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Akkermansia muciniphila: key target for improving ulcerative colitis with active components of Chinese medicine

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Abstract: The onset of ulcerative colitis (UC)is closely related to intestinal flora imbalance, with a significant decrease in the abundance of *Akkermansia muciniphila* being a key feature. Recent studies have found that active components of Chinese medicine can improve UC symptoms by significantly increasing the abundance of *Akkermansia muciniphila*, regulating short-chain fatty acid levels, enhancing the intestinal mucosal barrier, and reducing the levels of inflammatory factors. This article systematically reviews the role of *Akkermansia muciniphila* in the treatment of UC and the mechanism by which active components of Chinese medicine regulate *Akkermansia muciniphila* to improve UC, providing a new theoretical basis for the development of UC adjuvant therapies based on intestinal flora intervention.

Keywords: *Akkermansia muciniphila*; Ulcerative colitis; Intestinal microecology; Chinese medicine; Active component; Gut microflora; Intestinal mucosal barrier
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Ulcerative colitis (UC) is a chronic recurrent inflammatory bowel disease closely associated with immune imbalance and intestinal microecological dysbiosis. Imbalanced composition of the human gut microbiota, characterized by reduced probiotics and expanded opportunistic or pathogenic bacteria, contributes to the pathogenesis of UC. *Akkermansia muciniphila* (*Akkermansia*) is a Gram-negative anaerobic bacterium colonized in the intestinal mucus layer. It can thrive within the mucus layer and directly participates in multiple physiological processes, including immune regulation, metabolism and inflammatory responses [1-2]. Clinical trials have demonstrated that the abundance of *Akkermansia* in fecal samples from UC patients is markedly lower than that in healthy individuals. Moreover, patients with active UC exhibit significantly reduced *Akkermansia* abundance compared with those in the remission phase [3-4]. In addition, UC patients with long-term clinical remission present gut microbiota profiles highly similar to healthy populations, and *Akkermansia* abundance is positively correlated with disease remission.

Decreased fecal *Akkermansia* abundance may serve as a potential biomarker for predicting UC flare-ups and disease activity [5]. Additional clinical studies have explored the alterations and underlying mechanisms of *Akkermansia* in UC patients (**Table 1**), further indicating that *Akkermansia* may represent a promising therapeutic target for UC [6-10].

China is abundant in traditional Chinese medicine (TCM) resources. Accumulating studies have verified that bioactive components derived from TCM can effectively alleviate UC symptoms, and remodeling of gut microbiota represented by *Akkermansia* plays a critical role in such therapeutic effects [11-12]. This review summarizes the regulatory role of *Akkermansia* in the improvement of UC mediated by TCM active ingredients, aiming to provide novel adjuvant therapeutic strategies for UC management.

1 Mechanisms by Which *Akkermansia* Ameliorates UC

1.1 Effects of Akkermansia and Its Outer Membrane Components

Animal experiments have confirmed that oral supplementation of *Akkermansia* increases colonic mucus thickness in mice [13]. Bian *et al.* [14] reported that *Akkermansia* supplementation alleviated dextran sulfate sodium (DSS)-induced colitis in mice and reduced the levels of proinflammatory cytokines [tumor necrosis factor-α (TNF-α), interleukin (IL)-1, IL-6] and chemokines in serum and colonic tissues. Zhai *et al.* [15] conducted experiments using distinct *Akkermansia* strains and confirmed anti-inflammatory effects of both strains *in vitro*. Consistently, both strains downregulated the expression of proinflammatory interferon-γ (IFN-γ) and TNF-α in the colon of colitic mice *in vivo*. Liu *et al.* [16] found that toll-like receptor 4 (TLR4) deficiency led to a dramatic depletion of intestinal *Akkermansia*, accompanied by decreased counts of retinoic acid-related

orphan receptor γt (RORγt)$^+$ regulatory T cells (Tregs) and exacerbated intestinal inflammation. Intervention with *Akkermansia* restored the proportion of RORγt$^+$ Tregs and activated Treg-mediated immune responses, thereby mitigating colitis in TLR4-deficient mice. Furthermore, *Akkermansia* treatment suppressed colonic TNF-α and IL-1β expression, while increasing goblet cell numbers and mucin 2 (MUC2) production in UC mice [17]. Collectively, *Akkermansia* attenuates colonic inflammation by reducing proinflammatory cytokine release and reinforcing intestinal mucosal barrier function.

Amuc_1100 and Amuc_2109 are two pivotal outer membrane proteins of *Akkermansia*. Oral administration of pasteurized *Akkermansia* or purified Amuc_1100 in UC patients and colitic mice attenuated inflammatory cell infiltration and relieved DSS-induced colonic injury [18]. Emerging evidence has shown that both *Akkermansia* and Amuc_1100 repair 5-fluorouracil (5-FU)-induced intestinal mucosal damage, reduce TNF-α and IL-6 concentrations, inhibit NLRP3 inflammasome activation, and restore intestinal barrier integrity [19]. Qian *et al.* [20] demonstrated that Amuc_2109 alleviated DSS-induced colitis via suppressing NLRP3 inflammasome activation and reducing the secretion of proinflammatory mediators including TNF-α, IL-1β and IL-6. In conclusion, both viable *Akkermansia* and its outer membrane proteins exert potent anti-inflammatory activities in the intestinal tract.

1.2 Metabolites Produced by Akkermansia

1.2.1 Short-Chain Fatty Acids (SCFAs)

SCFAs are organic acids generated by gut microbial fermentation of dietary fibers. Reduced fecal SCFA concentrations are commonly detected in UC patients compared with healthy controls [21]. SCFAs serve as the primary energy source for intestinal epithelial cells, promote mucosal repair, maintain intestinal barrier homeostasis, and defend against pathogenic invasion. As a typical mucus-degrading probiotic, *Akkermansia* produces abundant SCFAs (e.g., acetate, propionate, butyrate) with multiple physiological functions to relieve UC-related symptoms. Recent studies have revealed that the clinically isolated *Akkermansia* strain Akk ONE significantly elevates cecal SCFA contents and ameliorates experimental colitis in mice [22]. SCFAs activate the aryl hydrocarbon receptor (AhR)/IL-22 signaling axis, alleviate colonic pathological damage, suppress inflammatory cascades, and modulate tight junction protein expression, thereby exerting protective effects against UC [23]. Wang *et al.* [24] validated that SCFAs reversed the T helper 17 (Th17)/Treg imbalance, a core pathological feature of UC. In addition, SCFAs upregulate anti-inflammatory cytokine levels, decrease proinflammatory IL-8 secretion, and preserve epithelial tight junction integrity [25]. Hong *et al.* [26] illustrated that SCFAs relieved colitis through binding to G-protein-coupled receptor 43 (GPR43) on intestinal epithelial cells. Mechanistically, propionate derived from *Akkermansia* metabolism interacts with epithelial GPR43, upregulating the tight junction proteins occludin and zonula occludens-1 (ZO-1) to strengthen intestinal epithelial barrier function [27].

