
MICROBIOME-DIRECTED PHYTOBIOTICS IN GASTROINTESTINAL DISORDERS: SYNERGISTIC THERAPEUTIC POTENTIAL OF PROBIOTICS AND FOENICULUM VULGARE

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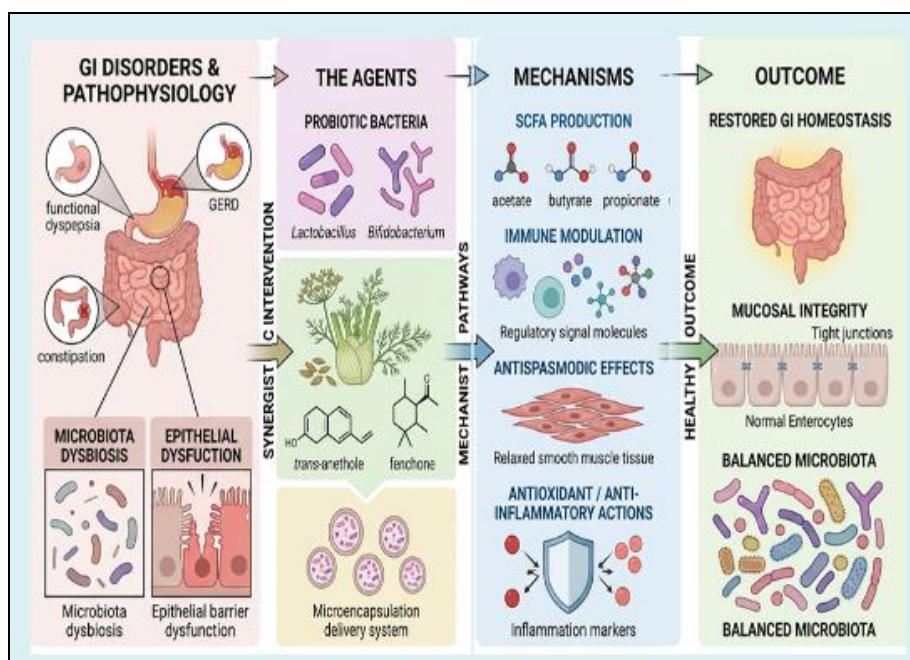
ABSTRACT.

The prevalence of gastrointestinal diseases such as irritable bowel syndrome, functional dyspepsia, constipation, inflammatory bowel diseases, and gastroesophageal reflux disease is increasing globally and are now being associated with the dysbiosis of gut microbiota, dysfunction of the epithelial barrier, immunological imbalance, and alterations in the gut-brain axis. While conventional pharmacotherapies may offer temporary relief but can be problematic due to side effects and lack the ability to reverse microbial dysbiosis. This review aims at critically examining the therapeutic application of probiotics and *Foeniculum vulgare* (fennel) as a phytobiotic approach for managing the gut microbiome and gastrointestinal disorders. Literature searches were performed in PubMed, Scopus, Web of Science, and Google Scholar databases up to 2025 with the use of key terms such as gut microbiome, probiotics, *Foeniculum vulgare*, phytobiotics, synbiotics, and gastrointestinal disorders. Peer-reviewed scientific publications on the topic have been chosen and studied concerning their mechanisms, efficiency, and synergy. The use of probiotics, like *Lactobacillus* and *Bifidobacterium*, promotes a healthier digestive tract through maintaining the microbial balance, formation of short-chain fatty acids, increase in epithelial cell integrity, and regulation of immune reactions. *Foeniculum vulgare* is endowed with trans-anethole, fenchone, flavonoids, and phenolic acids and features the ability to perform as an antispasmodic agent, have antimicrobial effects, act as an antioxidant, reduce inflammation,

and serve as a prebiotic. It may be expected that their synergy can result in better efficacy owing to inflammation reduction, better mucus protection, and proper bacterial metabolic processes. Using advanced drug delivery methods, such as microencapsulation, can promote better results as well. Nevertheless, clinical trials and standardization are necessary for developing this new treatment method.

KEYWORDS: Constipation, Epithelial barrier, *Foeniculum vulgare*, Functional dyspepsia, Gastroesophageal reflux disease.

GRAPHICAL ABSTRACT: Synbiotic Modulation of Gut Microbiota: Mechanisms and Therapeutic Outcomes in Gastrointestinal Disorders.



INTRODUCTION

The GI conditions that contribute to increased morbidity include IBS, functional dyspepsia, inflammatory bowel disease, gastroesophageal reflux disease, and constipation among others. The impact of such disorders on quality of life, health costs, and productivity cannot be overemphasized. Gut-brain dysfunction occurs among 40% of the world's population. On the other hand, the incidence of functional dyspepsia has been increasing in recent years owing to changing dietary patterns, stress, antibiotic abuse, and lack of physical activities. Poor outcomes of GI diseases are especially evident in lower income nations since early diagnosis and appropriate care for the conditions are often inaccessible. (Sperber et al., 2021; Ford et al., 2015).

