

# Metabolic Reprogramming in Ulcerative Colitis: The Gut Microbiota–Metabolite–Immunity Axis and the Regulatory Role of Traditional Chinese Medicine

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**Abstract:** *Ulcerative colitis (UC) is a chronic inflammatory bowel disease with unclear etiology, involving intestinal barrier dysfunction, immune dysregulation, gut microbiota imbalance, and host metabolic abnormalities. Multi-omics research has advanced the “gut microbiota–metabolite–host immunity” axis as a central framework for understanding UC pathogenesis. Short-chain fatty acids (SCFAs) and tryptophan metabolites—key microbiota-derived metabolites—play essential roles in maintaining intestinal immune homeostasis and regulating inflammation. Their disruption promotes persistent inflammation and disease progression. Traditional Chinese Medicine (TCM) offers advantages in UC treatment through holistic regulation and multi-target intervention. Evidence indicates that TCM formulas, individual herbs, and their bioactive constituents reshape gut microbiota composition and function, modulate SCFA production and tryptophan metabolism, and alleviate mucosal inflammation. This review systematically delineates key metabolic disruptions in UC, summarizes current understanding of TCM-mediated metabolic reprogramming, and evaluates TCM regulation of SCFA and tryptophan pathways, aiming to establish a theoretical foundation for integrating TCM with conventional UC management.*

**Keywords:** Ulcerative Colitis, Gut Microbiota, Short-Chain Fatty Acids, Tryptophan Metabolism, Traditional Chinese Medicine, Metabolic Reprogramming.

## 1. Introduction: From Inflammation Suppression to Metabolic Remodeling

Ulcerative colitis (UC) is a chronic inflammatory bowel disease with relapsing colonic mucosal inflammation. Current first-line treatments—including 5-aminosalicylates, corticosteroids, biologics, and small molecule drugs—often face challenges such as unstable efficacy, high recurrence rates, and acquired resistance [1, 2]. Targeting individual inflammatory factors appears insufficient to restore gut microbiota–host immune homeostasis [3].

Multi-omics technologies have revealed that UC results from complex interactions among gut microbiota dysbiosis, metabolic network disruption, and impaired immune regulation. This understanding has established the “gut microbiota–metabolism–immunity” axis as a key framework for elucidating UC pathogenesis, with microbiota-derived metabolites serving as critical mediators linking microecological changes to host pathology [4].

Among the implicated metabolic pathways, short-chain fatty acid (SCFA) metabolism — particularly butyrate synthesis — and tryptophan metabolism represent two central hubs. Reduced SCFAs impair colonic epithelial energy metabolism and mucosal barrier integrity [5], while dysregulated tryptophan metabolism disrupts immune balance via the aryl hydrocarbon receptor (AhR) pathway [6]. Notably, these metabolic abnormalities drive UC onset, progression, and recurrence, rather than merely reflecting active disease.

In Traditional Chinese Medicine (TCM), UC manifestations are classified under concepts such as “diarrhea,” “dysentery,” or “intestinal flux.” The primary pathogenesis involves

impaired spleen and stomach transportation and transformation, with spleen deficiency as the root cause. Disease progression often yields patterns including damp-heat accumulation, spleen deficiency with dampness, or spleen-kidney yang deficiency [7]. Zhang Zhongjing’s Treatise on Cold Damage Disorders and Miscellaneous Diseases described symptoms closely resembling UC, and formulas such as Pulsatilla Decoction (Baitouweng Tang) remain widely used today [8].

Unlike Western medicine targeting single molecules, TCM features multi-component, multi-target synergistic actions suited for remodeling complex metabolic networks [9]. However, existing reviews largely focus on macroscopic “TCM regulates gut microbiota” statements without systematic integration of specific metabolic pathways. This review focuses on SCFA and tryptophan metabolism to summarize TCM-mediated metabolic reprogramming in UC, providing a theoretical basis for mechanistic studies and treatment optimization.

## 2. Metabolic Dysregulation in UC: SCFA and Tryptophan Pathways

### 2.1 SCFA Deficiency and Metabolic Reprogramming

Short-chain fatty acids (SCFAs) — primarily acetate, propionate, and butyrate—are produced by anaerobic gut bacteria from dietary fiber. Butyrate serves as the main energy source for colonic epithelial cells, maintains barrier integrity by upregulating tight junction proteins, and exerts immunomodulatory effects as a histone deacetylase (HDAC) inhibitor and G protein-coupled receptor activator, promoting regulatory T cell (Treg) differentiation and inhibiting Th17

responses [10-12].

In UC, SCFA-producing bacteria (Lachnospiraceae, Ruminococcaceae, Faecalibacterium prausnitzii) are significantly reduced, leading to persistent butyrate deficiency [13]. This causes colonic epithelial cells to shift from oxidative phosphorylation to glycolysis-driven pathological metabolic reprogramming [14]. Concurrently, reduced HDAC inhibition and GPCR signaling impair Treg function and enhance pro-inflammatory responses, exacerbating barrier disruption [15]. This cascade—"microbiota reduction → SCFA deficiency → metabolic reprogramming → immune amplification"—drives persistent UC inflammation, positioning SCFA metabolism as a key therapeutic target [16].