1.2.2 Other Metabolites

Other metabolic products of *Akkermansia* include γ-aminobutyric acid, creatinine and ornithine lipids. However, the direct causal relationship between these metabolites and UC remission remains poorly elucidated. Creatinine has been reported to enhance intestinal ecosystem homeostasis and improve mucosal barrier function [28], while the regulatory effects of other *Akkermansia*-derived metabolites on UC require further investigation..

Tab.1 Changes and possible mechanisms of Akk bacteria in UC patients

Sample size	Key findings	Possible mechanisms of changes in *Akkermansia* abundance	References
33 cases (19 patients with active UC and 14 healthy controls)	The abundance of *Akkermansia* in the intestinal tract of UC patients was decreased.	The decreased content of mucin 2 (MUC2) in the intestinal mucosa leads to a reduction in *Akkermansia* abundance, which uses MUC2 as the sole carbon source.	[6]
54 cases (20 patients with active UC, 14 patients with quiescent UC, and 20 healthy controls)	The abundance of *Akkermansia* in the intestinal tract of patients with active UC was lower than that in patients with quiescent UC and healthy controls.	A decrease in the relative proportion of sulfated mucins in the mucus gel layer may lead to a reduction in *Akkermansia* abundance.	[7]
185 cases (41 UC patients and 144 healthy controls)	The abundance of *Akkermansia* in fecal samples of UC patients was decreased.	In the intestinal tract of UC patients, the content of mucin, which serves as an energy source for *Akkermansia*, is reduced.	[8]
163 cases (66 patients with UC in remission and 97 healthy controls)	The abundance of *Akkermansia* in fecal samples of UC patients was decreased.	—	[9]
10 cases (6 UC patients and 4 healthy controls)	The abundance of *Akkermansia* in fecal samples of UC patients was decreased.	—	[10]

1.3 Akkermansia-Derived Extracellular Vesicles (EVs)

Kang *et al.* [29] found that EVs secreted by *Akkermansia* enhanced colonic epithelial stability, reduced inflammatory cell infiltration, and alleviated tissue injury in mice with 2% DSS-induced colitis.

Subsequent research by Zheng *et al.* [30] further confirmed these findings. *Akkermansia* EVs improved mucus layer integrity, reduced intestinal permeability by upregulating goblet cell-derived MUC2 expression, and substantially strengthened intestinal barrier function.

In summary, *Akkermansia* alleviates UC inflammation and clinical manifestations through multiple mechanisms: inhibiting proinflammatory cytokines and inflammasome activation, producing beneficial SCFAs, and reinforcing intestinal mucosal barrier function.The detailed regulatory mechanisms are illustrated in **Figure 1.**

