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Benefits and mechanisms of polysaccharides derived from traditional Chinese medicine for ulcerative colitis treatment (Review)

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Abstract. Ulcerative colitis (UC) is a chronic inflammatory bowel disease characterized by abdominal pain, diarrhea and bloody mucopurulent stools. The UC global incidence is rising and conventional therapies remain limited. Therefore, there is an urgent need for novel treatments. Polysaccharides derived from traditional Chinese medicine (TCM) have emerged as promising candidates due to their multifaceted bioactivities. Preclinical studies have demonstrated that these polysaccharides can regulate immune system pathways, thereby reducing intestinal inflammation and oxidative stress. This protects the intestinal mucosal barrier, enhances tight junction protein expression and modulates the gut microbiota. However, their precise molecular targets and structure-activity associations remain to be fully elucidated. Translational advancement is currently constrained by challenges such as undefined mechanisms, poor oral bioavailability and a lack of clinical validation. Therefore, the present review focused on a number of polysaccharides derived from TCM herbs. The aim of the present review was to systematically analyze their functions and mechanisms for UC prevention and treatment, thus underscoring the necessity for integration of mechanistic discovery with innovative delivery strategies to facilitate the clinical translation of TCM polysaccharides in UC management.

Contents

1. Introduction

Ulcerative colitis (UC) is a chronic inflammatory disease that affects the inner layers of the colon and rectum. Its clinical features are manifested as varying degrees of non-infectious inflammation of the colonic mucosa. Currently, clinical treatment primarily relies on immunosuppressive strategies that may be effective to some extent, but also may cause serious side effects, such as bone marrow suppression, drug-induced hepatitis and pancreatitis (1). The UC global incidence has exhibited a sustained upward trend over the past few decades (2). In 2023, the prevalence of UC was estimated to be 5 million cases globally (3), which has led to considerable healthcare and social costs.

UC is a chronic inflammatory condition that has the potential to develop at any stage of an individual's lifespan. However, statistical data and clinical observations have indicated that the majority of UC cases are most frequently diagnosed during the second and third decades of life, specifically between ages 20-30 years (4). Currently, the pathogenesis of UC is not clearly

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understood. However, it is believed to be associated with a variety of factors that include genetic predisposition, diet, environmental factors, drugs, gut microbiota and immune response. Primary UC treatment methods include amino-salicylic acid, glucocorticoids, immunomodulatory agents and biological therapies. However, issues including hormone dependence, adverse reactions and drug resistance associated with these treatments persist. Therefore, creating safe and effective treatments continues to pose a notable challenge. High treatment costs also remain an unresolved issue. Consequently, it is important to pursue a new therapeutic approach.

Polysaccharides derived from traditional Chinese medicine (TCM) have received extensive attention (5-7) in recent years as potential candidate drugs for UC treatment (8). Polysaccharides are important biological macromolecules found in all organisms and are commonly sourced from plants, animals and fungi. They have been extensively researched (9-11) as potential therapeutic agents for chronic diseases due to their biodegradability and biocompatibility. Their favorable safety profile has increasingly positioned natural polysaccharides as a research focus in UC disease (12). The TCM polysaccharide is a type of aldose or polymer composed of aldose extracted from Chinese medicine. A large number of studies (13-15) have shown that polysaccharides can treat UC by regulating immune function, oxidative stress, the gut microbiota and the mucosal barrier. However, their specific roles and mechanisms have not been systematically summarized (16).

Existing peer-reviewed studies have provided valuable insights into the application of polysaccharides and TCM treatment for UC, covering natural polysaccharides from diverse sources as well as their core anti-inflammatory and intestinal barrier-protective mechanisms. Guo *et al* (17) has offered a comprehensive overview of natural polysaccharides for UC, covering their structural characteristics, pharmacological activities and mechanisms of action. In addition, Wang *et al* (18) presented a holistic summary of TCM interventions for UC, including compound prescriptions, single Chinese herbs and diverse active ingredients, in which polysaccharides were briefly introduced as one important category of bioactive components. Arora *et al* (19) also systematically summarized natural polysaccharides from diverse sources for UC treatment, clarifying their key anti-inflammatory and intestinal barrier-protective pathways. Building upon these studies, the present review specifically focused on TCM polysaccharides, systematically integrating 38 experimental studies, supplementing comprehensive information on the botanical origins, medicinal extraction parts and crude drug profiles for each polysaccharide and further elaborating upon the therapeutic mechanisms of 22 TCM polysaccharides against UC.

The aim of the present study was to comprehensively summarize the demonstrated benefits of TCM polysaccharides in UC models and elucidate their intricate molecular and cellular mechanisms of action. The present results will therefore provide a foundation for future research and development.

2. Polysaccharides derived from Chinese medicinal herbs for UC

Polysaccharides derived from Chinese medicinal herb rhizomes. Astragalus polysaccharide (APS) is a primary active component of *Astragali Radix* (AR). It has been reported to reduce oxidative stress and inflammatory response by downregulating pro-inflammatory cytokines (TNF-α, IL-6, IL-1β) and myeloperoxidase (MPO) activity, decreasing malondialdehyde (MDA) level, and restoring superoxide dismutase (SOD) activity (20). Colonic cell infiltration in rats treated with AR was shown to be markedly reduced compared with that of the model group. In addition, the intestinal mucosa was repaired, suggesting that the AR therapeutic effect on colitis was associated with a reduction in intestinal inflammation, promotion of mucosal repair and improvement of the membrane barrier function (21).

The *Scutellaria baicalensis Georgi* polysaccharide is utilized in TCM theory to clear heat and dampness, purge fire and facilitate detoxification (22). Polysaccharides are notable components of *Scutellaria baicalensis Georg*, with a previous study having demonstrated that a polysaccharide derived from *Scutellaria baicalensis Georgi* alleviated UC by inhibiting NF-κB signaling and NLR family pyrin domain containing 3 inflammasome activation (23). An additional homogeneous polysaccharide, known as SP2-1, was also shown to reduce the levels of key pro-inflammatory cytokines, including IL-6, IL-1β and TNF-α (24).

Ginger polysaccharides have also been reported to alleviate UC symptoms by inhibiting the levels of key pro-inflammatory cytokines, including TNF-α, IL-6, IL-1β, IL-17A and IFN-γ, thereby regulating intestinal inflammation. In addition, they appear to aid in the repair of the intestinal barrier, as evidenced by occludin-1 and zonula occludens-1 (ZO-1) expression levels and gut microbiota modulation (25).

The Chinese yam polysaccharide (CYP) is derived from *Dioscorea opposita L.* and has been shown to alleviate colitis symptoms in dextran sulfate sodium (DSS)-treated mice. This effect was associated with enhanced IL-10 production, pro-inflammatory cytokine suppression (IL-1β and TNF-α) and reduced MPO activity. The CYP was also shown to have preserved intestinal barrier integrity by upregulating tight junction protein (ZO-1 and occludin) and mucin (MUC)-2 expression levels (26).

Polysaccharides derived from *Dendrobium huoshanense* (DHP) have been shown to alleviate UC symptoms and improve the colonic mucosal barrier function in mouse models (27). Previous studies have further indicated that DHP exerts anti-inflammatory effects by modulating the NF-κB signaling pathway, and the specific regulatory mechanism involves inhibiting the expression of NF-κB p65 in colon tissues, subsequently reducing the serum levels of key pro-inflammatory cytokines, including IL-1β, TNF-α, IL-17 and TGF-β, and ultimately blocking the inflammatory cascade in UC (28).

