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Berberine as a Dual-Target Therapeutic for Ulcerative Colitis

Berberine in ulcerative colitis

Dharmendra Kumar Maurya, Prashasti Sharma

Abstract

Ulcerative colitis (UC) is a chronic inflammatory bowel disease (IBD) characterized by dysregulated immune response, gut microbiota imbalance, and disruption of the epithelial barrier disruption. Preclinical studies using dextran sulfate sodium (DSS)-induced colitis models, which mimic UC pathology have highlighted the therapeutic potential of berberine, a bioactive isoquinoline alkaloid derived from traditional Chinese medicine. The efficacy of berberine is attributed to a dual mechanism involving microbiota remodeling and direct inhibition of gasdermin D (GSDMD), which collectively suppress the pyroptosis and intestinal inflammation. Through these actions, berberine restores tight junction proteins (e.g., ZO-1, claudin-1), reduces pro-inflammatory cytokines (IL-1β, IL-6, TNF-α), and improves disease-associated clinical outcomes. Importantly, this dual-target profile distinguishes berberine from conventional single-pathway agents, as it simultaneously modulates luminal microbial communities and epithelial inflammasome signaling, thereby targeting a critical interface linking microbial dysbiosis, epithelial cell death, and immune activation. However, current evidence is largely derived from acute experimental models and indirect modulation of GSDMD, highlighting the need for deeper mechanistic and translational validation. Thus, with further clinical optimization, berberine emerges as a promising adjunct therapeutic candidate for the inflammation- and barrier-centric treatment of UC This opinion-review therefore emphasizes not only what berberine does, but why its combined microbiota GSDMD/pyroptosis targeting represents a conceptually compelling strategy for UC management.

Key Words: Ulcerative colitis; Inflammatory bowel disease; Berberine; Traditional Chinese medicine; Fecal microbiota transplantation; Gasdermin D

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Core Tip: Berberine ameliorates ulcerative colitis by modulating gut microbiota dysbiosis and inhibiting gasdermin D-mediated pyroptosis. It enriches beneficial taxa producing short-chain fatty acids (SCFAs), suppresses proinflammatory cytokines (*e.g.*, IL-1β, TNF-α), and restores epithelial tight junctions (ZO-1, claudin-1). Preclinical DSS mouse models demonstrate reduced inflammation, histological damage, and clinical scores.

INTRODUCTION

Ulcerative colitis (UC) is a chronic inflammatory bowel disease characterized by relapsing inflammation primarily affecting the colonic mucosa, presenting with symptoms such as diarrhea, rectal bleeding, and weight loss, and often associated with extra-intestinal manifestations [1]. Its pathogenesis involves genetic susceptibility, environmental triggers, epithelial barrier defects, dysregulated mucosal immunity, and gut microbiota dysbiosis, culminating in aberrant responses to luminal antigens [2]. Key mechanisms include Toll-like receptor activation, dysregulated mucosal immune responses involving Th2-like, Th17, and innate immune pathways (*e.g.*, IL-13, IL-17, and TNF-α), and leukocyte recruitment mediated by chemokines such as CXCL8 and adhesion molecules including MadCAM-1 [3-5]. Oxidative stress related epithelial injury has also been proposed to contribute to mucosal inflammation and neutrophilic infiltration [6]. Inflammasomes, a multi-protein complexes that sense microbial signals drive pyroptosis *via* gasdermin D (GSDMD) cleavage, releasing IL-1β and IL-18 to amplify inflammation [7]. Induction therapy uses 5-aminosalicylates or corticosteroids; maintenance employs immunomodulators or biologics such as anti-TNF agents [8-10]. Colectomy cures pancolitis but risks pouchitis [11,12].

Recently Huang *et al* (2024) [13] reviewed the literature in the databases to obtain information on the relationship between natural compounds and UC and found that flavonoids and polysaccharides help in epithelial repair and possess anti-TNF effects in DSS models. They restore the key molecules ZO-1, occludin, and reduce MPO activity, indicating the translational potential of natural compounds [13]. In another recent review Long *et al* (2025)[14] showed that arbutin, berberine, curcumin, and aloe polysaccharides

inhibiting STAT3 phosphorylation in TNBS (2,4,6-trinitrobenzene sulfonic acid) colitis models. These compounds suppress JAK/STAT signaling, reducing inflammation and histological scores. Preclinical data support their multi-target efficacy, offering safer alternatives to biologics for induction and maintenance therapy [14]. In another study Li *et al* (2025)[15] showed that probiotic metabolites like short chain fatty acids (SCFAs) from natural sources correct dysbiosis, down-regulating IL-17 and upregulating Treg cells in UC models.

