

REVIEW ARTICLE

The gut microbiome–immune axis in inflammatory bowel disease: Microbial mechanisms and therapeutic implications

Nooreen Kazi¹, Nesa Ansari¹, Aleena Zobairi¹, and Mansoor Ali Vaali Mohammed^{2*}

¹General Medicine Practice Program, Batterjee Medical College, Jeddah, Saudi Arabia

²Colorectal Research, College of Medicine, King Saud University, Riyadh, Saudi Arabia

Abstract

The human gut microbiome makes up a highly diverse microbial ecosystem that is crucial for host metabolism, immunological modulation, and intestinal barrier integrity. The bacteria phyla *Firmicutes*, *Bacteroidetes*, *Proteobacteria*, and *Actinobacteria* dominate the intestinal microbiota, contributing to metabolic processes such as dietary polysaccharide fermentation and the synthesis of bioactive microbial metabolites. Dysbiosis, or disruptions in microbial composition and function, has been linked to the development of autoimmune disorders. Microbial mechanisms that relate dysbiosis to disease include the growth of pro-inflammatory microbial taxa, decreased synthesis of short-chain fatty acids (SCFAs), altered microbial metabolic pathways, and loss of epithelial barrier integrity. Among autoimmune disorders, inflammatory bowel disease (IBD), which encompasses Crohn's disease and ulcerative colitis, is one of the best-studied cases of microbiome-associated pathology. In this review, we focus on the role of gut microbiome alterations in the pathogenesis of IBD, highlighting microbial dysbiosis, changes in microbial metabolites, and host–microbiome interactions that contribute to intestinal inflammation. This review also examines microbiome-targeted therapeutic strategies, including probiotics, prebiotics, fecal microbiota transplantation, and postbiotics, alongside emerging artificial intelligence–based approaches to personalized treatment, and consider how comorbid systemic conditions may shape microbial homeostasis in IBD patients. Understanding these microbial pathways may open new possibilities for microbiome-based diagnostics and therapeutic approaches in IBD.

Keywords: Gut microbiome; Dysbiosis; Inflammatory bowel disease; Autoimmune disease

***Corresponding author:**
Mansoor Ali Vaali Mohammed
(mansooralicytogene@gmail.com)

Citation: Kazi N, Ansari N, Zobairi A, Mohammed MAV. The gut microbiome–immune axis in inflammatory bowel disease: Microbial mechanisms and therapeutic implications. *Microbes & Immunity*. doi: 10.36922/MI026120027

Received: March 19, 2026

Revised: August 11, 2026

Accepted: September 1, 2026

Published online: September 11, 2026

Copyright: © 2026 Author(s). This is an Open-Access article distributed under the terms of the Creative Commons Attribution License, permitting distribution, and reproduction in any medium, provided the original work is properly cited.

Publisher's Note: AccScience Publishing remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.

1. Introduction

The history of inflammatory bowel disease (IBD) has evolved from a rare disease with prevalence in early industrialized regions during the twentieth century to its current status as a global health challenge with millions affected worldwide. Through a population-based study published from 1920 to 2024, IBD epidemiology has evolved

through distinct phases, starting with an emergence phase with low incidence (0.1–1.2 per 100,000), followed by accelerating incidence and compounding prevalence (362.9–660.1 per 100,000). Prevalence in North American and European populations is projected to reach 1.0%–1.6% by the 2040s, while rapid rises in incidence are now being reported in newly industrialized regions in Asia and Latin America.¹

This global epidemiological change has highlighted the importance of environmental factors in the pathogenesis of IBD, and among which, the gut microbiome has emerged as a key mediator. The human gastrointestinal system hosts trillions of microorganisms known as the gut microbiome. These microbial communities contribute to one of the most densely populated microbial ecosystems in the human body, with a gene pool that vastly exceeds that of the human genome. Microbial colonization starts early in infancy and progresses through dynamic interactions with host physiology, nutrition, and environmental exposure. The bacterial phyla *Firmicutes* and *Bacteroidetes* dominate the gut microbiota of healthy people, with Actinobacteria and Proteobacteria contributing as well. These microbial populations play important roles in a variety of physiological processes, including food metabolism, vitamin production, and immune response modulation.^{2,3}

The study of the gut microbiome has been transformed by developments in high-throughput sequencing methods like 16S rRNA sequencing, metagenomics, and metatranscriptomics. These methods provide unprecedented levels of detail for characterizing the composition of microbial communities and functional metabolic pathways. Numerous studies have shown that while the makeup of microbial species varies between individuals, the fundamental metabolic processes of microorganisms involved in the fermentation of carbohydrates and the creation of metabolites are mostly maintained throughout populations. Beyond immunological development, pathogen resistance, and epithelial barrier integrity, the gut microbiota maintains a symbiotic relationship with the host. However, dysbiosis can result from disruptions in the organization of microbial communities, which are often marked by a decrease in microbial diversity and an increase in opportunistic species. Numerous inflammatory and autoimmune disorders have been linked to dysbiosis, suggesting that complex host-microbe interactions underlie microbial imbalance in disease pathogenesis.^{4,5}

Thus, understanding the microbial mechanisms that lead to dysbiosis and, subsequently, intestinal inflammation is important for developing novel therapies. The objective

of this review is to synthesize current evidence on the gut microbiome–immune axis in IBD, with a specific focus on three areas: (i) the compositional and functional alterations of the gut microbiome observed in Crohn's disease and ulcerative colitis; (ii) the mechanistic pathways, including epithelial barrier disruption, altered metabolite signaling, and innate and adaptive immune dysregulation, through which dysbiosis contributes to chronic intestinal inflammation; and (iii) emerging microbiome-targeted therapeutic strategies, including probiotics, prebiotics, fecal microbiota transplantation, and precision microbial interventions, along with their current clinical evidence and limitations. By integrating mechanistic and translational perspectives, this review aims to clarify how microbiome research can inform future diagnostic and therapeutic approaches in IBD.

2. Methodology

2.1. Search strategy

A narrative literature search was conducted across PubMed/MEDLINE, Scopus, Web of Science, and Google Scholar for articles published between 2000 and 2026. The search combined keywords and Medical Subject Headings (MeSH) terms including “inflammatory bowel disease,” “Crohn's disease,” “ulcerative colitis,” “gut microbiome,” “dysbiosis,” “microbiota,” “16S rRNA sequencing,” “metagenomics,” “gut-immune axis,” and “microbiome-targeted therapy,” combined using Boolean operators (AND/OR). Reference lists of relevant articles and prior reviews were also manually screened to identify additional eligible studies.

2.2. Inclusion and exclusion criteria

Studies were included if they reported original data or synthesized findings on gut microbiome composition, function, or microbiome-immune interactions in the context of Crohn's disease, ulcerative colitis, or unclassified IBD. Eligible study designs included human clinical and cohort studies, animal models of intestinal inflammation, *in vitro* and *ex vivo* mechanistic studies, and bioinformatic or computational analyses of microbiome datasets, provided they employed high-throughput sequencing methods (16S rRNA sequencing, shotgun metagenomics, or metatranscriptomics) or other well-characterized experimental approaches. Studies were required to be published in peer-reviewed, English-language journals. Studies were excluded if they were case reports, conference abstracts without full-text availability, non-English publications, or focused exclusively on non-microbial etiologic factors without reference to microbiome involvement.

3. Gut microbiome composition and immune homeostasis

The maintenance of intestinal immune homeostasis is a complex process governed by the continuous interaction between commensal microorganisms and the host's innate and adaptive immune systems.⁶ Central to this interaction are short-chain fatty acids (SCFAs), primarily acetate, propionate, and butyrate, which are produced through the fermentation of non-digestible dietary fibers by specific bacterial taxa.⁷ These metabolites serve as primary signaling molecules that influence host gene expression and cellular function through both receptor-mediated and epigenetic mechanisms.⁸ The specific composition of the gut microbiota, particularly the abundance of butyrate-producing guilds, serves as a predictive marker for the stability of the host's immune tone.⁹

Butyrate, in particular, has been identified as a cornerstone of gut health due to its dual role as a metabolic fuel for colonocytes and a potent immunomodulator.^{10,11} At the metabolic level, evidence from colonocyte culture and murine models indicates that butyrate oxidation provides the primary energy source for intestinal epithelial cells, supporting the maintenance of the physical barrier by upregulating tight junction proteins such as occludin and zonula occludens-1.^{11,12} Beyond its role in barrier integrity, *in vitro* and murine studies show that butyrate exerts profound epigenetic effects by acting as a histone deacetylase (HDAC) inhibitor.⁸ This inhibition results in the remodeling of host transcriptional programs, favoring the expression of anti-inflammatory factors like interleukin-10 (IL-10) and promoting the differentiation of regulatory T cells (Tregs) through the acetylation of the Foxp3 locus, a mechanism established primarily in murine colitis models and human cell-culture systems rather than confirmed in human clinical trials.¹³ This epigenetic reprogramming is essential for the induction of oral tolerance and the prevention of inappropriate immune responses to dietary antigens, though extrapolation of these findings to human physiology remains an active area of investigation.¹⁴

The signaling capacity of SCFAs is further mediated by G protein-coupled receptors (GPCRs), specifically G protein-coupled receptor 41 (GPR41), also known as free fatty acid receptor 3 (FFAR3), G protein-coupled receptor 43 (GPR43), also known as free fatty acid receptor 2 (FFAR2), and G protein-coupled receptor 109A (GPR109A), also known as hydroxycarboxylic acid receptor 2 (HCA2), which are highly expressed on various immune cells, including macrophages, dendritic cells, and neutrophils.¹⁵ Activation of GPR43 by acetate and propionate has been shown to suppress the nuclear factor kappa B (NF- κ B) signaling pathway, thereby dampening

the production of pro-inflammatory cytokines such as tumor necrosis factor alpha (TNF- α) and interleukin-6 (IL-6).¹⁵ Additionally, *in vivo* murine and human tissue co-culture data indicate that the binding of butyrate to GPR109A induces the production of antimicrobial peptides (AMPs) and interleukin-22 (IL-22).¹² A recent mouse model of radiation proctopathy, corroborated by correlative human fecal and serum sampling, identified 3-hydroxybutyrate (3HB) as a ligand that blocks GPR43-mediated pro-inflammatory IL-6 signaling to maintain mucosal health, though this mechanism has not yet been tested in a controlled human intervention.¹⁶ Research has also highlighted the regulatory role of the microbiome in modulating pattern recognition receptors (PRRs).² For instance, a piglet model demonstrated that probiotics like *Lactiplantibacillus argenteratensis* induce the expression of host defense peptides through TLR2 recognition, alleviating inflammatory stress¹⁷; whether this extends to the human gut-immune axis remains untested. Furthermore, *in vitro* experiments using isolated human macrophages have shown that, under concurrent TLR stimulation, butyrate and propionate can activate the NLRP3 inflammasome through a caspase-8-dependent mechanism, leading to IL-1 β release.¹⁸ This finding, while mechanistically well-characterized at the cellular level, has not yet been validated *in vivo* or in human patients with active inflammation, and should be interpreted as proof-of-concept rather than established clinical pathology. It is important to note that much of the mechanistic evidence discussed above is derived from murine models or *in vitro* human cell systems rather than controlled human clinical studies; where human data exist, they are frequently correlative rather than causal, and this distinction should inform the interpretation of the proposed pathways.