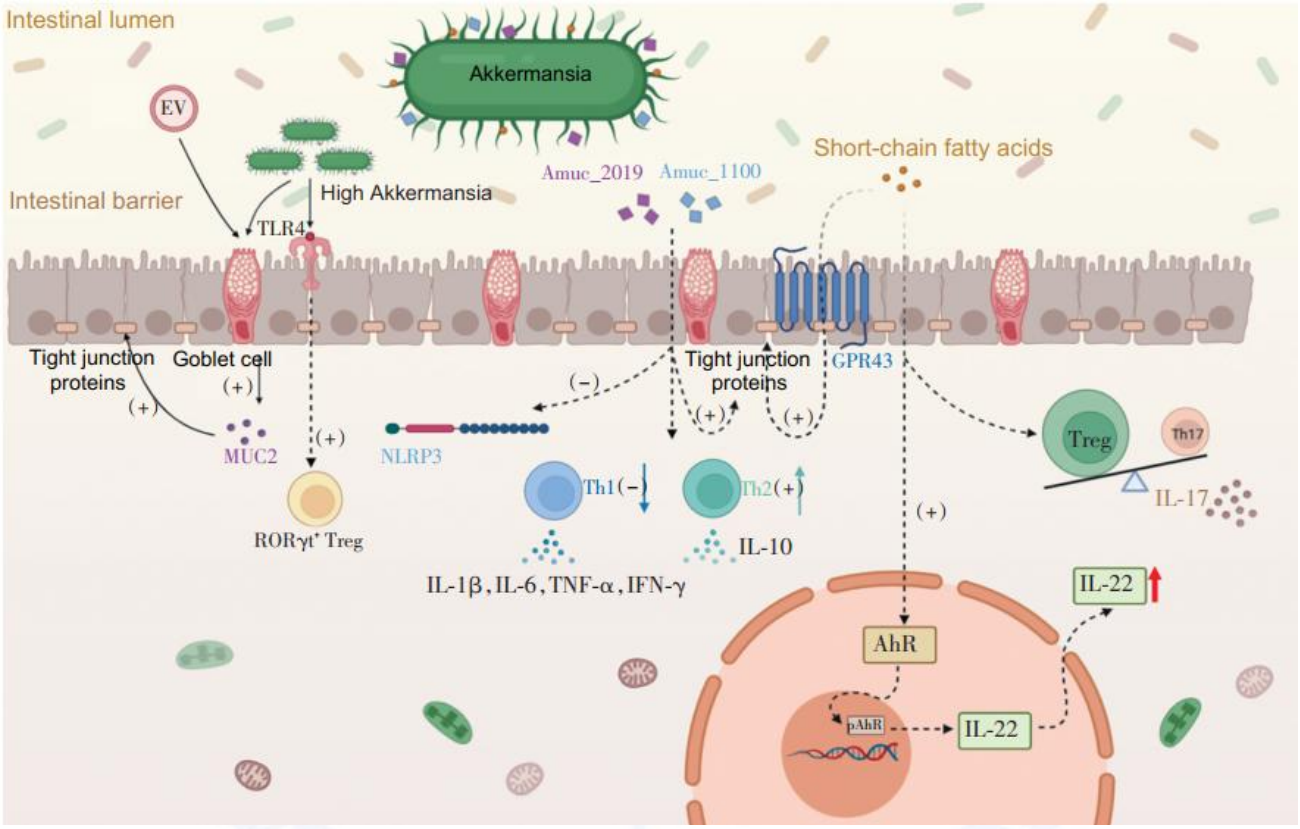

Fig.1 Mechanism of Akk bacteria in improving UC

2 Regulatory Effects of *Akkermansia* in TCM Active Ingredient-Mediated UC Treatment

2.1 Alkaloids

Berberine is an isoquinoline alkaloid extracted from *Coptis chinensis* and other TCM herbs. Yang *et al.* [31] observed that berberine intervention markedly increased the intestinal abundance of *Akkermansia*, *f_Muribaculaceae*, *Bacteroides*, *Dubosiella* and *Allobaculum* in DSS-induced UC mice. Independent validation confirmed that intestinal mucosal *Akkermansia* was highly enriched in the high-dose berberine group. Berberine suppressed arachidonic acid metabolism and reduced inflammation-related metabolites via modulating the abundance of *Bacteroides* and *Akkermansia*. Moreover, berberine attenuated intestinal epithelial apoptosis and restored barrier integrity in UC mice in an *Akkermansia*-dependent manner. These findings suggest that berberine alleviates intestinal inflammation and enhances mucosal barrier function by elevating *Akkermansia* abundance in UC.

Jatrorrhizine, another isoquinoline alkaloid isolated from *Coptis chinensis* and *Phellodendron chinense*. Zhang *et al.* [32] found that jatrorrhizine could significantly increase the abundance of *Akkermansia* in the intestinal tract of UC mice. In addition, the expression of nitric oxide synthase 2 (NOS2) in colonic tissues of mice was markedly downregulated after jatrorrhizine treatment, and its expression level was negatively correlated with the relative abundance of *Akkermansia*. Inhibition of NOS2 could alleviate intestinal inflammation. These findings suggest that jatrorrhizine may exert anti-UC effects by elevating the abundance of *Akkermansia*, reducing the relative abundance of pathogenic bacteria, and thereby attenuating intestinal inflammatory responses.

Protopine, a major anti-inflammatory isoquinoline alkaloid from *Macleaya cordata*, selectively enriches beneficial *Akkermansia* and reduces the abundance of detrimental Proteobacteria, *Escherichia coli* and *Enterococcus*. Protopine administration effectively

attenuated DSS-induced colonic injury and inhibited proinflammatory cytokine production [33]. Mechanistically, protopine relieves experimental UC by upregulating *Akkermansia*, reducing TNF-α, IL-1β and IL-6 levels, and restoring tight junction proteins ZO-1 and occludin.

Matrine is a bioactive alkaloid extracted from *Sophora flavescens*, *Sophora alopecuroides* and *Sophora subprostrata*. Matrine supplementation reversed the reduction of gut microbiota diversity in UC mice and increased the abundance of *Akkermansia* and *Lactobacillus* [34]. It ameliorated DSS-triggered colonic oxidative stress and suppressed the production of proinflammatory cytokines including TNF-α, IL-6, IL-17A and IL-1β. Matrine also corrected Treg/Th17 imbalance, repaired colonic tissue damage and restored goblet cell function in colitic mice. Additionally, matrine upregulated the expression of tight junction proteins occludin and ZO-1. Collectively, matrine improves UC by enriching *Akkermansia*, enhancing colonic barrier integrity, suppressing intestinal inflammation and restoring Treg/Th17 homeostasis.

2.2 Polyphenols

Resveratrol is a plant-derived bioactive polyphenol primarily isolated from *Polygonum cuspidatum*. In 2,4,6-trinitrobenzenesulfonic acid (TNBS)-induced UC mice, resveratrol treatment elevated the abundance of *Akkermansia* and *Ruminococcus gnavus* while reducing *Bacteroides acidifaciens* [35]. Resveratrol restored gut microecological balance, suppressed systemic inflammation and aberrant T cell activation. It also increased intestinal acetate and isobutyrate levels to exert protective effects against colitis. Resveratrol exerts anti-UC activity via enriching *Akkermansia*, inducing anti-inflammatory IL-10, inhibiting proinflammatory Th1/Th17 cell responses, and elevating endogenous SCFA production.

Chlorogenic acid (ChA) is a core antibacterial and antiviral bioactive component of *Lonicera japonica*. ChA intervention significantly increased the proportion of intestinal *Akkermansia* in DSS-induced colitic mice. It inhibited NF-κB pathway activation and reduced the secretion of proinflammatory IFN-γ, TNF-α and IL-6, thereby alleviating acute colonic injury [36]. The intestinal protective effects of ChA against UC are closely associated with *Akkermansia* enrichment and subsequent attenuation of local and systemic inflammation.

2.3 Flavonoids

Icariin, a major flavonoid extracted from *Epimedium* species, reshaped gut microbiota composition in DSS-induced colitic mice. Icariin markedly increased beneficial bacteria including *Akkermansia*, *Lachnospiraceae* and *Lactobacillus*, whereas decreasing the abundance of *Helicobacteriaceae*, *Bacteroides* and *Turicibacter* [37]. Moreover, icariin enhanced the biological activity of *Akkermansia* and alleviated colonic inflammatory tissue damage. Icariin ameliorates DSS-induced UC by enriching and activating *Akkermansia*, reducing tissue injury and downregulating proinflammatory IL-6 and TNF-α.

Total flavonoids of *Abelmoschus esculentus* (TFA) exhibit potent anti-inflammatory, analgesic and antioxidant properties. High-dose TFA (TFA-H) restored DSS-induced gut microbiota dysbiosis and induced dramatic enrichment of intestinal *Akkermansia* [38]. TFA-H alleviated colonic shortening and histological damage in experimental colitis and restored MUC2 and ZO-1 expression to physiological levels. TFA ameliorated colonic inflammation and corrected intestinal epithelial barrier dysfunction. In vitro assays further confirmed that TFA directly promoted the growth of *Akkermansia*. TFA relieves UC by robustly increasing *Akkermansia* abundance, strengthening intestinal barrier function, and suppressing multiple proinflammatory cytokines including TNF-α, IL-6, IFN-γ, IL-1β and IL-17a.

Apigenin is a naturally occurring flavonoid abundant in traditional Chinese medicines such as *Plantago asiatica*, *Trachelospermum jasminoides* and *Agastache rugosa*. Fu *et al.* [39] reported that apigenin treatment significantly increased the abundance of *Akkermansia* and *Faecalibaculum* in UC mice. Apigenin prevented intestinal barrier destruction in colitic mice, with superior therapeutic efficacy to sulfasalazine at high doses. It also markedly elevated intestinal SCFA concentrations. Mechanistically, apigenin improves UC through two key pathways mediated by *Akkermansia* enrichment: increasing SCFA synthesis to promote anti-inflammatory IL-10 expression and inhibit TNF-α, IL-1β and IL-6 secretion; upregulating tight junction proteins ZO-1, claudin-1 and occludin to restore intestinal barrier integrity.

