Chinese Journal of Natural Medicines

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Citation: Yating Shao, Bo Li, Yongfang Wang, Chuanjie Zhou, Yunlong Qiao, Xinglishang He, Shengqiang Tong, Guiyuan Lv, Suhong Chen, An overview of the advantageous effects and underlying mechanisms of natural polysaccharides in inflammatory bowel disease, Chinese Journal of Natural Medicines, 2026, 24(1), 45–58. doi: 10.1016/S1875–5364(26)61076–X.

View online: https://doi.org/10.1016/S1875–5364(26)61076–X

Chinese Journal of Natural Medicines 24 (2026) 45-58

Contents lists available at ScienceDirect

Chinese Journal of Natural Medicines

journal homepage: www.cjnmcpu.com/

Review

An overview of the advantageous effects and underlying mechanisms of natural polysaccharides in inflammatory bowel disease

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ARTICLE INFO

Article history:
Received 24 January 2025
Revised 5 April 2025
Accepted 11 June 2025
Available online 20 January 2026

Keywords:
Natural polysaccharides
Inflammatory bowel disease
Pathogenesis
Therapeutic effect
Research progress

ABSTRACT

Inflammatory bowel disease (IBD), which includes Crohn's disease (CD) and ulcerative colitis (UC), is a chronic inflammatory condition affecting the gastrointestinal tract. The global incidence and prevalence of IBD continue to increase. While multiple clinical treatments exist, conventional therapies frequently present limitations and adverse effects. Natural polysaccharides (PSs) have emerged as a significant focus of research interest due to their therapeutic potential and applications in functional foods and health products. This review synthesizes current understanding of IBD pathophysiology and the mechanisms by which natural PSs counter IBD, including their capacity to restore immune homeostasis and intestinal barrier function, modulate gut microbiota and metabolites, reduce oxidative stress, and address irregularities in autophagy and endoplasmic reticulum stress (ERS). The review examines the structure-activity relationships of PSs demonstrating anti-IBD effects and identifies promising therapeutic products. The discussion encompasses pharmacokinetics, safety evaluations, and clinical applications of these compounds. This comprehensive review establishes a theoretical foundation for developing natural PS-based therapeutic approaches for IBD management.

1. Introduction

The intestine serves a critical function in nutrient absorption and waste elimination. Major intestinal disorders associated with inflammation include inflammatory bowel disease (IBD) and irritable bowel syndrome (IBS). IBD, a chronic and recurring gastrointestinal inflammatory condition characterized by immunological dysfunction [1], has multiple contributing factors, and approximately 20% of affected individuals may subsequently develop colon cancer [2]. The two primary forms of IBD, ulcerative colitis (UC) and Crohn's disease (CD), manifest through symptoms including weight loss, mucopurulent bloody stools, diarrhea, and abdominal pain (Fig. 1). Epidemiological studies indicate that IBD affects approximately 0.5% of populations in Europe and the United States, where incidence rates have stabilized; however, IBD cases continue to rise substantially in developing regions, particularly in East Asia and South America [3]. This worldwide increase in IBD prevalence creates significant challenges for healthcare systems globally.

Polysaccharide (PS) is a naturally occurring polymeric compound consisting of more than 20 sugar units formed through condensation and dehydration reactions between monosaccharides, establishing glycosidic bonds [4]. As shown in Table S1, PSs occur extensively in nature, present in higher plants, algae, fungi, and animals [5]. Along with lipids, proteins, and nucleic acids, PSs constitute fundamental biological macromolecules essential for maintaining diverse biological functions. Research has demonstrated multiple biological benefits of PSs, including immune system regulation [6], anti-aging properties [7], and gastrointestinal protection [8]. The abundant sources, stability, absence of drug resistance, cost-effectiveness, and additional beneficial characteristics of PSs render them promising candidates for pharmaceutical development [9].

While the precise etiology of IBD remains undetermined, research indicates that immune dysregulation, gut microbiota and metabolite imbalances, autophagy impairment, oxidative stress, endoplasmic reticulum stress (ERS), intestinal epithelial barrier disruption, and genetic predisposition all contribute to IBD onset [10]. Current clinical management of IBD primarily relies on immunosuppressants, glucocorticosteroids, and aminosalicylic acid derivatives; however, these treatments frequently cause substantial side effects and may trigger serious adverse reactions, with limited efficacy and high relapse rates [2, 11]. Given these therapeutic limitations, natural products have emerged as promising alternative approaches for IBD management.

This review aims to establish a foundation and direction for future research on developing novel IBD medications utilizing

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https://doi.org/10.1016/S1875-5364(26)61076-X

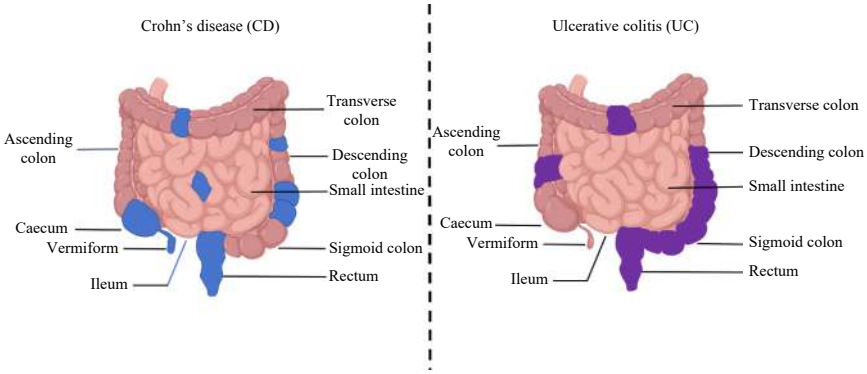

Fig. 1 Graphical representation of the two primary IBD types. CD lesions are discontinuous and may involve the entire GI tract; UC lesions tend to appear in the sigmoid colon and rectum and might impact the entire colon.

PSs as primary therapeutic agents by examining and analyzing the advantages and limitations of natural PSs in IBD therapy.

2. Pathogenesis of IBD

As illustrated in Fig. 2, multiple factors contribute to IBD pathophysiology. This paper examines the classical mechanisms of IBD, including intestinal barrier impairment, immune system dysfunction, intestinal flora disruption, oxidative stress, dysregulated autophagy, ERS, and genetic susceptibility. Additionally, non-classical mechanisms are addressed, such as increased formation of neutrophil extracellular traps (NETs), exosomal interventions, iron death, and altered expression of cell adhesion molecules (CEACAMs).

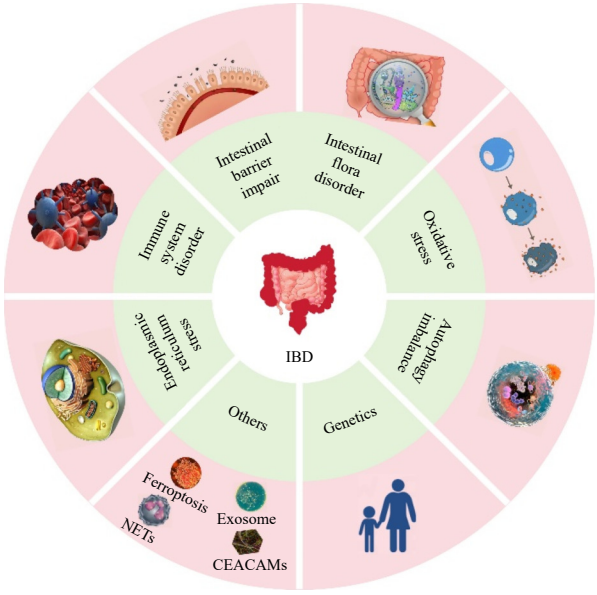

Fig. 2 Pathogenesis of IBD. NETs: neutrophil extracellular traps; CEACAMs: cell adhesion molecules.

