The Egyptian Journal of Hospital Medicine (July 2025) Vol. 100, Page 4382-4386

Role of Berberine Nanoparticles in Treatment of Ulcerative Colitis: A Comprehensive Review

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ABSTRACT

Background: Ulcerative colitis, a form of inflammatory bowel disease, involves repeated episodes of inflammation and ulcer formation in the colon. Its development is influenced by a combination of genetic predisposition, age, sex, and environmental conditions. The isoquinoline alkaloid berberine (BBR), which is frequently used as an antidiarrheal, is extracted from the rhizome of the Ranunculaceae plant Coptis chinensis, also known as "Huang-Lian" in Chinese. The use of BBR and its derivatives to treat irritable bowel disease (IBD) has recently been investigated. It is important to remember that BBR may reduce intestinal inflammation in a variety of ways. The effectiveness and bioavailability of BBR are probably going to be enhanced by nanoparticles.

Objective: This article aimed to investigate the potential therapeutic benefits of berberine nanoparticles in the management of ulcerative colitis.

Methods: We searched PubMed, Google Scholar, and Science Direct for Ulcerative colitis, Berberine nanoparticles, MAPK signaling pathway, Interleukin-6 and Nrf2 signaling pathway. Only the most recent or thorough investigation, from 2013 to 2023 was taken into account. The writers evaluated relevant literature references as well. Documents written in languages other than English have been ignored. Papers that were not regarded as significant scientific research included dissertations, oral presentations, conference abstracts, and unpublished manuscripts were excluded.

Conclusion: The observed downregulation of INOS2 and MAPK 14 mRNA expression in colon specimens treated with BBR NP accounted for the anti-inflammatory action of both BBR NP. Additionally, the strong Nrf2/HMOX1 pathway activation of BBR demonstrated its antioxidant impact.

Keywords: Ulcerative colitis, Berberine nanoparticles, MAPK signaling pathway, Interleukin-6, Nrf2 signaling pathway.

INTRODUCTION

Ulcerative colitis, a type of inflammatory bowel disease, is characterized by recurrent inflammation and ulceration in the colon. Its development is thought to result from an interaction of multiple contributors, including hereditary predisposition, demographic factors such as age and sex, as well as environmental influences [(1)].

Berberis vulgaris and other similar species, such as Berberis aristata, Berberis croatica, and Berberis aquifolium, are the primary sources of berberine (BBR), a naturally occurring alkaloid [(2)].

Numerous pharmacological characteristics, including anti-inflammatory, anti-cancer, antidiabetic, and antioxidant activities, are displayed by this phytochemical. BBR's therapeutic role in managing inflammatory illnesses is supported by evidence from several studies indicating it has strong anti-inflammatory effects by increasing anti-inflammatory cytokines and decreasing proinflammatory ones [(3)].

Berberis vulgaris itself is a widely recognized medicinal plant distributed across Asia and Europe [(4)]. Its roots, bark, leaves, and fruits have all yielded bioactive extracts with a variety of medicinal properties, and it has long been used as a culinary ingredient [(5)]. Particularly, Berberis species including B. aristata, B. croatica, and B. aquifolium have larger amounts of BBR in their roots, rhizomes, stems, and barks [(6)].

Recent advancements in pharmaceutical formulations suggest that nanoparticle-based delivery systems could significantly enhance both the bioavailability and therapeutic efficacy of BBR.

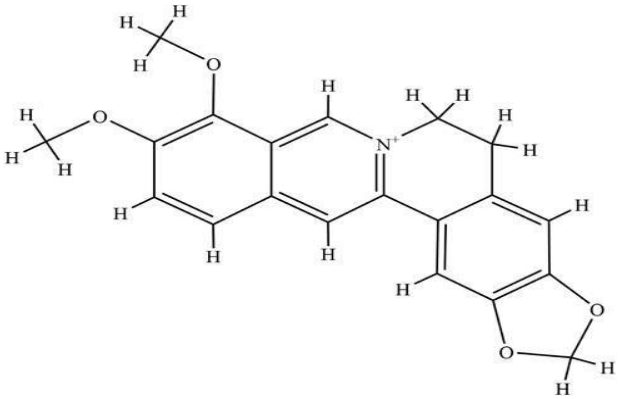

Fig (1): The chemical structure of berberine.

