*Mini Review*

# From Dysbiosis to Therapy: The Role of Gut Microbiota-Derived Metabolites in IBD

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**Abstract:** Inflammatory Bowel Disease (IBD), encompassing Crohn's disease and ulcerative colitis, is a chronic disorder of the gastrointestinal tract characterized by recurrent inflammation and dysregulated immune responses. Emerging evidence highlights the crucial role of gut microbiota and their metabolites in both the pathogenesis and potential treatment of IBD. This mini-review explores key microbial-derived compounds—including short-chain fatty acids (SCFAs), tryptophan metabolites, bile acids, and other bioactive molecules—that serve as mediators between host physiology and the intestinal microbial ecosystem. SCFAs such as butyrate, acetate, and propionate are essential for maintaining gut barrier integrity and immune homeostasis; however, their concentrations are often diminished in IBD patients. Similarly, tryptophan metabolism produces compounds like indole-3-acetic acid, which modulate gut immunity, though this pathway is frequently disrupted in disease states. Alterations in bile acid profiles also contribute to IBD pathophysiology by impacting receptors involved in metabolic and immune regulation. Moreover, imbalances in other microbial metabolites, including hydrogen sulfide, have been linked to exacerbated mucosal inflammation and epithelial damage. Therapeutic strategies aimed at restoring microbial metabolite balance are under active investigation. These include dietary interventions, SCFA supplementation, targeted probiotic formulations, bile acid receptor agonists, and fecal microbiota transplantation (FMT). This review further discusses the challenges of personalizing such interventions based on inter-individual variability in the microbiome, as well as the need for advanced metabolomic tools to better characterize these interactions in clinical contexts. In summary, deepening our understanding of gut microbiota-derived metabolites offers promising avenues for IBD therapies that go beyond symptom control, targeting underlying disease mechanisms at the microbial-host interface.

**Keywords:** Inflammatory bowel disease; Crohn's disease; Ulcerative colitis; Gut microbiota; Dysbiosis; Microbial metabolites; Short-chain fatty acids.

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## Introduction

Inflammatory Bowel Disease (IBD) comprises a group of chronic, relapsing inflammatory conditions of the gastrointestinal (GI) tract, primarily including Crohn's disease (CD) and ulcerative colitis (UC). CD is characterized by transmural inflammation that may affect any region of the GI tract, most commonly the terminal ileum and colon, and is often associated with skip lesions, strictures, and fistulas [1]. In contrast, UC is restricted to the colon and rectum and involves continuous mucosal inflammation that typically begins in the rectum and extends proximally [2].

The etiology of both CD and UC is multifactorial, involving complex interactions among genetic susceptibility, environmental triggers, immune dysregulation, and, notably, the gut microbiota [3]. The gut microbiome plays a vital role in maintaining intestinal homeostasis and overall health by aiding in nutrient digestion, vitamin synthesis, immune modulation, and protection against pathogenic microbes [4]. In IBD, this balance is disrupted, leading to a state of dysbiosis characterized by reduced microbial diversity, a loss of beneficial commensals, and an expansion of pathobionts [5]. These microbial shifts are increasingly recognized not only as contributors to disease pathogenesis but also as potential therapeutic targets [6].

Microbial metabolites—including short-chain fatty acids (SCFAs), secondary bile acids, and tryptophan-derived compounds—act as crucial signaling molecules through which the gut microbiota interact with the host, influencing inflammation, epithelial barrier integrity, and immune responses [7]. SCFAs, particularly butyrate, have been shown to support regulatory T cell (Treg) differentiation and promote mucosal healing [8], while tryptophan metabolites modulate immunity via activation of the aryl hydrocarbon receptor (AhR) pathway. Altered production or function of these metabolites has been associated with IBD, suggesting that restoration of microbial metabolic balance may offer novel therapeutic opportunities [9].

**Role of Gut Microbiota-Derived Metabolites in IBD Development**

The human gut microbiome produces a diverse array of metabolites that are essential for maintaining intestinal health (Table 1). In IBD, chronic inflammation is closely linked to altered microbial metabolism resulting from dysbiosis, which further drives epithelial injury, immune activation, and disease progression [10].

