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Research Progress on the Regulation of the Gut Microbiota-Metabolism Axis by Probiotics for the Treatment of Inflammatory Bowel Disease

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Abstract

Inflammatory bowel disease (IBD), which primarily includes ulcerative colitis (UC) and Crohn's disease (CD), has seen a rapid rise in incidence in China in recent years. Traditional medications and biologics still face limitations such as limited targeting and a high risk of relapse upon discontinuation. Gut microbiota dysbiosis and the resulting metabolic disturbances are key pathological mechanisms underlying intestinal barrier damage and mucosal immune imbalance in IBD. This article focuses on the microbiota-metabolism axis to elucidate the physiological functions of three core metabolic pathways—short-chain fatty acids, bile acids, and tryptophan—and their pathological alterations in IBD. In addition, the regulatory mechanisms and clinical evidence of typical probiotics such as Clostridium butyricum, Escherichia coli, Faecalibacterium prausnitzii, Bifidobacterium and Limosilactobacillus reuteri on the above pathways were sorted out. Existing studies have shown that probiotics can play an anti-inflammatory role by refilling the exhausted metabolic pathways, repairing the intestinal epithelial barrier and regulating mucosal immunity, which is a safe and good auxiliary intervention for IBD. This article systematically reviews the above evidence to provide a reference for the subsequent mechanism research and clinical application of probiotics in IBD.

Keywords

inflammatory bowel disease, probiotics, gut microbiota-metabolic axis, short-chain fatty acids, bile acids, tryptophan

1. Introduction

Inflammatory bowel disease (IBD) is a chronic non-specific inflammatory disease affecting the gastrointestinal tract, mainly including ulcerative colitis (UC) and Crohn's disease (CD). The etiology of IBD is still unclear, but it is known that a variety of factors are involved in its pathogenesis, including genetic susceptibility, environmental triggers, intestinal immune disorders and intestinal flora disorders [1]. At present, as a newly industrialized country, China is experiencing a period of rapid increase in the incidence of IBD. If this trend continues, it is expected that the incidence of IBD in China will reach 12 to 26 cases per 100 000 people in the next 30 years, which will bring a heavy burden to the society [2]. Although current traditional medications, small-molecule inhibitors, and biologics can control clinical symptoms in some patients, they still have limitations such as limited targeting ability and recurrence after drug withdrawal, and it is urgent to develop safer adjuvant intervention methods in clinical practice [3].

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In this context, probiotics have received extensive attention due to their high safety and low side effects. Probiotics are live microorganisms that are beneficial to the host, and a number of pre-clinical and clinical studies have proved the good role of probiotics in IBD [4], which is closely related to intestinal microecology: intestinal microecological disorder is an important pathogenic link in the occurrence and development of IBD. Intestinal flora under normal conditions can produce key signaling molecules such as short-chain fatty acids, tryptophan-derived indole derivatives, and secondary bile acids [5]. These metabolites can act on intestinal epithelial cells and immune cells, and participate in the maintenance of intestinal barrier and the regulation of intestinal immune homeostasis. However, in the state of IBD, the levels of the above metabolites are significantly perturbed, which in turn magnifies the inflammatory damage of the intestine. Therefore, targeted repair of the microbiota-metabolism axis has also become a highly concerned direction in the field of IBD intervention research [6].

Accordingly, this paper takes the microbiota-metabolism axis as its central theme to elucidate the fundamental association between this axis and intestinal inflammation. It systematically reviews research progress on how probiotics regulate metabolic pathways involving short-chain fatty acids, bile acids, and tryptophan, analyzes the characteristics of synergistic interactions across multiple metabolic axes, and systematically summarizes the mechanisms of action of probiotic interventions in IBD, thereby providing a theoretical framework for subsequent investigations into the fundamental mechanisms and clinical applications of probiotics.

2. Mechanisms Linking the Gut Microbiota-Metabolism Axis to Intestinal Inflammation

2.1 Characteristics of Gut Microbiota Dysbiosis in IBD

Inflammatory bowel disease is primarily classified into two subtypes: ulcerative colitis and Crohn's disease. Patients with both conditions exhibit characteristic gut microbiota dysbiosis, and the disruption of microbiota homeostasis is involved throughout the entire process of IBD onset and disease progression [6]. Compared to healthy individuals, IBD patients exhibit a significant decrease in gut microbial α-diversity and a marked shift in overall microbial community structure. A vicious cycle develops between inflammatory damage and microbial dysbiosis; this imbalance is not limited to changes in individual bacterial species but represents a disturbance at the level of the community's overall function [7].