Traditional Chinese medicine (TCM) formulas like Gegen Qinlian decoction, Huangqin decoction, and Baitouweng decoction offers promising adjunctive therapy for UC by alleviating the symptoms by repairing the intestinal mucosal barrier, modulating gut microbiota, and reducing inflammation [16-18]. In addition to herbal formulations, emerging evidence also suggests potential benefits of nutritional interventions. *Scutellaria baicalensis*, a traditional Chinese medicinal herb, shows promise as a safer alternative by targeting inflammation, immunity, intestinal barrier integrity, oxidative stress, and gut microbiota [19]. *Scutellaria* improves UC symptoms largely by modulating lipid peroxidation and controlling intestinal epithelial ferroptosis through the GPX4/ASCL4 pathway [20]. A recent double-blind placebo-controlled trial demonstrated that coconut water supplementation induced clinical remission in patients with mild-to-moderate UC, highlighting the growing interest in complementary strategies targeting mucosal healing and inflammation [21]. Berberine, a bioactive isoquinoline alkaloid from TCM herbs like Coptis chinensis (Huanglian), used for treating dysentery, has gained significant scientific attention for its wide-ranging anti-inflammatory, antimicrobial, antioxidant, metabolic, and anticancer activities[22-25]. Berberine exhibits potent anti-inflammatory effects relevant to UC management, making it a promising candidate for future therapeutic development [21]. Berberine suppresses pro-inflammatory cytokines (TNF-α, IL-1β, IL-6) by inhibiting NF-κB activation, MAPK signaling, and STAT3 phosphorylation in colitis models [26]. It promotes Nrf2-mediated antioxidant responses, restoring epithelial barrier integrity and modulating gut microbiota dysbiosis common in UC [27]. In a recent study, Yang *et al* (2026) [28] explored the berberine's dose-

dependent protection in DSS colitis model [29] as evidenced by reduced disease activity index (DAI), preserved colon length, and attenuated histopathology. Fecal microbiota transplantation (FMT) and cohousing confirm microbiota dependence, while molecular docking reveals berberine-GSDMD binding (energy -7.3 kcal/mol), validated by molecular dynamics simulations and disulfiram reversal. These dual pathways i.e microbiota mediated barrier enhancement and pyroptosis blockade, position berberine uniquely. Yang *et al* (2026)[28] study showed that male C57BL/6 mice treated with 3% DSS in drinking water for 6 days to induce acute colitis and administration of Berberine orally at 50 mg/kg b.wt (low dose) or 100 mg/kg b.wt (high dose) daily. It was observed that berberine dose-dependently reduced DSS-induced weight loss, DAI scores, colon shortening, spleen enlargement, and histological damage (*e.g.*, epithelial disruption, infiltration). It lowered proinflammatory cytokines and restored ZO-1/claudin-1 expression, enhancing barrier integrity. Gut microbiota analysis *via* 16S rRNA sequencing revealed DSS-induced dysbiosis i.e reduced alpha diversity, depleted Bacteroidetes/Lactobacillus, and enriched Proteobacteria/Escherichia-Shigella, which berberine reversed, boosting Prevotellaceae and Lachnospiraceae. FMT from berberine donors and cohousing transferred protection, affirming microbiota indispensability. Cohousing experiments further validated this contagion effect [30]. GSDMD pathways showed DSS upregulated cleaved GSDMD and ASC; berberine suppressed both *via* western blot and immunohistochemistry. GSDMD focus shone through docking (hydrogen bonds with VAL383, LYS52, ILE467), 100-ns MD simulations (stable RMSD/RMSF, ΔG -19.41 kcal/mol), and a western blot showing normalized cleaved GSDMD. Disulfiram (GSDMD inhibitor, 10 mg/kg b.wt) abolished berberine's benefits, elevating DAI and pathology. Berberine acts dually i.e microbiota remodeling promotes beneficial bacteria and metabolites (*e.g.*, short-chain fatty acids), restoring homeostasis and barrier function; direct GSDMD binding inhibits pyroptosis/inflammation. These pathways synergize, with microbiota influencing GSDMD thresholds. This aligns with prior targets like NEK7-NLRP3 but highlights GSDMD as novel. The finding of Yang *et al* (2026)[28] align well with reports i.e berberine enhances enteric glia-intestinal

