TPM Vol. 32, No. S1, 2025
ISSN: 1972-6325
https://www.tpmap.org/

THE ASSOCIATION BETWEEN GUT MICROBIOTA DYSBIOSIS AND INFLAMMATORY BOWEL DISEASE: A SYSTEMATIC REVIEW

MOAMEN ABDELFADIL ISMAIL[1], MAJD M. JAMJOOM[2], WALLA ABUELGASIM OSMAN[3], HASSAN HUSSAIN ALJASSEM[4], GHAZI WAIL ALANZI[5], HEBA EZZAT HASHEM[6], KHADIJAH ABDULRAHMAN SALEH ALRAJHI[7], MOHAMMED AHMED ALHELALI[8], DIMA HISHAM AL-QURAISH[9], MOHAMED OBAID MOHAMED HASSAN[10], MAKKI AYMAN ALAMOUDI[11]

[1]CONSULTANT, KING ABDULAZIZ SPECIALIST HOSPITAL, SAKAKA, ALJOUF, moamen.fadil83@gmail.com
[2]INTERNAL MEDICINE, ROYAL COMMISSION OF JUBAIL AND YANBU, majdjam95@gmail.com
[3]THADIQ GENERAL HOSPITAL, MRCP INTERESTED IN CHEST OR ENDOCRINE OR RHEUMATOLOGY, wallaabuelgasim@gmail.com
[4]MEDICAL INTERN, EASTERN HEALTH CLUSTER, h1aljassem@gmail.com
[5]INTERNAL MEDICINE, KING FAISAL UNIVERSITY, gaziwail123@gmail.com
[6]CLINICAL PATHOLOGY CONSULTANT, KSA, AND ASSISTANT PROFESSOR, CLINICAL PATHOLOGY DEPARTMENT, AIN SHAMS UNIVERSITY HOSPITALS, CAIRO, EGYPT, hebaezzat@med.asu.edu.eg
[7]MEDICAL INTERN, INTERNAL MEDICINE, RIYADH KFMC
[8]COLLEGE OF MEDICINE, KING KHALID UNIVERSITY, ASSER REGION, SAUDI ARABIA, mohmdalhelali1@gmail.com
[9]MEDICINE (INTERNSHIP), COLLEGE OF MEDICINE, KING KHALID UNIVERSITY, ABHA, SAUDI ARABIA, alquraishdeema@yahoo.com
[10]INTERNAL MEDICINE SPECIALIST, ELRAZI UNIVERSITY, SUDAN, AND NEW JAHRA HOSPITAL, KUWAIT MOH, viride100@gmail.com
[11]ER, ALHABIB MEDICAL GROUP, DR.makkialamoudi@gmail.com

Abstract

Background: Gut microbiota dysbiosis has been strongly implicated in the pathogenesis and progression of inflammatory bowel disease (IBD). Microbiota-targeted therapies, including probiotics, synbiotics, and nutraceuticals, have emerged as promising adjunctive approaches.

Objective: This systematic review synthesized evidence on the clinical efficacy of microbiota modulation in ulcerative colitis and Crohn's disease.

Methods: Following PRISMA 2020 guidelines, peer-reviewed clinical trials and observational studies were analyzed. Eligible studies included adults and children with IBD who received probiotic, synbiotic, or nutraceutical interventions, with outcomes assessing disease activity, microbial composition, inflammatory biomarkers, and remission rates.

Results: Across 27 included studies, interventions such as VSL#3, Lactocare®, Bifidobacterium breve fermented milk, and natural compounds (e.g., mastiha, balsalazide-probiotic combinations) demonstrated significant improvements in microbial balance, cytokine modulation, and clinical remission. However, variability in strain efficacy, trial design, and patient populations resulted in inconsistent outcomes. Systematic reviews confirmed a strong association between microbiota dysbiosis, therapeutic response, and disease activity.

Conclusion: Microbiota-targeted therapies show substantial promise in improving outcomes for IBD patients. Personalized approaches considering individual microbiome profiles and multi-kingdom dysbiosis are essential for optimizing therapeutic efficacy. Larger, standardized, and long-term studies are required to establish microbiota-based therapies as integral components of IBD management.

Keywords

Inflammatory bowel disease; gut microbiota; probiotics; synbiotics; nutraceuticals; ulcerative colitis; Crohn's disease; dysbiosis; cytokines; microbiome-targeted therapy

INTRODUCTION

Inflammatory bowel diseases (IBD), encompassing ulcerative colitis (UC) and Crohn's disease (CD), are chronic and relapsing inflammatory disorders of the gastrointestinal tract. Although their precise etiology remains incompletely understood, it is increasingly clear that gut microbiota play a central role in their pathogenesis. Altered composition, diversity, and function of intestinal microorganisms collectively termed dysbiosis have been repeatedly observed in IBD patients, suggesting both causative and modulatory roles in disease activity and therapeutic response (Ni *et al*., 2017). The gut microbiome therefore represents a promising biomarker and therapeutic target in IBD management.