Turmeric polysaccharides (TPSs) are derived from ginger and have been shown to ameliorate pathological phenotypes, reinstate intestinal barrier integrity and suppress colonic inflammation. A 16S ribosomal RNA-based microbiota analysis further revealed that TPSs ameliorated DSS-induced gut microbiota dysbiosis by enriching tryptophan metabolism-associated probiotics (such as *Lactobacillus* and Clostridia-UCG-014) and promoting microbial tryptophan catabolism (29).

Atractylodes macrocephala Koidz. (AM), commonly known as Baizhu, is traditionally used in East Asian medicine for its spleen-invigoration, dampness-resolution and anti-inflammatory properties. Its polysaccharides (AMPs) have been identified as key bioactive components contributing to its therapeutic efficacy in treating UC treatment. A previous study evaluated the effects of AM and AMPs on DSS-induced UC in mice, with results demonstrating that AMP markedly ameliorated DSS-induced weight loss and mitigated colonic injury (30).

The *Platycodon grandiflorus* polysaccharide (PGP) derived from *P. grandiflorus* exhibits anti-inflammatory and antioxidant properties through colonic immune response modulation mediated by mesenteric lymphatic circulation (31). In addition, the pectic polysaccharide from *Smilax china L.* has been shown to mitigate colonic histological injury and reduce the production of key pro-inflammatory mediators, including MPO, IL-1β, IL-6 and TNF-α in DSS-induced UC mouse models. Galectin-3 has also been recognized for its role in inflammation promotion in UC (32).

Codonopsis Radix is a qi-tonifying and spleen-strengthening TCM herb that helps enhance physical strength, reduce fatigue, promote digestion and absorption and boost immunity (33). The *Codonopsis Radix* polysaccharide (CRP) has shown promise in UC treatment. CRP nanoparticles have exhibited enhanced colon adhesion and retention in DSS-induced colitis mice, thus alleviating disease severity, reducing pro-inflammatory cytokine levels and restoring the gut microbiota diversity, likely through inhibition of the toll-like receptor 4 (TLR4)/NF-κB pathway (34).

Bletilla striata has been demonstrated to quickly stop bleeding and promote wound healing (35). This makes it a viable therapeutic option for conditions such as hemoptysis in tuberculosis, gastrointestinal ulcers and skin ulcers. The *Bletilla striata* polysaccharide (BSP) has been formulated into a thermosensitive hydrogel using chitosan and loaded with puerarin-loaded thiolated hyaluronic acid nanoparticles. This composite hydrogel has been shown to adhere strongly to the colonic mucosa and provide sustained drug release at body temperature.

This therefore markedly ameliorated disease activity in murine UCmodels, accelerated colonic mucosal repair, downregulated pro-inflammatory cytokines (TNF-α, IL-1β and IL-6) and upregulated the anti-inflammatory cytokine IL-10, thereby validating its efficacy as a localized therapeutic strategy for UC (36).

Polysaccharides derived from Chinese medicinal herb fruits. Amomum villosum Lour. is an edible plant that can alleviate symptoms such as diarrhea, gastric distension and abdominal bloating (37). The *A. villosum* polysaccharide (AVLP) has demonstrated potential antioxidant and glycosidase inhibitory activities. AVLP administration also helped maintain the intestinal barrier function by upregulating the ZO-1 protein expression. A gut microbiota analysis further indicated that AVLP protective effects against colitis were associated with intestinal bacteria regulation (38).

Lycium barbarum L. has also been found to have certain benefits in UC treatment. *Lycium barbarum* polysaccharides have been demonstrated to markedly reduce disease activity index scores and alleviate colon structural distortion. In addition, they have been shown to effectively decrease colonic pro-inflammatory cytokine levels (including IFN-γ, IL-17A and IL-22) and modulate colonic microbiota composition by reducing the relative abundance of colitis-enriched genera *Turicibacter* and *Lachnospira*, while elevating the relative abundance of *Ruminiclostridium_9* (39,40).

Polysaccharides derived from Chinese medicinal herb flowers. Lonicera japonica Thunb. was first referenced during the Jin Dynasty in Ge Hong's 'Zhouhou Beiji Fang', a manual of first-aid medical prescriptions and aids in clearing heat and detoxification for bacterial dysentery, bronchitis and other infectious disease treatment in TCM (41). A previous study demonstrated that the *Lonicera japonica* Thunb. polysaccharide is an active ingredient that can ameliorate intestinal dysbiosis and enhance immune function in UC. Furthermore, it may elevate the activity of natural killer cells and cytotoxic T lymphocytes while promoting the proliferation of intestinal probiotics (*Bifidobacterium* and *Lactobacillus*) and suppressing pathogenic bacteria (*Escherichia coli* and *Enterococcus*) (42).

Yunnan pine pollen is the dried pollen of *Pinus yunnanensis*, a forest tree species native to southwestern China (43). The crude polysaccharide, PPM60, precipitated using 60% ethanol and its sulfated derivative (SPPM60) in the pollen of Yunnan pine, are the primary active components (44). This beneficial effect may be attained by restoration of the T helper (Th)-17/regulatory T cell (Treg) balance, reinforcement of colonic tight junctions, blocking of receptor interacting serine/threonine kinase 3-dependent necroptosis and stabilization of the gut microbiome and serum metabolome (45,46).

Polysaccharides derived from Chinese medicinal herb fungi. Poria polysaccharides are primary active ingredients in *Poria cocos*. Carboxymethylated *Poria* polysaccharides have been reported to exhibit therapeutic effects on UC by alleviating the infestation of inflammatory factors in colonic tissues and regulating gut microbiota dysbiosis (47,48). *Poria cocos* polysaccharides (PCPs) can enhance MUC-2, β-defensin and secretory IgA expression levels in intestinal tissues associated with the biochemical barrier. Furthermore, PCPs regulate the immunological barrier by enhancing TGF-β and IFN-γ production and increase short-chain fatty acid (SCFA) concentrations in the contents of the small intestine. PCPs influence the intestinal barrier function by modifying the microbial makeup of the gut. PCPs may also preserve the intestinal barrier integrity by enhancing the production of Wnt/β-catenin and low-density lipoprotein receptor-related protein 5 (49).

Ganoderma atrum has been widely used as a functional food or dietary supplement for centuries (50-52). Its polysaccharide, PSG-1, is recognized as a major bioactive constituent and can alleviate DSS-induced UC by protecting the physical barrier regulated by apoptosis/autophagy and the immune barrier associated with dendritic cells (53). An additional active substance, known as the *Ganoderma lucidum* polysaccharide, is primarily composed of β-glucan and has been reported to alleviate DSS-induced colitis. This effect is mediated by increasing the abundance of SCFA-producing bacteria (such as *Ruminococcus_1*) and reducing enteric pathogens (including *Escherichia-Shigella*) in the rat small intestine and cecum (54).