Disbiosis, which entails microorganism imbalance and lack of microbial diversity, is one factor closely related to IBS, IBD, colon inflammation, and dysmotility disorders, hence making microbiome-based interventions highly beneficial. (Belkaid & Hand, 2014; Sanders et al., 2019)

This has brought about the need for integrative therapies. Microbiome-directed nutraceutical interventions involving probiotics, prebiotics, and plant-derived phytochemicals have emerged as promising alternatives. Probiotic strains such as *Lactobacillus* and *Bifidobacterium* improve gut health through microbial modulation, immune regulation, and epithelial barrier enhancement. *Foeniculum vulgare* (fennel), rich in trans-anethole, fenchone, and flavonoids, possesses antispasmodic, antimicrobial, antioxidant, anti-inflammatory, and prebiotic properties (Rather et al., 2016).

Although there is growing scientific support for the use of microbiome-targeting therapies, there are only few literature reviews on the combined use of probiotics and *Foeniculum vulgare* as a phytotherapy approach for treating gastrointestinal diseases. The purpose of this review is to critically evaluate the scientific justification and therapeutic potential of using probiotics in conjunction with fennel for gastrointestinal disease management. Particular attention will be paid to issues related to gut microbial modulation, SCFA metabolism, maintenance of tight junction integrity, regulation of inflammatory responses, and gut motility. (Rather et al., 2016).

METHODOLOGY

A systematic literature review was carried out utilizing databases such as PubMed, Scopus, Web of Science, and Google Scholar for literature published from 2005 to 2025. The use of keywords like “gut microbiome,” “probiotics,” “*Foeniculum vulgare*,” “fennel,” “phytochemicals,” “synbiotics,” and “gastrointestinal disorders” using Boolean operators such as AND/OR helped to narrow the search. The inclusion criteria included peer-reviewed scientific articles, review articles, clinical trials, and meta-analysis related to the role of probiotics and *Foeniculum vulgare* on gastrointestinal health. (Rather et al., 2016).

Duplicate papers, conference abstracts, editorials, non-English papers, and papers that were irrelevant scientifically or mechanistically, were all excluded from consideration. Selection of papers proceeded using a modified PRISMA procedure which involved identifying papers, screening papers, determining their suitability for use, and inclusion of selected papers. This was then followed by critical evaluation of the selected literature (Hill et al., 2014; Plaza-Diaz et al., 2019).

Gut Microbiota and Gastrointestinal Health

The gut microbiota is noted for its high degree of complexity with a community dominated by four distinct phyla of bacteria namely Firmicutes, Bacteroidetes, Actinobacteria, and Proteobacteria. The human microbiota comprises of trillions of microorganisms, whose collective gene pool is much larger and more complex than that of humans (Human Microbiome Project Consortium, 2012). Probiotics including *Lactobacillus* and *Bifidobacterium* are essential to sustaining gastrointestinal health. Such microorganisms facilitate nutrient absorption, regulation of immunity, mucus layer maintenance, and epithelial lining. It is noteworthy that decreased diversity within the microbiota is linked to inflammatory conditions and metabolic diseases, hence the need for probiotic therapy. (Belkaid & Hand, 2014; Sanders et al., 2019). Dysbiosis denotes the imbalance in the microbiota due to loss of beneficial bacteria, decreased diversity, and dominance of opportunistic bacteria. Dysbiosis is associated with the development of diseases like irritable bowel syndrome, inflammatory bowel disease, antibiotic-induced diarrhea, and colonic inflammation. The prevalence of harmful bacteria like *Escherichia coli* and a decrease in bacteria that produce butyrate are noted in dysbiosis. Dysbiosis leads to poor mucosal barrier integrity, immune stimulation, and intestinal motility. (Dale et al., 2019; Didari et al., 2015; Ford et al., 2014).

Probiotic treatment restores balance through the stimulation of the growth of friendly bacteria and the inhibition of pathogenic bacteria while increasing short chain fatty acid production. (Sanders et al., 2019; Ouwehand et al., 2002). Furthermore, phytochemical components of the plant *Foeniculum vulgare* have antimicrobial, anti-inflammatory, and antispasmodic effects which can help in alleviating symptoms of dysbiosis (Rather et al., 2016; Badgujar et al., 2014).

The gut-brain axis refers to the interaction between the brain and the microbial ecosystem within the digestive tract via neurological, hormonal, immunological, and metabolic interactions. Additionally, microbial products such as short-chain fatty acids also have an effect on vagus nerve activity and neuroinflammation. (Cryan & Dinan, 2012; Carabotti et al., 2015). The probiotic strain *Lactobacillus plantarum* is known for its psychobiotic properties, whereas *Foeniculum vulgare* has some mild anxiolytic and antispasmodic properties (Cryan & Dinan, 2012; Rather et al., 2016).

Table 1: Gut Microbiota: Composition & Diversity.

