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REVIEW

The Role of Gut Microbiota on Intestinal Fibrosis in Inflammatory Bowel Disease and Traditional Chinese Medicine Intervention

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Abstract: Inflammatory bowel disease (IBD) is a chronic, relapsing inflammatory disorder of the intestine, frequently complicated by intestinal fibrosis. As fibrosis progresses, it can result in luminal stricture and compromised intestinal function, significantly diminishing patients' quality of life. Emerging evidence suggests that gut microbiota and their metabolites contribute to the pathogenesis of IBD-associated intestinal fibrosis by influencing inflammation and modulating immune responses. This review systematically explores the mechanistic link between gut microbiota and intestinal fibrosis in IBD and evaluates the therapeutic potential of traditional Chinese medicine (TCM) interventions. Relevant studies were retrieved from PubMed, Web of Science, Embase, Scopus, CNKI, Wanfang, and VIP databases. Findings indicate that TCM, including Chinese herbal prescriptions and bioactive constituents, can modulate gut microbiota composition and microbial metabolites, ultimately alleviating intestinal fibrosis through anti-inflammatory, immunemodulatory, and anti-fibrotic mechanisms. These insights highlight the potential of TCM as a promising strategy for targeting gut microbiota in the management of IBD-associated fibrosis.

Keywords: inflammatory bowel disease, intestinal fibrosis, intestinal inflammation, gut microbiota, traditional Chinese medicine

Introduction

Inflammatory bowel disease (IBD), encompassing Crohn's disease (CD) and ulcerative colitis (UC), is a chronic inflammatory disorder of the intestine. Although its exact cause remains unclear, genetic susceptibility, environmental factors, and immune dysregulation are known to contribute to its onset.[1] The gut microbiota plays a vital role in maintaining intestinal homeostasis, supporting gut barrier integrity, and regulating systemic inflammation. Numerous studies have demonstrated that the intestinal microbiota can exert either detrimental or beneficial effects on disease progression.[2,3] Gut microbiota dysbiosis can promote intestinal inflammation, impaire barrier function, and stimulate the overgrowth of pathogenic bacteria, all of which may contribute to gastrointestinal disorders. The gut microbiota and its metabolites directly or indirectly interact with the intestinal epithelium, influencing intestinal immunity, inflammatory responses, and mucosal barrier function. This dysbiosis leads to intestinal dysfunction and plays a role in the onset and progression of intestinal diseases. Furthermore, the intestinal microbiota of patients with intestinal fibrosis differs significantly from that of healthy individuals.[4] Animal models have also demonstrated that specific intestinal bacteria can induce intestinal fibrosis.[5] Intestinal microbiota metabolites influence intestinal function and are closely associated with IBD.[6] While intestinal microbiota and their metabolites contribute to the onset and advancement of intestinal fibrosis, certain microbiota elements might be beneficial.[7]

Intestinal fibrosis is the main manifestation of structural damage in IBD patients.[8] IBD-associated intestinal fibrosis primarily occurs in CD but is less commonly seen in UC, which is typically considered an inflammatory process confined to the mucosal and submucosal layers. However, recent research has shown that chronic inflammation in UC can lead to

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localized fibrosis.[9] A study of 706 UC tissue cross-sections identified submucosal fibrosis exclusively in inflamed regions, with colectomy samples showing a strong correlation between fibrosis and inflammation.[10] These findings suggest that submucosal fibrosis and thickening of the muscularis mucosae are prevalent pathological features of progressive UC. Patients who underwent surgery to relieve intestinal stricture still experienced recurrence of stenosis in 70% of cases, with more than half requiring additional surgery. This recurrent issue significantly impacts their quality of life.[11,12] Excessive accumulation of extracellular matrix (ECM) is a hallmark of intestinal fibrosis and a primary cause of structural damage in IBD.[13] The pathogenesis of intestinal fibrosis in IBD is complex, involving chronic inflammation, microbial factors, and even dietary influences that provide the body with persistent harmful stimuli. In response to tissue injury, the body initiates a self-repair process.[14] Intestinal microbiota dysbiosis, impaired barrier function, and the activation of cytokines and growth factors, along with the triggering of immune responses, all contribute to excessive ECM deposition and metabolic imbalance (Figure 1). Currently, there are no clinically effective therapies for intestinal fibrosis, making prevention the most viable strategy.[14] Although IBD treatments like aminosalicylates and immunosuppressants can reduce inflammation, they do not relieve fibrostenotic obstruction. Biologics, such as anti-tumor necrosis factor, may promote ulcer healing but could also contribute to fibrostenosis.[15] Therefore, urgent research is needed to find effective treatments for IBD-related intestinal fibrosis. Emerging evidence suggests that modulating gut microbiota balance holds promise as a potential therapeutic approach.

Traditional Chinese Medicine (TCM), rooted in the principles of holism and syndrome differentiation, has been widely used to treat gastrointestinal disorders with proven therapeutic efficacy. The ancient Chinese medical texts record numerous formulas that are still used in clinical practice today. With the development of modern research techniques, the mechanisms by which Chinese medicine exerts its effects are gradually being explained, and many bioactive compounds from Chinese herbs have been extracted and applied. Recent studies have demonstrated that TCM formulations and bioactive compounds possess

