizawa et al., “Coinfection of *Helicobacter pylori* and *Neisseria subflava* is closely associated with lymph follicle formation in human stomach,” *Alimentary Pharmacology & Therapeutics*, vol. 24, pp. 207–213, 2006.

[72] Y. Michigami, J. Watari, C. Ito et al., “Long-term effects of *H. pylori* eradication on epigenetic alterations related to gastric carcinogenesis,” *Scientific Reports*, vol. 8, no. 1, article 14369, 2018.

[73] S. Shichijo and Y. Hirata, “Characteristics and predictors of gastric cancer after *Helicobacter pylori* eradication,” *World Journal of Gastroenterology*, vol. 24, no. 20, pp. 2163–2172, 2018.

[74] B. N. Parsons, U. Z. Ijaz, R. D’Amore et al., “Comparison of the human gastric microbiota in hypochlorhydric states arising as a result of *Helicobacter pylori*-induced atrophic gastritis, autoimmune atrophic gastritis and proton pump inhibitor use,” *PLoS Pathogens*, vol. 13, no. 11, article e1006653, 2017.

[75] S. Sjostedt, A. Heimdahl, L. Kager, and C. E. Nord, “*Microbial colonization of the oropharynx, esophagus and stomach in* BioMed Research International
patients with gastric diseases,” *European Journal of Clinical Microbiology*, vol. 4, no. 1, pp. 49–51, 1985.

[76] I. Polakovicova, S. Jerez, I. A. Wichmann, A. Sandoval-Bórquez, N. Carrasco-Véliz, and A. H. Corvalán, “Role of micro-RNAs and exosomes in Helicobacter pylori and Epstein-Barr virus associated gastric cancers,” *Frontiers in Microbiology*, vol. 9, p. 636, 2018.

[77] M. Albanese, T. Tagawa, A. Buschle, and W. Hammerschmidt, “MicroRNAs of Epstein-Barr virus innate and adaptive antiviral immunity,” *Journal of Virology*, vol. 91, no. 16, article e01667, 2017.

[78] J. Biller and I. Okereke, “Impact of environmental and pharmacologic changes on the upper gastrointestinal microbiome,” *Biomedicine*, vol. 9, no. 6, p. 617, 2021.

[79] L. Engstrand and M. Lindberg, “Helicobacter pylori and the gastric microbiota,” *Best Practice & Research. Clinical Gastroenterology*, vol. 27, no. 1, pp. 39–45, 2013.

[80] J. Dicksved, M. Lindberg, M. Rosenquist, H. Enroth, J. K. Jansson, and L. Engstrand, “Molecular characterization of the stomach microbiota in patients with gastric cancer and in controls,” *Journal of Medical Microbiology*, vol. 58, no. 4, pp. 509–516, 2009.

[81] G. Nardone and D. Compare, “The human gastric microbiota: is it time to rethink the pathogenesis of stomach diseases?,” *United European Gastroenterology Journal*, vol. 3, no. 3, pp. 255–260, 2015.

[82] X.-X. Li, G. L.-H. Wong, K.-F. To et al., “Bacterial microbiota profiling in gastritis without Helicobacter pylori infection or non-steroidal anti-inflammatory drug use,” *PLoS One*, vol. 4, no. 11, article e7985, 2009.

[83] G. Ozbey, E. Sproston, and A. Hanafiah, “Helicobacter pylori infection and gastric microbiota,” *European Journal of Gastroenterology and Hepatology*, vol. 10, no. 1, pp. 36–41, 2020.

[84] J. Liu, Y. Xue, and L. Zhou, “Detection of gastritis-associated pathogens by cultivating of gastric juice and mucosa,” *International Journal of Clinical and Experimental Pathology*, vol. 11, no. 4, pp. 2214–2220, 2018.

[85] S. Zhang and D. C. Chen, “Facing a new challenge: the adverse effects of antibiotics on gut microbiota and host immunity,” *Chinese Medical Journal*, vol. 132, no. 10, pp. 1135–1138, 2019.

[86] Y. Y. Hsieh, S. Y. Tung, H. Y. Pan et al., “Increased abundance of Clostridium and Fusobacterium in gastric microbiota of patients with gastric cancer in Taiwan,” *Scientific Reports*, vol. 8, no. 1, p. 158, 2018.

