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REVIEW

Targeting the Gut Microbiota with Herbal Compounds from Traditional Chinese Medicine: A Mechanistic Synthesis of a Novel Therapeutic Approach for Ulcerative Colitis

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Abstract: Ulcerative colitis (UC) represents a chronic relapsing inflammatory bowel disease characterized by substantial unmet clinical needs and limited curative modalities. Accumulating evidence implicates gut microbiota dysbiosis as a pivotal pathogenic driver, positioning microbiota-targeted interventions as promising therapeutic strategies. This review systematically delineates the mechanisms by which herbal compounds from Traditional Chinese Medicine ameliorate UC through the restoration of microbial and metabolic homeostasis—including the modulation of beneficial commensals and their bioactive metabolites—thereby reinforcing intestinal barrier integrity and dampening mucosal inflammation. Although translational bottlenecks persist, integrative multi-omics frameworks coupled with advanced pharmaceutical engineering offer viable pathways to bridge preclinical findings and clinical application. Taken together, deciphering the bidirectional crosstalk between herbal compounds and the gut microbiome paves the way for mechanism-based, personalized botanical therapeutics in UC management.

Keywords: ulcerative colitis, herbal compounds, gut microbiota, intestinal barrier, translational challenges

Introduction

Ulcerative colitis (UC), a chronic, relapsing inflammatory bowel disease (IBD) characterized by mucosal inflammation of the colon and rectum,[1] has emerged as a major global health challenge due to its increasing incidence and prevalence worldwide,[2,3] debilitating clinical outcomes, and the inadequacy of current therapeutic strategies. A systematic review demonstrated that UC incidence has increased by 2 to 5 fold over the past three decades in newly industrialized regions, including East Asia and Latin America, while prevalence in Western countries remains elevated at 50–200 cases per 100,000 population.[4] Clinically, UC imposes a significant burden due to its chronic relapsing course, which often leads to complications such as severe diarrhea, rectal bleeding, and malnutrition,[5,6] and confers a 1.7-fold increased lifetime risk of colorectal cancer in long-standing cases.[7,8] Economically, UC imposes a substantial global healthcare burden, with high direct costs arising from hospitalization for disease flares and long-term medication use, as well as significant indirect costs due to productivity losses.[9] Despite the availability of conventional therapeutic classes including 5-aminosalicylic acid compounds, corticosteroids, immunosuppressants, and biologic agents such as anti-tumor necrosis factor monoclonal antibodies,[10] a substantial proportion of patients (up to 30%) fail to achieve sustained remission, underscoring a critical efficacy gap in current management strategies. Furthermore, long-term use of these agents is associated with serious adverse effects, including opportunistic infections, osteoporosis, and an elevated risk of lymphoma, which collectively

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contribute to the significant limitations of existing pharmacologic approaches.[11] These efficacy and safety gaps underscore the urgent imperative for novel therapies that target the core pathogenic pathways of UC.[12]

Intestinal microbiota dysbiosis is a well-established central driver in the pathogenesis of ulcerative colitis.[13] Clinical and animal studies consistently identify hallmark features of UC-associated dysbiosis, including a decreased relative abundance of Firmicutes alongside an expansion of Proteobacteria.[14,15] Expanded Proteobacteria, particularly Enterobacteriaceae, elevate luminal lipopolysaccharide (LPS) levels,[16] activates Toll-like receptor 4 (TLR4) on epithelial and immune cells, triggering a nuclear transcription factor-κB (NF-κB)-mediated production of pro-inflammatory cytokines such as interleukin-6 (IL-6) and tumor necrosis factor-α (TNF-α).[17,18] This process directly links microbial dysbiosis to the inflammatory cascades characteristic of ulcerative colitis flares. Concurrently, the depletion of butyrate-producing commensals results in diminished luminal butyrate levels, which is a short-chain fatty acid (SCFA) that serves as the primary energy source for colonocytes and critically regulates the expression and function of tight junction proteins.[19] This impairment of butyrate-mediated epithelial homeostasis directly compromises intestinal barrier integrity, leading to increased permeability and mucosal damage that characterizes active ulcerative colitis.[20] Evidence from germ-free mouse models demonstrates that colonization with microbiota derived from UC patients can induce severe colitis, confirming the pathogenic potential of dysbiotic communities,[21] while clinical studies show that fecal microbiota transplantation (FMT) from healthy donors achieves symptom alleviation and clinical remission in a significant proportion of refractory UC cases, further substantiating the causal role of microbiota imbalance in disease pathogenesis.[22,23]

Traditional Chinese Medicine (TCM) has been utilized for millennia to treat gastrointestinal disorders, and contemporary preclinical and clinical research now substantiates its efficacy in promoting gut health.[24] Ancient TCM texts, such as the *Huangdi Neijing* and *Shennong Bencao Jing*, document the use of herbal formulas like Scutellaria Decoction (*Huangqin Tang*) for treating symptoms analogous to UC, with efficacy in ameliorating intestinal inflammation and restoring gut barrier function demonstrated in murine colitis models.[25] In dextran sulfate sodium (DSS)-induced mice models of colitis, herbals like *Scutellaria baicalensis* (*Huangqin*) significantly reduce intestinal inflammation and improve barrier integrity,[26,27] while *Astragalus membranaceus* (*Huangqi*) modulate key inflammatory pathways such as NF-κB and NOD-like Receptor Pyrin domain containing 3 (NLRP3) inflammasome activation.[28,29] Meta-analyses of randomized controlled trials have established that TCM interventions, particularly herbal medicines, significantly improve clinical remission rates in UC patients when combined with conventional therapy,[30] thereby providing robust clinical validation for TCM's efficacy in gut health management.

Despite the well-established association of gut microbiota dysbiosis in UC pathogenesis[13] and the historical application of herbal remedies for gastrointestinal disorders,[24] the mechanistic connections between herbal compounds, gut microbiota modulation, and UC resolution remain incompletely elucidated. To address this gap, this review synthesizes mechanistic evidence to clarify the relationship between the microbiota and UC pathogenesis, links herbal compounds to gut microbiota modulation, and ultimately elucidates how herbal compounds improve UC by regulating the microbiota. Furthermore, we critically examine the translational bottlenecks between preclinical findings and clinical implementation of herbal therapeutics. Integrating contemporary technological advances, we propose that multi-omics frameworks coupled with advanced pharmaceutical delivery systems represent pivotal strategies to bridge this translational divide and drive future breakthroughs in microbiota-targeted UC management.

The Gut Microbiota in Health and UC

Normal Gut Microbiota: Composition, Functions, and Host-Microbe Symbiosis

The normal gut microbiota is a complex and dynamic community, predominantly composed of trillions of microorganisms from the phyla *Firmicutes, Bacteroidetes, Actinobacteria, Proteobacteria*, and *Verrucomicrobia* (Figure 1). These microorganisms engage in a mutually beneficial symbiotic relationship with the host, performing critical metabolic, immune-modulatory, and barrier-supporting functions. *Firmicutes* (eg., *Lactobacillus, Faecalibacterium prausnitzii, Roseburia* spp.) and *Bacteroidetes* (eg., *Bacteroides thetaiotaomicron, Prevotella copri*) collectively account for approximately 90% of the adult gut microbiota. *Actinobacteria* (eg., *Bifidobacterium* spp)., *Proteobacteria* (eg., *Escherichia coli*), and *Verrucomicrobia* (*Akkermansia muciniphila*) represent the remaining minority.[31]