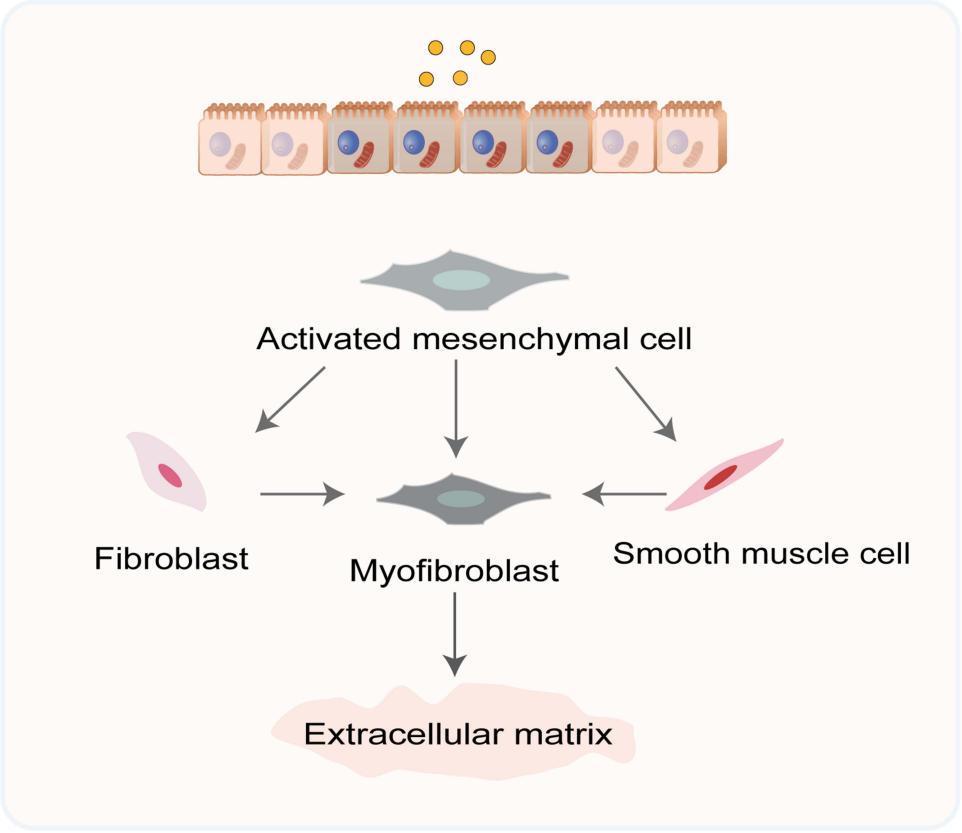

Figure 1 Activated mesenchymal cells and extracellular matrix. Intestinal fibroblasts proliferate and become activated in response to persistently harmful stimuli. It expedites the conversion of smooth muscle cells and fibroblasts into myofibroblasts, as well as the conversion of endothelial and epithelial cells into mesenchymal cells, leading to an accumulation of extracellular matrix products.

therapeutic potential for various fibrotic diseases. Several studies suggest that TCM interventions modulate intestinal microbiota and their metabolites, which are closely linked to inflammation and fibrosis. Beyond microbiota regulation, other strategies for managing IBD-related fibrosis include inhibiting profibrotic signaling pathways and modulating immune responses. This review aims to explore the role of gut microbiota in the pathogenesis of intestinal fibrosis in IBD and evaluate the therapeutic potential of TCM in addressing this complex condition.

Methods

To ensure a thorough and systematic review of TCM in modulating gut microbiota and its metabolites for the treatment of intestinal fibrosis in IBD, we searched multiple electronic databases, including PubMed, Web of Science, Embase, Scopus, China National Knowledge Infrastructure (CNKI), and Wanfang. The search was conducted up to September 2024, with no language constraints. The following search terms and combinations were used: ("inflammatory bowel disease" OR "IBD" OR "Crohn's disease" OR "ulcerative colitis") AND ("intestinal fibrosis" OR "fibrosis" OR "stenosis") AND ("traditional Chinese medicine" OR "Chinese herbal medicine" OR "Chinese medicine formula" OR "TCM monomers" OR "bioactive components") AND ("gut microbiota" OR "intestinal microbiota" OR "microbial metabolites"). Inclusion Criteria: Research on the effects of TCM, Chinese herbal formulations, or active components of Chinese herbs on intestinal fibrosis in IBD; Original research publications, covering in vitro, in vivo, and clinical trials. Systematic reviews and meta-analyses on the topic. Exclusion criteria: The exclusion criteria include studies that are unrelated to IBD-associated intestinal fibrosis; Case studies, conference abstracts, letters, editorials, and non-peer-reviewed papers; Studies with insufficient experimental data or mechanistic insights. Two reviewers conducted the selection procedure independently in order to verify accuracy and minimize bias. Discrepancies were handled by discussing or consulting with a third reviewer. Furthermore, the references of selected research were manually checked for potentially relevant literature.

Intestinal Fibrosis and the Role of the Gut Microbiota

Intestinal Microbiota Dysbiosis in IBD

Microbiota in the human intestine have an important effect on both health and disease.[16] Alterations in the diversity and composition of the gut microbiota are major contributors to IBD.[17,18] The mucosal barrier in the non-inflamed ileum of UC patients becomes impaired, leading to reduced mucus secretion, enhanced bacterial infiltration, and a reduction in bacterial diversity due to mucosal barrier defects and aberrant bacterial colonization.[19] The microbiological, chemical, mechanical, and immunological barriers constituting the mucosal layer of the intestine collaboratively contribute to the development and prevention of IBD (Figure 2). Intestinal barrier failure is a major cause of illness recurrence in individuals with IBD.[20] The gut microbiota acts as a biological barrier and regulates the production of important chemical barriers, such as mucin and antimicrobial peptides (AMPs).[21] The intestinal microbiota compositions of healthy individuals and those with IBD are different. Studies have shown that individuals with IBD have a higher percentage of pathogenic bacteria such as *Bacteroides fragilis, Escherichia coli*, and *Clostridium clostridioforme*, and a lower proportion of beneficial bacteria, such as *Bifidobacterium* and *Lactobacillus*.[22–24] Research on the potentially harmful microbiota associated with intestinal fibrosis has been ongoing for many years, with initial tests demonstrating that bacterial suspensions applied to the intestinal wall elevate tissue levels of transforming growth factor-β1 (TGF-β1) and collagen.[25] Myofibroblasts and fibrocytes which respond to flagellin, a bacterial component, secrete large amounts of ECM.[26] However, some bacteria can exert beneficial effects. *Lactobacillus acidophilus* can reduce α-smooth muscle actin (α-SMA) levels and collagen I accumulation.[27] The microbiota plays a critical role in the progression of IBD, with its metabolites potentially acting as key regulators of the disease's pathogenesis.[28] The intestinal microbiota produces several metabolites, including lipopolysaccharide (LPS), bile acids (BAs), tryptophan, and short-chain fatty acids (SCFAs), which significantly influence intestinal inflammation and fibrosis. Individuals with IBD exhibit disruption in BA metabolism. According to previous research, IBD patients have a different fecal BA pool than healthy controls, caused by an increase in primary bile acids and a reduction in secondary bile acids (SBAs).[22] Supplementation with SBAs can reduce intestinal inflammation in murine models of colitis.[29] In patients with IBD, inflammatory cells and dysbacteriosis are elevated, along with reduced levels of SCFAs.[30] Enema fluid containing butyrate or glutamine reduces