2.1. Damaged intestinal barrier

The intestinal barrier functions as a critical defense against external infections entering the body, comprising chemical, mechanical, immunological, and biological barriers [12].

The mechanical barrier consists of intestinal epithelial cells (IECs) and tight junctions (TJs) between them. TJs function as essential regulators of paracellular permeability and direct targets and modulators of various signaling pathways. Their composition includes occludin, claudins, ZO-1, junctional adhesion molecules (JAM), and the cytoskeleton [13]. IECs complete their renewal every 4–5 days, with stem cells in the intestinal crypts continuously proliferating to replace lost cells. As depicted in Fig. 3, under pathological conditions, IEC turnover becomes disrupted, TJ expression becomes irregular, intestinal epithelial barrier integrity decreases, and permeability increases. Consequently, IBD may develop when macromolecules such as proteins and pathogens penetrate the compromised mechanical barrier and invade the lamina propria [14-16].

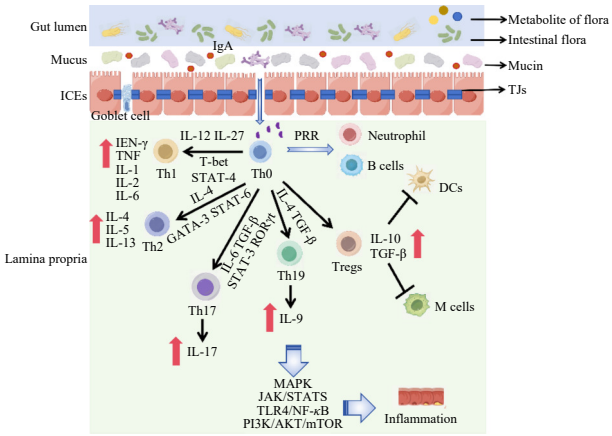

Fig. 3 Mechanisms of IBD development due to impaired intestinal barrier. B cells: B lymphocytes; M cells: macrophages; DCs: dendritic cells; IgA: immunoglobulin A; PRR: pattern recognition receptor; Th0: helper T cells; RORγt: vitamin A acid-related orphan receptor γt.

The mucus layer, adhering tightly to IECs and positioned between luminal microorganisms and the intestinal epithelium, constitutes the chemical barrier. It primarily comprises immunoglobulin A (IgA), anti-microbial peptides (AMPs), and mucin (MUC), secreted by goblet cells (GCs). The chemical barrier enhances the physical barrier formed by cells and their interconnecting TJs [17]. MUC2 represents the primary component of the double-layered mucus system protecting IECs from bacteria [18]. As shown in Fig. 3, during initial inflammation, pathogen invasion disrupts intestinal crypts, reduces GCs with altered phenotypes (abnormal MUC post-translational modification, decreased MUC2 glycosylation), and diminishes MUCs, leading to further deterioration of the intestinal mucus layer [19]. This results in increased infiltration of intestinal luminal microbial components contacting the colon epithelium, thereby exacerbating IBD [20-22].

2.2. Immune system disorders

IBD primarily results from an imbalance in the gut immune system, involving both innate and adaptive immune responses. As illustrated in Fig. 3, innate immune cells serve as the body's first line of defense against pathogens. These cells express pat-

tern recognition receptors (PRRs), including toll-like receptors (TLRs) and NOD-like receptors (NLRs), which recognize pathogen-associated molecular patterns (PAMPs) and damage-associated molecular patterns (DAMPs), triggering the release of cytokines and chemokines that initiate inflammation [23]. The development of IBD has been associated with the activation of DCs, M1 macrophages, T lymphocytes, and B lymphocytes in the intestinal mucosal lymphoid tissue (GALT) and lamina propria, leading to TJ damage, epithelial cell apoptosis, and compromised intestinal barrier integrity. Neutrophils contribute to prolonged intestinal inflammation by disrupting epithelial barrier function and releasing inflammatory mediators [24]. Although intestinal endocrine IgA (SIgA), IgE, IgG, IgM, and other antibodies typically aggregate intestinal luminal bacteria, reduce bacterial adhesion, prevent bacterial translocation, enhance intestinal mucus secretion, accelerate mucus layer migration, and decrease pathogenic bacterial colonization [19], IBD conditions increase the probability of bacterial adhesion and translocation [25].

Adaptive immunity exhibits high selectivity, with various helper T (Th)-cell subpopulations maintained through controlled polarized production of cytokines or effector cytokines [26]. The Th1/Th2 balance maintains intestinal immune homeostasis through mutual cytokine-mediated regulation. Th1 cells produce IBD. APS reduced inflammatory cytokines [interferon (IFN)-γ], inhibiting Th2 cell proliferation, while Th2 cells secrete interleukin (IL)-4, counteracting Th1 cell differentiation [27, 28]. Th17, considered a major pathogenic factor in IBD, secretes IL-17, which binds to the IL-17 receptor, activates nuclear factor κB (NF-κB), and promotes pro-inflammatory factor production [29]. Elevated levels of Th17 cells and IL-17 are present in the inflammatory intestinal mucosa of CD and UC patients [30]. Research has revealed significantly higher levels of PU.1IL-9Th9 cells in the colonic lamina propria [31] and increased *IL-9* mRNA expression [1] in IBD patients. Tregs produce IL-10, which suppresses immune responses [28] and promotes Treg proliferation through signal transducer and activator of transcription 3 (STAT3) activation [32, 33]. Transforming growth factor β (TGF-β), another crucial Treg secretion, activates intracellular mediators SMAD3 and SMAD4 to suppress pro-inflammatory responses [34]. UC associates with Th-2 cells, characterized by normal IFN-g levels and elevated IL-4, IL-5, and IL-13, while CD presents as a Th-1-dominant inflammatory condition, induced by IL-12 producing substantial IFN-g and tumor necrosis factor (TNF) [35].

As depicted in Figs. 3 and 5, multiple signaling pathways affecting normal intestinal function, including TLR4/MyD88/NF-κB, Janus kinase (JAK)/STATS, nuclear factor erythroid 2-related factor 2 (Nrf2)/PPAR-γ/SIRT1, phosphatidylinositol 3-kinase (PI3K)/protein kinase B (AKT)/mammalian target of rapamycin (mTOR), mitogen-activated protein kinase (MAPK), Wnt, Notch, and Hippo, may contribute to IBD development [36-40].

2.3. Disorders of intestinal flora

Firmicutes, *Bacteroidetes*, *Proteobacteria*, and *Actinobacteria* constitute the majority of the intestinal flora. More than 90% of the intestinal flora in healthy adults comprises primarily *Firmicutes* and *Bacteroides* [41]. Research has demonstrated that individuals with UC exhibit dysregulated intestinal flora, characterized by altered host-microbe interactions, reduced biodiversity, abnormal composition, and modified spatial distribution [15]. Studies indicate that *Lactobacillus*, *Fungus*, *Enterococcus faecalis*, *Bifidobacterium*, and *Escherichia coli* are potential pathogenic microorganisms associated with IBD [42]. Several mechanisms explain the impact of intestinal flora dysregulation in IBD: first, deoxyribonucleic acid (DNA) methylation reprogramming upregulates colitis-related gene expression (e.g., *FRA1*, *AP1*, and *FOSL2*) [43]; second, microbial metabolite dysregulation affects intestinal barrier function and immune homeostasis [44]; third, dysregulation of intestinal innate lymphocytes ILC3 and ILC1 increases pro-inflammatory cytokines IFN-γ, IL-17, and IL-22 [45]; fourth, adaptive immunity dysregulation manifests through increased pro-inflammatory Th17 cells, which produce IL-17 and IL-22 cytokines, and decreased anti-inflammatory Treg cells, which produce IL-10 and TGF-β.

