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Fucoidan as a therapeutic agent for ulcerative colitis: mechanisms of action and modulation of the gut microbiota

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Ulcerative colitis (UC), a chronic inflammatory bowel disease driven by gut dysbiosis, immune dysregulation, and oxidative stress, lacks universally effective therapies. Fucoidan (FCD), a sulfated polysaccharide derived from brown algae, has emerged as a multifaceted therapeutic candidate due to its anti-inflammatory, antioxidant, and immunomodulatory properties. This review synthesizes FCD's mechanisms in UC pathogenesis, emphasizing its suppression of NF- κ B and MAPK signaling pathways to reduce proinflammatory cytokines (e.g., IL-6, TNF- α) and regulate TLR-mediated macrophage polarization. FCD enhances intestinal barrier integrity via upregulation of tight junction proteins (Claudin-1, ZO-1) and mucin MUC2 expression, while remodeling gut microbial ecology through enrichment of SCFAs-producing bacteria (e.g., Ruminococcaceae) and suppression of pathogens (*Escherichia coli*, *Candida albicans*). Preclinical studies highlight LMWF as a superior candidate, demonstrating enhanced bioavailability and efficacy in mitigating DSS-induced colitis. Despite its promise, challenges persist in structural heterogeneity (source- and extraction-dependent), scalable production of LMWF, and insufficient pharmacokinetic data. Emerging strategies—including nanoparticle-based delivery systems and structural modifications (cross-linking, covalent bonding)—aim to overcome bioavailability limitations. This review underscores FCD's potential as a functional food or adjuvant therapy for UC, while advocating for rigorous clinical validation to bridge translational gaps. Enrichment of SCFAs-producing taxa and suppression of pathobionts (*Escherichia coli*, *Candida albicans*), mediated through prebiotic fermentation. Suppression of NF- κ B activation via I κ B α stabilization and inhibition of p65 nuclear translocation, and downregulation of MAPK phosphorylation (ERK1/2, JNK, p38), reducing proinflammatory cytokines (IL-6, TNF- α , IL-1 β). FCD can be used as a potential treatment for UC.

KEYWORDS

Fucoidan, ulcerative colitis, gut microbiota, toll-like receptors (TLRs), oxidative stress, inflammation

1 Introduction

Inflammatory bowel disease (IBD), which includes ulcerative colitis (UC) and Crohn's disease (CD), is a chronic, relapsing inflammatory disorder of the gastrointestinal tract. While the specific etiology and pathogenesis of IBD remain elusive, gut microbiota dysbiosis is a hallmark feature. Patients with IBD exhibit reduced microbial diversity compared with healthy individuals, characterized by decreased beneficial taxa such as *Lactobacillus* spp. and increased abundance of *Aspergillus* spp. IBD onset spans all age groups, although diagnosis peaks in the third decade of life, particularly in Western industrialized nations. In northern Europe, the annual incidence rates range from 35–50 UC cases and 30–100 CD cases per 100,000 individuals. Global estimates indicate UC burdens of 7.6–245 annual cases and incidence rates of 1.2–20.3 per 100,000 people (The global, regional, and national burden of inflammatory bowel disease in 195 countries and territories, 1990–2017: a systematic analysis for the Global Burden of Disease Study 2017, 2020). Le Berre et al. reported in The Lancet that approximately 5 million people worldwide had UC in 2023 (Le Berre et al., 2023).

Dysbiosis-driven disruption of host–microbiota interactions is central to IBD pathogenesis (Becker et al., 2023). The high inter- and intraindividual variability of the intestinal microbiome influences host susceptibility to immune-mediated disorders, with IBD being particularly sensitive to these perturbations. Immune autophagy plays a pivotal role in maintaining intestinal homeostasis by modulating crosstalk among the gut microbiota, innate/adaptive immunity, and host defense mechanisms (Forbes et al., 2018). Macrophages, key regulators of intestinal inflammation and homeostasis, perform critical functions, including pathogen clearance and dead cell removal. However, in autoimmune disorders, hyperactivated macrophages exacerbate intestinal barrier dysfunction through excessive proinflammatory cytokine production and tissue infiltration (Zhang et al., 2023).

UC is characterized by distal rectal inflammation extending proximally with variable lengths, resulting in a sharp transition between inflamed and noninflamed mucosa. The disease follows a relapsing–remitting clinical course, with over 90% of patients experiencing recurrent flares after initial onset. Early recurrence within the first two years strongly predicts progressive disease severity. While no definitive diagnostic biomarker exists for UC, fecal calprotectin >250 µg/g serves as the most reliable noninvasive marker to screen for IBD, warranting confirmatory endoscopy (Reenaers et al., 2018). Other metalloproteins in the gut microbiota may influence disease progression (Ma Y et al., 2023). However, biomarkers such as fecal lactoferrin (<7.25 µg/g normal threshold) remain insufficiently validated (Ministro and Martins, 2017; Xiao L et al., 2023).

Microbiome profiling of IBD patients with active disease has revealed that intestinal dysbiosis is marked by diminished microbial diversity (particularly within the Firmicutes phylum), reduced community stability, and overrepresentation of Proteobacteria (e.g., *Enterobacteriaceae*) and fungal Ascomycetes relative to healthy controls (Devkota et al., 2012; Gevers et al., 2014;

Machiels et al., 2014; Nishino et al., 2018). Dysbiotic shifts correlate directly with intestinal pathology exacerbation. Reactive oxygen species (ROS) serve as key drivers of gut barrier impairment and proinflammatory signaling. Microbiota-derived short-chain fatty acids (SCFAs) reduce the luminal pH, suppressing pathogenic expansion while promoting beneficial taxa to reestablish mucosal homeostasis (Guo et al., 2021). Therapeutic strategies to reconstitute beneficial microbiota include (1) the administration of defined bacterial strains and probiotic formulations that secrete antimicrobial peptides to combat pathogens and (2) enzymatic modulation by probiotics to stimulate symbiotic microbial proliferation, thereby enhancing intestinal homeostasis (Zhou et al., 2019). Probiotics demonstrate multimodal efficacy in IBD management by rectifying dysbiosis, fortifying mucosal barrier integrity, improving microecological niches, and modulating local/systemic immunity—providing a novel therapeutic approach.

Marine seaweed, a vital biological resource, synthesizes diverse bioactive compounds—including polysaccharides, proteins, and polyphenols—with significant pharmaceutical potential. Among these polysaccharides, structurally complex marine polysaccharides have garnered extensive research interest. Functionally, these biopolymers play dual roles: as structural and metabolic reservoirs in marine organisms and as endogenous antioxidants. Algal-derived polysaccharides present across marine flora and fauna exhibit immunomodulatory, anti-inflammatory, antioxidant, and antiviral properties (Smith et al., 2018; Cui et al., 2019; Corino et al., 2021; Jayawardena et al., 2022). Preclinical studies have demonstrated that seaweed polysaccharides and extracts protect the gastric mucosal barrier and attenuate inflammation, highlighting their therapeutic potential for gastrointestinal disorders (Lajili et al., 2019; Wang et al., 2019; Li R. et al., 2024). Notably, algal polysaccharides resist degradation by host digestive enzymes and act as prebiotic substrates for probiotic fermentation, positioning them as promising candidates for managing intestinal inflammatory diseases such as IBD (Xie et al., 2019).