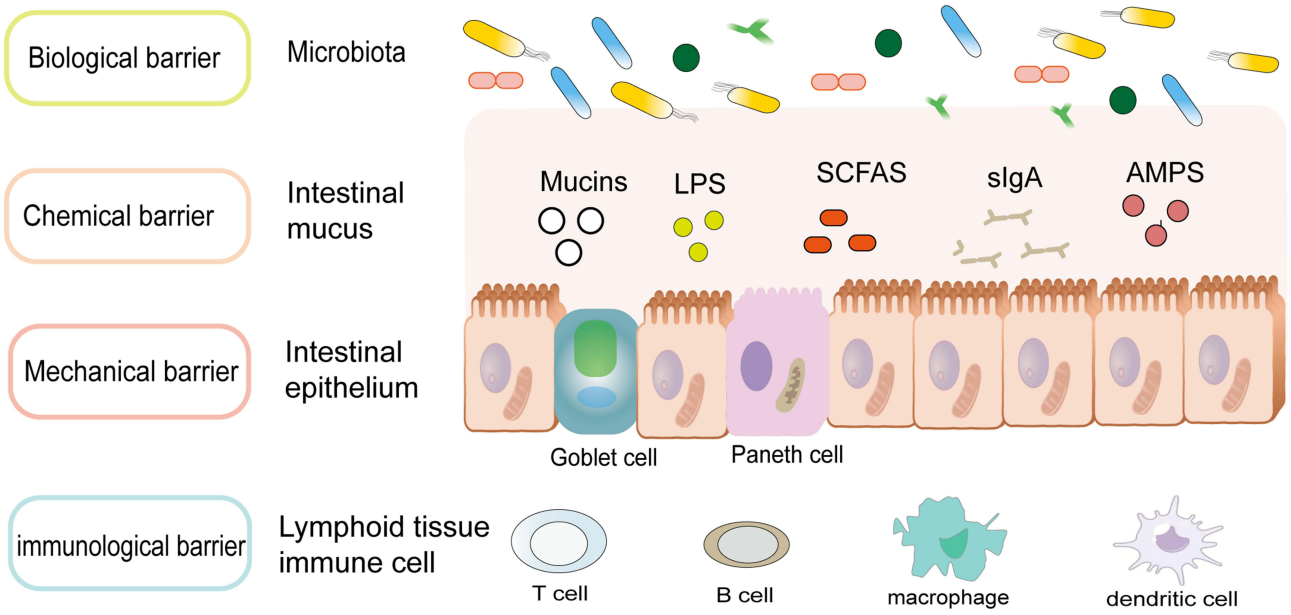

Figure 2 Intestinal mucosal barriers. The intestinal mucosal barrier consists of four components: microbial, mechanical, chemical, and immunological barriers, which function synergistically to maintain intestinal homeostasis and are critically involved in the development and management of inflammatory bowel disease.

fibrosis and inflammation in experimental diverted colitis.[31] Alterations in tryptophan metabolism are associated with gut microbial dysbiosis and the severity of illness.[32] LPS activates intestinal fibroblasts, leading to increased collagen synthesis.[33] Therefore, the gut microbiota and its metabolites are closely associated with the pathogenesis of IBD.

Mechanisms Underlying Gut Microbiota-Mediated Intestinal Fibrosis

Intestinal microbiota plays a crucial role in the initiation and progression of intestinal fibrosis by influencing barrier function, immune responses, and fibroblast activation.[18] An imbalance in the host‘s intestinal flora, characterized by a significant increase in pathogenic bacteria, leads to the production of harmful molecules that directly damage the intestinal cells. The intestinal mucosa and epithelial cells are severely damaged, making them more susceptible to microbial damage. These processes involve the activation of fibroblasts and the excessive accumulation of extracellular matrix. Research on intestinal fibrosis commonly uses bacteria-induced IBD models, such as *Adherent-invasive Escherichia coli* (AIEC) and *Salmonella enterica serovar* infection mouse models.[34] AIEC infection has been shown to cause persistent intestinal inflammation and fibrosis in mice.[35] AIEC may suppress exosomal miRNA lethal-7b (let-7b) produced by intestinal epithelial cells, thereby facilitating the fibrotic phenotype of intestinal macrophages and, consequently, fibrosis.[36] Elimination of the myeloid differentiation primary response gene 88 in a *Salmonella*-induced colitis model reduces intestinal fibrosis.[37] Creeping fat is closely associated with intestinal fibrosis.[38] *Clostridium innocuum* in mesenteric adipose tissue induces M2 macrophages, which secrete pro-fibrotic factors like TGF-β.[39] The intestinal microbiome directly and indirectly activates fibroblasts via epithelial or immune cells.[40] Certain molecules from the microbiota can affect fibroblast transcription, leading to intestinal fibrosis.[37,41] Myofibroblasts and fibrocytes that react to flagellin, a bacterial component, secrete large amounts of ECM. Consequently, it appears that potential pathogens contribute significantly to intestinal fibrosis. Furthermore, symbiotic bacteria can transform into pathogenic forms, penetrating the epithelium and triggering immune responses that disrupt junctional proteins, thereby increasing permeability and promoting a “leaky gut”.[42] “Leaky gut” is associated with intestinal inflammation, which exposes mesenchymal cells to luminal components and inflammatory mediators.[43] Prolonged exposure of mesenchymal cells to this inflammatory environment can lead to their activation and contribute to the development of intestinal fibrosis. In addition, the induction of cytokines may contribute to microbiota-driven intestinal fibrosis.[44] Cytokine induction contributes to microbiota-driven fibrosis, with TL1A-mediated fibroblast activation correlating with specific bacterial presence. Th17 cells produce amphiregulin, further driving fibrosis.[45,46] The formation of multiple ECMs proteins is

significantly induced by TGF-β1. As an essential part of the TGF-β/Smad signaling pathway, the Smad protein family acts as a signal converter and is located downstream of TGF-β. Matrix metalloproteinases (MMPs) and tissue inhibitors of matrix metalloproteinases (TIMPs) are among the pro- and anti-fibrotic factors that regulate intestinal degradation and repair.[47] To a substantial extent, the ECM can be broken down by MMPs and TIMPs control MMPs' activity. TGF-β may affect the balance between MMPs and TIMPs. Endogenous antimicrobial peptides suppress TGF-β1, insulin-like growth factor-1 (IGF-I), and collagen production through mitogen-activated protein kinase (MAPK)-dependent pathways.[48,49]

Microbial metabolites also play a key role. LPS stimulates the nuclear factor κ-B (NF-κB) pathway via Toll-like receptor 4 (TLR4), while TLR4 deficiency reduces fibrosis, TGF-β levels, and collagen synthesis.[50] High levels of serum succinate and succinate receptor 1 (SUCNR1) were found in excised intestinal tissue and intestinal fibroblasts from CD patients. SUCNR1 signaling has been shown to exacerbateinflammation and fibroblast activation in patients with CD.[51] The link between CD and reduced hydrogen sulfide (H2S) synthesis, as well as enhanced intestinal microbial hydrogen sulfide production, is mediated by assimilatory sulfate reduction (ASR). The microbial ASR-mediated metabolism of dietary sulfate is crucial for colitis.[52] Low H2S levels reduce inflammation, whereas excessive H2S disrupts mucus integrity.[53] Although some metabolites are associated with intestinal fibrosis in IBD, research indicates that specific metabolites can mitigate intestinal inflammation and alleviate fibrosis. Beneficial metabolites like indoleacrylic acid (IA) from Peptostreptococcus enhance epithelial barrier integrity, while aryl hydrocarbon receptor (AHR) activation by tryptophan and SCFAs influences inflammation.[54,55] Regulatory T (Treg) cells play a key role in maintaining immune balance in the gut and controlling excessive pro-inflammatory responses. Normal BAs metabolism is essential for the regulation of TH17 and Treg differentiation.[56] Indole-3-propionic acid (IPA) inhibits pregnane X receptor (PXR) to reduce inflammation,[57] while SCFAs enhance forkhead transcription factor p-3 (Foxp3) expression and Treg function via G protein-coupled receptor 43 (GPR43) protecting against colitis.[58,59] IBD fibrosis results from interactions among metabolites and pathways, encompassing pro- and anti-inflammatory as well as pro- and anti-fibrotic mechanisms at various stages of the disease.[60] The microbiota and its metabolites influence the intestinal barrier, activate the inflammatory response, and disrupt the immune system, leading to fibroblast activation and excessive ECM production (Figure 3). Potential treatments may involve modulating microbial metabolites by enhancing beneficial ones, reducing harmful ones, or targeting their receptors. Further research is needed to optimize microbiota-based therapies for IBD fibrosis.