Mulberry anthocyanins are water-soluble natural flavonoid pigments extracted from *Mori Fructus*.Mulberry anthocyanin treatment significantly elevated the relative abundance of beneficial *Akkermansia*, *Muribaculaceae* and *Allobaculum*, while depleting the opportunistic pathogenic genus *Escherichia-Shigella* [40]. It suppressed inflammatory responses and enhanced antioxidant defense to block UC progression. Mulberry anthocyanins protected mucus layer integrity by preventing MUC2 downregulation in colitic mice, thereby reinforcing intestinal barrier function. Mulberry anthocyanins alleviate colitis by enriching *Akkermansia*, reducing proinflammatory TNF-α, IL-1β and IL-6, increasing anti-inflammatory IL-10, and restoring colonic tight junction protein (ZO-1, occludin, claudin-3) expression.

Dihydroquercetin is a natural bioflavonoid derived from medicinal plants including *Taxus chinensis* and *Silybum marianum*. In UC mice transplanted with fecal microbiota from healthy donors, dihydroquercetin treatment resulted in higher intestinal *Akkermansia* abundance compared with the control group [41]. Dihydroquercetin reduced intestinal mucosal damage and

inflammatory cell infiltration, and increased fecal butyrate and isobutyrate levels. It alleviates UC symptoms by modulating *Akkermansia* abundance, enhancing SCFA production, and suppressing colonic TNF-α, IL-1β and IL-6 expression.

2.4 TCM Polysaccharides

Carthamus tinctorius polysaccharide is a key bioactive ingredient of *Carthamus tinctorius*. The therapeutic effects of safflower polysaccharide on DSS-induced UC are dose-dependent [42]. Safflower polysaccharide remodeled gut microbiota structure, significantly increased the abundance of *Akkermansia* and *Limosilactobacillus*, and inhibited the expansion of *Bacteroides*. Notably, the abundance of *Akkermansia* in the high-dose group was approximately 5 times that in the model control group. Safflower polysaccharide upregulated mucin 1 (MUC1) and MUC2 expression, repaired abnormal intestinal mucosal injury and restored epithelial structural integrity. It also attenuated pathological tissue damage and reduced inflammatory cell infiltration. Safflower polysaccharide improves UC by enriching *Akkermansia*, reducing proinflammatory IL-1β, IL-6, IL-8 and TNF-α, and enhancing intestinal barrier function.

Lycium barbarum polysaccharide (LBP) is the major bioactive extract of *Lycium barbarum*. Li *et al.* [43] demonstrated that LBP intervention increased the abundance of beneficial *Akkermansia*, *Ruminococcaceae*, *Lactobacillus* and *Butyricicoccus*, while reducing UC-associated opportunistic pathogens *Mucispirillum* and *Sutterella*. LBP significantly mitigated intestinal inflammation, improved colonic histological morphology, upregulated tight junction proteins claudin-1 and ZO-1, and elevated intestinal SCFA contents. LBP ameliorates UC via enriching *Akkermansia*, increasing SCFA production, suppressing proinflammatory cytokines, and reinforcing intestinal barrier function, showing great potential as a novel adjuvant agent for UC prevention and treatment.

Codonopsis pilosula polysaccharide is an essential active component of *Codonopsis pilosula*. In UC mice, codonopsis polysaccharide treatment significantly increased the abundance of beneficial bacteria including *Akkermansia* and *Lactobacillus*, elevated the Firmicutes/Bacteroidetes ratio, and increased intestinal acetate and butyrate levels [44]. Elevated SCFAs bind to GPR family proteins and inhibit NLRP3 inflammasome activation, ultimately reducing intestinal inflammation. Codonopsis polysaccharide exerts anti-colitis effects by upregulating *Akkermansia*, promoting SCFA synthesis and blocking NLRP3 inflammasome-mediated inflammatory cascades.

Hericium erinaceus low-molecular-weight polysaccharide (HEP10) is a characteristic bioactive extract of *Hericium erinaceus*. HEP10 reversed DSS-induced alterations in gut microbial community structure via significant enrichment of *Akkermansia* and restored fecal SCFA depletion in colitic mice [45]. In addition, HEP10 inhibited the production of proinflammatory cytokines (TNF-α, IL-1β, IL-6), inducible nitric oxide synthase (iNOS) and cyclooxygenase-2 (COX-2) in colonic tissues. It also suppressed the activation of NLRP3 inflammasome, nuclear factor kappa-B (NF-κB) and MAPK signaling pathways to alleviate acute DSS-induced colitis. HEP10 exerts anti-UC activity by enriching *Akkermansia*, restoring SCFA metabolism, and inhibiting inflammatory cytokine secretion and NLRP3 inflammasome activation.

3 Conclusion and Prospect

Multiple bioactive components derived from traditional Chinese medicine alleviate UC and intestinal inflammation through multiple core mechanisms driven by *Akkermansia* enrichment: balancing gut microecology, promoting SCFA biosynthesis, enhancing intestinal barrier integrity via upregulating tight junction proteins, and suppressing the expression of proinflammatory cytokines and NLRP3 inflammasome. At present, the precise molecular mechanisms by which TCM ingredients regulate *Akkermansia* to improve UC remain incompletely clarified globally. Therefore, the development of innovative technologies to further elucidate the *Akkermansia*-mediated regulatory network of TCM active components in UC treatment is urgently required. Recently, an oral *Akkermansia*-mimetic nanotherapeutic agent (AM@HMPB@E) has been developed, which relieves UC by repairing intestinal epithelial barrier damage and eliminating excessive reactive oxygen/nitrogen species [46]. Combined with modern biotechnologies, including 16S rDNA sequencing, fecal microbiomics and metagenomic sequencing, the regulatory effects of TCM active ingredients on gut microbiota can be analyzed with high precision to optimize individualized UC treatment strategies. Novel nanomaterial technologies and advanced molecular detection methods will facilitate in-depth exploration of the *Akkermansia*-dependent mechanisms of TCM, providing innovative insights for the clinical management of ulcerative colitis.