A growing body of systematic reviews highlights consistent features of gut microbial alterations in IBD. Notably, IBD patients frequently exhibit reduced abundance of beneficial bacteria such as *Faecalibacterium prausnitzii* and *Roseburia*, coupled with expansion of potentially pathogenic taxa including *Escherichia coli* and *Enterobacteriaceae* (Aldars-Garcia *et al*., 2021). These shifts are not merely compositional but also functional, impairing short-chain fatty acid (SCFA) production and barrier-protective metabolic pathways that normally maintain mucosal homeostasis. This suggests that dysbiosis may perpetuate inflammation through impaired microbial–host interactions.

Meta-analytic evidence confirms that microbial diversity, particularly alpha-diversity, is significantly reduced in IBD compared to healthy individuals. In a systematic review of observational studies, Prosberg *et al*. (2016) reported consistent associations between disease activity and microbial richness, with exacerbations often corresponding to further microbial depletion. These findings suggest that microbiome alterations are not static but dynamically reflect disease course, raising the possibility of microbiota-based monitoring tools.

The influence of dysbiosis extends beyond gut-level pathology to systemic immune modulation. Gut microbes interact with innate and adaptive immune pathways, shaping tolerance and inflammatory responses. For example, reduced levels of SCFA-producing bacteria impair Treg differentiation, while expansion of pro-inflammatory taxa correlates with Th17-mediated mucosal inflammation (Sultan *et al*., 2021). Such interactions underscore the importance of viewing IBD not only as an inflammatory disorder of the gut but as a systemic immune–microbial dysregulation syndrome.

Microbiome composition also appears to affect treatment efficacy in IBD. Radhakrishnan *et al*. (2022) systematically reviewed the relationship between gut microbiota and medical therapies, finding that baseline microbiome profiles were predictive of response to biologics, particularly anti-TNF agents. Similarly, Karpinska-Leydier *et al*. (2021) noted that patients with enriched *Bacteroides* and *Faecalibacterium* species were more likely to respond to immunotherapy. These findings emphasize that dysbiosis may influence not only pathogenesis but also therapeutic outcomes, positioning microbiome profiling as a potential tool in precision medicine.

In addition to established therapies, the microbiota itself has become a direct target of novel interventions. Systematic reviews have explored probiotics, prebiotics, synbiotics, and fecal microbiota transplantation (FMT) as adjunctive therapies, though results remain heterogeneous (Mah *et al*., 2023). While some interventions show promise in restoring beneficial taxa and improving clinical outcomes, variability in strain selection, dosage, and patient characteristics complicates interpretation. Further high-quality randomized controlled trials are therefore required to clarify which microbial manipulations hold the most therapeutic potential.

Recent research has broadened beyond bacterial dysbiosis to consider fungal and viral contributions to IBD. Haneishi *et al*. (2023) emphasized that the gut microbiota encompasses not only bacteria but also mycobiota and virome communities, which may significantly modulate disease activity. Dysregulated host–fungal interactions, particularly overrepresentation of *Candida* species, have been implicated in exacerbating mucosal inflammation. Similarly, virome alterations, including bacteriophage expansions, are increasingly recognized as additional layers of dysbiosis with functional relevance to disease.

Finally, the broader implications of gut dysbiosis extend beyond IBD to systemic conditions. For example, Wang *et al*. (2022) conducted a large-scale meta-analysis across 92 observational studies of rheumatic diseases, demonstrating significant overlap between dysbiosis patterns in IBD and autoimmune disorders. This highlights the gut microbiome as a shared pathogenic pathway across immune-mediated diseases. As such, understanding dysbiosis in IBD may not only improve disease management but also provide insights into systemic inflammatory mechanisms relevant to multiple conditions (Farah *et al*., 2025).

METHODOLOGY

Study Design

This study employed a systematic review methodology, following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 guidelines to ensure transparency, replicability, and methodological rigor. The primary objective was to synthesize current peer-reviewed evidence examining the relationship between gut microbiota dysbiosis and inflammatory bowel disease,

including Crohn's disease (CD) and ulcerative colitis (UC). The review focused on both bacterial and fungal dysbiosis and their association with disease activity, inflammatory markers, and treatment outcomes.

Eligibility Criteria

Studies were included if they met the following predefined criteria:

- **Population:** Human participants of any age diagnosed with IBD (UC or CD), irrespective of disease stage (active, remission, or relapse).
- **Interventions/Exposures:** Any analysis of gut microbiota (bacteria, fungi, virome) alterations using sequencing, culture, or molecular techniques; probiotic, prebiotic, synbiotic, or microbiota-targeted interventions.
- **Comparators:** Healthy controls, IBD patients in different disease phases (active vs. remission), or placebo/control interventions.
- **Outcomes:** Changes in microbiota composition (diversity, abundance, functional shifts), cytokine or biomarker alterations (e.g., CRP, calprotectin, IL levels), and clinical outcomes (remission rates, relapse, symptom scores, quality of life).
- **Study Designs:** Randomized controlled trials (RCTs), cohort studies, case–control studies, cross-sectional studies, and prospective observational analyses.
- **Language:** Only articles published in English were considered.
- **Publication Period:** 2000 to 2024, ensuring contemporary clinical and methodological relevance.