epithelial-immune crosstalk in UC[31]. GSDMD restrains cGAS inflammation in macrophages during colitis; its loss worsens disease [32]. Berberine similarly curbs PLA2-COX-2-PGE2 *via* microbiota in DSS models [33]. Berberine's colitis protection aligns with meta-analyses of animal studies, showing reduced DAI, myeloperoxidase, and TNF-α across 20+ models. A 2024 systematic review affirmed berberine+5-ASA superiority over 5-ASA alone in UC remission (RR = 1.35), without added adverse events [34]. Network pharmacology studies implicate berberine in TLR4/NF-κB/HIF-1α inhibition, complementing GSDMD targeting [34,35]. Microbiota modulation echoes reports of berberine enriching SCFA producers like Lactobacillus, attenuating dysbiosis in IBD. In DSS models, berberine activated tuft cell-bitter taste signaling and AhR *via* tryptophan metabolites [36]. GSDMD's role bifurcates: Macrophage GSDMD restrains cGAS inflammation in colitis, yet epithelial GSDMD drives mucus secretion and barrier integrity. Berberine's direct pore blockade offers non-pyroptotic regulation [37].

This opinion-review therefore emphasizes not only what berberine does, but why its combined targeting of the gut microbiota and GSDMD-mediated pyroptosis represents a conceptually compelling therapeutic strategy for UC. By simultaneously reshaping dysbiotic microbial communities and suppressing epithelial pyroptotic injury, berberine addresses two upstream drivers of UC that are often treated separately in current pharmacologic approaches. This dual-target paradigm aligns with emerging systems-biology models of IBD, which view epithelial barrier integrity, inflammasome activation, and luminal microbial networks as tightly interconnected processes rather than isolated pathways. Targeting this shared axis has the potential to break the cycle of barrier loss, immune overstimulation, and microbial dysregulation that perpetuates chronic colitis. With further optimization of delivery systems, biomarker-guided patient selection, and mechanistic validation in genetic and clinical settings, berberine stands out as a promising adjunct therapy. Its capacity to integrate microbiota modulation with epithelial protection positions it uniquely within the inflammation- and barrier-centric management framework for UC.

RELEVANCE OF BERBERINE IN ULCERATIVE COLITIS PATHOBIOLOGY

UC arises from initial epithelial injury that compromises barrier integrity, allowing luminal microbiota and their products to access the lamina propria and activate innate immune pathways [38,39]. This exposure triggers pattern-recognition receptors and promotes assembly of the NLRP3 inflammasome, leading to caspase-1 activation and subsequent cleavage of gasdermin D (GSDMD) [40,41]. The N-terminal fragment of GSDMD forms membrane pores that drive pyroptotic cell death, resulting in epithelial cell lysis and release of pro-inflammatory mediators such as IL-1β and IL-18[42]. This process amplifies mucosal inflammation and perpetuates tissue damage. Interestingly, GSDMD also exhibits context-dependent protective roles; controlled pore formation can facilitate mucus secretion from goblet cells and contribute to antimicrobial defense [43]. Moreover, GSDMD-mediated signaling intersects with the cGAS–STING pathway, linking cytosolic DNA sensing to innate immune activation [44]. Thus, GSDMD functions as a double-edged regulator, contributing both to inflammatory injury and to maintenance of intestinal homeostasis depending on the extent and context of its activation [32]. Berberine's novelty emerges in direct GSDMD docking, mimicking NEK7-NLRP3 blockade, disrupting inflammasome assembly and restoring barrier integrity. UC dysbiosis (↓Faecalibacterium/Roseburia, ↑Proteobacteria) parallels DSS models, where berberine recapitulates probiotic benefits by enriching short-chain fatty acid producers. Meta-analyses confirm berberine+5-ASA superiority (RR 1.22 for efficacy, reduced Baron/DAI scores) [34]. Molecularly, berberine exhibits a uniquely broad interaction profile, targeting several regulatory nodes that converge on inflammation, epithelial homeostasis, and microbial ecology. Its ability to modulate RXR/β-catenin signaling [45], initially characterized in cancer contexts, has important implications for UC, where aberrant β-catenin activity contributes to impaired epithelial renewal and barrier instability. Berberine's inhibition of EIF2AK2 (PKR), a key stress-response kinase driving cytokine production, inflammasome activation, and epithelial injury, provides an additional layer of anti-inflammatory control that directly aligns with UC pathobiology [46]. Moreover, the interaction with microbial enzyme FtfL highlights berberine's

