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The Role of Non-Helicobacter Pylori Bacteria in the Pathogenesis of Gastric Diseases

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Abstract In the context of dysbiosis, chronic inflammation, and carcinogenesis, non-Helicobacter pylori bacteria are becoming more widely acknowledged as significant contributors to stomach diseases. The stomach contains a variety of bacterial communities, including *Fusobacterium nucleatum*, *Streptococcus species*, *Lactobacillus species*, *Prevotella species*, *Veillonella species*, and *Propionibacterium acnes*, according to studies employing next-generation sequencing. Because of adaptation processes like urease activity, acid-tolerant metabolism, and biofilm development, these organisms can survive in acidic environments. While some, like *Lactobacillus*, can create metabolites like lactic acid that may impact carcinogenic nitrosation reactions, others, including *F. nucleatum* and *Streptococcus*, cause inflammation through immune activation and cytokine production. A known stomach carcinogen, N-nitroso compound, may be formed more frequently if nitrate-reducing bacteria proliferate. Following *H. pylori* eradication, dysbiosis frequently involves elevated abundance of these taxa, which may impact stomach cancer risk and mucosal integrity. The need for more comprehensive microbiome-targeted therapeutic approaches is highlighted by mounting evidence that non-*H. pylori* bacteria interact either antagonistically or synergistically with *H. pylori* and host factors, causing intestinal metaplasia, gastritis, and tumour progression, even though causality is still being investigated.

Keywords Non-*H. pylori* bacteria, Dysbiosis, Chronic inflammation, Carcinogenesis, Urease Activity

Introduction

A substantial worldwide health burden is attributed to gastrointestinal disorders, which include ailments including peptic ulcers, chronic gastritis, and stomach cancer. Helicobacter pylori (*H. pylori*) have long been known to be a major pathogenic bacterium among the etiological organisms linked to various disorders. *H. pylori* have radically changed our knowledge of gastric pathophysiology and gastrointestinal microbiology since Marshall and Warren discovered it in the early 1980s and showed that it could colonize the stomach's acidic environment. Due in great part to the action of urease, which neutralizes stomach acid and permits the organism to flourish in an otherwise hostile environment, this spiral-shaped, Gram-negative bacteria bacterium has evolved specifically to live

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in the gastric mucosa. Peptic ulcer disease, mucosa-associated lymphoid tissue (MALT) lymphoma, chronic gastritis, and non-cardia stomach cancer have all been closely connected with its colonization [1,2].

Vacuolating cytotoxin A (vacA), cytotoxin-associated gene A (cagA), adhesins, and outer membrane proteins are among the virulence components that contribute to *H. pylori* 's pathogenicity [3]. These components allow the bacterium to stick to the stomach epithelial cells, cause inflammation, and occasionally interfere with the function of the host cell or cause cellular transformation. A persistent inflammatory response brought on by a chronic infection usually damages the stomach epithelium and promotes the development of cancer [4]. Consequently, *H. pylori* have been designated as a Group 1 carcinogen by the World Health Organization [5].

Despite significant regional, socioeconomic, and hygiene-related variations in infection rates and clinical effects, global epidemiological studies have revealed that more than 50% of the world's population carries *H. pylori* [6]. Even though *H. pylori* are so common, not everyone who has the infection goes on to experience symptoms. Host genetics, immunological response, environmental factors (including nutrition), and—most importantly—interactions with other gastric microbiota members are all elements that affect how a disease manifests [7].

Recent developments in high-throughput sequencing technology and molecular diagnostics have allowed for a more thorough investigation of the human gastric microbiome, exposing a rich and varied bacterial population that co-exists in the stomach with or without *H. pylori*. The long-held belief that the stomach is sterile outside of *H. pylori* colonization has been called into question by these findings [8]. The most extensively researched stomach bacterium remains *Helicobacter pylori*; however, growing evidence suggests that other microbial taxa may also contribute to the development of gastric disorders [9]. Indeed, various studies now link non–*H. pylori* genera such as *Streptococcus*, *Lactobacillus*, *Fusobacterium*, *Prevotella*, and *Veillonella* to mucosal inflammation and neoplastic transformation in the stomach (Table 1) [10].

The widespread use of antibiotics and successful *H. pylori* eradication may create ecological niches that allow non–*H. pylori* bacteria with pathogenic potential to flourish, sparking concern over their roles in stomach disease progression [11]. *Prevotella spp.* have been linked to chronic inflammatory responses that may speed up the precancerous cascade; *Lactobacillus* and *Veillonella* may secrete lactic acid in excess, lowering the pH microenvironment and fostering carcinogenesis; *Streptococcus* spp. can facilitate nitrosation reactions leading to N-nitroso compound formation; and *Fusobacterium nucleatum* has been linked to activation of NF-κB signalling and modulation of immune responses that promote tumour growth. There are significant clinical ramifications when these other pathogenic pathways are identified. It implies that the gastric microbiome is a dynamic ecosystem where changes in the relative abundance and activity of several microbial species, in addition to the presence of a single dominating pathogen, cause disease. This emphasizes the necessity of both therapy approaches that target modifying microbial populations rather than eliminating specific species and diagnostic techniques that go beyond *H. pylori* detection to incorporate thorough microbial profiling (Figure 1). Clarifying the causal links between non-*H. pylori* bacteria and stomach disorders will be essential as the area of gastric microbiome research develops in order to incorporate these discoveries into individualized preventive, monitoring, and treatment plans [12]. For example, gastric cancer tissues have been found to contain higher concentrations of *Fusobacterium nucleatum*, a microbe that has been linked to colorectal cancer in the past, especially in situations where *H. pylori* are not present [13].

Following the removal of *H. pylori*, some of these bacteria may function as opportunistic pathogens, flourishing in the changed mucosal habitats, or they may work in concert with host immunity or stomach epithelial cells to produce their effects.

Non-*H. pylori* bacteria can cause gastric disease in a number of ways, including (i) directly interfering with epithelial signalling or repair pathways; (ii) producing reactive oxygen and nitrogen species that damage DNA; (iii) producing carcinogenic compounds like N-nitroso compounds through nitrate reduction; and (iv) causing chronic inflammation by activating innate immune receptors like toll-like receptors (TLRs) [14,15].

Both ambient influences and gradual pathological alterations in the stomach mucosa have an impact on the extremely dynamic composition of the gastric microbiota. By modifying stomach pH and favouring particular taxa, dietary habits, the use of proton pump inhibitors (PPIs), and the administration of antibiotics are known to change microbial communities. Particularly, PPI medication raises the pH of the stomach and breaks down the acidic barrier, which causes the overall microbial diversity to decrease and oral-derived bacteria including *Streptococcus*, *Veillonella*, and *Prevotella* to

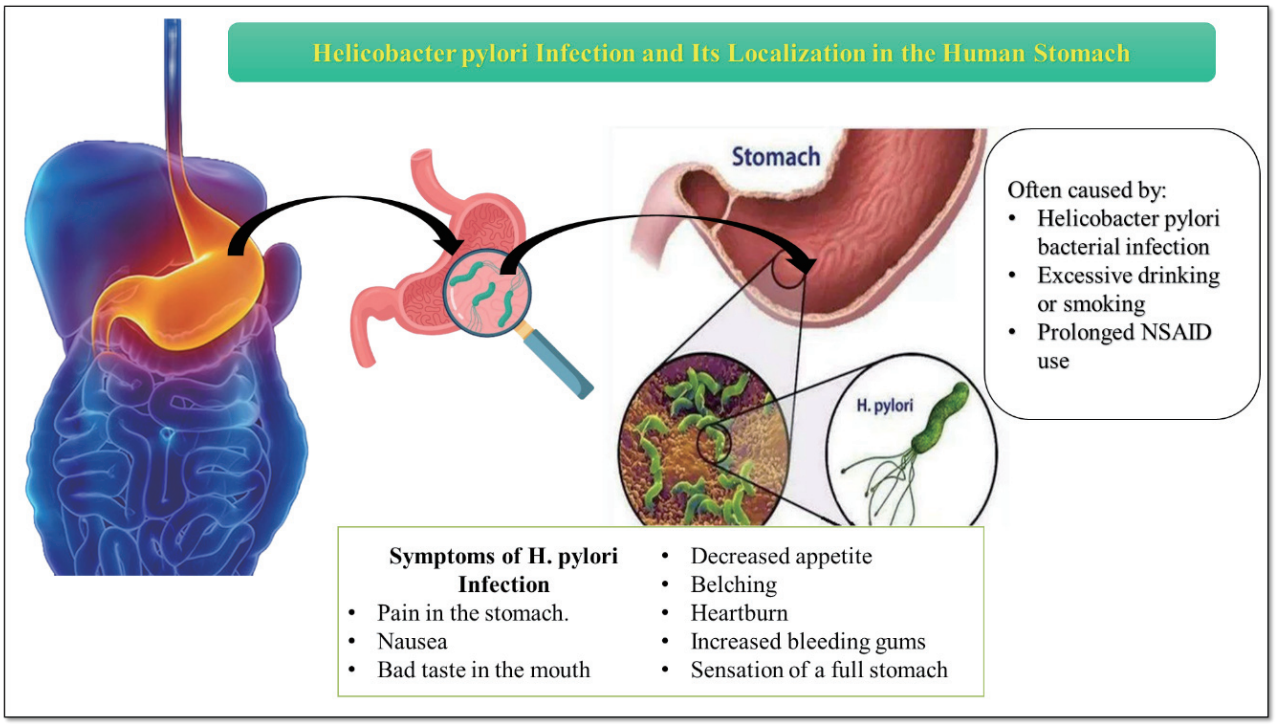

Figure 1: Localization and Clinical Impact of Helicobacter pylori Infection in the Human Stomach
This figure illustrates the colonization of the human stomach by Helicobacter pylori, a spiral-shaped, gram-negative bacterium that survives in the gastric mucosa. The diagram highlights the anatomical localization of the infection, beginning with ingestion and subsequent adherence of the bacteria to the stomach lining. The magnified inset shows H. pylori embedded within the gastric mucosal layer, where it releases urease and other virulence factors that neutralize gastric acid, damage epithelial cells, and promote inflammation.

overrepresent [16, 17]. Similarly, the administration of broad-spectrum antibiotics has been linked to the enrichment of opportunistic bacteria that can survive in changed stomach conditions and the temporary loss of commensal species [18]. As gastric disease progresses from chronic gastritis to atrophic gastritis, intestinal metaplasia, and ultimately adenocarcinoma, longitudinal studies have documented a gradual shift in community composition, with decreased Helicobacter abundance and enrichment of taxa such as *PeptoStreptococcus*, *Parvimonas*, and *Rothia* [19].