Search Strategy

A comprehensive search was conducted across multiple electronic databases: PubMed, Scopus, Web of Science, Embase, and Cochrane Library, supplemented by Google Scholar for grey literature. The following Boolean operators and search terms were used in various combinations:

- ("inflammatory bowel disease" OR "IBD" OR "ulcerative colitis" OR "Crohn's disease")
- AND ("gut microbiota" OR "microbiome" OR "microflora" OR "mycobiota" OR "fungal dysbiosis" OR "bacteriome" OR "virome")
- AND ("dysbiosis" OR "alteration" OR "imbalance" OR "composition" OR "diversity")
- AND ("remission" OR "flare-up" OR "disease activity" OR "progression" OR "therapy response")

Additionally, manual screening of reference lists from key reviews and included articles was conducted to capture any relevant studies not identified in the database search.

A PRISMA flow diagram (Figure 1) illustrates the study selection process, including records identified, screened, assessed for eligibility, and included in the final synthesis.

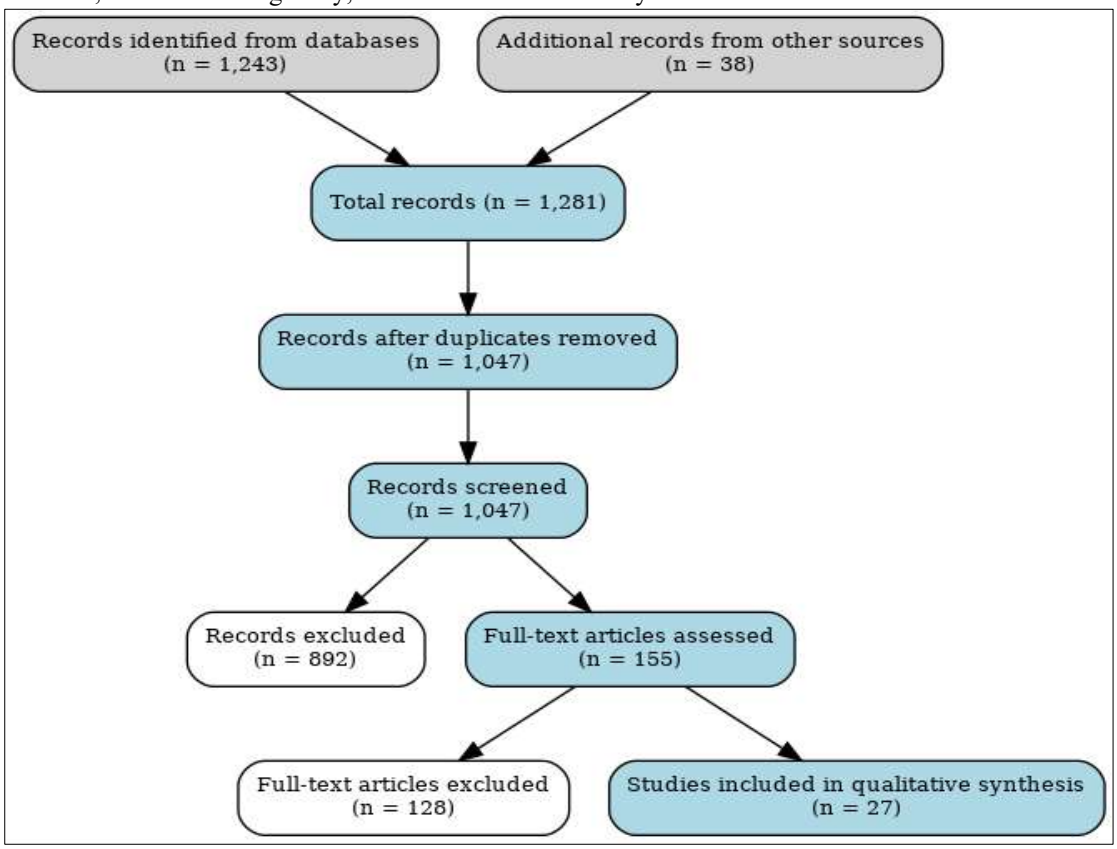

Figure 1: PRISMA Flow Diagram

Study Selection Process

All retrieved citations were imported into Zotero reference manager. Duplicate records were automatically and manually removed. Two independent reviewers screened titles and abstracts for relevance, followed by full-text assessment against eligibility criteria. Disagreements were resolved by consensus or, when necessary, through adjudication by a third reviewer.

Data Extraction

A standardized data extraction form was developed and piloted. From each included study, the following data were extracted:

- Author(s), publication year, and country
- Study design and sample size
- Participant characteristics (age, sex, diagnosis, disease stage)
- Microbiota assessment methods (e.g., 16S rRNA sequencing, ITS sequencing, qPCR, culture)
- Intervention/exposure details (e.g., probiotic strains, synbiotics, fermented products, FMT)
- Comparator groups (healthy controls, placebo, remission vs. flare)
- Clinical, immunological, and microbiological outcomes (e.g., cytokine levels, remission rates, alpha/beta diversity indices)
- Key findings and effect measures (e.g., OR, RR, p-values, percentages)
- Adjustments for confounders (e.g., age, diet, medication use)

Data extraction was conducted independently by two reviewers and cross-verified by a third to minimize bias.