In terms of microbial abundance changes, commensal bacteria with anti-inflammatory metabolic functions are generally depleted: the abundance of Firmicutes such as Faecalibacterium and Roseburia, which produce short-chain fatty acids, is significantly reduced; populations of Bifidobacterium and Lactobacillus, which participate in bile acid metabolism, have shrunk; and Faecalibacterium and Lactobacillus, which mediate tryptophan metabolism to produce indole signaling molecules, are also downregulated [8]. At the same time, potential pro-inflammatory pathogens—such as adherent and invasive Escherichia coli (AIEC), Klebsiella pneumoniae, Staphylococcus mediterraneus, and Bacillus hypophilus—proliferate extensively [9]. These bacteria release pro-inflammatory components that disrupt tight junctions in the intestinal epithelium, continuously activate the mucosal immune response, further inhibit the colonization of beneficial commensal bacteria, and amplify intestinal inflammatory damage.

2.2 Three Major Microbiota-Metabolic Axes

Disruption of microbiota homeostasis directly alters the overall metabolic capacity of the gut microbiota, resulting in changes in the three major microbiota-metabolic axes: short-chain fatty acids, bile acids, and tryptophan. This section describes the normal physiological functions of these three metabolic axes and the pathological changes in these pathways in the context of IBD-associated microbiota dysbiosis.

2.2.1 Short-Chain Fatty Acid Metabolic Axis

In the gut of a healthy human, commensal anaerobic bacteria such as Bacteroides and Roseburia ferment indigestible dietary fiber to produce short-chain fatty acids (SCFAs) such as acetic acid, propionic acid, and butyric acid. SCFAs exert protective effects on the gut through two key pathways: on the one hand, they act as ligands to bind to G protein-coupled receptors (GPCRs) such as GPR41 and GPR43, and other G protein-coupled receptors; on the other hand, by inhibiting histone deacetylases (HDACs), they jointly regulate the

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differentiation of regulatory T cells (Tregs), maintain mucosal immune tolerance, and simultaneously upregulate tight junction proteins to ensure the integrity of the intestinal epithelial barrier [10]. Furthermore, SCFAs can regulate mucus secretion by goblet cells and the secretion of antimicrobial peptides, stabilize the gut microbiota, and suppress excessive inflammatory responses [11].

Compared with healthy individuals, multi-omics analyses show that SCFA biosynthetic pathways are significantly reduced in IBD patients, particularly those responsible for butyrate and acetate production—a finding consistent with the significant reduction in Faecalibacterium prausnitzii and the Roseburia genus [12]. However, butyrate is the primary energy supply substrate of colonic epithelial cells, and its insufficient content can cause energy metabolism disorders of colonic epithelial cells, inhibit intestinal epithelial cell proliferation and damage repair, down-regulate the expression of tight junction protein, increase intestinal mucosal permeability, and form a state of "intestinal leakage" [13]. In the absence of butyric acid-mediated epithelial protection, bacterial antigens and pathogen-associated molecular patterns in the intestinal lumen can penetrate the damaged epithelial barrier and invade the lamina propria of the mucosa, activate innate immune cells such as macrophages and dendritic cells, and then drive the release of TNF-α, IL-6, IL-17 and other pro-inflammatory factors, which directly destroy tight junction proteins. It further aggravates the occurrence of inflammation [14], forming a vicious cycle of flora derangement, metabolite deficiency and inflammation aggravation.

2.2.2 Bile Acid Metabolism Axis

Under normal conditions, bile acids are primarily exert physiological regulatory effects through two core receptors—FXR and TGR5—forming a multidimensional intestinal protective mechanism. Among them, FXR is widely expressed in intestinal epithelial cells, which can precisely regulate the absorption and synthesis of bile acids and maintain the homeostasis of intestinal bile acid pool by regulating the expression and activation of apical sodium-dependent bile acid transporter (ASBT) [15]. GPBAR1 (TGR5), as a G protein-coupled receptor, is highly expressed in the distal ileum and colon and can be preferentially activated by secondary bile acids such as LCA and DCA. TGR5 is dependent on immune cells such as macrophages and induces macrophage phenotype transformation from M1 to M2 through PKA-CREB signaling pathway, down-regulates IL-6, TNF-α, IFN-γ and increases IL-10, thus playing an anti-inflammatory role [16].