Normal Gastric Microbiota

Characterization of the Gastric Microbiota in Healthy Individuals

When *H. pylori* were discovered in the early 1980s, this long-standing paradigm was called into question [20], an acidophilic bacterium that can colonize the stomach mucosa and cause persistent infections in about 50% of people worldwide. Recent developments in culture-independent molecular technologies, particularly 16S rRNA gene sequencing, metagenomics, and meta transcriptomics, have disproved the notion of a sterile gastric niche by revealing a surprisingly complex and varied microbial community living in healthy people's stomachs in addition to *H. pylori* [21]. Recent molecular investigations have shown that a complex microbial community lives within the gastric niche, defying previous theories that the human stomach is sterile because of its extremely acidic environment. Five primary bacterial phyla—*Proteobacteria*, *Firmicutes*, *Bacteroidetes*, *Actinobacteria*, and *Fusobacteria*—dominate the ecology in healthy persons. *Prevotella*, *Streptococcus*, *Veillonella*, *Rothia*, and *Haemophilus* are the most commonly found organisms at the genus level and collectively make up the core stomach microbiota. These results provide insight into gastric homeostasis and possible disease-related dysbiosis by demonstrating that a dynamic and structured microbial population endures in the healthy stomach even in the face of adversity [22]. Compared to the colon, which normally supports 10^{10} to 10^{12} colony-forming units (CFU)/mL, the stomach has a relatively sparse microbial community, with classic culture-based research suggesting a load between 10^{2} and 10^{4} CFU per millilitre of gastric juice [23]. However, the

stomach is home to a diverse range of microorganisms with unique ecological traits adapted to the severe physicochemical circumstances [24]. In addition to being temporary visitors, these microorganisms actively interact metabolically and ecologically with their hosts and other microbial community members [25].

Numerous host factors, such as age, food, geography, usage of drugs (particularly proton pump inhibitors), and either the presence or the absence of *H. pylori*, affect the richness of the stomach microbiota [26–27]. The microbial landscape is dominated by *H. pylori* during infection, although the microbiota of non-infected people is more varied and stable.[28]. By controlling local immune responses, affecting gastric physiology, and possibly acting as a barrier against pathogenic invasion, the gastric microbiota is essential for preserving the homeostasis of the stomach mucosa.

Table 1: Associations Between Non-Helicobacter Pylori Gastric Microbes and Gastric Tumorigenesis

S. No.	Study	Bacterial Species/ Group	Findings	Mechanisms of Pathogenesis	Reference
1	INS-GAS Mouse Model Study	*Lactobacillus murinus*, *Clostridium, Bacteroides*	Colonization led to gastric intraepithelial neoplasia (GIN) independent of H. pylori	Induced inflammation and upregulation of cancer-related genes	[32]
2	Human Gastric Cancer Study	Lactic acid bacteria (*Streptococcus*, *Lactobacillus*, *Bifidobacterium*, *Lactococcus*)	Increased abundance in gastric cancer patients	Production of reactive oxygen species (ROS), N-nitroso compounds, and lactate promoting inflammation and angiogenesis	[33]
3	Nitrate-Reducing Bacteria Analysis	*Neisseria*, *Clostridium*, *Staphylococcus*	Elevated in gastric cancer tissues	Enhanced nitrate and nitrite reductase activity leading to carcinogenic N-nitroso compound formation	[34]
4	Gastric Microbiota Diversity Study	Actinobacteria, Bacteroidetes, Firmicutes, Fusobacteria, non-*H. pylori* Proteobacteria	Inverse relationship with H. pylori abundance; higher microbial diversity associated with gastric cancer risk	Microbial dysbiosis contributing to carcinogenesis	[35]
5	Lipopolysaccharide (LPS) Activity Study	Non-*H. pylori* Gram-negative bacteria	LPS stimulated IL-8 secretion from gastric epithelial cells	Induced neutrophil recruitment and ROS production leading to DNA damage	[36]
6	Acid Suppression Therapy Study	Various non-*H. pylori* bacteria	Increased colonization in patients on proton pump inhibitors (PPIs)	Altered gastric pH facilitating bacterial overgrowth and potential carcinogenesis	[37]
7	Nitrosating Bacteria Study	*Veillonella*, *Haemophilus*, *Staphylococcus*, *Streptococcus*, *Neisseria*	Identified as contributors to N-nitroso compound formation	Nitrosation processes leading to DNA damage and cancer risk	[38]
8	Gastric Microbiota and Cancer Progression	*Lactobacillus coleohominis*, Lachnospiraceae	Increased abundance correlated with progression from gastritis to gastric cancer	Potential role in promoting carcinogenesis through microbial imbalance	[39]

According to studies, the stomach's commensal bacteria can influence the immune system, encourage a healthy inflammatory response and strengthen the epithelial barrier. Furthermore, the stomach microbial community has the ability to outcompete harmful microbes for ecological niches, preventing colonization and lowering the risk of infection [29].

In addition to bacteria, studies have shown that the stomach microbiota also includes fungus, viruses (including bacteriophages), and archaea, albeit the latter two are still little understood in this niche [30]. The way the gastrointestinal microbial population is arranged shows how it has adapted to changes in acidity, oxygen tension, and nutrient availability. Acid-sensitive bacteria can live in sheltered niches provided by mucosa-associated biofilms. These biofilms produce microenvironments with different pH, oxygen concentrations, and nutrition availability, which enable a variety of bacteria communities to flourish in the hostile environment of the stomach. Preventing pathogenic incursions and preserving gastric homeostasis depend on these adaptations [31]. All of these results highlight the fact that a dynamic microbial ecosystem that is essential to gastrointestinal health is present in the healthy stomach.

Common bacterial phyla and genera in the stomach

The stomach microbiota is mostly composed of five major bacterial phyla: Firmicutes, Proteobacteria, Bacteroidetes, Actinobacteria, and Fusobacteria, according to high-throughput sequencing research [40–42]. These phyla's relative abundance varies greatly from person to person and is impacted by exposure to the environment and physiological variables (Figure 2).

Firmicutes

The most prevalent phylum seen in the normal stomach microbiome is frequently Firmicutes. [43]. The genus Streptococcus is often prominent in this phylum. Acid-tolerant Streptococcus species, such S. mitis and S. salivarius, aid in the fermentation of carbohydrates and produce lactic acid as a metabolic byproduct [44]. Through competitive exclusion and the synthesis of antimicrobial peptides, these lactic acid-producing bacteria can prevent colonization by possible pathogens and regulate the pH of the surrounding environment.

Among the other genera in Firmicutes is *Lactobacillus*, which is well-known for its probiotic qualities and resilience to acid [45]. Short-chain

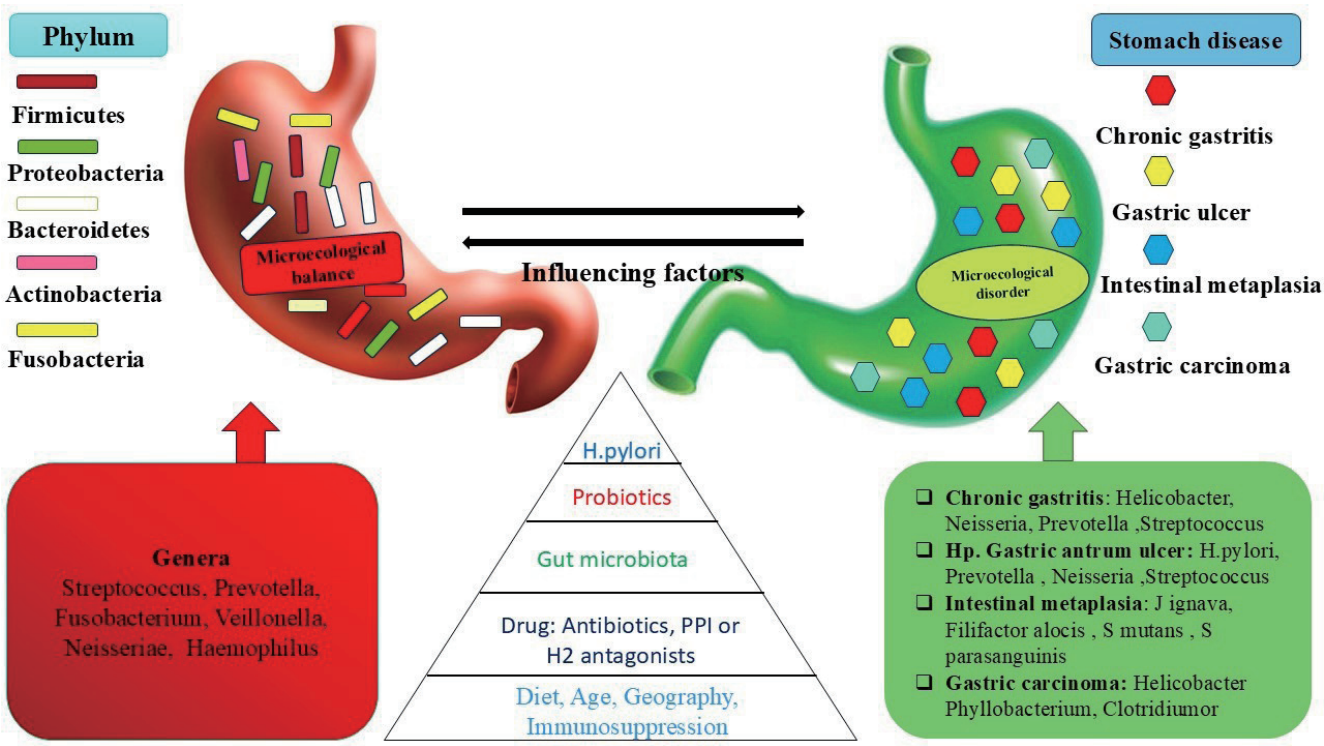

Figure 2: Influence of Gastric Microbiota on Stomach Health and Disease Progression
This figure illustrates the role of gastric microbial communities in maintaining microecological balance and how disruption of this balance contributes to the development of stomach diseases.

fatty acids (SCFAs), which have anti-inflammatory properties and strengthen the mucosal barrier, are produced by lactobacilli through fermentation processes. Moreover, Clostridium members from clusters XIVa and IV have been found to participate in metabolic interaction and cross-feeding in the stomach niche [46].