Short-chain fatty acids (SCFAs), tryptophan (TRP) metabolites, and bile acids (BA) represent three crucial intestinal bacterial metabolites [46]. As illustrated in Fig. 4, SCFAs, including acetic acid, propionic acid, and butyric acid, enhance gut microbiota harmony by reducing intestinal pH, thus inhibiting pathogenic microbe proliferation while promoting beneficial bacteria growth [47]. Butyrate undergoes *β*-oxidation to generate adenosine triphosphate (ATP), providing energy for the electron transport chain and tricarboxylic acid cycle (TCA cycle), while regulating TJ protein expression [15, 48]. As depicted in Fig. 4, TRP influences gut

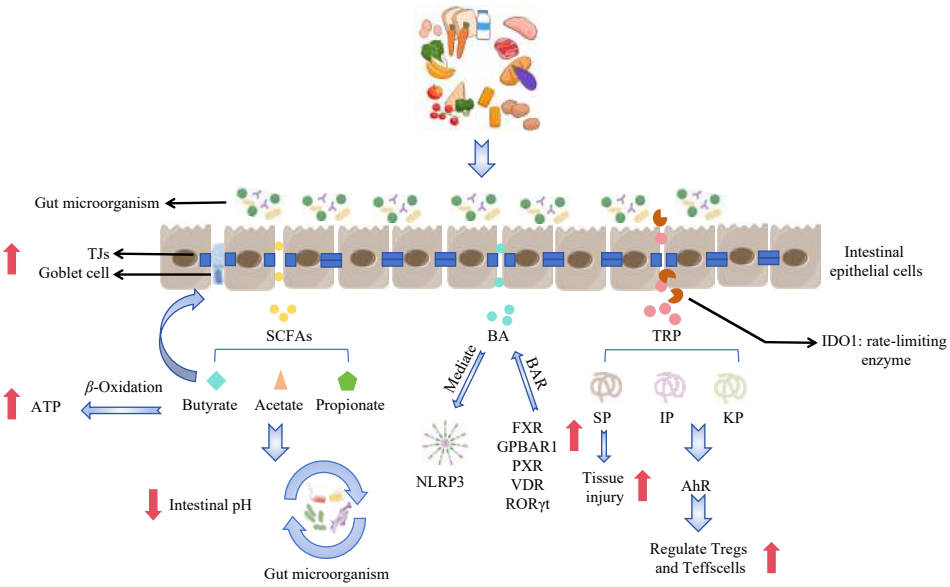

Fig. 4 Effect of gut microbial metabolites on intestinal remission. TJs: tight junctions; BA: bile acids; TRP: tryptophan; BAR: bile acid activation receptor; SP: intestinal chromaffin cell's serotonin pathway; IP: microbial-mediated indole pathway; IDO1: indole amine 2,3-dioxygenase 1; PXR: pregnane X receptor; FXR: farnesol X receptor; VDR: vitamin D receptor; GPBAR1: G protein-coupled bile acid receptor 1.

function through three distinct metabolic pathways: the serotonin pathway in enterochromaffin cells, the microbially mediated indole pathway, and the kynurenine pathway (KP), with KP accounting for approximately 90% of catabolism reactions [49]. Most indole metabolites and kynurenine (Kyn) bind to the aryl hydrocarbon receptor (AhR), which modulates IL-22 and IL-10 production, regulating Tregs and Teffs differentiation and activity [50], thereby alleviating colitis and preventing colorectal cancer. However, the serotonin system promotes colorectal cancer cell proliferation and metastasis [51]. IBD patients demonstrate elevated Kyn and Kyn/TRP ratios, indicating enhanced KP activity in TRP metabolism [52]. Additionally, IBD patients frequently experience BA malabsorption [53], exhibiting higher conjugated BA levels and reduced secondary BA concentrations [54]. Intestinal inflammation negatively regulates BA-activated receptor (BAR) expression and function, resulting from either BA or BAR dysregulation [53, 55-57]. Furthermore, BA demonstrates anti-colitis effects through modulation of NLRP3 inflammasome activation [58, 59].

2.4. Oxidative stress

As shown in Fig. 5, elevated reactive oxygen species (ROS) levels induce oxidative stress and intensify intestinal inflammation by damaging the intestinal mucosa through various mechanisms, including lipid peroxidation, protein denaturation, DNA damage, activation of relevant signaling pathways, intestinal bacterial invasion, epithelial cell apoptosis, and increased inflammatory mediator release (e.g., cytokines and chemokines) [60, 61].

One of the primary symptoms of IBD in animal models was an elevation in ROS in the colonic mucosa; the ROS level demonstrated strong correlation with disease severity and alterations in biomarkers, including glutathione (GSH), active aldehyde, and superoxide dismutase (SOD) [62, 63]. As shown in Fig. 5, polymorphonuclear neutrophils (PMNs) and macrophages are activated by invasive pathogens to produce inflammatory factors and other pro-oxidative stress mediators; these mediators generate ROS, which not only severely damage IECs but also stimulate leukocytes (primarily PMNs) to enhance detrimental immune responses [64].

2.5. Autophagy dysregulation

Autophagy is a biological process wherein cells utilize membrane vesicles to perform lysosomal degradation of misfolded or over-accumulated proteins and damaged organelles in the cytoplasm [65, 66]. By targeting the degradation of the claudin-2 protein, autophagy can enhance the effectiveness of the intestinal epithelial TJ barrier and reduce paracellular leakage while maintaining the intestinal barrier's normal function [67].

Research has demonstrated a significant association between aberrant autophagy and immune response disorders, inflammatory response imbalances, and injury to the intestinal mucosa [68]. The autophagy-associated gene (*ATG*) is essential for intestinal homeostasis, and *ATG16L1*, *IRGM*, and *NOD2* are among the genes most susceptible to IBD [69]. Cong's investigation revealed that the autophagy inducer Torkinib (pp242) may ameliorate intestinal barrier damage induced by TNF-α through triggering autophagy, although abnormalities in autophagy genes could cause harm to the intestinal barrier [70]. The severity of celiac disease increases substantially in IBD mice due to the loss of *ATG16L1*, resulting in altered macrophage function and an imbalance between pro- and anti-inflammatory factors [71].

2.6. ERS

Sustained exposure to dynamic microenvironments and complex networks with abundant stimulatory effects predisposes IECs to the accumulation of unfolding and misfolded proteins in the ER and triggers unfolded protein response (UPR), also known as ERS [12]. By reducing the quantity of unfolded proteins, enhancing the production of molecular chaperone proteins, and increasing the activity of the endoplasmic reticulum folding enzyme, UPR may mitigate ERS [12]. Apoptotic pathways may be activated or internal homeostasis restored depending on the duration and intensity of UPR [12].

The UPR activates when the ER chaperone-binding immunoglobulin (BiP) dissociates from the luminal structural domains of the three UPR-initiating sensors on the ER membrane due to the accumulation of unfolded/misfolded proteins under stress. Through IEC apoptosis, mucosal barrier disruption, and pro-inflammatory response activation, excessive ERS and impaired UPR signaling can trigger IBD [72]. Pathological examination in mice with acute colitis induced by dextran sulfate sodium salt (DSS) revealed decreased intestinal mucosal permeability, increased crypt cell apoptosis, and severe intestinal mucosal damage, all triggered by ERS [73].