Polysaccharides derived from Chinese medicinal herb leaves. Portulacae Oleracea L. (POL) is a plant with homologous medicinal and food sources. In TCM, POL is classified as a non-toxic herb characterized by its ability to clear heat, reduce swelling, detoxify the body and stop bleeding. In addition, it is utilized for removing dampness, treating diarrhea and eliminating parasites, with no marked side effects having been found (55,56). Polysaccharides derived from POL (POLPs) have been shown to elevate anti-inflammatory cytokine IL-10 levels while reducing the concentration of proinflammatory cytokines including IL-6 and TNF-α. In addition, POLPs may increase the abundance of intestinal probiotics, specifically *Bifidobacterium* and *Lactobacillus*. These findings indicate that POLPs contribute to UC treatment through their anti-inflammatory properties, the attenuation of hyperactive immune responses and intestinal dysbiosis modulation (57). Wang *et al* (58) also found that POLPs could alleviate UC symptoms through the NF-κB signal pathway by inhibiting IκBα degradation.

AL-I is an acidic polysaccharide fraction composed primarily of pectic polysaccharides. It was originally isolated from *Aconitum carmichaelii* leaves and has demonstrated immunomodulatory activity and attenuated intestinal inflammation *in vitro* (59). AL-I possesses numerous pharmacological effects that include anti-tumor, immune regulation, anti-depressive and cardiomyocyte protection. In addition, it has been associated with fewer adverse reactions and an increased safety profile. AL-I has also been demonstrated to ameliorate clinical symptoms and pathological damage in the colons of colitis mice. In addition, it modulates inflammatory markers in both the serum and colonic tissue, with AL-I administration having been shown to attenuate intestinal barrier impairment in mice by upregulating tight junction protein expression and restoring both colonic SCFA and branched-chain fatty acid production (59).

Crude polysaccharides from *Schisandra chinensis* (SCPs) are composed of eight monosaccharides dominated by galacturonic acid, galactose, arabinose and rhamnose. These are characteristic constituents of pectic polysaccharides. SCP administration has been shown to preserve the colonic mucus layer integrity and goblet cell abundance in DSS-challenged mice. Furthermore, SCP treatment has been shown to restore DSS-suppressed SCFA production, with butyrate levels exhibiting marked elevation (60).

Polysaccharides derived from whole Chinese medicinal herbs. Scutellaria barbata is an established perennial herb used in TCM and valued for its ability to clear heat and toxins, promote blood circulation, remove blood stasis and induce diuresis to reduce edema (61). Recent pharmacological studies have substantiated its properties, including its anticancer effects, bacteriostatic action, antiviral capabilities, anti-inflammatory benefits, antioxidative properties and ability to enhance immunity (61-63). *S. barbata* polysaccharides (PSBs) attenuate colonic inflammatory cytokine levels, including those of TNF-α, IFN-γ, IL-1β, IL-6 and IL-18. PSB administration has been shown to inhibit DSS-induced activation of the NF-κB and STAT3 signaling pathways. In addition, enrichment of beneficial bacterial genera (*Lachnospiraceae_NK4A136_group, Ruminococcus, Bacteroides, Parasutterella* and *Eisenbergiella*) following PSB treatment has been associated with reduced intestinal inflammation. These findings demonstrate the therapeutic potential of PSBs in UC and other dysbiosis-associated conditions (64).

Euphorbia humifusa is a medicinal and edible plant traditionally used to treat diarrhea and intestinal disorders. It exhibits anti-inflammatory, hemostatic and hepatoprotective properties. Its polysaccharides (EHPs) are primarily composed of galactose, glucose and glucuronic acid. In DSS-induced UC mice, EHP administration has been shown to alter gut microbiota composition by increasing the relative abundances of *Bifidobacterium* and *Holdemanella* while reducing *Escherichia-Shigella, Tyzzerella* and *Parasutterell*a. Furthermore, EHP administration has been shown to downregulate pro-inflammatory cytokine levels (IL-6 and IL-17) and upregulate anti-inflammatory IL-10 levels to markedly attenuate colon tissue damage (65).

3. Polysaccharide mechanisms to maintain the intestinal barrier integrity

Upregulation of tight junction protein expression. Herbal polysaccharides have garnered attention for their potential to protect the intestinal mucosal barrier, which is important in maintaining overall health. Recent studies have highlighted the multifaceted role these natural compounds serve in enhancing the gut barrier function (66-68). A previous study showed that APSs may increase the number of goblet cells and promote MUC secretion, thereby enhancing the stability of the intestinal mucosal barrier and reducing the intestinal inflammatory response. These polysaccharides may also upregulate the expression of tight junction proteins, such as ZO-1 and occludin, further strengthening intestinal barrier function (69).

Cui *et al* (24) also found that a homogenous polysaccharide isolated from *Scutellaria baicalensis Georgi* exhibited the ability to repair the intestinal barrier. This was achieved by increasing ZO-1, occludin and claudin-5 expression levels, all of which are important in maintaining intestinal epithelium structural integrity. Xiao *et al* (70) found that *Tremella fuciformis* polysaccharides markedly alleviated symptoms in a DSS-induced UC mouse model. This treatment notably reduced the infiltration of inflammatory cells and restored the integrity of the intestinal epithelial barrier by enhancing the expression of intestinal barrier-related genes and proteins (TJP1/ZO-1 and OCLN/occludin) and mucus barrier-associated molecules (Muc-2 and Clca1). The *Eucommia ulmoides* polysaccharide, modified with nano-selenium particles, has also been shown to improve DSS-induced intestinal barrier function by notably increasing the expression of tight junction proteins occludin, claudin-1, claudin-3 and ZO-1 (13).

Repair of the mucous layer and activation of the goblet cell. In a DSS-induced colitis model, polysaccharides were shown to restore the reduced thickness of the mucus layer due to inflammation. In addition *Astragalus membranaceus* polysaccharides have been shown to markedly increase MUC-2 secretion to form a protective mucus layer (71). MUC-2 is secreted by intestinal goblet cells to form a major constituent of the mucus layer. This layer serves a key role in segregating the epithelial surface from the contents within the intestinal lumen. Patients with UC often experience pathological changes such as thinning of the mucus layer and interruption of its continuity (72).

Scavenging of reactive oxygen species (ROS) to regulate antioxidant signaling pathways. Oxidative stress constitutes a key pathological element in UC, arising from an overabundance of ROS and dysfunction of the antioxidant system. SOD1 deficiency exacerbates oxidative stress in the DSS-induced acute colitis mouse model, resulting in significant body weight loss, intestinal epithelial barrier disruption and reduced activities of core antioxidant enzymes, including total SOD, glutathione peroxidase (GPx), catalase and glutathione (GSH) (73). A previous study also demonstrated a marked increase in colonic MDA concentrations in patients with UC, in contrast to a marked decline in the activity of antioxidant enzymes such as GPX, catalase and SOD (74).

There is a clear structure-activity association between the antioxidant activity of polysaccharides and their structural characteristics. Studies on longan polysaccharides have shown that purified acidic polysaccharide components exhibit stronger free radical scavenging and metal ion chelating activities, which are associated with their uronic acid content and molecular weight distribution (75-77).

Dictyophora indusiata polysaccharides exhibit notable antioxidant activity through their unique structural characteristics, including direct free radical scavenging and enhancing the endogenous antioxidant enzyme system (78). APS is derived from *Astragalus mongholicus* Bunge and suppresses DSS-induced colitis by suppressing the Nrf2/HO-1 axis, thereby upregulating GPX4, ferritin heavy chain-1 and GSH-Px4 activity. Consequently, Fe^{2+} accumulation and lipid ROS are reduced, leading to ferroptosis inhibition in intestinal epithelial cells (79). Huaier polysaccharide (HP), extracted from *Trametes robiniophila* Murr., has been shown to notably attenuate DSS-induced weight loss, the elevated disease activity index and colonic shortening. Mechanistically, HP decreases colonic MDA levels, restores GSH and SOD activity and preserves epithelial barrier integrity by enhancing MUC-2 expression. Metabolomics has further revealed that HP remodels the gut microbiota and promotes antioxidant phospholipid metabolites (80). Network pharmacology coupled with *in vivo* validation in trinitrobenzene sulfonic acid-ethanol colitis rats has demonstrated that the Dang Shen polysaccharide downregulated PI3K/Akt signaling, decreased pro-inflammatory cytokine production (IL-6 and TNF-α) and concurrently reduced Fe^{2+}, MDA and MPO levels while enhancing GPX4, GSH activity and SOD (81).