Aspect	Simple Explanation	Examples	Importance
Main Bacteria Type	Most common bacteria in gut	Firmicutes, Bacteroidetes	Help in digestion
Good Bacteria	Helpful microbes	Lactobacillus, Bifidobacterium	Improve gut health, protect from disease
Harmful Bacteria	Can cause problems if increased	E. coli, Salmonella	Cause infections/inflammation
Other Microbes	Not just bacteria	Fungi, viruses	Maintain balance in gut

Probiotics in Gastrointestinal Health

Probiotic definition is described as live microorganisms which confer health benefits on the host by contributing to the intestinal microbial balance. Probiotics include not only bacteria probiotics like lactobacilli and other anaerobes, but also non-bacteria probiotics like yeasts. Probiotics are grouped according to their physiological traits including acid and bile resistance, adherence to intestinal epithelial cells, and metabolic interaction with host microbiota. New approaches in this field have been developed taking into account genomic specificity of probiotic strains because of high strain-specific variability even among representatives of the same species (Hill et al., 2014).

Among probiotics with clinical significance, *Lactobacillus* strains have been well-studied for their capacity to attach to the mucus layer and synthesize antimicrobial agents. Prominent species include *Lactobacillus rhamnosus* GG, *Lactobacillus plantarum*, and *Lactobacillus reuteri*, which are often employed in diseases affecting the gastrointestinal tract. Anaerobic *Bifidobacterium* strains, including *Bifidobacterium longum*, *Bifidobacterium breve*, and *Bifidobacterium animalis*, form the bulk of the colon's microflora and serve an important function in fermenting carbohydrates and stabilizing the gut's microflora balance. The probiotic yeast *Saccharomyces boulardii* is especially useful in avoiding antibiotic-related diarrhea and chronic intestinal infections because it survives antibiotic treatment (Sanders et al., 2019; Goldenberg et al., 2017).

Another mechanism for probiotics is competition with pathogenic bacteria. The impact of probiotics becomes more pronounced when they are used alongside phytobiotics, such as *Foeniculum vulgare* (Plaza-Diaz et al., 2019; Rather et al., 2016). Probiotics are able to modulate immune functions through interactions with epithelial cells, dendritic cells, and gut-associated lymphoid tissue. Probiotics increase IgA production while lowering the levels of

pro-inflammatory cytokines such as TNF- α and IL-6, while increasing anti-inflammatory cytokines such as IL-10. Certain strains of probiotics can activate T-regulatory cells, which are important for inflammatory bowel disease and functional gastrointestinal disorders (Plaza-Diaz et al., 2019; Markowiak & Śliżewska, 2017). However, butyrate plays a crucial role in promoting intestinal homeostasis and repair (Koh et al., 2016; Ríos-Covián et al., 2016). The formation of short-chain fatty acids can additionally potentiate the influence of fennel compounds on microbiota (Cardona et al., 2013; Rowland et al., 2018).

They also increase the production of mucin, which shields the epithelium and enhances its function as a barrier. This effect is especially significant in cases involving the “leaky gut” syndrome, like IBS and IBD (Plaza-Diaz et al., 2019).

There are some clinical studies that suggest the benefits of using probiotics for the treatment of some gastrointestinal conditions. They have strain-specific effects. (Ford et al., 2014; Didari et al., 2015). Two strains of probiotics known to be effective in preventing antibiotic-induced and infectious diarrhea are *Lactobacillus rhamnosus* GG and *Saccharomyces boulardii*. The use of multi-strain probiotics is effective in alleviating abdominal pain, bloating, and bowel problems in patients with IBS. Also, probiotics can help in achieving remission in cases of inflammatory bowel disease (Ford et al., 2014; Dale et al., 2019). The use of both probiotics and phytobiotics like *Foeniculum vulgare* with its antispasmodic, antioxidant, and anti-inflammatory properties may prove to be a promising treatment approach (Rather et al., 2016).

***Foeniculum vulgare* (Fennel): Botanical and Ethnopharmacological Overview**

Foeniculum vulgare Mill. is the botanical name for fennel. It is a perennial, aromatic herb from the family Apiaceae (Umbelliferae) and order Apiales. Fennel originates from the Mediterranean regions but is now grown in large quantities in Asia, Europe, and India due to its culinary, nutritive, and medicinal uses. Its seeds are rich in volatile oils, trans-anethole, fenchone, and estragole, among other compounds, which contribute to its unique aroma and pharmacological effects.

The use of *Foeniculum vulgare* in traditional medicine dates back centuries. This herb is a key ingredient in various formulations prescribed in Ayurveda, Unani, and Greco-Arab medicine. Fennel seeds are often taken after meals to treat distension, flatulence, abdominal cramps, and dyspepsia. The decoction of fennel seeds is popular in treating infantile colic and mild cases of diarrhea. Additionally, the plant is known to increase digestive secretions and reduce intestinal spasms, thereby increasing digestive capacity. Thus, *Foeniculum vulgare* is

useful in the treatment of functional gastrointestinal conditions such as IBS (Rather et al., 2016; Badgujar et al., 2014).

Nutritionally speaking, fennel has been classified as a functional food owing to the fact that it contains dietary fiber, calcium, potassium, iron, and phenolic antioxidants (Mehra et al., 2021). Fennel seeds and bulbs are commonly employed in the preparation of herbal tea and fermented foods. Prebiotics in these preparations can have an influence on the composition of the intestinal microbiota. The presence of polyphenols and essential oils enables fennel to promote the development of probiotic microorganisms in the intestines (Cardona et al., 2013; Rafieian et al., 2024).

