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STRAIN-SPECIFIC EFFECTS OF PROBIOTICS IN GASTROESOPHAGEAL REFLUX DISEASE: A COMPREHENSIVE REVIEW

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ABSTRACT

Gastroesophageal reflux disease (GERD) is one of the most prevalent gastrointestinal disorders worldwide and represents a significant burden on healthcare systems due to its high prevalence, chronic course, and impact on patients' quality of life. Although proton pump inhibitors (PPIs) remain the cornerstone of GERD treatment, a considerable proportion of patients continue to experience persistent symptoms, and concerns regarding the long-term use of acid-suppressive therapy have increased interest in complementary therapeutic approaches. Recent advances in microbiome research have highlighted the potential role of gut and esophageal microbiota in the pathogenesis of GERD, suggesting that probiotics may offer therapeutic benefits beyond conventional treatment. This review summarizes current evidence regarding the strain-specific effects of probiotics in GERD, focusing on commonly investigated strains, including *Lactobacillus reuteri*, *Lactobacillus rhamnosus* GG, *Lactobacillus acidophilus*, and *Bifidobacterium* species. Available studies indicate that these probiotics may improve upper gastrointestinal symptoms through modulation of the intestinal microbiota, enhancement of epithelial barrier function, regulation of inflammatory responses, and improvement of gastrointestinal motility. Emerging evidence also suggests that certain *Bifidobacterium* strains may indirectly influence glucagon-like peptide-1 (GLP-1) secretion via the production of short-chain fatty acids, although the clinical significance of this mechanism in GERD has not yet been established. Overall, current findings support the use of probiotics as a promising adjunct to standard GERD therapy; however, their effects remain highly strain-specific, and the available evidence is limited by heterogeneous study designs and relatively small patient populations. Further well-designed randomized controlled trials are required to determine the most effective probiotic strains, optimal treatment regimens, and their long-term role in the management of GERD.

KEYWORDS

Gastroesophageal Reflux Disease (GERD), Probiotics, *Lactobacillus reuteri, Lactobacillus rhamnosus* GG, Bifidobacterium, Gut Microbiota, Esophageal Microbiota, Proton Pump Inhibitors (PPIs), Glucagon-Like Peptide-1 (GLP-1)

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1. Introduction

Gastroesophageal reflux disease (GERD) is one of the most prevalent gastrointestinal disorders worldwide, affecting approximately 10-20% of the adult population in Western countries and showing an increasing incidence in developing regions. The condition is characterized by the reflux of gastric contents into the esophagus, resulting in troublesome symptoms such as heartburn, regurgitation, chest discomfort, and, in some cases, extraesophageal manifestations including chronic cough, laryngitis, and asthma. Persistent reflux may lead to complications such as erosive esophagitis, Barrett's esophagus, and esophageal adenocarcinoma, significantly impairing patients' quality of life and increasing healthcare utilization.

The pathogenesis of GERD is multifactorial and involves transient lower esophageal sphincter relaxations, impaired esophageal clearance, delayed gastric emptying, hiatal hernia, and increased intra-abdominal pressure. Although gastric acid has traditionally been considered the primary factor responsible for symptom development and mucosal injury, growing evidence suggests that inflammatory mechanisms, host immune responses, and alterations in the gastrointestinal microbiota may also contribute to disease progression.

Current treatment strategies for GERD include lifestyle modifications, pharmacological therapy, and surgical interventions. Proton pump inhibitors (PPIs) remain the cornerstone of medical treatment and are highly effective in reducing gastric acid secretion and promoting mucosal healing. However, a substantial proportion of patients continue to experience symptoms despite adequate PPI therapy. Furthermore, concerns regarding the long-term use of acid-suppressive medications, including potential associations with nutrient

deficiencies, enteric infections, and alterations in gut microbial composition, have stimulated interest in complementary and alternative therapeutic approaches.

Recent advances in microbiome research have highlighted the important role of the gastrointestinal microbiota in maintaining digestive health and regulating immune and inflammatory processes. While most studies have focused on the intestinal microbiome, increasing attention has been directed toward the esophageal microbiota and its potential involvement in GERD pathophysiology. Several investigations have demonstrated that patients with reflux disease exhibit distinct microbial profiles compared with healthy individuals, suggesting that microbial dysbiosis may contribute to mucosal inflammation and symptom generation.

Probiotics, defined as live microorganisms that confer health benefits when administered in adequate amounts, have emerged as a promising strategy for modulating the gastrointestinal microbiome. Various probiotic strains, particularly species belonging to the genera Lactobacillus and Bifidobacterium, have demonstrated beneficial effects in several gastrointestinal disorders through mechanisms including enhancement of epithelial barrier function, modulation of immune responses, inhibition of pathogenic microorganisms, and improvement of gastrointestinal motility. However, probiotic effects are highly strain-specific, and clinical outcomes may differ considerably depending on the microorganism used, dosage, treatment duration, and patient population.