Pharmacokinetics and Excretion of Berberine

Absorption: Although BBR demonstrates significant therapeutic benefits against multiple disorders, its clinical use remains restricted due to limited oral absorption and overall low bioavailability. While intravenous administration can raise plasma concentrations, clinical investigations have reported severe adverse reactions such as hypotension and respiratory depression [(7)]. For this reason, oral intake is considered the preferred route of administration. However, studies in rats have shown that the absolute bioavailability of BBR is less than 1%. Poor membrane permeability, P-glycoprotein (P-gp)-mediated efflux,

Received: 30/04/2025
Accepted: 30/06/2025

hepatobiliary re-excretion, and self-aggregation are some of the causes of the decreased absorption. Its poor systemic availability is also a result of the liver's and the intestines' significant first-pass metabolism [8].

Distribution: Research findings indicate that following oral intake, BBR tends to accumulate predominantly in body tissues rather than in plasma. After intragastric administration, the compound is rapidly distributed, with the highest concentrations detected in the liver, followed by the kidneys, muscles, lungs, brain, heart, pancreas, and adipose tissue. Among these, the liver represents the primary site of deposition. Pharmacokinetic evaluations further demonstrated that four hours after dosing, BBR concentrations in tissues were nearly 70-fold higher than in plasma, and levels remained relatively stable in organs such as the liver, muscle, brain, heart, and pancreas [8].

Metabolism: Extensive experimental evidence shows that BBR is rapidly metabolized in vivo, with the liver and intestinal microbiota acting as the primary sites of transformation. During this process, much of the parent compound is converted into derivative metabolites, leading to alterations in its concentration and chemical structure. The main metabolic routes involve phase I reactions such as demethylation, demethylenation, reduction, and hydroxylation, followed by phase II processes including glucuronidation, sulfation, and methylation. The importance of gut bacteria in influencing BBR metabolism following oral ingestion is further supported by study. These microorganisms drive a series of biotransformation steps that significantly influence both the nature and amount of BBR absorbed. Experimental studies have identified demethoxylation and hydrogenation as the principal metabolic pathways initiated by intestinal flora. Specifically, microbial nitroreductases (NRs) convert BBR into dihydroberberine, a more absorbable intermediate, which is subsequently re-oxidized back into BBR within intestinal tissues before entering systemic circulation [8].

Excretion: Studies have shown that BBR is eliminated primarily through the kidneys, with excretion occurring in both urine and feces, as well as via bile. The biliary route is relatively slow because of enterohepatic circulation. It has been discovered that the excretion profile is affected by differences in the species (humans, mice, rats and rabbits) and the mode of delivery (oral gavage, oral ingestion, or intravenous injection). In rats, experimental results demonstrated that fecal elimination is predominant after oral or gavage administration, whereas urinary excretion is the main pathway following intravenous delivery [9].

Originally introduced as an antibacterial compound, BBR has since been recognized for its wide range of pharmacological activities. These include anticancer, antidiabetic, antioxidant, and anti-inflammatory effects, as well as protective roles in the liver, heart, and nervous system, in addition to anti-obesity properties [10]. BBR is a viable treatment option for neurodegenerative diseases including Parkinson's disease (PD) and Alzheimer's disease (AD) due to its capacity to pass the blood–brain barrier (BBB) [2]. Experimental data also indicate that berberine hydrochloride suppresses the production of heat shock proteins (HSPs) in various cancer types, including nerve, prostate, colon, gastric, pulmonary, and uterine cancers. Since HSP overexpression is often associated with poor prognosis and lymph node metastasis, this effect highlights the potential of berberine hydrochloride in limiting cancer progression [11]. Despite its wide spectrum of pharmacological actions and therapeutic promise, the clinical performance of BBR is often compromised by its poor bioavailability [12]. Limited absorption and rapid metabolic transformation are considered the main reasons behind this drawback, prompting research efforts to improve its systemic availability [13].

Structurally, BBR contains a quaternary base, and for clinical applications it is usually formulated as salts such as berberine sulfate or berberine chloride, with these forms showing acceptable efficacy in clinical trials [2]. In recent years, advanced drug delivery systems (DDS) based on nanotechnology have been developed to enhance the therapeutic profile of BBR. These systems are intended to reduce systemic toxicity, enhance solubility and stability, boost bioavailability, provide regulated drug release, and encourage drug accumulation at target locations. Such strategies have significantly advanced therapeutic approaches for inflammatory bowel disease (IBD) and related conditions [14].