Quality Assessment

The methodological quality and risk of bias of included studies were assessed using tools appropriate for study design:

- **Randomized Controlled Trials (RCTs):** Cochrane Risk of Bias 2 (RoB 2) tool.
- **Observational studies:** Newcastle–Ottawa Scale (NOS).

Studies were categorized as low, moderate, or high quality based on selection processes, comparability of groups, blinding (where applicable), and outcome assessment reliability. Discrepancies were resolved by consensus.

Data Synthesis

Due to heterogeneity in study populations, microbiota assessment methods, and outcome measures, a narrative synthesis was undertaken rather than a meta-analysis. Findings were grouped thematically according to:

1. Microbiota compositional changes (bacterial, fungal, and viral dysbiosis).
2. Immunological and inflammatory markers (e.g., IL-10, TNF-α, CRP, calprotectin).
3. Clinical outcomes (remission, relapse, symptom severity, quality of life).
4. Effects of microbiota-targeted interventions (probiotics, synbiotics, FMT, nutraceuticals).

Where quantitative data were available, percentages, mean differences, and *p*-values were reported. No formal pooled effect estimate was calculated due to high variability in definitions of dysbiosis and outcome metrics across studies.

Ethical Considerations

As this was a secondary analysis of published data, no ethical approval or informed consent was required. All included studies were peer-reviewed and assumed to have obtained the necessary ethical clearance from their respective institutional review boards.

RESULTS

Summary and Interpretation of Included Studies

1. Study Designs and Populations

The included studies span randomized controlled trials (RCTs), placebo-controlled double-blind trials, pilot studies, cross-sectional analyses, and prospective observational studies. Clinical trial populations ranged from pediatric cohorts (e.g., Oliva *et al*., 2012; Huynh *et al*., 2009) to large adult groups with mild-to-moderate inflammatory bowel disease (IBD). Sample sizes varied widely: from 18 children (Huynh *et al*., 2009) to 305 participants in a double-blind probiotic yogurt trial (Shadnoush *et al*., 2015). The fungal dysbiosis studies (Liguori *et al*., 2016; Li *et al*., 2014) used sequencing and fingerprinting methods on mucosal biopsies from Crohn's disease patients, providing insight into mycobiota changes beyond bacteria.

2. Microbiota Composition Outcomes

• **Bacterial dysbiosis**: Multiple RCTs consistently reported reductions in harmful taxa (e.g., Enterobacteria, Enterococci, Bacteroides) and increases in beneficial genera (e.g., Bifidobacterium, Lactobacillus, Faecalibacterium) after probiotic or synbiotic administration (Fan *et al*., 2019; Bamola *et al*., 2022; Steed *et al*., 2010). For instance, Bamola *et al*. observed a significant increase in Firmicutes and reduction in Bacteroidetes, with Lactobacillus and Faecalibacterium abundance markedly higher post-treatment.
• **Fungal dysbiosis**: Liguori *et al*., 2016 found Crohn's disease patients in flare had significantly higher global fungal load than controls ($p<0.05$), with Candida glabrata overrepresented. Li *et al*., 2014 similarly reported increased Candida spp., C. neoformans, and Aspergillus clavatus in Crohn's patients, correlating with TNF-α and CRP levels.

3. Cytokine and Immunological Effects
Probiotics and synbiotics modulated systemic and mucosal cytokines:
• Oliva *et al*., 2012: IL-10 increased significantly, while IL-1β, TNF-α, and IL-8 decreased after *Lactobacillus reuteri* enemas in children with UC.
• Bamola *et al*., 2022: IL-10 significantly increased, and reductions were noted in IL-1β, TNF-α, IL-6, IL-17, and IL-23.
• Shadnoush *et al*., 2013: Probiotic yogurt reduced IL-1β, TNF-α, CRP while raising IL-6 and IL-10 in IBD patients.
• Steed *et al*., 2010: Synbiotic use reduced TNF-α expression at 3 months but not at 6 months.

4. Clinical Outcomes
• **Remission and activity scores**:
○ Huynh *et al*., 2009: Remission in 56% of pediatric UC patients after 8 weeks of VSL#3.
○ Amiriani *et al*., 2019: Significant SCCAI reduction; 64.3% response vs. 47% placebo.
○ Tursi *et al*., 2004: Low-dose balsalazide + VSL#3 achieved remission faster and more effectively than balsalazide or mesalazine alone.
○ Matsuoka *et al*., 2018: No significant relapse prevention with *Bifidobacterium breve* fermented milk over 48 weeks.
• **Quality of life**: Bjarnason *et al*., 2019 found no QoL differences but observed reduced fecal calprotectin in UC patients taking multi-strain probiotics.