2.7. Genetic susceptibility

IBD risk demonstrates significant variation by race and genetics. The disease was first identified in Western nations; it currently affects over 2 million individuals in North America, with projections indicating 4 million cases by 2030 [74]. IBD has

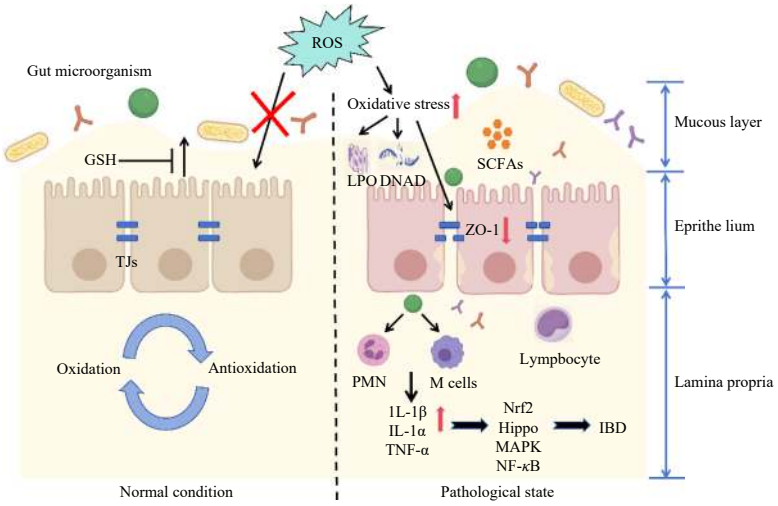

Fig. 5 Excess reactive oxygen species (ROS) exacerbate intestinal inflammation. GSH: glutathione; TJs: tight junctions between epithelial cells; LPO: lipid peroxide; DNAD: DNA damage; M cells: macrophages.

emerged in newly industrialized nations in recent decades due to dietary modifications, and its prevalence is increasing globally. The incidence and prevalence of IBD have risen markedly in China over the past 20 years. For example, Taiwan, China experienced an increase in CD and UC prevalence from 0.6 and 2.1 to 3.9 and 12.8 (per 100 000 individuals) between 2001 and 2015. Additionally, UC and CD affected 24.5 and 18.6 persons per 100 000 in Hong Kong, China in 2014 [75].

Approximately 240 loci account for 20%–25% of the genetic factors associated with IBD, including *CARD9*, *CD40*, *IL10*, *NCF4*, *SLC9A3*, *STAT1*, and *STAT3* [76]. Multiple studies have shown that specific genetic factors, such as those related to autophagy (e.g., *ATG16L1*) [77], upstream signaling (e.g., *NOD2* and *IL22*) [78, 79], and chemokine (e.g., *CCL2*) [80], may increase the likelihood of IBD occurrence.

2.8. Others

Beyond the previously described pathogenesis mechanisms, IBD develops through alterations in non-classical factors including enhanced formation of NETs [81], exosomal interventions [82, 83], iron death [84], and modified expression of CEACAMs [85]. NETs have been implicated in IBD development through multiple mechanisms: increasing inflammatory mediators (including TNF-α, IL-1β, and IL-6), compromising intestinal epithelial barrier function, promoting extracellular matrix (ECM) degradation, elevating protein hydrolysis activity, increasing thrombosis risk, and disrupting intestinal microbiota [81, 86]. Exosomes derived from intestinal immune cells, microbiota, and IECs facilitate IBD development by mediating interactions among these components [87]. Additionally, certain exosomes and their constituents show promise as potential diagnostic and therapeutic targets for IBD [88]. Iron death regulation centers on diminished glutathione peroxidase 4 (GPX4) activity, lipid peroxidation, disrupted iron metabolism, and GSH depletion, which significantly contribute to inflammatory disorders and colonic injury [89]. Enhanced CEACAM expression, which recognizes pathogenic factors including adherent-invasive *Escherichia coli* (AIEC), intensifies intestinal epithelial inflammation due to the inflammatory environment induced by IBD triggers [85].

3. Structure-activity relationship of natural PSs

PSs constitute macromolecular carbohydrates comprising multiple monosaccharides (n > 10) connected through α- or β-glycosidic bonds. These essential biological macromolecules function as energy sources (such as starch and glycogen), structural components (including cellulose and chitin), and biological process regulators, particularly in cell recognition and signal transduction. The biological activities of natural PSs correlate strongly with their chemical structure, molecular weight, and higher-order structure.

3.1. Chemical structure

PSs represent high-molecular-weight polymers constructed from monosaccharides joined by glycosidic linkages, including (1→3), (1→2), (1→4), and (1→6), in various α and β conformations [90]. The biological activities of PSs are substantially influenced by their chemical structural characteristics, encompassing branching degree, side chain length, monosaccharide composition, glycosidic linkages, and the quantity and position of functional groups [2].

The polysaccharide from *Dendrobium officinale* (DOPS), primarily containing mannose (Man), glucose (Glc), and arabinose (Ara), demonstrates efficacy in reducing β-arrestin1 and NLRP3 inflammasome activation, restoring pro- and anti-inflammatory factor balance, and ameliorating colon pathology in UC animal models [91]. SHPS-1, a heteropolysaccharide isolated from *Phellinus baumii* fruiting bodies, possesses a 46-kDa molecular weight and comprises Ara, Man, Glc, and galactose. Its structure features a 1,3-linked β-D-glucopyranosyl backbone and 1,6-linked α-D-galactopyranosyl residues, with arabinofuranose, mannopyranose, and galactopyranose as oligosaccharide side chains. SHPS-1 reduces STAT-1 phosphorylation and *STAT-1* target gene expression, promotes tissue repair through pro- and anti-inflammatory factor balance, and alleviates IBD [92]. SUSP-4, an acidic PS from *Selaginella uncinata*, consists of a primary chain structure of →4)-α-D-GalAp-(1→ and →6)-β-D-Galp-(1→, with a branched chain of →5)-α-L-Araf-(1→. SUSP-4 modulates thiamine metabolism by affecting *Akkermansia* and inhibiting macrophage activation, thereby controlling oxidative stress and inflammation *via* NF-κB/Nrf2/COX-2 [93]. Additionally, *Eucommia* ulmoides polysaccharide (EUP-SeNP) improves intestinal barrier and anti-oxidant capacity, modifies gut microbiota composition, and inhibits the TLR4/NF-κB signaling pathway to mitigate DSS-induced colitis [94]. Moreover, carboxymethyl polysaccharide (CMP33) from *Poria cocos* demonstrates potential in reducing colitis severity by decreasing pro-inflammatory cytokines while enhancing anti-inflammatory cytokine production [95].

3.2. Molecular weight

Molecular weight significantly influences the biological functions of PSs. High-molecular-weight PSs demonstrate more stable structures, enhanced recognition by specific cell surface receptors, and greater anti-inflammatory and immunomodulatory activities [96]. Studies show that low-molecular-weight sulfated polysaccharides (LMW-ulvan) from seaweed mitigate IBD by reducing inflammatory factors, enhancing TJ protein expression, and improving oxidative stress levels [97]. Although low-molecular-weight and short-chain β-glucans are generally considered biologically inactive, high-molecular-weight β-glucans demonstrate significant immune response modulation [8]. Research comparing oat β-glucans revealed that low-molecular-weight forms more effectively reduced inflammation markers and modulated chemokine and cytokine pathways, while high-molecular-weight forms demonstrated superior inhibition of lymphocyte infiltration and stronger anti-inflammatory effects in a rat model of 2,4,6-trinitrobenzenosulfinic acid (TNBS)-induced colitis [98]. Furthermore, after isolation from *Smilax china*, both neutral PS SCLP1 (42.1 kDa) and acidic PS SCLP3-2 (16.8 kDa) substantially reduced NO, IL-6, and TNF-α levels in lipopolysaccharides (LPS)-induced RAW264.7 cells, with SCLP3-2 additionally inhibiting the Gal-3/NLRP3 inflammasome/IL-1β pathway, thus alleviating UC [99].