Regulating the Microbiota to Alleviate Intestinal Fibrosis

Current evidence suggests that diet plays a dual role in IBD, influencing disease risk and activity by modulating gut microbiota and intestinal inflammation. Due to impaired immune response, intestinal permeability, and changes in the mucosal layer, diet may cause microbial dysbiosis and intestinal inflammation.[61] Western diets, rich in sugar, fat, and processed ingredients, contribute to microbial dysbiosis, increased intestinal permeability, and fibrosis progression.[62–65] In contrast, specific dietary interventions, such as the Crohn's Disease Exclusion Diet (CDED), Crohn's disease-TREAT (CD-TREAT) diet,[66] Ulcerative Colitis Exclusion Diet (UCED),[67] and the Mediterranean diet,[68] have been shown to restore microbial balance and support intestinal health. Suskind et al found that switching to a low-"fermentable oligo-, di-, and mono-saccharides and polyols" (FODMAP) diet drastically affected the microbiota composition.[69] Additionally, nutrients with anti-fibrotic properties can target key receptors like γ (PPARγ),[70] AhR,[71] and VDR,[72] offering potential therapeutic benefits. While unhealthy diets may exacerbate intestinal fibrosis, dietary modifications can help mitigate these effects by reshaping gut microbiota and its metabolites.

A decrease in beneficial microbiota is more strongly linked to the onset of IBD than an increase in pathogenic microbiota. Beneficial microbes, including those involved in butyrate generation, such as *Faecalibacterium, Ruminococcus Christensenellaceae, Methanobrevibacter*, and *Butyricicoccus*, were much less abundant in CD patients than in normal controls.[23,73] Butyrate preserves epithelial cell integrity and intestinal homeostasis, which are essential for preventing intestinal diseases.[74,75] *Akkermansia muciniphila*, crucial for gut barrier integrity, has emerged as a potential therapeutic target.[76] Probiotics like *Lactobacillus plantarum LC27* and *Bifidobacterium longum LC67* can restore microbial balance, reduce inflammation, and enhance IBD therapy outcomes.[77] *Bifidobacterium breve (B. breve) H4-2* and *H9-3* can alleviate colitis induced by dextran sulfate sodium (DSS).[78] Prebiotics, including oligosaccharides and

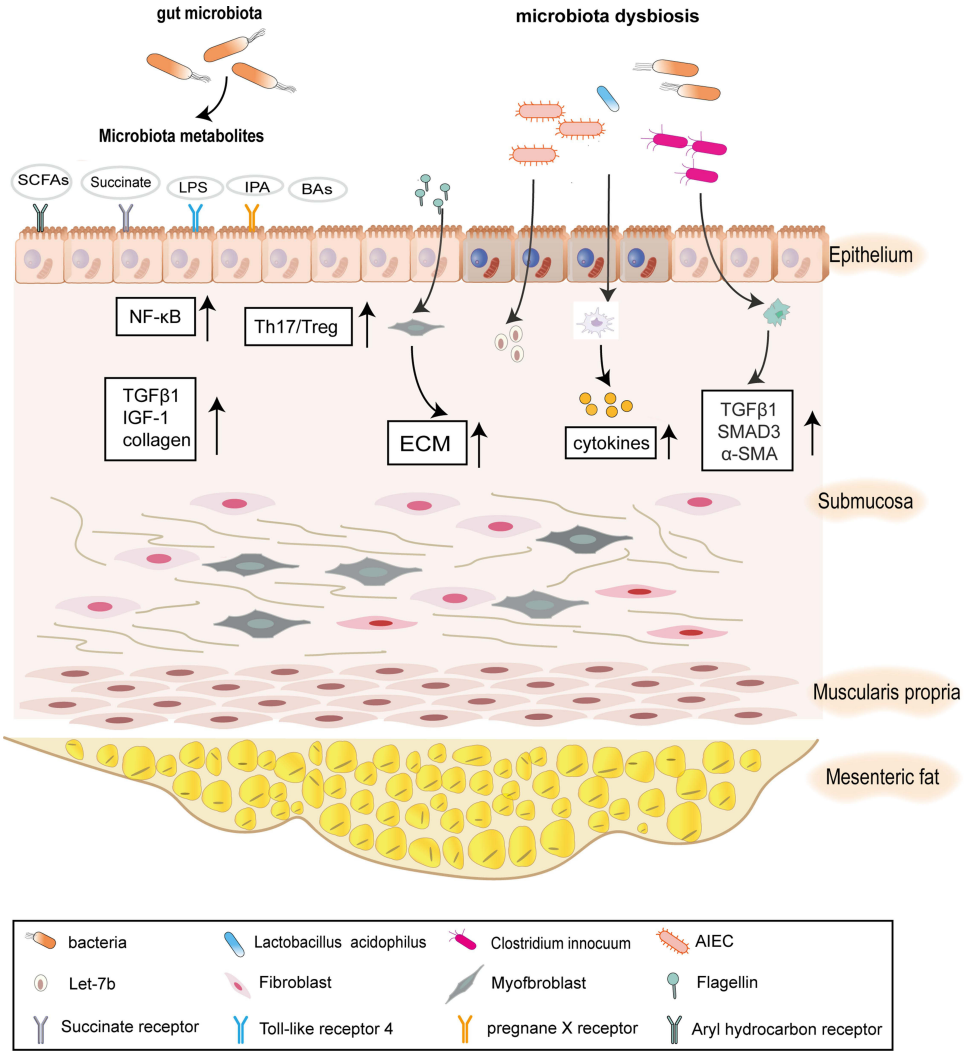

Figure 3 The microbiota and intestinal fibrosis. The intestinal microbiota affects the initiation and advancement of intestinal fibrosis in multiple ways. *Lactobacillus acidophilus* and other advantageous intestinal bacteria decrease, while pathogenic bacteria proliferate, leading to increased levels of SMA and collagen deposition. *Clostridium innocuum* causes intestinal fibrosis by inducing M2 macrophages, which inducepro-fibrotic substances like TGF-β. *Adherent-invasive Escherichia coli* (AIEC) promotes fibrosis. Myofibroblasts and fibrocytes that react to flagellin, a bacterial component, secrete increased amounts of ECM. Microbiota-derived metabolites may significantly influence fibrotic outcomes. Succinate, via the succinate receptor (SUCNR1) signaling, intensifies inflammation and fibroblast activity. LPS interacts with Toll-like receptor 4, thereby activating NF-κB and enhancing collagen production. Tryptophan metabolites, SCFAs, and other compounds may modulate inflammation through pathways involving AHR activation. The intestinal fibrosis and fibroblast proliferation mediated by tumor necrosis factor-like cytokine A (TL1A) are contingent upon the microbiota.