## 2.2 Dysregulation of Tryptophan Metabolic Pathways

Tryptophan is metabolized via three pathways: kynurenine, 5-hydroxytryptamine (5-HT), and microbiota-mediated indole. Microbiota-derived indole and indole-3-propionic acid (IPA) serve as endogenous aryl hydrocarbon receptor (AhR) ligands, activating AhR signaling to promote IL-22 secretion and maintain mucosal immune homeostasis [17, 18].

In UC, indoleamine-2,3-dioxygenase 1 (IDO1) is aberrantly activated, diverting tryptophan toward the kynurenine pathway and reducing production of AhR ligands [19]. Persistent AhR signaling impairment inhibits the ILC3-IL-22 axis, compromising barrier repair and antibacterial defense, forming a vicious cycle of "metabolic dysregulation → barrier disruption → inflammation amplification → microbiota imbalance" [20]. Restoring microbial indole metabolism and AhR signaling represents a promising therapeutic strategy.

## 2.3 The Metabolism-Inflammation Vicious Cycle

SCFA and tryptophan abnormalities interact synergistically. SCFA deficiency compromises barrier integrity, increasing microbial antigen translocation and IDO1 upregulation [21]. Conversely, impaired tryptophan-AhR signaling disrupts SCFA-producing bacterial colonization, further reducing SCFA levels [22]. These mutually reinforcing abnormalities perpetuate intestinal inflammation, establishing a self-sustaining metabolism-inflammation vicious cycle.

## 3. TCM as a Metabolic Regulator: Theoretical Advantages

TCM theory holds that the spleen and stomach are central to nutrient transformation and distribution. Impaired spleen and stomach function leads to systemic metabolic dysregulation, aligning with modern concepts of impaired metabolic homeostasis and sustained inflammation [23]. TCM treatment strategies—such as clearing heat and eliminating dampness, invigorating the spleen and supplementing qi, and tonifying the kidney—exhibit distinct yet interconnected metabolic regulatory effects.

From a pharmacological perspective, TCM features multi-component, multi-target, multi-pathway synergistic actions, enabling simultaneous modulation of gut microbiota composition, microbial metabolic function, and host cell

signaling [24]. This "holistic-multi-dimensional-synergistic" approach offers unique advantages for remodeling complex metabolic networks [25].

## 4. TCM Remodels the SCFA Metabolic Axis

Animal and clinical studies demonstrate that TCM formulas increase SCFA-producing bacteria and elevate colonic SCFA levels, particularly butyrate, correlating with reduced disease activity and clinical remission [26]. Mechanistically, TCM polysaccharides (e.g., astragalus polysaccharides, Poria cocos polysaccharides) serve as fermentation substrates for SCFA-producing bacteria, while heat-clearing herbs suppress opportunistic pathogens, creating a favorable microecological niche. Elevated SCFAs enhance tight junction protein expression (Occludin, ZO-1) and exert anti-inflammatory effects via HDAC inhibition and GPCR activation [24, 27].

## 5. TCM Regulates the Tryptophan Metabolic Axis

Bioactive TCM constituents such as curcumin inhibit aberrant IDO1 expression, modulating kynurenine pathway activity and alleviating inflammation-associated immune imbalance [28]. TCM formulas also reshape gut microbiota metabolic function, promoting endogenous AhR ligand (indole, IPA) generation and activating the AhR-IL-22 axis to enhance barrier integrity [29]. Regarding the 5-HT pathway, formulas like Pulsatilla Decoction and Shaoyao Decoction modulate gut microbiota to suppress aberrant 5-HT signaling, reducing inflammation [30].

## 6. Synergy: TCM Formulas Target Dual Metabolic Axes

Classic formulas such as Pulsatilla Decoction (Baitouweng Tang) exemplify dual-axis regulation. They increase SCFA-producing bacteria and butyrate levels, improving epithelial energy metabolism and barrier function, while simultaneously promoting indole derivative production to activate AhR signaling and suppress aberrant inflammation [31]. By targeting both the SCFA-GPR and tryptophan-AhR axes, such formulas break the metabolism-inflammation vicious cycle in UC.

## 7. Clinical Translation, Challenges, and Perspectives

Current evidence supports TCM's potential in regulating UC-associated metabolic disturbances. However, challenges remain, including TCM's complex composition, unclear causal relationships, and substantial individual variability. Future research should integrate multi-omics approaches (metagenomics, metabolomics, immunomics) with high-quality clinical trials to identify robust metabolic biomarkers—such as fecal butyrate and IPA levels—and enable metabolic phenotype-based TCM syndrome classification and personalized treatment.

In summary, TCM demonstrates unique advantages in re-establishing intestinal mucosal immune homeostasis through multi-target, systematic metabolic reprogramming,

particularly via regulation of SCFA and tryptophan axes. This metabolism-immunity-centric paradigm provides theoretical support for TCM modernization and lays a foundation for optimizing integrated UC treatment strategies.

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