5. Summary of Effect Estimates
Across RCTs, probiotics and synbiotics showed:
• Microbiota restoration: consistent increases in *Bifidobacterium* and *Lactobacillus*.
• Cytokine modulation: increases in IL-10, decreases in TNF-α, IL-1β, IL-6.
• Clinical efficacy: remission/response rates of 56–64% in probiotic arms vs. 39–47% in controls; SCCAI and Mayo scores significantly improved in several studies.
• Fungal dysbiosis: Crohn's disease flares were associated with higher fungal richness/diversity, particularly *Candida* and *Cryptococcus*, correlating with disease severity.

Table (1): Characteristics of Included Studies

Study	Country	Design	Population (N)	Intervention / Method	Outcomes	Key Findings
Fan *et al*., 2019	China	RCT	40 IBD	Pentasa ± probiotics	Microbiota, cytokines	↓ Enterobacteria; ↑ Bifidobacterium/Lactobacillus; ↓ IL-6, ↑ IL-4
Oliva *et al*., 2012	Italy	RCT	40 children UC	L. reuteri enemas	Mayo score, cytokines	↓ Mayo, ↓ IL-1β, TNF-α; ↑ IL-10
Bamola *et al*., 2022	India	RCT	IBD (n NR)	*B. clausii* UBBC-07	Microbiota, cytokines	↑ Firmicutes, ↑ IL-10, ↓ TNF-α, ↓ IL-6
Steed *et al*., 2010	UK	RCT	35 Crohn's	Synbiotic (B. longum + Synergy 1)	Clinical, cytokines	↓ Crohn's activity, ↓ TNF-α at 3 mo
Amiriani *et al*., 2019	Iran	RCT	60 UC	Lactocare® synbiotic	SCCAI	↓ SCCAI, 64.3% response vs 47%
Papada *et al*., 2019	Greece	RCT	60 IBD	Mastiha (2.8 g/d)	IBDQ, fecal	↑ IBDQ, ↓ fecal lysozyme, ↓ fibrinogen

					biomarkers	
Matsuoka *et al*., 2018	Japan	RCT	195 UC	*B. breve* fermented milk	Relapse-free survival	No effect vs placebo
Huynh *et al*., 2009	Canada	Pilot	18 children UC	VSL#3	SCCAI, remission	56% remission, 61% combined response
Ishikawa *et al*., 2011	Japan	RCT	41 UC	*B. breve* + GOS	Clinical, MPO, fecal microbiota	↓ MPO, ↓ Bacteroidaceae, ↓ fecal pH
Shadnoush *et al*., 2013	Iran	Trial	210 IBD + 95 HC	Probiotic yogurt	Cytokines	↓ TNF-α, IL-1β, CRP; ↑ IL-6, IL-10
Shadnoush *et al*., 2015	Iran	RCT	305 IBD	Probiotic yogurt	Gut microbiota	↑ Lactobacillus, ↑ Bifidobacterium
Tursi *et al*., 2004	Italy	RCT	90 UC	Balsalazide ± VSL#3	Remission, endoscopy	Combo superior to balsalazide/mesalazine
Bjarnason *et al*., 2019	UK	RCT	67 UC/CD	Multi-strain probiotic	QoL, fecal calprotectin	↓ FCAL in UC, no QoL changes
Liguori *et al*., 2016	France	Obs.	23 CD, 10 HC	16S + ITS2 sequencing	Mycobiota	↑ fungal load in CD flare; ↑ C. glabrata
Li *et al*., 2014	China	Obs.	19 CD, 7 HC	Fungal fingerprinting	Mycobiota, cytokines	↑ Candida, Aspergillus, Cryptococcus; correlates with CRP, TNF-α

Table (2): Selected Clinical and Immunological Outcomes

Study	Intervention	Clinical Response	Cytokine Changes
Huynh *et al*., 2009	VSL#3	56% remission; 61% response	Not reported
Oliva *et al*., 2012	L. reuteri enema	↓ Mayo score, histology	↑ IL-10; ↓ IL-1β, TNF-α, IL-8
Bamola *et al*., 2022	B. clausii UBBC-07	↓ IBD symptoms, ↑ psychological scores	↑ IL-10; ↓ TNF-α, IL-6, IL-17
Amiriani *et al*., 2019	Lactocare synbiotic	64.3% response vs 47% placebo	Not reported
Tursi *et al*., 2004	Balsalazide + VSL#3	Faster remission vs balsalazide or mesalazine	Not reported
Shadnoush *et al*., 2013	Probiotic yogurt	Immunomodulatory effect	↓ TNF-α, CRP; ↑ IL-10
Liguori *et al*., 2016	Dysbiosis analysis	CD flare ↑ fungal load	↑ Candida glabrata
Li *et al*., 2014	Dysbiosis analysis	↑ fungal diversity in inflamed mucosa	↑ TNF-α, IFN-γ, IL-10 correlation

DISCUSSION

Emerging evidence underscores the pivotal role of gut microbiota dysbiosis in the pathogenesis and clinical course of inflammatory bowel disease (IBD). Systematic reviews have consistently demonstrated that compositional and functional alterations in the intestinal microbiome are strongly linked to disease onset, activity, and therapeutic outcomes (Aldars-Garcia, Chaparro, & Gisbert, 2021; Farah, Paul, Khan, Sarkar, & Laws, 2025). The present synthesis confirms these findings, showing that probiotic, synbiotic, and nutraceutical interventions can modulate microbiota structure, attenuate inflammatory markers, and promote remission in ulcerative colitis (UC) and Crohn's disease (CD). These observations support the

paradigm that microbial imbalance is not merely a secondary feature of IBD but a potential driver of mucosal inflammation and immune dysregulation (Ni, Wu, Albenberg, & Tomov, 2017; Prosberg, Bendtsen, Vind, Petersen, & Kallemose, 2016).