inulin,[79,80] support beneficial bacteria, while synbiotics facilitate probiotic colonization.[81] Research indicates that fecal microbiota transplantation (FMT) is an efficacious intervention for IBD worsened by *Clostridium difficile* infection and reinstates a variety of intestinal microbiota.[82] By promoting short-chain fatty acid production, modulating inflammatory responses, and reinforcing the intestinal barrier, probiotics, prebiotics, and synbiotics present promising strategies for alleviating intestinal inflammation and fibrosis.[83]

Several pharmaceuticals have shown anti-fibrotic effects in animal studies (Table 1). The *Lactococcus lactis*-derived Hsp65 antigen reduced IL-6 and TGF-α while increasing IL-10 in chronic intestinal inflammation models, suggesting potential therapeutic benefits.[84] TL1A activates fibroblasts and regulates the intestinal immune response and tissue remodeling, while TL1A-induced intestinal fibrosis relies on the intestinal microbiome.[45] The anti-TL1A antibody (PRA023) has demonstrated higher endoscopic response and clinical remission rates in moderate-to-severe Crohn's disease. Nicotinamide mononucleotide (NMN) therapy modulates gut microbiota and mitigates radiation-induced intestinal fibrosis.[85] Fibroblast growth factor 19 (FGF19) deficiency in Crohn's disease affects microbiome composition and inflammation, while FGF19-M52, via FXR, alters bile acid metabolism and protects against intestinal

Table 1 Anti-Intestinal Fibrosis Drugs Based on Microbiota

Agent	Mechanism	Reference
Hsp65	*Lactococcus lactis* antigen; IL-6 and TGF-α↓, IL-10↑.	[84]
PRA023	TL1A-induced intestinal fibrosis relies on the intestinal microbiome. Anti-TL1A antibody.	[45]
NMN	Changing the intestinal microbiota and regulating microorganism's metabolic function.	[85]
FGF19	Intestinal microbiota; BAs.	[86]
EVs secreted by L. john	*Lactobacillus johnsonii* EVs; EVs activate M2 macrophages, thereby inhibiting NLRP3 activation in intestinal epithelial cells.	[87]

inflammation.[86] *Lactobacillus johnsonii* extracellular vesicles (EVs) suppress NLRP3 activation, contributing to anti-fibrotic effects. Exploring gut microbiota-related antifibrotic therapies remains a promising research direction.[87] Therefore, exploring antifibrotic therapies targeting gut microbiota and its metabolic byproducts offers a promising and feasible approach for treating IBD-associated intestinal fibrosis.

The Effect of TCM on Gut Microbiota and Intestinal Fibrosis

The Intestinal Microbiota as a Target in TCM for Treating Organ Fibrosis

As research on anti-fibrosis treatments has progressed, the benefits and unique aspects of TCM in the treatment of fibrotic disorders have become increasingly apparent. TCM believes that chronic inflammation is accompanied by latent pathogenic factors that hinder the flow of qi, blood, and water, leading to the formation of pathological products. Qi stagnation, blood stasis, and phlegm-dampness are key pathological factors in fibrotic diseases, and the elimination of these factors has become a central concept in TCM for the treatment of such disorders.[88] Cryptotanshinone (CPT), a major biologically active component in the roots of *Salvia miltiorrhiza*, modulates radiation-induced intestinal microbiota and BAs metabolism in mice, reducing pulmonary inflammation and fibrosis.[89] Certain compounds present in herbs, such as polyphenols and polysaccharides, can assist the body in producing beneficial metabolites like SCFAs and tryptophan, thereby alleviating liver fibrosis and inflammation[90] Danggui Shaoyao San has been shown to help treat CCl4-induced hepatic fibrosis by influencing the intestinal microbiota and its metabolites (SCFAs and BAs).[91] Ethanol extracts of *Ganoderma lucidum* ameliorated hepatic fibrosis and enhanced the interaction between metabolites and the intestinal microbiota through the NF-κB and TGF-β1/Smad pathways.[92] Betanin decreased streptozotocin-induced fibrosis in a diabetic nephropathy model by altering the expression of EMT-associated markers.[93] Ootheca mantidis reduced renal fibrosis in mice by suppressing apoptosis and boosting the intestinal bacteria *Akkermansia muciniphila* while modifying glutamine metabolism.[94] The occurrence and progression of fibrotic disorders are directly linked to the intestinal microbiota. From single herbs to compounds, and from crude extracts to monomer components, the biological foundations of TCM's anti-fibrotic activity are gradually being uncovered.

The Impact of TCM Prescriptions on Intestinal Flora and Fibrosis

Traditional Chinese medicine compounds, single herbs, and monomers can alleviate IBD and intestinal fibrosis by modulating gut microbiota and their metabolites.[95,96] Table 2 summarizes the specific mechanisms of various TCM formulas and their effects on gut microbiota and metabolic products. Gut microbiota imbalance plays a crucial role in the onset and progression of intestinal fibrosis in IBD. TCM formulas can restore gut microbiota balance by inhibiting harmful bacteria and promoting beneficial bacteria. In addition, traditional Chinese medicine can exert therapeutic effects by modulating the levels of microbial metabolites.[97] Kuijieyuan Decoction (KJYD) decreases *Escherichia-Shigella* and *Desulfovibrio*, while increasing *Alloprevotella, Treponema*, and *Prevotella*, leading to the suppression of the PI3K/AKT/NF-κB pathway and the alleviation of colitis.[98] Similarly, Huanglian Jiedu Decoction (HLJD) suppresses *Alistipes, Prevotella*, and *Bacteroides*, while increasing *Oscillibacter* and *Lactobacillus*, thereby restoring microbial homeostasis and modulating Csf1r/Src signaling to mitigate inflammation.[99,100] Additionally, Yiyi Fuzi Baijiang Powder (YFBP) reduces *Prevotella_9*, while enhancing

Table 2 Chinese Medicine Compound in the Treatment of Intestinal Fibrosis

Prescription	Mechanism	Reference
Kuijieyuan decoction	*Alloprevotella, Treponema* and *Prevotella*↑; *Escherichia_Shigella* and *Desulfovibrio*↓; PI3K/AKT/NF-κB↓.	[98]
Huanglian Jiedu Decoction	*Oscillibacter, Lactobacillus*↑; *Alistipes, Prevotella, Bacteroides*↓; Csf1r/Src.	[99,100]
Yiyi Fuzi Baijiang Powder	*Prevotella_9*↓; *Lachnospiraceae_NK4A136_group*↑; TLR4/NF-κB/NLRP3.	[101]
Gegen Qinlian Decoction	*Lactobacillus*↑; *Lachnospiraceae_NK4A136_group*↑; SCFAs↑; Treg/Th17.	[102]
Rhubarb Peony Decoction	*Butyricicoccus pullicaecorum*↑; SCFAs↑; Treg/Th17.	[103]
Anchang Yuyang Decoction	*Romboutsia, Monoglobus*↑; *Bacteroides, Alistipes*↓; SCFAs↑.	[104]
Baitouweng Tang	*Lactobacillus, Clostridium*↑; FXR and TGR5↑; Regulate the balance of BAs.	[105]
San Wu HuangQin decoction	*Escherichia-Shigella*↓; LPS↓.	[106]
Qingchang Wenzhong Decoction	IL-17, NF-κB and TLR4↓.	[107]
Xue-jie-San	Autophagy; EndoMT, EMT↓.	[108,109]
Wumei Wan	α-SMA, collagen I, MMP-9↓.	[110]
Qingchang Tongluo Decoction	TGF-β1/Smad; Collagen I and VEGF-A↓.	[111]