3.3. Conformational feature

PSs demonstrate distinctive conformational structures in their sugar chains, including spherical, helical, flexible, and rod-like chains, among other complex arrangements. Essential conformational parameters, including z-average molar mass (Mz), number-average molar mass (Mn), weight-average molar mass (Mw), hydrodynamic radius (Rh, z), root mean square radius (Rg, z), intrinsic viscosity ([η]), and specific conformation parameters such as α, v, and ρ, are crucial for understanding their biological activities [90]. Peach gum PS (DPG2) exhibits conformational properties including Mw of 5.21×10^5 g·mol^{-1}, Mn of 3.15×10^5 g·mol^{-1}, Rg, z of 19.0 nm, and Rh, z of 16.1 nm, displaying a flexible coil-like structure. DPG2 notably increased levels of NO, T-SOD, and MPO, repaired oxidative damage in the colonic mucosa, and decreased pro-inflammatory cytokine release, thereby ameliorating DSS-induced colitis in mice [100]. Black jujube polysaccharide (BJP-4), examined under atomic force microscopy (AFM),

presents a spherical mass with molecular aggregation; under X-ray diffraction (XRD), it shows both crystalline and amorphous structures, and circular dichroism spectrum (CD) analysis indicates the absence of a triple-helical structure. BJP-4 mediates the MyD88/NF-κB/NLRP3 signaling pathway, maintains balanced pro-inflammatory cytokine production, protects against oxidative stress, supports the intestinal barrier, restores gut microbiota composition, and promotes SCFA synthesis, contributing to its anti-colitic effects [101].

4. Natural PS intervention in IBD

Natural PSs have attracted considerable attention globally due to their extensive pharmacological activity and therapeutic potential [15]. As illustrated in Fig. 6, recent studies confirm that natural PSs can repair damaged intestines, modulate immune responses, balance gut flora diversity and abundance, alleviate oxidative stress, and regulate autophagy and ERS to address IBD pathogenesis [102, 103].

4.1. Natural PSs repair intestinal mechanical and chemical barriers

In patients with IBD, abnormal expression of TJ proteins increases mucosal permeability and compromised mucus function disrupts the intestinal barrier (section 2.1). Research indicates that natural PSs can restore TJ protein expression and repair mechanical barrier integrity in IBD.

Dimocarpus longan polysaccharide (LPIIa) decreases claudin-2 expression while increasing ZO-1 expression in Caco-2 cells, thus promoting intestinal health in IBD [104, 105]. Chitosan (CS) demonstrates protective effects on the intestinal barrier in UC mice exposed to sodium glucan sulfate (DSS) through enhancing TJ proteins including MUC1, occludin, and ZO-1 while reducing TNF-α [106]. PS GLP, derived from *Ganoderma lucidum*, substantially elevates occludin levels in the rat ileum, reduces epithelial permeability, and enhances the mechanical barrier function of the intestinal mucosa [107].

Research indicates that natural PSs effectively address GC reduction, mucus layer thinning, and MUC deficiency in IBD. *Schisandra chinensis* PSs minimize crypt structure and colon tissue damage, promote mucus secretion, enhance GC density, increase MUC2 expression, and strengthen the intestinal barrier [108]. Kai's research demonstrates that PSs from *Atractylodes macrocephala* enhance MUC (MUC1, MUC2) expression in DSS-damaged colon tissues, facilitating mucus barrier restoration [109]. MAP effectively inhibits MUC1 expression, thereby reducing colitis-associated carcinogenesis in mice [110]. Furthermore, jellyfish-sulfated PSs strengthen the mucus layer, increase GC count, repair mucosal damage, and enhance Tff3 and MUC2 expression in UC models, contributing to intestinal barrier health.

4.2. Natural PSs repair the immune barrier and regulate the immune system

Natural PSs ameliorate intestinal damage in IBD by stimulating immune cell growth including M cells, DC cells, T cells, and B cells and modulating the synthesis of pro-inflammatory proteins, cytokines, and chemokines [111]. Through signaling pathways including MAPK, NF-κB, and TLR, natural PSs activate M cells to regulate the release of pro- and anti-inflammatory cytokines, thereby enhancing immune responses. Lentinan reduces pro-inflammatory cytokines such as IL-13 and CD30L, inhibits the TLR4/NF-κB pathway, reduces inflammatory cell infiltration, and alleviates inflammatory symptoms, suggesting potential therapeutic applications for colitis-related cancer and IBD [112]. *Dictyophora indusiata* polysaccharide (DIP) inhibits M1 macrophage activation, enhances M2 macrophage polarization, increases IL-10 levels, and reduces IL-6, IL-18, IL-1β, and TNF-α levels, collectively alleviating colitis in mice [113]. DC cells connect innate and specific immunity [114], and natural PSs influence signaling pathways such as PRR, PI3K/AKT, MAPK, NF-κB, and Dectin-1/Syk on DC cell surface to promote immune cell maturation, metabolism, antigen uptake and presentation, T cell activation, and other essential functions [115]. Moreover, natural PSs maintain Th1/Th2 and Th17/Treg cell ratios, preventing excessive pro-inflammatory responses [8]. For instance, *Rehmannia glutinosa* polysaccharide (RGP) promotes DC maturation *via* TLR4, elevates *IFN-γ* and *T-bet* mRNA levels, increases Th1 cell populations, and regulates Th1/Th2 balance [116]. *Astragalus mongholicus* polysaccharide (APS) decreases IL-17 levels and promotes Treg cells, ameliorating colitis symptoms in experimental models [117].

4.3. Natural PSs regulate intestinal flora and metabolites

Studies indicate that PSs can modify gut microbiota composition, optimizing microbial diversity, abundance, and balance in the colon and cecum to benefit IBD [13]. In colitis mice, GLP increases Shannon and Chao1 indices, demonstrating positive effects on the gut microbial community [118]. *Rehmannia glutinosa* PS maintains intestinal flora balance by enhancing microbial diversity, decreasing harmful bacteria and protozoa, increasing *Firmicutes* abundance, and promoting SCFAs [119]. PSs in *Moringa*

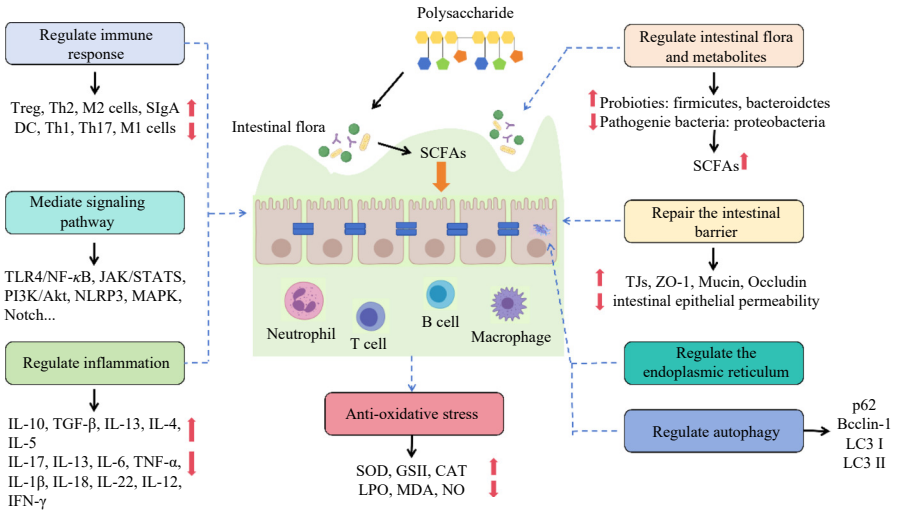

Fig. 6 Therapeutic mechanism of PSs in IBD. DCs: dendritic cells; M1 cells: M1 macrophages; CAT: catalase; MDA: malondialdehyde.

oleifera leaves similarly improve gut flora by promoting SCFA-producing bacteria and reducing pathogenic species [120]. In UC mouse models, *Atractylodes macrocephala* polysaccharide (AMP) restores disrupted intestinal flora, increases microbial richness, enhances lactic acid bacteria, and reduces *Actinobacillus*, *Akkermansia*, *Anaerobic bacteria*, *Bifidobacterium*, *Beauveria bassiana*, *Parabacteroides*, and *Parabacteroides parvulus*, while promoting SCFAs [121]. Additionally, flaminella polysaccharide (FVP) stimulates probiotic growth, inhibits pathogens, increases SCFA (particularly butyrate) production, and restores intestinal function, thereby alleviating IBD symptoms [103].