2 Physiological processes and factors affecting Fucoidan absorption and metabolism

2.1 Brief description of FCD

Marine macroalgae (seaweeds), among the ocean's most biologically valuable resources, are taxonomically classified into three groups—brown (Phaeophyceae), red (Rhodophyta), and green (Chlorophyta) algae—on the basis of pigmentation, monosaccharide profiles, molecular weight distributions, and structural polysaccharide composition (Xu et al., 2017). Fucoidan (FCD), a sulfated polysaccharide predominantly abundant in brown algae, coexists with other characteristic biopolymers, such as alginates and laminarin. FCD-producing species span diverse marine taxa, including *Laminaria hyperborea*, *Sargassum stenophyllum*, *Hizikia fusiforme*, *Ascophyllum nodosum*, *Fucus*

spp. (*F. evanescens*, *F. serratus*, *F. distichus*, *F. vesiculosus*), *Analipus japonicus*, *Caulerpa racemosa*, *Chorda filum*, *Padina gymnospora*, *Kjellmaniella crassifolia*, and *Dictyota menstrualis*.

FCD, a sulfated polysaccharide with the molecular formula $(C_6H_{10}O_7S)_n$, contains sulfate groups as integral components of its structural composition. Predominantly isolated from brown algae, this biopolymer consists primarily of sulfated fucose residues (Koh et al., 2019), with minor constituents, including xylose, mannose, galactose, rhamnose, arabinose, glucose, glucuronic acid, and acetyl groups (Jin et al., 2019; Koh et al., 2019; Usoltseva et al., 2019). Located in the cell walls of brown algae, FCD contributes to structural integrity by preventing tissue dehydration and stabilizing cell membranes (Lakshmana Senthil, 2024).

Structurally, FCD exhibit species-specific variations. Two common α -L-fucopyranose backbone motifs are observed (1): a 1,3-linked framework and (2) alternating 1,3- and 1,4-linked residues. Sulfation typically occurs at the C-2 or C-4 positions of the fucose residues (Figure 1) (Jia et al., 2025). While brown algal FCD share conserved backbone structures, they diverge in their sulfation patterns and glucuronic acid contents. For example, *Fucus serratus* (silky brown algae), *Fucus distichus* (pteridophyte brown algae), and *Pelvetia canaliculata* (tubular brown algae) exhibit similar core skeletons but differ in their branching complexity and monosaccharide diversity, which are correlated with functional distinctions (Ale et al., 2011; Wang et al., 2021; Obluchinskaya et al., 2023). Notably, certain FCD (e.g., from *Bifurcaria* and *Himanthalia elongata*) deviate from these canonical frameworks, suggesting additional structural heterogeneity (Sanjeeva et al., 2017).

The sulfate groups of FCD confer distinct biological activities. Studies have demonstrated its ability to mitigate intestinal barrier dysfunction through three mechanisms (1): enhancing tight junctions (TJs) and adherens junctions (AJs) protein interactions in epithelial cells (2), restoring the gut microbiota composition, and (3) suppressing proinflammatory cytokine production (Iraha et al., 2013; Shi et al., 2017; Luo et al., 2021). Both fucose-oligomeric polyphenol conjugates and desulfated FCD—structurally distinct precursors—alleviate dextran sulfate sodium (DSS)-induced acute colitis by suppressing inflammatory cytokine signaling (Lean et al., 2015). FCD has also been extensively studied for its antitumor, anticoagulant, and antioxidant activities; ability to modulate glucose and cholesterol metabolism; and potential hepatoprotective and nephroprotective effects.

The key bioactive properties of FCD are primarily attributed to its sulfated polysaccharide structure. Due to its complex structure, FCD cannot be predicted or classified. FCD exerts significant immunomodulatory, antitumor, and anti-inflammatory effects. Notably, FCD demonstrates pronounced impacts on intestinal function. An *in vitro* study by Chen et al. demonstrated that FCD modulates gut microbiota composition by altering SCFAs production (Chen et al., 2023). Furthermore, in a DSS-induced IBD model, Ye et al. showed that FCD intervention restructured gut microbial communities, enhanced colonic barrier integrity through upregulation of tight junction proteins (e.g., claudin-1, occludin),

and suppressed colonic inflammation via the TLR4/NF- κ B signaling pathway (Ye et al., 2024). Collectively, these findings highlight the therapeutic potential of FCD in IBD management.

2.2 Pharmacokinetics of FCD

Preclinical studies have characterized the absorption, distribution, metabolism, and excretion (ADME) properties of FCD. Absorption is quantified via enzyme-linked immunosorbent assay (ELISA) using FCD-specific antibodies (Torode et al., 2015; Pozharitskaya et al., 2018). In rats, oral administration of 737 kDa FCD resulted in peak serum concentrations at 4 hours postadministration, with renal deposition observed in nephrons (Nagamine et al., 2014). Systemic accumulation in extrarenal organs has also been documented (Nagamine et al., 2014). Notably, low-molecular-weight FCD (LMWF) has enhanced therapeutic potential; comparative pharmacokinetic analyses between LMWF and medium-molecular-weight FCD (MMWF) have shown superior bioavailability and tissue uptake of LMWF, supporting its clinical applicability. While FCD exhibits a favorable pharmacokinetic profile with minimal toxicity, inadequate data exist regarding its systemic redistribution.

A recent study by Kadena et al. (Kadena et al., 2018) evaluated FCD absorption via oral administration. The authors proposed that dietary seaweed consumption influences FCD uptake. In their trial, 396 participants consumed up to 3 g of *Cladosiphon okamuranus* (Okinawan Mozuku), with urinary FCD detected in 385 individuals. In addition, Ikeda-Ohtsubo et al. (Ikeda-Ohtsubo et al., 2020) investigated the *in vitro* modulation of the gut microbiota by FCD. High-purity (>95%) brown seaweed FCD (49.8 kDa), which was isolated from *C. okamuranus* cultivated in Japan, was administered to adult zebrafish at a 1:1 (w/w) feed ratio for 21 days. Pro- and anti-inflammatory cytokine levels were quantified via quantitative PCR (qPCR), while microbiota shifts were assessed by 16S rRNA sequencing. Compared with control zebrafish, FCD-supplemented zebrafish presented significantly reduced IL-1 β (proinflammatory) expression. Additionally, FCD enhanced intestinal microbial diversity and altered community composition, favoring beneficial taxa.

While additional investigations are needed to elucidate the mechanisms of intestinal FCD absorption, multidisciplinary approaches remain critical to comprehensively characterize its pharmacokinetic behavior. The systematic accumulation of these data will establish a robust foundation for the translation of FCD into clinically viable therapeutics.

3 The gut microbiota and UC

Short-chain fatty acids (SCFAs), metabolites generated by the gut microbiota, reduce the intestinal pH (Jiang MZ et al., 2024), suppress pathogenic bacterial growth, and promote beneficial taxa, thereby stabilizing microbial communities (Guo et al., 2021). Dysbiosis triggers gut inflammation by enabling harmful bacterial