Conflict of Interest: None

Reference

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· 炎症性肠病专题·研究进展 ·

Akk菌：中草药活性成分改善溃疡性结肠炎的关键靶点

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摘要：溃疡性结肠炎（UC）的发病与肠道菌群失调密切相关，其中嗜黏蛋白阿克曼菌（*Akkermansia muciniphila*，Akk菌）的丰度下降是重要特征。近年来研究发现，中草药活性成分可通过显著提升Akk菌丰度，调控短链脂肪酸水平、增强肠黏膜屏障、降低炎症因子水平等，进而改善UC症状。本文系统综述了Akk菌在UC治疗中的作用以及中草药活性成分调控Akk菌改善UC的机制，为开发基于肠道菌群干预的UC辅助疗法提供新的理论依据。

关键词：嗜黏蛋白阿克曼菌；溃疡性结肠炎；肠道微生态；中草药；活性成分；肠道菌群；黏膜屏障

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Akkermansia muciniphila: key target for improving ulcerative colitis with active components of Chinese medicine

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Abstract: The onset of ulcerative colitis (UC) is closely related to intestinal flora imbalance, with a significant decrease in the abundance of *Akkermansia muciniphila* being a key feature. Recent studies have found that active components of Chinese medicine can improve UC symptoms by significantly increasing the abundance of *Akkermansia muciniphila*, regulating short-chain fatty acid levels, enhancing the intestinal mucosal barrier, and reducing the levels of inflammatory factors. This article systematically reviews the role of *Akkermansia muciniphila* in the treatment of UC and the mechanism by which active components of Chinese medicine regulate *Akkermansia muciniphila* to improve UC, providing a new theoretical basis for the development of UC adjuvant therapies based on intestinal flora intervention.

Keywords: *Akkermansia muciniphila*; Ulcerative colitis; Intestinal microecology; Chinese medicine; Active component; Gut microflora; Intestinal mucosal barrier

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溃疡性结肠炎（ulcerative colitis，UC）是一种慢性复发性疾病，与免疫失衡和肠道微生态失调有着密切的关系。人类肠道微生物群的组成失衡（如益生菌减少、机会致病菌或病原菌增加）与UC发病有关。嗜黏蛋白阿克曼菌（*Akkermansia muciniphila*，Akk菌）是一种定植于肠道黏液层的革兰阴性厌氧菌，可在黏液层中生长，直接参与免疫、代谢、炎症等生理功能[1-2]。临床试验发现，UC患者粪便中Akk菌的丰度显著低于健康人群，且处于UC活动期患者的Akk菌丰度明显低于静止期[3-4]。此外，处于长期缓解期的UC患者，其粪便菌群组成更接近于健康人群，Akk菌的丰度与缓解期呈正相关。粪便样

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本中 Akk 菌的丰度降低可能作为预测 UC 发作或疾病活动性的潜在生物标志物[5]。还有其他临床研究也探索了 UC 患者中 Akk 菌的变化及可能的机制(表 1),进一步提示 Akk 菌可能是治疗 UC 的靶点之一[6-10]。

我国中草药资源相当丰富,多项研究发现中草药活性成分可有效改善 UC 症状,改变以 Akk 菌为代表的肠道菌群在改善 UC 症状中发挥重要作用[11-12]。本文探讨了 Akk 菌介导中草药活性成分改善 UC 的机制,以期为 UC 患者提供新的辅助治疗策略。

1　Akk 菌改善 UC 的机制

1.1　Akk 菌及其外膜成分的作用　一项动物实验发现补充 Akk 菌后,可使小鼠结肠黏液的厚度增加[13]。Bian 等[14]发现 Akk 菌可改善 3% 葡聚糖硫酸钠(DSS)诱导的小鼠结肠炎,降低血清和组织中的炎性细胞因子[肿瘤坏死因子-α(tumor necrosis factor-α,TNF-α)、白细胞介素(interleukin,IL)-1、IL-6]和趋化因子水平。Zhai 等[15]利用不同的 Akk 菌菌株实验发现,体外两种 Akk 菌株均有抗炎作用,体内二者均可下调小鼠结肠中促炎细胞因子干扰素-γ(interferon-γ,IFN-γ)和 TNF-α的表达。Liu 等[16]研究发现,Toll 样受体 4(Toll-like receptor,TLR4)的缺失会导致 Akk 菌显著减少,同时也会使维甲酸相关孤儿受体γt(RORγt)$^+$调节性 T 细胞(Treg)水平下降,炎症反应增加。给予 Akk 菌干预后,可增加 RORγt$^+$ Treg 细胞比例并激活其介导的免疫反应,从而改善 TLR4 缺失小鼠的结肠炎。此外,Akk 菌可降低 UC 小鼠结肠中 TNF-α和 IL-1β的表达,同时增加结肠中杯状细胞的数量和 MUC2 的表达[17]。因此,Akk 菌可降低炎症因子的水平以及增加肠黏膜屏障作用,从而改善结肠炎症。

Amuc_1100 和 Amuc_2109 均是 Akk 菌的外膜蛋白。对 UC 患者和结肠炎小鼠口服补充巴氏灭活的 Akk 菌或 Amuc_1100,可减少炎性细胞的浸润,改善 DSS 诱导的 UC 症状[18]。另有研究发现,Akk 菌和 Amuc_1100 能够修复由 5-氟尿嘧啶(5-FU)导致小鼠肠黏膜的损伤,降低 TNF-α和 IL-6 的水平以及抑制 NLRP3 炎症小体的激活,并恢复肠道屏障功能[19]。Qian 等[20]发现 Amuc_2109 通过抑制 NLRP3 炎症小体的表达以及抑制炎症因子(TNF-α、IL-1β、IL-6)改善 DSS 诱导的结肠炎。由此可见,Akk 菌以及其外膜蛋白在小鼠肠道中都表现出良好的抗炎作用。

1.2　Akk 菌产生的代谢物

1.2.1　短链脂肪酸(SCFAs)　SCFAs 是一类由肠道细菌发酵膳食纤维产生的有机酸。研究发现,UC 患者粪便中的 SCFAs 水平较健康人群降低[21]。SCFAs 为肠上皮细胞提供能量,促进肠道黏膜的修复,维持肠道屏障功能,免受病原体侵害。Akk 菌作为可降解黏液的益生菌,其产生的 SCFAs(如乙酸、丙酸、丁酸等)具有多种生理功能,可缓解 UC 患者症状。最新研究发现,从健康人粪便中分离的 Akk 菌株(Akk ONE)可显著增加小鼠盲肠中 SCFAs 的含量,进而缓解小鼠 UC 症状[22]。还有研究表明,SCFAs 可激活 AhR/IL-22 通路,改善结肠病理损伤、抑制炎症反应并调节肠道紧密连接蛋白的表达,发挥抗 UC 作用[23]。Wang 等[24]研究发现,SCFAs 可逆转 Treg/辅助性 T 细胞(Th17)细胞失衡,从而改善 UC。此外,SCFAs 的产生还可以提高抗炎细胞因子水平,而使促炎细胞因子 IL-8 的水平下降,同时改善上皮紧密连接的完整性[25]。Hong 等[26]研究发现,SCFAs 可通过上皮细胞上 G 蛋白偶联受体 43(GPR43)来缓解结肠炎。进一步研究表明,补充 Akk 菌后产生的丙酸与肠上皮细胞表面的 GPR43 结合,增强紧密连接蛋白 occludin 和人紧密连接蛋白(ZO-1)的表达,从而改善肠上皮屏障完整性[27]。