Although the use of probiotics in GERD remains an evolving area of research, several studies have reported improvements in reflux-related symptoms, upper gastrointestinal comfort, and overall digestive function following probiotic supplementation. Nevertheless, the available evidence remains heterogeneous, and the relative effectiveness of individual probiotic strains has not yet been comprehensively established.

Therefore, the aim of this review is to evaluate current evidence regarding the strain-specific effects of probiotics in gastroesophageal reflux disease. Particular attention is given to the mechanisms of action of individual probiotic strains, their clinical efficacy, safety profiles, and potential role as adjunctive therapies in the management of GERD. By synthesizing available data, this review seeks to provide a comprehensive overview of the current state of knowledge and identify directions for future research in this rapidly developing field.

2. Methods

This narrative review was conducted to summarize the current evidence regarding the strain-specific effects of probiotics in the management of gastroesophageal reflux disease (GERD). A comprehensive literature search was performed using the PubMed, Scopus, and Web of Science databases. Publications published between January 2010 and March 2026 were considered for inclusion.

The search strategy included combinations of the following keywords: "gastroesophageal reflux disease", "GERD", "probiotics", "Lactobacillus", "Bifidobacterium", "gut microbiota", "esophageal microbiota", "proton pump inhibitors", "GLP-1", "gut-brain axis", and "short-chain fatty acids".

Priority was given to systematic reviews, meta-analyses, randomized controlled trials, prospective clinical studies, and relevant experimental investigations published in English. Additional references were identified by manually screening the bibliographies of selected articles.

Studies focusing on the effects of probiotics on GERD symptoms, gastrointestinal microbiota, esophageal microbiota, epithelial barrier function, inflammatory responses, gastric motility, and microbiota-related signaling pathways were included. Publications with insufficient methodological quality, duplicate records, conference abstracts, and non-English articles were excluded.

The collected evidence was critically analyzed and organized according to the biological mechanisms of probiotic action, strain-specific characteristics, and available clinical evidence supporting probiotic supplementation as an adjunctive therapy in patients with GERD.

3. GERD Pathophysiology and the Gastrointestinal Microbiota

3.1. Pathophysiology of GERD

Gastroesophageal reflux disease (GERD) develops due to the reflux of gastric contents into the esophagus. The most important mechanism involved is dysfunction of the lower esophageal sphincter (LES), particularly transient LES relaxations. Other contributing factors include impaired esophageal clearance, delayed gastric emptying, increased intra-abdominal pressure, and hiatal hernia. Repeated exposure of the esophageal mucosa to gastric acid and other gastric components can lead to inflammation and tissue damage.

3.2. The Esophageal Microbiota

Recent studies have demonstrated that the esophagus contains a distinct microbial community. In healthy individuals, the microbiota is dominated by Gram-positive bacteria, particularly species of *Streptococcus*. In patients with GERD, alterations in microbial composition have been observed, including an increased abundance of Gram-negative bacteria. These changes may promote inflammation and contribute to disease progression.

3.3. The Gut–Esophagus Axis

The gastrointestinal microbiota plays an important role in regulating immune responses, epithelial barrier function, and gastrointestinal motility. Disturbances in microbial balance may contribute to GERD symptoms and esophageal inflammation. Increasing evidence suggests that modulation of the microbiota may represent a promising therapeutic strategy in GERD management.

4. Mechanisms of Probiotic Action in GERD

The therapeutic potential of probiotics in gastroesophageal reflux disease (GERD) is attributed to several biological mechanisms that contribute to maintaining gastrointestinal homeostasis. Although probiotics are not considered a primary treatment for GERD, increasing evidence suggests that they may support conventional therapy by improving microbial balance, strengthening the mucosal barrier, and modulating immune responses. Importantly, these effects are highly strain-specific, highlighting the importance of selecting appropriate probiotic microorganisms for clinical use.

4.1. Modulation of the Gastrointestinal Microbiota

One of the primary mechanisms of probiotic action is the restoration of a balanced gastrointestinal microbiota. Probiotic microorganisms compete with pathogenic bacteria for nutrients and adhesion sites while producing antimicrobial substances such as organic acids and bacteriocins. This competitive activity helps maintain microbial homeostasis and may reduce dysbiosis associated with GERD and long-term proton pump inhibitor (PPI) therapy.

4.2. Enhancement of Epithelial Barrier Function

Probiotics contribute to the maintenance of epithelial integrity by promoting the production of mucus and strengthening tight junction proteins between epithelial cells. Improved barrier function limits the penetration of harmful microorganisms and inflammatory mediators, thereby protecting the gastrointestinal mucosa from injury. These effects may reduce mucosal inflammation and support tissue repair in patients with reflux disease.