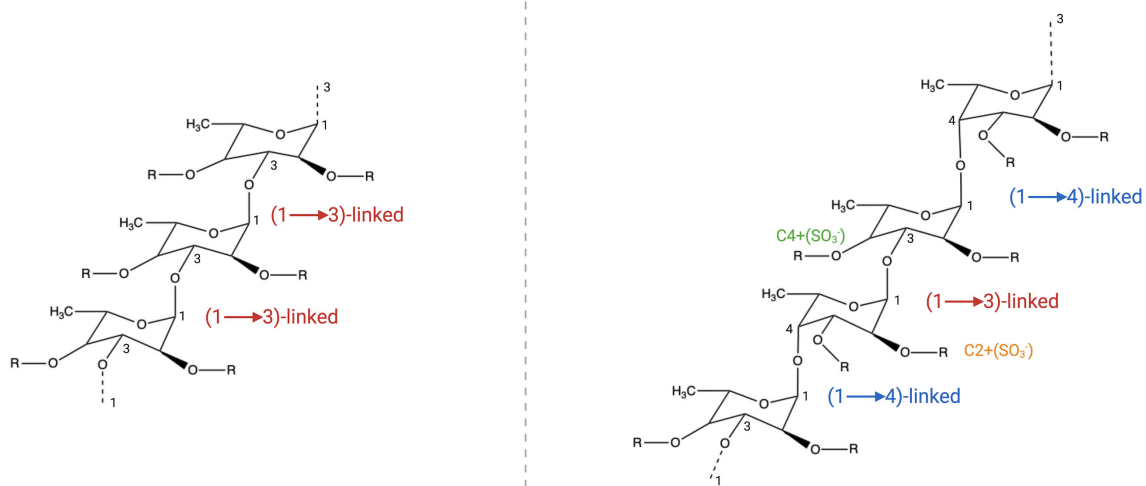


FIGURE 1

FCD structural diversity. Two predominant backbone motifs are observed (1): a 1,3-linked α -L-fucopyranose backbone and (2) a heteroglycosidic framework with alternating 1,3- and 1,4-linked α -L-fucopyranose residues. The C-2 and C-4 positions of these fucose residues are susceptible to sulfation (SO_3^- substitution), contributing to structural variability.

overgrowth. This imbalance increases enterotoxin release, which increases mucosal permeability and immunosuppressive protein production, ultimately disrupting immune homeostasis. Subsequent antigen-presenting cell activation drives T-cell subset polarization toward proinflammatory phenotypes, exacerbating tissue damage (Tang et al., 2019).

The gut microbiota sustains host homeostasis by regulating metabolic processes, epithelial barrier integrity, and immune system development and function (Luthuli et al., 2019; Sittipo et al., 2019). Gut microbiota-derived metabolites, such as SCFAs (e.g., butyrate, propionate, acetate), circulate systemically to organs, including the gut, spleen, liver, and pancreas. These metabolites regulate gastrointestinal hormone secretion, modulate blood glucose and lipid metabolism, and attenuate insulin resistance and inflammation, exerting broad physiological and immunomodulatory effects (Schoeler and Caesar, 2019; Liu et al., 2022). SCFAs additionally activate intestinal epithelial cells, reduce susceptibility to inflammatory disorders, and fine-tune innate and adaptive immune responses.

Commensal gut microbes competitively inhibit pathogenic bacteria via the production of antimicrobial compounds (Peng et al., 2024), such as bacteriocins and hydrogen peroxide. Coevolution with the host immune system has enabled sophisticated discrimination between the commensal microbiota and pathogens, preserving antimicrobial defense capacity. The microbiota critically shapes both innate and adaptive immune response maturation and activity (Matson et al., 2021).

Patients with inflammatory bowel disease (IBD) exhibit a dysbiotic gut microbiota marked by increased abundances of *Mycobacterium avium* (Naser et al., 2014) and *Escherichia coli* (Cho et al., 2022), alongside diminished levels of butyrate and other SCFAs (Akhtar et al., 2022). These SCFAs suppress histone

deacetylase (HDAC) activity (Fawad et al., 2022), modulate gene expression and cellular proliferation, and regulate immune responses. Notably, adherent-invasive *E. coli* strains demonstrate enhanced mucosal adhesion and invasion, triggering pathogenic immune activation. Emerging evidence highlights microbial metabolites—particularly SCFAs such as butyrate—as critical mediators of gastrointestinal barrier integrity and mucosal homeostasis rather than microbiota composition alone.

Butyrate serves as the primary energy source for colonic epithelial cells, promoting stem cell proliferation and anti-inflammatory macrophage polarization via HDAC inhibition and histone acetyltransferase activation. Conversely, butyrate depletion exacerbates colonic inflammation by impairing regulatory T (Treg) cell differentiation and reducing macrophage antimicrobial activity. The severity of microbial dysbiosis is directly correlated with IBD progression.

Patients with active IBD display reduced microbial diversity compared with non-IBD controls. Proteobacteria levels are significantly elevated during active UC (UC) but decline during remission. Active UC is further associated with increased abundances of *Klebsiella*, *Enterococcus*, and *Haemophilus*, whereas remission correlates with enrichment of *Roseburia*, *Faecalibacterium*, *Bradyrhizobium*, and *Enterococcus faecalis*.

3.1 *Escherichia coli*

UC-associated pathogens include diverse *Escherichia coli* strains, such as diffuse adherent *E. coli* (DAEC) (Walczuk et al., 2019) and extraintestinal pathogenic *E. coli* (ExPEC) (Figure 2). In 1987, Burke and Axon demonstrated that fecal isolates from UC patients predominantly comprised DAEC strains exhibiting

enterotoxigenic and enteropathogenic traits, unlike those from healthy individuals. ExPEC strains harbor virulence genes encoding toxins (e.g., α -hemolysin) and adhesins (e.g., FimH) (Figure 2) (Mirsepasi-Lauridsen et al., 2016; Mirsepasi-Lauridsen et al., 2019). Unlike pathogens that target small intestinal epithelia, these strains produce hemolysins that compromise intestinal epithelial cell (IEC) tight junction integrity, exacerbating colitis in murine models (Mirsepasi-Lauridsen et al., 2016; Mirsepasi-Lauridsen et al., 2020; Yang et al., 2020).

3.2 *Bacteroides vulgatus*

The genus *Bacteroides*, particularly *Bacteroides vulgatus*, is enriched in the colonic submucosal microbiota of UC patients. Notably, elevated serum titers of OmpA antibodies targeting *Brucella* outer membrane proteins are observed in a subset of individuals with UC (Figure 2) (Sharma et al., 2022).

3.3 *Candida albicans* (fungi)

Candida albicans is a key fungal commensal in the human gut microbiota that contributes to immune system development through mechanisms such as systemic antifungal IgG production (Figure 2) (Doron et al., 2021; Shao et al., 2022a). However, this fungus exacerbates intestinal inflammation via a self-reinforcing cycle: low-grade gut inflammation promotes fungal colonization, whereas *C. albicans* overgrowth amplifies inflammatory responses. Inflammation-driven *C. albicans* proliferation worsens colitis by lysing macrophages and secreting candidalysin, a hyphal exotoxin. Candidalysin directly induces intestinal inflammation, and *in vitro* studies have demonstrated that IL-1 β production is correlated with UC severity (Doron et al., 2021; Shao et al., 2022a).

Systemic antifungal IgG production depends on the CARD9 signaling pathway (Figure 2) (Doron et al., 2021). The DSS-induced murine colitis model recapitulates the clinical and histopathological features of human UC (Yang and Merlin, 2024). *Card9*-deficient mice exhibit impaired immune responses, including reduced expression of IL-6, IL-17A, and IL-22 and regenerating islet-derived protein 3 γ (RegIII γ) after DSS challenge (Sokol et al., 2013).

Candida albicans, a pathobiont of the gut microbiota, exacerbates UC via mycelium-associated hemolysin production (Moyes et al., 2016; Li et al., 2022). Strain-dependent variations in *C. albicans* macrophage lytic activity further modulate disease progression (Figure 2) (Li et al., 2022). While *C. albicans* has been implicated in the severity of Crohn's disease, recent studies have associated its abundance with chronic prostatitis progression, with increased colonization in advanced cases (Li et al., 2022; Hidalgo-Vico et al., 2024).