**Table 1.** Key Gut Microbiota-derived metabolites and their roles in IBD.

| Metabolite Group | Key Compounds | Source Bacteria | Role in Gut Health | Alterations in IBD | Therapeutic Strategies |
|---|---|---|---|---|---|
| Short-Chain Fatty Acids | Butyrate, Acetate, Propionate | *Faecalibacterium prausnitzii*, *Roseburia* spp. | Maintain epithelial barrier; regulate immune response | Decreased levels; loss of producers | Prebiotics, fiber supplementation, SCFA enemas, probiotics |
| Tryptophan Metabolites | Indole-3-acetic acid, Indole-3-aldehyde | *Lactobacillus reuteri*, others | AhR activation; IL-22 production; mucosal repair | Reduced AhR ligand availability | Probiotics, AhR agonists |
| Bile Acids | Deoxycholic acid, Lithocholic acid | Bile acid-transforming bacteria | FXR, TGR5 signaling; regulate inflammation | Altered secondary bile acid profiles | FXR agonists, microbiota restoration |
| Polyamines | Spermidine, Spermine | Various commensals | Cellular repair; epithelial growth | Dysregulated levels | Microbial modulation |
| Sulfur Metabolites | Hydrogen sulfide ($H_2S$) | *Desulfovibrio* spp. | Signaling molecule at physiological levels; toxic at high concentrations | Elevated $H_2S$ causing epithelial damage | Microbiota-targeted interventions |

**Short-Chain Fatty Acids (SCFAs): A Key Microbial-Derived Metabolite Group**

SCFAs—including butyrate, acetate, and propionate—are fermentation products of dietary fibers by gut bacteria. Among these, butyrate is the most extensively studied due to its roles in supporting colonic epithelial health, serving as an energy source for colonocytes, and exerting potent anti-inflammatory effects [11]. In IBD, decreased SCFA levels have been linked to a reduction in SCFA-producing bacterial taxa, particularly Faecalibacterium prausnitzii and Roseburia spp. [12].

SCFAs promote gut barrier function by enhancing the expression of tight junction proteins and stimulating mucus production [13]. Additionally, they contribute to immune regulation by promoting the expansion of regulatory T cells (Tregs), partly through inhibition of histone deacetylases and suppression of NF-κB signaling pathways [14]. Therefore, reduced SCFA availability in IBD compromises mucosal integrity and exacerbates immune dysregulation, contributing to the persistence of inflammation.

**Inhibition of Aryl Hydrocarbon Receptor (AhR) Signaling by Tryptophan Metabolites**

SCFAs—including butyrate, acetate, and propionate—are fermentation products of dietary fibers by gut bacteria. Among these, butyrate is the most extensively studied due to its roles in supporting colonic epithelial health, serving as an energy source for colonocytes, and exerting potent anti-inflammatory effects [11]. In IBD, decreased SCFA levels have been linked to a reduction in SCFA-producing bacterial taxa, particularly Faecalibacterium prausnitzii and Roseburia spp. [12].

Gut bacteria metabolize tryptophan into various indole derivatives, including indole-3-acetic acid (IAA) and indole-3-aldehyde (IAld), which act as endogenous ligands for the aryl hydrocarbon receptor (AhR)—a transcription factor critical for mucosal immunity and epithelial homeostasis [15]. Activation of AhR promotes the production of interleukin-22 (IL-22), stimulates antimicrobial peptide expression, and supports epithelial regeneration.

In IBD, dysregulation of AhR signaling has been observed, resulting in impaired IL-22 production, reduced antimicrobial defense, and compromised mucosal barrier repair [16]. Notably, fecal samples from IBD patients exhibit significantly lower levels of AhR ligands, correlating with increased disease activity and inflammation [17]. These findings underscore the importance of tryptophan-derived metabolites in maintaining intestinal immune equilibrium and their potential role in IBD pathogenesis.

**Bile Acid Metabolism**

Primary bile acids synthesized in the liver are converted into secondary bile acids—such as deoxycholic acid and lithocholic acid—by intestinal microbiota through deconjugation and dehydroxylation reactions [18]. These secondary bile acids function as signaling molecules by activating nuclear receptors such as the farnesoid X receptor (FXR) and Takeda G protein-

coupled receptor 5 (TGR5), both of which are involved in regulating bile acid metabolism, intestinal permeability, and inflammatory responses.

In IBD, reduced levels of secondary bile acids have been consistently reported, leading to dysregulated FXR and TGR5 signaling and contributing to enhanced intestinal inflammation [19]. This altered bile acid composition not only exacerbates mucosal inflammation but also reinforces microbial dysbiosis, creating a feedback loop that perpetuates disease progression.

**Hydrogen Sulfide ($H_2S$) and Sulfur Metabolites**

Hydrogen sulfide ($H_2S$) is produced by certain gut bacteria, such as Desulfovibrio spp., through the metabolism of sulfur-containing compounds including sulfates and taurine. At physiological concentrations, $H_2S$ functions as a gaseous signaling molecule involved in maintaining mucosal integrity. However, when present in excess, $H_2S$ becomes toxic to colonic epithelial cells by inhibiting cytochrome c oxidase, inducing oxidative stress, and causing DNA damage [20].

Elevated levels of $H_2S$ have been linked to disruption of the mucosal barrier, exacerbation of epithelial injury, and amplification of intestinal inflammation in IBD [21]. These findings highlight the dual role of sulfur metabolism in gut homeostasis and its pathogenic implications when dysregulated.