4. Immune regulation mechanisms

Th17/Treg pathway. TCM polysaccharides have multi-target and bidirectional balance characteristics that regulate the differentiation and function of numerous immune cells. The immune imbalance of UC causes an abnormal increase in the ratio of Th17 to Tregs, which is a core pathological feature. Th17 cells are differentiated and developed from $CD4^+$ T cells and their cell membranes express high levels of C-C motif chemokine receptor 6 that can migrate to the intestinal mucosa (82). IL-17 can stimulate macrophages, epithelial cells and fibroblasts to produce a variety of cytokines, such as IL-1β, IL-6 and TNF-α. This leads to inflammatory response amplification, with IL-17 triggering the release of IL-6, thus further activating the STAT3 pathway. The NF-κB pathway is then activated and implicated in the occurrence and development of the immune response (79). This pathway helps maintain this response when the host needs to fight off infection, as often an abundance of inflammatory cytokines causes colonic damage (83).

Eomesodermin and forkhead box P3 are two key nuclear transcription factors implicated in modulating Treg cell development and promoting the secretion of anti-inflammatory cytokines, including IL-10, IL-35 and TGF-β1 (84,85). IL-10 enhances Treg cell differentiation and function through STAT3 signaling, further inhibiting Th17 cell differentiation. IL-35 can also inhibit RAR-related orphan receptor γ-t activation, restrict IL-17 expression and reduce Th17 cell activity, which is conducive to inducing the proliferation of Treg cells (86,87). In the intestinal mucosa of patients with UC, the positive chemotaxis of IL-10, IL-35 and TGF-β on Treg cell proliferation and the inhibition of the Th17-type immune response has been shown to jointly maintain the Th17/Treg immune balance (88,89).

An *in vivo* study demonstrated that PGPs effectively lower Th17-associated cytokines and transcription factors, as well as enhance Treg-associated cytokines and transcription factors by modulating the Th17/Treg balance (31). APS markedly upregulated peripheral blood Treg cells in mice with DSS-induced colitis, reshaping the Th17/Treg homeostasis to treat UC (21). In addition, according to an additional study, SCFA levels were elevated in UC mice following APS treatment and this was mediated by reorganization of the intestinal microbiota structure and enrichment of SCFA-producing microbes. These changes support the gut barrier, mitigate inflammation and sustain the balance between Th17 and Treg cells (86,90).

TLR4/NF-κB signaling pathway inhibition. As a key target, the TLR4/NF-κB signaling pathway is a mechanism through which polysaccharides (derived from TCM) exert their immunomodulatory effects (91). As a pattern recognition receptor, TLR4 detects pathogens in the gut and activates the NF-κB pathway. This triggers the release of IL-1β, IL-6 and TNF-α, which further contribute to chronic intestinal mucosal inflammation (92). In UC animal models, TCM polysaccharide treatments have been shown to notably reduce the expression levels of the key proteins p50 and p100 in the NF-κB pathway (84). An additional *in vivo* experiment demonstrated that POLPs markedly downregulated TLR4, myeloid differentiation primary response 88 and NF-κB protein expression levels in the colonic tissues of mice with DSS-induced colitis. This suggested that the effect of POLP on UC may be associated with the suppression of TLR4 activation and its subsequent downstream signaling proteins (93).

NF-κB serves an important role in the pathological mechanism of UC. Through a number of pathways, it participates in the regulation of the inflammatory response, the maintenance of the intestinal barrier function and the balance of intestinal microecology. *In vitro*, NF-κB inhibitors have been shown to reduce apoptosis of intestinal epithelial cells and enhance their barrier function (94). In addition, studies on macrophages and T cells have shown that NF-κB activity inhibition reduces pro-inflammatory cytokine secretion and decreases immune response strength (95). Following a stimulus signal, NF-κB signaling is activated through a series of signaling cascades (classical and non-classical NF-κB signaling pathways). Thus, two independent *in vivo* experiments have shown that DHP and the *Scutellaria baicalensis Georgi* polysaccharide SP1-1, notably reduced NF-κB p65 expression, suggesting that DHP and SP1-1 can inhibit the NF-κB signaling pathway and reduce pro-inflammatory factor expression to treat UC (23,28). The pectin polysaccharide from the fruit of *Prunus salicina* has also been shown to markedly reduce the expression of Cemip, a cancer-promoting gene associated with colorectal cancer, by inhibiting the NF-κB pathway (96).

Reduction of inflammatory responses. Regulation of the inflammatory factor network by TCM polysaccharides is particularly important. Herbal polysaccharides have been shown to mitigate inflammatory responses and oxidative stress (66,95), both of which can compromise the mucosal barrier (97). Numerous bioactive polysaccharides, including those derived from *Plantago asiatica*, *Lycium barbarum*, *Spirulina* spp. and *Coix lacryma-jobi*, can suppress pro-inflammatory cytokine expression levels (including those of IL-6, IL-8, IL-12 and TNF-α). These actions collectively enhance epithelial barrier integrity by reducing inflammation and stabilizing paracellular permeability (98-101). Wang *et al* (102) demonstrated that polysaccharides derived from astragalus and ginseng mitigated lipopolysaccharide-induced intestinal barrier damage in weaned piglets. In a murine sepsis model generated by cecal ligation and puncture, polysaccharides derived from *Zizyphus jujuba* cv. Muzao were also found to ameliorate impairment of the intestinal epithelial barrier. This protection was achieved through the downregulation of pro-inflammatory cytokines and TLR4/NF-κB signaling pathway inhibition (103). *Rhodiola rosea* polysaccharides have been shown to exert therapeutic effects by reducing pro-inflammatory factors, such as IL-6, TNF-α and IL-1β, in the intestines of mice with colitis (104) and according to the findings of this research, polysaccharides exhibit the ability to regulate a number of signaling pathways, allowing them to limit the release of pro-inflammatory cytokines and preserve a damaged intestinal barrier. Therefore, the chronic inflammatory state of UC has been associated with the abnormal activation of numerous signaling pathways, including the TLR4/NF-κB signaling pathway, which mediates the excessive secretion of pro-inflammatory cytokines and further compromises intestinal mucosal barrier function.

5. Polysaccharides regulate gut microbiota and metabolites

Microbiota regulation mechanism. Intestinal dysbiosis is an important part of UC pathogenesis. Harmful bacteria penetrate the damaged intestinal epithelial barrier and activate the intestinal immune system. This leads to the release of pro-inflammatory factors that form part of the harmful 'microbiota-immune axis' cycle (105). Beneficial gut microbiota growth is also positively influenced by polysaccharides. Furthermore, they can enhance the proliferation and metabolism of immune cells within the gut, contributing to the wider defense mechanisms against pathogens (106). However, the mechanisms that underlie their protective effects are not fully understood and warrant further investigation.