Proteobacteria

The second most prevalent phylum is Proteobacteria, which includes genera like Helicobacter, Haemophilus, and Neisseria [47]. Because of its involvement in gastritis, peptic ulcers, and gastric cancer, *H. pylori* are the most thoroughly researched gastric colonizer [48]. One of the most prevalent bacterial groups in the human stomach, proteobacteria are important for both health and illness. By interacting with the host immune system and competitively excluding pathogens, Proteobacteria cohabit with other phyla including Firmicutes, Actinobacteria, and Bacteroidetes in healthy humans, helping to maintain gastric homeostasis [49]. In patients with atrophic gastritis, chronic gastritis, and gastric cancer, dysbiosis marked by an elevated relative abundance of Proteobacteria has been noted, indicating their possible role in the course of the disease [50].

Bacteroidetes

Anaerobic and suited to mucin-rich environments include members of the phylum bacterial species, which includes *Prevotella* and *Porphyromonas* [51]. Monosaccharides and other metabolites that sustain cross-feeding networks are released when complex carbohydrates and mucin glycoproteins are broken down by these taxa [52]. By modifying T-cell responses, Prevotella species have been associated with immunological homeostasis and mucosal integrity maintenance [53]. The presence of Bacteroidetes suggests that the stomach supports intricate ecological interactions rather than just acting as a passageway for ingested bacteria.

Actinobacteria

Despite making up a small portion of the gastric microbiota, actinobacteria are essential for preserving gastric homeostasis. According to studies, people who are *H. pylori* -negative have higher levels of Actinobacteria, which may have a preventive effect against stomach disorders. On the other hand, diseases like stomach cancer have been shown to have a decline in Actinobacteria, suggesting possible dysbiosis. By affecting microbial diversity and regulating the local immune response, these bacteria support the stomach environment and may have an effect on the course of disease and the effectiveness of treatment [54]. These bacteria may aid in the degradation of environmental substances and the regulation of mucosal immunity due to their wide metabolic flexibility [55]. Research on their functions in gastric health is still ongoing.

Fusobacteria

Despite their low prevalence, *Fusobacteria*—most notably *Fusobacterium nucleatum* and related species—are noteworthy for their function in biofilm development and possible connection to mucosal inflammation [56]. The oral cavity is the primary home of the Gram-negative, obligatory anaerobe *Fusobacterium nucleatum*. It may play a part in gastric disorders, as recent research has found that it is present in stomach biopsies even when *Helicobacter pylori* infection is not present. Notably, regardless of *H. pylori* status, a study found that *F. nucleatum* was present in stomach biopsies from patients with a variety of gastroduodenal conditions, including gastric cancer. The conventional wisdom that *H. pylori* is the main bacterial cause of stomach cancer is called into question by this discovery. Additionally, study by explores the possible methods that *F. nucleatum* may impact gastric carcinogenesis, such as immune response modulation and inflammatory pathway activation. These findings highlight how crucial it is to take into account the gastric microbiota in addition to *H. pylori* in order to comprehend gastric etiology and possible treatment targets [57].

Other Microbial Groups

In addition to bacteria, current research has found trace amounts of several fungal communities, including Candida spp., and archaea, including Methanobrevibacter species [58,59]. Although these elements are not as well understood, the stomach virome, which includes bacteriophages, affects the genetic exchange and the organization of bacterial communities [60].

Microbial Shifts in Gastric Disease States

Our knowledge of the human microbiome has significantly increased over the last ten years, demonstrating that resident microbial communities may be found in even the stomach and other organs with harsh physicochemical circumstances. In the past, it was thought that the stomach was practically sterile due to the high concentrations of gastric acid (pH values range from 1 to 3). Nevertheless, developments in culture-independent sequencing technology have shown that even in such unfavourable circumstances,

a varied, albeit low-biomass, microbial community may thrive. The delicate balance that is established in the healthy stomach by the interaction of microbial colonization, mucosal defence mechanisms, and acid secretion is essential for immunological regulation, digestive function, and general homeostasis. When this equilibrium is upset, whether by inflammatory conditions, viral agents, or pharmaceutical treatments, significant microbial changes can occur, which aid in the etiology of a number of stomach illnesses (Figure 3) [61-62].

According to recent studies, there are notable changes in the makeup and function of the gastric microbiota along the transition from chronic gastritis via intestinal metaplasia to gastric cancer. Stomach dysbiosis is not just a result of illness; it actively contributes to the development of cancer from a benign inflammatory condition. Additionally, the use of PPIs and broad-spectrum antibiotics, two prevalent therapy techniques for gastrointestinal diseases, are becoming more widely acknowledged as having two sides. These treatments may unintentionally disturb the complex microbial population, creating an environment that is favourable to dysbiosis, even as they reduce symptoms and eliminate pathogens like *H. pylori*.

The nature of dysbiosis in gastritis, metaplasia, and gastric cancer; the dynamics of bacterial richness and diversity in relation to disease progression; and the effects of antibiotics and PPIs on the gastric microbiota are the three interconnected topics covered in detail in this review. Our goal is to create a framework for comprehending the pathophysiological importance of microbial alterations in the stomach and to discover potential for novel diagnostic and therapeutic approaches by combining insights from current investigations [63].

The Gastric Microenvironment: Acidity, Mucosal Structure, and Microbial Homeostasis

The stomach's acidic lumen and unique mucosal defences play a major part in its function as a first line of defence against ingested microorganisms (Table 2). Only bacteria that have developed defences against low pH levels may survive in the environment created by gastric acid, which is produced by parietal cells (e.g., *H. pylori*) [64]. The microbial population of the human stomach is distinct, low-diversity, and mostly made up of species that can withstand acidity. The gastric

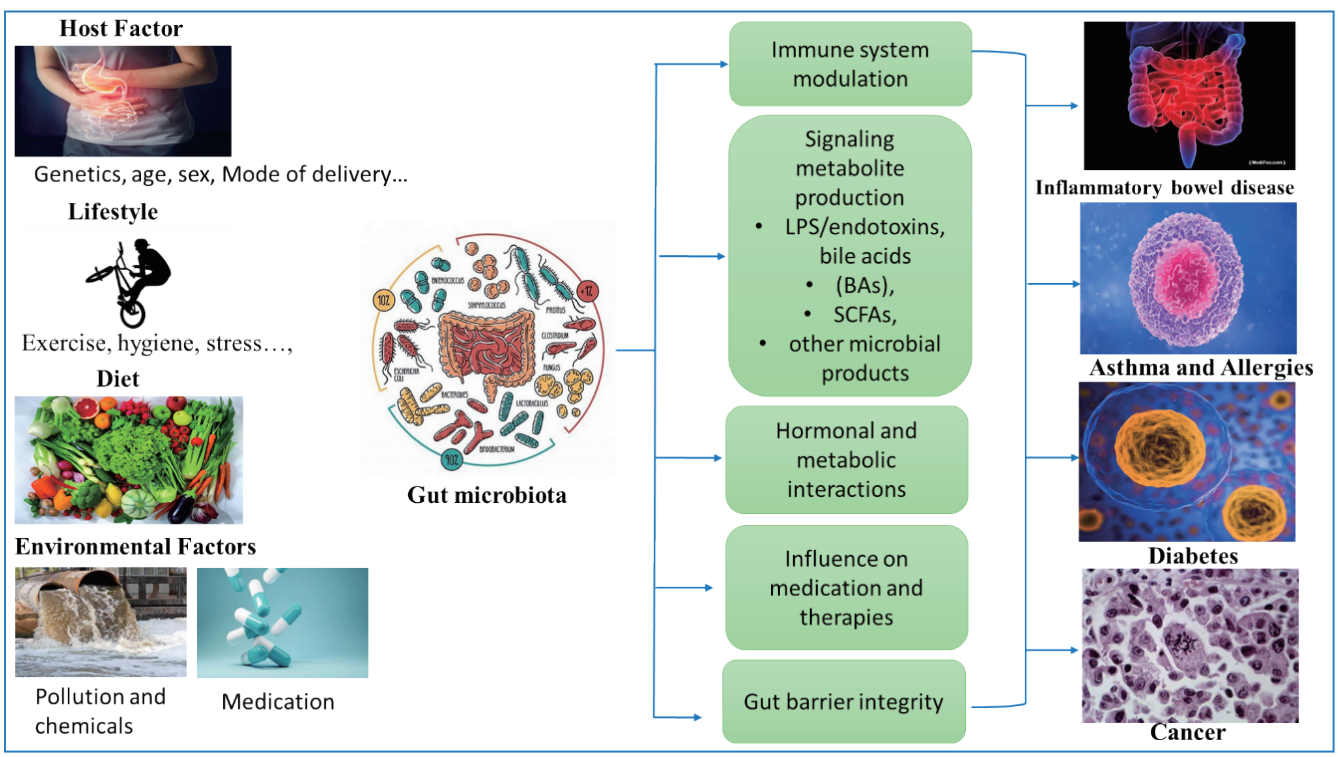

Figure 3: Determinants, functions, and disease links of the human gut microbiota.
The schematic summarizes how multiple upstream influences shape the intestinal microbial community and, in turn, host health.

mucosal barrier, which consists of tight junction proteins, antimicrobial peptides (AMPs), and mucus generated by epithelial cells, significantly influences this microbial composition. By limiting microbial adhesion and invasion, these elements work together to maintain stomach homeostasis. Epithelial cells' tight connections create a vital physical barrier that controls permeability and stops dangerous substances from passing through. Further defence against harmful microorganisms is provided by AMPs with bactericidal activity, such as defensins and cathelicidins, which are generated by epithelial cells. Rich in mucins, the mucus layer serves as a diffusion barrier, keeping microorganisms from coming into direct contact with the surface of the epithelium [65].