4.3. Immunomodulatory Effects

Several probiotic strains have demonstrated the ability to regulate both innate and adaptive immune responses. They can reduce the production of pro-inflammatory cytokines, including tumor necrosis factor-α (TNF-α) and interleukin-6 (IL-6), while promoting anti-inflammatory mediators such as interleukin-10 (IL-10). Through these immunomodulatory mechanisms, probiotics may attenuate chronic low grade inflammation associated with gastrointestinal disorders, including GERD.

4.4. Effects on Gastrointestinal Physiology

Beyond their influence on the microbiota and immune system, probiotics may also affect gastrointestinal physiology through interactions with microbial metabolites, epithelial cells, and neuroendocrine pathways. Experimental evidence suggests that these interactions may influence gastric motility, intestinal permeability, and communication along the gut–brain axis. In addition, certain probiotic strains have been associated with metabolic signaling pathways involving short-chain fatty acids (SCFAs) and glucagon-like peptide-1 (GLP-1). Although these mechanisms remain under investigation, they represent promising areas for future research and are discussed in greater detail in the following chapter.

5. Strain-Specific Effects of Probiotics in GERD

5.1. Lactobacillus reuteri

Among the probiotic strains investigated in gastrointestinal disorders, *Lactobacillus reuteri* is one of the most extensively studied. This strain exhibits antimicrobial activity through the production of reuterin and other bioactive compounds that inhibit the growth of pathogenic microorganisms. Furthermore, *L. reuteri* has been shown to improve mucosal barrier integrity and modulate local immune responses.

Several clinical studies have reported beneficial effects of *L. reuteri* supplementation on upper gastrointestinal symptoms, including regurgitation, gastric discomfort, and functional dyspepsia. In infants, supplementation with *L. reuteri* DSM 17938 has been associated with reduced regurgitation frequency and improved gastric emptying. Although evidence specifically addressing GERD remains limited, these findings suggest that *L. reuteri* may contribute to symptom improvement through modulation of gastrointestinal function and microbial homeostasis.

5.2. Lactobacillus rhamnosus GG

Lactobacillus rhamnosus GG is one of the best characterized probiotic strains and has demonstrated beneficial effects in numerous gastrointestinal conditions. Its mechanisms of action include enhancement of epithelial barrier function, stimulation of mucus production, and regulation of inflammatory pathways.

Experimental studies indicate that *L. rhamnosus* GG may reduce intestinal permeability and promote mucosal healing. These properties are particularly relevant in gastrointestinal disorders associated with chronic inflammation. Although direct evidence in GERD patients is currently limited, its ability to support epithelial integrity and modulate immune responses may provide indirect benefits in reflux disease.

5.3. Lactobacillus acidophilus

Lactobacillus acidophilus is frequently included in probiotic formulations due to its ability to maintain microbial balance within the gastrointestinal tract. This strain produces lactic acid and antimicrobial substances that inhibit the growth of potentially harmful bacteria while supporting the proliferation of beneficial microorganisms.

Clinical studies have suggested that *L. acidophilus* may alleviate symptoms such as bloating, nausea, and indigestion, which often coexist with GERD. Furthermore, its favorable safety profile and long history of clinical use support its potential role as an adjunctive component of reflux management strategies.

5.4. Bifidobacterium Species and Potential Interactions with GLP-1

Species belonging to the genus *Bifidobacterium*, particularly *Bifidobacterium lactis* and *Bifidobacterium breve*, have attracted increasing attention due to their immunomodulatory properties and their influence on host metabolism. These bacteria contribute to the maintenance of intestinal barrier integrity and promote the production of short-chain fatty acids (SCFAs), including acetate and butyrate.

Recent studies suggest that SCFAs may stimulate enteroendocrine L-cells to increase the secretion of glucagon like peptide 1 (GLP-1), hormone involved in glucose metabolism, gastric emptying, appetite regulation, and gastrointestinal motility. Through this mechanism, *Bifidobacterium* species may indirectly influence upper gastrointestinal function.

The relationship between GLP-1 signaling and GERD remains complex. Increased GLP-1 activity is associated with delayed gastric emptying, which could theoretically increase gastric retention and promote reflux in some individuals. Conversely, improved metabolic regulation, reduced inflammation, and enhanced barrier function may exert beneficial effects on gastrointestinal health. At present, there is insufficient clinical evidence to conclude whether probiotic-induced modulation of GLP-1 has a direct impact on GERD symptoms.

Nevertheless, the interaction between *Bifidobacterium* species, microbial metabolites, and enteroendocrine signaling represents a promising area for future research.