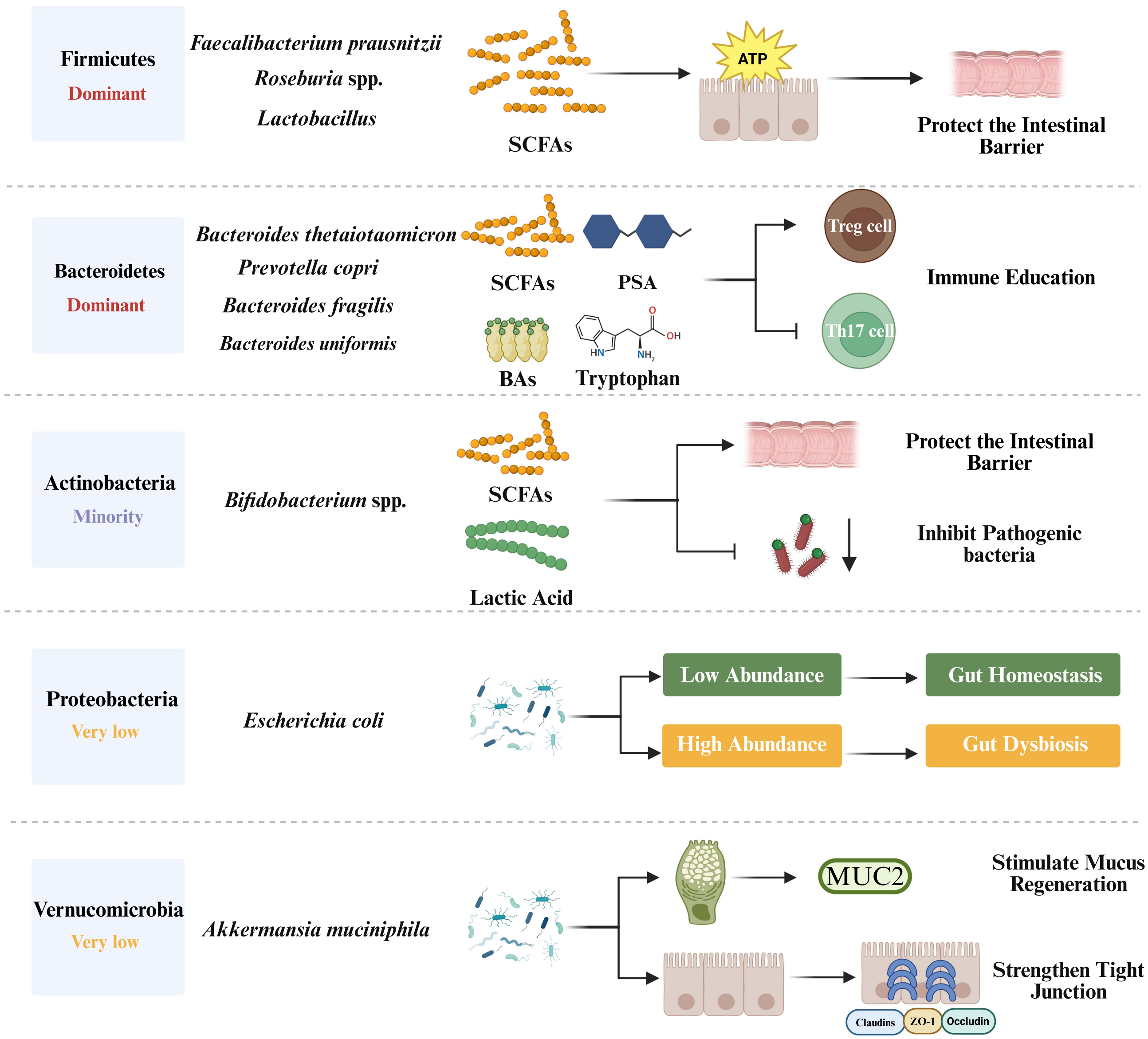

Figure 1 The core gut microbiota in health and its symbiotic influence on the host.

This microbial community establishes a mutualistic symbiosis with the human host, representing an integral component of intestinal anatomy and physiology. The human gastrointestinal tract provides a unique ecological niche for these microorganisms, characterized by a strictly anaerobic environment, stable temperature, controlled pH gradients, and a continuous supply of nutrients derived from the diet (indigestible fibers, resistant starches) and host secretions (mucins, sloughed epithelial cells). In return, these commensal microbes actively shape intestinal function through their metabolic output, immunomodulatory signals, and competitive exclusion of pathogens, thereby forming a functional meta-organism essential for host homeostasis.[32]

A primary function of the gut microbiota is the metabolic biotransformation of indigestible dietary components and host-derived substrates into a diverse array of bioactive metabolites that regulate host physiology. Central to this metabolic capacity is the fermentation of dietary fibers and complex carbohydrates, which evade host enzymatic digestion in the small intestine and reach the distal gut intact. Microbial carbohydrate-active enzymes, including polysaccharidases and glycosidases, hydrolyze these complex glycans into five- or six-carbon monosaccharides that undergo catabolism via the pentose phosphate pathway or Embden–Meyerhof–Parnas glycolysis to phosphoenolpyruvate

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and pyruvate. These intermediates subsequently fuel multiple anaerobic fermentation pathways to produce short-chain fatty acids (SCFAs; predominantly acetate, propionate, and butyrate) as terminal end products. Concurrently, the microbiota engages in extensive protein fermentation, wherein microbial proteases hydrolyze dietary and host-derived proteins into amino acids that undergo dissimilatory catabolic reactions, generating not only SCFAs and branched-chain fatty acids (BCFAs) but also ammonia, phenolic compounds, and indole derivatives. Furthermore, microbial bile salt hydrolases deconjugate primary bile acids, enabling subsequent 7α/β-dehydroxylation, epimerization, and oxidation reactions that yield diverse secondary bile acid pools, while tryptophanase activity directly transforms tryptophan into indole and its derivatives.[33]

Beyond metabolism, the normal gut microbiota plays a vital role in educating the host immune system by promoting immunoregulatory responses. For example, non-toxigenic *Bacteroides fragilis* produces polysaccharide A (PSA), which induces Foxp3$^+$ regulatory T cells (Tregs) and enhances interleukin-10 (IL-10) secretion, thereby suppressing excessive pro-inflammatory responses and supporting intestinal immune homeostasis.[34] Similarly, *Bacteroides uniformis* modulates intestinal bile acid metabolism[35] and restores the expression of intestinal immune barrier proteins by suppressing T-helper 17 (Th17) cell differentiation in colonic epithelial cells and inhibiting downstream NF-κB and MAPK inflammatory signaling pathways.[36]

In addition to immune modulation, beneficial commensals from minority phyla are pivotal in maintaining physical barrier integrity. Beneficial commensals from minority phyla, including *Actinobacteria* and *Verrucomicrobia*, reinforce the intestinal barrier through distinct but complementary mechanisms. *Bifidobacterium* spp. (*Actinobacteria*) produce acetate and lactate to lower luminal pH and inhibit pathogen growth, while generating exopolysaccharides that strengthen the mucus layer and competing with detrimental microorganisms for nutrients and adhesion sites.[37–40] Concurrently, *A. muciniphila* (*Verrucomicrobia*) enhances barrier integrity by degrading mucin to stimulate goblet cell production and upregulating tight junction proteins (zonula occludens-1 (ZO-1), occludin, and claudin-1), thereby maintaining epithelial tightness.[41]

Finally, the symbiotic equilibrium depends on the proper management of even low-abundance phyla, such as *Proteobacteria* (eg., *E. coli*). At baseline levels, these bacteria contribute to metabolic functions and microbial balance; however, their overgrowth transforms them into opportunistic pathogens that drive inflammatory pathology.[42]

Gut Dysbiosis in UC: Altered Diversity, Metabolism, and Immune Interactions

Gut dysbiosis in UC represents a profound disruption in the composition and balance of the gut microbiota, which alters microbial metabolism, undermines epithelial function, and perpetuates chronic intestinal inflammation.[13,43] One of the most notable changes in UC is the depletion of beneficial microbes, particularly those belonging to the *Firmicutes phylum*, which are key producers of SCFAs, especially butyrate.[44] The depletion of these key SCFA-producing bacteria, initiates a cascade of detrimental effects. It deprives colonocytes of their primary metabolic fuel, leading to an energy crisis that impairs cellular function and survival. Crucially, the loss of SCFA signaling undermines multiple protective mechanisms: it compromises epithelial barrier integrity by reducing the expression of tight junction proteins (eg., claudin-1) and mucin (MUC2), weakens the colonic hypoxic barrier favorable to commensals, and diminishes the production of antimicrobial peptides (AMPs). Furthermore, the absence of SCFAs, notably butyrate and propionate, disrupts immunomodulation by failing to inhibit histone deacetylases (HDAC) and activate receptors like G-protein-coupled receptor 43 (GPR43) and GPR109a on immune cells. This results in diminished anti-inflammatory cytokine production (eg., IL-10, TGF-β1), impaired differentiation of Tregs, and a consequent loss of braking mechanisms on the mucosal immune system, thereby directly fueling and perpetuating chronic inflammation[45] Beyond SCFA production, *F. prausnitzii* also plays a crucial role in suppressing NF-κB activation, which regulates the release of pro-inflammatory cytokines; its depletion thus worsens both inflammation and impedes mucosal healing.[46] Similarly, *Roseburia* species help reinforce the mucus barrier and promote Treg differentiation, vital for maintaining immune tolerance.[47]