In terms of pharmacology, fennel is known to be characterized by strong antispasmodic, anti-inflammatory, antioxidant, antimicrobial, and protective properties of mucosa. According to experimental findings, fennel extract contributes to strengthening the intestine barrier due to increased production of tight junction protein, inhibition of inflammatory responses through blocking STAT1 signaling pathway (Das et al., 2022). Such outcomes become especially significant for inflammatory bowel diseases and other conditions caused by epithelial abnormalities. Trans-anethole is one of the most active substances in fennel that plays an essential role in promoting smooth muscle relaxation and regulating gut motility. Consequently, such characteristics make fennel a beneficial phytobiotic supplement when taken along with probiotics (Rather et al., 2016; Badgujar et al., 2014).

Phytochemistry of *Foeniculum vulgare*.

Phytochemically, *Foeniculum vulgare* is rich in a variety of phytochemicals that are believed to account for its gastroprotection and beneficial effects on the gut microbiota. The main phytochemicals found in *Foeniculum vulgare* include phenylpropanoids, flavonoids, phenolic acids, terpenoids, coumarins, sterols, and derivatives of fatty acids. Out of all these phytochemicals, trans-anethole is the most active compound since it is endowed with strong antimicrobial, carminative, antioxidant, and anti-inflammatory properties. Other phytochemicals include estragole, fenchone, quercetin, kaempferol, apigenin, and rosmarinic acid which are also known to synergistically work to protect the gut and reduce inflammation. Their concentrations will depend on the variety and growing conditions of *Foeniculum vulgare*.

Phenylpropanoid ethers constitute the main volatile phytochemicals of *Foeniculum vulgare*; they are commonly referred to as anethole and account for 15% to 90% of *Foeniculum*

vulgare essential oil content. Other volatile phytochemicals found in *Foeniculum vulgare* include estragole (methyl chavicol) and fenchone (Rather et al., 2016; Badgujar et al., 2014). The phenolic compounds found in fennel are chlorogenic acid, caffeic acid, ferulic acid, p-coumaric acid, and rosmarinic acid, which are excellent free radicals and antioxidants. Flavonoids like quercetin, kaempferol, apigenin, and their glycoside derivatives play a crucial role in maintaining the integrity of the mucous lining and lowering oxidative stress. Additionally, they regulate inflammation by altering signaling pathways in the gastrointestinal system. It is essential to note that phenolic acids can be utilized as substrates for metabolic processes by beneficial bacteria in the gastrointestinal system (Cardona et al., 2013; Slavin, 2013).

Apart from volatiles fractions, fennel comprises other phytochemicals including monoterpenoids, sesquiterpenoids, diterpenoids, sterols, coumarins, and aromatic molecules like anisaldehyde and methyl ketones. The above secondary metabolites increase microbial cell wall permeability and exhibit antimicrobial properties, thereby promoting probiotic colonization in phytobiotics. (Kwon et al., 2002; Rather et al., 2016).

Total phenol and flavonoids can be estimated using spectrophotometric techniques including the Folin-Ciocalteu and aluminum chloride methods. More advanced chemometric methods coupled with GC-MS are being employed to differentiate chemotypes of fennel for therapeutic and microbiome targets (Rather et al., 2016; Badgujar et al., 2014).

Table 2: Major bioactive compounds.

Class	Key Compounds	Microbiome Action	GI Benefit
Phenylpropanoids	Trans-anethole, Estragole	Antimicrobial, antibiofilm	Relieves gas, improves digestion
Monoterpenes	Fenchone, Limonene	Modulate gut flora	Anti-inflammatory, mucosal protection
Flavonoids	Quercetin, Kaempferol	Promote beneficial bacteria	Antioxidant, gut protection
Phenolic acids	Caffeic & p-Coumaric acid	Increase SCFA production	Improve gut barrier
Coumarins	Furanocoumarins	Antimicrobial	Control pathogens
Fiber (prebiotic)	Soluble fiber	Feeds beneficial microbes	Improves bowel movement
Probiotic metabolites	SCFAs, bacteriocins	Enhance microbiota balance	Boost gut immunity

Gastrointestinal Pharmacological Activities of Fennel

Foeniculum vulgare (fennel) has traditionally been utilized as a carminative herb, which promotes the digestive function through alleviation of intestinal gases, enhancement of

gastric evacuation, and promotion of digestive fluid secretion. The active components of fennel oil include trans-anethole and fenchone, which promote gastrointestinal motility and alleviate problems such as bloating, indigestion, and post-meal discomfort. The effects of fennel make it a powerful phyto-biotic for targeted digestive treatment through maintenance of the intestinal ecosystem (Rather et al., 2016; Badgujar et al., 2014).

Fennel's antispasmodic action can be primarily linked to its capacity to suppress smooth muscle contraction in response to stimulation by acetylcholine and histamine. In vitro experiments have indicated that fennel extracts possess antioxidant properties; in particular, fennel extracts increase superoxide dismutase and catalase activities, which play important roles in scavenging oxygen free radicals. Additionally, fennel decreases malondialdehyde levels. The mentioned effects are particularly significant for gastrointestinal conditions due to their role in microbiome disruption and epithelial malfunction (Choi & Hwang, 2004; Rather et al., 2016).