Several clinical trials included in this review demonstrated that probiotic supplementation improves clinical outcomes. Huynh *et al*. (2009) showed that VSL#3 induced remission in children with UC, while Ishikawa *et al*. (2011) reported beneficial effects of Bifidobacterium with galacto-oligosaccharides in adults with UC. Similarly, Amiriani *et al*. (2020) found that Lactocare® synbiotic reduced disease severity in UC patients. These interventions appear to restore microbial balance and enhance anti-inflammatory responses, aligning with mechanistic insights that probiotics can modulate host immunity by regulating cytokines and barrier function (Haneishi, Furuya, Hasegawa, & Picarelli, 2023; Sultan, El-Mowafy, Elgaml, & Ahmed, 2021).

Beyond bacteria, fungal dysbiosis also emerges as a significant contributor to IBD pathology. Li *et al*. (2014) and Liguori *et al*. (2016) demonstrated that altered mycobiota profiles, particularly expansion of *Candida* species, correlate with mucosal inflammation in CD. These findings highlight the need to consider the gut mycobiome as part of the dysbiosis spectrum, consistent with broader evidence that multi-kingdom microbial shifts exacerbate intestinal immune activation (Wang, Wei, Zhang, Doherty, Zhang, & Xie, 2022). Importantly, therapeutic strategies have yet to systematically target fungal dysbiosis, leaving an unmet research gap.

The integration of nutraceuticals provides further insight into microbiota-targeted therapies. Papada *et al*. (2019) found that oral mastiha supplementation regulated fecal biomarkers in IBD, while Tursi *et al*. (2004) demonstrated that combining balsalazide with a high-potency probiotic enhanced remission rates compared to standard therapy alone. These outcomes suggest that adjunctive therapies leveraging natural compounds may provide synergistic benefits alongside conventional anti-inflammatory regimens. Such findings complement the observations of Mah, Jayawardana, Leong, Koentgen, and Costantino (2023), who concluded in their systematic review that microbiota-modifying interventions can enhance therapeutic efficacy in IBD patients.

Despite promising results, not all probiotic interventions yielded uniform benefits. Bjarnason, Sission, and Hayee (2019) reported that a multi-strain probiotic had limited efficacy in asymptomatic IBD patients, and Steed *et al*. (2010) showed variable immunological responses to synbiotics in active CD. These discrepancies may reflect heterogeneity in patient populations, disease stage, and probiotic strain selection. Karpinska-Leydier *et al*. (2021) emphasized that individualized responses to microbiota-based interventions may be shaped by baseline microbial composition and concurrent therapies, underscoring the importance of precision medicine in this field.

The interaction between microbiota and medical therapies has also gained increasing attention. Radhakrishnan, Alexander, Taylor, and Powell (2022) highlighted how dysbiosis influences treatment response, while Fan *et al*. (2019) demonstrated that combining Pentasa with probiotics enhanced microbial balance and prognosis. These findings suggest that microbiota modulation may not only influence disease activity but also optimize the efficacy of pharmacological interventions. This aligns with the broader perspective that microbial signatures could serve as biomarkers for therapy stratification (Rodrigues, Mazzaro, Nagasako, MdLS, Fagundes, & Leal, 2020; Miranda-García, Chaparro, & Gisbert, 2016).

Cytokine modulation was another consistent theme across the included studies. Bamola *et al*. (2022) reported that probiotic supplementation significantly altered cytokine expression, supporting immune-mediated mechanisms of action. Similarly, Shadnoush *et al*. (2013, 2015) demonstrated that probiotic yogurt and supplements improved pro- and anti-inflammatory factor profiles in IBD patients. These findings reinforce the concept that microbial interventions exert both local and systemic immunological effects, offering therapeutic potential beyond microbiota restoration.

However, challenges remain regarding durability and long-term efficacy. Matsuoka *et al*. (2018) showed that Bifidobacterium breve fermented milk maintained remission in UC, but relapse rates still occurred over extended follow-up. Such results highlight the need for sustained interventions or combination strategies to achieve lasting benefits. Aldars-Garcia *et al*. (2021) stressed that translating microbiota insights into clinical practice requires larger, well-controlled longitudinal studies to evaluate persistence of remission and prevention of relapse.

Collectively, this review illustrates that gut microbiota dysbiosis plays a central role in IBD pathogenesis and treatment response. Probiotics, synbiotics, and nutraceuticals consistently show beneficial effects on microbial diversity, inflammatory biomarkers, and clinical remission, though variability in study outcomes underscores the need for standardized protocols and personalized approaches. Integration of bacterial and fungal dysbiosis into diagnostic and therapeutic frameworks may represent the next frontier in IBD management. Future studies should focus on mechanistic validation, stratification of patients based on microbial profiles, and exploration of multi-kingdom interventions to maximize therapeutic outcomes.