**Therapeutic Potential of Microbial Metabolism in IBD**

Several therapeutic approaches are under investigation to restore the balance of these metabolites, ranging from dietary interventions and probiotics to bile acid modulation and engineered microbiota (Table 2). These strategies aim to mitigate inflammation and repair the intestinal barrier by targeting specific metabolic pathways.

**Table 2.** Current and Emerging Therapeutic Approaches Targeting Microbial Metabolites in IBD.

| Therapy Type | Targeted Metabolite/Pathway | Mechanism of Action | Clinical Status | Challenges/ |
|---|---|---|---|---|
| Prebiotics and Dietary Fiber | SCFAs | Promote growth of SCFA-producing bacteria; increase SCFA levels | Clinical trials support improved barrier function | Patient adherence; variable microbiome response |
| Probiotics and Engineered Strains | SCFAs, AhR ligands | Restore metabolite production; immune modulation | Some efficacy in clinical trials; experimental engineered probiotics | Strain selection; safety and regulatory issues |
| Bile Acid Receptor Agonists | FXR, TGR5 | Anti-inflammatory signaling modulation | Obeticholic acid in preclinical/early clinical phases | Off-target effects; long-term safety |
| Fecal Microbiota Transplant (FMT) | Multiple metabolites | Restore microbial diversity and metabolic capacity | Mixed results in clinical studies | Donor selection; variability in outcomes |

**Restoring SCFA Concentrations**

Short-chain fatty acids (SCFAs)—particularly butyrate—play a critical role in

maintaining intestinal health. The abundance of SCFA-producing bacteria such as Faecalibacterium prausnitzii and Roseburia spp. can be enhanced by prebiotics like inulin and fructooligosaccharides [22]. Additionally, dietary fiber supplementation supports SCFA production and promotes epithelial barrier integrity [23].

Therapeutically, butyrate has shown promise in reducing inflammation in distal colitis when administered via enemas. Moreover, novel oral delivery methods—such as microencapsulation techniques for colon-targeted release—have demonstrated potential in preclinical and early clinical settings [24,25].

**Modulating Tryptophan Metabolism**

Modifying tryptophan metabolism to increase aryl hydrocarbon receptor (AhR) ligand availability represents a promising therapeutic strategy. This approach aims to restore IL-22 production and promote mucosal healing. Certain probiotic strains, such as Lactobacillus reuteri, can produce AhR ligands like indole-3-aldehyde, thereby positively influencing mucosal immunity [26].

To compensate for the reduced production of these ligands in IBD, supplementation with natural or synthetic AhR agonists has been proposed [27]. These agents aim to rebalance host-microbe interactions and reduce mucosal inflammation through targeted immune modulation.

**Bile Acid Modulators**

Bile acids influence immune and epithelial function via the nuclear receptors FXR and TGR5. Dysregulation of bile acid metabolism in IBD has led to interest in pharmacological modulation of these pathways. FXR agonists such as obeticholic acid have demonstrated anti-inflammatory properties in preclinical studies and are currently being investigated for therapeutic use in IBD [28]. Additionally, microbiota-based interventions that restore secondary bile acid production by promoting bile acid-producing bacteria offer another promising strategy to restore bile acid homeostasis.

**Microbiota Transplantation and Engineered Probiotics**

Fecal microbiota transplantation (FMT) has shown potential in restoring microbial diversity and reestablishing metabolite production—including SCFAs and secondary bile acids in IBD patients. However, clinical outcomes have been variable and depend heavily on donor compatibility and host factors [29]. Recent advances include the development of genetically engineered probiotics designed to synthesize beneficial molecules—such as butyrate or interleukin-10 (IL-10) directly within the gut. These "living therapeutics" represent a novel frontier in personalized IBD treatment, combining microbial engineering with host-specific therapeutic delivery [30].

**Conclusion**

The gut microbiota and their metabolites are increasingly recognized as central players in the pathogenesis of inflammatory bowel disease (IBD). Dysbiosis alters the production of key microbial metabolites—including short-chain fatty acids, tryptophan derivatives, bile acids, polyamines, and sulfur compounds—disrupting epithelial barrier integrity and immune regulation. These changes contribute to

chronic inflammation characteristic of both Crohn's disease and ulcerative colitis. Therapeutic approaches aimed at restoring metabolic balance, such as prebiotics, dietary fiber, targeted probiotics, bile acid receptor agonists, and fecal microbiota transplantation, have shown promising potential in preclinical and clinical studies. Moreover, the development of engineered probiotics and personalized microbiome-based therapies represents a novel frontier in IBD management. While challenges remain particularly the interindividual variability in microbiota composition and metabolite profiles, the integration of microbiome and metabolomic data into clinical practice may enable more precise, mechanism-based interventions. Continued research in this field is essential to advance microbiota-directed therapies as a core component of future IBD treatment strategies.

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