Studies have demonstrated the critical role of yeast morphology in *Candida albicans* adaptation (1): Deletion of EFG1 (Enhanced Filamentous Growth Protein 1) (Park et al., 2020) or FLO8 (Flocculation Protein 8, key regulators of filamentation) (Hidalgo-Vico et al., 2024) enhances fungal colonization in the antibiotic-

treated murine gut (2). Heterologous expression of UME6 (Transcriptional Repressor UME6, a hyphal transition driver) (Shao et al., 2022b) reduces colonization capacity (3). ZCF8 (Zinc Finger Transcription Factor UME6-interacting Protein 2), TRY4 (Trypsin-4), and ZFU2 (Zinc Finger Transcription Factor UME6-interacting Protein 2) —negative regulators of filamentation—are essential for fungal survival in abiotic environments (Böhm et al., 2017) (4). Null mutations in HMS1 (Hyphal Morphology and Stress Response Protein 1) (Wakade et al., 2023) and CPH2 (cAMP-dependent Protein Kinase Homolog 2, yeast morphology promoters under anaerobic conditions) impair colonization (5). Yeast morphology is dominant in murine gut symbionts, suggesting fitness for intestinal niches (Zhang et al., 2025).

While yeast forms thrive in the gut, filamentous morphotypes may colonize other mucosae. For example, hyphal structures are prevalent in the oral mucosa (Jin et al., 2019), although their presence does not inherently indicate pathogenicity.

3.4 Probiotics (Lactobacilli)

Probiotic efficacy requires survival in the gastrointestinal (GI) tract, gastric acid tolerance, the absence of antibiotic resistance genes, and demonstrable host benefits (Nya, 2022). Among probiotic candidates, *Lactobacillus* spp. remain the most widely utilized and studied (Figure 2).

Lactobacilli modulate GI immune responses by enhancing intestinal barrier integrity and inhibiting pathogen colonization (Kong et al., 2020). These effects are mediated through interactions with innate and adaptive immune cells via microbe-associated molecular patterns (MAMPs), which engage pattern recognition receptors (PRRs), such as Toll-like receptors (TLRs), nucleotide-binding oligomerization domain (NOD)-like receptors, and C-type lectins (Veiga et al., 2010). Additionally, *Lactobacillus* species secrete immunoregulatory proteins. For example, *Lactobacillus rhamnosus* GG (ATCC 53103) secretes p40 and p75 proteins, which activate the Akt signaling pathway and inhibit TNF- α -induced epithelial cell apoptosis in human and murine colonic epithelial cells (Figure 2).

Synbiotic approaches combining *Bifidobacterium lactis* with lactobacilli reduce colitis severity and Enterobacteriaceae levels—a family associated with colitogenic potential—during early disease stages (Veiga et al., 2010). Many *Lactobacillus* species negatively correlate with UC severity. DeMarco et al. (De Marco et al., 2018) demonstrated that the probiotic strains *Lactobacillus acidophilus*, *L. casei*, *Lactococcus lactis*, *L. reuteri*, and *Saccharomyces boulardii* exert anti-inflammatory effects by selectively modulating the production of cytokines—including IL-10, IL-1 β , TNF- α , PGE-2, and IL-8—in HT-29 intestinal epithelial cells. Jia et al. alleviated colitis by increasing intestinal macrophage proportions and IL-10 secretion via *Lactobacillus johnsonii* (Jia et al., 2022). Sun et al. attenuated DSS-induced UC through *L. plantarum*-12 administration, enhancing barrier function by upregulating Mucin 2 (MUC2) protein expression (Sun et al., 2020).

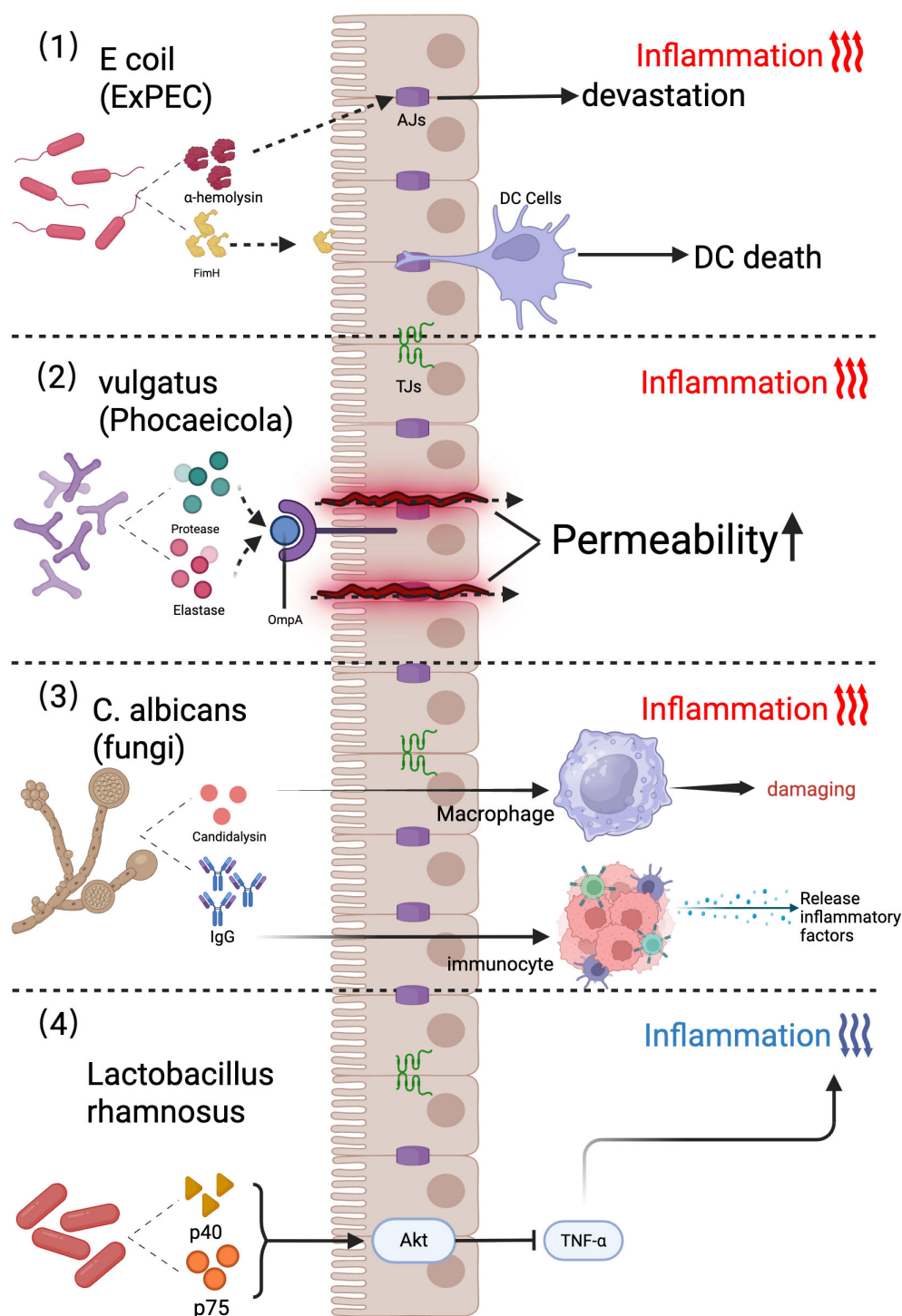


FIGURE 2

Mechanisms of gut microbiota in promoting and suppressing ulcerative colitis. (1) *Escherichia coli* strains harboring ExPEC virulence genes, such as FimH (mediating intestinal epithelial cell [IEC] adhesion) and α -hemolysin (disrupting IEC tight junctions), promote epithelial barrier dysfunction, DC infection, and host cell death. (2) The gut commensal bacterium *Phocaeicola vulgatus* (formerly *Bacteroides vulgatus*) acts as a patient-specific biomarker, secreting proteases and elastases that increase intestinal permeability and correlate with UC severity. (3) Mechanisms Underlying *Candida albicans*-Induced Inflammation. (4) The probiotic *Lactobacillus rhamnosus* attenuates inflammation by secreting the p40 and p75 proteins, which activate the Akt signaling pathway to suppress TNF- α -induced epithelial apoptosis in human colonic epithelia and murine models. ExPEC, Extraintestinal Pathogenic; OmpA, Outer Membrane Protein A; DC Cells, Dendritic Cells; Akt, Ak strain transforming; TNF- α , Tumor Necrosis Factor alpha; AJs, Adherens Junctions; TJs, Tight Junctions; FimH, Fimbrial tip adhesin subunit H; IgG, Immunoglobulin G.