5.4.1. SCFA Production and GLP-1 Secretion

One of the most important mechanisms through which *Bifidobacterium* species may exert beneficial effects is the production of short-chain fatty acids (SCFAs), particularly acetate, propionate, and butyrate. These metabolites are generated during the fermentation of dietary fibers and play a key role in maintaining intestinal homeostasis. SCFAs serve as signaling molecules by activating G-protein-coupled receptors, including GPR41 and GPR43, located on enteroendocrine L-cells. Activation of these receptors stimulates the secretion of glucagon-like peptide-1 (GLP-1), an incretin hormone involved in glucose metabolism and gastrointestinal function.

In addition to its metabolic effects, GLP-1 has been shown to influence gastric emptying, intestinal motility, and epithelial barrier integrity. Through indirect stimulation of GLP-1 secretion, *Bifidobacterium* species may contribute to improved gastrointestinal homeostasis and reduced mucosal inflammation. However,

current evidence supporting this mechanism is derived mainly from experimental and metabolic studies rather than clinical trials involving patients with GERD. Therefore, although the microbiota–SCFA–GLP-1 axis represents a promising therapeutic target, its direct role in reflux disease remains to be established.

5.4.2. Effects on Gastric Emptying

Gastric emptying plays an important role in the pathophysiology of GERD. Delayed gastric emptying increases gastric volume and intragastric pressure, thereby promoting reflux episodes. Several probiotic strains have been reported to improve gastric motility and accelerate gastric emptying, potentially reducing gastric distension and the frequency of reflux events.

Experimental studies suggest that probiotics may influence gastrointestinal motility through interactions with the enteric nervous system, microbial metabolites, and gastrointestinal hormones, including GLP-1. Although increased GLP-1 secretion is generally associated with delayed gastric emptying, the overall effects of probiotics on gastric motility appear to depend on complex interactions between different microbial metabolites and host regulatory pathways. Consequently, further clinical studies are needed to clarify the relationship between probiotic supplementation, GLP-1 signaling, and gastric emptying in patients with GERD.

5.4.3. Modulation of Gut–Brain Signaling

Emerging evidence indicates that probiotics may influence the bidirectional communication between the gastrointestinal tract and the central nervous system through the gut–brain axis. This interaction involves neural, endocrine, immune, and microbial pathways that regulate gastrointestinal function and symptom perception.

Several *Lactobacillus* and *Bifidobacterium* strains have demonstrated the ability to modulate neurotransmitter production, reduce systemic inflammation, and influence vagal nerve signaling. These mechanisms may contribute to improved gastrointestinal motility, reduced visceral hypersensitivity, and better regulation of digestive function. Since stress and psychological factors are recognized contributors to GERD symptom severity, modulation of the gut–brain axis may represent an additional mechanism through which probiotics improve patient outcomes.

Although current evidence remains preliminary, the interaction between probiotics, microbial metabolites, gastrointestinal hormones, and neural signaling pathways represents a rapidly expanding area of research. Future studies are required to determine the clinical significance of these mechanisms in the management of GERD.

5.5. Multi-Strain Probiotic Formulations

Multi-strain probiotic formulations containing combinations of *Lactobacillus* and *Bifidobacterium* species have gained increasing attention in recent years. Such formulations are designed to provide synergistic effects through multiple mechanisms, including microbial modulation, enhancement of epithelial barrier function, and regulation of immune responses.

Several clinical studies have reported improvements in upper gastrointestinal symptoms, including heartburn, regurgitation, bloating, and abdominal discomfort following supplementation with multi-strain probiotics. However, substantial heterogeneity exists among studies regarding probiotic composition, dosage, and treatment duration.

Overall, current evidence suggests that probiotic supplementation may provide symptomatic benefits in some patients with GERD. Nevertheless, further well designed randomized controlled trials are required to identify the most effective strains and clarify the mechanisms responsible for their clinical effects.

5.6. Emerging Probiotic Candidates and Future Directions

Although most clinical studies have focused on *Lactobacillus* and *Bifidobacterium* species, increasing attention has recently been directed toward next generation probiotics with potential applications in gastrointestinal diseases. Advances in microbiome research have identified several commensal microorganisms that may exert beneficial effects through mechanisms distinct from those of conventional probiotic strains.

Among the most promising candidates is *Akkermansia muciniphila*, a mucin-degrading bacterium associated with improved intestinal barrier function, reduced inflammation, and enhanced metabolic homeostasis. Experimental studies suggest that *A. muciniphila* may strengthen epithelial integrity and promote the production of beneficial microbial metabolites, although its role in GERD has not yet been investigated in clinical trials.

Another microorganism attracting considerable interest is *Faecalibacterium prausnitzii*, one of the major butyrate producing bacteria in the healthy human gut. This species exhibits potent anti-inflammatory properties and contributes to epithelial barrier maintenance through the production of short-chain fatty acids,

particularly butyrate. Reduced abundance of *F. prausnitzii* has been reported in several inflammatory gastrointestinal disorders, suggesting that restoration of its population may provide therapeutic benefits.