Lachnospiraceae_NK4A136_group, contributing to the inhibition of TLR4/NF-κB/NLRP3 and the restoration of the intestinal barrier.[101] Several TCM formulas exert protective effects by increasing beneficial bacteria, which promote SCFA production and regulate immune balance. For example, Gegen Qinlian Decoction (GGQL) increases *Lactobacillus* and *Lachnospiraceae_NK4A136_group*, leading to higher SCFA levels and improved Treg/Th17 balance, which helps alleviate experimental colitis.[102] Similarly, Rhubarb Peony Decoction (RPD) upregulates *Butyricicoccus pullicaecorum*, restoring SCFA levels and regulating the Th17/Treg ratio, thereby exerting anti-inflammatory and intestinal barrier-protective effects.[103] Anchang Yuyang Decoction (AYYD) increases *Romboutsia* and *Monoglobus*, contributing to higher SCFA levels and improved intestinal barrier function.[104] Beyond modulating gut microbiota composition, some formulas exert their effects by regulating bile acid metabolism and LPS production. Baitouweng Tang (BTW) enhances *Lactobacillus* and *Clostridium*, increasing FXR and TGR5 expression and regulating bile acid metabolism, which contributes to gut microbiota balance and symptom relief in DSS-induced colitis.[105] Furthermore, San Wu Huangqin Decoction (SWHQD) lowers *Escherichia-Shigella* abundance and reduces LPS production, thereby restoring epithelial MUC2 secretion and colonic tight junction integrity.[106] In addition to microbiota modulation, some TCM formulas directly regulate fibrosis-related pathways. Qingchang Wenzhong Decoction (QCWZD) alleviates fibrosis by inhibiting IL-17, NF-κB, and TLR4, reducing inflammation and fibrosis progression.[107] Meanwhile, Xue-jie-San (XJS) inhibits Notch1 and FGL-1 signaling, thereby suppressing autophagy, endothelial-to-mesenchymal transition (EndoMT), and EMT, mechanisms implicated in Crohn's disease-related fibrosis.[108,109] Similarly, Wumei Wan (WMW) mitigates fibrosis by downregulating α-SMA, collagen I, and MMP-9, slowing fibrosis progression[110] Qingchang Tongluo Decoction (QTD) inhibits intestinal fibroblast proliferation and collagen deposition via suppression of the TGF-β1/Smad pathway, making it a promising treatment for CD-related intestinal fibrosis.[111] Taken together, these findings suggest that TCM interventions can modulate gut microbiota balance, as well as influence metabolites such as SCFAs, bile acids, and LPS production. Additionally, they directly regulate fibroblast activity and fibrosis-related pathways, collectively contributing to the prevention and treatment of IBD-associated intestinal fibrosis.

Monomers of TCM Alleviate Intestinal Fibrosis by Modulating the Intestinal Microbiota

Natural plant chemicals have long served as sources of medicinal compounds and structural foundations for the development of pharmaceuticals. Evidence suggests that Chinese medicinal monomers can modulate fibroblast activity and decrease the progression of intestinal fibrosis through fibrosis-related molecular signals, inflammatory cytokines, and other mechanisms.

These TCM monomers can also alleviate IBD-associated intestinal fibrosis by regulating the intestinal microbiota and its metabolites (Table 3). For instance, the sesquiterpene atractylenolides from *Atractylodes macrocephala* can modulate the intestinal microbiota by increasing beneficial bacteria such as *Lactobacillus* and restoring the intestinal barrier, offering potential treatment for UC.[112] Rhein, a bioactive compound primarily found in *Rheum palmatum*, has garnered increasing attention for its potential anti-fibrotic properties across various organs.[113,114] Notably, Rhein affects the intestinal microbiota, indirectly influencing colonic purine metabolism and alleviating colitis.[115] Puerarin, found in *Pueraria lobatae* Radix, exerts strong anti-inflammatory effects by reducing *Akkermansia muciniphila*, inhibiting macrophage M1 polarization, and thereby alleviating colitis in UC-like animal models.[116] Ginsenoside Rg1, derived from *Panax ginseng*, aids in treating colitis and repairing the intestinal mucosal barrier by regulating the microbiota and inflammatory cytokine levels.[117] Polysaccharides from *Dendrobium officinale* increase the variety of microbes in the intestine and stimulate the colon to produce SCFAs.[118] *Poria cocos* polysaccharide (PCP) increases small-intestinal SCFAs and strengthens the intestinal barrier.[119] *Schisandra chinensis* polysaccharide (SCP) can balance intestinal microbiota and boost SCFAs levels.[120] *Patrinia Scabiosifolia* extract can restore gut microbiota balance, reduce the expression of β-defensin 2, and decrease the expression of TGF-β and α-SMA, thereby exerting a therapeutic effect on TNBS-induced intestinal fibrosis.[121] TCM monomers influence signaling pathways, reduce inflammatory factors, and decrease collagen production, thus mitigating intestinal fibrosis in IBD patients. Nrf2 activators, for example, can be used to maintain this molecule during the early stages of IBD, preventing the onset of cancer and fibrosis. Maggot extracts alleviate inflammation-induced intestinal fibrosis by enhancing Nrf2 expression and inhibiting the TGF-β1/SMADs pathway.[122]

Recent research has also focused on the improving efficacy of active substances in traditional Chinese medicine. For example, MIR2911 from *Lonicera japonica* can be generated in host small extracellular vesicles and absorbed through diet, directly influencing intestinal bacteria, reducing *Escherichia -Shigella*, and improving colitis symptoms.[123] TGF-β, a key factor in EMT, plays a significant role in fibrosis induction[124,125] Calycosin, by inhibiting the TGF-β/Smad pathway, prevents intestinal fibrosis.[126] Furthermore, curcumin has been shown to reduce intestinal fibrosis in a TNBS-