Microbial homeostasis is not established in isolation, and its interpretation is often complicated by comorbid conditions that are highly prevalent among IBD patients and independently reshape the gut ecosystem. Type 2 diabetes mellitus (T2DM), which co-occurs with IBD at elevated rates, is associated with depletion of butyrate-producing genera such as *Faecalibacterium* and expansion of pro-inflammatory taxa, a compositional shift that compounds the SCFA deficits already characteristic of IBD and further impairs glucose-immune crosstalk.¹⁸ Colorectal malignancy, a recognized long-term complication of chronic IBD, is itself driven in part by dysbiotic enrichment of genotoxic pathobionts such as *Fusobacterium nucleatum* and polyketide synthase-positive *Escherichia coli*, which promote epithelial DNA damage and immune evasion independently of the inflammatory mechanisms discussed above.^{19,20} Cardiovascular comorbidity, increasingly recognized in IBD populations due to chronic systemic

inflammation, is linked to microbial production of trimethylamine-N-oxide (TMAO), a metabolite that antagonizes the protective effects of SCFAs and promotes atherogenesis through pathways distinct from the epithelial and epigenetic mechanisms detailed in this review.^{21,22} Pulmonary comorbidities, particularly chronic obstructive pulmonary disease (COPD), have a bidirectional relationship with intestinal dysbiosis termed the “gut-lung axis,” in which reduced circulating SCFAs correlate with impaired regulatory T-cell output in the airway mucosa, mirroring but mechanistically distinct from the Treg dysregulation observed in the intestinal compartment.^{23,24} Taken together, these comorbidities indicate that microbial homeostasis in IBD patients must be interpreted within a broader systemic context, as extra intestinal disease burden can independently alter the microbial and metabolic landscape under study.

4. Microbial dysbiosis and mechanisms of autoimmune activation

Microbial dysbiosis, defined as a disruption in the composition and function of the gut microbiota, is a primary driver of immune dysregulation and autoimmune activation.¹ This state is typically characterized by the depletion of beneficial, SCFA-producing taxa and the simultaneous expansion of pro-inflammatory pathobionts.²⁵ Taxa such as *Faecalibacterium prausnitzii* and *Akkermansia muciniphila* are frequently reduced in autoimmune contexts, leading to a significant decrease in the availability of immunomodulatory metabolites like butyrate and its derivatives.³ The reduction in these taxa is often accompanied by an increase in Proteobacteria, which are known to contribute to systemic inflammation through the release of potent endotoxins.²⁶

The loss of these beneficial species compromises the intestinal barrier, allowing translocation of microbial products into the systemic circulation, a phenomenon often referred to as “leaky gut,” into the systemic circulation.^{27,28,12} For instance, the expansion of Proteobacteria leads to elevated levels of lipopolysaccharide (LPS), which activates the TLR4/MyD88/NF- κ B pathway, triggering chronic low-grade inflammation.²⁹ This persistent inflammatory environment can facilitate the activation of autoreactive T cells through mechanisms such as molecular mimicry or bystander activation.¹ Molecular mimicry occurs when microbial antigens share structural similarities with host proteins, leading to cross-reactive immune responses that target the host's tissues.² Alternatively, bystander activation involves the non-specific stimulation of autoreactive cells due to the high concentration of cytokines and co-stimulatory signals present during a state of microbial imbalance.¹

Furthermore, human cohort data link dysregulated SCFA levels with heightened susceptibility to autoimmune disorders.⁸ Murine and *in vitro* evidence suggests that in the absence of sufficient butyrate to inhibit HDAC activity, Treg differentiation is impaired while Th17 differentiation is enhanced.¹³ This shift in T-cell balance is observed as a correlative hallmark in various human autoimmune conditions, including systemic lupus erythematosus and rheumatoid arthritis, though causal direction (whether dysbiosis drives disease or results from it) has not been established in longitudinal human studies.³ [Figure 1](#) summarizes the characteristics and mechanism of microbial dysbiosis.

5. Microbial alterations in inflammatory bowel disease

Inflammatory bowel disease (IBD), including Crohn's disease and ulcerative colitis, is characterized by a profound and systemic dysregulation of the gut microenvironment.²⁵ Metagenomic and metabolomic analyses have revealed consistent microbial signatures in IBD patients, most notably a marked reduction in the diversity of the *Firmicutes* phylum and an overrepresentation of adherent-invasive *Escherichia coli* (AIEC).^{25,30} These alterations lead to a significant shift in the gut's metabolic profile, characterized by reduced concentrations of SCFAs and an accumulation of detrimental metabolites that damage the epithelial lining and promote fibrosis.³¹⁻³⁴

The reduction of *Faecalibacterium prausnitzii*, a major butyrate producer, is particularly strongly associated with IBD activity and relapse.²⁵ The resulting deficit in butyrate impairs colonocyte health and barrier function, facilitating the entry of pathobionts like AIEC that directly stimulate pro-inflammatory responses through the activation of TLR and NLR pathways.^{25,35} Interestingly, *in vitro* evidence using human macrophages suggests that the poor tolerance to fiber-rich diets observed in some IBD patients may be linked to the paradoxical activation of the NLRP3 inflammasome by SCFAs under conditions simulating chronic inflammation.¹⁸ In this cellular model, butyrate and propionate triggered IL-1 β release from macrophages via epigenetic suppression of cellular FLICE-like inhibitory protein (cFLIP) and IL-10, potentially exacerbating intestinal inflammation rather than resolving it.¹⁸ It is important to note that this represents an isolated *in vitro* mechanism and has not been directly demonstrated in IBD patient tissue or animal colitis models, so the clinical relevance of this pathway to human fiber intolerance in IBD remains inferential. The neuroimmune interactions within the gut also play a significant role in IBD pathogenesis.¹⁴ Dysbiosis-induced changes in the gut microbiota can

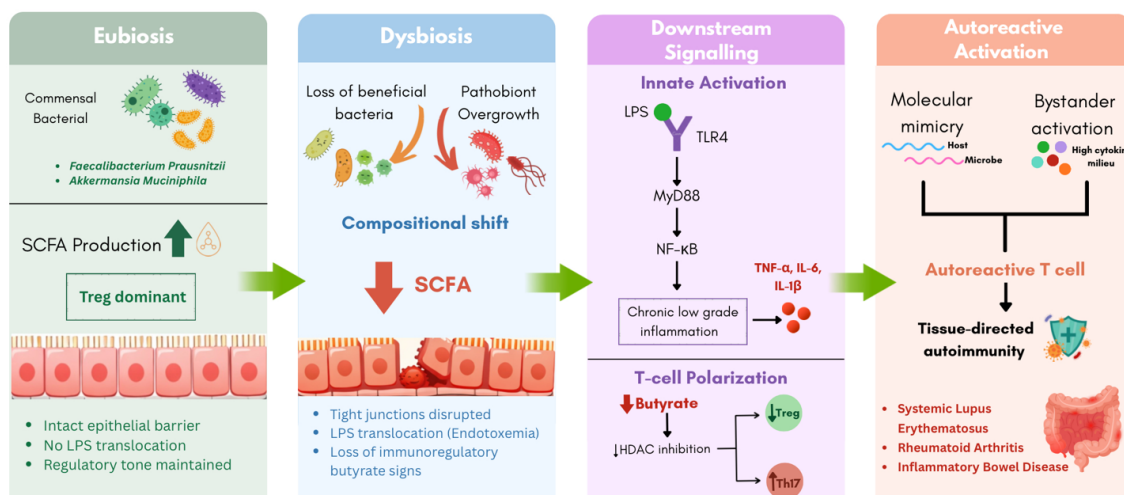


Figure 1. Illustration showing the characteristics and mechanisms of dysbiosis. Image created by the authors.

alter the production of neurotransmitters and neuroactive metabolites, which in turn modulate intestinal motility and immune cell activity via the enteric nervous system.² For instance, the activation of the host-microbiota-immune axis can influence the secretion of neuropeptides that regulate the permeability of the intestinal barrier and the recruitment of inflammatory cells into the lamina propria.^{33,36,37} Beyond local neuroimmune signaling, this gut-brain crosstalk operates bidirectionally at a systemic level: circulating pro-inflammatory cytokines, dysbiosis-altered microbial metabolites (e.g., SCFAs, tryptophan-kynurenine derivatives), vagal/sympathetic signaling, and HPA-axis dysregulation together form a self-reinforcing inflammatory cycle linking intestinal disease activity to comorbid anxiety and depression.³⁸ Furthermore, IBD involves altered intestinal immune responses in which SCFAs are critical modulators, and therapeutic strategies now aim to restore SCFA-producing bacteria to recalibrate the immune response.¹³ Together, these findings emphasize that IBD is not merely a consequence of microbial presence but rather a result of a multifaceted collapse in the signaling networks encompassing metabolic, epigenetic, and neuroimmune axes that normally support the host-microbe symbiosis.¹⁴

