# Regulatory Mechanisms of Berberine in Inflammatory Bowel Disease: Postprint

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## Abstract

Inflammatory bowel disease (IBD) is a chronic intestinal inflammatory disease prone to relapse, causing significant harm to both humans and animals, with no curative pharmacological treatment available to date. As a natural product, berberine exhibits diverse physiological functions and unique pharmacological properties, demonstrates considerable therapeutic efficacy for IBD, and holds potential advantages for its prevention and treatment. This article introduces the types and properties of berberine, the fundamental characteristics of IBD, explores the regulatory mechanisms through which berberine modulates IBD, and provides a scientific basis for its practical application.

## Full Text

## Regulatory Mechanisms of Berberine in Inflammatory Bowel Disease

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### Abstract

Inflammatory bowel disease (IBD) is a recurrent chronic intestinal inflammatory disorder that poses severe threats to both humans and animals, and no curative treatment currently exists. As a natural product, berberine exhibits diverse physiological functions and unique pharmacological properties, demonstrating considerable therapeutic potential for IBD prevention and treatment. This review introduces the types and properties of berberine, describes the fundamental characteristics of IBD, and explores the regulatory mechanisms through which berberine modulates IBD, providing a scientific basis for its practical application.

**Keywords:** berberine; inflammatory bowel disease; regulation mechanism

## 1. Types and Properties of Berberine

Berberine is the principal active constituent found in the roots, stems, and bark of medicinal plants from families including Berberidaceae, Papaveraceae, Ranunculaceae, Rutaceae, Menispermaceae, and Rhamnaceae. Common sources include *Coptis chinensis*, *Phellodendron amurense*, *Berberis aquifolium*, *Berberis vulgaris*, and *Berberis aristata*. As the primary pharmacologically active component in the dried rhizomes of perennial herbs from the Ranunculaceae family —*Coptis chinensis*, *Coptis deltoidea*, or *Coptis teeta*—berberine is also known as coptisine.

Chemically, berberine is an isoquinoline alkaloid with the molecular formula C H NO , a molecular weight of 336 u, and a melting point of 85–86°C. It appears as yellow needle-shaped crystals, is odorless, and has an extremely bitter taste. Berberine is soluble in hot water or methanol, slightly soluble in water or ethanol, very slightly soluble in chloroform, and insoluble in ether or benzene. For clinical applications, it is primarily used as hydrochloride or sulfate salts, now mainly obtained through chemical synthesis. Treatment with different bases yields three forms of berberine: quaternary ammonium, aldehyde, and alcohol, with the quaternary ammonium form being the most stable.

## 2. Basic Characteristics of IBD

IBD encompasses ulcerative colitis (UC) and Crohn' s disease (CD), representing recurrent chronic intestinal inflammatory disorders that cause abdominal pain, diarrhea, and the passage of mucoid or bloody stools in both humans and animals. These conditions are notoriously difficult to treat and can cause significant morbidity [3]. UC is a nonspecific inflammatory disease typically localized to the colon, whereas CD is a chronic granulomatous inflammatory disease commonly affecting the terminal ileum and proximal colon.

The etiology of IBD remains incompletely understood, with pathogenesis involving multiple interacting factors including genetic susceptibility, lifestyle disruptions, adverse environmental conditions, and intestinal microbiota dysbiosis [4]. Research indicates close interactions between the immune and nervous systems, which communicate through direct contact between enteric glial cells and intestinal epithelial cells, eosinophils, or mast cells, as well as through signaling via cytokines such as histamine, neurokinins, and serotonin, thereby inducing inflammation and motility disorders in IBD and pain modulation [5]. Interactions among the gut, environment, and cytokines can trigger excessive mucosal immune responses, leading to IBD development [6]. Disruption of the intestinal mucosal epithelial barrier results in imbalance between anti-inflammatory and pro-inflammatory factors, triggering a cascade of antigen-specific immune

reactions and inflammatory changes with massive release of cytokines and inflammatory mediators. This provokes excessive mucosal immune responses in normal or already damaged intestinal tissues, exacerbating mucosal injury and promoting IBD initiation and progression [7]. Additionally, dysregulation of the mucosal immune system can induce excessive immune responses to intestinal microbiota, also triggering IBD.

Current therapeutic options for IBD primarily include aminosalicylate preparations, corticosteroids, and immunosuppressants. However, these drugs are expensive and can only alleviate inflammation and limit complications without providing a complete cure [1].

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## 3. Regulatory Effects and Mechanisms of Berberine on IBD

From safety and efficacy perspectives, natural products represent a compelling approach for IBD prevention and treatment. Numerous in vivo studies have demonstrated berberine' s therapeutic potential against IBD induced by agents such as acetic acid, indomethacin, trinitrobenzene sulfonic acid (TNBS), and dextran sulfate sodium (DSS) in rodent models [8]. Berberine' s pharmacological properties—including antimicrobial, anti-inflammatory, lipid-regulating, glucose-lowering, antitumor, antioxidant, blood pressure-reducing, antithrombotic, analgesic, smooth muscle-stimulating, and immunomodulatory effects—may all contribute to its regulatory mechanisms against IBD.