1.2.2　其他　Akk 菌的代谢产物还有γ-氨基丁酸、肌酐、鸟氨酸脂质等,但目前尚未明确这些代谢产物与 UC 缓解存在直接关联。有研究发现肌酐可能与增强肠道生态系统稳态和改善肠道屏障功能有关[28],而 Akk 菌的其他代谢产物对 UC 的作用有待进一步研究。

1.3　Akk 菌细胞外囊泡(EV)　Kang 等[29]发现 Akk 菌分泌的 EV 处理后可增强结肠壁上皮稳定性和减少炎性细胞浸润,从而改善 2%DSS 诱导的小鼠结肠炎,减少结肠组织损伤。后续 Zheng 等[30]研究不仅证实了此观点,还发现 Akk 菌的 EV 可通过提高杯状细胞分泌的 MUC2 的表达,改善黏液完整性和降低肠道通透性,显著增强肠道屏障的作用。

综上所述,Akk 菌可通过抑制炎症因子和炎症小体的表达、产生 SCFAs 和增强肠道黏膜屏障,改善 UC 症状,缓解炎症反应。具体机制见图 1。

表 1　UC 患者中 Akk 菌的变化及可能的机制

Tab.1　Changes and possible mechanisms of Akk bacteria in UC patients

样本量	主要发现	Akk 菌变化的可能机制	参考文献
33 例(活动期 UC 患者 19 例与健康对照 14 例)	UC 患者肠道中 Akk 菌的丰度降低	肠黏膜中的黏蛋白 2(MUC2)的含量下降,导致以 MUC2 作为唯一碳源的 Akk 菌的丰度下降	[6]
54 例(活动期 UC 患者 20 例、静止期 UC 患者 14 例与健康对照 20 例)	活动期 UC 患者肠道中的 Akk 菌的丰度低于静止期 UC 患者与健康对照人群	黏液凝胶层中硫酸化粘蛋白的相对比例降低可能会导致 Akk 菌的丰度降低	[7]
185 例(UC 患者 41 例与健康对照 144 例)	UC 患者的粪便样本中 Akk 菌的丰度降低	UC 患者肠道中,作为 Akk 菌能量来源的黏蛋白含量减少	[8]
163 例(缓解期 UC 患者 66 例与健康对照 97 例)	UC 患者的粪便样本中 Akk 菌的丰度降低	—	[9]
10 例(UC 患者 6 例与健康对照 4 例)	UC 患者的粪便样本中 Akk 菌的丰度降低	—	[10]

注:"—"代表原文献中未提及 Akk 菌变化的可能机制。

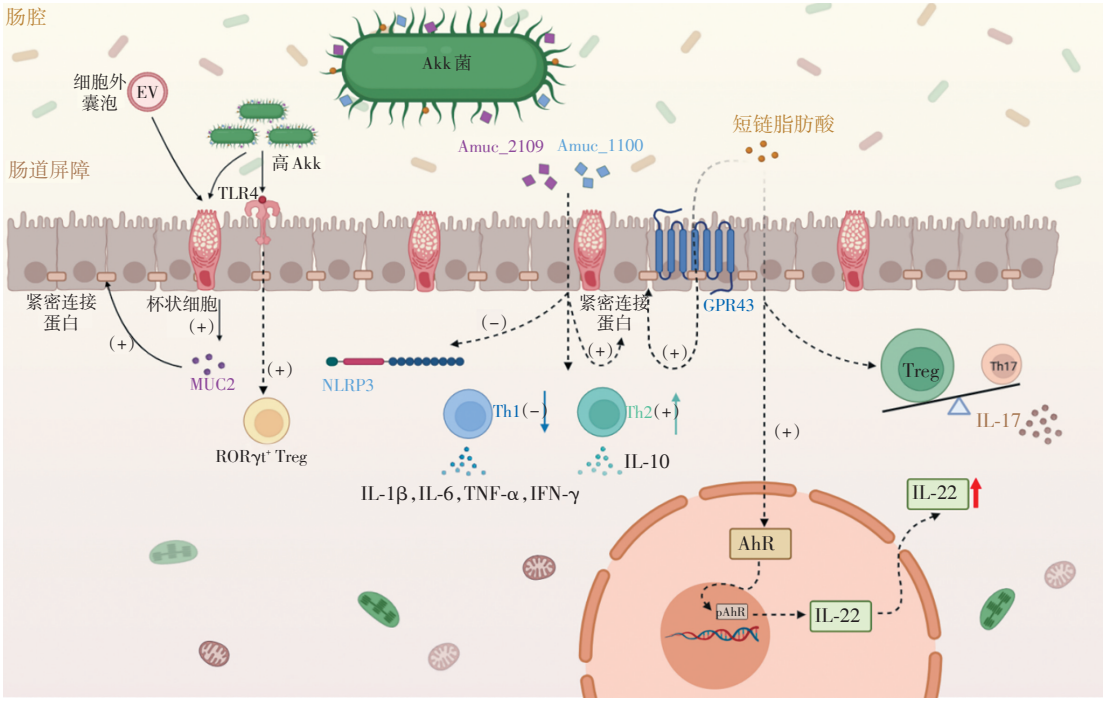

图 1　Akk 菌改善 UC 的作用机制

Fig.1　Mechanism of Akk bacteria in improving UC

2　Akk 菌在中草药活性成分治疗 UC 中的作用

2.1　*生物碱类*　小檗碱是从中草药黄连等植物中提取并分离得到的一类异喹啉类生物碱。Yang 等[31]研究发现，使用小檗碱后，DSS 诱导的 UC 小鼠模型肠道中 Akk 菌、*f_Muribaculaceae*、*Bacteroides*、*Dubosiella* 和 *Allobaculum* 的丰度显著增加。随后单独验证发现 Akk 菌是在高剂量小檗碱组中的肠黏膜内显著富集。此外，还发现小檗碱通过增加 *Bacteroides* 和 Akk 菌的丰度，抑制血清中花生四烯酸的代谢，并减少炎症相关的代谢物。同时，小檗碱通过增加 Akk 菌的丰度，有效改善 UC 小鼠小肠上皮细胞的凋亡，增强肠道屏障功能。提示小檗碱可能通过增加 Akk 菌的丰度，减轻炎症反应并增强肠道屏障功能，改善 UC 炎症。