Collectively, these findings demonstrate that probiotics attenuate inflammation by suppressing proinflammatory cytokines (e.g., IL-1 β and TNF- α) and enhancing anti-inflammatory mediators (e.g., IL-10) through PRR- and Akt-dependent pathways.

4 Inflammation in UC

UC is characterized by intestinal barrier dysfunction, which originates from epithelial cell impairment or structural defects in the intestinal epithelium. Dysregulated immune mediators and aberrant cellular activity in the lamina propria further compromise barrier integrity, triggering a cascade of inflammation that drives disease chronicity.

An extensive network of dendritic cells resides beneath the intestinal epithelium. When substantial quantities of *Aspergillus* bacteria breach the mucus barrier, pathogen-associated molecular patterns (PAMPs), such as lipopolysaccharides and flagellin, on the fungal surface are detected by TLRs on dendritic cells (Figure 3) (Kawai and Akira, 2011; Wells et al., 2011). Immature dendritic

cells secrete IL-23, driving localized intestinal inflammation (Dewayani et al., 2021). Cytokine-activated natural killer (NK) cells adhere to affected vascular smooth muscle cells (VSMCs), releasing cytotoxic granules that induce apoptosis. IL-1 β further stimulates innate lymphoid cells (ILCs) to produce IFN- γ , IL-17, and other proinflammatory cytokines, amplifying the inflammatory cascade (Figure 3) (Bishop et al., 2014).

The progression of UC is driven by dysregulated pro- and anti-inflammatory chemokine signaling networks. Oxidative stress exacerbates intestinal inflammation in UC by activating nuclear factor erythroid 2-related factor 2 (Nrf2), which triggers nuclear translocation to induce antioxidant response pathways (Figure 3). Furthermore, Nrf2 enhances mucosal barrier integrity through the transcriptional regulation of intestinal tight junction proteins, thereby suppressing UC pathogenesis.

5 FCD and UC

FCD exerts multifaceted effects across the inflammatory cascade in UC. These include (1) inhibition of lymphocyte adhesion and

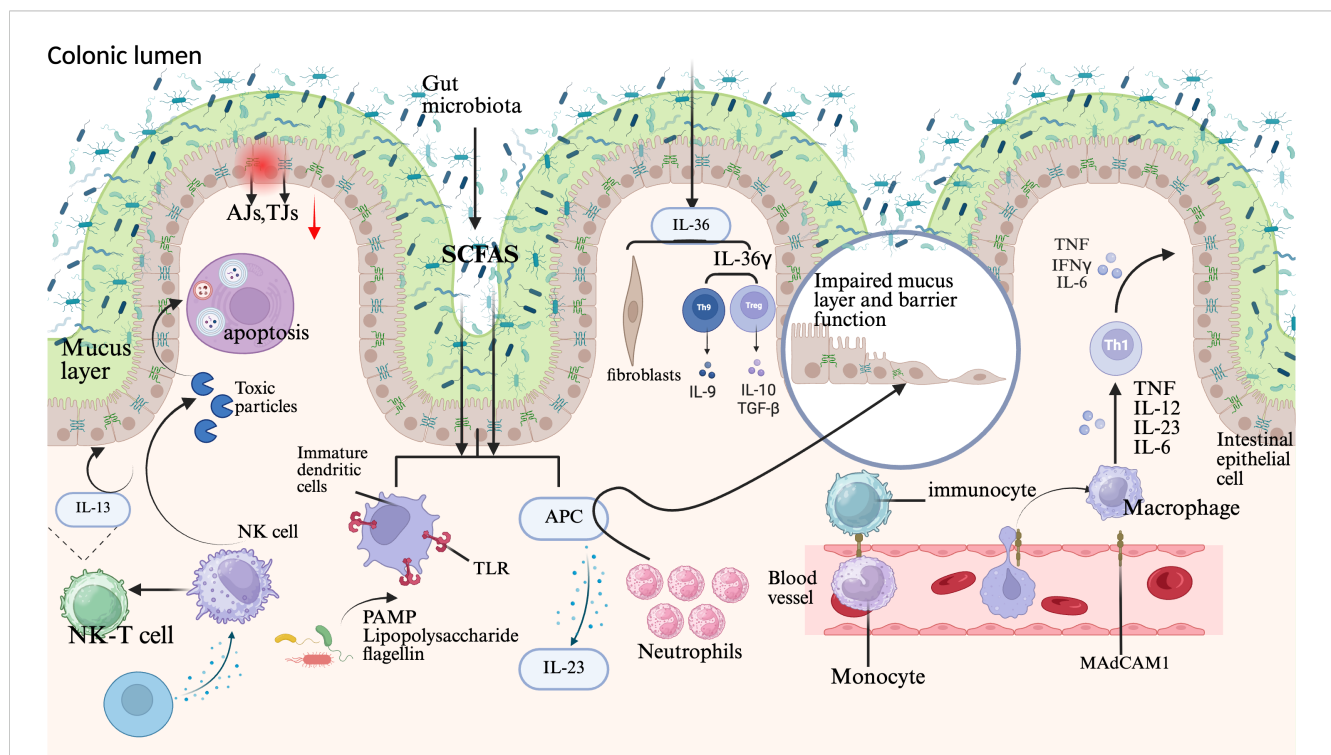


FIGURE 3

Pathophysiology of UC. UC pathophysiology involves multifactorial contributors, including reduced intestinal microbiota diversity and metabolic alterations such as diminished SCFAs production. In UC patients, the colonic mucus layer is compromised due to decreased synthesis of MUC2. These microbiota shifts and mucus layer thinning disrupt intestinal barrier integrity, facilitating microbial translocation to the epithelial barrier. Focal apoptosis and dysregulated TJs protein expression further degrade the intestinal epithelium, enabling microbiota penetration. This breach activates macrophages and APCs, triggering chemokine production and neutrophil recruitment. Neutrophils mediate primary cellular defense via neutrophil extracellular trap (NET) formation, whereas immune cell infiltration occurs through vascular epithelium-expressed adhesion molecules. Infiltrating monocytes differentiate into macrophages that secrete TNF, IL-12, IL-23, and IL-6, driving TH1 cell polarization. Concurrently, epithelial-derived IL-36 γ suppresses Treg cells and promotes IL-9-producing TH9 cell polarization, whereas IL-36 activates fibrogenic genes. Additionally, IL-13 released by NKT cells exacerbates barrier dysfunction. AJs, Adherens junctions; TJs, Tight junctions; SCFAs, Short-chain fatty acids; NK cell, Natural killer cell; NK-T cell, Natural killer T cell; MAdCAM-1, Mucosal vascular addressin cell adhesion molecule 1; TLR, Toll-like receptor; IFN γ , Interferon gamma; TNF, Tumor necrosis factor; IL-12, Interleukin-12; IL-23, Interleukin-23; IL-6, Interleukin-6; IL-9, Interleukin-9; IL-10, Interleukin-10; TGF- β , Transforming growth factor beta; IL-13, Interleukin-13; APC, Antigen-presenting cell; IL-36, Interleukin-36; IL-36 γ , Interleukin-36 gamma.

infiltration (2); suppression of enzymatic activity, notably matrix metalloproteinases (MMPs) and the complement cascade (3); modulation of inflammation-associated gene expression and transcriptional regulation; and (4) induction of apoptotic cell death. FCD also effectively prevents inflammatory lesion formation *in vitro* (Pomin, 2015; Apostolova et al., 2020; Ahmad et al., 2021) and influences critical therapeutic targets implicated in the pathogenesis and progression of inflammatory disorders (Wu et al., 2022).