F. vulgare's antimicrobial effect has been demonstrated to be effective against various pathogens that infect the gastrointestinal tract, like *H. pylori*, *E. coli*, and other enteric bacteria. Bioactive substances, anethole and estragole, destroy the cell membranes of microbes, prevent their proliferation, and restrict colonization of the pathogen. The mechanism of selective antimicrobial activity may help to promote an environment suitable for probiotic microorganisms (Kwon et al., 2002; Badgujar et al., 2014).

The extract from fennel has been proven to have gastroprotective effects on experimental models of stomach ulcers. It can prevent the formation of lesions in the stomach, maintain the integrity of the mucous lining, and provide protection against oxidative stress due to the presence of antioxidants in the body. The extract is also capable of stimulating the production of mucus in the stomach and preventing inflammation of the gastric mucosa (Birdane et al., 2007; Rather et al., 2016).

Microbiome-Modulating Potential of Fennel Phytochemicals

Foeniculum vulgare (Fennel) plays an important role in the modulation of gut microbiota due to the presence of dietary fibers and phytochemicals that help in promoting richness, diversity, and equilibrium of the microbes. The fiber content in fennel plays a crucial role in helping commensal bacteria flourish while restraining the growth of dysbiotic and opportunistic microbes. However, the effects become more pronounced when fennel is used alongside probiotics. (Makki et al., 2018; Cardona et al., 2013).

The prebiotic effects of fennel are primarily attributed to the indigestible carbohydrates, such as inulin-type fructans and soluble fibers, contained in fennel. They promote the proliferation of healthy bacteria like Lactobacilli and Bifidobacteria that assist in maintaining the integrity of the intestinal lining as well as suppressing the growth of disease-causing organisms. Moreover, some polyphenols found in fennel remain unabsorbed in the upper GI system and make their way to the colon to be metabolized by bacteria. Their effects are comparable to those of prebiotics (Gibson et al., 2017; Cardona et al., 2013).

Probiotics with the prebiotic components from fennel are synbiotic because they improve the fecal metabolic profile via the production of beneficial bacteria that produce SCFAs. Beneficial bacteria in the microbiome are capable of interacting with the phytochemicals in the fennel and enhancing the efficacy of the probiotics. This is through metabolism of the polyphenols to small molecules by gut microbes. This makes a very solid scientific basis for developing probiotics using *Foeniculum vulgare* (Cardona et al., 2013).

Probiotic–Fennel Synergy: Concept of Phytobiotics

Phytobiotics can be described as bioactive substances derived from plants, including polyphenols, flavonoids, terpenoids, and essential oils. The uniqueness of phytobiotics is associated with their effect on gut microbial activity and their capacity to lower intestinal inflammation and oxidative stress. Unlike traditional nutraceuticals, phytobiotics have a direct influence on microbial communities, making them good partners to probiotics in complementary therapy. This gives rise to a new aspect of synbiotics, where plant and microbial components can coexist in symbiosis (Markowiak & Śliżewska, 2017).

Foeniculum vulgare is considered a potential phyto-biotic due to its relatively high trans-anethole, fenchone, flavonoid, and oligosaccharide content from fibers. These compounds have antimicrobial, anti-inflammatory, antioxidant, and prebiotic activity, respectively, and do not negatively affect friendly microflora. As such, fennel is an excellent candidate for use along with probiotics in targeted microbiome (Rather et al., 2016; Badgujar et al., 2014).

The interplay between probiotics and fennel is synergetic from different angles of view. The probiotic species, like *Lactobacillus* and *Bifidobacterium*, release SCFAs that contribute to the reduction of intestinal pH and protection against pathogenic microbes. On the other hand, fennel extracts decrease oxidative stress and inflammation and destroy pathogenic bacteria by disrupting their membranes. In this way, fennel plays a role of microbial modulator rather than antibacterial agent (Plaza-Diaz et al., 2019; Rather et al., 2016).

Moreover, fennel also has non-digestible carbs and fiber components, which assist in the survival of probiotics while passing through the GI tract. Such elements contribute to better adherence of probiotics to the intestinal mucosa, promoting their colonization. The antioxidant activity of phytochemicals present in fennel is also helpful in protecting the probiotic cells against oxidative stress during the journey through the gut (Malos et al., 2025; Li et al., 2023).

In addition, the effect of *Foeniculum vulgare* on the modulation of microbiomes is enhanced due to its selective stimulation of favorable microbial communities along with inhibiting the action of inflammatory microbial signatures. Studies have shown that consumption of fennel leads to the increase of growth of *Lactobacillus* and *Bifidobacterium* along with lowering microbial inflammation patterns. The interaction between the probiotic and fennel shows promising potential for future developments of gastro therapeutics (Yadav et al., 2024; Rather et al., 2016).