This limited microbial profile minimizes inflammation and aids in immunological tolerance under normal physiology. Significant changes in the local microbiota can result from even minor alterations in stomach physiology, whether brought on by aging, persistent inflammation, or medication-induced acid suppression. For example, atrophic gastritis and hypochlorhydria (lower acid secretion), which are prevalent in the elderly and in people with chronic inflammation, cause the stomach's antibacterial capacity to decline. Bacteria that are normally transitory members of the upper gastrointestinal tract, as well as those that originate from the mouth cavity and intestines, can colonize and flourish due to this loss of acid-mediated selection [66].

The microbial population of the human stomach is distinct, low-diversity, and mostly made up of species that can withstand acidity. In addition to external factors including infection, drug exposure, and nutrition, the host's mucosal and acid defences also affect this microbial composition. The stomach's microbiome is an ecosystem that sustains homeostasis through intricate interactions between host factors and microbial populations, as evidenced by the development of metataxonomic and metagenomic studies, which show that these bacterial communities respond dynamically to changes in the physicochemical environment [72].

Dysbiosis in Gastric Disease States

Table 2: Site-Specific Composition of microbiota and Clinical Implications of Gastrointestinal

S.No.	Compartment	Location	Dominant Microbes	Key Features	Clinical/Functional Relevance	Reference
1	Oral Microbiota	Oral cavity (tongue, teeth, gingiva, saliva)	*Streptococcus*, *Actinomyces*, *Veillonella*, *Fusobacterium*, *Prevotella*	High microbial biomass; biofilm formation on mucosal surfaces and teeth; entry point to GI tract	Implicated in periodontal disease, dental caries, and as a source for gastric and intestinal colonization	[67]
2	Gastric Juice Microbiota	Gastric lumen (acidic pH, ~1.5–3.5)	*Streptococcus*, *Lactobacillus*, *Veillonella*, *Prevotella*, *Haemophilus*	Transient microbiota; reflects swallowed oral taxa; sensitive to gastric acid and medications	Modified by PPIs and antibiotics; associated with reflux, dyspepsia, and gastric microbiome shifts	[68]
3	Gastric Mucosal Microbiota	Stomach lining (mucus layer and epithelium)	*Helicobacter pylori*, *Streptococcus*, *Lactobacillus*, *Propionibacterium*	More stable and adherent; adapted to low pH; immune system interface; lower diversity than lumen	Key in gastritis, atrophic changes, metaplasia, and gastric cancer; triggers local immune responses	[69]
4	Intestinal Microbiota	Small and large intestine (mucosa and lumen)	*Bacteroides*, *Firmicutes* (e.g., *Clostridium*, *Lactobacillus*), *Escherichia coli*	Highest diversity and density; vital for digestion, immunity, and SCFA production	Associated with IBD, metabolic syndrome, colorectal cancer, systemic inflammation, and immune modulation	[70,71]

Gastritis and Early Inflammatory Changes

A common early warning sign for the development of stomach disorders is chronic gastritis. Even though *Helicobacter pylori* is still a known cause of the illness, new studies show that other microbial populations also play a part. One of the hallmarks of gastritis is dysbiosis, which is defined by an imbalance between opportunistic pathogens and protective commensals. The gastric microbiota of patients with non-*H. pylori* gastritis has been found to vary; species including Sphingomonas and Ralstonia are abundant in chronic atrophic gastritis, indicating that they may be early microbial markers of mucosal changes. Through mechanisms involving pathogen-associated molecular patterns (PAMPs), which trigger innate immune responses and cause mucosal damage, these microbial changes are thought to worsen local inflammation [73].

Intestinal Metaplasia: A Prelude to Malignancy

An intestine-like lining replaces the typical stomach epithelium in intestinal metaplasia, a histological alteration. This change is thought to represent a precancerous state that acts as a link between benign inflammation and malignant development. Surprisingly, intestinal metaplasia is linked to an additional gastric microbiota rearrangement. In comparison to normal mucosa, several investigations have shown that metaplastic tissues contain higher levels of microbial richness and beta diversity; taxa that are prevalent in the lower intestine or oral cavity become more prevalent in the metaplastic milieu. It is believed that the emergence of these exogenous bacterial species is due to a reduction in the selective pressures exerted by high acid secretion, which permits the colonization of non-native microorganisms. Furthermore, the altered glycosylation patterns and surface proteins of the metaplastic epithelium might offer new attachment sites that help these bacteria persist. A pro-inflammatory milieu that encourages genomic instability and dysplasia may be a result of these microbial alterations [74].

Gastric Cancer: The End Stage of Microbial Imbalance

Often occurring in the context of chronic inflammation and metaplasia, gastric adenocarcinoma is the last stage in the chain of gastric pathology. The dysbiotic state is significantly more noticeable in the tissues of stomach cancer. Research shows that in addition to an elevated overall bacterial burden, there is also a further disruption in the structure of the community, with a notable decrease in beneficial commensals and an increase in taxa with recognized procarcinogenic characteristics [75]. For example, microbial communities that were once minor components in healthy tissues may become dominant in individuals with established stomach cancer. This might change local metabolic processes and trigger inflammatory signalling pathways, which promotes the growth of the tumour [76]. Changes in xenobiotic degradation, vitamin metabolism, and pathways linked to cell growth and apoptosis are examples of such modifications in microbial metabolic activity. Through complex interactions between microbial products and host cell signalling pathways, these findings collectively imply that dysbiosis in gastric cancer is not merely a bystander occurrence but rather an active player in tumour genesis and progression [77].

Changes in Bacterial Richness and Diversity During Disease Progression

High-throughput 16S rRNA gene sequencing has been used in longitudinal studies to shed light on how the richness and diversity of the stomach microbiota change as the disease progresses. A comparatively limited range of bacterial species are enforced by the hostile stomach environment under normal circumstances. However, the microbial community experiences significant changes as acid secretion and the mucosal barrier's integrity decline [78].

Alterations in Alpha and Beta Diversity

The gastric microbiota frequently shows enhanced alpha diversity in chronic gastritis, especially after *Helicobacter pylori* eradication. This indicates a higher number of species within a sample. This gain, though, might not always be a sign of improved health. Rather, it might indicate a dysbiotic environment where the native microbial equilibrium is upset by the introduction of alien species from the intestines or mouth cavity. Healthy people and those with advanced gastric pathology are clearly separated by beta diversity analyses, which evaluate the compositional variations across microbial communities across samples. This distinction highlights how the microbial composition significantly changes in response to pathophysiological changes in the stomach [79]. The use of acid suppression medications, for instance, is linked to notable variations in alpha and beta diversity, as shown by Lee et al., highlighting the significance of gastric pH as a basic determinant of microbial taxonomy and structure [80].

Successional Dynamics and Community Reordering

The dynamic character of stomach microbial populations as disease advances has been revealed by recent time-series analysis. Because of strong mucosal defences and acid secretion, the bacteria populations in the stomach are stable in healthy people. However, a "successional" reordering takes place in diseases like metaplasia and gastritis, where some microbial clusters grow more common while others become less so. Stable areas of the stomach mucosa exhibit considerable asynchrony and strong resilience, according to studies, suggesting species-specific temporal responses. On the other hand, progressive sites show little asynchrony and convergence, indicating the possibility of pathogenic species dominating and reducing ecological diversity and community variation. Due to the lack of species interactions and competitive restrictions, this convergence may make opportunistic infections easier [81].

Functional Implications: Metabolic Shifts and Immune Modulation

As the disease progresses, the stomach microbiome's functional capacity is also significantly changed, going beyond simple taxonomic alterations. Changes in pathways linked to signal transduction, amino acid metabolism, and xenobiotic degradation have been found by metagenomic and metabolomic investigations. By producing free radicals and other reactive intermediates, bacterial populations in atrophic and neoplastic tissues, for example, exhibit an overrepresentation of genes involved in xenobiotic metabolism, a shift that may lead to chronic inflammation and carcinogenesis.

Concurrently, shifts in the production of short-chain fatty acids (SCFAs) and other microbial metabolites can impact epithelial cell proliferation, immune modulation, and barrier function. These functional alterations, coupled with the loss of beneficial commensals, create a self-perpetuating cycle of inflammation and tissue damage that can ultimately drive disease progression [82].

Impact of Antibiotics and Proton Pump Inhibitors on the Gastric Microbiota

Antibiotics and their collateral damage

Antibiotics are essential for treating bacterial infections like gastritis caused by *H. pylori*, but using them causes major changes to the gut microbiota and the stomach. Because broad-spectrum antibiotics are unable to distinguish between commensals and pathogens, resident bacterial populations are frequently rapidly reduced. Microbial diversity is immediately reduced as a result of this "collateral damage," which also creates ecological niches that are later occupied by opportunistic and frequently less advantageous bacteria [75,77]. For instance, research has demonstrated that following antibiotic exposure, the stomach frequently experiences a brief bloom of intestinal and oral commensals, which are microorganisms that are typically inhibited by a low pH. Such alterations have been linked to a higher chance of recurring infections, chronic inflammation, and potentially a long-term propensity for neoplastic transformation.