capacity to reshape luminal metabolic outputs, promoting the growth of beneficial commensals and enhancing SCFA production, both crucial for mucosal repair[47]. By simultaneously influencing these molecular pathways, berberine integrates seamlessly into the gut-immune axis, targeting interconnected mechanisms rather than isolated endpoints [48,49]. This multi-target molecular signature reinforces its potential as a holistic therapeutic adjunct for UC.

BERBERINE MEDIATED MICROBIOTA REMODELING AND GSDMD INHIBITION

Berberine's dual mechanism centers on two complementary but interdependent axes i.e reshaping the gut microbiota and directly inhibiting gasdermin D-driven pyroptosis [28]. DSS-induced colitis models show that berberine enriches saccharolytic and short-chain-fatty-acid (SCFA)-producing microbiota while reducing pro-inflammatory or bile-acid-metabolizing taxa, thereby improving microbial homeostasis and metabolite output[28]. This microbial remodeling indirectly dampens inflammasome activation and mucosal immune stimulation, which feeds into its anti-inflammatory effects [50]. Concurrently, berberine directly inhibits GSDMD, the terminal executor of pyroptotic cell death. By restraining GSDMD-mediated pore formation, berberine reduces epithelial pyroptosis, limits the release of danger-associated molecules (including IL-1β), and curbs a major amplifier of sterile inflammation in UC-like colitis. Thus, at a mechanistic level, berberine acts as a "gatekeeper" at two levels i.e it strengthens the microbial side of the barrier equation and tightens control over the inflammasome-driven epithelial death program [48]. The functional outcome of this dual-target action is restoration of intestinal barrier integrity and suppression of pro-inflammatory cytokine networks. In DSS-UC models, berberine increases expression of tight junction proteins such as ZO-1 and claudin-1, reduces epithelial erosion, and improves histological scores. Concomitantly, it lowers colonic levels of IL-1β, IL-6, and TNF-α, which are signature cytokines in human UC and are tightly linked to inflammasome and NF-κB signaling [51]. This pattern suggests that berberine's dual-target profile is not merely additive but potentially synergistic i.e microbiota remodeling reduces the luminal "inflammatory drive," while

GSDMD inhibition directly cuts the inflammasome-pyroptosis cascade at its executioner node (Scheme 1). The result is an improvement in clinical disease activity indices, colon length, and microscopic architecture, all of which align with UC-relevant endpoints such as mucosal healing [52].

Scheme 1: *Berberine's dual pathway in Ulcerative colitis. In the microbiota arm, dysbiosis elevates Proteobacteria, prompting berberine intervention that boosts Lactobacillus and Bacteroidetes populations, enhancing short-chain fatty acid (SCFA) production. Elevated SCFAs upregulate tight junction proteins ZO-1 and claudin-1, restoring intestinal barrier integrity. Concurrently, the GSDMD arm activates the NLRP3 inflammasome and caspase-1, cleaving GSDMD to form membrane pores that release IL-1β and IL-18, driving pyroptosis. Berberine directly binds GSDMD, occluding pores and curbing cytokine release. Crosstalk amplifies protection as microbial metabolites inhibit NLRP3 activation, synergistically suppressing GSDMD-mediated pyroptosis and fortifying gut homeostasis.*

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MECHANISM OF BERBERINE'S ACTION