6. Molecular mimicry and microbial antigen-cross reactivity

A significant proposed mechanism by which microbial antigens contribute to inflammatory and autoimmune disorders is molecular mimicry, a largely theoretical and structurally inferred framework in which microbial antigens or proteins are hypothesized to closely resemble

host proteins, potentially resulting in cross-reactive immune responses.^{39,40} This mechanism is supported chiefly by *in silico* structural homology analyses and observational associations between specific microbial taxa and autoimmune phenotypes, rather than by direct experimental demonstration of causality in humans.³⁹⁻⁴¹ Antigen-presenting cells, such as dendritic cells, process bacterial antigens and deliver them to T lymphocytes during an infection or microbial dysbiosis. Activated immune cells may mistakenly attack host tissues if these microbial antigens mimic the host molecules, which leads to inflammation and persistent immune activation.^{39,40}

The pathophysiology of IBD has been increasingly linked to this mechanism. When the intestinal barrier is disrupted in these patients, microbial antigens gain greater access to the mucosal immune system. Cross-reactive antibody production and autoreactive T-cell responses can be triggered by structural similarities between microbial and host intestinal proteins. Consequently, the immune system may target intestinal epithelial components as well as microbial antigens, causing tissue damage and persistent intestinal inflammation.³⁹⁻⁴¹ However, direct evidence that this process drives rather than merely accompanies tissue damage in IBD patients is still lacking, and the current literature relies on correlative and bioinformatic evidence.³⁹⁻⁴¹

7. Therapeutic approaches targeting the gut microbiome

Microbiome-targeted therapeutic approaches are gaining popularity as the role of gut microbial dysbiosis in autoimmune diseases becomes better understood. By

enhancing intestinal barrier integrity, these treatments seek to regulate immunological responses and restore microbial balance. Probiotics, prebiotics, fecal microbiota transplantation, and postbiotics are some of the potential methods for altering the gut microbiome and affecting the course of disease.^{42,43}

7.1. Probiotics

Probiotics are live microorganisms that, when administered in adequate amounts, provide health benefits to individuals.⁴⁴ In the context of IBD, probiotics are speculated to restore the disrupted microbial equilibrium characteristic of dysbiosis by re-establishing colonization resistance, reinforcing epithelial barrier integrity, and rebalancing mucosal immune responses.⁴⁵ However, it should be noted at the outset that the clinical evidence for probiotics is markedly disease specific: the most robust data exist for ulcerative colitis, whereas evidence for Crohn's disease remains largely inconclusive.^{46,47}

The immunomodulatory effects of probiotics are exerted through several well-characterized cellular and molecular pathways. Firstly, they enhance innate immunity and modulate pathogen-induced inflammation via Toll-like receptors (TLR) and downstream signaling pathways, which include NF- κ B, mitogen-activated protein kinases (MAPKs), and Akt.⁴⁵ Secondly, probiotics promote the differentiation of regulatory T cells and increase the production of anti-inflammatory cytokines such as IL-10, while simultaneously suppressing pro-inflammatory mediators, including TNF- α , IL-6, and IL-1 β .^{43,48,49} Furthermore, probiotics strengthen the intestinal epithelial barrier by upregulating tight junction proteins, particularly ZO-1, ZO-2, and claudin-14, and by downregulating claudin-2, which is pore-forming.

Beyond these direct effects, probiotics produce antimicrobial substances including bacteriocins, lactic acid, hydrogen peroxide, and acetic acid; these substances exclude pathogenic organisms by competing for adhesion sites and nutrients on the intestinal epithelium.^{50,47} Through a cross-feeding relationship with the symbiotic bacteria, such as butyrate-producing species, certain probiotic strains can also indirectly increase SCFA synthesis, which promotes anti-inflammatory pathways and epithelial energy homeostasis.⁴⁸⁻⁵² These mechanisms are strain-specific; different probiotic organisms operate through distinct, sometimes non-overlapping, molecular pathways, which partly explains the clinical outcomes observed across studies.^{45,49}

7.1.1. Clinical evidence in ulcerative colitis and Crohn's disease

According to clinical evidence, probiotics are more

effective in treating ulcerative colitis than Crohn's disease. While the multispecies VSL#3 (which has eight bacterial strains from the genera *Lactobacillus*, *Bifidobacterium*, and *Streptococcus*) has shown advantages in both producing and sustaining remission in patients with mild-to-moderate illness, *E. coli* Nissle 1917 (EcN) has shown effectiveness in ulcerative colitis that is equivalent to mesalazine (5-ASA) for inducing or maintaining remission.^{48,50,53,54} Probiotics significantly increased the likelihood of achieving clinical remission in ulcerative colitis (OR 2.00; 95% CI 1.28–3.11), according to a recent meta-analysis that corroborated these findings.⁴⁸ Combination therapy using probiotics and 5-ASA showed additional benefits in certain patients, although heterogeneity among studies remains significant.⁴⁸

Additionally, probiotics have shown significant effectiveness in avoiding pouchitis recurrence after ileal pouch-anal anastomosis; the most researched formulation is VSL#3.^{48,50,55} Conversely, there is still little data to support the use of probiotics in Crohn's disease. Meta-analyses have not found a substantial decrease in disease recurrence, including after ileocecal resection, and randomized controlled studies have typically failed to show significant advantages in inducing or sustaining remission.^{48,54} While Crohn's disease is characterized by transmural inflammation, frequent small intestinal involvement, and more significant changes in gut microbial diversity, ulcerative colitis is limited to the colonic mucosa, where probiotic organisms can directly interact with inflamed tissue. These differences may reflect the distinct pathophysiology of the two conditions.^{47,55,56} Although *Saccharomyces boulardii* has shown limited adjunctive benefit in maintaining remission, current evidence remains insufficient to recommend routine probiotic therapy for Crohn's disease.⁴⁷

7.1.2. Safety considerations

Although probiotics are considered generally safe in general populations, with mild gastrointestinal side effects (bloating, diarrhea, flatulence) reported in approximately 3%–5% of users, this perception requires important qualifications in immunocompromised individuals, particularly within the IBD population.^{52,55} Several lines of key evidence raise safety concerns:

A systematic review of case reports and case series documented 93 cases of infectious complications associated with probiotic use, including fungemia (37.6%), sepsis (31.2%), bacteremia (20.4%), endocarditis, and abscess formation, with an overall mortality rate of 19.6%.⁵⁷ The species involved in most cases were *Saccharomyces* species, and most affected patients were immunocompromised, critically ill, or had central venous catheters.^{57,58} IBD

patients frequently receive immunosuppressive therapies (corticosteroids, anti-TNF biologics), which places them in the higher-risk category for opportunistic infections from probiotic organisms.^{59,60} Cases involving *Lactobacillus bacteremia* have been reported in patients with underlying immunosuppressive conditions, and genome-level analysis has confirmed clonal transmission of ingested probiotic strains into the bloodstream. The World Gastroenterology Organization recommends that immunocompromised individuals restrict probiotic use to strains and indications with proven efficacy. Another species, *Saccharomyces boulardii*, while effective in antibiotic-associated diarrhea, has been linked to fungemia in critically ill IBD patients with rare fatal outcomes reported.⁵⁷ This is particularly relevant because *S. boulardii* is often co-prescribed with antibiotics in IBD patients during infectious complications.

7.1.3. Patient heterogeneity and limitations of current evidence

Several factors contribute to the considerable heterogeneity in probiotic treatment outcomes across clinical settings:

Strain-specificity: Not all probiotics possess identical therapeutic effects. Different strains of the same species can exert vastly different immunomodulatory and barrier-protective functions.^{49,58} Clinical trials that use poorly characterized or inconsistently formulated products make cross-study comparisons difficult and may explain some contradictory findings.⁴⁸

Dose and formulation variability: Effective doses range widely across studies, from 10^8 to 10^{11} colony-forming units (CFU) per day, and both single and multi-strain formulations have been used. The meta-analysis found that only multi-strain formulations achieved statistically significant results in ulcerative colitis, suggesting that synergistic interactions between multiple species may be necessary for clinical efficacy.⁴⁸ A key limitation is that negative Crohn's disease data may reflect the wrong strain or dose rather than true lack of effect, since trial designs rarely incorporate strain selection based on mechanistic or microbiome data.

Methodological limitations: Many existing trials are characterized by small sample size, short follow-up durations, insufficient reporting of adverse effects, and lack of standardization in outcome measures. The overall certainty of evidence, as assessed using the GRADE framework, remains low for most outcomes in probiotic IBD research.⁴⁸ Publication bias cannot be excluded, particularly for maintenance of remission studies.