The anti-inflammatory properties of FCD have been extensively investigated, primarily through *in vitro* studies using murine RAW 264.7 macrophages. Liyanage et al. (Liyanage et al., 2023) demonstrated that FCD suppresses lipopolysaccharide (LPS)-induced prostaglandin E2 (PGE2) production in these cells, highlighting its central role in mediating anti-inflammatory effects. Additionally, FCD prevented the nuclear translocation of NF- κ B p65, stabilized I κ B α against degradation, and inhibited the MAPK signaling pathway. In Murraya-derived FCD, reduced secretion of TNF- α and IL-1 β , along with suppressed neutrophil infiltration, further underscored its efficacy in attenuating early-phase inflammation (Liyanage et al., 2023).

The intestinal barrier is structurally defined by intestinal epithelial cells (IECs) interconnected via AJs, TJs, and associated complexes (Bhat et al., 2018). TJs interface with the cytoskeletal framework, forming a dynamic barrier system. FCD enhances gut barrier integrity by (1) increasing transmembrane protein activity (2), activating TJ-associated signaling pathways, and (3) reducing paracellular permeability in IECs. Intestinal PRRs, including TLRs and nucleotide-binding oligomerization domain-like receptors (NLRs), bind FCD and trigger signaling cascades that modulate inflammatory cytokines and immune mediators. These interactions culminate in upregulated expression of barrier-protective genes and proteins, reinforcing intestinal immunity (Bhat et al., 2018).

FCD fermentation in the colon enhances microbial diversity, increases SCFAs production (e.g., acetate, succinate), and mitigates colitis severity in murine models (Fan LJ et al., 2023). Specifically, FCD supplementation elevates fecal acetate and succinate levels in colitis-prone mice, counteracting antibiotic-induced dysbiosis (Wang et al., 2020). *Arthrospira*-derived FCD increases the abundance of *Lactobacillus*, a genus critical for intestinal immunity and epithelial renewal (Shang et al., 2016; Lee et al., 2018). Dietary FCD also enriches *Ruminococcaceae*, the primary producers of SCFAs that modulate the Th1/Treg cell balance to maintain gut homeostasis (Smith et al., 2013; Sun et al., 2018). Additionally, the alga FCD strengthens mucosal immunity by increasing mucin and secretory IgA production in the intestinal lumen (Takahashi et al., 2020). Collectively, these findings position dietary FCD as a potent modulator of microbiota composition, with broad implications for gastrointestinal health (Li R. et al., 2024; Li S. et al., 2024).

FCD modulates the composition of the gut microbiota by enhancing intestinal probiotic populations and stimulating epithelial cells to secrete SCFAs, antimicrobial peptides (AMPs), and MUC2—a gel-forming mucin critical for the colonic and small intestinal mucus layers. These IEC secretory complexes inhibit

bacterial adhesion in the intestinal lumen (Sicard et al., 2017; Paone and Cani, 2020). Conversely, increased intestinal permeability (a risk factor for bacterial translocation and disease pathogenesis) is counteracted by the reinforcement of the intestinal chemical barrier by FCD. Furthermore, FCD induces the synthesis of autoimmune mediators, including secretory immunoglobulin A (sIgA), which is produced by lamina propria plasma cells and serves as the predominant immunoglobulin in intestinal secretions. sIgA prevents pathogen invasion and strengthens the microbial barrier, thereby strengthening gut immune homeostasis. Notably, FCD from *Acaudina molpadioides* ameliorated cyclophosphamide (CPA)-induced mucosal damage by reducing intestinal inflammation, increasing TJ protein expression, and enriching SCFAs-producing microbiota (*Coprococcus*, *Rikenella*, and *Butyricicoccus*).

5.1 NF- κ B pathway

The NF- κ B transcription factor exists as homo or heterodimeric complexes (e.g., p50/p65) bound to the inhibitory protein I κ B α under basal conditions. Upon stimulation, I κ B α is phosphorylated and ubiquitinated, leading to proteasomal degradation and subsequent release of NF- κ B subunits (e.g., p65), which translocate to the nucleus to activate proinflammatory target genes (Figure 4) (Hu et al., 2018). In a murine chronic colitis model, *Cladosiphon okamuranus* Tokida-derived FCD inhibited NF- κ B pathway activation, reducing IL-6 and IFN- γ levels and ameliorating disease severity (Matsumoto et al., 2004). This compound also suppressed LPS-induced secretion of nitric oxide (NO), prostaglandin E2 (PGE2), TNF- α , and IL-1 β in macrophages without inducing cytotoxicity. Notably, low-dose FCD enhanced the production of NO, inducible nitric oxide synthase (iNOS), ROS, and cytokines (IL-1 β , IL-6, IL-12, and TNF- α) by macrophages, whereas high-dose FCD attenuated these mediators, revealing a concentration-dependent biphasic anti-inflammatory response.

NF- κ B signaling is central to inflammatory pathogenesis (Zahan et al., 2022). FCD attenuated the LPS-induced nuclear translocation of NF- κ B p65 and the accumulation of intracellular ROS in RAW 264.7 macrophages (Figure 4). Furthermore, it reversed CPA-induced immunosuppression by reducing ROS levels and downregulating proinflammatory cytokines (IL-6, IL-1 β , and IL-12) via NF- κ B pathway inhibition, thereby restoring intestinal immune homeostasis (Zahan et al., 2022).

Mounting evidence demonstrates FCD's inhibitory effects on NF- κ B signaling. K.K. Asanka Sanjeewa et al. isolated FCD from *Padina commersonii* and stimulated RAW264.7 cells, revealing that FCD significantly downregulates mRNA and protein expression of TLR2, TLR4, and MyD88 in LPS-induced inflammation, thereby suppressing inflammatory responses (Asanka Sanjeewa et al., 2019). In an *in vivo* model of UC induced by a fiber-deficient diet, Weiyun Zheng et al. found that FCD inhibits NF- κ B pathway activation, reduces intestinal LPS levels, ameliorates inflammatory cell infiltration, and preserves gut barrier integrity, collectively mitigating UC pathology (Zheng et al., 2024).