The gut microbiota includes the phyla Firmicutes (such as *Lactobacillus, Enterococcus, Clostridium* and *Bacillus*) and Bacteroidetes (including *Bacteroides* and *Prevotella*), as well as the phyla Actinobacteria (such as *Bifidobacterium*) and Ascomycetes (including *Escherichia coli*) (107). Gut microbiota imbalances have been shown to be associated with digestive system inflammatory diseases, including inflammatory bowel disease, non-alcoholic steatohepatitis and metabolic dysfunction-associated steatohepatitis, and with the application of macro-genomic analyses, an association between the gut microbiota and UC is gradually emerging (108-112).

Herbal polysaccharides derived from TCM are macromolecular compounds that generally cannot be absorbed into the blood through intestinal mucosa; hence, their pharmacological effect is perhaps associated with a change in the gut microbiota composition and metabolites (113). Arabinogalactan from *Lycium barbarum* (114), AMPs (30) and polysaccharides from *Chrysanthemum morifolium* Ramat (115) have been shown to increase both Chao1 and Abundance-based Coverage Estimator indices, two critical metrics that quantify the community richness of gut microbiota (30), as well as increase the abundance and diversity of gut microbiota in UC rats/mice. In addition, DHP has been shown to restore gut microbiota β diversity (27).

At the phylum level, SP2-1 and EHPs markedly elevate the total abundance of Firmicutes, a dominant polysaccharide-fermenting phylum in the gut that can efficiently degrade indigestible polysaccharides and convert them into SCFAs. This phylum is negatively associated with intestinal inflammation and the reduced abundance of Firmicutes is a key feature of intestinal dysbiosis in patients with UC (24). In addition, SP2-1 and EHPs reduce the relative abundance of Proteobacteria, a phylum enriched with opportunistic pathogens whose growth can disrupt the intestinal barrier and activate inflammatory responses (24,61). At the genus level, *Chrysanthemum* polysaccharides, SP2-1 and EHPs restore the abundance of *Bifidobacterium* and *Lactobacillus* that exert anti-UC effects by inhibiting pro-inflammatory cytokine secretion and enhancing the epithelial barrier function (61,88,115). SP2-1 notably upregulates *Roseburia*, which directly alleviates colonic inflammation by promoting Treg differentiation, enhancing the secretion of anti-inflammatory cytokines (such as IL-10 and TGF-β) and suppressing pro-inflammatory cytokines, including IL-1β, IL-6 and TNF-α. In addition, SP2-1 notably inhibits the proliferation of the genera *Bacteroides* and *Staphylococcus*, both of which are capable of disrupting the intestinal immune homeostasis and aggravating epithelial injury (24). By contrast, EHPs reduce the abundances of *Escherichia-Shigella*, *Tyzzerella* and *Parasutterella*, thereby decreasing endotoxin release and pro-inflammatory signaling activation (61).

Enrichment effect of SCFA-producing bacteria. Chinese herbal polysaccharides markedly promote the proliferation of SCFA-producing bacteria by regulating the gut microbiota composition. SCFAs (such as butyric acid, propionic acid and acetic acid) are primary metabolites of dietary fiber fermented by the gut microbiota, possessing marked anti-inflammatory properties and being regarded as key protective factors against inflammatory bowel disease (116). SCFAs are the primary energy substrate in colonic tissue and they directly affect the gastrointestinal tract of the host by altering the colonic epithelial cell phenotype. In particular, butyric acid can activate the energy metabolism regulator, adenosine monophosphate-activated protein kinase, which can regulate both cellular energy homeostasis and metabolic stress to improve the function of the UC intestinal mucosal barrier (117). Ginseng polysaccharides, such as *A. senegalensis*, increase the tryptophan metabolic level of the host and promote indole derivative generation (66). These findings are important to consider as microbiota remodeling is associated with metabolite changes. Overall, TCM polysaccharides regulate the microbiota composition and affect its metabolic functions, thereby generating beneficial metabolites.

Tryptophan metabolism regulation. Tryptophan metabolism is an additional important avenue through which TCM polysaccharides regulate the gut-immune axis. Tryptophan is converted into indole and its derivatives under the action of the bacterial community, activating the AhR signaling pathway. Ginseng neutral polysaccharides have been shown to markedly increased the content of indole derivatives in the intestines of aged mice and activate the AhR pathway (66). After activation, AhR can promote IL-22 secretion, stimulate the proliferation of intestinal epithelial cells and mucus production, enhance tight junction protein expression, reduce intestinal permeability, inhibit the NF-κB signaling pathway, alleviate intestinal inflammation and promote intestinal stem cell self-renewal and differentiation (66). These metabolites act as ligands for AhRs and serve a key role in the regulation of the intestinal immune balance, forming a complete functional chain of ‘polysaccharide-microbiota-metabolite-host’.

6. Clinical translational research and challenges

Systematic review of the existing clinical trial evidence. A number of preclinical studies have shown that TCM polysaccharides have a notable therapeutic effect on UC (118,119). Huangqin Decoction (HQD) and Gegen Qinlian Decoction (GQD) are classic TCM formulas recorded in Shang Han Lun, which have been extensively applied in gastrointestinal diseases and show marked efficacy against UC. HQD, consisting of four herbal ingredients, alleviates UC by regulating gut microbiota, amino acid metabolism, mTOR signaling and the intestinal epithelial barrier. GQD and its modified preparation ameliorate chronic UC through repairing intestinal mucus barriers, inhibiting NLRP3 inflammasome activation and reducing pro-inflammatory γδT17 cell responses. However, the majority of recent studies remain at the animal experimental stage, lacking large-scale randomized controlled clinical trial data to verify the exact efficacy and safety of these polysaccharide components.

Optimization of bioavailability and drug delivery systems. Therapeutic application of TCM polysaccharides in UC remains largely confined to animal models and preclinical studies. This limited progress may be attributed to a number of key factors (120), such as their large molecular size and high hydrophilicity, which notably reduce their transmembrane efficiency. In addition, structural damage and activity loss caused by exposure to gastric acid, bile salts and digestive enzymes, may lead to diminished efficacy. Lastly, a lack of colon-targeting specificity hinders their enrichment at inflammatory sites to achieve effective therapeutic concentrations.

With regard to the oral route, polysaccharides can be engineered into charge-targeted nanoparticles. A representative approach may involve the development of amphiphilic prodrug nanoparticles from the *Codonopsis* polysaccharide (34). This design exploits the positively charged, protein-rich microenvironment of the inflamed colonic mucosa to markedly enhance nanoparticle adhesion and retention. With a typical diameter of ~180 nm, these nanoparticles readily penetrate the mucus layer and accumulate in diseased tissues through the enhanced permeability and retention effect. Consequently, systemic circulation is markedly prolonged. This is evidenced by an extended half-life of ~25 h. In addition, bioavailability is notably improved, with this being reflected by an increase in the area under the curve value. In parallel, rectal administration uses *in situ* thermosensitive gelling systems such as hydrogels composed of BSP, chitosan and β-glycerophosphate (35). These systems undergo a reversible sol-to-gel transition at body temperature, completely avoiding upper gastrointestinal degradation and hepatic first-pass metabolism. In addition, the incorporation of mucoadhesive components, such as thiolated hyaluronic acid, enables the formation of disulfide bonds with the colonic mucus layer. This interaction extends local retention beyond 48 h and ensures controlled drug release.