Formulation Strategies for Probiotic–Fennel Combinations

The pairing of probiotics and *Foeniculum vulgare* (fennel) is considered a novel approach in the field of nutraceuticals and functional foods development for the modulation of the microbiome. The bioactive compounds found in fennel such as trans-anethole, flavonoids, and phenolic acids aid in promoting a healthy microbiome by contributing to bacterial homeostasis, anti-inflammation, and strengthening epithelial barriers. Fennel is used as a phytobiotic in modern formulations for its beneficial properties on the microbiome, whereas the probiotics like *Lactobacillus* and *Bifidobacterium* provide additional benefits to the intestines and immunity and increase the production of short-chain fatty acids. (Malos et al., 2025; Rather et al., 2016).

Microencapsulation is key in the formulation of probiotics-fennel blends because both probiotics and plant-based constituents are highly susceptible to adverse effects caused by exposure to oxygen, moisture, heat, and mechanical damage (Cook et al., 2012; Malos et al., 2025).

One of the key difficulties in formulating probiotics is ensuring that the microorganisms remain viable beyond the threshold dose level of 10^6 - 10^7 CFU/g. Microencapsulation enhances the survival rate of probiotics by shielding the organisms from acidic conditions, bile salts, oxidants, and heat. Phytoconstituents present in fennel may serve as antioxidants by minimizing oxidative stress on probiotic membranes (Cook et al., 2012; Li et al., 2023).

The controlled-release system aims at delaying the liberation of probiotics and phytochemicals until their arrival in the intestine, where environmental pH levels are suitable for colonization. Core-shell nanoparticles, mucoadhesive layers, and non-digestible carbohydrate carriers help in facilitating more effective colonization of the microbes by providing targeted delivery to the colon. In probiotic-fennel-based products, the process of delayed release enables an enhanced response from the combination of probiotics and fennel metabolites, leading to improved antimicrobial and anti-inflammatory effects (Cook et al., 2012; Malos et al., 2025).

Therapeutic Applications in Gastrointestinal Disorders

Phytobiotic therapies targeting the microbiome with probiotics and *Foeniculum vulgare* show great potential for treating conditions that affect the digestive tract. In irritable bowel syndrome (IBS), this approach helps to adjust the gut microbiota composition, alleviate visceral hyperalgesia, and soothe intestinal spasm. Probiotics like lactobacilli and bifidobacteria can treat problems like abdominal pain, gas, and erratic bowel movements, whereas volatile oils derived from fennel seeds, especially anethole, can relax smooth muscles and treat intestinal spasms. The multi-strain probiotics regimen over an extended period of time is more effective when IBS arises due to dysbiosis (Ford et al., 2014; Didari et al., 2015; Rather et al., 2016).

For functional dyspepsia, probiotics can aid the conditions of upper abdominal fullness, postprandial distress, and early satiety by restoring the balance of bacteria and reinforcing the mucosa. The use of fennel will complement this treatment by utilizing its effects as a carminative, decreasing gas production, and increasing gastric emptying. These are particularly effective for dyspepsia that is more focused on bloating because of bacterial imbalance and slow digestion (Zhang et al., 2020; Rather et al., 2016).

In terms of bowel irregularities like constipation and diarrhea, the probiotics regulate transit time through the increase in short-chain fatty acids and maintaining the water balance in the gut epithelium. The role of probiotics in constipation is that they enhance colon movements and increase stool movements. For diarrhea, probiotics have an effect on the inhibition of the pathogens and enhancing barrier functions. Fennel contributes to bowel regulation through its prokinetic action and anti-spasmodic activity (Dale et al., 2019; Rather et al., 2016).