In contrast, patients with IBD exhibit significantly reduced gut microbial diversity, with a marked decrease in the abundance of key microbial communities encoding BSH and BAI. This impedes the processes of bile acid deconjugation and 7α-dehydroxylation in the gut, leading to a significant decline in microbial metabolic capacity [17]. These pathological changes directly result in the abnormal accumulation of primary and conjugated bile acids (CA, CDCA, TCA, GCA) in the patients' intestines, while secondary bile acids (DCA, LCA) with anti-inflammatory activity are significantly reduced. This has become a core characteristic of bile acid metabolism disorders in IBD, and this abnormal phenotype has been validated by multiple cohort studies in both adult and pediatric patients with CD and UC [18–20].

2.2.3 Tryptophan metabolism axis

In the physiological state, the direct metabolic pathway is the conversion of tryptophan to derivatives such as indole, indole-3-propionic acid, and indole-3-aldehyde by intestinal microorganisms. These derivatives are aryl hydrocarbon receptor (AHR) ligands. AHR is a ligand-dependent transcription factor that plays an important role in maintaining intestinal homeostasis. Indole derivatives can activate AhR signaling pathway, promote epithelial cell renewal, maintain the integrity of intestinal mucosal barrier, and act on many types of immune cells. In addition to the direct metabolic pathway, there are two tryptophan metabolic pathways in the host: the kynurenine pathway can be mediated by IDO1 to produce kynurenine and its downstream products. The end products of the pathways are involved in the regulation of a variety of host biological processes, involving inflammation and immune response. While the products of 5-HT pathway are mainly synthesized by enterochromaffin cells, which are involved in the regulation of intestinal peristalsis and endocrine signaling [21]. The above two pathways can be indirectly regulated by intestinal flora and cooperate with the indole-ahr pathway to maintain the stability of intestinal homeostasis.

In the IBD state, the ability of microorganisms to convert tryptophan to indole derivatives is impaired. Clinical cohort studies have shown that fecal tryptophan metabolites such as IPA, indole-3-acetic acid, and 3-indole-butyric acid in active IBD patients are significantly reduced, accompanied by a decrease in the

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abundance of IPA producing bacteria such as Peptostreptococcus and Clostridium [22], which is further confirmed by the summary of observational studies. A synthesis of observational studies further confirmed that serum levels of tryptophan and various microbiota-derived indoles are reduced in patients with IBD [23]. AhR ligand deficiency weakens the activation of AhR signaling in epithelial cells, and the epithelial repair and mucosal immune protection mediated by it is decreased. At the same time, intestinal inflammation upregulates mucosal IDO1 expression and enhances kynurenine pathway metabolism, leading to an increase in Kyn/Trp ratio and further destroying intestinal homeostasis [24].

In summary, the three microbiota-metabolic axes involving SCFAs, bile acids, and tryptophan play irreplaceable roles in maintaining intestinal immune homeostasis, barrier integrity and microecological balance. The above pathological mechanisms provide a clear theoretical basis for targeted intervention of probiotics.

3. The regulatory effects of probiotics on the three microbiota-metabolic axes and the effectiveness of intervention

In view of the pathological changes of the above three metabolic axes in IBD, the following is to elaborate how typical probiotics of each axis regulate the corresponding metabolic axis, and their clinical effects or future prospects.

3.1 Probiotics regulate the SCFA metabolic axis

Although UC and CD both belong to IBD, there are differences in the characteristics of bacterial dysbiosis, the phenotype of SCFA metabolic disorder and the evidence of probiotic intervention. Therefore, this section describes how probiotics regulate the SCFA metabolic axis separately in UC and CD.

3.1.1 Regulation of the Short-Chain Fatty Acid Metabolic Axis in UC by Probiotics

Patients with UC exhibit reduced gut microbiota diversity and depletion of SCFA-producing bacteria; a meta-analysis has quantitatively confirmed that levels of SCFAs, such as butyrate, are significantly reduced in the feces of IBD patients [25]. Insufficient short-chain fatty acid (SCFA) supply leads to impaired energy metabolism in colonic epithelial cells, downregulation of tight junction proteins, and increased mucosal permeability, which constitute the pathological targets for probiotic intervention. The following section introduces two typical probiotics whose core mechanism involves the SCFA metabolic axis.