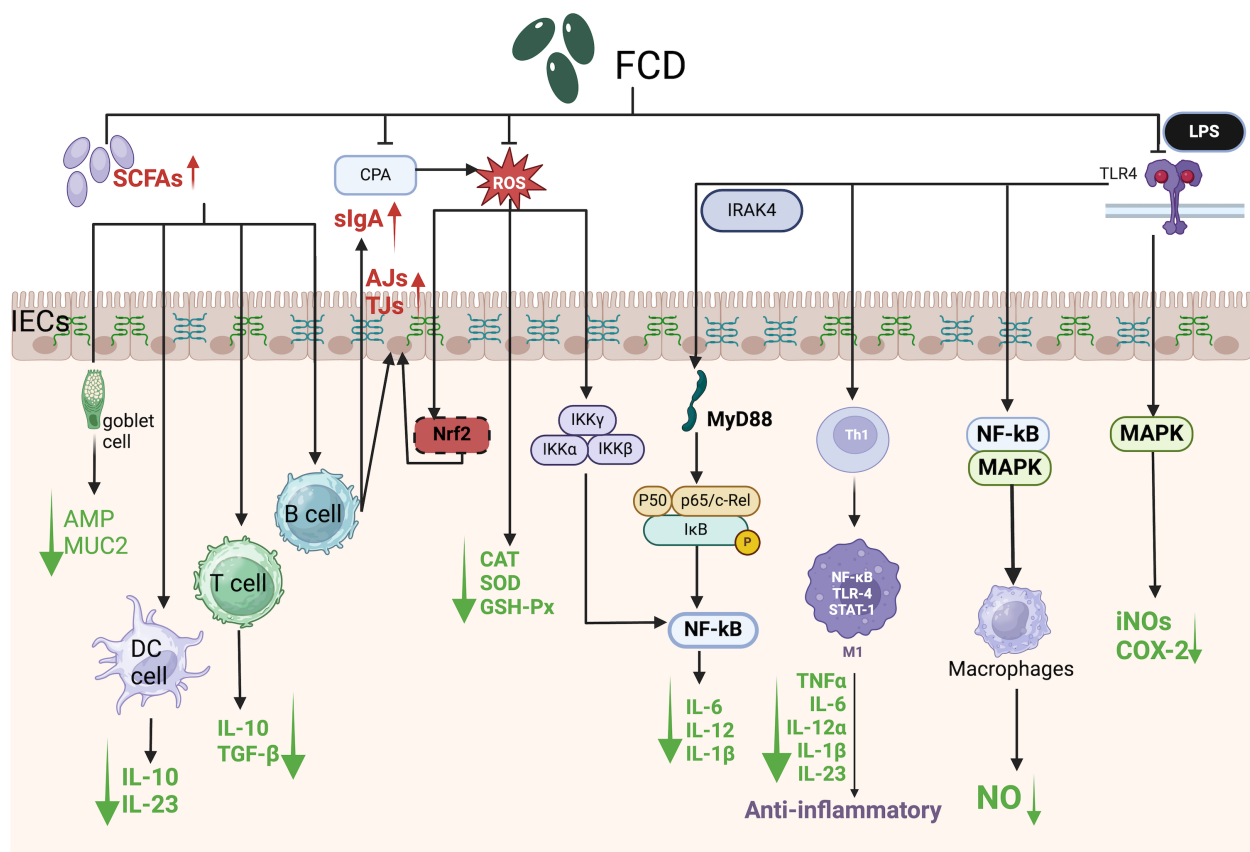


FIGURE 4

Schematic of signaling pathways mediating the protective effects of algal polysaccharides against intestinal damage. SCFAs, Short-chain fatty acids; CPA, Cyclophosphamide; ROS, Reactive oxygen species; LPS, Lipopolysaccharide; TLR4, Toll-like receptor 4; sIgA, Secretory immunoglobulin A; IRAK4, Interleukin-1 receptor-associated kinase 4; IECs, Intestinal epithelial cells; AJs, Adherens junctions; TJs, Tight junctions; AMP, Antimicrobial peptide; MUC2, Mucin 2; DC cell, Dendritic cell; T cell, T lymphocyte; B cell, B lymphocyte; Nrf2, Nuclear factor erythroid 2-related factor 2; IKK α , Inhibitor of nuclear factor kappa-B kinase subunit alpha; IKK β , Inhibitor of nuclear factor kappa-B kinase subunit beta; IKK γ , Inhibitor of nuclear factor kappa-B kinase subunit gamma; MyD88, Myeloid differentiation primary response 88; I κ B, Inhibitor of kappa B; Th1, T helper 1 cell; M1, Classically activated macrophage; STAT-1, Signal transducer and activator of transcription 1; IL-10, Interleukin-10; IL-23, Interleukin-23; TGF- β , Transforming growth factor beta; CAT, Catalase; SOD, Superoxide dismutase; GSH-Px, Glutathione peroxidase; IL-6, Interleukin-6; IL-12, Interleukin-12; IL-1 β , Interleukin-1 beta; TNF α , Tumor necrosis factor alpha; IL-12 α , Interleukin-12 subunit alpha; iNOS, Inducible nitric oxide synthase; COX-2, Cyclooxygenase-2; NO, nitric oxide.

5.2 Mitogen-activated protein kinase pathway

The MAPK family comprises phosphotransferases that regulate cytosolic signaling cascades via the phosphorylation of serine/threonine residues (Braicu et al., 2019). Researchers have quantified the expression of three MAPK isoforms: extracellular signal-regulated kinase 1/2 (ERK1/2), phosphorylated c-Jun N-terminal kinase (JNK), and phosphorylated p38. In IBD, colonic macrophages predominantly exhibit the proinflammatory M1 phenotype, which drives disease progression through the secretion of mediators such as IL-1 β , IL-6, IL-12 α , IL-23, and TNF (Zhao et al., 2022). Classically activated macrophage (M1 macrophages) are polarized by Th1 cytokines (e.g., interferon- γ) and Toll-like receptor (TLR) ligands (e.g., LPS). In DSS-induced

colitis, ERK signaling is activated, which is correlated with increased M1 macrophage infiltration (Figure 4).

LPS binds to TLR4, triggering MAPK pathway activation and upregulating proinflammatory mediators, including TNF- α , NO, inducible NO synthase (iNOS), and cyclooxygenase-2 (COX-2) (Figure 4). FCD dose-dependently suppressed ERK1/2 and p38 phosphorylation, reduced iNOS and COX-2 protein levels, and attenuated TNF- α and IL-1 β production, demonstrating potent MAPK pathway inhibition.

FCD in the MAPK pathway remains relatively unexplored, particularly in UC. However, FCD's anti-inflammatory effects via MAPK inhibition are established. Junhan Cao et al. investigated sea cucumber-derived FCD, demonstrating its suppression of *Helicobacter pylori*-induced gastritis through MAPK/NF- κ B signaling and gut microbiota modulation. Specifically, FCD

significantly enhanced biosynthesis of microbial metabolites including butyrate, isobutyrate, hexanoate, and phospholipids, thereby attenuating gastric inflammation (Cao et al., 2025).

5.3 Toll-like receptor pathway

TLRs constitute an essential class of PRRs that orchestrate innate immune responses against microbial pathogens (Yang et al., 2015). TLR4, the principal receptor for LPS signaling, regulates cytokine cascades and caspase activation while pathogen-associated molecular patterns (PAMPs) are detected, thereby bridging pathogen detection and inflammatory signaling in innate immunity (Kawasaki and Kawai, 2014). Upon ligand binding, TLR activation initiates intracellular signaling via recruitment of the adaptor protein myeloid differentiation primary response 88 (MyD88), enabling IRAK-4 association with the receptor–ligand complex. This cascade activates the I κ B kinase (IKK) complex, triggering I κ B phosphorylation and proteasomal degradation, which enables NF- κ B nuclear translocation and subsequent transcription of proinflammatory genes (Figure 4) (Kawasaki and Kawai, 2014; Vaamonde-García et al., 2021). FCD derived from *Ascophyllum nodosum* suppresses LPS-induced macrophage inflammation by inhibiting TLR4/NF- κ B signaling (Figure 4). Specifically, FCD attenuated LPS-stimulated NO production (IC₅₀: 27.82 μ g/mL), iNOS, and COX-2 expression in RAW 264.7 macrophages in a dose-dependent manner (Fernando et al., 2017).