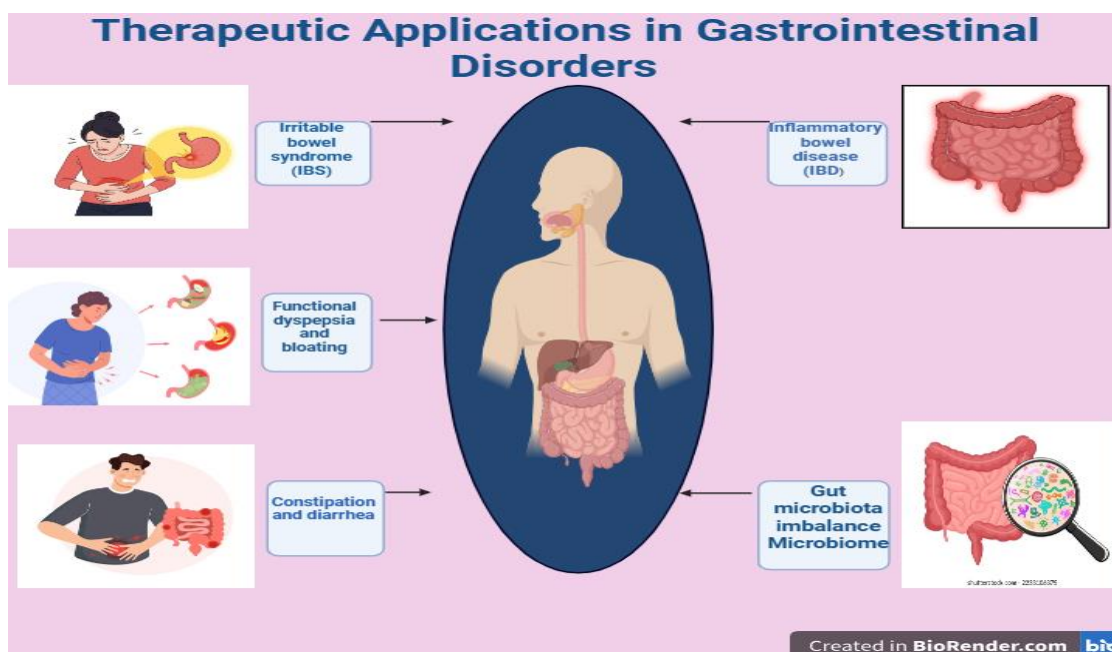


Figure 1: Therapeutic Applications in Gastrointestinal Disorders.

Safety, Toxicological, and Regulatory Considerations

Probiotic strains employed in GI applications are considered to be safe if they are characterized strains like *Lactobacillus*, *Bifidobacterium*, and *Saccharomyces boulardii* that are applied in sufficient quantities. Nevertheless, the safety of probiotics is determined by proper identification of strains, lack of virulence properties, antibiotic resistance profile, genetic stability, and proper quality assurance. The international consensus for probiotics requires that probiotics should not be pathogenic and possess no transferable antimicrobial resistance genes (Araya et al., 2002; Hill et al., 2014). Though rare, there have been cases documented of bacteremia and fungemia occurring in immunocompromised patients, critically ill subjects, and neonates. Patient selection and safety assessment thus continue to be very important, particularly when considering more advanced products (Hill et al., 2014). For synbiotics and phytobiotics, the compatibility of the probiotic with other bioactive phytochemicals in the formulation should not be overlooked. Some phytochemicals can affect the viability, metabolism, and colonization efficacy of probiotics. This means that a strain compatibility test has to be carried out first for therapeutic efficacy and microbial stability (Plaza-Diaz et al., 2019).

The *Foeniculum vulgare* plant species produces both volatile and non-volatile phytoconstituents such as trans-anethole, estragole, fenchone, flavonoids, and phenolic acids, which are responsible for its gastrointestinal function. This herb possesses anti-spasmodic, carminative, and anti-inflammatory action, which is useful for promoting digestion;

nevertheless, toxicological testing is recommended for some of the constituents like estragole, an element found in fennel essential oil. Toxicological studies have established the genotoxic and hepatocarcinogenic activity of estragole at high doses in experiments, but the dietary intake from regular fennel consumption is much less. Extracts from fennel contain antioxidants, which can offset the toxicity of this herb (Rather et al., 2016; Badgujar et al., 2014).

Regulatory classification of probiotic-fennel products differs by country. While probiotics can be considered food, dietary supplement, or live biotherapeutics products, fennel belongs to the category of medicinal herbs or nutraceuticals. In the case of modern microbiome-directed phytobiotics, clinical validation and safety have become crucial factors in achieving regulatory approval (Szajewska & Vinderola, 2024).

Clinical Evidence and Translational Potential

Probiotics have been widely used in clinical settings to demonstrate their health benefits in gastrointestinal conditions like irritable bowel syndrome, bloating, constipation, and other functional bowel disorders. Several randomized controlled trials have demonstrated that probiotic therapy effectively reduces abdominal discomfort, stool consistency, bloating symptoms, and quality of digestive health (Kim et al., 2025; Dale et al., 2019). Improvements in beneficial gut bacteria such as *Faecalibacterium prausnitzii* and *Blautia stercoris* further support the role of probiotics in restoring microbial balance and reducing symptoms (Dizman et al., 2020; Didari et al., 2015).

Larger studies using synbiotics have also reported marked reductions in symptoms of bloating, gas production, and discomfort in adults suffering from functional disorders of the gut. While no larger clinical trial has compared the co-administration of probiotics along with *Foeniculum vulgare*, fennel extracts have been observed to produce favorable results in infants with colic, dyspepsia, abdominal pain, and IBS-related discomfort owing to their antispasmodic and motility-modulatory actions (Alexandrovich et al., 2003; Rather et al., 2016).

The use of probiotics in conjunction with fennel can be justified very well in terms of complementary actions. Probiotics function by transient colonization of gut microbes, competitive inhibition of pathogenic microorganisms, production of short chain fatty acids, and increasing the intestinal barrier strength. They facilitate the growth of anti-inflammatory microbes and inhibit the growth of unfavorable ones. Fennel adds to this activity by virtue of

its active components like anethole, fenchone, and flavonoids (Sanders et al., 2019; Rather et al., 2016).

Although there is strong mechanistic evidence in support, there are several challenges associated with its translation to clinical settings. First, most of the probiotic experiments involve the use of heterogeneous strains, dosing, and duration of treatment, which can make comparisons between various studies challenging. The same limitation can be found among the fennel-related research, with most studies emphasizing symptomatic relief rather than a direct assessment of its effects on the microbiome. Moreover, large-scale randomized clinical trials using probiotics along with fennel are not yet available (Sanders et al., 2019).