Conversely, UC is marked by the expansion of pathogenic bacteria, particularly within the *Proteobacteria* phylum.[48] Pathobionts such as adherent-invasive Escherichia coli (AIEC) thrive in the inflammatory milieu of the UC colon.[49] These bacteria exploit nitrate and oxygen radicals, byproducts of the host's inflammatory response, to fuel their growth.[50] The overgrowth of these pathogens leads to epithelial invasion and triggers the activation of TLR4 via LPS binding. This activation subsequently stimulates the NLRP3 inflammasome, leading to the production of potent pro-inflammatory cytokines like IL-1β and TNF-α. This initiates a self-perpetuating inflammatory loop, intensifying mucosal immune activation and driving UC progression.[51]

Beyond these dominant phyla, multifaceted taxonomic perturbations further compromise mucosal homeostasis. *Bacteroidetes* exhibits strain-level heterogeneity with divergent pathogenic potentials: enterotoxigenic *B. fragilis* strains which highly secrete the highly pro-inflammatory *B. fragilis* toxin expand in the UC microenvironment to drive epithelial cleavage and exacerbate mucosal inflammation[52], whereas beneficial mucin-degrading species such as *B. thetaiotaomicron*, critical for mucus production and SCFA generation, are significantly depleted, weakening epithelial barrier integrity.[53] Concurrently, *Akkermansia muciniphila* (*Verrucomicrobia*), a specialized mucin-degrading bacterium that produces acetate and propionate essential for colonic mucus maintenance, is reduced in UC, resulting in diminished sulfated mucins and increased susceptibility to bacterial translocation.[54] Similarly, immunoregulatory *Actinobacteria*, particularly *Bifidobacterium* species (eg., *B. longum, B. adolescentis*) that modulate Th1/Th2 and Th17/Treg balance, are depleted, impairing immune tolerance and Treg mitochondrial fitness.[55–57] Lastly, sulfate-reducing *Desulfovibrionaceae* (*Proteobacteria*) perpetuate epithelial damage through hydrogen sulfide-mediated cytotoxicity, compromising colonocyte viability and mucosal integrity.[58]

In conclusion, UC-associated dysbiosis is characterized by a complex shift in the gut microbiota. This involves the depletion of beneficial microbes, such as SCFA-producing *Firmicutes* and immunoregulatory *Actinobacteria*; the expansion of pro-inflammatory pathogens from the *Proteobacteria* and specific *Bacteroides* strains; and the loss of mucin-degrading *Verrucomicrobia*. These profound microbial imbalances disrupt critical metabolic processes and immune regulation, ultimately leading to a breakdown in epithelial energy homeostasis, severe barrier dysfunction, and chronic intestinal inflammation.

The Pathogenic Role of the Gut Microbiota in Ulcerative Colitis

Compelling evidence from preclinical models,[59] human interventional trials,[60] and observational studies collectively validates the gut microbiota as a primary driver of ulcerative colitis pathogenesis, thereby underscoring its potential as a viable therapeutic target.[61] Germ-free (GF) mice, which entirely lack a gut microbiota, consistently demonstrate significantly attenuated colitis severity-exhibiting up to 60% lower disease activity indices, reduced epithelial damage, and diminished pro-inflammatory cytokine levels-when challenged with UC-inducing agents such as DSS or trinitrobenzene sulfonic acid (TNBS),[62,63] and this attenuated phenotype is reversed upon reconstitution with a complex microbiota.

Beyond compositional shifts, specific strains have been causally implicated in UC pathogenesis. *Proteus mirabilis*, detected at significantly higher frequencies in UC patients (65.9% vs. controls), exacerbates DSS-induced colitis in mice by downregulating IL-18-mediated mucin production.[64] Similarly, specific strains of *Streptococcus mutans*, isolated more frequently from UC patients, aggravate colitis in murine models through hepatic interferon-γ activation.[65] Additionally, *Enterococcus faecalis* strain OG1RF worsens experimental colitis through a glucosamine phosphotransferase system that enhances metabolic fitness.[66]

Conversely, FMT from UC patients into GF or antibiotic-treated mice has been shown to recapitulate UC-like phenotypes, including epithelial damage, immune infiltration, and elevated pro-inflammatory cytokine expression,[21,67] directly implicating dysbiotic microbiota in the induction of ulcerative colitis. In human interventional trials, FMT achieves clinical remission in approximately 30–50% of patients with refractory UC, with responders exhibiting restored microbial diversity and enrichment of anti-inflammatory taxa such as *F. prausnitzii*.[68,69]

Specifically, a recent randomised, double-blind, placebo-controlled trial showed that oral lyophilised FMT following antibiotic conditioning induced corticosteroid-free clinical remission with endoscopic response in 53% of active UC patients at week 8, compared with 15% in the placebo group (difference 38.3%, 95% CI 8.6–68.0; p=0.027), with sustained benefits observed at week 56 in patients continuing maintenance therapy.[70]

Furthermore, longitudinal cohort studies substantiate this relationship, demonstrating that individuals with pre-existing dysbiosis which is characterized by a reduced abundance of butyrate-producing bacteria exhibit a significantly elevated risk of developing UC, while cross-sectional analyses reveal that disease severity correlates with the degree of microbial disruption.[71]

Collectively, these findings unequivocally establish the gut microbiota as a central driver in UC pathogenesis, establishing microbial modulation as a viable therapeutic target. This mechanistic foundation necessitates a detailed examination of how TCM herbal compounds engage with and modulate the gut microbial ecosystem to exert therapeutic effects.

Interaction Between Herbal Compounds and Gut Microbiota

Herbal compounds derived from TCM can be systematically classified according to their distinct structural frameworks, which fundamentally determine their bioavailability, metabolic fate, and interactions with gut microbiota. These interactions are critical in mediating the pharmacological activities of TCM, as many compounds undergo microbial biotransformation prior to exerting systemic effects[72] (Table 1).

Flavonoids, defined by their characteristic benzopyrone core and multiple phenolic hydroxyl groups,[73] represent one of the most abundant classes of bioactive molecules in medicinal plants. Representative compounds include baicalin from *Scutellaria baicalensis* (*Huangqin*), luteolin from *Reseda odorata* (*Muxicao*), chrysanthemin from *Chrysanthemum indicum* (*Yejuhua*), perillaldehyde from *Perilla frutescens* (*Zisu*), and cardamonin from *Alpinia katsumadai* (*Caodoukou*).[74] These compounds primarily exist as glycosides, which must be hydrolyzed by microbial β-glucosidases in the colon to yield absorbable aglycones.[75,76] Such enzymatic activation underscores the indispensable role of gut microbiota in flavonoid bioavailability.[77] These aglycones have been shown to alleviate UC through inhibition of the NF-κB pathway, modulation of cytokine secretion, and enhancement of antioxidant defense.[75]

Polysaccharides, characterized as high-molecular-weight carbohydrate polymers with complex branched structures, constitute major bioactive constituents of numerous TCM herbals,[78] including *Astragalus polysaccharides* (APS) from *Astragalus membranaceus* (*Huangqi*), ginseng polysaccharides from *Panax ginseng* (*Renshen), lycium barbarum* polysaccharides (LBP) from *Lycium barbarum* (*Gouqi*), and lentinan from *Lentinus edodes* (*Xianggu*).[79] Due to their large molecular size, these compounds resist upper gastrointestinal absorption and reach the colon intact, where they serve as selective fermentable substrates for beneficial commensals (eg., *Bifidobacterium, Faecalibacterium*).[80] Specifically, APS increases *F. prausnitzii* abundance 2.5-fold in fecal samples from UC patients, whereas ginseng and LBP promote proliferation of Bifidobacterium and Lactobacillus species. Microbial fermentation of these substrates generates SCFAs such as butyrate, which confer anti-inflammatory and barrier-protective effects.[81]

Alkaloids, characterized by nitrogen-containing heterocyclic structures and basic properties, are predominantly isolated from TCM herbals such as *Coptis chinensis* (*Huanglian*) and *Sophora flavescens* (*Kushen*).[82–84] Berberine and matrine represent prototypical examples whose lipophilic nature and relatively small molecular size enable direct antimicrobial activity against enteric pathogens, including *E. coli* and *Klebsiella* species frequently overrepresented in dysbiotic UC microbiota.[85–87] Beyond direct bactericidal effects, these alkaloids remodel microbial composition, enriching beneficial taxa such as *Akkermansia muciniphila* and *Barnesiella intestinihominis* while reducing *Helicobacter* colonization.[88,89] This ecological shift elevates fecal concentrations of SCFAs, including butyrate, acetic acid, and propionic acid, while attenuating harmful LPS levels.[90] Consequently, these compounds suppress pro-inflammatory cytokine production, enhance intestinal barrier integrity, and restore mucosal homeostasis.