Table 3 Chinese Medicine Monomer in the Treatment of Intestinal Fibrosis

Monomer	Main source	Mechanism	Reference
Atractylenolides	*Atractylodes macrocephala*	*Lactobacillus*↑; Regulate the expression of Nrf2;	[112]
Rhein	*Rheum palmatum*	*Lactobacillus*↑;	[115]
Puerarin	*Puerariae Lobatae* Radix	*Akkermansia muciniphila*↓; Macrophage M1 polarization↓.	[116]
Ginsenoside Rg 1	*Panax ginseng*	*Lachnospiraceae*↑; *Staphylococcus, Bacteroides and Ruminococcaceae_UCG_014*↓.	[117]
Polysaccharides	*Dendrobium officinale*	*Bacteroides, Lactobacillus* and *Ruminococcaceae*↑; *Proteobacteria*↓ SCFAs (acetate and butyrate)↑.	[118]
	Poria cocos	*Muribaculaceae, Bacteroides*↑; SCFAs↑.	[119]
	Schisandra chinensis	*Alloprevotella*↑; SCFAs↑.	[120]
Patrinia Scabiosifolia Extracts	*Patrinia Scabiosifolia*	Restore gut microbiota balance; β-defensin 2, TGF-β and α-SMA↓.	[121]
Maggot Extracts	Maggot	*Lactobacillus*↑; *Bacteroides*↓; TGF-β1/SMADs; Nrf2↑.	[122]
MIR2911	*Lonicera japonica*	*Escherichia -Shigella*↓	[123]
Calycosin	*Astragalus membranaceus*	p-Smad2, p-Smad3, Smad4, and TGF-β1↓; Smad7↑.	[126]
Curcumin	*Curcuma longa*	PPAR-γ and E-cadherin; MMP-3, MMP-3/TIMP-1↑; Fibronectin; α-SMA↓.	[127,128]
GENs	*Panax ginseng*	*Lactobacillus, Alistipes*↑; *Helicobacter, Odoribacter*↓. Pro-inflammatory cytokines↓;.	[129]
Total flavone	*Abelmoschus manihot*	Th17/Treg; α-SMA, TGF-β, and TIMP-1↓; MMPs↑; ECM↓.	[130]

induced rat model by elevating PPAR-γ and E-cadherin levels and altering the MMP-3/TIMP-1 ratio, while also decreasing the levels of α-SMA and fibronectin.[127,128] Plant-derived exosome-like nanoparticles (GENs) derived from *Panax ginseng* may improve colitis by controlling pro-inflammatory cytokines, balancing the intestinal microbiota, and enhancing the intestinal barrier.[129] Additionally, the total flavone from *Abelmoschus manihot* can correct the Th17/Treg imbalance, decrease α-SMA, TGF-β, and TIMP-1 production, enhance MMPs, and prevent ECM deposition.[130] Chinese medicine components with anti-fibrotic activity are becoming increasingly recognized due to expanding research and technological advancements, leading to a broader understanding of their mechanisms of action.

Discussion

Inflammatory bowel disease arises from the complex interplay of genetic predisposition, environmental influences, and immune dysregulation, with gut microbiota playing an important role in disease progression[131,132] An imbalance in the immune response of the intestinal mucosa can occur due to microbiota dysregulation, metabolite changes, and pathogenic bacterial invasion, all of which disrupt the normal intestinal mucosal barrier.[133,134] This immune activation promotes the secretion of cytokines and molecular mediators, leading to the differentiation of mesenchymal-like cells and ECM deposition, which ultimately contributes to intestinal fibrosis. Despite its significant impact on patient prognosis, intestinal fibrosis remains an unmet clinical challenge, as no clinically approved treatment options are available for intestinal fibrosis. Existing therapeutic strategies primarily focus on inhibiting myofibroblast proliferation, reducing ECM accumulation, and targeting pro-fibrotic signaling pathways. While some experimental antifibrotic agents have demonstrated efficacy in animal models and early-phase clinical trials, their translation into effective therapies is limited by concerns regarding efficacy, safety, and long-term outcomes. Novel approaches, such as gene regulation and stem cell therapy, show promise but require further validation, particularly concerning cost-effectiveness and patient safety. Patients with IBD are increasingly pursuing complementary and alternative therapies. Given the growing recognition of the gut microbiota in IBD-related fibrosis, targeting the gut microbiota has emerged as a potential therapeutic strategy. Several interventions, including dietary modifications and probiotic supplementation, have been proposed to restore microbial balance and mitigate fibrosis. However, there remain critical gaps in understanding how specific bacterial species and their metabolites directly influence fibrotic pathways. Additionally, the bidirectional relationship between gut microbiota and pharmacological interventions is increasingly acknowledged. The gut microbiota can affect drug metabolism and efficacy, while certain drugs can reshape microbial composition and function, underscoring the need for microbiota-informed precision medicine.

Traditional Chinese medicine has gained attention for its multicomponent and multitarget therapeutic properties, offering a promising approach to modulating gut microbiota and ameliorating intestinal fibrosis. Evidence suggests that TCM can restore microbial homeostasis by increasing beneficial bacteria, reducing pathogenic species, and influencing microbial-derived metabolites, thereby enhancing intestinal barrier integrity and improving intestinal inflammation, all of which have demonstrated antifibrotic effects. Additionally, TCM preparations regulate fibroblast activity and suppress pro-fibrotic signaling pathways, thus alleviating IBD-related fibrosis. Although there is limited direct evidence on the role of TCM in regulating gut microbiota for the treatment of intestinal fibrosis, we hypothesize that TCM formulas and bioactive components of Chinese medicine may alleviate IBD-associated intestinal fibrosis through modulation of the intestinal microbiota. Three key factors support this hypothesis: (1) TCM can improve intestinal microbiota dysbiosis by increasing beneficial bacteria, decreasing pathogenic bacteria, and enhancing gut barrier integrity. A key factor in the persistence of inflammation and fibrosis in IBD is the disruption of the intestinal barrier. (2) TCM regulates intestinal microbiota metabolites, some of which play a role in the pathogenesis of IBD-related fibrosis, while others have direct therapeutic potential. (3) TCM has the potential to modulate immune responses via the gut microbiota. The interaction between the gut microbiota and host immunity plays a pivotal role in the onset and progression of inflammatory disorders. The gut microbiota and immune system can activate signaling pathways, generate cytokines, influence fibroblasts, alter the ECM, and produce anti-fibrotic substances.

Although TCM-based therapies show potential, several challenges hinder their clinical application: (1) Limited mechanistic studies. While preclinical evidence supports the antifibrotic effects of TCM, the precise molecular mechanisms remain incompletely understood. Future research should focus on targeted validation of microbiota-mediated