However, the favorable safety profile of probiotics observed in controlled trials must be interpreted cautiously given the elevated infection risk in immunosuppressed

IBD patients.^{60,61} Future research should prioritize well-designed, adequately powered randomized controlled trials with standardized probiotic formulations, strain-specific dosing protocols, and predefined subgroup analyses based on disease phenotype, baseline microbiome composition, and concurrent immunosuppressive therapy. The integration of multi-omics approaches to identify biomarkers of probiotic responsiveness represents a promising avenue toward personalized probiotic therapy in IBD.^{48,50,55}

7.2. Prebiotics

Prebiotics are non-digestible components of food that stimulate the growth and activity of beneficial microbes in the gut. Examples of prebiotics include inulin, fructooligosaccharides, and resistant starch, which are dietary fibers fermented by beneficial microbes to produce SCFAs. SCFAs include acetate, propionate, and butyrate. SCFAs help maintain intestinal epithelium integrity, modulate inflammatory and immune responses, and reduce susceptibility to autoimmune diseases.^{50,62-64}

The therapeutic rationale for prebiotics in IBD centers on restoring SCFAs production, which is frequently compromised in patients with active disease.^{63,64} IBD patients demonstrate reduced abundance of SCFA-producing bacteria, particularly butyrate-producing Firmicutes, leading to diminished availability of butyrate and impaired epithelial barrier function. Prebiotics counteract this deficiency by promoting the proliferation of beneficial commensals, thereby enhancing in IBD, where barrier failure permits translocation of luminal antigens and microbial metabolites, driving persistent immune activation.⁶⁵⁻⁶⁷

7.2.1. Clinical evidence, differential efficacy between ulcerative colitis and Crohn's disease

A critical distinction emerges when evaluating prebiotic efficacy across IBD subtypes. The pathophysiology of Crohn's disease and ulcerative colitis differs fundamentally: Crohn's disease typically involves transmural inflammation affecting any part of the gastrointestinal tract with a Th1/Th17-dominant immune response, whereas ulcerative colitis is restricted to the colonic mucosa with Th2-mediated inflammation. These differences influence therapeutic responses to microbiota-based interventions.^{66,68}

Clinical evidence demonstrates that prebiotics show greater promise in ulcerative colitis than in Crohn's disease. Studies utilizing oligofructose-enriched inulin, germinated barley foodstuff, and psyllium have reported modest benefits in patients with active ulcerative colitis or ulcerative colitis in remission. A randomized controlled trial of synbiotic

therapy combining *Bifidobacterium longum* with Synergy 1 (inulin-oligofructose) demonstrated significant reduction in sigmoidoscopy scores, TNF- α , and IL-1 α in active ulcerative colitis patients, alongside downregulation of human β -defensins 2, 3, and 4.⁶⁵ Conversely, clinical trials in Crohn's disease have yielded disappointing results. A Cochrane review found insufficient evidence to support probiotics or prebiotics for inducing remission in Crohn's disease, with only one small study meeting inclusion criteria.⁶⁷ Similarly, prebiotic supplementation studies in Crohn's disease have not consistently demonstrated improvements in bacterial modulation or inflammatory response.⁶⁹

7.2.2. Safety and tolerability considerations

Prebiotics are generally regarded as safe, with a favorable side effect profile compared to immunosuppressive therapies. However, gastrointestinal symptoms including bloating, flatulence, and abdominal discomfort are common, particularly at higher doses. A randomized controlled trial investigating FODMAP (Fermentable Oligosaccharides, Disaccharides, Monosaccharides, and Polyols) intake (which includes naturally occurring prebiotics) in quiescent Crohn's disease found that while increasing FODMAPs enhanced butyrate-producing *Clostridium* cluster XIVa and *Akkermansia muciniphila* abundance, symptom severity doubled compared to low FODMAP intake.⁶⁴ This finding underscores a critical paradox: prebiotic-induced microbiological improvements may come at the cost of exacerbating functional gastrointestinal symptoms, necessitating individualized dose titration.⁶⁴

7.2.3. Patient heterogeneity and response variability

The heterogeneity of prebiotic responses reflects multiple factors including baseline microbiota composition, disease severity, genetic background, and concomitant medications. Patients with distinct microbial signatures may respond differently to identical prebiotic interventions, as the capacity for SCFA production depends on the presence of specific fermentative taxa.⁶⁸ Furthermore, the severity of dysbiosis at treatment initiation likely influences therapeutic outcomes, with patients exhibiting more profound microbial depletion potentially requiring adjunctive strategies to establish engraftment of prebiotic-responsive communities.

7.2.4. Immune modulation and mechanistic insights

Beyond microbial composition changes, prebiotics exert immunomodulatory effects on the gut mucosa. Fermentation metabolites inhibit pro-inflammatory signaling pathways and reduce production of cytokines

central to IBD pathogenesis, including IL-6 and TNF- α .⁵⁰ Additionally, prebiotics may promote regulatory T cell differentiation, enhance immunological tolerance, and attenuate excessive inflammatory responses.⁶⁸ SCFAs mediate these effects through multiple mechanisms including histone deacetylase inhibition, activation of G-protein coupled receptors (GPR43, GPR109a), and stabilization of hypoxia-inducible factors, collectively suppressing NF- κ B activation and pro-inflammatory cytokine production.⁶³

7.2.5. Microbial diversity and clinical outcomes

Prebiotic treatment has been associated with increases in gut microbial diversity, which is characteristically reduced in IBD patients. Greater microbial diversity enhances ecosystem resilience and may reduce the likelihood of disease flare-ups. However, clinical outcomes remain inconsistent because prebiotic efficacy depends on variables including illness severity, dietary habits, and baseline microbiota composition.⁶⁶ A systematic review of 23 randomized controlled trials examining fiber supplementation in IBD found limited evidence for efficacy in ulcerative colitis (3/10 studies showing benefit) and no evidence in Crohn's disease (0/12 studies), though favorable physiological outcomes including fecal butyrate and calprotectin were observed.⁶⁹

7.2.6. Limitations of current evidence

Despite compelling mechanistic rationale, several limitations constrain definitive conclusions regarding prebiotic efficacy in IBD. The prebiotic literature is the weakest methodologically. A systematic review of 23 randomized trials found that fiber improved disease outcomes in only 3 of 10 ulcerative colitis trials, none of 12 Crohn's disease trials, and the single pouchitis trial, with benefit confined largely to physiological surrogates such as fecal butyrate and calprotectin rather than disease activity.⁶⁹ The most cited positive trial was a small pilot ($n = 18$) using a synbiotic in active ulcerative colitis, in which sigmoidoscopy scores improved only marginally ($p = 0.06$) but inflammatory markers including TNF- α , IL-1 α , and β -defensins 2-4 fell significantly.⁶⁵ The Crohn's disease crossover trial adds a further caution: increasing fermentable fiber shifted the microbiota toward butyrate producers but doubled symptom severity, underscoring tolerability limits and the overlap with FODMAP sensitivity.⁶⁴ Heterogeneity in fiber type, dose, and fermentation capacity, together with the absence of adequately powered trials, keeps the level of evidence low.^{63,69} Well-designed, adequately powered randomized controlled trials with standardized endpoints are essential

to establish the role of prebiotics as adjunctive therapy in IBD management.⁶⁶

7.3. Fecal microbiota transplantation

Fecal microbiota transplantation (FMT) is the transfer of microbiota from the feces of a healthy donor into the gastrointestinal tract of a patient, aiming to restore a balanced microbiota composition. This therapeutic option has shown promising results in treating recurrent *Clostridioides difficile* infections, a gram-positive, anaerobic and spore-forming bacterium. FMT is also being investigated as a potential therapeutic option for autoimmune and inflammatory disorders. This therapeutic option has the potential to restore the balance of the microbiota, leading to the re-establishment of immune tolerance, thereby alleviating the symptoms of these disorders.^{50,70,71}

7.3.1. Efficacy in ulcerative colitis versus Crohn's disease

FMT has been investigated as a strategy to restore microbial diversity and correct dysbiosis in IBD. However, efficacy differs substantially between ulcerative colitis and Crohn's disease.⁷² Ulcerative colitis is characterized by continuous mucosal inflammation restricted to the colon with Th2-mediated immune responses, whereas Crohn's disease involves transmural, skip lesions affecting any gastrointestinal segment with Th1/Th17-dominant inflammation. These pathophysiological distinctions influence therapeutic responses to FMT.⁷³ Multiple randomized controlled trials have evaluated FMT in ulcerative colitis.⁷² A landmark multicenter, double-blind trial demonstrated that anaerobically prepared donor FMT achieved steroid-free remission in 32% of ulcerative colitis patients compared to 9% receiving autologous transplant at 8 weeks ($p = 0.03$), with 42% of responders maintaining remission at 12 months. Similarly, a study reported that donor FMT induced remission in 25% of ulcerative colitis patients versus 5% receiving autologous feces in a randomized, double-blind trial.⁷² These findings establish moderate but consistent efficacy for FMT in ulcerative colitis. Conversely, evidence for FMT in Crohn's disease remains limited and less encouraging.^{72,74}

A pilot randomized controlled trial found that while FMT was safe and improved endoscopic scores, none of the Crohn's disease patients achieved donor microbiota engraftment as the primary endpoint, though steroid-free remission rates were numerically higher in the FMT group (50% vs. 33%).⁷⁵ A systematic review, similarly, reported no significant improvement among Crohn's disease patients following FMT, with only transient remission observed in a minority.⁷⁶ The transmural nature of Crohn's disease,

its segmental distribution, and fibrotic complications may reduce FMT efficacy compared to the mucosal-limited inflammation of ulcerative colitis.

7.3.2. Mechanisms of therapeutic action

The therapeutic effect of FMT is attributed to restoration of a diverse microbial community capable of re-establishing metabolic processes, including SCFA production, while inhibiting pro-inflammatory bacterial taxa.^{70,73} Specifically, successful FMT engraftment increases Firmicutes abundance, particularly butyrate-producing species such as *Faecalibacterium prausnitzii* and *Roseburia intestinalis*, which are characteristically depleted in IBD.^{77,78} Concurrently, FMT reduces the relative abundance of Proteobacteria and pathobionts including AIEC.