4.4. Natural PSs regulate oxidative stress

Patients with IBD frequently exhibit increased effector lymphocyte activity, infiltration of various immune cells [122, 123], and elevated levels of pro-inflammatory mediators, resulting in chronic inflammation and excessive ROS production. ROS accumulate in inflamed areas, causing cellular and molecular damage that worsens tissue deterioration. ROS functions as signaling molecules involved in immune modulation within inflamed intestinal mucosa [124]. *Porphyra haitanensis* polysaccharides (PHP) exhibit strong 1,1-diphenyl-2-picrylhydrazyl radical (DPPH) and hydroxyl radical scavenging activity, suggesting their potent antioxidant capacity helps restore the mucosal layer and cuprocyte regeneration, strengthens TJs and adhesion junctions, and reduces mucosal damage [125]. Moreover, acute colitis may be effectively treated with *Dendrobium officinale* PSs, as they decrease hydrogen peroxide-induced macrophage apoptosis, protect cell morphology and structure from oxidative damage by H_2O_2 treatment [126], downregulate the TNF-α signaling pathway, and activate the Nrf-2 signaling pathway [127]. Additionally, pectin oligosaccharides (POS) regulate anti-oxidant and anti-inflammatory signaling pathways, such as AMPK, Nrf2, and NF-*κ*B, which enhance anti-oxidant biomarker levels and decrease oxidative biomarkers, potentially inhibiting colon cancer [128].

4.5. Natural PSs regulate autophagy dysregulation

Research increasingly demonstrates a connection between autophagy dysfunction and IBD, where impaired autophagy contributes to epithelial barrier disruption, aberrant immune responses, and increased pro-inflammatory and chemokine release, initiating inflammation [129, 130]. PSs from *Strongylocentrotus nudus* eggs (SEP) can regulate autophagy-related factors in IECs through the CD36-PI3K/AKT pathway, decrease Th17/Treg cell ratios and inflammatory factors, restore the intestinal barrier, improve gut flora, and alleviate symptoms in UC mice [131]. *Pycnoporus sanguineus* polysaccharides (PPS) ameliorate IBD by upregulating proliferating cell nuclear antigen (PCNA), *E*-cadherin, ZO-1, and autophagy markers (p62, LC3 I, and beclin-1), while downregulating Th2, Th17, and Treg cell ratios [132]. The AhR, a key transcription factor, plays a role in maintaining immune homeostasis and inflammation balance in the intestinal barrier [133]. In colitis-affected mice, APS activates AhR-dependent autophagy, increases Becn1, occludin, and claudin-1 levels, reduces p62, promotes LC3B-I to LC3B-II conversion, supports crypt cell proliferation, repairs intestinal mucosa, and balances pro- and anti-inflammatory cytokines [134].

4.6. Natural PSs regulate ERS

ERS plays a crucial role in IBD pathogenesis [135], with ER function affected by various physiological and pathological changes, particularly in DSS-induced colitis models [136]. Natural PSs, being safe and renewable biological resources, provide distinct advantages for managing ERS, reducing IEC apoptosis, and restoring the intestinal barrier. Neutral PSs from *Larix gmelinii* roots (AG-40-I-II) inhibit IRE1α-mediated splicing of XBP1 *via* the ERS pathway, reduce H_2O_2-induced apoptosis and MDA levels, and increase SOD activity in IEC-6 cells, effectively decreasing ROS production [137]. In clostridium-damaged IPEC-J2 cells, pectin PSs from *Lycium barbarum* in Xinjiang (XLBP-I-I) reduce ERS and the UPR, protecting IPEC-J2 cells from ERS-induced apoptosis [138]. PSs from *Poria cocos*, functioning through ERS inhibition, substantially reduce intestinal mucosal permeability, mitigate tissue injury and inflammation, and enhance occludin and ZO-1 expression in intestinal tissues, supporting barrier integrity [139].

5. Potential natural PS drugs with therapeutic effects in IBD

Natural PSs have attracted considerable attention as potential therapeutic agents for IBD. Despite showing substantial promise in preclinical studies, their clinical applications remain limited, primarily concentrating on their use with specialized carriers for treating colorectal diseases [140]. This section examines natural PSs and their derivatives–derived from plants, animals, and microorganisms that demonstrate therapeutic potential for IBD, establishing a foundation for future drug development.

5.1. Pectin

Pectin, a heterogeneous heteropolysaccharide, exists primarily in the intercellular layer and adjacent cell walls of plants [141]. Pectin exhibits multiple therapeutic effects, including GC stimulation to produce MUC, thereby enhancing the mucous layer. It also modulates TLR signaling pathways to reduce inflammation, promotes SCFA production, maintains gut flora homeostasis, and enhances epithelial barrier integrity by increasing TJ levels [142]. Wu et al. [143] demonstrated that pectin from *Rubus chingii* and *Lycium barbarum* ameliorates colitis by reducing tissue damage, enhancing immune organ indices, inhibiting TNF-α, IL-17β, and IL-6 production, improving anti-oxidant status, and increasing SCFA concentrations. Lemon-derived pectin has been shown to ameliorate colitis by enhancing fermentation products, while galactosan-rich pectin influences anti-inflammatory cytokines and intestinal barrier function. Lemon pectin containing abundant arabinan side chains reduces IL-6 release.

Green plum pectin significantly enhances anti-oxidant enzymes including GSH, SOD, CAT, and GPx while reducing pro-inflammatory cytokines such as TNF-α, IL-6, and IFN-γ, and upregulating anti-inflammatory IL-10 [144]. It also alleviates intestinal inflammation in mice by increasing TJ levels. Notably, low-ester pectin demonstrates stronger anti-inflammatory effects compared to high-fat pectin. Overall, pectin exhibits comprehensive therapeutic benefits in IBD, including immune modulation, intestinal barrier repair, anti-inflammatory and anti-oxidant effects, and maintenance of intestinal flora balance. However, additional research is necessary to understand its specific mechanisms of action and optimize clinical applications.

5.2. Guar gum

Guar gum, although its high viscosity limits its use as a dietary fiber, represents a promising water-soluble galactomannan among dietary fibers. It functions as a thickening and binding agent in food preparation and serves as an essential nutritional supplement [145, 146]. Intestinal flora metabolizes guar gum into SCFAs, which promote *Bacteroides* growth, maintain bacterial homeostasis, and contribute to IBD prevention and treatment [147]. Partially hydrolyzed guar gum (PHGG) significantly reduces MPO activity and promotes healing of colonic mucosa damage in COVID mice. It also increases SCFA concentrations, thereby regulating gut microbiota diversity and abundance [148]. Additional stud-

ies reveal that PHGG activates Rho and ERK1/2 kinases and MAPK pathways, promoting actin polymerization in YAMC cells, which supports wound healing in colonic epithelial cells. These findings highlight guar gum's therapeutic potential for IBD treatment [149].

5.3. Fructan

Fructan, commonly known as inulin, is a water-soluble PS consisting of fructose molecules connected by *β*-1,2-glucoside bonds [150]. Although minimally digested and absorbed in the stomach and small intestine, fructan reaches the large intestine where beneficial bacteria such as *Lactobacillus* and *Bifidobacterium* ferment it. This fermentation process promotes gut flora proliferation, generates SCFAs, and suppresses harmful bacteria and pathogens [151]. Studies show that inulin-type fructan from *Codonopsis pilosula* (CP-A) inhibits mTOR/p70S6K signaling pathway activation, thereby reducing colon damage, IL-8 and TNF-α levels, and intercellular adhesion molecule expression. It concurrently increases IL-10 and TGF-β levels, thus ameliorating UC [152]. Burdock fructooligosaccharide (BFO) maintains intestinal barrier function by minimizing crypt deformation and enhancing GC numbers. It also reduces inflammatory cytokine overexpression and secretion (TNF-α, IL-1β, IL-6, and MCP-1), inhibits MPO activity, and eliminates excess ROS, effectively reducing intestinal inflammation [153]. Furthermore, inulin modulates intestinal flora composition in IBD mice, preferentially supporting probiotic *Lactobacillus* and *Bifidobacterium* growth while inhibiting *Proteobacteria* proliferation [154]. Given its dual function in gut microbiota regulation and inflammation reduction, fructan serves as an important natural supplement for IBD prevention and remission.