[87] D. Shao, E. Vogtmann, A. Liu et al., “Microbial characterization of esophageal squamous cell carcinoma and gastric cardioadrenaecarcinoma from a high-risk region of China,” *Cancer*, vol. 125, no. 22, pp. 3993–4002, 2019.

[88] R. M. Ferreira, J. Pereira-Marques, I. Pinto-Ribeiro et al., “Gastric microbial community profiling reveals a dysbiotic cancer-associated microbiota,” *Gut*, vol. 67, no. 2, pp. 226–236, 2018.

[89] D. M. Lilly and R. H. Stillwell, “Probiotics: growth-promoting factors produced by microorganisms,” *Science*, vol. 147, no. 3659, pp. 747–748, 1965.

[90] S. H. Podolsky, “Methchnikoff and the microbiome,” *Lancet*, vol. 380, no. 9586, pp. 1810–1811, 2012.

[91] FAO/WHO, *Guidelines for the Evaluation of Probiotics in Food. Report of a Joint FAO/WHO Working Group on Drafting Guidelines for the Evaluation of Probiotics in Food*, World Health Organization, London, Ontario, Canada, 2002.

[92] C. Hill, F. Guarnier, G. Reid et al., “The International Scientific Association for Probiotics and Prebiotics consensus statement on the scope and appropriate use of the term probiotic,” *Nature Reviews. Gastroenterology & Hepatology*, vol. 11, no. 8, pp. 506–514, 2014.

[93] A. M. Cain and K. D. Karpa, “Clinical utility of probiotics in inflammatory bowel disease,” *Alternative Therapies in Health and Medicine*, vol. 17, no. 1, pp. 72–79, 2011.

[94] W. S. Hong, Y. P. Chen, and M. J. Chen, “The anti-inflammatory effect of kefir lactobacilli,” *Journal of Food Science*, vol. 75, no. 8, pp. H244–H253, 2010.

[95] E. Isolauri, Y. Sütas, P. Kankaanpää, H. Arvilommi, and S. Salminen, “Probiotics: effects on immunity,” *The American Journal of Clinical Nutrition*, vol. 73, Supplement 2, pp. 444S–450S, 2001.

[96] P. T. Shyu, G. G. Oyong, and E. C. Cabrera, “Cytotoxicity of Probiotics from Philippine Commercial Dairy Products on Cancer Cells and the Effect on Expression of cfos and cjun Early Apoptotic-Promoting Genes and Interleukin-1β and Tumor Necrosis Factor-α Proinflamatory Cytokine Genes,” *BioMed Research International*, vol. 2014, Article ID 491740, 9 pages, 2014.

[97] K. L. Erickson and N. E. Hubbard, “Probiotic immunomodulation in health and disease,” *The Journal of Nutrition*, vol. 130, no. 2, pp. 403S–409S, 2000.

[98] G. T. Rijkers, S. Bengmark, P. Enck et al., “Guidance for substantiating the evidence for beneficial effects of probiotics: current status and recommendations for future research,” *The Journal of Nutrition*, vol. 140, no. 3, pp. 671S–676S, 2010.

[99] L. Boyanova, G. Gergova, R. Markovska, D. Yordanov, and I. Mitov, “Bacteriocin-like inhibitory activities of seven Lactobacillus delbrueckii subsp. bulgaricus strains against antibiotic susceptible and resistant Helicobacter pylori strains,” *Letters in Applied Microbiology*, vol. 65, no. 6, pp. 469–474, 2017.

[100] P. K. Singh and I. P. Kaur, “Synbiotic (probiotic and ginger extract) loaded floating beads: a novel therapeutic option in an experimental paradigm of gastric ulcer,” *The Journal of Pharmacy and Pharmacology*, vol. 64, no. 2, pp. 207–217, 2012.

[101] P. Dharmani, C. De Simone, and K. Chadee, “The probiotic mixture VSL#3 accelerates gastric ulcer healing by stimulating vascular endothelial growth factor,” *PLoS One*, vol. 8, no. 3, article e58671, 2013.

[102] O. V. Virchenko, T. M. Falalyeyeva, T. V. Beregova, M. Y. Spivak, L. M. Lazarenko, and O. M. Demchenko, "EFFECTS of mono-, poly- and composite probiotics on the ulceration caused by restraint stress,” *Fiziologicheskii Zhurnal*, vol. 61, no. 1, pp. 35–41, 2015.