Terpenoids, comprising diverse isoprene-derived hydrocarbons ranging from monoterpenes to triterpenes, form another major class of TCM metabolites. Typical representatives include artemisinin from *Artemisia annua* (*Qinghao*), ginsenosides from *Panax ginseng* (*Renshen*), ginkgolides from *Ginkgo biloba* (*Yinxing*), and tanshinones from *Salvia miltiorrhiza* (*Danshen*).[91,92] Owing to their lipophilicity, terpenoids exhibit high intestinal permeability and are readily subjected to microbial oxidation, reduction, or hydrolysis, generating metabolites with enhanced bioavailability and bioactivity.[93] These compounds have been shown to modulate immune balance (eg., promoting Treg differentiation) and inhibit inflammatory pathways such as NF-κB, largely through microbially mediated transformation.[94,95]

Polyphenols and phenolic acids, characterized by aromatic rings bearing one or more hydroxyl groups, encompass a structurally heterogeneous group of metabolites ranging from simple phenolic acids to polymerized tannins. Representative examples include rhein from *Rheum palmatum* (*Dahuang*), curcumin from *Curcuma longa* (*Jianghuang*), chlorogenic acid from *Lonicera japonica* (*Jinyinhua*), and polyphenolic extracts from *Portulaca oleracea* (*Machixian*) and *Origanum vulgare* (*Niuzhicao*).[96] Their partial hydrophilicity allows prolonged retention in the colon, where they undergo extensive microbial catabolism into low-molecular weight phenolic metabolites.[97] These

Table 1 The Interaction Between Herbal Compounds and UC

Structural Class	Structural Features	Herbal Compounds	Source	Associated Mechanisms
Polysaccharides	High-molecular weight carbohydrate polymers with complex branched structures.	*Codonopsis pilosula polysaccharides* *Scutellaria baicalensis Georgi polysaccharide* *Astragalus polysaccharides* *Turmeric polysaccharide* *Lycium barbarum polysaccharides* *Lentinan*	*Codonopsis pilosula* *Scutellaria baicalensis* Georgi Astragalus membranaceus *Curcuma longa* *Lycium barbarum* *Lentinus edodes*	Serve as selective fermentable substrates • Enrich beneficial commensals (*F. prausnitzii, Bifidobacterium, Lactobacillus*). • Generate SCFAs to confer anti-inflammatory and barrier-protective effects.
Alkaloids	Nitrogen-containing heterocyclic structures and basic properties.	*Berberine* *Matrine*	*Coptis chinensis* *Sophora flavescens*	Exert direct antimicrobial activity against enteric pathogens (*E. coli, Klebsiella*) and attenuate LPS levels. • Remodel microbiota to enrich *Akkermansia muciniphila* and *Barnesiella intestinihominis* • Elevate SCFA production and suppress pro-inflammatory cytokines.
Flavonoids	Characteristic benzopyrone core and multiple phenolic hydroxyl groups.	*Baicalin* *Luteolin* *Chrysanthemin* *Perillaldehyde* *Cardamonin* *Mulberry anthocyanins*	*Scutellaria baicalensis* *Reseda odorata* *Chrysanthemum indicum* *Perilla frutescens* *Alpinia katsumadai* Morin	Undergo hydrolysis by microbial β-glucosidases into highly absorbable bioactive aglycones. • Alleviate inflammation via inhibition of the NF-κB pathway. • Modulate cytokine secretion and enhance antioxidant defense.
Terpenoids	Diverse isoprene-derived hydrocarbons, ranging from monoterpenes to triterpenes.	*Artemisinin* *Ginsenosides* *Ginkgolides* *Tanshinones*	*Artemisia annua* *Panax ginseng* *Ginkgo biloba* *Salvia miltiorrhiza*	Readily subjected to microbial oxidation, reduction, or hydrolysis to generate bioactive metabolites. • Modulate immune balance by promoting Treg cell differentiation. • Inhibit inflammatory cascades, including the NF-κB pathway.

(*Continued*)

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Table 1 (Continued).

Structural Class	Structural Features	Herbal Compounds	Source	Associated Mechanisms
Polyphenols and Phenolic Acids	Aromatic rings bearing one or more hydroxyl groups.	*Rhein* *Curcumin* *Chlorogenic acid* *Purslane Polyphenols*	*Rheum palmatum* *Curcuma longa* *Lonicera japonica* *Portulaca oleracea*	Undergo extensive microbial catabolism into low-molecular-weight phenolic metabolites. • Scavenge reactive oxygen species (ROS) for potent antioxidant effects. • Inhibit Cyclooxygenase-2 (COX-2) and suppress the growth of pathogenic *E. coli*.
Other Key Compounds	Includes glycosides, tannins, coumarins, and lignans.	*Angelicin* *Schisandrin* *Paeoniflorin* *Geniposide* *Rosavin*	*Angelica dahurica* *Schisandra chinensis* *Paeonia veitchii* Radix *Gardenia jasminoides* Fructus *Rhodiola rosea* L.	Participate in the precise taxonomic diversification and specific ecological modulation of the gut microbiota.

biotransformation processes are associated with antioxidant (eg., reactive oxygen species scavenging),[98] anti-inflammatory (eg., Cyclooxygenase-2 inhibition),[99] and antimicrobial effects (eg., suppression of *E. coli* growth).[100] Consequently, the gut microbiota serves as a pivotal intermediary that converts polyphenols into bioactive forms with systemic health benefits.

Furthermore, other crucial compounds, such as glycosides (eg., salidroside),[101] tannins (eg., dimeric proanthocyanidins),[102] coumarins (eg., angelicin),[103] and lignans (eg., schisandrin),[104] also participate in the diversification and precise modulation of gut microbiota.

Collectively, the structural diversity of herbal compounds governs their microbial accessibility, metabolic conversion, and downstream physiological effects. The dynamic interplay between these phytochemicals and the gut microbiome represents a key mechanistic basis for the therapeutic efficacy of TCM in inflammatory and metabolic disorders.

Restoring Multi-Tiered Intestinal Barrier Integrity: The Role of Herbal Compounds and Microbial Metabolites in UC Therapy

A healthy intestinal mucosal barrier is essential to maintain the physiological processes. There are four parts of the complete intestinal mucosal barrier: mechanical, chemical, immune, and biological barriers.[105] The pathogenesis of UC is characterized by the progressive disruption of the four-tiered intestinal mucosal barrier, a structural breach that perpetuates chronic inflammation[106] (Figure 2 and Supplementary Table S1).

Targeting the Biological Barrier: Reversing Dysbiosis and Reinstating Colonization Resistance

The intestinal biological barrier comprises a dynamic commensal microbial ecosystem that excludes pathogens to maintain mucosal homeostasis.[107] In UC, this microecological equilibrium collapses, manifesting as reduced microbial diversity, depletion of beneficial commensals, and expansion of opportunistic pathogens.[108] Herbal compounds intervene within this microenvironment through antimicrobial, prebiotic, and ecological restoration mechanisms to reinstate colonization resistance.[17]

Alkaloids, characterized by lipophilic nitrogen-containing heterocycles, exhibit potent antimicrobial activity against gut pathobionts while preserving commensal networks.[109] In vitro and in vivo studies demonstrate that Berberine effectively suppresses proliferation of UC-associated pathogens *E. coli* that are aberrantly enriched in dysbiotic microbiota, thereby limiting luminal LPS accumulation.[110] Similarly, matrine reduces *Helicobacter* colonization while enriching beneficial taxa such as *Barnesiella intestinihominis*, attenuating microbial triggers of mucosal inflammation.[88]