7. Critical appraisal and future directions

It has been established that the ‘black box’ nature of polysaccharide pharmacology presents a notable challenge. While TCM polysaccharides exert multi-target effects through modulation of the Th17/Treg balance, inhibition of the TLR4/NF-κB pathway and reshaping of the gut microbiota, their precise molecular targets, binding affinities and structure-activity associations remain elusive. The bioactivity of TCM polysaccharides is associated with their structural characteristics, including their molecular weight, monosaccharide composition, glycosidic linkage types, branching degree and higher-order spatial conformation. The common lack of detailed structural characterization in natural product extracts, coupled with inherent batch-to-variability, hinders reproducibility, standardization and the establishment of reliable structure-activity associations, which are key in rational drug design and optimization. Future research should therefore aim to employ multi-omics approaches (metabolomics, metagenomics and glycomics) combined with network pharmacology and artificial intelligence-driven target prediction to decipher the specific receptors and signaling nodes through which TCM polysaccharides act. Concurrently, it is important to establish standardized extraction protocols and advanced structural characterization techniques to ensure batch consistency. Semi-synthetic modifications or enzymatic hydrolysis techniques should be explored to obtain low-molecular-weight fragments with enhanced bioactivity, thereby overcoming the limitations posed by the heterogeneity of natural polysaccharides.

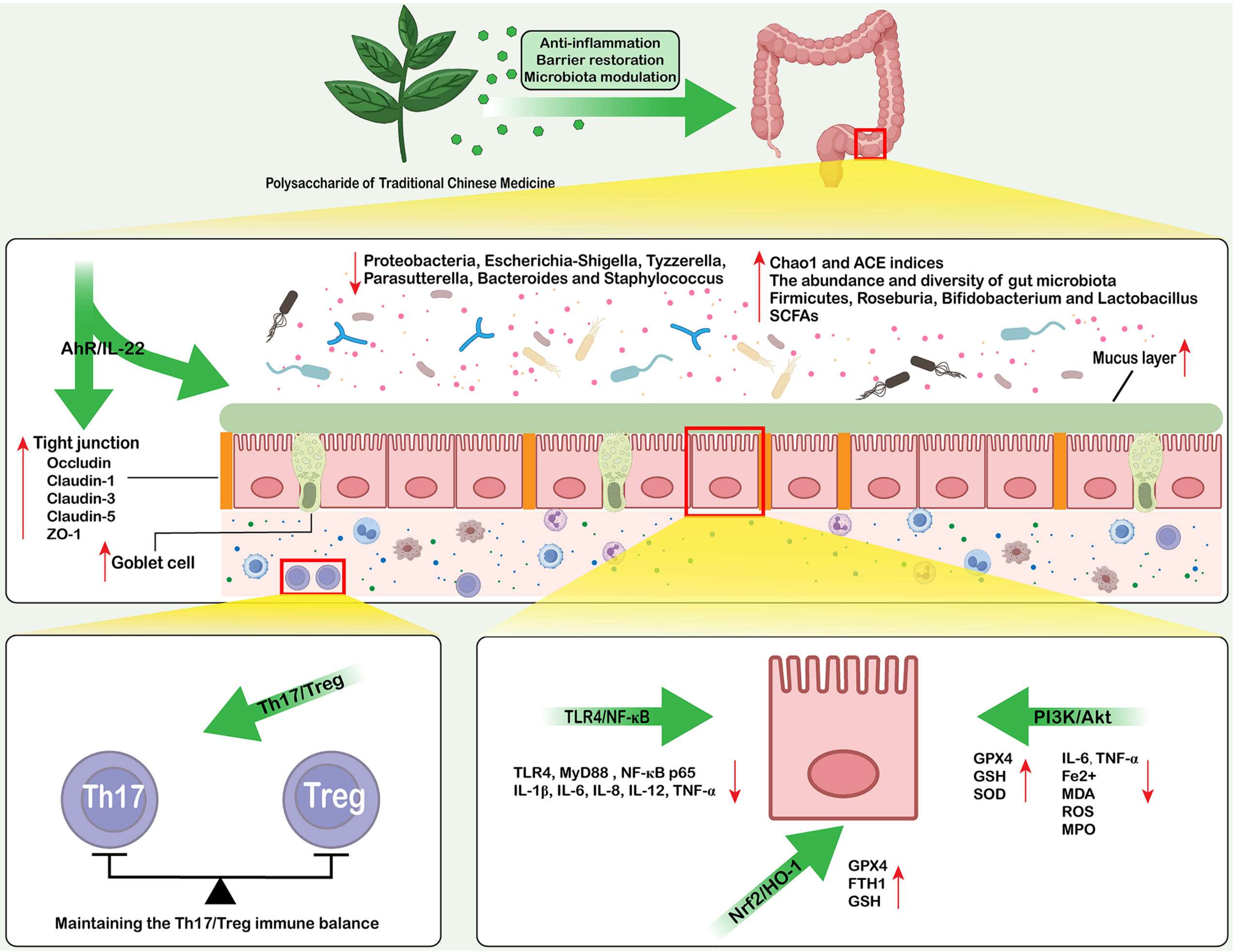

Figure 1. Effects of polysaccharides from Traditional Chinese Medicine on ulcerative colitis. AhR, aromatic hydrocarbon receptor; ZO-1, zonula occludens-1; ACE, Abundance-based Coverage Estimator; SCFA, short-chain fatty acid; Th17, T helper 17 cell; Treg, T regulatory cell; TLR4, toll-like receptor 4; ROS, reactive oxygen species; MyD88, myeloid differentiation primary response 88; Nrf2, nuclear factor erythroid 2-related factor 2; HO-1, heme oxygenase-1; GSH, glutathione; GPX4, GSH peroxidase 4; FTH1, ferritin heavy Chain 1; SOD, superoxide dismutase; MDA, malondialdehyde; MPO, myeloperoxidase.

The current evidence base primarily originates from animal models and *in vitro* cell cultures. Therefore, to the best of our knowledge, there are currently no randomized controlled trials or large-scale clinical studies specifically dedicated to evaluating purified TCM polysaccharides in UC with the aim of determining their exact efficacy, safety or optimal dosage. Therapeutic effects have been observed in clinical practice (121) with TCM formulations that contain polysaccharide components, however the specific contribution of polysaccharides to these clinical benefits remains unclear due to the complexity of the formulations. This reliance on preclinical models raises concerns regarding their translational relevance, as rodent colitis models often fail to adequately recapitulate the chronic, relapsing-remitting nature and complex immunopathology of human UC (122). This may have led to an overestimation of the therapeutic benefits. Research should therefore aim to shift away from traditional rodent models toward patient-derived organoids, 3D co-culture systems that incorporate intestinal epithelial cells, immune cells and microbiota or humanized microbiota mouse models to better mimic the human UC microenvironment. Phased clinical research should be initiated to address the gap in dedicated UC clinical trials for TCM polysaccharides. Initially, small-scale pilot trials are required to assess the safety, tolerability and preliminary efficacy of purified polysaccharides in patients with mild-to-moderate UC. The endpoints should include clinical remission rates, mucosal healing and inflammatory marker levels. Subsequently, large-scale randomized controlled trials with long-term follow-ups should be designed to compare polysaccharide-based therapies with conventional treatments or combination therapies. These should focus on long-term efficacy and safety.