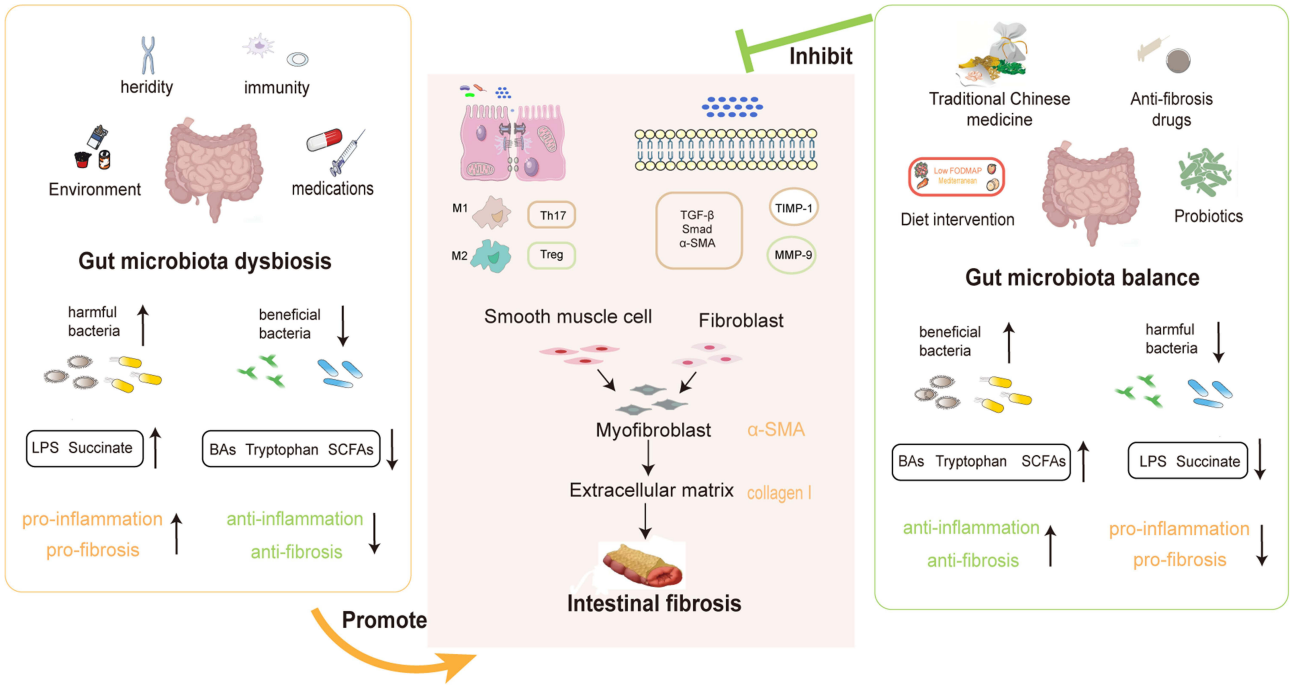

Figure 4 Treatment of IBD intestinal fibrosis through intestinal microbiota and metabolites regulation. An imbalance in the immune response of the intestinal mucosa can occur as a result of microbiota dysregulation, metabolite changes, and pathogenic bacterial invasion, all of which disrupt the normal intestinal mucosal barrier. The immune system activates and releases cytokines or molecular mediators to generate and activate mesenchymal-like cells, which can boost submucosal ECM secretion. Diet, probiotics, anti-fibrotic drugs, and traditional Chinese medicine can modulate the equilibrium of the gut bacteria, improve the production of advantageous metabolites, diminish deleterious metabolites, regulate intestinal immunity, strengthen intestinal barrier integrity, elevate anti-inflammatory and anti-fibrotic molecules, and inhibit the deposition of extracellular matrix, thereby facilitating the treatment of inflammatory bowel disease fibrosis.

pathways and their interactions with TCM compounds. (2) Heterogeneity in TCM formulations. The lack of standardized nomenclature and inconsistent dosage compositions affect reproducibility and hinder cross-study comparisons. Establishing standardized formulations and dose optimization is essential for advancing TCM-based treatments. (3) Limited high-quality clinical evidence. Most studies on TCM interventions for intestinal fibrosis rely on animal models, with minimal evidence from well-designed randomized controlled trials (RCTs). High-quality clinical research is needed to validate the efficacy and safety of TCM formulas in human patients. To bridge these gaps, future research should prioritize multidisciplinary approaches that integrate microbiome analysis, omics technologies (metabolomics, transcriptomics) to elucidate microbiota-driven fibrotic mechanisms. Additionally, well-designed RCTs evaluating the efficacy of microbiota-targeted therapies, including TCM, are crucial for translating preclinical insights into clinical applications. In summary, intestinal microbiota and their metabolites play a notable role in IBD-associated intestinal fibrosis. Strategies that modulate gut microbiota represent a promising therapeutic avenue, with TCM offering unique advantages in restoring microbial balance and mitigating fibrosis (Figure 4). However, rigorous research is necessary to optimize TCM interventions, address current limitations, and establish a robust foundation for future clinical applications.

Conclusion

Intestinal fibrosis is a common and challenging complication of IBD, with gut microbiota dysbiosis playing a crucial role in its development. Accumulating evidence suggests that alterations in gut microbiota composition and its metabolites contribute to intestinal fibrosis through multiple mechanisms. Targeting the gut microbiota and its metabolites has emerged as a promising strategy for managing intestinal fibrosis in IBD. TCM has shown efficacy in regulating the intestinal microbiota, influencing the production of intestinal microbiota metabolites, and providing notable benefits in alleviating intestinal fibrosis. TCM formulas, single herbs, and monomers exert beneficial effects by enriching beneficial bacteria, inhibiting pathogenic species, and regulating key metabolic pathways. These findings highlight the potential of

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TCM as a therapeutic approach for IBD-associated fibrosis. Further studies are warranted to elucidate the precise mechanisms and optimize microbiota-targeted interventions for improved clinical outcomes.

Abbreviations

IBD, Inflammatory Bowel Disease; CD, Crohn's Disease; UC, Ulcerative Colitis; ECM, extracellular matrix; TGF-β1, transforming growth factor-β1; AIEC, *Adherent-invasive Escherichia coli*; α-SMA, α-smooth muscle actin; AMPs, antimicrobial peptides; LPS, lipopolysaccharide; Bas, bile acids; SCFAs, short-chain fatty acids; SBAs, secondary bile acids; IA, indoleacrylic acid; AHR, aryl hydrocarbon receptor; MMPs, matrix metalloproteinases; TIMPs, tissue inhibitors of matrix metalloproteinases; IGF-I, insulin-like growth factor-1; MAPK, mitogen-activated protein kinase; let-7b, exosomal miRNA lethal-7b; SUCNR1, succinate receptor 1; NF-κB, nuclear factor κ-B; TLR4, Toll-like receptor 4; H2S, hydrogen sulfide; ASR, sulfate reduction; Treg, regulatory T; TH17, T helper cells 17; IPA, Indole-3-propionic acid; PXR, pregnane X receptor; Foxp3, forkhead transcription factor p-3; GPR43, G protein-coupled receptor 43; HFD, high-fat diets; CDED, Crohn's Disease Exclusion Diet; PEN, partial enteral nutrition; CD-TREAT, Crohn's Disease-TREAT; EEN, Exclusive Enteral Nutrition; UCED, Ulcerative colitis exclusion diet; FODMAP, fermentable oligo-, di-, and mono-saccharides and polyols; PPARγ, peroxisome proliferator-activated receptor γ; DSS, dextran sulfate sodium-induced; FMT, fecal microbiota transplantation; NMN, nicotinamide mononucleotide; FGF19, fibroblast growth factor 19; EVs, extracellular vesicles; NLRP3, NOD like receptor thermal protein domain associated protein 3; FGL-1, fibrinogen-like protein 1; EndoMT, endothelial-to-mesenchymal transition; GENs, exosome-like nanoparticles; RCTs, randomized controlled trials.

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Disclosure

The authors report no conflicts of interest in this work.

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