In contrast to alkaloid bactericidal activity, high-molecular-weight polysaccharides resist upper gastrointestinal digestion, reaching the colon intact to serve as selective fermentable substrates. For instance, polysaccharides derived from both *Codonopsis pilosula* and *Astragalus membranaceus* synergistically stimulate the proliferation of *Faecalibacterium prausnitzii*, a major butyrate-producing commensal that is characteristically depleted in the inflamed mucosa of UC patients.[111] Similarly, LBP drive the expansion of keystone genera like *Bifidobacterium* and *Lactobacillus*, which selectively ferment these substrates to yield elevated SCFAs.[112] These SCFAs serve as obligate bioenergetic substrates for colonocyte proliferation and epithelial repair.[113]

Beyond targeted taxonomic modulation, herbal interventions restore the macroscopic architecture of the gut microbiome, which in UC is universally compromised by collapsed α-diversity and skewed *Firmicutes/Bacteroidetes* (F/B) ratios.[114] Terpenoids, such as ginsenoside Rg1, restore this macroscopic composition in murine models, increasing α-diversity and normalizing dysregulated F/B ratios.[115] Importantly, this architectural restoration is not limited to isolated monomers but is a shared characteristic of broad-spectrum herbal therapies. Recent studies demonstrate that the classic herbal pair *Polygonum hydropiper L*. and *Coptis chinensis* comprehensively reverses DSS-induced ecological collapse, restoring α-diversity to near-healthy baseline levels and stabilizing the microbial network[116] Similarly, polysaccharides derived from *Poria cocos* promote microbial richness and diversity, correlating directly with intestinal barrier repair and mucosal inflammation suppression.[117]

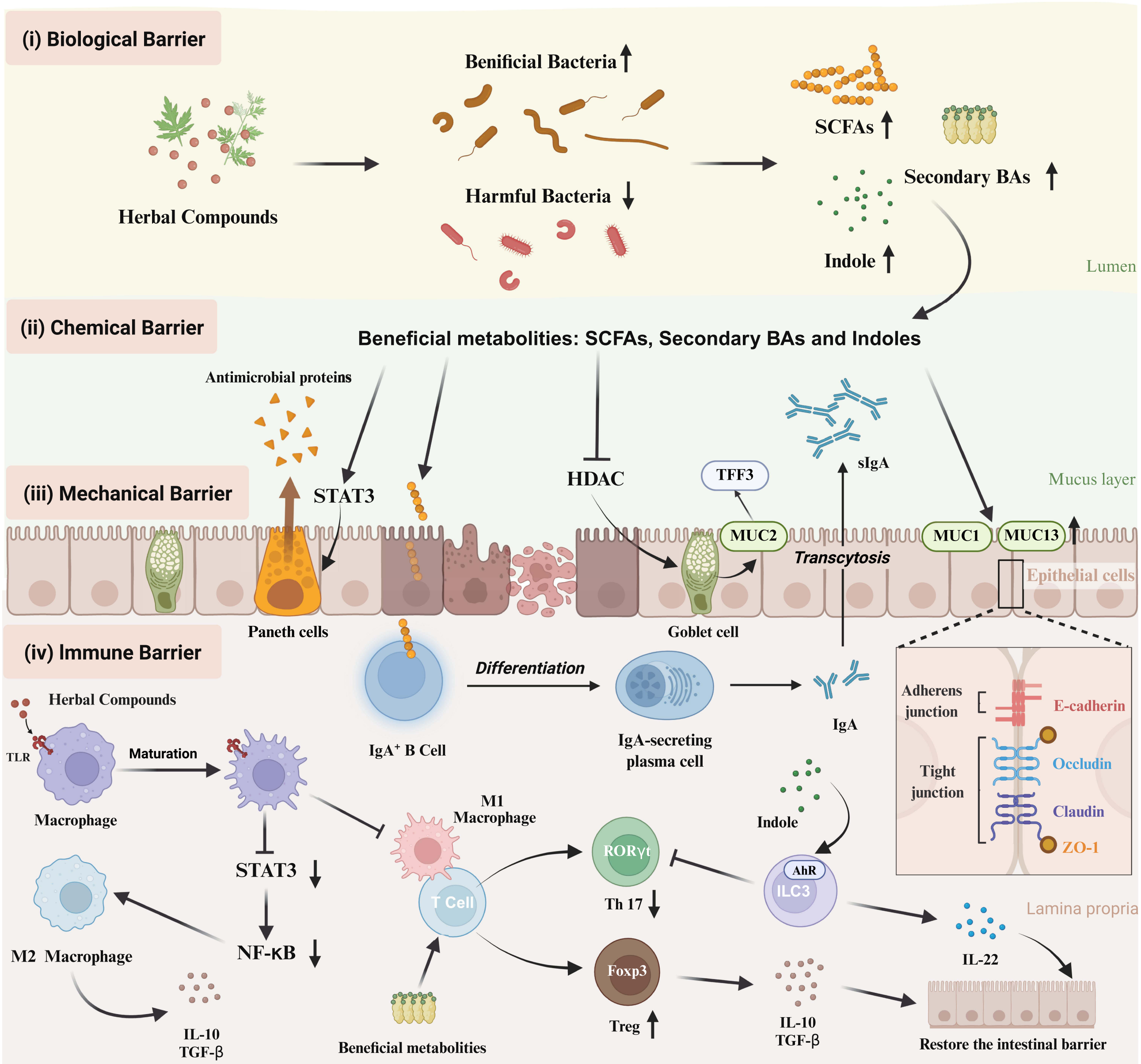

Figure 2 Multidimensional restoration of the intestinal barrier mediated by gut microbiota and their metabolites. Herbal compounds restore intestinal barrier integrity through four hierarchical layers: (i) Biological barrier: Restructuring gut microbiota to enrich beneficial bacteria and suppress pathogens, thereby increasing production of SCFAs, secondary bile acids, and indole derivatives. (ii) Chemical barrier: Metabolites fortify the mucus layer by upregulating MUC2 and trefoil factor 3 (TFF3), enhance secretory IgA (sIgA) production, and stimulate Paneth cells to release antimicrobial proteins via STAT3 signaling. (iii) Mechanical barrier: Metabolites drive assembly of apical junctional complexes, preserving tight junctions (occludin, claudin, ZO-1) and adherens junctions (E-cadherin) to seal paracellular spaces. (iv) Immune barrier: In the lamina propria, compounds and metabolites reprogram immune networks—suppressing STAT3/NF-κB to shift macrophages from M1 to M2 phenotypes, modulating Th17/Treg balance toward Foxp3+ Treg differentiation, stimulating IgA production, and activating AhR on ILC3 cells to induce IL-22 release. Collectively, this microbiome-dependent metabolic network resolves colonic inflammation and restores mucosal homeostasis.

Fortifying Intestinal Chemical Barrier: Enhancing Mucin Networks and Antimicrobial Defenses

The intestinal chemical barrier constitutes a biochemical interface comprising mucins, trefoil factors, secretory IgA (sIgA), AMPs, and electrolytes that segregates the epithelium from luminal microbiota.[118] In UC, this defensive framework undergoes multifaceted compromise, manifesting as goblet cell depletion, mucin hyposulfation, and diminished antimicrobial secretions.[119] Herbal compounds exert therapeutic effects through distinct yet convergent mechanisms targeting secreted mucin networks, antimicrobial factor production, and transmembrane glycocalyx stability.[120]

As principal gel-forming constituents, MUC2 and trefoil factor 3 (TFF3) are critical for mucus viscosity and epithelial repair.[121,122] Diverse herbal compounds restore mucus barrier integrity by fundamentally reprogramming microbiota-host metabolic interactions. Multi-omics studies demonstrate that Polyphenols such as quercetin remodel gut microbiota to enrich protective metabolites (eg., isovanillic acid, SCFAs), which reduce the expression of MUC2, thereby restoring mature mucin synthesis and secretion.[123] Concurrently, these interventions re-establish the mucin-foraging feedback loop: berberine enrich *Akkermansia muciniphila*, which catabolizes mucin glycans to generate propionate SCFAs and upregulate MUC2 expression in colonic epithelium.[124] In addition to SCFA-mediated mechanisms, multi-omics analyses reveal that berberine actively upregulates the colonic expression of TFF3 to accelerate mucosal repair. This upregulation is intricately linked to berberine-induced microbiota remodeling; specifically, berberine significantly enriches beneficial genera such as Megasphaera, whose abundance exhibits a strong positive correlation with enhanced TFF3 transcription and overall barrier fortification.[125]