Clostridium butyricum is a Gram-positive bacillus and a butyrate-producing commensal bacterium in the human gut [26]. As a key probiotic, Clostridium butyricum is widely used in many regions and exerts its anti-inflammatory effects primarily through the SCFA pathway. In intestinal metabolism, Clostridium butyricum produces SCFAs, primarily butyrate. SCFAs promote Treg differentiation by activating G protein-coupled receptor 41 and inhibiting HDAC function; they also induce the production of anti-inflammatory B10 cells, thereby enhancing intestinal immune regulation; simultaneously, Clostridium butyricum and SCFAs regulate inflammatory factors via the NF-κB and TLR4 signaling pathways; activation of TLR4 enhances the production of anti-inflammatory cytokines such as IL-10, suppresses pro-inflammatory mediators such as IL-1β and IL-6, and reduces the release of pro-inflammatory chemokines, thereby curbing the migration of immune cells to sites of inflammation and alleviating intestinal inflammation and tissue damage [27].

The anti-inflammatory mechanisms mediated by the SCFA axis described above provide a theoretical basis for Clostridium butyricum intervention in ulcerative colitis, and its clinical efficacy has also been validated. The randomized controlled trial conducted by Lin Jinxiang et al. on 122 UC patients showed that Clostridium butyricum monotherapy or combined with infliximab treatment could significantly improve the clinical remission rate, reduce the recurrence rate, and the overall treatment safety was good [28]. A 24-month randomized controlled trial conducted by Yasueda et al. in patients who underwent IPAA for UC showed that Clostridium butyricum MIYA-BM (9 tablets/day) significantly reduced the number of Escherichia coli in the intestine, regulated the microbial composition, and lowered the incidence of postoperative pouchitis [29].

Escherichia coli Nissle (EcN) 1917 is a nonpathogenic Gram-negative strain widely used in the treatment of various gastrointestinal diseases, particularly ulcerative colitis; it is also the only probiotic recommended in the ECCO guidelines as an effective alternative to mesalazine [30]. Mechanistic studies have shown that EcN improves mucosal barrier function by increasing SCFA levels in the intestine: Römermann et al. demonstrated

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in a mouse model of chronic inflammatory diarrhea that EcN-mediated increases in SCFA levels promote goblet cell proliferation and mucus secretion, enhance the expression of tight junction proteins, and thereby improve intestinal mucosal barrier function and alleviate mucosal inflammation; Acetic acid itself can also increase fluid absorption in the proximal colon and alkalinize the lumen, thereby maintaining normal colonic homeostasis [31]. These findings suggest that SCFA metabolism may be one of the key mechanisms through which EcN exerts its intestinal protective effects. Meanwhile, clinical studies have demonstrated the therapeutic value of EcN in maintaining remission in UC: a multicenter randomized controlled trial conducted by Kruis et al. showed that the relapse rate during maintenance of UC remission with EcN (2 capsules/day) was 36%, which was not statistically different from the 34% relapse rate observed with mesalazine (1,500 mg/day) [32]; A Phase II dose-finding randomized controlled trial conducted by Matthes et al. was the first to investigate the local therapeutic effect of rectal administration of EcN enema (Mutaflor) on distal UC; the results showed that the clinical remission rate (DAI ≤ 2) in the 40 mL dose group increased in a dose-dependent manner, and the time to remission was significantly shortened [33]. The above studies indicate that EcN demonstrates good efficacy and tolerability, whether used for oral maintenance of remission or rectal enema administration to induce remission in active distal UC. Its mechanism of action involves the regulation of the intestinal mucosal barrier through SCFA metabolism, providing multifaceted clinical evidence for probiotic intervention in UC.

In summary, there is already substantial clinical evidence supporting intervention targeting the SCFA metabolic axis in UC. The two strains mentioned above offer clinical options for probiotic intervention in UC at different mechanistic levels; further exploration of strain-specific mechanisms and personalized application strategies is still needed in the future.

3.1.2 Regulation of the Short-Chain Fatty Acid Metabolic Axis in CD by Probiotics

Compared with UC patients, CD patients exhibit a more pronounced decrease in fecal butyrate levels; butyrate is even considered a candidate metabolic biomarker for distinguishing CD from UC [34].