7.3.3. Immunomodulatory effects

FMT may facilitate immune regulation by reducing mucosal inflammation and promoting regulatory immunological pathways. Restoration of healthy microbiota diminishes activation of pro-inflammatory signaling pathways, including NF- κ B and mitogen-activated protein kinase cascades, while reducing gut immune system exposure to pathogenic microbial antigens.⁷⁶ Additionally, FMT enhances regulatory T cell differentiation and increases production of anti-inflammatory cytokines such as IL-10, contributing to restoration of immunological tolerance in the gut environment.⁷²

7.3.4. Donor factors and engraftment

A critical determinant of FMT success is donor microbiota quality. A study demonstrated that donor species richness and the number of transferred phylotypes were significantly associated with treatment success, identifying persistently elevated C-reactive protein at two weeks post-transplant as predictive of response failure.⁷⁶ These findings suggest that standardized donor screening and selection of donors with high microbial diversity may optimize outcomes. Furthermore, a study reported that absence of donor microbiota engraftment was associated with disease flare, underscoring the importance of successful microbial transplantation for therapeutic benefit.⁷⁵

7.3.5. Clinical evidence, safety concerns and adverse events

FMT carries the strongest evidence of the four approaches. Two randomized trials in ulcerative colitis, Costello *et al.*⁷⁴ (anaerobically prepared pooled donor stool, $n = 73$) and Rossen *et al.*⁷² ($n = 50$), reported higher steroid-free remission with donor FMT, with the difference reaching statistical significance only in the larger trial (32% vs 9% at week 8, OR 5.0). Even here, heterogeneity is considerable:

donor selection, aerobic versus anaerobic stool processing, delivery route, number of infusions, and outcome definitions all differ, and donor microbial richness appears to predict success.^{74,76} In Crohn's disease, the evidence is far weaker: the only sham-controlled pilot ($n = 17$) failed its primary engraftment endpoint, although endoscopic severity improved after FMT and absence of engraftment predicted flare.¹¹ An uncontrolled cohort found no benefit in Crohn's disease and endoscopic remission in only 2 of 8 ulcerative colitis patients⁷⁶, while a step-up strategy in steroid-dependent ulcerative colitis achieved clinical improvement in 57% of patients.⁷⁸ Safety data remain limited to short follow-up, with serious adverse events reported sporadically; overall, the level of evidence is moderate for ulcerative colitis and very low for Crohn's disease.

Despite its promise, FMT faces safety considerations that limit widespread clinical adoption. Serious adverse events, including bacteremia and aspiration pneumonia, have been reported in immunocompromised patients, though incidence remains low.⁷³ Transmission of multidrug-resistant organisms and unknown pathogens represents a significant concern, particularly with long-term follow-up data limited. Donor screening protocols have become increasingly rigorous, yet cannot eliminate all infectious risks. Additionally, gastrointestinal side effects including abdominal pain, bloating, diarrhea, and transient fever are common but typically self-limiting.⁷⁵

7.3.6. Patient heterogeneity and response predictors

Heterogeneity in FMT response reflects multiple factors including baseline microbiome composition, disease severity, concomitant immunosuppressive therapy, and genetic background. Patients with more severe dysbiosis may require repeated FMT procedures or combined therapeutic approaches.⁷⁸ A step-up FMT strategy, involving escalating treatment intensity for non-responders, demonstrated that 57% of steroid-dependent ulcerative colitis patients achieved clinical improvement, though only 29% maintained long-term remission.⁷⁸ This variability underscores the need for personalized approaches to patient selection and treatment protocols.

7.3.7. Standardization challenges and future directions

Several barriers impede FMT standardization: variability in donor microbiota composition between stool banks, lack of uniform preparation and administration protocols, and insufficient long-term safety data.⁷⁶ The optimal FMT dose, frequency, and delivery route remains undefined, with studies utilizing colonoscopic infusion, nasojejunal tubes, enemas, and oral capsules with variable success.⁷⁶ Well-

designed, adequately powered randomized controlled trials with standardized endpoints, longer follow-up periods, and defined patient stratification criteria are essential to establish FMT's role in IBD management. Development of defined microbial consortia as alternatives to crude fecal preparations may address standardization challenges while maintaining efficacy.^{73,74}

7.4. Postbiotics

The term postbiotics describes the beneficial physiological effects exerted by bioactive metabolites or cell components, such as SCFAs, or cell wall components, produced during bacterial metabolism. Unlike probiotics, postbiotics do not require the administration of live microbes, offering a potential advantage given the safety and stability concerns associated with live formulations.^{50,73} Recent studies have shown that postbiotics have the potential to modulate the immune system, strengthen the intestinal barrier, and downregulate the inflammatory response. As understanding of postbiotics' role grows, they have the potential to become a targeted therapeutic option with fewer side effects.^{50,68}

7.4.1. Mechanisms of action in intestinal homeostasis

Postbiotics may provide a targeted strategy for restoring intestinal homeostasis in IBD by directly supplying bioactive substances frequently depleted during dysbiosis. Short-chain fatty acids, particularly butyrate, are essential for preserving epithelial integrity through multiple mechanisms: they serve as primary energy substrates for colonocytes, enhance mitochondrial respiration and biogenesis, and increase production of tight junction proteins including occludin, claudins, and zonula occludens.⁷⁹ Additionally, butyrate modulates mucosal immune responses through histone deacetylase inhibition, epigenetic regulation of gene expression, and activation of G-protein coupled receptors (GPR43, GPR109a), collectively promoting regulatory T cell differentiation and inhibiting pro-inflammatory cytokine production.⁶⁸ Tryptophan-derived postbiotics, including indole derivatives and kynurenine metabolites, activate the aryl hydrocarbon receptor on innate lymphoid cells, stimulating IL-22 secretion that enhances mucosal barrier function and antimicrobial peptide production.⁸⁰

7.4.2. Differential effects in Crohn's disease versus ulcerative colitis

The immunological heterogeneity between Crohn's disease and ulcerative colitis influences postbiotic therapeutic potential. Crohn's disease is characterized by Th1/Th17-dominant immune responses with transmural inflammation, whereas ulcerative colitis exhibits Th2-

mediated mucosal inflammation restricted to the colon.⁸¹ These pathophysiological differences suggest that postbiotic interventions may have distinct efficacy profiles across IBD subtypes.

Emerging evidence indicates that butyrate-producing bacteria, particularly *Faecalibacterium prausnitzii* and *Roseburia intestinalis*, are preferentially depleted in Crohn's disease, contributing to reduced butyrate availability and impaired epithelial barrier function.⁸² This metabolic deficit may be particularly amenable to postbiotic supplementation in Crohn's disease patients. Conversely, ulcerative colitis-associated dysbiosis involves broader microbial perturbations affecting multiple metabolite pathways, including tryptophan catabolism and bile acid metabolism.⁸³ A comparative study demonstrated that postbiotics derived from *Bifidobacterium adolescentis* exhibited stronger modulatory effects on gut microbiota composition and metagenomic potential than corresponding probiotics in a colitis model, suggesting that postbiotics may offer distinct therapeutic advantages irrespective of IBD subtype.⁸⁰

7.4.3. Safety profile and advantages over probiotics

Postbiotics offer several safety advantages over live microbial therapies. They eliminate risks of bacteremia, fungemia, and systemic infection that occasionally complicate probiotic administration, particularly in immunocompromised IBD patients.⁸¹ The well-defined chemical composition of postbiotics enables precise dosing, standardization, and quality control, addressing the inherent batch-to-batch variability observed with probiotic preparations.⁸² Additionally, postbiotics demonstrate superior stability under diverse storage conditions and gastrointestinal environments, potentially improving bioavailability and therapeutic consistency.

However, postbiotics are not devoid of safety considerations. High-dose butyrate supplementation may paradoxically promote inflammation in specific contexts, particularly when administered to damaged epithelium with compromised barrier function where high local concentrations may recruit neutrophils.⁶⁸ Tryptophan catabolites, while generally anti-inflammatory, may exert context-dependent effects depending on the balance between protective indole derivatives and potentially toxic kynurenine pathway metabolites.⁸² These findings underscore the importance of formulation optimization and dose-response characterization.

7.4.4. Clinical evidence and limitations

Despite compelling preclinical data, clinical evidence for postbiotic efficacy in IBD remains limited. Postbiotics are mechanistically attractive because they address the safety

and standardization problems of live biotherapeutics, but human data are scarce.^{50,79} The only clinical signals are small and largely negative: a phase 2 randomized trial of a GPR43 antagonist in mild-to-moderate ulcerative colitis showed no clinical benefit despite *in vitro* anti-inflammatory activity, and butyrate enemas produced only minor effects in ulcerative colitis patients in remission.⁶⁸ Supportive evidence comes from *ex vivo* organ culture, where a postbiotic downregulated inflammation in IBD tissue, and from a mouse colitis model in which postbiotics modulated the microbiota more strongly than the parent probiotic strain.^{80,81} The level of evidence is therefore preclinical, and the key design questions for future trials are which metabolite class, what dose and formulation, which delivery route, and how to stratify patients, for example, by baseline butyrate-producing capacity.^{68,79}

7.4.5. Patient heterogeneity and response variability

Response to postbiotic interventions varies considerably among IBD patients, reflecting differences in baseline microbiome composition, disease severity, genetic background, and concomitant medications.^{68,81} Patients with profound depletion of SCFA-producing bacteria may require higher doses or combination approaches to achieve therapeutic benefit, whereas those with preserved metabolic function may derive minimal additional effect.⁵⁰ Furthermore, the interplay between host genetics (including polymorphisms in *NOD2*, *CARD9*, and *IL23R*) and postbiotic metabolism remains poorly characterized, limiting the ability to predict therapeutic responses.⁶⁸

7.4.6. Future directions and precision therapeutics

Postbiotics represent a promising frontier in precision microbiome-based therapeutics for IBD.⁸³ Development of next-generation postbiotic formulations incorporating defined metabolite combinations, targeted delivery systems, and personalized dosing algorithms may address current limitations.⁸³ Integration of metabolomic profiling with host genetic analysis could enable patient stratification and identification of individuals most likely to benefit from specific postbiotic interventions.⁷⁹ Additionally, combination strategies pairing postbiotics with prebiotics or conventional immunosuppressive agents may enhance therapeutic efficacy while reducing adverse effects. Continued investment in well-designed, adequately powered clinical trials with standardized endpoints is essential to establish postbiotics' role in IBD management.^{50,68}

7.5. Comparative clinical and therapeutic implications

The clinical evidence supporting microbiota-directed therapies in IBD varies considerably across the four

therapeutic approaches and between ulcerative colitis and Crohn's disease. Probiotics have been investigated most extensively, with selected formulations demonstrating greater clinical benefit in ulcerative colitis than Crohn's disease. Although substantial heterogeneity in strains, doses, formulations, and treatment outcomes limits direct comparisons. Evidence for prebiotics remains limited and inconsistent, while FMT has demonstrated more promising results in ulcerative colitis but remains insufficiently

studied in Crohn's disease. In contrast, postbiotics are at an earlier stage of clinical development, with most evidence derived from preclinical or small exploratory studies. These differences highlight the importance of considering disease phenotype, treatment formulations, patient characteristics, and study design when interpreting the therapeutic potential of microbiota-directed interventions. A summary of the current clinical evidence and major limitations is presented in [Table 1](#).