5.4 FCD inhibits lipid peroxidation damage

ROS, including superoxide, hydroxyl radicals, hydroperoxyl radicals, NO, and singlet oxygen, are key mediators of oxidative damage in inflamed tissues (Bassoy et al., 2021). ROS amplify inflammation by upregulating factors linked to innate and adaptive immune responses, exacerbating mucosal injury (Tian et al., 2017). Sustained ROS release in inflammatory microenvironments induces cytosolic and metabolic dysfunction, driving tissue damage through lipid peroxidation (LPx), enzyme inactivation, and DNA oxidation (Schieber and Chandel, 2014; Esmaeeli et al., 2023; Liu et al., 2023). In IBD, oxidative stress (OS) arises from an imbalance between oxidant production and antioxidant defenses (Bourgonje et al., 2020). ROS directly activate proinflammatory signaling pathways, including the NF- κ B, MAPK, and signal transducer and activator of transcription 3 (STAT3) pathways. Leukocyte infiltration in inflamed mucosa further amplifies ROS generation, perpetuating cellular and tissue injury (Wang et al., 2016).

Excessive ROS production induces compensatory antioxidant responses to counteract oxidative damage. The NADPH oxidase (NOX) family serves as the primary enzymatic generator of ROS in mammalian cells, with NF- κ B activation driven by ROS-dependent activation of the I κ B kinase α/β (IKK α/β) complex (Figure 4). Cyclophosphamide (CPA), an immunosuppressant employed in

cancer therapy, paradoxically exacerbates oxidative stress through ROS overproduction and the downregulation of antioxidant enzymes—including catalase (CAT), superoxide dismutase (SOD), and glutathione peroxidase (GSH-Px)—in the spleen and thyroid tissues (Xu and Zhang, 2015; Li et al., 2017). ROS disrupt intestinal epithelial barrier integrity by redistributing TJs and AJs proteins through PKC-, MAPK-, JNK-, and ERK-dependent mechanisms (Figure 4). FCD counteracts these effects by inhibiting ROS-driven lipid peroxidation. For example, polysaccharide fractions from the seaweed *Solieria filiformis* exhibit dose-dependent antioxidant activity, scavenging 2,2-diphenyl-1-picrylhydrazyl (DPPH) free radicals with an IC₅₀ of 1.77 mg/mL (Sousa et al., 2016).

5.5 Role of FCD in UC

FCD ameliorates intestinal disorders by restoring intestinal barrier integrity, attenuating lipid peroxidation, and suppressing proinflammatory mediators. FCD modulates the gut microbiota composition, enhances SCFAs production by commensal bacteria, and reverses dysbiosis in UC patients, thereby mitigating disease progression. Through synergistic interactions with the gut microbiota, FCD inhibits the NF- κ B and MAPK signaling pathways, downregulates proinflammatory cytokines (e.g., IL-12, IL-23, IL-6, IL-36 γ , and IL-13), and counteracts oxidative stress-induced intestinal damage by reducing ROS accumulation. Concurrently, FCD upregulates TJs proteins, MUC2, and sIgA, collectively enhancing mucosal protection in UC.

6 Conclusion

This review synthesizes current knowledge on IBD etiology, UC pathogenesis, and the therapeutic mechanisms of FCD in modulating the gut microbiota and inflammation. Dysregulated host–microbiota interactions, particularly in UC, drive immune dysfunction and sustain the upregulation of proinflammatory factors, exacerbating disease severity. FCD acts as a prebiotic agent, restoring intestinal epithelial homeostasis, suppressing inflammation, neutralizing oxidative stress, and rectifying microbial dysbiosis, all of which contribute to its beneficial effects on UC. Despite these advances, key challenges remain: the precise etiology of IBD is unresolved, the structural heterogeneity of FCD (which is dependent on algal species and extraction methods) complicates standardization, and scalable production of low-molecular-weight FCD (LMWF) and identification of specific prebiotic targets for IBD require further investigation. Owing to its anti-inflammatory, antitumor, and immunomodulatory properties, FCD holds promise as a functional food or therapeutic agent for managing IBD and associated malignancies.

The limited clinical translation of FCD as a therapeutic agent stems primarily from its poor bioavailability. Historically, this sulfated polysaccharide has been utilized in traditional Chinese medicine (TCM) to treat diverse pathologies (Shen et al., 2018). In

oncology, preclinical studies have extensively investigated FCD's anticancer properties, with robust evidence demonstrating its dose-dependent cytotoxic effects on colon cancer cells (HT29, Caco-2) via ROS-mediated apoptosis induction (Vishchuk et al., 2013; Usoltseva et al., 2017; Narayani et al., 2019). LMWF has been used as a complementary therapy for patients with metastatic colorectal cancer (Tsai et al., 2017). Despite its suboptimal bioavailability, significant efforts have focused on structural modifications—including cross-linking, ionic interactions, covalent bonding, electrostatic stabilization, and physical entrapment—to enhance its bioactivity. Encapsulation strategies, particularly nanoparticle (NP)-based drug delivery systems, improve FCD's stability and targeted release at lesion sites (Deepika et al., 2019). Nevertheless, critical gaps persist in pharmacokinetic profiling and bioavailability optimization, requiring further experimental validation to advance clinical translation. Notably, FCD exhibits extraordinary chemopreventive potential due to its pleiotropic modulation of both classical and non-classical signaling pathways.

Currently FDA-approved therapeutics for UC primarily comprise traditional aminosalicylates and glucocorticoids, yet their associated adverse effects and complications remain inadequately resolved (D'Haens, 2016). Consequently, identifying and developing low-toxicity therapeutics with reduced side-effect profiles represents a critical research priority. Polyphenols and polysaccharides, natural products exhibiting anti-inflammatory and antioxidant properties with favorable toxicity profiles at appropriate doses, are considered promising candidates for inflammatory disorders. However, limitations in bioavailability and undefined safety dosage ranges restrict their clinical translation.

Nanoparticle-based drug delivery has emerged as a prominent strategy to address these challenges. Utilizing targeted carriers enables selective drug release at disease sites, minimizes systemic absorption, prevents off-target delivery to healthy tissues, enhances bioavailability, and reduces adverse effects. Mingxiao Cui et al. demonstrated enhanced therapeutic efficacy in UC through nano-encapsulated delivery of Phragmites polysaccharide (RP) to the intestinal tract (Cui et al., 2022). In a comprehensive review, Cui et al. summarize polysaccharide delivery via nanocarriers, highlighting that encapsulation protects polysaccharides from gastrointestinal degradation, improves stability, promotes localization to inflamed intestinal regions, reduces side effects, and enhances bioavailability through targeted colonic delivery (Cui et al., 2021).

While nanocarrier systems represent one approach to improve polysaccharide bioavailability, alternative strategies—including chemical modification and enzyme inhibitors—constitute

emerging UC therapeutics. Further clinical validation is required to assess their applicability.

Author contributions

YZ: Conceptualization, Data curation, Formal Analysis, Funding acquisition, Investigation, Methodology, Project administration, Resources, Software, Supervision, Validation, Visualization, Writing – original draft, Writing – review & editing.

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Conflict of interest

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