药根碱是一种从多种植物中分离提取的异喹啉生物碱，可从黄连和黄柏中提取得到。Zhang 等[32]发现，药根碱可显著增加 UC 小鼠肠道中 Akk 菌的丰度。此外，药根碱治疗后小鼠的结肠组织中一氧化氮合酶 2（NOS2）的表达显著降低，其表达水平与 Akk 菌的相对丰度呈负相关，抑制 NOS2 可以缓解肠道炎症。提示药根碱可能通过增加 Akk 菌的丰度和降低病原菌的相对丰度，减轻肠道炎症反应，发挥抗 UC 作用。

原阿片碱是一种异喹啉生物碱，是中药博落回的主要抗炎成分之一。原阿片碱显著增加了 Akk 菌有益细菌的丰度，以及减少变形菌、大肠杆菌和肠球菌的丰度；此外，原阿片碱给药能有效缓解 DSS 诱导的小鼠结肠炎症状，并抑制炎症因子的表达[33]。提示原阿片碱可能通过增加 Akk 菌的丰度，降低炎症因子 TNF-α、IL-1β、IL-6 的水平以及升高紧密连接蛋白 ZO-1 和 occludin 的表达水平，从而有效缓解 DSS 诱导的 UC。

苦参碱存在于中药苦参、苦豆子和广豆根中。研究表明，苦参碱能缓解 UC 小鼠肠道菌群多样性的下降，增加 Akk 菌和乳酸杆菌的丰度[34]。苦参碱不仅能有效改善 DSS 诱导的小鼠结肠组织氧化应激，还能减少炎症细胞因子 TNF-α、IL-6、IL-17A 和 IL-1β 的产生。此外，苦参碱可通过调节 Treg/Th17 细胞失衡来治疗小鼠结肠炎。同时，苦参碱可逆转 DSS 诱导的肠道损伤和杯状细胞的数量，并上调结肠中紧密连接蛋白 occludin 和 ZO-1 的表达。提示苦参碱可能通过增加 Akk 菌的丰度增强结肠屏障完整性、抑制肠道炎症和减少 Treg/Th17 细胞失衡，从而改善 UC 症状。

2.2　*多酚类*　白藜芦醇是一种植物衍生的生物活性多酚，主要来源于中药虎杖。研究报道，在 2,4,6−三硝基苯磺酸诱导的 UC 小鼠中，白藜芦醇治疗后 Akk 菌和 *Ruminococcus gnavus* 的丰度显著增加，*Bacteroides Acidifaciens* 的丰度降低[35]。白藜芦醇通过恢复肠道菌群失调，降低炎症反应并抑制 T 细胞反应。此外，白藜芦醇治疗后能提高乙酸和异丁酸水平，对 UC 小鼠起保护作用。表明白藜芦醇可能通过增加 Akk 菌的丰度，诱导抗炎因子 IL-10 的产生并抑制炎症性 Th1/Th17 细胞以及提高 SCFAs 水平，发挥抗 UC 作用。

绿原酸（ChA）是中药金银花的主要抗菌、抗病毒有效药理成分之一。研究提示，ChA 干预后显著增加了 DSS 诱导结肠炎小鼠中 Akk 菌的比例，并通过抑制 NF-κB 信号通路的活性和炎性细胞因子 IFN-γ、TNF-α 和 IL-6 的分泌，改善 DSS 诱导的急性结肠炎[36]。提示 ChA 对 UC 的保护作用可能与 Akk 菌的丰度增加后，导致肠道和全身炎症减轻有关。

2.3　*黄酮类*　淫羊藿苷是从小檗科淫羊藿属植物中提取的一种黄酮类化合物。研究表明，在淫羊藿苷干预下，DSS 诱导

的结肠炎小鼠肠道菌群中，有益菌 Akk 菌、*Lachnospiraceae* 和 *Lactobacillus* 显著增加，而 *Helicobacteriaceae*、*Bacteroides* 和 *Turicibacter* 减少[37]。同时，淫羊藿苷可增加 Akk 菌等有益菌的活性。此外，淫羊藿苷治疗后可以缓解结肠组织的炎症损伤。提示淫羊藿苷可能通过增加 Akk 菌的丰度和活性，减轻组织损伤和降低炎症因子 IL-6 和 TNF-α的水平，以改善 DSS 诱导的 UC。

黄秋葵总黄酮（TFA）是从黄秋葵花中提取的化合物，具有显著的抗炎、镇痛和抗氧化活性。研究发现，高剂量 TFA（TFA-H）可显著恢复 DSS 诱导的肠道菌群失调，并极大地富集了 Akk 菌[38]。TFA-H 还可减轻 DSS 诱导的实验性结肠炎结肠缩短和组织学损伤，且 TFA-H 处理后使 MUC2 和 ZO-1 的表达恢复到正常水平。此外，TFA 显著改善结肠炎症反应和肠上皮屏障功能障碍；TFA 在体外直接促进 Akk 菌的生长。提示 TFA 可能通过大幅增加 Akk 菌的丰度，增强肠道屏障和降低炎症因子 TNF-α、IL-6、IFN-γ、IL-1β和 IL-17A 的水平，进而减轻 UC。

芹菜素是天然存在的一种黄酮类化合物，在车前子、络石藤、藿香等中药中含量较高。Fu 等[39]研究发现，在 UC 小鼠模型中，芹菜素治疗后显著提高了 Akk 菌和 *Faecalibaculum* 的丰度。此外，芹菜素可预防结肠炎小鼠的肠道屏障损伤，并且大剂量芹菜素比柳氮磺胺吡啶具有更好的治疗效果。芹菜素也可显著增加 SCFAs 水平。提示芹菜素可能通过增加 Akk 菌丰度，一方面提高小鼠肠道中 SCFAs 含量，促进抗炎因子 IL-10 的表达并抑制促炎因子 TNF-α、IL-1β及 IL-6 表达；另一方面上调紧密连接蛋白 ZO-1、claudin-1 和 occludin 的表达，以恢复肠道屏障的完整性，从而在改善 UC 上起到一定的作用。