Furthermore, a number of variables, such as the antibiotic class, dosage, delivery method, and length of treatment, affect how much the microbial populations are disturbed. Different antibiotics can cause varying degrees of dysbiosis, according to research by Yang et al., with broad-spectrum medicines generating more significant changes than narrow-spectrum ones. These findings emphasize the need of antibiotic stewardship since maintaining the integrity of the stomach microbiota may be essential to avoiding long-term negative consequences [82].

Proton Pump Inhibitors as Modulators of the Gastric Ecosystem

Because they efficiently lower the production of gastric acid, proton pump inhibitors (PPIs) are frequently used to treat graft-related conditions such peptic ulcer disease and gastroesophageal reflux disease (GERD). By increasing the intragastric pH, acid suppression modifies the stomach's inherent defence systems while also reducing acid-related mucosal damage. By allowing bacteria that are often restricted to the oral cavity and distal intestine to colonize, this weakening of the acidity barrier increases the diversity and richness of microorganisms in the stomach. According to Jackson et al., long-term PPI usage is linked to a decrease in the abundance of "protective" gut commensals as well as an increase in mouth taxa such Streptococcaceae.

A number of epidemiological studies have also connected long-term PPI usage to a higher risk of gastrointestinal infections, such as Clostridium difficile infection, and possibly to a higher risk of gastric neoplasia [73,76]. Acid suppression and disruption of the microbial ecosystem interact in a complicated

way. PPIs are commonly used in conjunction with antibiotics to treat *H. pylori* infections; however, this combination therapy may worsen microbial imbalance and make the recovery of the native microbiota even more difficult. The idea that PPIs should be used sparingly has been reaffirmed by recent meta-analyses, especially in groups that are already at risk for problems from dysbiosis [76].

Combined Effects and the Role of Therapeutic Interventions

Maintaining microbial equilibrium is made more difficult by the concurrent use of PPIs and antibiotics, particularly when treating *H. pylori* infections. According to studies, compared to using either medication alone, combining these two can result in a more severe and long-lasting dysbiosis. Giordan et al. showed that patients who received both PPIs and antibiotics had a considerably lower overall and progression-free survival rate, which was partially caused by altered immune responses brought on by microbial dysregulation. This brings up crucial questions about treatment plans and emphasizes the possible necessity of supplemental treatments like particular probiotics or prebiotics to lessen the negative effects on the stomach microbiota [83].

Probiotic supplements, dietary changes, and even fecal microbiota transplantation (FMT) have been used in attempts to reestablish microbial equilibrium following disturbance. Targeted restoration of the gut and stomach microbial communities may be able to enhance mucosal integrity, lower inflammation, and partially reverse dysbiosis, according to preliminary clinical trials. Research is still ongoing to have a better understanding of these therapies' long-term effects and how best to apply them in clinical settings [84, 85].

Non-*H. pylori* Bacteria of Interest in Gastric Disease

While *H. pylori* remain, the principal bacterial agent implicated in gastric diseases, emerging evidence highlights the significant roles of non-*H. pylori* bacteria in gastric pathophysiology. The gastric microbiota, once thought nearly sterile due to low pH, harbors diverse bacteria including *Fusobacterium nucleatum*, *Streptococcus spp.*, *Lactobacillus spp.*, *Prevotella*, *Veillonella*, and *Propionibacterium acnes. F. nucleatum* has been associated with chronic inflammation and may promote tumorigenesis via modulation of immune responses and activation of pro-inflammatory pathways. Streptococci and lactobacilli influence gastric pH, mucosal integrity, and local immune signaling, with lactobacilli exhibiting both protective and potentially pathogenic roles depending on abundance and host context. Obligate anaerobes such as *Prevotella* and *Veillonella* produce short-chain fatty acids that modulate mucosal immunity, while P. acnes have been implicated in chronic gastric inflammation linked to atrophic gastritis and cancer. Collectively, these non-*H. pylori* bacteria contribute to gastric disease through immune modulation, production of genotoxic metabolites, and interactions with other microbes, including *H. pylori*. Understanding these complex microbial networks is critical for developing targeted diagnostics and therapeutic strategies in gastric disease management [86].

Fusobacterium nucleatum: Inflammation and Tumor Association

The gram-negative, anaerobic bacterium *Fusobacterium nucleatum*, which is mainly found in the oral cavity, has attracted a lot of attention when it comes to gastrointestinal cancers, especially colorectal and stomach cancers. Although it has historically been disregarded in the stomach because it is anaerobic, more and more data indicates that it continues to colonize even in the acidic gastric environment, particularly when mucosal damage or atrophic gastritis is present and causes hypochlorhydria [87-88]. By activating pattern recognition receptors including Toll-like receptor 4 (TLR4), which triggers nuclear factor-kappa B (NF-κB) signalling and the synthesis of pro-inflammatory cytokines like IL-6, IL-8, and TNF-α, *F. nucleatum* is known to worsen inflammation [89-90]. Angiogenesis, immune cell infiltration, and the epithelial-mesenchymal transition (EMT) are all signs of a tumor-promoting milieu that can be facilitated by these pro-inflammatory pathways [91].

Notably, *F. nucleatum* alters cell signalling and host immunity to induce carcinogenesis. By binding E-cadherin on epithelial cells and triggering β-catenin signalling, the bacterium's FadA adhesin increases the production of oncogenes such MYC and cyclin D1 [92,93]. Additionally, its outer membrane vesicles (OMVs) are linked to NK cell activity suppression, which permits tumour immune evasion [94]. According to clinical research, F. nucleatum is more abundant in stomach cancer tissues than in the nearby non-cancerous mucosa, which may indicate that it plays a role in the development and spread of the disease [95-96]. Furthermore, microbial sequencing studies have demonstrated that *F. nucleatum* co-

occurs with other pathogenic species, forming biofilms that enhance mucosal colonization and host defence resistance [94]. These results have established *F. nucleatum* as a marker and possible cause of inflammation linked to tumours in the gastric niche [97].

Streptococcus spp.: Mucosal Damage and Acid Tolerance

One of the most frequently found non-*H. pylori* taxa in the human stomach are Streptococcus species, particularly those belonging to the *Streptococcus mitis*, *S. salivarius*, and *S. anginosus* families. This is especially true in situations where the stomach's acidity is increased, like atrophic gastritis or the use of proton pump inhibitors (PPIs) [98-100]. Because of their exceptional acid tolerance, these facultative anaerobes can endure in the low pH of the stomach lumen. The generation of urease-independent ammonia, the stimulation of stress response genes like groEL and dnaK, and the development of F1F0-ATPases to extrude protons and maintain intracellular pH are examples of acid resistance mechanisms [101].

Streptococcus species have a variety of harmful potential in the stomach environment. By producing cytotoxins like hydrogen peroxide and enzymes that break down extracellular matrix components like hyaluronidase and neuraminidase, these microbes are known to contribute to the collapse of the mucosal barrier [102,103]. *Streptococcus anginosus's* involvement in gastric inflammation and possible link to chronic gastritis and gastric cancer have been brought to light by recent research. Acute gastritis in mouse models caused by *S. anginosus* colonization was typified by neutrophilic infiltration and increased levels of pro-inflammatory cytokines, such as interleukin-8 (IL-8). This acute inflammation eventually developed into diseases linked to a higher risk of gastric cancer, including chronic gastritis, parietal cell atrophy, mucinous metaplasia, and dysplasia. Its possible involvement in gastric carcinogenesis is further supported by the discovery of *S. anginosus* in the gastric mucosa of patients with gastric cancer. [104]. *Streptococcus spp.* abundance and increased expression of genes involved in DNA repair and cellular proliferation inside the gastric epithelium have been linked to early tumorigenic processes in recent metagenomics and transcriptomics investigations [105].

Lactobacillus spp.: Paradoxical Role—Probiotic vs. Cancer-Promoting Species

Historically thought of as probiotics and commensals having positive effects on gut health, *Lactobacillus* species exhibit contradictory behaviour in the gastric environment. Although some *Lactobacillus* strains, like *L. rhamnosus* GG and *L. reuteri*, have been demonstrated to produce bacteriocins, organic acids, and immunomodulatory compounds that have anti-inflammatory properties and prevent *H. pylori* colonization, other research has linked these bacteria to gastric carcinogenesis under particular circumstances [106]. The context-dependent dual nature of *Lactobacillus* is impacted by the strain in question, host characteristics, and the composition of the microbial community. Increased lactic acid production and a hypoxic tumour microenvironment that supports the survival and growth of cancer cells have been associated with elevated levels of *Lactobacillus*, specifically *L. fermentum*, *L. paracasei*, and *L. salivarius*, in patients with gastric cancer [107]. In addition to providing tumour cells with energy through the lactate shuttle, lactic acid also regulates angiogenesis by promoting the expression of vascular endothelial growth factor (VEGF) and stabilizing hypoxia-inducible factor-1α (HIF-1α) [108,109]. Additionally, by causing DNA damage through reactive oxygen species (ROS) and aiding in immunological suppression through the activation of regulatory T cells (Treg), these species may contribute to carcinogenesis. The difference between the pathogenic and probiotic functions of *Lactobacillus* species emphasizes how crucial strain-specific identification and host-contextual assessment are for determining their impact on the stomach [110, 111].