Berberine exerts its multi-layered protective effects within the gut ecosystem through four interconnected arms i.e i) the luminal arm where berberine reshapes the gut microbiota toward a more saccharolytic, SCFA-producing profile, restoring bile-acid homeostasis and lowering pro-inflammatory microbial cues[53]; ii) the epithelial arm where it suppresses inflammasome-dependent activation of GSDMD, thereby reducing pyroptotic cell death and limiting IL-1β release[52,54]; iii) the barrier arm highlights berberine's ability to reinforce epithelial structure by upregulating tight-junction proteins such as ZO-1 and claudin-1, which collectively reduce bacterial translocation and downstream immune stimulation[55]; and iv) the immune arm which integrate different upstream events, showing how diminished microbial and pyroptotic signals translate into lower IL-6, TNF-α, and related cytokines, alongside a rebalanced Treg/Th17 response[55]. Altogether, berberine reshapes the luminal microbiota toward a saccharolytic, SCFA-rich community and normalizes bile-acid metabolism. Within the

epithelium, it suppresses inflammasome activation, inhibits GSDMD-mediated pyroptosis, and reduces IL-1β release. At the barrier level, berberine enhances tight-junction protein expression and limits bacterial translocation. These upstream effects synergistically reduce pro-inflammatory cytokines, restore Treg/Th17 balance, and attenuate chronic intestinal inflammation (Scheme 2) [56].

Scheme 2. *Schematic illustration of the multilevel mechanism through which berberine protects the gut. Berberine reshapes the luminal microbiota toward a saccharolytic, SCFA-rich community and normalizes bile-acid metabolism. Within the epithelium, it suppresses inflammasome activation, inhibits GSDMD-mediated pyroptosis, and reduces IL-1β release. At the barrier level, berberine enhances tight-junction protein expression and limits bacterial translocation. These upstream effects synergistically reduce pro-inflammatory cytokines, restore Treg/Th17 balance, and attenuate chronic intestinal inflammation.*

CRITIQUE OF LIMITATIONS

Despite encouraging findings, several limitations temper the overall enthusiasm and warrant cautious interpretation. Most available data arise from acute DSS models, which reflect short-term inflammation but fail to capture the chronic, relapsing course of UC; chronic AOM/DSS paradigms better model fibrosis and cancer risk [54]. Microbiota-related conclusions rely heavily on antibiotics, FMT, or co-housing approaches, yet causality and functional shifts would be more convincingly demonstrated using germ-free mice, shotgun metagenomic sequencing, or quantitative SCFA profiling. Likewise, the evidence for GSDMD modulation remains largely non-genetic, relying on disulfiram (10 mg/kg IP), a non-specific inhibitor; validation in GSDMD-knockout mice, macrophage- versus epithelial-specific models, or cleaved-GSDMD immunohistochemistry is still required [57]. Furthermore, the mechanistic link between berberine and GSDMD is so far largely non-genetic (e.g., pharmacological inhibition or correlative expression changes), so causal validation in cell-type-specific or GSDMD-knockout models is still needed [51]. These limitations should be framed as

qualitative challenges rather than deal-breakers [53]. The reliance on acute, chemically induced models raises questions about berberine's effects in chronic, relapsing settings or in models with genetic susceptibility variants [52]. The non-genetic nature of the reported GSDMD modulation means that alternative upstream inflammasome or caspase-1–dependent mechanisms cannot be fully excluded [50]. Additional concerns include the exclusive use of C57BL/6 mice without genetic diversity, absence of human organoids or patient-derived FMT to support translational relevance, and omission of female mice despite known sex differences in microbiota and immunity. Berberine's poor bioavailability remains unaddressed, with no pharmacokinetic or toxicity data, including long-term effects on gut motility [58]. These limitations should be viewed as qualitative challenges rather than disqualifying flaws, as the mechanistic consistency across microbiota remodeling, barrier restoration, cytokine suppression, GSDMD-associated readouts, and clinical improvements still justifies deeper investigation in more advanced and genetically informed UC models. Therefore acknowledging these gaps while still arguing that the mechanistic consistency across multiple readouts (microbiota, barrier proteins, cytokines, GSDMD, clinical scores) supports further investigation rather than early dismissal [48].