Future probiotic research is expected to move beyond traditional formulations toward personalized microbiome-based interventions. Advances in metagenomics, metabolomics, and microbial sequencing technologies may enable the identification of individual microbial signatures associated with GERD susceptibility, symptom severity, and treatment response. Such approaches could facilitate the development of precision probiotic therapies tailored to the patient's microbiota composition rather than relying on universal probiotic preparations.

Although these next generation probiotics remain largely experimental in the context of GERD, they represent an important direction for future research and may contribute to the development of more effective microbiota-targeted therapies.

Probiotic strain	Main mechanisms of action	Potential effects in GERD	Level of evidence
Lactobacillus reuteri DSM 17938	Production of reuterin, inhibition of pathogenic bacteria, enhancement of epithelial barrier function, modulation of immune responses, improvement of gastric emptying	Reduced regurgitation, improved gastric motility, relief of upper gastrointestinal symptoms	Moderate (clinical studies)
Lactobacillus rhamnosus GG	Enhancement of tight junction integrity, stimulation of mucus production, immunomodulation, reduction of inflammatory cytokines	Protection of esophageal and intestinal mucosa, potential reduction of inflammation	Limited–Moderate
Lactobacillus acidophilus	Production of lactic acid, inhibition of pathogenic microorganisms, stabilization of gut microbiota	Improvement of dyspeptic symptoms, abdominal discomfort, and microbial balance	Limited
Bifidobacterium lactis	SCFA production, enhancement of epithelial barrier function, modulation of gut microbiota, regulation of immune responses	Potential modulation of GLP-1 secretion, improved gut homeostasis, reduction of inflammation	Limited (mainly experimental)
Bifidobacterium breve	SCFA production, improvement of intestinal permeability, anti-inflammatory activity	Potential support of gastrointestinal barrier function and metabolic regulation	Experimental
Multi-strain formulations (*Lactobacillus* + *Bifidobacterium*)	Synergistic modulation of gut microbiota, immune regulation, epithelial protection	Improvement of reflux symptoms, gastrointestinal comfort, and microbial diversity	Moderate

6. Clinical Evidence: Probiotics as Adjunctive Therapy to Proton Pump Inhibitors

Proton pump inhibitors (PPIs) remain the first line pharmacological treatment for gastroesophageal reflux disease (GERD) due to their effectiveness in suppressing gastric acid secretion and promoting mucosal healing. However, a considerable proportion of patients continue to experience persistent symptoms despite PPI therapy. In addition, long-term use of PPIs has been associated with alterations in the gastrointestinal microbiota, raising interest in complementary strategies aimed at restoring microbial balance.

In recent years, several studies have investigated the potential benefits of combining probiotics with PPI therapy. The rationale for this approach is based on the ability of probiotics to modulate the gastrointestinal microbiota, strengthen epithelial barrier function, and regulate immune responses. These mechanisms may complement the acid-suppressive effects of PPIs and contribute to improved symptom control.

A systematic review by Cheng and Ouwehand evaluated the effects of probiotics on GERD-related symptoms and reported that the majority of included studies demonstrated positive outcomes, including reductions in regurgitation, heartburn, abdominal discomfort, and other upper gastrointestinal symptoms. The authors concluded that probiotics may serve as a beneficial adjunctive therapy in patients with reflux disease, although further high quality clinical trials are required to confirm these findings.

More recently, a randomized double-blind placebo-controlled study examined the effects of a multi-strain probiotic administered alongside rabeprazole in patients with GERD. Compared with placebo, patients receiving probiotics showed significantly greater improvement in reflux symptoms and maintained symptom relief after discontinuation of PPI treatment. These benefits were accompanied by favorable changes in gut microbiota composition and microbial metabolites, suggesting that probiotics may help counteract PPI-associated dysbiosis.

Several probiotic strains, particularly species belonging to the genera *Lactobacillus* and *Bifidobacterium*, have been proposed as potential adjuncts to conventional GERD therapy. Although the available evidence remains heterogeneous, current findings suggest that probiotic supplementation may improve upper gastrointestinal symptoms, enhance patient comfort, and support microbial homeostasis during long-term PPI treatment.

Nevertheless, important limitations should be acknowledged. Existing studies differ considerably with regard to probiotic strains, dosages, treatment duration, and clinical endpoints. Furthermore, many trials include relatively small patient populations, making direct comparisons difficult. Consequently, additional randomized controlled trials on a large scale are needed to establish clear recommendations regarding the use of probiotics as adjunctive therapy in GERD.

Overall, current evidence indicates that probiotics may represent a promising complementary approach to conventional PPI therapy. Their ability to improve gastrointestinal symptoms and potentially mitigate microbiota disturbances associated with long-term acid suppression warrants further investigation.