Prevotella, *Veillonella*, *Propionibacterium*: Inflammation and Immune Modulation

Propionibacterium, *Veillonella*, and *Prevotella* are significant components of the gastric microbiota that affect immunological regulation and inflammation. In order to promote Th17 responses and neutrophil recruitment, which in turn lead to mucosal inflammation, *Prevotella* species can induce gastric epithelial cells to generate pro-inflammatory cytokines including IL-8 and IL-6. Despite being less well-studied, *Veillonella* species interact with other stomach bacteria and may intensify inflammatory cascades through the dynamics of microbial communities. Traditionally linked to the skin microbiota, Propionibacterium acnes have been found in the stomach and may alter host immunity, which could lead to long-term inflammation and epithelial alterations. Together, these bacteria affect mucosal integrity, stomach immune homeostasis,

and may contribute to the development of diseases including gastritis and early carcinogenic alterations. Developing medicines that target the microbiota in the management of gastrointestinal diseases requires an understanding of how they interact with the host immune system [112-113]. *Saccharolytic* bacteria called *Prevotella* species, which include *P. melaninogenica* and *P. intermedia*, can ferment carbohydrates to short-chain fatty acids (SCFAs), especially acetate and propionate, which alter host immune responses by inhibiting histone deacetylase and G-protein coupled receptors [114-115]. However, by boosting immunological tolerance and epithelial proliferation, high SCFA synthesis in inflammatory tissues may paradoxically encourage cancer [116].

Streptococcus and *Veillonella* species, mainly V. parvula, are known to co-aggregate and form biofilms, which promotes microbial persistence and epithelial attachment [117]. These bacteria also contribute to metabolite-driven immune regulation by converting lactate to propionate and succinate. Interestingly, *Veillonella* has been linked to TLR2 activation and neutrophil recruitment, which promote an inflammatory environment [118]. Propionibacterium species, such P. acnes, which are frequently linked to skin microbiota, have been found in stomach tissues. They are believed to cause chronic inflammation by activating the NLRP3 inflammasome and producing inflammatory mediators like IL-1β and IL-18 [119]. It's interesting to note that P. acnes DNA has been found in the tissues of stomach adenocarcinomas, which raises concerns about its possible role in microbially driven carcinogenesis. All together, these non-*H. pylori* genera engage in dynamic and context-dependent interactions with host cells and immunological pathways, influencing either illness or homeostasis based on the host environment, interactions within the microbial community, and the state of the immune system. To precisely define their mechanistic functions and therapeutic implications in stomach disorders, more research is required [120].

Mechanisms of Gastric Damage in Gastric Disease Pathogenesis

Environmental variables, host immunological responses, and *H. pylori* interact with other microbial communities to cause stomach mucosal injury that leads to chronic gastritis, metaplasia, and eventually gastric cancer. Apart from *H. pylori*, other bacterial species also play a role in gastric carcinogenesis by other methods, such as genotoxicity, immunological regulation, nitrosation responses, and virulence factor release. Here, we offer a thorough analysis of the four main pathways linked to gastrointestinal injury caused by bacteria [121,122].

Nitrosating Bacteria and the Formation of Carcinogenic N-Nitroso Compounds

The stomach microbiome's nitrosating bacteria play a major role in carcinogenesis by accelerating the production of powerful mutagens and carcinogens called N-nitroso compounds (NOCs). NOCs are produced by nitrosation processes, in which nitrites and secondary amines or amides combine to make nitrosamines and nitrosamides, which are substances that are known to cause mutagenesis and DNA alkylation [123]. NOCs are potent carcinogens implicated in various cancers, including gastric and esophageal cancers. These compounds are primarily formed through the nitrosation of amines and amides in the presence of nitrite, a process facilitated by nitrosating agents. While dietary intake of nitrates and nitrites contributes to NOC formation, the gastrointestinal tract also plays a crucial role in their endogenous production [124].

In the stomach, particularly under acidic conditions, dietary nitrates are reduced to nitrites by commensal bacteria such as *Nitrosospira*, *Nitrosomonas*, and certain *Clostridium* species. These bacteria possess nitrate and nitrite reductases, enabling them to convert dietary nitrate to nitrite in acidic or hypoxic stomach environments. Once nitrite is present, it can further react with amines and amides to form NOCs, especially in conditions of low gastric acidity or reduced gastric acid secretion, as seen in chronic gastritis or achlorhydria [125,126].

The formation of NOCs in the stomach is not solely a chemical process; it is significantly influenced by the gastric microbiota. Studies have shown that bacterial species such as *Propionibacterium acnes* can activate the NLRP3 inflammasome, leading to the production of inflammatory mediators like IL-1β and IL-18, which may contribute to chronic inflammation and neoplastic transformation in gastric tissues [127]. Furthermore, the presence of nitrosating bacteria and the subsequent formation of NOCs have been directly detected in the gastric juice and tissues of patients with gastric cancer and chronic gastritis [128].

Intragastric nitrite concentrations are raised by this microbial metabolism, particularly under hypochlorhydric conditions brought on by long-term *H. pylori* infection or proton pump inhibitor treatment [129]. According to metagenomic analysis, individuals

with stomach cancer have more nitrosating bacterial genes, which is associated with a higher chance of developing the disease [130].

Immune Evasion and Chronic Inflammation

It is commonly known that chronic inflammation has a role in the development of gastrointestinal disorders and carcinogenesis. Chronic inflammatory states are caused by persistent infections that are established by pathogens, especially bacteria in the stomach environment, which can elude host immune responses. A well-known example is *H. pylori*, which subverts both innate and adaptive immunity by interfering with host cell signalling, blocking phagocytosis, and modifying cytokine production through the use of mechanisms including the CagA protein and VacA toxin. [131]. Additionally, chronic inflammation and immune evasion are caused by non-*H. pylori* bacteria. Certain species, like *Streptococcus anginosus* and *Fusobacterium nucleatum*, can stick to the stomach mucosa and interfere with Toll-like receptor (TLR) signalling pathways, which increases the release of IL-8 and TNF-α while reducing the effectiveness of cytotoxic T-cell responses. This immunomodulation encourages a pro-inflammatory milieu that is favourable to tissue injury and carcinogenesis, as well as bacterial survival [132,133].

The persistent emission of reactive oxygen and nitrogen species (ROS/RNS) and the infiltration of neutrophils, macrophages, and lymphocytes are hallmarks of chronic inflammation caused by bacterial persistence. These reactive chemicals increase the risk of cancer by causing epithelial cells to undergo epigenetic changes, mutagenesis, and DNA damage [134].

Complex immune evasion strategies used by persistent bacteria to colonize the stomach mucosa promote chronic inflammation, a known predisposing factor to carcinogenesis [135]. The progression of gastric disease may be slowed by therapeutic strategies that target chronic inflammation by eliminating harmful bacteria, altering immunological signalling, or using anti-inflammatory drugs [136]. But other bacterial strains alter the structure of LPS lipid A or suppress the synthesis of flagellin, which reduces TLR4 and TLR5 activation and helps them avoid being detected by the innate immune system [137].

Bacterial persistence is made possible by this suppressed initial immune response. However, persistent bacterial stimulation of inflammasomes and the release of pro-inflammatory cytokines including IL-1β, TNF-α, and IL-6 sustain chronic immunological activation [138]. Reactive oxygen and nitrogen species (ROS and RNS) cause oxidative stress due to neutrophil, macrophage, and T lymphocyte infiltration in chronic gastritis, further destroying epithelium DNA and proteins [139, 140]. In addition to promoting gastric epithelial cell proliferation and apoptotic dysregulation, persistent inflammation also contributes to metaplastic and dysplastic alterations [141]. Crucially, certain bacteria, such as *Prevotella* species and *Fusobacterium nucleatum*, activate the NF-κB and STAT3 pathways, intensifying inflammatory signalling and creating a pro-tumorigenic milieu [142, 143].

Direct Genotoxic Effects of Bacterial Metabolites

In addition to indirect DNA damage caused by inflammation, several bacteria generate genotoxic chemicals that directly damage the DNA of stomach epithelial cells. Reactive oxygen species (ROS), reactive nitrogen species (RNS), and bacterial genotoxins like colibactin and cytolethal distending toxin (CDT) are examples of these metabolites [144,145]. By causing neutrophilic oxidative burst and secreting vacuolating cytotoxin A (VacA), which impairs mitochondrial function and produces ROS, *H. pylori* itself cause oxidative DNA damage [146]. Colibactin, a hybrid polyketide-nonribosomal peptide produced by other bacteria, such as *Escherichia coli* strains that have the pks genomic island, causes DNA interstrand cross links and double-strand breaks, which leads to genomic instability [147]. While the existence of colibactin in the gastric microbiota is still being studied, its genotoxicity in colorectal carcinogenesis is well documented, and it may play similar roles in gastric cancer [148].

Together with metabolic waste products like acetaldehyde and hydrogen sulphide, these poisons produce a genotoxic environment that encourages mutagenesis and malignant transformation [149, 150]. *In vivo*, bacterial strains that express genotoxin hasten the development of stomach cancer in mice [151].

Bacterial Toxins and Virulence Factors Affecting Epithelial Integrity

In order to induce carcinogenesis, bacterial virulence factors alter cell signalling and interfere with the function of the stomach epithelial barrier. The most well-characterized virulence factor causing epithelial damage and oncogenic signalling is the cytotoxin-associated gene A (CagA) protein produced by *H. pylori* and administered through a type IV secretion system [152]. As a result of CagA's interactions with

host kinases and phosphatases during translocation, pathways like SHP-2, β-catenin, and NF-κB are dysregulated, changing cell adhesion, promoting proliferation, and preventing apoptosis [153, 154]. Deeper bacterial invasion and more exposure to carcinogens are made possible by the loss of tight junction integrity and increased epithelial permeability that results from this [155].