At the microbiome level, the abundance of butyrate-producing bacteria in the Firmicutes phylum is significantly reduced in the intestines of CD patients. As the primary energy substrate for colonic epithelial cells, butyrate plays a crucial role in intestinal physiology, defense against pathogen invasion, and immune system regulation; a deficiency of this substance in the gut directly increases the risk of CD onset [35], which also provides a clear pathological basis for probiotic-targeted interventions in CD. Based on this target, existing research has primarily focused on preclinical studies of next-generation butyrate-producing bacteria, among which Faecalibacterium prausnitzii is the most iconic strain in CD research. In 2008, Sokol et al. found through analysis of the gut microbiota of CD patients that the abundance of Faecalibacterium prausnitzii was significantly reduced in both the mucosa and feces of these patients [36]. Subsequent mechanistic studies further confirmed that this bacterium can directly ferment dietary fiber to produce butyrate, providing the primary energy substrate for colonic epithelial cells; simultaneously, butyrate itself can alleviate intestinal mucosal inflammation through mechanisms such as inhibiting the activation of the NF-κB transcription factor, upregulating PPARγ, and suppressing interferon-γ (IFN-γ) [37]. It should be noted that European guidelines do not support the use of probiotics for the treatment of CD; compared to UC, the overall level of clinical evidence for probiotics related to CD is lower [24]. Furthermore, the strictly anaerobic and extremely oxygen-sensitive growth characteristics of Faecalibacterium prausnitzii pose dual challenges for large-scale production and oral delivery [38], and to date, no approved formulations have been brought to market.

In summary, interventions targeting the SCFA metabolic axis in CD currently remain primarily in the early stages of clinical exploration involving next-generation butyrate-producing bacteria. Butyrate-producing bacteria, represented by Faecalibacterium prausnitzii, represent an important future direction; however, their clinical translation urgently requires large-scale randomized controlled trials and technological breakthroughs in anaerobic formulation.

3.2 Probiotics Regulating the Bile Acid Metabolism Axis

Given the pathological characteristic of impaired microbial bile acid metabolism in IBD, Bifidobacteria with functional bile salt hydrolase (BSH) activity have become an important subject of research regarding probiotics' regulation of the bile acid metabolism axis. In IBD patients, this impairment is characterized by

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decreased intestinal BSH activity, elevated levels of primary bile acids, and reduced levels of secondary bile acids [39, 40]; supplementation with these bacteria can directly restore this impaired pathway.

Mechanistically, BSH expressed by Bifidobacterium hydrolyzes the C-24 N-acyl bond, deconjugating glycine- or taurine-conjugated bile acids to form free bile acids; this gateway reaction is a prerequisite for subsequent 7α/β-dehydroxylation and 7α-dehydrogenation, ultimately leading to the formation of secondary bile acids [39].

Xiao et al. gave B. longum CECT 7894 to DSS colitis mice, and targeted metabolomics confirmed that fecal secondary bile acids (LCA, UDCA, isoLCA, isoalloLCA, etc.) increased, and were positively correlated with the abundance of bacteria containing BSH and 7α-dehydroxylase genes [41].

The biological effects of the increase in secondary bile acids after bifidobacterium intervention need to be explained through the intestinal epithelial FXR/TGR5 receptor pathway. BA, as a signaling molecule, regulates intestinal inflammation and barrier function through intestinal epithelial nuclear receptor FXR and membrane receptor TGR5 pathways: FXR activation plays an anti-inflammatory role and maintains the integrity of intestinal barrier [39], and TGR5 signaling is also involved in the regulation of inflammation. Multi-omics analysis of UC patients with ileal pouches and FAP controls showed that LCA/DCA and the bacteria that produce them, Ruminococcaceae were decreased in UC patients. Secondary BA supplementation reduced inflammation in three murine colitis models, and this anti-inflammatory effect was partially dependent on the TGR5 receptor [42]. Together, the above evidence suggests that Bifidobacterium may regulate mucosal inflammation through the FXR/TGR5 axis by restoring BSH-mediated deconjugation and reconstructing the secondary bile acid pool.