6.1. Clinical Evidence in Adults

Most clinical studies investigating probiotics in gastroesophageal reflux disease have been conducted in adult populations. Although the number of randomized controlled trials remains limited, available evidence suggests that probiotic supplementation may improve several upper gastrointestinal symptoms associated with GERD, including heartburn, regurgitation, abdominal discomfort, nausea, and bloating.

A systematic review conducted by Cheng and Ouwehand analyzed 13 prospective clinical studies evaluating probiotic supplementation in patients with GERD or reflux-related symptoms. Approximately 79% of the included studies reported beneficial effects of probiotics, with reductions in regurgitation, heartburn, and dyspeptic symptoms being the most frequently observed outcomes. However, the authors emphasized the considerable heterogeneity among studies regarding probiotic strains, treatment duration, and clinical endpoints, preventing definitive conclusions regarding the most effective probiotic formulations.

Several studies have also suggested that probiotics may improve overall digestive function by reducing gas-related symptoms and promoting a healthier gastrointestinal microbiota. These findings support the hypothesis that probiotics may complement conventional GERD treatment, although additional randomized controlled trials are required before routine clinical use can be recommended.

6.2. Clinical Evidence in Pediatric Patients

Probiotics have also been investigated in pediatric patients with gastroesophageal reflux disease, particularly because prolonged proton pump inhibitor therapy may alter the intestinal microbiota and increase the risk of dysbiosis.

A randomized controlled trial by Belei et al. evaluated the administration of *Lactobacillus reuteri* DSM 17938 in children receiving PPI therapy for GERD. After 12 weeks of treatment, the prevalence of small intestinal bacterial overgrowth was significantly lower in children receiving probiotics compared with those treated with PPIs alone. These findings suggest that probiotic supplementation may help preserve microbial balance during long-term acid suppression therapy.

Additional evidence from systematic reviews indicates that probiotic supplementation may reduce the frequency of infant regurgitation and improve gastrointestinal comfort during early life. Although infant regurgitation is considered a physiological condition rather than true GERD in many cases, these findings support the potential role of probiotics in improving upper gastrointestinal function. Nevertheless, current evidence remains insufficient to recommend routine probiotic supplementation in all pediatric patients with GERD, and further clinical trials are needed to establish optimal strains, dosages, and treatment duration.

6.3. Probiotics as Adjunctive Therapy to Proton Pump Inhibitors

Proton pump inhibitors (PPIs) remain the cornerstone of pharmacological treatment for gastroesophageal reflux disease (GERD) because of their effectiveness in suppressing gastric acid secretion and promoting mucosal healing. However, approximately 20-40% of patients continue to experience persistent reflux symptoms despite adequate PPI therapy. In addition, long-term acid suppression has been associated with alterations in the composition of the gastrointestinal microbiota, which may contribute to dysbiosis and gastrointestinal complaints. These observations have increased interest in probiotics as a complementary therapeutic approach.

The rationale for combining probiotics with PPIs is based on their ability to restore microbial homeostasis, reinforce epithelial barrier integrity, inhibit the growth of pathogenic microorganisms, and modulate local immune responses. By improving microbial balance, probiotics may also help reduce gastrointestinal symptoms frequently reported during prolonged PPI treatment, including bloating, abdominal discomfort, nausea, and dyspepsia.

Evidence supporting adjunctive probiotic therapy has steadily increased in recent years. A systematic review by Cheng and Ouwehand, which included 13 prospective clinical studies, reported that most studies demonstrated improvements in reflux-related symptoms following probiotic supplementation. Beneficial effects were observed particularly for heartburn, regurgitation, epigastric discomfort, and overall gastrointestinal well-being. Nevertheless, the authors emphasized that differences in study design, probiotic strains, treatment duration, and outcome measures limited direct comparisons between studies.

More recently, randomized controlled trials have suggested that supplementation with multi-strain probiotics in combination with PPI therapy may provide greater symptom relief than PPI treatment alone. Patients receiving probiotics showed improved control of reflux symptoms, better gastrointestinal comfort, and favorable changes in gut microbial composition. Some studies also reported sustained symptom improvement after discontinuation of PPI therapy, indicating that restoration of microbial homeostasis may contribute to longer-term clinical benefits.

Despite these encouraging findings, the available evidence remains insufficient to support the routine use of probiotics in all patients with GERD. Clinical outcomes appear to depend on the specific probiotic strain, dosage, duration of supplementation, and individual patient characteristics. Consequently, probiotics should currently be regarded as an adjunct rather than a replacement for conventional acid-suppressive therapy.

Future large-scale, randomized, placebo-controlled studies are required to identify the most effective probiotic strains, establish standardized treatment protocols, and determine which patient populations are most likely to benefit from adjunctive probiotic therapy. Such studies will be essential for integrating probiotics into evidence-based clinical management of GERD.