[103] R. Francavilla, L. Polimeno, A. Demichina et al., “Lactobacillus reuteri strain combination in Helicobacter pylori infection: a randomized, double-blind, placebo-controlled study,” *Journal of Clinical Gastroenterology*, vol. 48, no. 5, pp. 407–413, 2014.

[104] G. Hauser, N. Salkic, K. Vukelic, A. Jajac Knez, and D. Stimac, "Probiotics for standard triple Helicobacter pylori eradication: a randomized, double-blind, placebo-controlled trial," *Medicine*, vol. 94, no. 17, 2015.

[105] M. Uchida, K. Shimizu, and K. Kurakazu, “Yogurt containing Lactobacillus gasseri OLL2176 (LG21 yogurt) accelerated the
healing of acetic acid-induced gastric ulcer in rats,” *Bioscience, Biotechnology, and Biochemistry*, vol. 74, no. 9, pp. 1891–1894, 2010.

[106] M. Uchida and K. Kurakazu, “Yogurt containing Lactobacillus gasseri OLL2716 exerts gastroprotective action against [correction of against] acute gastric lesion and antral ulcer in rats,” *Journal of Pharmacological Sciences*, vol. 96, no. 1, pp. 84–90, 2004.

[107] P. K. Singh, P. K. Deol, and I. P. Kaur, “Entrapment of Lactobacillus acidophilus into alginate beads for the effective treatment of cold restraint stress induced gastric ulcer,” *Food & Function*, vol. 3, no. 1, pp. 83–90, 2012.

[108] E. K. Lam, L. Yu, H. P. Wong et al., “Probiotic Lactobacillus rhamnosus GG enhances gastric ulcer healing in rats,” *European Journal of Pharmacology*, vol. 565, no. 1-3, pp. 171–179, 2007.

[109] E. K. Y. Lam, E. K. K. Tai, M. W. L. Koo et al., “Enhancement of gastric mucosal integrity by _Lactobacillus rhamnosus GG_,” *Life Sciences*, vol. 80, no. 23, pp. 2128–2136, 2007.

[110] P. Girard, M. C. Coppé, Y. Pansart, and J. M. Gillardin, “Gastroprotective effect of Saccharomyces boulardii in a rat model of ibuprofen-induced gastric ulcer,” *Pharmacology*, vol. 85, no. 3, pp. 188–193, 2010.

[111] S. Sakarya and N. Gunay, “Saccharomyces boulardii expresses neuraminidase activity selective for α2, 3-linked sialic acid that decreases Helicobacter pylori adhesion to host cells,” *APMIS*, vol. 122, no. 10, pp. 941–950, 2014.

[112] C. Alexander, K. S. Swanson, G. C. Fahey, and K. A. Garleb, “Perspective: physiologic importance of short-chain fatty acids from nondigestible carbohydrate fermentation,” *Advances in Nutrition*, vol. 10, no. 4, pp. 576–589, 2019.

[113] J. Liu, J. Wang, Y. Shi et al., “Short chain fatty acid acetate protects against ethanol-induced acute gastric mucosal lesion in mice,” *Biological & Pharmaceutical Bulletin*, vol. 40, no. 9, pp. 1439–1446, 2017.

[114] J. Liu, F. Wang, H. Luo et al., “Protective effect of butyrate against ethanol-induced gastric ulcers in mice by promoting the anti-inflammatory, anti-oxidant and mucosal defense mechanisms,” *International Immunopharmacology*, vol. 30, pp. 179–187, 2016.

[115] J. G. LeBlanc, F. Chain, R. Martin, L. G. Bermúdez-Humarán, S. Courau, and P. Langella, “Beneficial effects on host energy metabolism of short-chain fatty acids and vitamins produced by commensal and probiotic bacteria,” *Microbial Cell Factories*, vol. 16, no. 1, p. 79, 2017.

[116] M. Nagaoka, S. Hashimoto, T. Watanabe, T. Yokokura, and Y. Mori, “Anti-ulcer effects of lactic acid bacteria and their cell wall polysaccharides,” *Bioscience, Biotechnology, and Biochemistry*, vol. 58, no. 8, pp. 1012–1017, 1994.

[117] P. Louis and H. J. Flint, “Formation of propionate and butyrate by the human colonic microbiota,” *Environmental Microbiology*, vol. 19, no. 1, pp. 29–41, 2017.