**3.1 Antimicrobial and Antidiarrheal Effects** IBD pathogenesis is associated with bacterial or viral infections, making antimicrobial and antiviral interventions crucial for prevention and treatment. Berberine is a positively charged compound that directly interacts with lipopolysaccharides (LPS), bacterial cell wall components, and cell surface proteins, exhibiting broad-spectrum antimicrobial activity against various multidrug-resistant bacteria [9]. Due to poor absorption following oral administration, berberine remains in the intestinal lumen at high concentrations, creating favorable conditions for antimicrobial action. Berberine can reverse the trend of increased *Escherichia coli* and *Enterococcus* alongside decreased *Lactobacillus* and *Bifidobacterium* observed in IBD model animals [1]. Chae et al. [10] found that berberine inhibits resident human intestinal bacteria, showing stronger suppression of harmful bacteria such as *Clostridium* species while exerting weaker effects on beneficial bacteria like *Lactobacillus*. Lv et al. [11] reported that berberine administration effectively inhibited Enterobacteriaceae proliferation in C57BL/6 mice with *Clostridioides difficile* infection-induced intestinal injury and colitis, offsetting vancomycin side effects, modulating intestinal microbiota, preventing recurrence, and improving survival rates.

Berberine' s antimicrobial action relates to its effects on bacterial metabolism and enhanced calcium ion permeability of intestinal mucosal epithelial cell walls.

A primary symptom of IBD is the formation of gaps between intestinal epithelial cells, leading to water and electrolyte exudation and causing diarrhea. Berberine directly affects water and electrolyte secretion induced by bacterial toxins. Chen et al. [12] demonstrated that berberine regulates water and sodium absorption by upregulating sodium-hydrogen exchanger 3 (NHE3) and aquaporin 4 in intestinal epithelial cells, while inhibiting intestinal smooth muscle motility to prolong intestinal transit time, thereby reducing diarrhea frequency in IBD patients. Berberine' s antimicrobial effects can be antagonized by multidrug resistance efflux pumps and related proteins that bacteria develop against antibiotics, resulting in relatively poor in vitro antimicrobial efficacy. However, berberine' s combined actions make it not only an effective anti-IBD agent but also a widely used antimicrobial and antidiarrheal drug for both humans and animals.

**3.2 Analgesic Effects** Pain is a common symptom of IBD that should be alleviated alongside effective disease treatment. Berberine' s analgesic and antidepressant properties play important roles in IBD therapy [13]. Chen et al. [14] reported that berberine reversed intestinal hypermotility and hypersecretion in mice with diarrhea-predominant irritable bowel syndrome by increasing expression of - and -opioid receptors in intestinal neurons, thereby reducing pain perception. Tang et al. [15] suggested that nitric oxide (NO) plays a significant role in pain transmission, and berberine can reduce visceral hypersensitivity-induced pain through NO mediation. Kim [8] found that berberine' s anti-inflammatory and antioxidant effects could alleviate pain caused by chronic constriction injury of the sciatic nerve in rats. Jiang et al. [16] reported that berberine reduced pain from recurrent aphthous ulcers. Additionally, berberine can relieve pain induced by cold temperature or mechanical injury, as well as reserpine-induced pain and depression [1].

**3.3 Inhibition of Oxidative Stress** Oxidative stress, a detrimental effect of reactive oxygen species (ROS) generation, is closely associated with various diseases including IBD. When the balance between ROS production and clearance is disrupted, oxidative damage occurs [17]. Therefore, inhibiting oxidative stress represents a viable therapeutic strategy for IBD. Berberine can inhibit ROS generation, induce antioxidant defense construction, and trigger oxidative stress in diseased cells, possessing the characteristics of an ideal antioxidant [18]. In vitro, berberine directly quenches ROS and chelates redox-active transition metals, indirectly preventing ROS formation [19]. In vivo, berberine inactivates ROS and interferes with enzyme systems involved in ROS generation by inhibiting oxidases to block ROS production pathways [20]. Simultaneously, berberine induces antioxidant defense construction by regulating endogenous antioxidant enzyme activity and maintaining endogenous non-enzymatic antioxidant levels [21]. Furthermore, berberine specifically interferes with ROS generation and detoxification in diseased cells, exhibiting pro-oxidant effects in pathological cells while demonstrating antioxidant properties in normal cells [22].