Author (Year)	Study design	Study population	Probiotic strain(s)	Main findings
Cheng & Ouwehand (2020)	Systematic review (13 studies)	Adults and children with GERD or reflux-related symptoms	Various *Lactobacillus* and *Bifidobacterium* strains	Approximately 79% of studies reported improvement in heartburn, regurgitation, dyspepsia, or overall gastrointestinal symptoms.
Belei et al. (2018)	Randomized controlled trial	Children receiving PPI therapy for GERD	*Lactobacillus reuteri* DSM 17938	Significantly reduced prevalence of small intestinal bacterial overgrowth (SIBO) during PPI treatment.
Indrio et al. (2014)	Randomized controlled trial	Healthy infants with functional regurgitation	*Lactobacillus reuteri* DSM 17938	Reduced regurgitation episodes and accelerated gastric emptying compared with placebo.
Zhang et al. (2026)	Randomized, double-blind, placebo-controlled trial	Adults with GERD	Multi-strain probiotic combined with rabeprazole	Greater symptom relief, improved gut microbiota composition, and sustained benefits following discontinuation of PPI therapy.
Hungin et al. (2013)	Systematic review	Patients with functional gastrointestinal disorders	Various probiotic strains	Improvement in abdominal bloating, nausea, and upper gastrointestinal discomfort; evidence for GERD remained limited.

7. Safety and Limitations

7.1. Safety of Probiotic Supplementation

Probiotics are generally recognized as safe for use in healthy individuals and have been extensively investigated in the prevention and management of gastrointestinal disorders. Clinical studies evaluating probiotic supplementation in patients with upper gastrointestinal diseases have consistently reported a favorable safety profile. The most frequently observed adverse events are mild and transient, including abdominal bloating, flatulence, or changes in bowel habits, which usually resolve without discontinuation of treatment.

Serious adverse events associated with probiotic use are extremely rare and are primarily reported in severely immunocompromised patients, critically ill individuals, or patients with central venous catheters. Consequently, probiotic supplementation should be used with caution in these populations. For the majority of patients with GERD, however, currently available evidence indicates that probiotic therapy is safe and well tolerated when administered at recommended doses.

7.2. Limitations of Current Evidence

Despite encouraging findings, the available evidence regarding probiotics in GERD remains limited. One of the major challenges is the relatively small number of randomized controlled trials specifically investigating patients with gastroesophageal reflux disease. Many published studies evaluate broader functional gastrointestinal disorders or upper gastrointestinal symptoms, making it difficult to draw conclusions that are directly applicable to GERD.

Another important limitation is the substantial heterogeneity among studies. Differences in probiotic strains, dosages, treatment duration, patient characteristics, and clinical outcome measures complicate comparisons between individual studies and limit the development of evidence-based recommendations. Furthermore, most available clinical trials include relatively small sample sizes and short follow-up periods, reducing the strength of the current evidence.

The relationship between probiotics and novel mechanisms, including modulation of the microbiota–SCFA–GLP-1 axis and gut–brain signaling, is also based largely on experimental and preclinical studies. Therefore, the clinical relevance of these mechanisms in GERD remains to be confirmed.

7.3. Challenges in Strain-Specific Research

An important consideration in probiotic research is that beneficial effects are highly strain-specific. Even closely related bacterial strains within the same species may differ substantially in their biological activity, metabolic properties, and clinical efficacy. Therefore, positive results obtained with one probiotic strain cannot be generalized to all members of the same bacterial species.

Future studies should focus on identifying the probiotic strains that provide the greatest therapeutic benefit for patients with GERD and clarifying their mechanisms of action. Particular attention should be given to interactions between probiotics, the esophageal and intestinal microbiota, microbial metabolites, gastrointestinal hormones such as GLP-1, and the gut–brain axis. Standardization of probiotic formulations and clinical endpoints will be essential for comparing study results and translating research findings into clinical practice.

Addressing these challenges will facilitate the development of personalized microbiota-based therapies and improve the quality of evidence supporting probiotic use in the management of gastroesophageal reflux disease.

8. Future Perspectives

Growing advances in microbiome research have significantly expanded our understanding of the relationship between microbial communities and gastrointestinal diseases, including gastroesophageal reflux disease (GERD). Although probiotics have demonstrated promising therapeutic potential, current evidence indicates that their clinical efficacy is highly strain-specific and depends on multiple host-related factors. Future research should therefore focus on identifying probiotic strains with the greatest potential to improve reflux symptoms and restore gastrointestinal homeostasis.