The majority of TCM polysaccharides are hydrophilic macromolecules with low oral bioavailability due to poor intestinal absorption, susceptibility to degradation by gastric acid and digestive enzymes and a lack of targeted delivery to colonic inflammatory sites. The effective concentrations demonstrated in *in vitro* cell cultures are often far beyond physiologically achievable levels *in vivo*. Therefore, there is an urgent need for innovative delivery strategies for TCM polysaccharides. As aforementioned, charge-mediated nanoparticles and *in situ* thermosensitive gelling systems represent promising novel routes. These approaches can enhance local bioavailability, prolong retention at the disease site and circumvent systemic

Table I. Effects of polysaccharides from Traditional Chinese Medicine on ulcerative colitis.

First author, year	Source	Compound name	Molecular weight, Da	Models	Mechanisms	(Refs.)
Hao *et al*, 2022	*Zingiber officinale*	Ginger polysaccharides	7.47x10^{5}	DSS-induced colitis in mice	Upregulation of occludin-1, ZO-1, SCFAs, *Muribaculaceae*, *Bacteroidaceae* and *Lactobacillaceae*; downregulation of IL-2, IL-4, TNF-α, *Rikenellaceae* and *Lachnospiraceae*	(25)
Yu *et al*, 2022	*Dendrobium huoshanense*	Polysaccharides of *Dendrobium huoshanense*	2.20x10^{4}	DSS-induced colitis in rats	Downregulation of TNF-α, IL-1β, IL-17, TGF-β and NF-κB	(27)
Gu *et al*, 2021				DSS-induced colitis in mice	Downregulation of TNF-α, IL-1β, IL-6, *Desulfobacterota* and *Clostridioides*; upregulation of ZO-1, occludin, IL-10, *Alistipes* and *Rikenella*	(28)
Yang *et al*, 2021	Turmeric	Turmeric polysaccharides		DSS-induced colitis in mice	Upregulation of *Lactobacillus*, *Clostridia*-UCG-014, IAA, AhR, ZO-1, occludin and IL-22	(29)
Pan *et al*, 2022	*Smilax china* L.	*Smilax china* L. polysaccharide	1.60x10^{6}	DSS-induced colitis in mice and LPS stimulated THP-1 cells	Downregulation of IL-6, TNF-α, galectin-3 and NLRP3	(32)
Dong *et al*, 2024	*Codonopsis pilosula*	*Codonopsis Radix* polysaccharide-A	3.60x10^{3}	DSS-induced colitis in mice	Downregulation of IL-6, IL-1β, IFN-γ, TNF-αTLR4, PI3K, Akt and p65; upregulation of *Akkermansia* and *Bacteroides*	(34)
Zhao *et al*, 2024	*Bletilla striata*	*Bletilla striata* polysaccharide	2.36x10^{5}	DSS-induced colitis in mice	Downregulation of TNF-α, IL-1β and IL-6; upregulation of IL-10	(36)
Wu *et al*, 2022	*Scutellaria barbata* D. Don	Polysaccharides from *Scutellaria barbata* D. Don	1.25x10^{4}	DSS-induced colitis in mice	Downregulation of TNF-α, IFN-γ, IL-1β, IL-6, IL-18, NF-κB, STAT3 and *Bacteroides*; upregulation of *Firmicutes*	(64)
Zhao *et al*, 2016	*Astragali Radix*	Astragalus polysaccharide	1.70x10^{6}; 1.20x10^{6}	TNBS-induced colitis in rats	Upregulation of Treg cells and TGF-β; downregulation of IL-2, IL-6, IL-17 and IL-23	(129)
Lv *et al*, 2017				DSS-induced colitis in mice	Downregulation of TNF-α, IL-1β, IL-6, IL-17, MPO and NF-κB	(130)

Table I. Continued.

First author, year	Source	Compound name	Molecular weight, Da	Models	Mechanisms	(Refs.)
Yang *et al*, 2014				TNBS-induced colitis in rats	Downregulation of TNF-α and IL-1β; upregulation of Nfatc4	(131)
Yan *et al*, 2020				Colon mucosal tissue sensitization and TNBS-ethanol in rats	Upregulation of ZO-1 and occludin	(132)
Chen *et al*, 2021				DSS-induced colitis in mice and RSL3-treated Caco-2 cells	Upregulation of HO-1 and Nrf2; downregulation of ROS, lipid, peroxidation and ferroptosis	(133)
Zhang *et al*, 2025				DSS-induced colitis in mice	Downregulation of IL-2, IL-6, IL-12, p70, IL-23, TNF-α, TGF-β1, Tfh1, Tfh17, Tfh21, Blimp-1, Bcl-6 and IL-21; upregulation of Tfh10 and Tfr	(90)
Zhang *et al*, 2025				DSS-induced colitis in mice	Downregulation of NF-κB, IL-17 and IL-6; upregulation of IL-10 and SCFA	(90)
Cui *et al*, 2019	*Scutellaria baicalensis Georgi*	SP1-1	$4.56x10^5$	DSS-induced colitis in mice and LPS-stimulated THP-1-derived macrophages	Downregulation of IL-1β, IL-18, TNF-α, NF-κB and NLRP3	(23)
Cui *et al*, 2021		SP2-1	$3.72x10^6$	DSS-induced colitis in mice	Upregulation of ZO-1, occludin, claudin-5, facetic acid, propionic acid, butyric acid, *Bifidobacterium*, *Lactobacillus* and *Roseburia*; downregulation of *Bacteroides*, Proteobacteria and *Staphylococcus*	(24)
Xiao *et al*, 2024		*Scutellaria baicalensis Georgi* polysaccharide	$4.56x10^5$	DSS-induced colitis in mice	Upregulation of AGR2, FUT2, ST6GAL1, B3GNT6, ATOH1, occludin, claudin-1 and ZO-1; downregulation of HES1, Notch1, p-IκBα, p-NF-κB p65, p-MLC, MLC and NMIIA	(134)
Lu *et al*, 2023	*Dioscoreae Rhizoma*	Chinese yam polysaccharide	$2.09x10^3$	DSS-induced colitis in mice	Upregulation of MUC-2, ZO-1, occludin, IL-10, *Alistipes*, *Bacteroides* and SCFAs; downregulation of ET, LBP, MPO, TNF-α and IL-1β	(26)

Table I. Continued.

First author, year	Source	Compound name	Molecular weight, Da	Models	Mechanisms	(Refs.)
Feng *et al*, 2020	*Atractylodes macrocephala* Koidz.	*Atractylodes macrocephala* Koidz. polysaccharides	2.39x10^{4}	DSS-induced colitis in mice	Downregulation of TNF-a, IL-18 and IL-1β; upregulation of *Butyricicoccus* and *Lactobacillus* with decreasing *Actinobacteria*, *Akkermansia*, *Anaeroplasma*, *Bifidobacterium*, *Erysipelatoclostridium*, *Faecalibaculum*, *Parasutterella*, *Parvibacter*, *Tenericutes* and *Verrucomicrobia*; upregulation of 5-aminopentanamidevaline, leucine and 2-hydroxyisocaproic acid	(30)
Liu *et al*, 2023	*P. grandiflorus*	*Platycodon grandiflorum* polysaccharide	1.02x10^{4}	DSS-induced colitis in mice	Downregulation of T-bet, ROR-γ, TIFN-γ, IL17, Th1 and Th17; upregulation of GATA-3, Foxp3, Th2 and Treg	(31)
Luo *et al*, 2022	*Amomum villosum* Lour.	*A. villosum* polysaccharide	4.16x10^{5}	DSS-induced colitis in mice	Upregulation of ZO-1, *Halomonas*, *Adlercreutzia*, *Nocardia*, *Clostridium*, *Streptococcus*, *Parabacteroides*, *Helicobacter*, *Odoribacter* and *Alistipe*; downregulation of IL-6, TNF-α and *Polynucleobacter*	(38)
Lian *et al*, 2022	*Lycium barbarum*	*Lycium barbarum* polysaccharides	7.48x10^{6}-4.62x10^{7}	DSS-induced colitis in rats	Downregulation of IFN-γ, IL-17A and IL-22; upregulation of *Ruminiclostridium_9* and *Ruminoclostridium_1*	(39)
Chen *et al*, 2022					Downregulation of MDA, IL-6, TNF-α, TRPV and TRPA1	(40)
Ye *et al*, 2023				DSS-induced colitis in mice	Downregulation of IL-1β, IL-6, iNOS, TNF-α and claudin-2; upregulation of IL-10, occludin, ZO-1, Nrf2, SCFAs, *Ruminococcaceae*, *Lactobacillus*, *Butyricicoccus* and *Akkermansia*	(13)