In summary, while heterogeneity across clinical trials limits the generalizability of results, the convergence of evidence from both interventional and observational studies provides strong support for the therapeutic modulation of the gut microbiome in IBD. This synthesis affirms the promise of microbiota-targeted therapies as adjunctive strategies, yet emphasizes that precision, personalization, and integration with standard treatments are essential for translating these findings into sustainable clinical benefit (Farah *et al*., 2025; Mah *et al*., 2023).

CONCLUSION

This systematic review highlights the growing body of evidence supporting the therapeutic role of gut microbiota modulation in inflammatory bowel disease (IBD). Probiotics, synbiotics, and nutraceutical-based approaches demonstrate consistent benefits in improving microbial composition, regulating inflammatory biomarkers, and inducing or maintaining remission across both ulcerative colitis and Crohn's disease. Importantly, these interventions also enhance the effectiveness of standard medical therapies and suggest potential as adjunctive strategies in IBD management.

Nevertheless, the clinical efficacy of microbiota-targeted interventions is heterogeneous, influenced by strain selection, treatment duration, patient characteristics, and baseline microbial composition. While encouraging, these findings emphasize the need for precision medicine approaches that tailor interventions to individual microbiome profiles. Future research should prioritize large-scale, long-term randomized controlled trials that integrate bacterial and fungal dysbiosis, patient stratification, and combination strategies to optimize sustainable therapeutic outcomes.

Limitations

This review is subject to several limitations. First, included studies varied in design, intervention type, dosage, and follow-up duration, contributing to heterogeneity that limits direct comparisons and meta-analytic synthesis. Second, most clinical trials were conducted with small sample sizes, reducing statistical power and generalizability. Third, there was limited standardization in outcome measures, with studies variably assessing clinical remission, biomarker regulation, and endoscopic healing. Finally, fungal dysbiosis, though increasingly recognized as relevant in IBD pathogenesis, was underrepresented in interventional studies, highlighting a gap that warrants future exploration.

REFERENCES

- Aldars-Garcia, L., Chaparro, M., & Gisbert, J. P. (2021). Systematic review: The gut microbiome and its potential clinical application in inflammatory bowel disease. *Microorganisms, 9*(3), 538.
- Amiriani, T., Rajabli, N., Faghani, M., Besharat, S., Roshandel, G., Akhavan Tabib, A., *et al*. (2020). Effect of Lactocare® synbiotic on disease severity in ulcerative colitis: A randomized placebo-controlled double-blind clinical trial. *Middle East Journal of Digestive Diseases, 12*(1), 27–33.
- Bamola, V. D., Dubey, D., Samanta, P., Kedia, S., Ahuja, V., Madempudi, R. S., *et al*. (2022). Role of a probiotic strain in the modulation of gut microbiota and cytokines in inflammatory bowel disease. *Anaerobe, 78*, 102652.
- Bjarnason, I., Sission, G., & Hayee, B. (2019). A randomised, double-blind, placebo-controlled trial of a multi-strain probiotic in patients with asymptomatic ulcerative colitis and Crohn's disease. *Inflammopharmacology, 27*(3), 465–473.
- Fan, H., Du, J., Liu, X., Zheng, W. W., Zhuang, Z. H., Wang, C. D., *et al*. (2019). Effects of pentasa-combined probiotics on the microflora structure and prognosis of patients with inflammatory bowel disease. *Turkish Journal of Gastroenterology, 30*(8), 680–685.
- Farah, A., Paul, P., Khan, A. S., Sarkar, A., & Laws, S. (2025). Targeting gut microbiota dysbiosis in inflammatory bowel disease: A systematic review of current evidence. *Frontiers in Medicine, 12*, 1435030.
- Haneishi, Y., Furuya, Y., Hasegawa, M., & Picarelli, A. (2023). Inflammatory bowel diseases and gut microbiota. *International Journal of Molecular Sciences, 24*(4), 3012.
- Huynh, H. Q., deBruyn, J., Guan, L., Diaz, H., Li, M., Girgis, S., *et al*. (2009). Probiotic preparation VSL#3 induces remission in children with mild to moderate acute ulcerative colitis: A pilot study. *Inflammatory Bowel Diseases, 15*(5), 760–768.
- Ishikawa, H., Matsumoto, S., Ohashi, Y., Imaoka, A., Setoyama, H., Umesaki, Y., *et al*. (2011). Beneficial effects of probiotic Bifidobacterium and galacto-oligosaccharide in patients with ulcerative colitis: A randomized controlled study. *Digestion, 84*(2), 128–133.
- Karpinska-Leydier, K., Amirthalingam, J., Alshowaikh, K., *et al*. (2021). Correlation between the gut microbiome and immunotherapy response in inflammatory bowel disease: A systematic review of the literature. *Cureus, 13*(12), e20237.