One of the most promising areas of investigation is the interaction between probiotics and host metabolic signaling pathways. Recent studies suggest that *Bifidobacterium* species may indirectly stimulate glucagon-like peptide-1 (GLP-1) secretion through the production of short-chain fatty acids (SCFAs). This microbiota SCFA-GLP-1 axis may influence gastrointestinal motility, epithelial barrier integrity, immune regulation, and metabolic homeostasis. Although these mechanisms have been demonstrated primarily in experimental models, their potential role in GERD warrants further investigation through well-designed clinical studies.

Another important direction for future research is the growing interest in the gut–brain axis. Communication between the intestinal microbiota, enteric nervous system, vagal pathways, and central nervous system may influence gastrointestinal motility, visceral sensitivity, and symptom perception. A better understanding of these interactions could contribute to the development of novel microbiota-based therapeutic strategies for patients with persistent reflux symptoms.

Future studies should also investigate the role of the esophageal microbiota in GERD pathogenesis. Advances in next-generation sequencing technologies may enable the identification of microbial signatures associated with disease severity, treatment response, and the risk of complications such as Barrett's esophagus. Such findings could facilitate the development of personalized therapeutic approaches based on individual microbial profiles.

Finally, large-scale randomized controlled trials with standardized probiotic formulations, treatment protocols, and clinical outcome measures are essential to establish evidence-based recommendations. Integrating microbiome profiling with clinical and molecular data may support the implementation of precision medicine in GERD management and allow probiotic therapy to be tailored to individual patient characteristics.

Overall, continued research into strain-specific probiotics, host–microbiota interactions, and microbiome-targeted therapies is expected to improve our understanding of GERD pathophysiology and may lead to more effective, personalized treatment strategies in the future.

9. Conclusions

Gastroesophageal reflux disease (GERD) remains one of the most prevalent gastrointestinal disorders worldwide, with a multifactorial pathogenesis involving lower esophageal sphincter dysfunction, impaired gastrointestinal motility, delayed gastric emptying, and alterations in the esophageal and intestinal microbiota. Although proton pump inhibitors (PPIs) continue to be the cornerstone of GERD management, their long-term use does not provide complete symptom relief in all patients and has raised concerns regarding potential adverse effects, including disturbances in the gastrointestinal microbial ecosystem. These limitations have stimulated growing interest in complementary therapeutic approaches aimed at restoring microbial homeostasis.

Recent advances in microbiome research have substantially improved our understanding of the relationship between the gut microbiota and upper gastrointestinal diseases. Increasing evidence suggests that dysbiosis may contribute to esophageal inflammation, impaired epithelial barrier function, and persistent reflux symptoms. Consequently, modulation of the microbiota has emerged as a promising strategy for supporting conventional GERD treatment.

The findings summarized in this review indicate that selected probiotic strains, particularly *Lactobacillus reuteri*, *Lactobacillus rhamnosus* GG, *Lactobacillus acidophilus*, and *Bifidobacterium* species, may exert beneficial effects through multiple biological mechanisms. These include restoration of microbial balance, inhibition of pathogenic microorganisms, enhancement of epithelial barrier integrity, modulation of inflammatory responses, and improvement of gastrointestinal motility. Clinical studies have also demonstrated that probiotic supplementation may reduce upper gastrointestinal symptoms such as heartburn, regurgitation, bloating, and abdominal discomfort, particularly when used as an adjunct to conventional PPI therapy.

An important aspect discussed in this review is the growing evidence linking probiotic activity with host metabolic signaling pathways. In particular, *Bifidobacterium* species may promote the production of short-chain fatty acids, which can stimulate glucagon-like peptide-1 (GLP-1) secretion by enteroendocrine L-cells. Although the precise role of the microbiota–SCFA–GLP-1 axis in GERD has not yet been fully established, this pathway represents a promising area of investigation that may provide new insights into microbiota-based therapeutic strategies. Likewise, emerging evidence regarding probiotic effects on gastric motility and the gut–brain axis further supports the concept that probiotics may influence reflux symptoms through mechanisms extending beyond simple microbial modulation.

Despite these encouraging findings, the available evidence remains limited by heterogeneous study designs, relatively small sample sizes, differences in probiotic strains and dosages, and inconsistent clinical outcome measures. Importantly, the beneficial effects of probiotics are strain-specific and cannot be generalized across different formulations. Therefore, future research should prioritize large, well-designed randomized controlled trials aimed at identifying the most effective probiotic strains, establishing standardized treatment protocols, and evaluating long-term clinical outcomes in diverse patient populations.

In conclusion, probiotics should currently be regarded as a promising adjunct rather than a replacement for standard GERD therapy. Their ability to influence the gastrointestinal microbiota, immune responses,

epithelial barrier function, and host metabolic signaling highlights their potential role in personalized approaches to GERD management. Continued research into strain-specific probiotic effects and microbiota-host interactions may contribute to the development of more targeted and effective therapeutic strategies for patients with gastroesophageal reflux disease.

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