Table I. Continued.

First author, year	Source	Compound name	Molecular weight, Da	Models	Mechanisms	(Refs.)
Zhou *et al*, 2021	*Lonicera japonica* Thunb.	*Lonicera japonica* Thunb. polysaccharide	$2.02x10^3$-$7.79x10^3$	DSS-induced colitis in mice	Upregulation of IL-2, TNF-α, IFN-γ, natural killer cells, CTL, *Bifidobacteria* and *Lactobacilli*; downregulation of *Escherichia coli* and *Enterococci*	(42)
Wang *et al*, 2023	Pine pollen	*Pinus yunnanensis* pollen polysaccharides	$3.16x10^5$	DSS-induced colitis in mice	Upregulation of IL-2, IL-10, IL-13 and *Lactobacillus*; downregulation of IL-1β, IL-6, TNF-α, *Akkermansia* and *Aerococcus*	(45)
Li *et al*, 2022		*Pinus yunnanensis* pollen polysaccharide III		DSS-induced colitis in mice	Downregulation of COX-2, iNOS, IL-6, IL-18, RIPK1, RIPK3 and MLKL; upregulation of ZO-1, occludin, claudin-1 and caspase-8,	(46)
Tan *et al*, 2023	*Poria cocos*	Carboxymethylated *Poria* polysaccharides I and II		DSS-induced colitis in mice	Downregulation of IL-1, IL-6,TNF-α and MPO; upregulation of IL-4 and SOD	(47)
Zheng *et al*, 2020		*Poria cocos* polysaccharides	$1.16x10^4$		Upregulation of IL-2, IL-4, IL-6, IL-10, TGF-β, IFN-γ, SCFAs, MUC2, β-defensin, SIgA, Wnt, β-catenin and LRP5	(53)
Zheng *et al*, 2020	*Ganoderma atrum*	*G. atrum* polysaccharide	$1.01x10^3$	DSS-induced colitis in mice	Upregulation of Bcl-2, ATG5, ATG7 and beclin-1; downregulation of caspase-3, caspase-9, p-Akt, p-mTOR and IL-10	(53)
Xie *et al*, 2019		*Ganoderma lucidum* polysaccharide		DSS-induced colitis in rats	Upregulation of *Ruminococcus_1*, CCL5, CD3E, CD8A, Il21R, LCK and TRBV; downregulation of *Escherichia-Shigella*, CCL3, GRO, IL-11, MHC2 and PTGS	(54)
Yang *et al*, 2023	*Portulaca oleracea* L.	*Portulaca oleracea* L. polysaccharide	$4.00x10^4$	DSS-induced colitis in mice	Downregulation of TLR4, MyD88 and NF-κB	(93)
Wang *et al*, 2020					Downregulation of COX-2, p-STAT3, PGE2 and IL-6	(135)

Table I. Continued.

First author, year	Source	Compound name	Molecular weight, Da	Models	Mechanisms	(Refs.)
Yang *et al*, 2018					Downregulation of NF-κB p65, Bcl-2 and survivin	(58)
Fu *et al*, 2022	*Aconitum carmichaelii* leaves	Polysaccharides from *Aconitum carmichaelii* leaves	2.60×10^4-2.70×10^5	DSS-induced colitis in mice	Downregulation of IL-1β, IL-6, TNF-α, NOD1 and TLR4; upregulation of ZO-1, occludin, SCFAs, BCFAs and IL-10	(59)
Son *et al*, 2022	*Saururus chinensis*	*Saururus chinensis*-derived crude polysaccharides	9.26×10^4	DSS-induced colitis in mice	Downregulation of IL-6, TNF-α and MPO	(60)

DSS, dextran sulfate sodium; TNBS, trinitrobenzene sulfonic acid.

degradation. Furthermore, screening for probiotic strains that exhibit optimal synergy with TCM polysaccharides and the employment of co-administration strategies, could yield synergistic effects greater than the sum of their parts (123). In addition, drug administration through colonic transendoscopic enteral tubing may represent an innovative and promising approach (124). This technique involves the colonoscopic placement of a specialized tube into the target area (such as the ileocecal region), its fixation to the intestinal wall using endoscopic clips and subsequent medication delivery through side openings in the tube. This would enable precise, repeated and whole-colon coverage drug delivery.

8. Conclusion

UC is a chronic, relapsing-remitting inflammatory bowel disease characterized by mucosal inflammation and impaired intestinal barrier function. Current therapeutic strategies, including aminosalicylates, corticosteroids, immunomodulators and biologics, often face limitations such as partial efficacy, systemic side effects and loss of response over time. Therefore, TCM polysaccharides have emerged as a promising multi-target and system-modulating approach that offers a complementary or alternative strategy for UC management.

Polysaccharides exhibit multi-target synergistic effects for UC treatment, primarily by regulating the immune system, inhibiting inflammatory pathways and repairing the intestinal barrier to achieve synergistic effects (Fig. 1). For example, polysaccharides can simultaneously downregulate pro-inflammatory factors and upregulate anti-inflammatory factors, thus alleviating colonic inflammation by inhibiting inflammasome signaling pathways (8,125,126). This multi-pathway synergy avoids the limitations of a single target and enhances the overall therapeutic effect (127). With regard to safety, polysaccharides are natural macromolecules that possess good biodegradability and biocompatibility. Their low reactivity and fewer side effects are markedly improved compared with traditional immunosuppressants (128), thus lowering the risk of systemic toxicity during long-term treatment (Table I) (23,26,30,31,38-40,42,45-47,53,54,59,60,129-135).

Overall, TCM polysaccharides represent a promising, multi-faceted therapeutic avenue for UC that are capable of modulating the complex immunoinflammatory and microbial disease landscape. By addressing the current challenges through mechanistic elucidation, pharmaceutical innovation and rigorous clinical validation, TCM polysaccharides may evolve from traditional herbal constituents into standardized, evidence-based biologics and represent promise for patients with UC.

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Availability of data and materials

The data generated in the present study may be requested from the corresponding author.

Authors' contributions

ZJ conceptualized the present study. YJ and ZJ prepared the original manuscript draft. GL wrote and reviewed the manuscript. LB edited the manuscript. LP reviewed the manuscript and provided guidance and supervision. All authors have read and approved the final version of the manuscript. Data authentication is not applicable.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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