Table 1. Summary of clinical evidence, key findings, and limitations of microbiota-directed therapeutic approaches in inflammatory bowel disease

Approach	Key studies	Populations	Main findings	Key limitations
Probiotics	Butterworth <i>et al.</i> (2008) ⁶⁷ ; EcN/VSL#3 trials ^{45,47}	UC and CD	More consistent benefit in UC; CD trials largely negative/inconclusive	Strain, dose, formulations, treatment duration, and outcome heterogeneity; many small trials
Prebiotics	Halmos <i>et al.</i> (2016) ⁶⁴ ; Furrie <i>et al.</i> (2005) ⁶⁵ ; Wedlake <i>et al.</i> (2014) ⁶⁹	UC and CD	Benefit observed in some UC studies, but not CD; inflammatory/microbiome changes do not consistently translate to clinical benefit	Small studies; variable fiber types/doses; tolerability
FMT	Rossen <i>et al.</i> (2015) ⁷² ; Costello <i>et al.</i> (2019) ⁷⁴ ; Sokol <i>et al.</i> (2020) ⁷⁵ ; Vermeire <i>et al.</i> (2016) ⁷⁶ ; Cui <i>et al.</i> (2015) ⁷⁸	Mainly UC; limited CD	Promising remission outcomes in UC; evidence in CD remains very limited	Donor variability, processing, delivery, engraftment and safety
Postbiotics	Butyrate studies ⁶⁸	Mainly UC; insufficient CD data	Preliminary evidence for effects on intestinal inflammation; clinical efficacy remains uncertain	Very few clinical trials; small samples; short follow-up; formulation/delivery uncertainty

Abbreviations: CD: Crohn's disease; UC: Ulcerative colitis.

8. Future directions

Precision medicine techniques, which seek to tailor treatment plans according to the unique microbial profiles, are being made possible by developments in microbiome research. Metagenomics, metabolomics, and transcriptomics are high-throughput sequencing-based technologies that have greatly advanced our understanding of the relationships between the gut microbiota and host immune responses, though further cohort studies are needed to expand the omics analysis. Complementing this, emerging computational platforms that integrate metagenomic, metatranscriptomic, and metabolomic data with enzyme-focused bioinformatics and machine learning are increasingly able to link specific gut microbial genes and enzymes to therapeutic outcomes, offering a more mechanistic route toward precision microbiome medicine. In autoimmune diseases, these multi-omics techniques may make it possible to identify

disease-specific microbial signatures that might function as biomarkers for early diagnosis, disease tracking, and therapy response prediction.⁸⁴ AI and machine learning approaches, including supervised classifiers and deep learning architectures, have further demonstrated the ability to identify disease-associated microbial signatures and predict host immune and treatment-related outcomes from high-dimensional microbiome datasets, suggesting similar frameworks could be adapted to stratify dysbiosis-driven inflammatory conditions such as IBD.⁸⁵ Additionally, a new approach including targeted nutritional treatments, microbiomes derived metabolites therapeutics, and engineered probiotics may offer more accurate and customized ways to modify immune function. Even with these encouraging findings and advancements, there are still several obstacles that have to be overcome, such as the necessity for standardized procedures, inter-individual heterogeneity in microbiome composition, and differentiation of causative linkages from correlations.

9. Conclusion

In conclusion, there is mounting evidence that the gut microbiota plays a significant role in controlling immune responses and causing IBD. Through processes including decreased microbial metabolite synthesis, increased gut permeability, and immunological activation, microbial dysbiosis can disrupt intestinal immune homeostasis. Molecular mimicry and microbial antigen cross-reactivity are two further processes that show how gut bacteria might affect chronic intestinal inflammation. These insights support a move towards personalised medicine: depending on the composition of their gut microbiota, each can benefit from a specific treatment that improves health while minimizing adverse effects, an approach made possible by innovations in genomics, artificial intelligence (AI)-powered data analysis, and biomedical technologies. Unlike the stability of the human genome, the gut microbiome is highly dynamic, shaped by external factors such as diet, antibiotics, lifestyle, and environmental exposures, so it both reflects an individual's health status and serves as a target for therapeutic intervention. Microbiological analysis of the gut microbiome remains a complex undertaking whose reliability varies across cohorts due to geographical and dietary differences in microbial signatures, and the current lack of standardized analysis workflows and sequencing methods still limits its clinical applicability. In IBD, specifically, microbial alterations reported in Crohn's disease and ulcerative colitis stem mainly from cross-sectional observational studies showing association rather than causation; longitudinal animal studies have offered mechanistic insight but require confirmation through large-scale randomized clinical trials, and microbiome-based diagnosis will require "multi-omics" data, AI tools, and standardized analyses. Given this current level of uncertainty, microbiome-targeted treatments—whether probiotics, dietary changes, or FMT—remain promising but highly unpredictable, and further study is required to fully comprehend host-microbiome interactions and to create safe, effective microbiome-based therapies for IBD.

Acknowledgments

None.

Funding

None.

Conflict of interest

The authors declare that there are no competing interests.

Author contributions

Conceptualization: Nooreen Kazi, Mansoor Ali Vaali

Mohammed

Writing—original draft: Nooreen Kazi, Nesa Ansari, Aleena Zobairi

Writing—review & editing: All authors

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Availability of data

All data analyzed in this study are derived from previously published articles, regulatory documents, and publicly accessible databases, as cited in the reference list. No new datasets were generated.

References

1. Ouyang H, Yang Y, Zhang X, Cui Y, Zhang Y. Microbial orchestration of neuroimmune crosstalk: from homeostasis to disease. *Front Immunol.* 2025;16:1679286. doi: 10.3389/fimmu.2025.1679286
2. Cortés M, Olate P, Rodriguez R, *et al.* Human microbiome as an immunoregulatory axis: mechanisms, dysbiosis, and therapeutic modulation. *Microorganisms.* 2025;13(9):2147. doi: 10.3390/microorganisms13092147
3. Han EJ, Ahn JS, Chae YJ, Chung HJ. Immunomodulatory roles of *Faecalibacterium prausnitzii* and *Akkermansia muciniphila* in autoimmune diseases: mechanistic insights and therapeutic potential. *Clin Rev Allergy Immunol.* 2025;68(1):77. doi: 10.1007/s12016-025-09093-8
4. Shan Y, Lee M, Chang EB. The gut microbiome and inflammatory bowel diseases. *Annu Rev Med.* 2022;73(1):455-468. doi: 10.1146/annurev-med-042320-021020
5. Nazir A, Hussain FHN, Nadeem Hussain TH, Al Dweik R, Raza A. Therapeutic targeting of the host-microbiota-immune axis: implications for precision health. *Front Immunol.* 2025;16:1570233. doi: 10.3389/fimmu.2025.1570233
6. Abavisani M, Faraji N, Ebadpour N, Kesharwani P, Sahebkar A. Beyond digestion: Exploring how the gut microbiota modulates human social behaviors. *Neuroscience.* 2025;565:52-62. doi: 10.1016/j.neuroscience.2024.11.068
7. Hays KE, Pfaffinger JM, Ryznar R. The interplay between gut microbiota, short-chain fatty acids, and implications for host health and disease. *Gut Microbes.* 2024;16(1):2393270.