TRANSLATIONAL DIRECTIONS AND POSITIONING AS AN ADJUNCT THERAPY

Positioning berberine within the broader therapeutic landscape of UC highlights its strongest potential as an adjunct rather than a standalone therapy, particularly in patients with mild-to-moderate disease or those exhibiting microbiota dysbiosis and barrier dysfunction [51]. Owing to its multi-targeted mechanism, future translational efforts should focus on identifying biomarker-driven subgroups such as individuals with heightened inflammasome activity, reduced short-chain fatty acid levels, or pronounced microbial imbalance that are most likely to benefit from berberine intervention [48]. Additionally, optimizing delivery strategies, including nanoformulations and colon-targeted systems, will be critical to enhance local drug bio-availability while minimizing systemic exposure [59]. Early-phase clinical trials should therefore be designed to

evaluate berberine in combination with standard UC therapies, incorporating endpoints such as mucosal healing, microbiota modulation, and GSDMD-associated biomarkers [54]. Collectively, these approaches underscore berberine's unique positioning at the interface of conventional pharmacology and microbiota-directed therapy. With further clinical refinement and mechanistic validation, particularly of its GSDMD-modulating effects, berberine holds promise as a valuable adjunct in inflammation- and barrier-focused management of UC [56].

FUTURE DIRECTIONS

To enhance berberine's therapeutic potential in UC, its delivery can be optimized using colon-targeted nanoparticles such as pH-responsive pectin-chitosan systems-to achieve site-specific GSDMD inhibition and improved interaction with the gut microbiota. Synergistic combinations with 5-ASA or probiotics, as supported by clinical evidence, should be explored. Preclinical evaluation in IL-10 knockout or T-cell transfer colitis models would help determine its efficacy in chronic inflammation [37]. In human studies, a Phase II trial in mild-to-moderate UC could position berberine as an adjunct therapy, with $GSDMD^{NT}$ levels in colonic biopsies serving as a pharmacodynamic biomarker. Analogue development such as dihydroberberine-may further address bioavailability constraints. Longitudinal FMT-based microbiome tracking after berberine treatment would help establish the durability of therapeutic responses. AI-guided docking pipelines could refine GSDMD-targeting candidates from TCM compound libraries, while multi-omics analyses should be incorporated to monitor long-term microbiome safety.

Network pharmacology and experimental data from Li *et al.* (2024)[60] show that berberine improves UC outcomes by suppressing the TLR4/NF-κB/HIF-1α axis, thereby reducing inflammation and correcting colonic pathology. Further, Ma *et al.* (2020)[32] report that GSDMD acts in macrophages as a negative regulator of cGAS-dependent inflammation, offering protection against colitis. These insights support the integration of intestinal organoid platforms for high-throughput screening of Berberine-microbiota-

GSDMD interactions, providing a translational pathway toward precision therapy for UC.

CONCLUSION

In conclusion, Berberine exemplifies precision traditional Chinese medicine (TCM) and emerges as a promising multi-target adjunct for ulcerative colitis management, leveraging microbiota remodeling and GSDMD inhibition to suppress pyroptosis, restore tight junctions (ZO-1, claudin-1), and curb cytokines (IL-1β, TNF-α). Preclinical DSS models affirm efficacy, yet limitations i.e acute inflammation focus and translation gaps necessitate TNBS colitis validation for Th1/Th17 insights and chronicity. Optimized nanoparticles enhancing bioavailability, coupled with microbiome-stratified patient cohorts, will bridge to clinical success, complementing biologics and transforming UC therapy paradigms. Preclinical studies, particularly DSS-induced colitis models, demonstrate improvement in disease severity and restoration of epithelial integrity. However, the DSS model primarily reflects acute epithelial injury and innate immune responses, whereas ulcerative colitis involves complex interactions between innate and adaptive immune pathways, which limits direct translation of these findings. Moreover, microbiota analyses in current studies largely rely on 16S rRNA sequencing, which provides compositional insights but does not fully capture functional microbial dynamics or metabolite profiles; future investigations incorporating shotgun metagenomics and quantitative metabolite analyses may help clarify the causal links between microbiota remodeling and berberine-mediated therapeutic effects. Although several clinical studies and meta-analyses suggest potential benefits of berberine, many trials are limited by relatively small sample sizes, heterogeneous study designs, and variable clinical endpoints. Another important limitation is that most clinical evidence currently originates from studies conducted in China, and large, well-designed multicenter trials from other regions remain scarce. In addition, berberine has not yet received regulatory approval for UC treatment from major agencies such as the United States Food and Drug Administration (FDA), the European Medicines Agency (EMA), or the Drugs Controller

General of India (DGCI). Future studies should therefore focus on well-powered randomized controlled trials, standardized outcome measures, and broader geographic representation to better define the therapeutic potential and clinical applicability of berberine in ulcerative colitis.