Research Gaps and Future Perspectives

Another area that requires more research in probiotic-based therapies is strain specificity in the effects that can be achieved by the use of probiotics. While some positive impacts are often observed, outcomes vary depending on the strain used in each instance. Some strains, such as *Lactobacillus rhamnosus* GG, *Bifidobacterium longum* 35624, and *Lactiplantibacillus plantarum* 299v, have proved to be effective in terms of producing desired effects on the digestive system, whereas other strains from the same species fail to achieve comparable results. When used together with phytochemicals, like fennel, strain compatibility and metabolites produced become critical factors (Sanders et al., 2019).

Another disadvantage is that the study still depends on traditional 16S rRNA analysis, which does not have adequate resolution to detect functional differences in microbes down to the species and strains level. Modern techniques such as shotgun metagenomic sequencing, metatranscriptomics, metabolomics, and single-cell genomics for microorganisms offer detailed insight into microbial metabolic pathways, microbe-host interactions, quorum sensing, and inflammation. They are especially useful when studying the impact of fennel bioactive molecules on the expression of genes in microbes, generation of short-chain fatty acids, and regulation of immune cells in the gut. (Plaza-Diaz et al., 2019).

The emerging future trends of therapies for the management of disorders of the gastrointestinal system will involve personalized medicine with an emphasis on the microbiome. Individual variations in terms of the composition of the microbiome, diet, immunity, and genetics have an important role in determining the success of treatment. The efficacy of conventional probiotics is unlikely to be the same across individuals, and similar probiotics may have different effects based on the composition of the microflora of individual

patients. Phytochemical components of fennel could help increase the precision of treatments through their effect on the microbiome and bowel movements (Zhang et al., 2020).

There are also promising opportunities for future generations of pharmaceuticals and nutraceuticals through the design of encapsulated synbiotics, gastro-resistant live biotherapeutic products, and controlled-release phytobiotics. There are also obstacles to overcome with respect to phytochemical standardization, probiotic stabilization during formulation, and regulatory approval of co-formulated live biotherapeutic products. It is recommended that future investigations focus on stability studies, pharmacokinetics of fennel phytochemicals, and controlled clinical trials assessing dose–response relationships (Hill et al., 2014; Plaza-Diaz et al., 2019).

Future Scope

The future studies need to concentrate on proving the efficacy of strain-specific probiotics, determining the phytochemical components of *Foeniculum vulgare* and performing large clinical randomized trials. Omics approaches, individual microbiota analysis, and AI-based therapeutics are critical for advancing the precision level of therapy. Moreover, the utilization of modern drug delivery techniques like nanoencapsulation and controlled release mechanisms along with regulatory standardization will facilitate the development of phytobiotic drugs for gastroenterological diseases.

CONCLUSION

Gastrointestinal disorders continue to be among the biggest problems worldwide owing to their wide prevalence, chronic nature, and considerable effect on people's quality of life and the healthcare system. Modern studies confirm that a disruption in the gut microbiota balance is a crucial factor involved in the development of both functional and inflammatory disorders of the gastrointestinal tract; therefore, the use of microbiome-focused treatments represents a major step forward compared to standard symptomatic therapy.

However, although standard pharmacological treatments allow patients experiencing relief, they do not ensure restoration of microbiome balance, gut integrity, and overall health of the gastrointestinal tract. Probiotics represent one of the most effective ways to normalize the balance of microorganisms, enhance barrier function, modulate the immune response, and stimulate the synthesis of short-chain fatty acids. Nevertheless, the effectiveness of such therapy depends greatly on the type of bacterial strains used and the characteristics of patients themselves. *Foeniculum vulgare* (fennel) is viewed as an efficient phytobiotic due to its

diverse phytochemistry. The use of probiotics together with fennel represents an effective synergetic approach whereby the probiotics help restore microbial and immunological homeostasis, whereas fennel is responsible for maintaining motility of the GI tract, lowering oxidative stress, alleviating inflammation, and targeting pathogenic microbes. Such a strategy may prove highly beneficial in the treatment of irritable bowel syndrome, functional dyspepsia, constipation, and inflammatory bowel diseases.

Further studies need to investigate strain-specific probiotic effects, develop standards for phytochemical content of fennel extracts, and conduct randomized controlled trials involving larger sample sizes. Incorporating omics technology, developing personalized medicine based on individual microbiomes, and using microencapsulation techniques to deliver probiotics and fennel components may facilitate their use in the management of gastrointestinal disorders.

Abbreviations

GI -Gastrointestinal; **IBS** - irritable bowel syndrome; **IBD** - Inflammatory Bowel Disease; **SCFA** - Short-Chain Fatty Acid; **GERD** - Gastroesophageal Reflux Disease; **FAO** - Food and Agriculture Organization; **WHO** – World Health Organization; **EFSA** -European Food Safety Authority; **RCT**- Randomized Controlled Trial; **GC-MS** -Gas Chromatography–Mass Spectrometry; **HPLC** - High-Performance Liquid Chromatography; **CFU** - Colony Forming Units.

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