- doi: 10.1080/19490976.2024.2393270
8. Zhao Y, Chen J, Qin Y, *et al.* Linking Short-Chain Fatty Acids to Systemic Homeostasis: Mechanisms, Therapeutic Potential, and Future Directions. *J Nutr Metab.* 2025;2025:8870958.
doi: 10.1155/jnme/8870958
 9. Zhao L. Guild-Level Response of the Gut Microbiome to Nutritional Signals: Advancing Precision Nutrition for Metabolic Health. *Annu Rev Nutr.* 2025;45(1):197-221.
doi: 10.1146/annurev-nutr-122424-022254
 10. Park B, Kim JY, Riffey OF, Walsh TJ, Johnson J, Donohoe DR. Crosstalk between butyrate oxidation in colonocyte and butyrate-producing bacteria. *iScience.* 2024;27(9):110853.
doi: 10.1016/j.isci.2024.110853
 11. Shaheen WA, Quraishi MN, Iqbal TH. Gut microbiome and autoimmune disorders. *Clin Exp Immunol.* 2022;209(2):161-174.
doi: 10.1093/cei/uxac057
 12. Tao M, Wu T, Zhou X, *et al.* Butyrate enhances gut dysbiosis by activating the cAMP/PKA/CREB signaling pathway to inhibit the progression of endometrial carcinoma. *BMC Microbiol.* 2025;25(1):516.
doi: 10.1186/s12866-025-04190-2
 13. Ventura I, Chomon-García M, Tomás-Aguirre F, *et al.* Therapeutic and Immunologic Effects of Short-Chain Fatty Acids in Inflammatory Bowel Disease: A Systematic Review. *Int J Mol Sci.* 2024;25(20):10879.
doi: 10.3390/ijms252010879
 14. Li Q. The gut microbiota as an actor in immunometabolism: impact in inflammatory bowel diseases. *Halscience.* 2025.
doi: 10.70675/f8e4bb82z869cz4996zaec0z0e1ab6c0a7d3.
 15. Chen C, Wang GQ, Li D, Zhang F. Microbiota-gut-brain axis in neurodegenerative diseases: molecular mechanisms and therapeutic targets. *Mol Biomed.* 2025;6(1).
doi: 10.1186/s43556-025-00307-1
 16. Ge Z, Chen C, Chen J, *et al.* Gut Microbiota-Derived 3-Hydroxybutyrate Blocks GPR43-Mediated IL6 Signaling to Ameliorate Radiation Proctopathy. *Adv Sci.* 2024;11(28):e2306217.
doi: 10.1002/advs.202306217
 17. Yoon KN, Choi YH, Keum GB, *et al.* Lactiplantibacillus argentoratensis AGMB00912 alleviates diarrhea and promotes the growth performance of piglets during the weaning transition. *BMC Microbiol.* 2024;24(1):404.
doi: 10.1186/s12866-024-03536-6
 18. Yu Y, Ding Y, Wang S, Jiang L. Gut Microbiota Dysbiosis and Its Impact on Type 2 Diabetes: From Pathogenesis to Therapeutic Strategies. *Metabolites.* 2025;15(6):397.
doi: 10.3390/metabo15060397
 19. Neagu AI, Bostan M, Ionescu VA, *et al.* The Impact of the Microbiota on the Immune Response Modulation in Colorectal Cancer. *Biomolecules.* 2025;15(7):1005.
doi: 10.3390/biom15071005
 20. Lan T, Hou Q, Zhao H, *et al.* Gut microbiota dysbiosis impairs TGF- β /Smad4 signaling to drive postoperative metastasis in colorectal cancer. *Front Microbiol.* 2025;16:1654227.
doi: 10.3389/fmicb.2025.1654227
 21. Yoo JY, Sniffen S, McGill Percy KC, Pallaval VB, Chidipi B. Gut Dysbiosis and Immune System in Atherosclerotic Cardiovascular Disease (ACVD). *Microorganisms.* 2022;10(1):108.
doi: 10.3390/microorganisms10010108
 22. Motte LRD, Giarritiello F, Sala LL, *et al.* A systematic review of TMAO, microRNAs, and the oral/gut microbiomes in atherosclerosis and myocardial infarction: mechanistic insights and translational opportunities. *J Transl Med.* 2025.
doi: 10.1186/s12967-025-07224-5
 23. Ni FX, Wang HX, Hu J, *et al.* The gut-lung axis in COPD: immunomodulatory roles of gut microbiota and novel therapeutic strategies. *Front Immunol.* 2026;17:1733726.
doi: 10.3389/fimmu.2026.1733726
 24. Lv J, Zhang Y, Liu S, Wang R, Zhao J. Gut-lung axis in allergic asthma: microbiota-driven immune dysregulation and therapeutic strategies. *Front Pharmacol.* 2025;16:1617546.
doi: 10.3389/fphar.2025.1617546
 25. Wang W, Dernst A, Martin B, *et al.* Butyrate and propionate are microbial danger signals that activate the NLRP3 inflammasome in human macrophages upon TLR stimulation. *Cell Rep.* 2024;43(9):114736.
doi: 10.1016/j.celrep.2024.114736
 26. Kou R, Guo Y, Qin Z, *et al.* Systemic dysregulation of the gut microenvironment plays a pivotal role in the onset and progression of inflammatory bowel disease. *Front Immunol.* 2025;16:1661386.
doi: 10.3389/fimmu.2025.1661386
 27. Wang X, Yuan W, Yang C, *et al.* Emerging role of gut microbiota in autoimmune diseases. *Front Immunol.* 2024;15:1365554.
doi: 10.3389/fimmu.2024.1365554
 28. Yu S, Zhang M, Dou Z, Tian B, Lu J. Gut microbiota metabolites in the immunoregulation of enteritis: research progress. *Front Immunol.* 2025;16:1706472.
doi: 10.3389/fimmu.2025.1706472
 29. Arron HE, Marsh BD, Kell DB, Khan MA, Jaeger BR, Pretorius E. Myalgic Encephalomyelitis/Chronic Fatigue Syndrome: the biology of a neglected disease. *Front*

- Immunol.* 2024;15:1386607.
doi: 10.3389/fimmu.2024.1386607
30. Andoh A, Nishida A. Alteration of the Gut Microbiome in Inflammatory Bowel Disease. *Digestion.* 2023;104(1):16-23.
doi: 10.1159/000525925
 31. Duan H, Xu B, Luo P, Chen T, Zou J. Microbial metabolites and their influence on the tumor microenvironment. *Front Immunol.* 2025;16:1675677.
doi: 10.3389/fimmu.2025.1675677
 32. Kaur N, Chen CC, Luther J, Kao JY. Intestinal dysbiosis in inflammatory bowel disease. *Gut Microbes.* 2011;2(4):211-216.
doi: 10.4161/gmic.2.4.17863
 33. Sultan S, El-Mowafy M, Elgaml A, Ahmed TAE, Hassan H, Mottawea W. Metabolic Influences of Gut Microbiota Dysbiosis on Inflammatory Bowel Disease. *Front Physiol.* 2021;12:715506.
doi: 10.3389/fphys.2021.715506
 34. Zheng J, Sun Q, Zhang J, Ng SC. The role of gut microbiome in inflammatory bowel disease diagnosis and prognosis. *United Eur Gastroenterol J.* 2022;10(10):1091-1102.
doi: 10.1002/ueg2.12338
 35. Bernardi F, D'Amico F, Bencardino S, *et al.* Gut Microbiota Metabolites: Unveiling Their Role in Inflammatory Bowel Diseases and Fibrosis. *Pharmaceuticals.* 2024;17(3):347.
doi: 10.3390/ph17030347
 36. Iliev ID, Ananthakrishnan AN, Guo CJ. Publisher Correction: Microbiota in inflammatory bowel disease: mechanisms of disease and therapeutic opportunities. *Nat Rev Microbiol.* 2025;23(8):541.
doi: 10.1038/s41579-025-01175-w
 37. Bajaj A, Markandey M, Kedia S, Ahuja V. Gut bacteriome in inflammatory bowel disease: An update on recent advances. *Indian J Gastroenterol.* 2024;43(1):103-111.
doi: 10.1007/s12664-024-01541-1
 38. Cui Y, Huang Y. The Gut-Brain Axis in Comorbidity of Inflammatory Bowel Disease and Anxiety/Depression: Mechanisms, Controversies, and Future Directions. *Int J Gen Med.* 2026;19:612029.
doi: 10.2147/IJGM.S612029
 39. Zhai J, Li Y, Liu J, Dai C. Neuroimmune interactions: The bridge between inflammatory bowel disease and the gut microbiota. *Clin Transl Med.* 2025;15(5):e70329.
doi: 10.1002/ctm2.70329
 40. Alem M, Abtahi Froushani SM, Hajighahramani N, Hosseini-Asl S, Pourfarzi F, Nemati R. Immuno-informatics voyage through molecular mimicry of Heat Shock Proteins: Potential IBD immunopathogenesis. *PLoS ONE.* 2025;20(10):e0333618.
doi: 10.1371/journal.pone.0333618
 41. Liu X, Lu B, Tang H, *et al.* Gut microbiome metabolites, molecular mimicry, and species-level variation drive long-term efficacy and adverse event outcomes in lung cancer survivors. *eBioMedicine.* 2024;109:105427.
doi: 10.1016/j.ebiom.2024.105427
 42. Muruganandam A, Migliorini F, Jeyaraman N, *et al.* Molecular Mimicry Between Gut Microbiome and Rheumatoid Arthritis: Current Concepts. *Med Sci.* 2024;12(4):72.
doi: 10.3390/medsci12040072
 43. Al-Habsi N, Al-Khalili M, Haque SA, Elias M, Olqi NA, Al Uraimi T. Health Benefits of Prebiotics, Probiotics, Synbiotics, and Postbiotics. *Nutrients.* 2024;16(22):3955.
doi: 10.3390/nu16223955
 44. Haneishi Y, Furuya Y, Hasegawa M, Picarelli A, Rossi M, Miyamoto J. Inflammatory Bowel Diseases and Gut Microbiota. *Int J Mol Sci.* 2023;24(4):3817.
doi: 10.3390/ijms24043817
 45. Ghouri YA, Richards DM, Rahimi EF, Krill JT, Jelinek KA, DuPont AW. Systematic review of randomized controlled trials of probiotics, prebiotics, and synbiotics in inflammatory bowel disease. *Clin Exp Gastroenterol.* 2014;7:473-487.
doi: 10.2147/CEG.S27530
 46. Yang X, Guo H, Zou M. Inflammatory bowel diseases: pathological mechanisms and therapeutic perspectives. *Mol Biomed.* 2026;7(1):2.
doi: 10.1186/s43556-025-00395-z
 47. Saez-Lara MJ, Gomez-Llorente C, Plaza-Diaz J, Gil A. The role of probiotic lactic acid bacteria and bifidobacteria in the prevention and treatment of inflammatory bowel disease and other related diseases: a systematic review of randomized human clinical trials. *Biomed Res Int.* 2015;2015:505878.
doi: 10.1155/2015/505878
 48. Estevinho MM, Yuan Y, Rodríguez-Lago I, *et al.* Efficacy and safety of probiotics in IBD: An overview of systematic reviews and updated meta-analysis of randomized controlled trials. *United Eur Gastroenterol J.* 2024;12(7):960-981.
doi: 10.1002/ueg2.12636
 49. Ng SC, Hart AL, Kamm MA, Stagg AJ, Knight SC. Mechanisms of action of probiotics: recent advances. *Inflamm Bowel Dis.* 2009;15(2):300-310.
doi: 10.1002/ibd.20602
 50. Roy S, Dhaneshwar S. Role of prebiotics, probiotics, and synbiotics in management of inflammatory bowel