Clinically, probiotics containing Bifidobacterium are effective in inducing remission in active UC but are ineffective in maintaining remission. A meta-analysis incorporating 6 randomized controlled trials involving 424 patients with active UC showed a relative risk of 1.73 for induction of remission (95% CI 1.23–2.43, p=0.002), indicating that such probiotics are effective in promoting remission in patients with active ulcerative colitis [43]; In contrast, the B-FLORA trial by Matsuoka et al., which enrolled 195 patients with UC in remission and followed them for 48 weeks, administered fermented milk containing the Bifidobacterium breve Yakult strain daily. The results showed that recurrence-free survival was not different from that of the placebo group (HR 1.16, 95% CI 0.63–2.14, p=0.643), and the study was terminated early due to lack of efficacy [44].

Unlike the short-chain fatty acid axis, which has candidate strains for both UC and CD, the current evidence for probiotics targeting the bile acid axis is limited to UC; while no clinical investigations of strains targeting this axis have been conducted for CD; furthermore, the endpoints of the aforementioned human trials were all clinical activity indices, CRP, or recurrence rates, and none simultaneously measured fecal or serum bile acid profiles. Therefore, the causal mechanism by which Bifidobacterium exerts its effects via the bile acid axis has not yet been established in humans, and whether it acts through the bile acid metabolism axis remains to be verified by clinical studies with the bile acid axis as the endpoint.

3.3 Probiotic Regulation of the Tryptophan Metabolic Axis

In patients with active IBD, levels of various microbiota-derived indoles in feces and serum are significantly reduced, and colonic expression of AhR and IL-22 is diminished [23, 45]; this defect in the ligand-AhR-IL-22 axis constitutes the pathophysiological basis for intervention in the tryptophan metabolic axis [46]. Among the probiotics known to exogenously produce indole, a relatively systematic body of evidence is available for Limosilactobacillus reuteri. Therefore, this bacterium will serve as the representative for the following discussion.

In the DSS colitis model, a relatively comprehensive mechanism has been elucidated for live L. reuteri D8 (the heat-inactivated strain does not exhibit this effect), confirming that its mucosal protective effect depends on the tryptophan metabolic pathway: D8 metabolizes dietary tryptophan into indole-3-aldehyde (IAld), which acts on AhR to stimulate IL-22 secretion; this effect can be blocked by the AhR inhibitor CH-223191.IL-22 subsequently induces STAT3 phosphorylation, accompanied by an increase in the number of $Lgr5^{+}$ intestinal stem cells and lysozyme-positive Paneth cells, thereby accelerating the proliferation of damaged epithelium and mucosal repair [46].

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Regarding the efficacy of IBD interventions, mouse studies have demonstrated that treatment with L. reuteri R2LC or 4659 significantly reduces intestinal mucosal inflammation in a DSS-induced UC mouse model. Furthermore, in probiotic therapy, treatment with L. reuteri can reverse DSS-induced thinning of the adherent mucus layer and significantly reduce inflammatory markers[47]. Clinically, a randomized controlled trial conducted by Oliva et al. enrolled 40 children with active distal UC. After 8 weeks of rectal infusion of L. reuteri ATCC 55730 (1×10^{10} CFU/day) in addition to mesalazine, the treatment group showed significantly better endoscopic and histological scores than the placebo group; the expression of pro-inflammatory factors in the rectal mucosa—TNF-α, IL-1β, and the chemokine IL-8—decreased significantly, while the mucosal expression of the anti-inflammatory factor IL-10 increased, indicating that treatment with L. reuteri alleviated inflammation in ulcerative colitis.However, this study did not concurrently measure the fecal indole profile or AhR target genes in the colon [48].

Overall, the causal chain by which L. reuteri modulates IBD via the tryptophan-AhR axis has currently been validated only in the DSS colitis model; its efficacy and mechanisms in humans still require confirmation through clinical studies using tryptophan metabolites and the AhR pathway as endpoints.