H. pylori secrete VacA, a strong toxin that causes mitochondrial dysfunction in gastric epithelial cells. Research has shown that VacA depolarizes the mitochondrial membrane, which releases cytochrome c and triggers the apoptotic process. Furthermore, VacA initiates autophagic activities, which, depending on the situation, may either promote cell death or provide protection. This dual function highlights how intricately VacA affects host cells [156]. Numerous Gram-negative bacteria produce CDT, a genotoxin that damages host cells' DNA. Particularly during the G2/M phase, the active CdtB subunit reaches the nucleus and causes DNA double-strand breaks, which trigger the DNA damage response and result in cell cycle arrest. Bacteria can alter host cell functioning through this technique, which promotes recurring infections and aids in the etiology of disease [157]. By breaking down mucins and extracellular matrix components, bacterial lipases and proteases reduce the protective mucus barrier and promote bacterial adhesion and biofilm development [158].

Interactions Between *Helicobacter pylori* and Other Microbes

Once thought to be sterile because of its high acidity, the stomach environment is now understood to support a dynamic and complex microbiota. The well-known gastric pathogen *Helicobacter pylori* (*H. pylori*) interact significantly with other microorganisms that live in the stomach and gastrointestinal system. These interactions may be antagonistic, which could restrict pathogenic consequences or allow for the restoration of microbial equilibrium, or they may be synergistic, which would accelerate the course of the disease. Comprehending these microbial interactions is essential for understanding the pathophysiology of disorders linked to *H. pylori* and for improving treatment approaches (Figure 4) [159,160].

Synergistic and Antagonistic Roles of *H. pylori* with Other Microbes

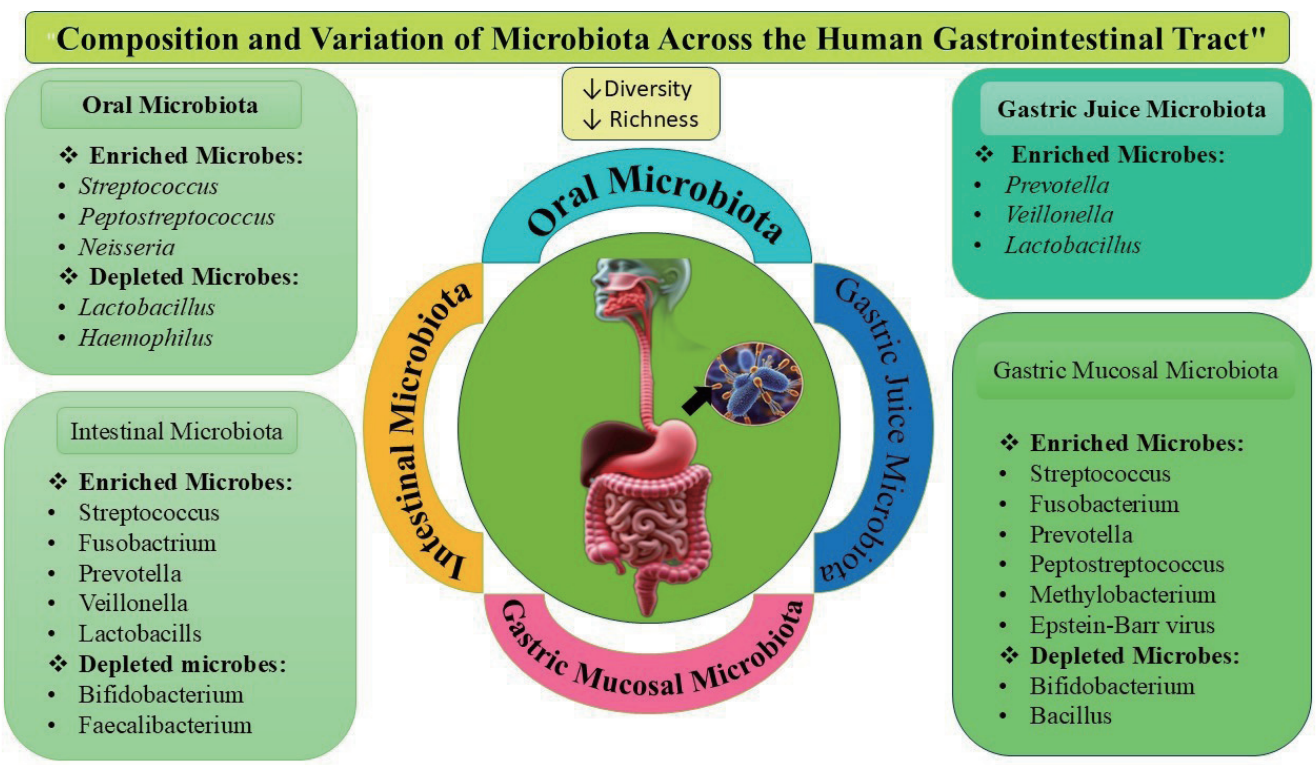

Figure 4: Composition and Variation of Microbiota Across the Human Gastrointestinal Tract
The figure illustrates the distribution, enrichment, and depletion of microbial communities across different sites of the human gastrointestinal tract, including the oral cavity, gastric juice, gastric mucosa, and intestine.

Synergistic Interactions

Numerous studies point out that *H. pylori* may contribute to gastric pathology by establishing a habitat that encourages the growth or virulence of other bacteria species. For instance, greater colonization by nitrate-reducing bacteria like Neisseria and *Streptococcus* species is linked to *H. pylori* infection. This can promote the production of carcinogenic N-nitroso compounds in hypochlorhydric circumstances caused by *H. pylori* [161,162]. This cooperative interaction might intensify damage to mucosal DNA and aid in the development of gastric cancer.

Additionally, the gastric milieu is altered by *H. pylori* -induced gastric inflammation, which facilitates the growth of opportunistic infections such as *Candida albicans* and *Fusobacterium nucleatum*. These bacteria have been linked to immune evasion and the promotion of epithelial-mesenchymal transition, which exacerbates damage to the stomach mucosa [163]. Specifically, *F. nucleatum* has the ability to attach themselves to stomach epithelial cells and work in concert with *H. pylori* to interfere with barrier function and increase inflammatory signalling [164].

Additionally, *H. pylori* produce substances like urease and VacA toxin that alter the pH and immune responses in the area, making it easier for bacteria and fungi that are sensitive to acid to co-colonize. It has been reported that *H. pylori* form cooperative biofilms with other bacteria, such as Staphylococcus and Pseudomonas, which shields *H. pylori* from antibiotics and human defences [165].

Antagonistic Interactions

On the other hand, *H. pylori* use direct antibacterial activity and competitive exclusion to negatively impact other gastric flora. The bacterium's strong urease activity temporarily raises the local pH, which makes the environment unfavourable for acidophilic bacteria and shapes the composition of the gastric microbiota [166].

Microbial Succession After *H. pylori* Eradication

Proton pump inhibitors (PPIs) and antibiotics are commonly used in eradication therapy, which significantly changes the gastric microbial environment in addition to eliminating *H. pylori*. A dynamic microbial succession characterized by greater diversity and colonization by commensals that are often inhibited during *H. pylori* infection is revealed by post-eradication research. Eradication therapy leads to significant shifts in gastric microbial communities. Non-*H. pylori* bacteria can expand in the absence of *H. pylori*, with increases in *Streptococcus*, *Prevotella*, and *Veillonella* reported in post-eradication patients. These successional changes may influence gastric mucosal healing, immune response, and long-term disease risk, emphasizing the importance of monitoring microbial dynamics during and after therapy [167].

Implications for Therapeutic Approaches

Therapeutic strategies should consider both *H. pylori* and non-*H. pylori* microbes. Approaches targeting biofilm disruption, microbial metabolites, and immune modulation may enhance eradication efficacy and prevent dysbiosis-related complications. Additionally, probiotics and prebiotics may support restoration of healthy microbial balance post-eradication, potentially reducing the risk of recurrent gastritis or neoplasia [168]. This change implies that eliminating *H. pylori* removes barriers to competition, enabling the growth of species that are typically inhibited. It's interesting to note that, depending on variables including host genetics, PPI use, and antibiotic regimen, the post-eradication microbiota may occasionally resemble that of healthy controls but may also retain dysbiosis indicators [169].

Functional Implications of Succession

Following *H. pylori* eradication, there are successional changes that affect stomach mucosal immunity and epithelial healing. For instance, restoring bacteria that produce butyrate, such as *Faecalibacterium* and *Roseburia*, can improve anti-inflammatory and mucosal healing [170]. The combination of proton pump inhibitors (PPIs) plus antibiotic medication might cause microbial succession in the gastrointestinal environment, which can upset the natural microbial balance and encourage the growth of opportunistic infections. PPIs lower stomach acidity, which makes it easier for acid-sensitive bacteria like Candida and Enterococcus species to colonize the stomach [171]. The necessity for treatment approaches that promote healthy microbiota recovery is highlighted by longitudinal studies that demonstrate that microbial succession following eradication is a lengthy process, occasionally taking months to years for microbiota normalization [172].

Antibiotic Therapy and Microbiota Perturbation

The mainstay of treatment for *Helicobacter pylori* infections and associated gastrointestinal conditions is

antibiotic therapy. Antibiotics are useful in eliminating harmful bacteria, but they can also significantly alter the gut and stomach microbiota, resulting in dysbiosis. Both short- and long-term clinical outcomes may be impacted by disruption of the microbial balance, which may encourage the growth of opportunistic infections, decrease microbial diversity, and compromise mucosal immunity [173]. In eradication regimens, broad-spectrum antibiotics like as metronidazole, amoxicillin, and clarithromycin are frequently utilized. These substances affect commensal bacterial populations in addition to *H. pylori*. Research indicates that the use of antibiotics decreases the number of good bacteria like *Lactobacillus* and Bifidobacterium while permitting potentially harmful bacteria like Enterococcus and Candida species to proliferate [174].

Probiotics and Microbiota Modulation

By reestablishing microbial balance, suppressing harmful bacteria, and boosting mucosal immunity, probiotics like *Lactobacillus* and Bifidobacterium species can alter the stomach and intestinal microbiota. It has been demonstrated that their usage in conjunction with antibiotic therapy for *H. pylori* infection improves eradication rates, lessens gastrointestinal side effects, and aids in preventing the establishment of opportunistic pathogens, all of which enhance the general health of the gastrointestinal tract [175].