5.4. Algal PSs

Algal PSs encompass a diverse group of physiologically active dietary fibers extracted from marine algae [155]. Seaweed, rich in dietary fiber, demonstrates effectiveness in modulating intestinal flora and alleviating colitis. Studies in acute colitis mouse models reveal that PSs from macroalgae (MPF, DP-MPF) substantially reduce colon MPO, NO, and MDA levels, increase anti-oxidant enzyme levels (SOD and CAT), and decrease pro-inflammatory cytokine levels [156]. Sodium alginate (SA), abundant in seaweed, is a natural polyanionic PS [157] possessing advantageous properties for IBD therapy, including non-toxicity, high biocompatibility, and simple gel formation. SA facilitates intestinal mucosal repair by enhancing TJ protein expression, lowering blood LPS and D-lactic acid (D-LA), and downregulating MAPK pathway and TLR4 expression. Additionally, SA increases beneficial gut bacteria (*Lactobacillus*, *Roseobacteria*, and *Lachnospiraceae NK4A136*) while reducing pathogenic bacteria including *Helicobacter pylori*, *Peptidococcus*, and *Tyzzerella* [158]. These characteristics establish algal PSs as promising candidates for future therapeutic and functional nutritional applications.

5.5. Homologous PSs of medicine and food from Chinese herbal PSs

PSs extracted from Chinese herbal medicines that serve both medicinal and edible purposes have attracted considerable attention due to their straightforward extraction process and diverse pharmacological effects, including anti-oxidant, immunomodulatory, and anti-viral properties. As illustrated in Fig. 7 and Table S2, various PSs from traditional Chinese medicines demonstrate effectiveness in IBD prevention and treatment. APS decreases inflammatory cytokines (IFN-γ, IL-6, TNF-α, IL-1β, and IL-17A) and ameliorates histological injury (inflammatory cell infiltration, colon epithelial cup cell loss, intestinal crypt destruction, sporadic colonic tissue ulcer) in colitis mice through Nrf2/HO-2 pathway inhibition [159]. *Arctium lappa* polysaccharide (ALP-1) maintains balance between pro-inflammatory (IL-1β, IL-10 cytokines while enhancing beneficial gut bacteria and inhibiting pathogenic bacteria in colitis models [160]. *Dendrobium officinale* polysaccharide (DOP) regulates hnRNPA2B1 to facilitate miR-433-3p loading into intestinal small extracellular vesicles (sEV), increasing miR-433-3p abundance, blocking MAPK signaling, and reducing inflammatory cytokine production, thus improving IBD symptoms [161].

5.6. CS

CS represents the sole naturally occurring positively charged alkaline amino PS, obtained through the deacetylation of chitin [162], which occurs abundantly in insect cuticles, fungal cell walls, and marine arthropod shells, particularly shrimp and crabs. As the second most prevalent renewable biomass material after cellulose, chitin's annual production exceeds 10 billion tons, offering advantages of cost-effectiveness, widespread availability, and minimal biological toxicity [163]. While traditionally utilized as

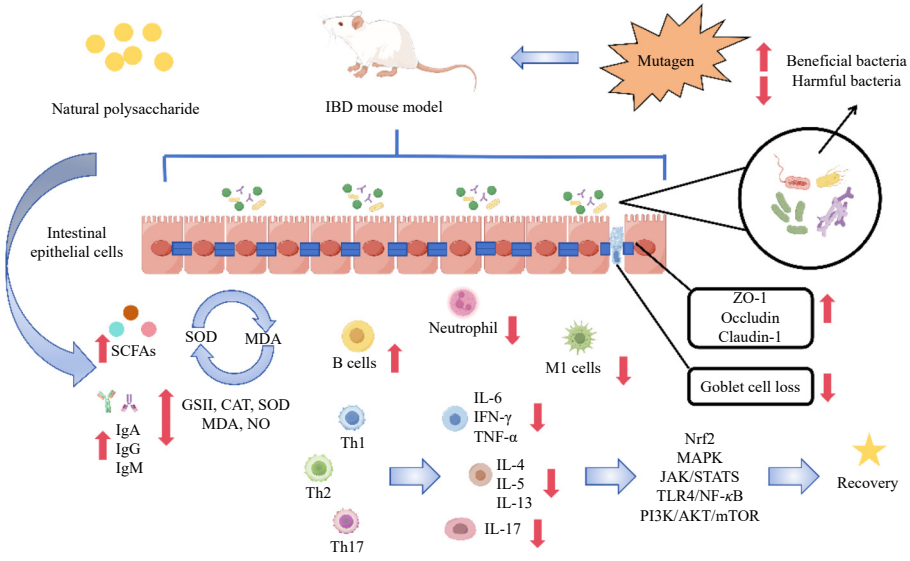

Fig. 7 The mechanism of improving IBD by natural PSs. DSS: dextran sodium sulfate salt; CAT: catalase; ZO-1: occlusion zone-1; M1 cells: M1 macrophages; B cells: B lymphocytes.

a drug excipient and carrier material, recent investigations have revealed CS's therapeutic potential for IBD [140, 164]. Wang et al. [165] demonstrated that chitosan oligosaccharide (COS) effectively restores MUC2 and occludin protein expression, enhances MUC2 secretion, and reduces mucus damage by mitigating intestinal barrier disruption in IBD mice. Additionally, it reinforces intestinal TJs by increasing occludin protein secretion and *OCLN* gene mRNA expression in Caco-2 cells, reducing submucosal edema and inflammatory cell infiltration. Research [166] has shown that CS diminishes tissue damage in UC mouse models while beneficially affecting intestinal flora and barrier function. CS inhibits TNF-α expression while enhancing MUC1, occludin protein, ZO-1, and other TJ proteins, thereby maintaining mucosal barrier integrity. Given its remarkable capacity to restore intestinal barrier function and maintain gut flora balance, CS emerges as a promising candidate for both functional food and health supplement applications in IBD prevention and treatment.

5.7. Hyaluronic acid (HA)

HA constitutes a non-sulfated glycosaminoglycan characterized by anionic properties. This macromolecular mucopolysaccharide comprises alternating units of *N*-acetylglucosamine and D-glucuronic acid [167]. Following synthesis in the cytoplasm, HA translocates to the cell surface, where it serves an essential function in vertebrates' ECM [168]. It demonstrates effective anti-oxidant properties. Low-molecular-weight HA (< 450 kDa) induces upregulation of matrix metalloproteinase genes, inflammatory mediators, and angiogenic factors, while high-molecular-weight HA (> 1450 kDa) inhibits cytophagocytosis [168]. Hyaluronic acid-bilirubin nanomaterials (HABN) demonstrate therapeutic potential for colitis through effective regulation of pro-inflammatory cytokines (e.g., IL-1b, TNF-a, IL-6) and anti-inflammatory cytokines (e.g., IL-10 and TGF-b). Furthermore, HABN restores ZO-1 and occludin-1 protein expression and mRNA levels in colitis mouse models while enhancing intestinal flora richness and diversity. These findings indicate HA's significant potential as a therapeutic agent for IBD management [169].