**3.4 Protection of Intestinal Mucosal Epithelial Barrier** Intestinal mucosal epithelial barrier dysfunction is a consequence of IBD. Berberine helps restore barrier function and suppress inflammatory responses, thereby mediating intestinal mucosal recovery. In Caco-2 monolayers, berberine reversed barrier dysfunction induced by tumor necrosis factor- (TNF- ), interferon- (IFN- ), hydrogen peroxide, and interleukin (IL)-1, reducing cell permeability and repairing intercellular tight junction damage [23]. Similar results were observed in HT-29/B6 human colon monolayers [24]. Berberine effectively inhibited endoplasmic reticulum stress in Caco-2 cells induced by TNF- , IFN- , and tunicamycin [25]. Li et al. [26] found that berberine suppressed elevated TNF- and IL-6 levels while increasing epithelial tight junction protein levels and permeability in rats with intestinal mucosal barrier damage induced by polymicrobial sepsis. Gu et al. [27] reported that berberine reversed lipopolysaccharide (10 mg/kg, intraperitoneal)-induced redistribution of tight junction proteins in colonic epithelium and membrane microdomains of mice with endotoxemia. Tan et al. [28] confirmed that intraperitoneal injection of berberine at 100, 150, and 200 mg/kg effectively ameliorated intestinal mucosal epithelial barrier damage induced by peritoneal air exposure. In DSS-induced intestinal injury and colitis mouse models, berberine suppressed colon tissue damage and shortening, upregulated tight junction proteins ZO-1 and occludin and anti-apoptotic protein expression, and downregulated apoptotic protein concentrations [29].

**3.5 Anti-inflammatory Effects** The dynamic balance between anti-inflammatory and pro-inflammatory factors in the body, when disrupted, triggers inflammation. Berberine modulates inflammatory responses by mediating Toll-like receptors (TLRs). TLRs expressed on epithelial cell surfaces recognize various pathogen- or damage-associated molecular patterns, initiating intracellular signal transduction that leads to effector molecule expression and secretion. Mogensen [30] found that berberine could affect TLR-2-mediated signaling pathways to regulate inflammatory factor expression. Li et al. [31] reported that berberine alleviated TNBS-induced IBD symptoms by modulating immune response balance while reducing IFN- , IL-17, IL-6, IL-1 , and TNF- levels in colonic mucosal epithelial cells and serum. Berberine also modulates cyclooxygenase-2 (COX-2) expression to regulate inflammatory responses and tissue damage. Kawano et al. [32] discovered that berberine inhibited COX-2 expression and activity in colonic epithelial cells and macrophages both in vitro and in vivo. Kuo et al. [33] reported that berberine suppressed dodecanoylphorbol acetate-induced COX-2 and prostaglandin E2 expression, thereby interfering with inflammatory responses.

**3.6 Regulation of T Helper (Th) Cells** IBD pathogenesis is closely related to cytokine responses, which are governed by T cell differentiation patterns. In T cell differentiation, Th1 cells primarily secrete IL-2, IL-12, and IFN- ; Th17 cells secrete IL-17A, IL-21, IL-6, IL-23, and TNF- ; and Th2 cells secrete IL-5, IL-13, IL-10, and IL-4. Anti-inflammatory cytokines such as IL-10 and IL-4 help main-

tain normal intestinal immune function, whereas pro-inflammatory cytokines including IL-1, IL-6, IL-8, and TNF- mediate IBD development [34]. Th1/Th2 and Th17/regulatory T cell imbalances also contribute to IBD pathogenesis, with Th17 being a major pro-inflammatory cytokine inducer—for instance, the release of pro-inflammatory cytokines from intestinal mucosal macrophages and lymphocytes in IBD patients is associated with Th17 [35]. Therefore, targeted cytokine intervention represents a therapeutic approach for IBD. Qin et al. [36] found that berberine inhibited Th1 and Th17 differentiation through direct action on the Janus kinase/signal transducer and activator of transcription (JAK/STAT) pathway, thereby preventing IBD. Cui et al. [37] demonstrated that berberine suppressed Th17 differentiation by activating extracellular signal-regulated kinase 1/2 while inhibiting Th1 differentiation through suppression of p38 mitogen-activated protein kinase and c-Jun N-terminal kinase activation, concurrently downregulating STAT1 and STAT4 activity. Li et al. [38] reported that berberine inhibited lymphocyte proliferation and downregulated Th1 and Th2 cytokines.

## 4. Conclusion

IBD poses severe threats to humans and animals, and current pharmacological therapies remain unable to achieve a cure. Both in vitro and in vivo studies have demonstrated berberine' s potent therapeutic capacity against IBD, which is attributable to its antimicrobial and antidiarrheal effects, analgesic and antispasmodic properties, antioxidant activity, epithelial barrier protection, anti-inflammatory actions, and Th cell regulatory functions. In terms of safety and efficacy, berberine offers significant potential advantages for IBD prevention and treatment. However, clinical cases utilizing berberine for IBD therapy remain scarce. Therefore, large-scale clinical trials and enhanced pharmaceutical chemistry research are warranted.

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