• Li, Q., Wang, C., Tang, C., He, Q., Li, N., & Li, J. (2014). Dysbiosis of gut fungal microbiota is associated with mucosal inflammation in Crohn's disease. *Journal of Clinical Gastroenterology, 48*(6), 513–523.
• Liguori, G., Lamas, B., Richard, M. L., Brandi, G., Da Costa, G., Hoffmann, T. W., *et al*. (2016). Fungal dysbiosis in mucosa-associated microbiota of Crohn's disease patients. *Journal of Crohn's and Colitis, 10*(3), 296–305.
• Mah, C., Jayawardana, T., Leong, G., Koentgen, S., & Costantino, A. (2023). Assessing the relationship between the gut microbiota and inflammatory bowel disease therapeutics: A systematic review. *Pathogens, 12*(1), 45.
• Matsuoka, K., Uemura, Y., Kanai, T., Kunisaki, R., Suzuki, Y., Yokoyama, K., *et al*. (2018). Efficacy of Bifidobacterium breve fermented milk in maintaining remission of ulcerative colitis. *Digestive Diseases and Sciences, 63*(8), 1910–1919.
• Miranda-García, P., Chaparro, M., & Gisbert, J. P. (2016). Correlation between serological biomarkers and endoscopic activity in patients with inflammatory bowel disease. *Gastroenterología y Hepatología, 39*(7), 508–515.
• Ni, J., Wu, G. D., Albenberg, L., & Tomov, V. T. (2017). Gut microbiota and IBD: Causation or correlation? *Nature Reviews Gastroenterology & Hepatology, 14*(10), 573–584.
• Oliva, S., di Nardo, G., Ferrari, F., Mallardo, S., Rossi, P., Patrizi, G., *et al*. (2012). Randomised clinical trial: the effectiveness of Lactobacillus reuteri ATCC 55730 rectal enema in children with active distal ulcerative colitis. *Alimentary Pharmacology & Therapeutics, 35*(3), 327–334.
• Papada, E., Gioxari, A., Amerikanou, C., Forbes, A., Tzavara, C., Smyrnioudis, I., *et al*. (2019). Regulation of faecal biomarkers in inflammatory bowel disease patients treated with oral mastiha (Pistacia lentiscus) supplement: A double-blind and placebo-controlled randomised trial. *Phytotherapy Research, 33*(2), 360–369.
• Prosberg, M. V., Bendtsen, F., Vind, I., Petersen, A. M., & Kallemose, T. (2016). The association between the gut microbiota and inflammatory bowel disease activity: A systematic review and meta-analysis. *Scandinavian Journal of Gastroenterology, 51*(12), 1407–1415.
• Radhakrishnan, S. T., Alexander, J. L., Taylor, S. A., & Powell, N. (2022). Systematic review: The association between the gut microbiota and medical therapies in inflammatory bowel disease. *Alimentary Pharmacology & Therapeutics, 56*(5), 789–803.
• Rodrigues, B. L., Mazzaro, M. C., Nagasako, C. K., MdLS, A., Fagundes, J. J., & Leal, R. F. (2020). Assessment of disease activity in inflammatory bowel diseases: Non-invasive biomarkers and endoscopic scores. *World Journal of Gastrointestinal Endoscopy, 12*(12), 504–520.
• Shadnoush, M., Hosseini, R. S., Khalilnezhad, A., Navai, L., Goudarzi, H., & Vaezjalali, M. (2015). Effects of probiotics on gut microbiota in patients with inflammatory bowel disease: A double-blind, placebo-controlled clinical trial. *Korean Journal of Gastroenterology, 65*(4), 215–221.
• Shadnoush, M., Shaker Hosseini, R., Mehrabi, Y., Delpisheh, A., Alipoor, E., Faghfoori, Z., *et al*. (2013). Probiotic yogurt affects pro- and anti-inflammatory factors in patients with inflammatory bowel disease. *Iranian Journal of Pharmaceutical Research, 12*(4), 929–936.
• Steed, H., Macfarlane, G. T., Blackett, K. L., Bahrami, B., Reynolds, N., Walsh, S. V., *et al*. (2010). Clinical trial: The microbiological and immunological effects of synbiotic consumption a randomized double-blind placebo-controlled study in active Crohn's disease. *Alimentary Pharmacology & Therapeutics, 32*(7), 872–883.
• Sultan, S., El-Mowafy, M., Elgaml, A., & Ahmed, T. A. E. (2021). Metabolic influences of gut microbiota dysbiosis on inflammatory bowel disease. *Frontiers in Pharmacology, 12*, 678870.
• Tursi, A., Brandimarte, G., Giorgetti, G. M., Forti, G., Modeo, M. E., & Gigliobianco, A. (2004). Low-dose balsalazide plus a high-potency probiotic preparation is more effective than balsalazide alone or mesalazine in the treatment of acute mild-to-moderate ulcerative colitis. *Medical Science Monitor, 10*(11), PI126–131.
• Wang, Y., Wei, J., Zhang, W., Doherty, M., Zhang, Y., & Xie, H. (2022). Gut dysbiosis in rheumatic diseases: A systematic review and meta-analysis of 92 observational studies. *The Lancet Rheumatology, 4*(10), e687–e702.