5.8. PSs from fungi and bacteria

Fungal PSs comprise active polymers derived from fungal mycelium, fermentation broths, and fruiting bodies. These compounds consist of more than ten monosaccharides connected *via* glycosidic bonds and exhibit various biological functions, including immune regulation and anti-oxidant effects [170]. HECP ameliorates colitis by inhibiting oxidative stress-related gene expression, reducing MPO, NO, MDA, and T-SOD levels, and decreasing pro-inflammatory cytokines including TNF-α, IL-6, and IL-1β. HECP additionally downregulates COX-2, iNOS, and phosphorylated NF-κB p65, IκB-α, MAPK, and Akt, while restoring intestinal flora and strengthening the intestinal barrier [104]. Lentinan [112], an extensively studied fungal PS, alleviates colitis through disruption of the TLR4/NF-κB signaling pathway, thereby reducing IL-13 and CD30L expression, minimizing tissue damage, and maintaining intestinal flora homeostasis. Moreover, bacterial PSs demonstrate therapeutic potential for IBD. Probiotic-derived PSs, particularly from *Lactobacillus*, facilitate macrophage transition from pro-inflammatory M1 to anti-inflammatory M2 phenotype. These compounds inhibit NF-κB signaling, reduce inflamed bowel tissue apoptosis, suppress IL-1β expression to decrease ROS production and restore intestinal flora balance. In conclusion, fungal and bacterial PSs show considerable promise in IBD treatment through modulation of intestinal flora, inflammatory cytokines, and oxidative stress levels, presenting a valuable avenue for therapeutic development [171].

6. Natural PSs' pharmacokinetic studies

The pharmacokinetic properties of natural PSs significantly constrain their efficacy in drug delivery and patient compliance [172]. These constraints primarily stem from their challenging and unstable oral absorption (classified as Class III under the biopharmaceutical classification system) and their hydrophilic and uncharged nature, resulting in limited *in vivo* absorption and rapid clearance. Following metabolism by gut microbiota into oligosaccharides, monosaccharides, and SCFAs, only a small fraction (< 2%) of natural PSs is absorbed. These metabolites may directly affect target organs to produce systemic pharmacological effects, while the majority remain in the intestine, providing local therapeutic benefits. Most oral PSs derived from traditional Chinese medicine demonstrate low bioavailability (< 5%) [173].

Natural PSs' charge, molecular weight, spatial conformation, and monosaccharide content influence their pharmacokinetics [174]. For instance, increased DA enhances CS's interaction with the intestinal epithelium, thereby improving bioavailability [175]. Higher Mw extends PSs' circulation time and increases their accumulation in the liver [174]. Positively charged PSs tend to accumulate in the liver, while negatively charged or neutral macromolecular PSs exhibit prolonged blood circulation times [174]. Additionally, single-chain dextran experiences faster blood clearance than triple-helix dextran under strongly alkaline and DMSO conditions [176-178]. Notably, the bioavailability of natural PSs can be enhanced through transformation into nano drug delivery systems (such as nanocrystals, liposomes, and nanoemulsions) [179], chemical and biochemical modification (such as phosphorylation, carboxymethylation, and sulfation) [180], and alternative administration routes (such as subcutaneous, intramuscular, and intranasal) [181, 182], among other methods.

7. Natural PSs' safety evaluation

Safety evaluation represents a crucial process designed to minimize risks associated with clinical drug use. This encompasses identifying toxic reactions through toxicology testing, predicting potential adverse effects, establishing clinical monitoring indicators, and determining clinical trial feasibility. Multiple studies have confirmed the favorable safety profile of natural PSs [8, 183, 184]. GLP demonstrated excellent safety in toxicity assessments. The acute oral maximum tolerated dose (MTD) in male and female mice exceeded 42.56 $g \cdot kg^{-1}$, which is 1290 times the recommended human dosage. The bacterial reverse mutation (Ames) test yielded negative results, indicating no mutagenic potential. Additionally, a 30-day feeding study revealed no significant effects on clinical signs, hematologic parameters, biochemical indices, or major organ coefficients. Histopathological analysis showed no observable pathological changes, toxic effects, or adverse reactions, confirming that GLP is safe for use [185]. Similarly, APS demonstrated a high safety margin. The acute oral MTD in male and female rats was greater than 15.0 $g \cdot kg^{-1}$, which is 300 times the recommended human daily intake, classifying it as a non-toxic substance. The Ames test, mouse sperm aberration assay, and bone marrow micronucleus test all produced negative results, showing no evidence of mutagenicity. Furthermore, a 30-day feeding study indicated no significant adverse effects on clinical signs, organ indices, or blood biochemical parameters. These findings suggest that long-term administration of APS is safe, with no apparent adverse reactions or toxic side effects [186].

8. Natural PSs' clinical application

Natural PSs have demonstrated significant utility in clinical

applications, particularly in wound healing and hemostatic gels [187], drug delivery vehicles [188], and vaccine adjuvants [189]. However, their application as primary active ingredients in pharmaceuticals and nutraceuticals remains limited. Lentinan, a PS extracted from *Lentinula edodes*, functions as a biological response modifier and immunostimulant available in tablet, capsule, and injectable forms. It has received approval for treating hepatitis, various cancers, and other diseases [190]. Additionally, it exhibits anti-inflammatory effects in the intestine by interrupting the activation of the TLR4/NF-κB pathway, thereby inhibiting inflammatory factor overexpression [191]. In 2015, the Chinese Food and Drug Administration approved the "polysaccharidum of *Poria cocos* oral solution" for treating hepatitis, certain malignancies, and other illnesses [192]. Studies have shown that *Poria cocos* PS can restore cellular TJ damage by inhibiting the NF-κB pathway, upregulating occludin and ZO-3 expression, and delivering significant preventive and therapeutic effects for gastrointestinal illnesses [193]. In addition to suppressing the JAK2/STAT1/NLPR3 inflammatory vesicle signaling pathway, which reduces colon tissue cytokine levels and enhances the body's anti-oxidant capacity to improve IBD [194], *Panax ginseng* PS injections serve as common complementary therapies for cancer [195].

9. Conclusion

This review provides a theoretical foundation for developing PS-based functional foods and health products and their application in IBD treatment. The review began by summarizing IBD pathogenesis and examining the structural-activity relationship of natural PSs. Subsequently, it explored natural PSs' mechanisms for treating IBD. Finally, it highlighted examples of natural PSs with anti-IBD activity, alongside an evaluation of their pharmacokinetics, safety, and clinical application. Natural PSs demonstrate substantial potential for advancement in IBD treatment.

Despite compelling evidence supporting the anti-IBD properties of natural PSs, their development into therapeutic drugs remains limited. This limitation stems from several challenges: first, their gradual and mild action obscures their holistic and synergistic therapeutic properties [172]; second, their unfavorable pharmacokinetic properties adversely affect their efficacy and clinical patient compliance; third, the extraction and purification production process requires significant time and resources [173]; fourth, the absence of accurate and reliable quantitative analysis methods, combined with their structural characteristics and large molecular weights, complicates standardization. Research into the therapeutic effects of natural PSs on IBD remains in its early stages, with limited available data. To address these challenges, additional studies are necessary. Specifically, further cellular, animal, and clinical experiments should investigate their mechanisms of action. Moreover, extensive clinical trials are crucial to validate their therapeutic efficacy.

Funding

This research was supported by the National Natural Science Foundation of China (Nos. 82003977, 82274134 and 82274139), the National Key Research and Development Plan (No. 2017YFC1702200), the Key Research and Development Program of Zhejiang Province (No. 2020C04020), and the Science and Technology Program of Zhejiang Province (No. 2025C02183).

Supporting information

Supporting information for this work can be obtained by contacting the corresponding authors *via* E-mail.

Conflicts of interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgement

Thanks to the following websites for graphic materials: https://www.figdraw.com/#/; https://image.baidu.com/. Thanks to the following websites for full botanical plant names (italics): http://mpns.kew.org; www.worldfloraonline.org.

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