桑椹花青素是从中药桑椹中提取的一种水溶性天然色素，属于黄酮类化合物。研究表明，桑椹花青素治疗可以大幅增加有益菌 Akk 菌、*Muribaculaceae* 和 *Allobaculum* 相对丰度和降低潜在有害细菌 *Escherichia-Shigella* 的水平[40]。此外，桑椹花青素可能具有抑制炎症反应和增强抗氧化防御能力，进而抑制 UC；同时，桑椹花青素通过抑制结肠炎小鼠结肠中 MUC2 的下调来保护黏膜层的完整性，从而增强肠道屏障功能，抑制结肠炎进展。提示桑椹花青素可能通过增加 Akk 菌的丰度，降低促炎因子 TNF-α、IL-1β和 IL-6 的水平并增加抗炎因子 IL-10 的水平，同时恢复结肠紧密连接蛋白 ZO-1、occludin 和 claudin-3 的表达，从而降低炎症反应、维持上皮完整性和保护屏障功能而改善 UC。

二氢槲皮素是一种可在红豆杉和水飞蓟药用植物中提取到的生物类黄酮。研究表明，采用二氢槲皮素处理移植健康小鼠粪便菌群的 UC 小鼠模型，与对照组相比，二氢槲皮素处理后小鼠肠道中 Akk 菌丰度相对较高[41]。此外，二氢槲皮素减少了小鼠的肠道黏膜损伤和炎性细胞浸润，并显著增加粪便中 SCFAs（丁酸和异丁酸）的水平。提示二氢槲皮素可能通过影响 Akk 菌的丰度，提升 SCFAs 水平以及抑制结肠组织中 TNF-α、IL-1β和 IL-6 的表达，对缓解 UC 的症状起到一定的作用。

2.4　中草药多糖类　红花多糖是中药红花中主要有效成分之一。研究表明，红花多糖对 DSS 诱发的 UC 症状的治疗效果呈剂量依赖性[42]。红花多糖可以调整肠道菌群结构，明显增加 Akk 菌和 *Limosilactobacillus* 的丰度，抑制 *Bacteroides* 的丰度。尤其是 Akk 菌，高剂量红花多糖处理组小鼠中 Akk 菌丰度约为模型对照组的 5 倍。此外，红花多糖处理后黏蛋白 1（MUC1）和 MUC2 的表达明显增加，有效改善肠黏膜的异常损伤，恢复上皮结构的完整性。红花多糖还可以减轻病理损伤和抑制肠道炎症细胞浸润。表明红花多糖可能通过增加 Akk 菌的丰度，降低炎症因子 IL-1β、IL-6、IL-8 和 TNF-α的水平及增强肠屏障功能，有效改善 UC 小鼠的症状。

枸杞多糖是药材枸杞中的有效提取物之一。Li 等[43]研究发现，给予枸杞多糖后，小鼠肠道内 Akk 菌、*Ruminococcaceae*、*Lactobacillus* 和 *Butyricicoccus* 的丰度显著增加，并且减少了与 UC 相关的机会致病菌 *Mucispirillum* 和 *Sutterella* 的丰度。同时枸杞多糖可显著降低小鼠肠道炎症反应，改善结肠组织结构，上调紧密连接蛋白 claudin-1 和 ZO-1 表达，并显著增加肠道中 SCFAs 含量。提示枸杞多糖可能通过增加 Akk 菌的丰度，增加 SCFAs 含量、降低炎症因子 IL-1β、IL-6 和 TNF-α的水平及增强肠屏障功能，来改善 UC 症状，有望作为预防和治疗 UC 的辅助药物。

党参多糖是党参中的一种重要活性成分。研究发现，党参多糖处理 UC 小鼠后肠道中 Akk 菌与乳杆菌等有益菌的丰度显著增加，并提高了厚壁菌门与拟杆菌门的比例，进一步增加肠道中 SCFAs（乙酸和丁酸）水平，进而使 SCFAs 与 GPR 蛋白结合抑制 NLRP3 炎症小体的激活，从而减轻肠道炎症[44]。提示党参多糖可能通过增加 Akk 菌的丰度，进一步增加 SCFAs 的产生，抑制 NLRP3 炎症小体的激活，发挥改善 UC 作用。

猴头菇低分子量多糖（HEP10）是中药材猴头菇的有效提取物之一。研究发现，HEP10 通过显著增加 Akk 菌的丰度，逆转了 DSS 诱导的肠道群落组成和结构的变化；同时，HEP10 干预后，小鼠粪便中 SCFAs 含量有所恢复[45]。此外，HEP10 一方面可抑制结肠炎小鼠结肠组织中 TNF-α、IL-1β、IL-6、诱导型 iNOS 及 COX-2 的产生；另一方面能显著抑制 NLRP3 炎性小体、核因子κB（nuclear factor kappa-B，NF-κB）及 MAPK 通路的激活，有效缓解 DSS 诱导的小鼠急性 UC 的症状。提示 HEP10 可能通过增加 Akk 菌的丰度，增加 SCFAs 的产生，抑制炎症因子 TNF-α、IL-1β、IL-6 及炎症小体 NLRP3 的表达，发挥抗 UC 作用。

3　结语与展望

多种中草药活性成分通过增加 Akk 菌丰度，进而调节肠道菌群平衡、促进 SCFAs 产生、增强肠道屏障功能（增加紧密连接蛋白表达）、抑制促炎细胞因子（TNF-α、IL-1β、IL-6 等）和炎症小体 NLRP3 的表达等多重机制，发挥改善 UC 症状和缓解肠道炎症作用。目前，国内外现有研究对中草药活性成分调节 Akk 菌丰度后，如何改善 UC 的具体作用机制尚未明确，因此，开发新的技术进一步揭示 Akk 菌在中草药活性成分中改善 UC 的作用机制显得尤为必要。近期有团队研发了一种

口服的仿肠道菌Akk菌的纳米治疗剂AM@HMPB@E，该纳米治疗剂通过修复肠上皮屏障和清除过量的活性氧/氮物质来改善UC症状[46]。结合现代生物技术，如16S rDNA测序、粪便微生物组学以及宏基因测序等手段，更准确地分析中草药活性成分对肠道菌群的影响，为UC患者提供更好的治疗。上述所提及的纳米颗粒技术以及现代生物检测技术都可有助于探索Akk菌在中草药活性成分改善UC的具体机制，为临床治疗UC提供新的思路。

利益冲突 无

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