Neutralization of luminal pathobionts depends upon abundant sIgA and AMPs secretion.[107] Longan pulp polysaccharide promotes the synthesis and secretion of intestinal SIgA through regulating IgA class switch recombination-related factors, facilitating gut homing of IgA+ plasma cells and upregulating polymeric immunoglobulin receptor (pIgR) and secretory component expression, thereby reinforcing the intestinal mucosal barrier function.[126] In a distinct regulatory pathway, total glucosides of peony (TGP) and its primary active component, paeoniflorin (PF), reduce the accumulation of microbial indole-3-lactate (ILA) to mitigate UC. As ILA serves as a negative regulator of intestinal epithelial autophagy, its suppression by TGP/PF effectively unleashes the protective autophagic machinery, thereby enhancing epithelial barrier robustness and suppressing inflammatory progression.[127]

Distinct from secreted mucins, transmembrane mucins (MUC1, MUC13) form the apical glycocalyx and transduce survival signals to underlying epithelium.[128] In UC, however, these structures are downregulated; specific herbal interventions effectively rescue this structural deficit. For instance, indigo naturalis-derived components function as potent AhR ligands to stimulate IL-22 production, driving STAT3-dependent transcriptional upregulation of MUC1 and MUC13 in colonic epithelium.[129] Concurrently, to prevent the inflammatory shedding of these mucin-anchored epithelial cells, flavonoids like baicalin actively suppress the NF-κB/Caspase-3-mediated apoptotic cascade, thereby preserving the physical cellular anchor required for transmembrane mucin stability.[130] Furthermore, specific polyphenols like resveratrol enhance the abundance of *A. muciniphila*, which in turn augments transmembrane mucin expression,[131] collectively stabilizing the epithelial-mucus interface and restoring chemical barrier homeostasis.

Repairing Intestinal Mechanical Barrier: Stabilizing Apical Junctions and Driving Stem Cell-Mediated Restitution

The intestinal mechanical barrier comprises a polarized epithelial monolayer sealed by apical junctional complexes (AJCs), including tight junctions (TJs) containing claudins, occludin, and ZO-1, supplemented by adherens junctions (eg., E-cadherin) and desmosomes.[132] In UC, inflammatory mediators drive downregulation of junctional proteins and accelerate epithelial apoptosis, resulting in a "leaky gut" architecture characterized by endotoxemia and mucosal ulceration.[133] Herbal compounds counteract this pathology through three convergent mechanisms: upregulating tight junction proteins, attenuating excessive epithelial shedding, and promoting stem cell-mediated restitution.[108]

TJs undergo dynamic assembly and disassembly to regulate paracellular permeability.[132] Herbal compounds fortify this physical barrier by modulating gut microbiota composition and enriching beneficial metabolites that upregulate TJ protein expression. For instance, mulberry anthocyanins ameliorate DSS-induced dysbiosis by reducing the abundance of Escherichia-Shigella and increasing beneficial taxa such as Akkermansia, Muribaculaceae, and Allobaculum.[134] These positive microbial shifts lead to the transcriptional upregulation of key tight junction proteins, including occludin, claudin-1, and ZO-1, thereby reducing pathological intestinal permeability. Similarly, polyphenol-rich Portulaca oleracea L. enriches Butyricoccus, Dorea, and Bifidobacterium, which elevate acetate and lactate production.[135,136] These metabolites serve as substrates for butyrate-producing bacteria like F. prausnitzii via cross-feeding interactions, resulting in increased colonic butyrate that activates GPR41 on intestinal epithelial cells. This triggers signaling pathways that transcriptionally upregulate occludin and claudin-1 and facilitate their functional assembly at the epithelial membrane, stabilizing junctional networks and restoring barrier integrity.[137,138]

Beyond reinforcing AJCs, herbal compounds attenuate pathological epithelial loss. In UC, pathobiont overgrowth elevates LPS, triggering epithelial shedding and mucosal denudation.[139] For instance, andrographolide minimizes epithelial loss by suppressing LPS-producing *Enterobacteriaceae* while deactivating NLRP3-mediated pyroptosis in intestinal epithelial cells (IECs).[140] Similarly, cardamonin inhibits the RIPK1/RIPK3/MLKL-dependent necroptotic pathway, a destructive form of inflammatory cell death that promotes barrier collapse. By disrupting necrosome formation, it helps maintain epithelial monolayer continuity.[141]

While halting excessive cell shedding is essential for damage control,[142] the ultimate restoration of barrier integrity necessitates active epithelial restitution driven by intestinal stem cells (ISCs).[143] Herbal compounds play a pivotal role in re-awakening this regenerative niche. For instance, Rosavin effectively repairs intestinal epithelial injury and restores barrier function by inhibiting inflammatory responses and apoptosis, significantly increasing the populations of Lgr5+ intestinal stem cells, Lyz1+ Paneth cells, and Muc2+ goblet cells. Intestinal organoid studies further demonstrate that Rosavin directly facilitates epithelial cell differentiation and protects against TNF-α-induced damage, with the underlying mechanism involving the upregulation of gene expression associated with cell proliferation and defensin secretion.[144] Additionally, notoginsenoside R1 has been shown to upregulates the Wnt/β-catenin cascade, amplifying the Lgr5+ stem cell pool to accelerate mucosal wound healing[145] Furthermore, epithelial repair is significantly regulated by IL-22, primarily produced by Innate Lymphoid Cells-Type 3 (ILC3s) in the colon.[146] In DSS-induced colitis mice, berberine restores gut microbial homeostasis by increasing probiotics (eg., *Lactobacillus/Lactococcus*) and decreasing pathobionts such as mouse intestinal Bacteroides, segmented filamentous bacteria, and Enterobacteriaceae. This immunomodulation is coupled with a suppression of ILC1 and an enhancement of ILC3s frequency and IL-22 production in colonic lamina propria lymphocytes, collectively promoting epithelial restitution.[147]

Reprogramming Intestinal Immune Barrier: Modulating Macrophage Polarization and Th17/Treg Homeostasis

The intestinal immune barrier comprises tissue-resident macrophages, T lymphocytes, B lymphocytes, and innate lymphoid cells (ILCs) distributed across intraepithelial compartments, lamina propria, and Peyer's patches.[148] In UC, chronic mucosal damage is driven by dysregulated macrophage polarization and disruption of the Th17/Treg balance.[149] Herbal compounds orchestrate mucosal healing by leveraging microbial biotransformation to reprogram innate macrophage polarization and recalibrate adaptive T-cell responses.

During active UC, pro-inflammatory M1 macrophages expand significantly, releasing cytokines (IL-6, TNF-α) that activate NF-κB signaling, thereby intensifying inflammatory infiltration and tissue damage.[150] This immune dysregulation is counteracted via a dual modulatory strategy. For instance, curcumin formulations suppress the TLR4/NF-κB inflammatory cascade while concurrently enriching SCFA-producing microbiota (eg., Lactobacillus).[151] The resulting elevation in microbial SCFAs, particularly butyrate, activates GPR43 on macrophages and functions as a HDAC inhibitor, driving polarization toward the tissue-repairing M2 phenotype.[152] Crucially, the immunomodulatory effects of herbal compounds are also highly dependent on the specific microbial context. While *Akkermansia muciniphila* is generally barrier-protective in homeostasis, its over-enrichment in the severely compromised mucosal niche of acute DSS colitis can pathologically trigger M1-like macrophage polarization via its secreted microbial protein Amuc_2172. In this specific pathological context, the administration of puerarin acts as a targeted immunomodulator.[153] It significantly attenuates the DSS-mediated over-enrichment of *A. muciniphila*, effectively inhibiting Amuc_2172-triggered M1 macrophage activation and ultimately halting disease progression. Similarly, Codonopsis pilosula polysaccharide enriches beneficial bacteria (eg., Ligilactobacillus, Akkermansia) to elevate cecal acetic and butyric acid levels, which bind GPR receptors to suppress NLRP3 inflammasome activation, thereby attenuating intestinal inflammation.[154]

Herbal compounds leverage complex host-microbe co-metabolism to directly intervene in T cell differentiation. Phytochemicals orchestrate mucosal healing by leveraging microbial biotransformation to reprogram innate macrophage polarization and recalibrate adaptive T-cell responses. UC is further characterized by pathological skewing toward