4. Conclusion and Outlook

In summary, dysbiosis and the resulting disruptions in the three metabolic axes—short-chain fatty acids, bile acids, and tryptophan—constitute a major pathological basis for intestinal barrier damage and mucosal immune imbalance in IBD, and represent a critical juncture in the vicious cycle of dysbiosis-induced inflammation amplification. In IBD, the depletion of SCFA-producing commensal bacteria not only impairs energy supply to and repair of the colonic epithelium but also weakens Treg differentiation and barrier protection; following intestinal barrier leakage, bacterial antigens penetrate the barrier, activating macrophages and dendritic cells to release pro-inflammatory factors such as TNF-α and IL-6. The atrophy of BSH and 7α-dehydroxylating microbiota leads to the accumulation of primary and conjugated bile acids and a reduction in secondary bile acids such as DCA and LCA. The role of FXR in maintaining bile acid pool homeostasis is disrupted. The anti-inflammatory signal of TGR5 promoting M2 polarization of macrophages and down-regulating pro-inflammatory factors through PKA-CREB was also lost. The decrease of indole-producing commensal bacteria leads to the lack of AhR ligands such as IPA and IAld, which weakens epithelial renewal and mucosal immune protection. Inflammation also up-regulated IDO1, enhanced kynurenine pathway compensation, and increased Kyn/Trp ratio. These three axes act synergistically to disrupt the barrier and amplify inflammation. Within this network, probiotics demonstrate intervention potential through distinct pathways: via the SCFA axis, Clostridium butyricum—which primarily produces butyrate—promotes the differentiation of Treg and B10 cells via GPR41/HDAC and inhibits the release of pro-inflammatory factors through the NF-κB/TLR4 pathway; EcN, meanwhile, promotes mucus secretion by goblet cells and the expression of tight junctions by elevating intestinal SCFA levels; Faecalibacterium prausnitzii, as a next-generation butyrate-producing bacterium, has also demonstrated anti-inflammatory activity in animal models, but has not yet been developed into a drug due to strict anaerobic growth requirements and delivery technology constraints. Via the bile acid axis, Bifidobacterium replenishes the secondary bile acid pool through BSH activity and modulates mucosal inflammation via the FXR/TGR5 pathway. Via the tryptophan axis, Lactobacillus reuteri metabolizes tryptophan to produce IAld, which accelerates epithelial repair through the AhR-IL-22-STAT3 pathway. The aforementioned strains have demonstrated efficacy in both animal models and small-sample clinical trials, suggesting that probiotics represent a class of adjunctive interventions for IBD with good safety profiles and well-defined targets.

However, gaps remain in the current evidence. First, the three axes are not independent pathways but are characterized by complex cross-regulation and synergistic interactions. Therefore, in addition to the single-strain probiotics explored in current studies, multi-strain probiotic combinations also represent a highly promising future research direction in this field. At the same time, meta-analyses suggest that multi-strain probiotic formulations are superior to single-strain formulations in inducing remission and preventing relapse in UC [24], indicating that multi-strain probiotics covering multiple metabolic axes may represent a more optimal approach; however, the combination and ratio of strains still require systematic optimization. Second, most human studies use clinical activity indices as endpoints, with few studies using concurrent measurements of fecal and serum SCFAs, bile acids, and indole profiles as endpoints; thus, the causal chain of probiotic effects via metabolic pathways has not yet been fully established in humans. Third, the evidence for probiotics

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in CD is weak: the ECCO notes that there is no clear evidence that probiotics can be used to induce remission in CD or prevent postoperative recurrence [49]. A systematic review by the AGA similarly indicates that there is no evidence supporting the ability of probiotics to induce or maintain disease remission in Crohn's disease in adults and children [50]. Therefore, the clinical value of probiotics in CD remains unclear. Fourth, there is significant individual variability in the efficacy of probiotics: due to differences in baseline microbiota, genetic background, and disease stage, responses to the same strain vary significantly among patients; at the same time, existing studies lack uniform standards for key parameters such as strain selection, optimal dosage, and treatment duration [51].

In the future, the application of probiotics in IBD is expected to evolve toward precision and multi-strain probiotic formulations. Individualized strain combinations based on patients' baseline microbiota and metabolic phenotypes will overcome the bottlenecks of significant interindividual variability in efficacy and the lack of unified standards for dosage and treatment duration; composite probiotics covering multiple metabolic axes, targeted delivery formulations for butyrate-producing anaerobes, and novel forms such as engineered bacteria and postbiotics are also expected to provide new treatment options for the CD population. Conducting mechanism-of-action studies with fecal and serum metabolomic profiles as endpoints will further clarify the causal chain through which these interventions exert their effects via the microbiota-metabolic axis, thereby enabling this adjunctive approach with a good safety profile to play a more definitive role in the comprehensive management of IBD.

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Conflicts of Interest

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