Targeting Microbial Interactions

A viable strategy to alter the stomach microbiota and enhance treatment results is to target microbial interactions. Enhancing antibiotic efficiency and lowering persistent infection can be achieved by preventing the formation of opportunistic pathogens or by breaking up synergistic biofilms between *H. pylori* and other bacteria. By selectively influencing microbial populations, techniques like bacteriophage therapy, quorum-sensing inhibitors, and microbiota-directed prebiotics or probiotics can restore equilibrium and lower the risk of disease [174].

Microbiome-based Diagnostics and Personalized Therapy

By comparing the gut microbiota before and after *Helicobacter pylori* (*H. pylori*) eradication, tailored treatment plans can be developed, which may improve eradication outcomes while maintaining beneficial microbes. Escherichia and Klebsiella genera emerged as the most common bacteria in the gut microbiome after eradication therapy, according to a study with 12 *H. pylori* positive participants. According to this metagenomic investigation, adjusting probiotic and antibiotic regimes according to each person's particular microbial makeup may maximize therapeutic results and reduce disturbances to the gut microbiota [176].

Significance in *H. pylori* -Negative Gastritis and Gastric Cancer Cases

A significant portion of instances of gastritis and gastric cancer occur without *H. pylori* infection, despite the fact that *H. pylori* infection is a major risk factor for gastric pathology. This suggests that other microbial agents and dysbiosis have a role in the pathophysiology of the disease. Studies have identified unique microbial signatures in *H. pylori* -negative gastritis, including higher abundances of *Streptococcus*, *Prevotella*, *Veillonella*, and Propionibacterium species. These species may be involved in mucosal inflammation by producing pro-inflammatory metabolites and activating the immune system [177]. It is crucial to expand diagnostics beyond *H. pylori* since bacteria other than *H. pylori* can also cause gastritis on their own. It is noteworthy that changes in the stomach microbiome, such as increased colonization by *Fusobacterium*, *Clostridium*, and *Peptostreptococcus*, which promote carcinogenesis through genotoxic and inflammatory pathways, are linked to *H. pylori* -negative gastric cancer. Additionally, the makeup of the stomach microbiota can affect how well a treatment works. While bacteria that form biofilms or are resistant to antibiotics, like Enterococcus and Staphylococcus, may decrease the effectiveness of therapy and raise the risk of recurrence, higher abundances of *Lactobacillus* and Bifidobacterium are associated with better rates of *H. pylori* eradication [178]. Moreover, dysbiosis can result from changes in microbiota brought on by proton pump inhibitors (PPIs) and antibiotics during treatment, which might affect adverse consequences like candidiasis and antibiotic-associated diarrhea [179]. There is growing evidence that the gut and stomach flora affect how patients react to radiation and chemotherapy. Tumour sensitivity or resistance may be impacted by certain bacterial metabolites that affect immunological responses and medication metabolism [180,181]. Probiotic supplementation has been demonstrated to improve treatment tolerance and lessen mucositis, however inflammation triggered by the microbiota may be a factor in chemoresistance.

Promising methods to increase therapy effectiveness include probiotics, prebiotics, and microbiome-based medicines that alter the stomach bacteria. Probiotics, for example, have been shown to decrease adverse effects and increase patient compliance during *H. pylori* eradication therapy. Faecal microbiota transplantation (FMT) and engineered microbial consortia are also being researched as possible strategies to lower the incidence of stomach cancer and restore microbial balance after treatment [182].

Therapeutic Perspectives

Therapeutic Perspectives in Gastric Microbiome Modulation

The pathophysiology of gastric disorders, such as gastritis, metaplasia, and gastric cancer, is influenced by the gastric microbiome, which is also essential for preserving the homeostasis of the stomach mucosa and regulating host immunological responses [183]. Although *Helicobacter pylori* are still the main pathogen linked to stomach problems, new research shows that non-*H. pylori* dysbiosis has a major influence on stomach health and the course of disease [184]. Probiotics, prebiotics, microbiome restoration after antibiotic usage, and bacterial metabolite targeting are therapeutic approaches that aim to alter the stomach microbiome. Probiotics, including species of *Lactobacillus* and *Bifidobacterium*, can improve treatment results, strengthen mucosal immunity, and restore microbial equilibrium. Non-digestible fibres called prebiotics, such as fructooligosaccharides and inulin, selectively activate good bacteria to support gut health.

Following antibiotic-induced dysbiosis, microbial diversity and function can be restored by restoring the microbiome using strategies like fecal microbiota transplantation (FMT) or synbiotics. Targeting bacterial metabolites, like short-chain fatty acids (SCFAs), can also affect the course of disease and modify immunological responses. By repairing and preserving a balanced stomach microbiota, these strategies together present possible ways to improve patient outcomes and therapeutic efficacy [185].

Probiotics and Prebiotics Targeting Non-*H. pylori* Dysbiosis

Following antibiotic therapy, a number of methods have been investigated to restore the gut microbiota. The potential of probiotics—live microorganisms that assist the host—to restore microbial balance has been extensively researched. Repopulating beneficial bacteria and preventing the establishment of pathogenic species have been demonstrated to be possible with certain strains of Bifidobacterium and *Lactobacillus*. However, not all probiotic formulations produce consistent outcomes, and the effectiveness of probiotics can vary depending on the strain. Symbiotic provide a synergistic approach to microbiome restoration by combining probiotics with prebiotics, which are indigestible food ingredients that encourage the growth of advantageous microbes. Through fermentable substrates, these combinations promote the growth of beneficial microorganisms and increase their chances of survival and colonization. A powerful treatment option for patients with recurrent Clostridium difficile infections is fecal microbiota transplantation (FMT). FMT has been shown in clinical trials to be effective in reestablishing microbial diversity and function, which improves clinical results. Furthermore, precision medicine techniques are being researched to customize microbiome restoration treatments according to patient profiles, which include genetic composition and particular microbial deficits [186].

Targeting Harmful Bacterial Metabolites: A Future Therapeutic Avenue

Targeting the metabolites that gut bacteria make offers a novel therapeutic approach in addition to restoring microbial diversity. Numerous metabolites, such as short-chain fatty acids (SCFAs), bile acids, and amino acid derivatives, are produced by the gut microbiota and are essential for host metabolism and immunological modulation. Nevertheless, dysbiosis can result in the synthesis of toxic metabolites, including secondary bile acids and certain derivatives of amino acids, which are linked to the etiology of illnesses like inflammatory bowel disease and colorectal cancer. Research is being done on interventions meant to alter the synthesis or activity of these toxic metabolites. For example, pharmaceutical medications may inhibit the enzymes responsible for the synthesis of toxic metabolites, whereas dietary changes may affect the formation of SCFAs. Additionally, a novel treatment strategy is represented by engineered probiotics that are made to either create advantageous metabolites or break down toxic ones [187].

Microbiome Restoration Therapies Post-Antibiotic Treatment

Despite being essential for eliminating *H. pylori* and other infections, antibiotics seriously disturb the gut and stomach microbiomes, which results in a decrease

in microbial diversity, an increase in opportunistic pathogens, and the loss of helpful commensals [188, 189]. Effective microbiome restoration techniques are necessary to restore microbial equilibrium and gastrointestinal barrier function since longitudinal studies reveal that microbiome disruptions might last for months after stopping antibiotics [190]. Transferring stool from a healthy donor to a recipient on antibiotics has transformed the treatment of recurrent Clostridium difficile infections and may help restore gut flora following antibiotic use. Although the lower gut is the primary target of FMT, new research indicates that systemic microbial modulation may also affect the stomach and other parts of the upper GI tract. In the future, specific therapeutic restoration may be possible with the development of targeted stomach microbiota transplantation [180, 185].

The repair of the microbiome with probiotic therapy after antibiotics is a topic of much research. Multi-strain probiotics help regulate gastric mucosal immunity, decrease drug-associated side effects, and speed up microbiome recovery when taken right after antibiotic treatment. Following antibiotic-induced depletion, dietary treatments high in fibre and polyphenols help to restore the resilience of the microbiome and encourage the colonization of beneficial bacteria. Pharmacological treatments like mucosal protectants and bile acid sequestrants may help lessen the toxicity and dysbiosis caused by antibiotics [134, 152, 190].

Conclusion

It is becoming more widely acknowledged that non-*Helicobacter pylori* bacteria play a major role in the development, course, and outcome of stomach disorders. These organisms, which were once thought to be minor or incidental colonizers, are now known to actively affect gastric health through a variety of mechanisms, such as altering the local pH, disrupting the integrity of the epithelium, producing metabolites that have the potential to cause inflammation, mutagenesis, or cancer, and modulating the gastric immune microenvironment. Species like Propionibacterium acnes, Streptococcus species, Lactobacillus species, Prevotella species, Veillonella species, and Fusobacterium nucleatum play a variety of ecological roles, from independently promoting mucosal damage and neoplastic transformation to synergistically enhancing *H. pylori* -induced pathology.

Their intricate relationships with *H. pylori*, one another, and host factors highlight the necessity of expanding diagnostic strategies beyond *H. pylori* detection alone. High-resolution analysis of gastric microbial populations is now possible thanks to advanced metagenomic sequencing, metabolomics, and systems biology techniques. This presents chances to find new biomarkers for early detection and to more precisely forecast the course of disease. From a therapeutic standpoint, incorporating knowledge about the microbiome into clinical practice may enable microbiota-targeted therapies, including dietary modification, precision probiotics, prebiotics, and suppression of detrimental bacterial metabolic pathways. In order to develop effective prevention and treatment measures, future research must attempt to demonstrate causal links between particular microbial alterations and illness outcomes. In the end, improving patient care in the management of gastric diseases and developing precision medicine will require taking into account the contributions of both *H. pylori* and non-*H. pylori* bacteria.

Authors' Contribution

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Conflict of Interest

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