RORγt-driven Th17 inflammatory phenotypes alongside functional impairment of FOXP3+ Treg networks.[155] Lycium barbarum polysaccharides stimulate Clostridium clusters (eg., C. butyricum) to produce propionate and butyrate, which epigenetically modify naïve CD4+ T cells by promoting acetylation of the Foxp3 promoter locus, thereby stabilizing Treg lineages.[156] Additionally, Astragalus polysaccharides restore SCFA-producing microbiota in a microbiota-dependent manner (validated by FMT from treated donors), with elevated SCFAs inhibiting NF-κB activation via TLR4 and HDAC3 pathways to improve Th17/Treg balance.[157] Furthermore, the Th17/Treg equilibrium is maintained through cross-talk with ILC3s.[158] Indirubin specifically activates AhR signaling within intestinal ILC3s, stimulating barrier-protective IL-22 release while restoring ILC3-dependent suppression of Th17 polarization, thereby shifting mucosal immunity toward Treg-mediated tolerance.[159]

Translational Challenges and Future Actionable Directions

Translational Challenges: Phytochemical Heterogeneity, Preclinical Model Limitations, and Therapeutic Safety Risks

The clinical translation of microbiota-targeted herbal compounds for UC is constrained by phytochemical heterogeneity and complex host metabolism. Botanical raw materials exhibit inherent compositional variability determined by geographic origin, cultivation conditions, and post-harvest processing[160–163] (Figure 3). For example, baicalin

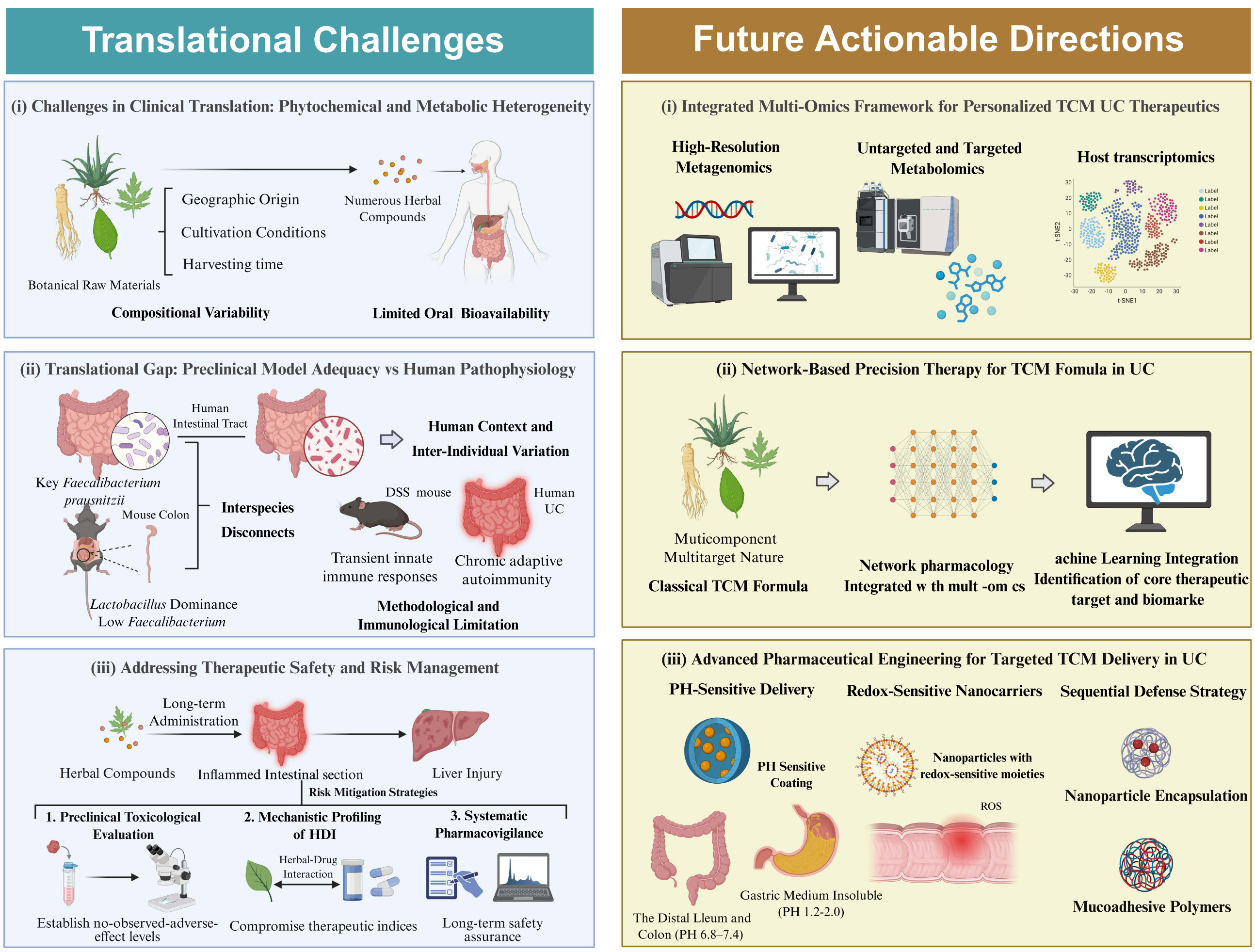

Figure 3 Translational challenges and future directions for TCM therapeutics in UC. (Left) Current translational bottlenecks: (i) phytochemical heterogeneity and limited bioavailability; (ii) discrepancies between preclinical models and human pathophysiology, including inter-individual microbiota variation; and (iii) safety concerns regarding long-term hepatotoxicity. (Right) Strategic solutions: (i) multi-omics frameworks for personalized therapeutics; (ii) network pharmacology integrated with machine learning to decode multi-component formulas; and (iii) stimuli-responsive nanocarriers (pH/redox-sensitive) for targeted colonic delivery.

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concentrations in *Scutellaria baicalensis* demonstrate significant inter-batch variation contingent on cultivation geography and harvest timing.[160,163] Expanding beyond flavonoids, this heterogeneity universally affects other structural classes. The molecular weight and monosaccharide composition of *Astragalus membranaceus* polysaccharides fluctuate extensively depending on specific extraction protocols, which directly alters their prebiotic consistency and efficacy.[164] Similarly, the precise ratios of bioactive ginsenosides in *Panax ginseng* are profoundly dictated by the plant's age (eg., 3-year versus 6-year roots) and processing techniques (eg., fresh versus steamed roots).[165] This variability is compounded by pharmacokinetic constraints: numerous TCM compounds exhibit limited oral bioavailability yet demonstrate clinical efficacy through microbiome-mediated biotransformation. Consequently, therapeutic outcomes depend on host-specific microbial enzymatic capacity, establishing a bidirectional relationship wherein baseline microbiota composition dictates drug bioactivation while the therapeutic agent concurrently reshapes microbial ecology.[166–168] This interplay between variable phytochemical inputs and individualized microbial metabolism renders therapeutic responses unpredictable without rigorous chemical standardization coupled with patient stratification based on microbial profiling.

Despite rapid advances in microbiome-targeted therapeutics for gastrointestinal disease, clinical translation remains substantially impeded by fundamental biological disconnects between preclinical models and human pathophysiology. Marked taxonomic incongruence characterizes these interspecies differences: keystone human butyrate-producers such as Faecalibacterium prausnitzii are essentially absent in murine systems, whereas *Lactobacillus* species dominate rodent microbiota yet constitute negligible proportions in human gut ecosystems.[169,170] These discrepancies are amplified by anatomical and physiological divergence, including differential mucus barrier architecture, distinct gastrointestinal transit kinetics, and divergent anatomical segregation of microbial fermentation—cecum-dominant in rodents versus distributed colonic fermentation in humans.[169,171] Methodologically, acute chemical injury models (eg., DSS) induce transient innate immune responses that fail to recapitulate the chronic, relapsing-remitting adaptive autoimmunity characteristic of human UC.[172] This translational gap is further exacerbated by the "hygiene problem" inherent to Specific Pathogen-Free housing, wherein artificially restricted microbial exposure generates immunologically naïve animals incapable of mimicking the antigen-experienced human immune system, potentially yielding artifactual efficacy signals reflecting toxicity resolution rather than true pharmacological modulation of chronic dysbiosis.[173,174] Transitioning to clinical contexts, these biological limitations converge with profound inter-individual variation in baseline gut microbiome composition and enzymatic capacity—specifically heterogeneous β-glucuronidase activity generating distinct patient metabotypes—which emerges as the primary determinant of divergent therapeutic outcomes, rendering universal treatment paradigms inherently inadequate.[175–177] This interplay between preclinical physiological inadequacy and patient-specific microbial enzymatic variation constitutes a pervasive bottleneck constraining clinical translation across microbiome-based therapeutics, demanding rigorous model standardization coupled with multi-omics-based stratification and mechanism-driven experimental frameworks to ensure therapeutic predictability.