- disease: Current perspectives. *World J Gastroenterol*. 2023;29(14):2078-2100.
doi: 10.3748/wjg.v29.i14.2078
51. Alvarez CS, Badia J, Bosch M, Giménez R, Baldomà L. Outer Membrane Vesicles and Soluble Factors Released by Probiotic *Escherichia coli* Nissle 1917 and Commensal ECOR63 Enhance Barrier Function by Regulating Expression of Tight Junction Proteins in Intestinal Epithelial Cells. *Front Microbiol*. 2016;7:1981.
doi: 10.3389/fmicb.2016.01981
 52. Yao S, Zhao Z, Wang W, Liu X. Bifidobacterium Longum: Protection against Inflammatory Bowel Disease. *J Immunol Res*. 2021;2021:1-11.
doi: 10.1155/2021/8030297
 53. Kruis W, Frick P, Pokrotnieks J, et al. Maintaining remission of ulcerative colitis with the probiotic *Escherichia coli* Nissle 1917 is as effective as with standard mesalazine. *Gut*. 2004;53(11):1617-1623.
doi: 10.1136/gut.2003.037747
 54. Schultz M. Clinical use of *E. coli* Nissle 1917 in inflammatory bowel disease. *Inflamm Bowel Dis*. 2008;14(7):1012-1018.
doi: 10.1002/ibd.20377
 55. Akutko K, Stawarski A. Probiotics, Prebiotics and Synbiotics in Inflammatory Bowel Diseases. *J Clin Med*. 2021;10(11):2466.
doi: 10.3390/jcm10112466
 56. Khan I, Ullah N, Zha L, et al. Alteration of Gut Microbiota in Inflammatory Bowel Disease (IBD): Cause or Consequence? IBD Treatment Targeting the Gut Microbiome. *Pathogens*. 2019;8(3):126.
doi: 10.3390/pathogens8030126
 57. Costa RL, Moreira J, Lorenzo A, Lamas CC. Infectious complications following probiotic ingestion: a potentially underestimated problem? A systematic review of reports and case series. *BMC Complement Altern Med*. 2018;18(1):329.
doi: 10.1186/s12906-018-2394-3
 58. Orel R, Kamhi Trop T. Intestinal microbiota, probiotics and prebiotics in inflammatory bowel disease. *World J Gastroenterol*. 2014;20(33):11505-11524.
doi: 10.3748/wjg.v20.i33.11505
 59. Bashir Yahya E, Abdulsamad AA, Suliman Aburowais MA, Abogmaza AF. Insights into microbiome-based therapeutics: engineered probiotics, bacteriophages, and microbiome-derived metabolites. *Biomed Res Ther*. 2025;12(12):8062-8071.
doi: 10.15419/35b1xn36
 60. Wang X, Peng J, Cai P, et al. The emerging role of the gut microbiota and its application in inflammatory bowel disease. *Biomed Pharmacother*. 2024;179:117302.
doi: 10.1016/j.biopha.2024.117302
 61. Parada Venegas D, De la Fuente MK, Landskron G, et al. Short Chain Fatty Acids (SCFAs)-Mediated Gut Epithelial and Immune Regulation and Its Relevance for Inflammatory Bowel Diseases. *Front Immunol*. 2019;10:277.
doi: 10.3389/fimmu.2019.00277
 62. Zhou J, Li M, Chen Q, et al. Programmable probiotics modulate inflammation and gut microbiota for inflammatory bowel disease treatment after effective oral delivery. *Nat Commun*. 2022;13(1):3432.
doi: 10.1038/s41467-022-31171-0
 63. Martyniak A, Medyńska-Przęczek A, Wędrychowicz A, Skoczeń S, Tomasiak PJ. Prebiotics, Probiotics, Synbiotics, Paraprobiotics and Postbiotic Compounds in IBD. *Biomolecules*. 2021;11(12):1903.
doi: 10.3390/biom11121903
 64. Halmos EP, Christophersen CT, Bird AR, Shepherd SJ, Muir JG, Gibson PR. Consistent Prebiotic Effect on Gut Microbiota With Altered FODMAP Intake in Patients with Crohn's Disease: A Randomised, Controlled Cross-Over Trial of Well-Defined Diets. *Clin Transl Gastroenterol*. 2016;7(4):e164.
doi: 10.1038/ctg.2016.22
 65. Furrie E, Macfarlane S, Kennedy A, et al. Synbiotic therapy (*Bifidobacterium longum*/Synergy 1) initiates resolution of inflammation in patients with active ulcerative colitis: a randomised controlled pilot trial. *Gut*. 2005;54(2):242-249.
doi: 10.1136/gut.2004.044834
 66. Looijer-van Langen MA, Dieleman LA. Prebiotics in chronic intestinal inflammation. *Inflamm Bowel Dis*. 2009;15(3):454-462.
doi: 10.1002/ibd.20737
 67. Butterworth AD, Thomas AG, Akobeng AK. Probiotics for induction of remission in Crohn's disease. *Cochrane Database Syst Rev*. 2008.
doi: 10.1002/14651858.CD006634.pub2.
 68. Russo E, Giudici F, Fiorindi C, Ficari F, Scaringi S, Amedei A. Immunomodulating Activity and Therapeutic Effects of Short Chain Fatty Acids and Tryptophan Post-biotics in Inflammatory Bowel Disease. *Front Immunol*. 2019;10:2754.
doi: 10.3389/fimmu.2019.02754
 69. Wedlake L, Slack N, Andreyev HJ, Whelan K. Fiber in the treatment and maintenance of inflammatory bowel disease: a systematic review of randomized controlled trials. *Inflamm Bowel Dis*. 2014;20(3):576-586.
doi: 10.1097/01.MIB.0000437984.92565.31
 70. Imdad A, Nicholson MR, Tanner-Smith EE, et al. Fecal

- transplantation for treatment of inflammatory bowel disease. *Cochrane Database Syst Rev*. 2018;2018(11):CD012774.
doi: 10.1002/14651858.CD012774.pub2
71. Zeng L, Deng Y, Yang K, Chen J, He Q, Chen H. Safety and efficacy of fecal microbiota transplantation for autoimmune diseases and autoinflammatory diseases: A systematic review and meta-analysis. *Front Immunol*. 2022;13:944387.
doi: 10.3389/fimmu.2022.944387
 72. Rossen NG, Fuentes S, van der Spek MJ, *et al*. Findings From a Randomized Controlled Trial of Fecal Transplantation for Patients With Ulcerative Colitis. *Gastroenterology*. 2015;149(1):110-118.e4.
doi: 10.1053/j.gastro.2015.03.045
 73. Boicean A, Birlutiu V, Ichim C, Anderco P, Birsan S. Fecal Microbiota Transplantation in Inflammatory Bowel Disease. *Biomedicines*. 2023;11(4):1016.
doi: 10.3390/biomedicines11041016
 74. Costello SP, Hughes PA, Waters O, *et al*. Effect of Fecal Microbiota Transplantation on 8-Week Remission in Patients With Ulcerative Colitis: A Randomized Clinical Trial. *JAMA*. 2019;321(2):156-164.
doi: 10.1001/jama.2018.20046
 75. Sokol H, Landman C, Seksik P, *et al*. Fecal microbiota transplantation to maintain remission in Crohn's disease: a pilot randomized controlled study. *Microbiome*. 2020;8(1):12.
doi: 10.1186/s40168-020-0792-5
 76. Vermeire S, Joossens M, Verbeke K, *et al*. Donor Species Richness Determines Faecal Microbiota Transplantation Success in Inflammatory Bowel Disease. *J Crohns Colitis*. 2016;10(4):387-394.
doi: 10.1093/ecco-jcc/jjv203
 77. Tan P, Li X, Shen J, Feng Q. Fecal Microbiota Transplantation for the Treatment of Inflammatory Bowel Disease: An Update. *Front Pharmacol*. 2020;11:574533.
doi: 10.3389/fphar.2020.574533
 78. Cui B, Li P, Xu L, *et al*. Step-up fecal microbiota transplantation strategy: a pilot study for steroid-dependent ulcerative colitis. *J Transl Med*. 2015;13:298.
doi: 10.1186/s12967-015-0646-2
 79. Prajapati SK, Yadav D, Katiyar S, Jain S, Yadav H. Postbiotics as Mitochondrial Modulators in Inflammatory Bowel Disease: Mechanistic Insights and Therapeutic Potential. *Biomolecules*. 2025;15(7):954.
doi: 10.3390/biom15070954
 80. Zhang T, Zhang W, Feng C, Kwok LY, He Q, Sun Z. Stronger gut microbiome modulatory effects by postbiotics than probiotics in a mouse colitis model. *npj Sci Food*. 2022;6(1):53.
doi: 10.1038/s41538-022-00169-9
 81. Tsilingiri K, Barbosa T, Penna G, *et al*. Probiotic and postbiotic activity in health and disease: comparison on a novel polarised ex-vivo organ culture model. *Gut*. 2012;61(7):1007-1015.
doi: 10.1136/gutjnl-2011-300971
 82. Banfi D, Moro E, Bosi A, *et al*. Impact of Microbial Metabolites on Microbiota-Gut-Brain Axis in Inflammatory Bowel Disease. *Int J Mol Sci*. 2021;22(4):1623.
doi: 10.3390/ijms22041623
 83. Štofilová J, Kvaková M, Kamlárová A, Hijová E, Bertková I, Guľašová Z. Probiotic-Based Intervention in the Treatment of Ulcerative Colitis: Conventional and New Approaches. *Biomedicines*. 2022;10(9):2236.
doi: 10.3390/biomedicines10092236
 84. Kharb A, Zhu X. Unlocking therapeutic impacts of the gut microbiota with computational tools. *Curr Opin Biotechnol*. 2026;97:103431.
doi: 10.1016/j.copbio.2025.103431
 85. Liu J, Zhao P, Jiang D, *et al*. Decoding the microbiome: artificial intelligence-targeted gut microenvironment breakthroughs in personalized cancer therapy. *Gut Microbes*. 2026;18(1):2672791.
doi: 10.1080/19490976.2026.2672791