Therapeutic safety requires rigorous scrutiny, particularly given documented contraindications and hepatotoxic risks associated with specific botanical compounds. *Indigo naturalis*, despite efficacy in refractory UC mucosal healing, induces dose-dependent hepatic dysfunction and pulmonary arterial hypertension upon chronic administration.[178,179] Mechanistically, macrophage-mediated translocation of insoluble indirubin from inflamed intestine to hepatic tissue precipitates oxidative stress-driven liver injury.[178] Similarly, baicalin-containing *Scutellaria baicalensis* formulations have been implicated in idiosyncratic drug-induced liver injury.[180] Mitigating these risks necessitates standardized preclinical toxicological evaluation following to establish no-observed-adverse-effect levels.[181] Additionally, mechanistic profiling of pharmacokinetic herb–drug interactions (HDI) is imperative given the polypharmacy prevalent in UC management; for instance, curcumin-mediated inhibition of intestinal BCRP/ABCG2 efflux transporters can substantially alter systemic exposure to conventional substrates such as sulfasalazine, potentially compromising therapeutic indices.[182] Long-term safety assurance further requires structured pharmacovigilance, such as employing validated hepatotoxicity assessment algorithms for objective causality adjudication of suspected herb-induced liver injury.[183] Integration of predictive toxicology, transporter-level HDI characterization, and systematic pharmacovigilance thus enables evidence-based risk stratification, ensuring that personalized therapeutic strategies are balanced against individualized safety profiles within precision medicine frameworks for UC.

Future Actionable Directions: Towards Precision Microbiome Therapies

To address the complexity of gut microbiota and phytochemical constituents constraining empirical TCM approaches, future UC therapeutics must adopt integrated multi-omics frameworks (Figure 3). Moving beyond descriptive microbiome surveys, research must systematically resolve the "active ingredient-microbiome-receptor" axis. High-resolution metagenomics enables precise delineation of patient- or syndrome-specific dysbiotic signatures establishing baseline microbial architectures.[25] Layered upon this, untargeted and targeted metabolomics capture dynamic functional outputs of microbial communities, specifically tracking TCM-microbe cometabolites. For instance, metabolomic profiling has traced microbial biotransformation of botanical compounds into SCFAs and tryptophan derivatives such as xanthurenic acid, which subsequently activate anti-inflammatory host receptors including the AhR.[184,185] Host transcriptomics completes this framework by providing phenotypic readouts mapping microbial cometabolite modulation of mucosal healing pathways and immune gene networks within intestinal epithelium.[186] Mathematical integration of metagenomic, metabolomic, and transcriptomic datasets enables predictive mechanistic modeling beyond associative correlations, facilitating truly personalized TCM interventions based on patient-specific multi-omic signatures.

The multicomponent, multitarget nature of TCM challenges conventional "one drug, one target" paradigms while aligning with the complex pathogenesis of UC. Network pharmacology integrated with multi-omics enables a shift toward network-based precision therapy.[187,188] Systems-level analyses reveal that classical formulas orchestrate synergistic modulation across multiple pathological pathways rather than isolated targets. Furthermore, machine learning integration refines core therapeutic target and biomarker identification, facilitating alignment of herbal compounds with distinct UC endotypes.[189,190] This data-driven framework transitions TCM from empirical practice to quantifiable precision medicine, advancing personalized therapeutic strategies.

Poor aqueous solubility and extensive first-pass metabolism of bioactive compounds (eg., curcumin, berberine), coupled with complex drug-microbiota metabolic networks, constrain therapeutic development and clinical application. To circumvent these limitations, advanced pharmaceutical engineering has developed targeted delivery systems that bypass the harsh upper gastrointestinal environment to achieve localized, high-concentration release at sites of colonic inflammation. These platforms predominantly employ stimuli-responsive mechanisms tailored to the physiological hallmarks of UC. pH-sensitive coatings (eg., methacrylic acid copolymers) remain insoluble in gastric medium (pH 1.2–2.0) while dissolving in the neutral-to-alkaline environment of the distal ileum and colon (pH 6.8–7.4), ensuring intestinal targeting.[191,192] Furthermore, nanoparticles functionalized with redox-sensitive moieties (eg., diselenide or thioketal linkers) exploit elevated reactive oxygen species levels in inflamed mucosa to enable site-specific payload release, maximizing bioavailability at sites of acute oxidative stress.[193,194] The integration of stimuli-responsive nanocarriers with other materials, such as cell membrane nanomaterials and enzymatically degradable polysaccharide-based hydrogels (eg., pectin or chitosan), establishes a synergistic, multi-level protective strategy. This sequential defense system first shields the active compounds from enzymatic degradation in the upper gastrointestinal tract; it then utilizes the specific enzymes produced by the colonic microbiome to precisely degrade the hydrogel matrix, thereby ensuring targeted payload release within the microbial-rich inflammatory microenvironment of the colon.[195–197] Collectively, these engineering strategies transform unstable phytochemicals into precision-targeted nanomedicines, fundamentally addressing bioavailability and site-specificity challenges in UC management.

Conclusion

This review systematically elucidates the multifaceted mechanisms by which herbal compounds alleviate UC symptoms by modulating the gut microbiota—promoting beneficial commensals, suppressing opportunistic pathogens, and restoring microbial diversity—thereby orchestrating improvements across mechanical, chemical, immune, and biological barrier functions. However, it is crucial to acknowledge that the current evidence base derives predominantly from preclinical models, necessitating cautious interpretation of causality until validated by rigorous human trials. To bridge this translational gap, future research must prioritize chemical standardization of raw materials, advanced pharmaceutical engineering to enhance bioavailability and colonic targeting, and the integration of multi-omics profiling to stratify patients according to baseline microbiome signatures and metabolic capacity, ultimately transforming empirical TCM application into precision microbiota-targeted therapeutics for UC.

Abbreviations

AhR, Aryl hydrocarbon receptor; AIEC, Adherent-invasive Escherichia coli; AJCs, Apical junctional complexes; AMPs, Antimicrobial peptides; APS, Astragalus polysaccharides; BCFAs, Branched-chain fatty acids; DSS, Dextran sulfate sodium; ER, Endoplasmic reticulum; F/B, Firmicutes/Bacteroidetes; FMT, Fecal microbiota transplantation; GF, Germ-free; GI, Gastrointestinal; GM, Gut microbiota; GPR43, G-protein-coupled receptor 43; HDAC, Histone deacetylase; HDI, Herb-drug interactions; IBD, Inflammatory bowel disease; IECs, Intestinal epithelial cells; IL-6, Interleukin-6; IL-10, Interleukin-10; ILA, indole-3-lactate; ILCs, Innate lymphoid cells; ILC3s, Group 3 innate lymphoid cells; IPA, Indole-3-propionic acid; ISCs, Intestinal stem cells; LBP, Lycium barbarum polysaccharides; LPS, Lipopolysaccharide; NF-κB, Nuclear transcription factor-κB; NLRP3, NOD-like Receptor Pyrin domain containing 3; pIgR, Polymeric immunoglobulin receptor; PSA, Polysaccharide A; SCFAs, Short-chain fatty acids; sIgA, Secretory IgA; TCM, Traditional Chinese Medicine; TFF3, Trefoil factor 3; Th17, T-helper 17; TJs, Tight junctions; TLR4, Toll-like receptor 4; TNBS, Trinitrobenzene sulfonic acid; TNF-α, Tumor necrosis factor-α; Tregs, Regulatory T cells; UC, Ulcerative colitis; ZO-1, Zonula occludens-1.

Data Sharing Statement

Data sharing is not applicable to this article as no data were created or analysed in this study.

Author Contributions

Junyi Chen: Conceptualization, Literature review, Investigation, Writing – original draft, Writing – review and editing. Jiaxv Chen: Conceptualization, Literature review, Investigation, Writing – original draft, Writing – review and editing. Zhenyi Wang.: Supervision, Validation, Writing – review and editing, Funding acquisition. All authors took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agreed to be accountable for all aspects of the work.

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Disclosure

The authors declare that they have no competing interests.

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