How Berberine affects inflammatory bowel disease and molecular pathways for treating colitis?

BBR exhibits strong anti-inflammatory properties, which supports its therapeutic potential in conditions linked to chronic inflammation, including inflammatory bowel disease (IBD) [2]. Administration of the compound promotes anti-inflammatory mediators, including interleukin-10 (IL-10) and transforming growth factor-β (TGF-β), while simultaneously suppressing pro-inflammatory cytokines such as interleukin-6 (IL-6), interleukin-1β (IL-1β), and tumor necrosis factor-α (TNF-α) [15].

Berberine has been shown to exert protective effects by regulating the Nrf2 signaling pathway. As a crucial cellular defense mechanism against oxidative stress, Nrf2 activation also supports anti-inflammatory responses, making it a valuable molecular target for managing colitis and related inflammatory conditions [16]. Additionally, berberine modulates the MAPK signaling pathway, which plays a central role in cytokine production. Activation of this pathway by inflammatory stimuli can increase pro-inflammatory mediators such as TNF-α, IL-1β, and IL-6, while affecting anti-inflammatory cytokines like IL-10.

Elevated MAPK activity has been associated with intestinal epithelial damage in inflammatory bowel disease. Earlier research further linked this activation to increased inducible nitric oxide synthase (iNOS) expression in gut inflammation [17].

Since the MAPK cascade governs the balance between pro- and anti-inflammatory cytokines, its dysregulation contributes to the pathogenesis of IBD, while restoring its equilibrium helps maintain gastrointestinal integrity. Notably, BBR treatment was found to significantly downregulate MAPK activity, thereby alleviating inflammatory responses [1]. Furthermore, by activating AMP-activated protein kinase (AMPK), BBR enhances the results of colitis. This happens via inhibiting oxidative phosphorylation, which in turn lowers CD4+ T cell production of IL-17A and interferon-γ (IFN-γ) [2].

In patients with ulcerative colitis (UC), alterations in gut microbiota composition contribute to impaired intestinal barrier function, resulting in enhanced epithelial permeability and activation of inflammatory responses [18]. Clinical observations also indicate a reduction in probiotic populations among UC patients, despite their established role in strengthening immune defense and promoting mucosal repair [19, 20]. Interestingly, treatment with BBR has been reported to modify gut microbial communities, leading to reduced diversity and a decline in specific bacterial groups such as Desulfovibrio, Eubacterium, and Bacteroides [21].

BBR exhibits powerful anti-inflammatory properties, and supplementing with it lowers important pro-inflammatory cytokines such TNF-α, IL-1, and IL-6 in colitis models [15]. At the molecular level, evidence suggests that BBR exerts therapeutic effects by upregulating STAT3 expression, which in turn suppresses the NF-κB signaling pathway, a critical mediator of intestinal inflammation [22].

Inflammatory cell infiltration, particularly by macrophages, plays a pivotal role in driving IBD pathology. These cells migrate into the intestinal mucosa, where they contribute to tissue damage through degradation of the extracellular matrix and the release of reactive oxygen and nitrogen metabolites [23]. Multiple studies have further shown that BBR alleviates colitis by preventing colon shortening, enhancing mucosal integrity, lowering inflammatory cytokine levels, and reducing the disease activity index (DAI) [24]. One of the major complications of chronic colitis is the heightened risk of developing colorectal cancer, which can arise as a long-term consequence of persistent inflammation [25].

Other therapeutic effects of berberine:

Antioxidant effect of berberine: Berberine's antioxidant action is mediated through the Nrf2 signaling pathway. Excessive reactive oxygen species buildup is a sign of oxidative stress, which damages DNA, proteins, and lipids both structurally and functionally. BBR has demonstrated considerable ability to counteract these harmful effects by reducing oxidative stress levels. The antioxidant activity of BBR is largely attributed to its regulation of the Nrf2 signaling pathway, which enhances the body's antioxidant defense mechanisms and provides protection against oxidative injury [26].

Hepatoprotective effect of berberine: BBR has been demonstrated to activate the Nrf2 signaling pathway in animal models of nonalcoholic fatty liver disease (NAFLD), which results in decreased body and liver weight, attenuation of hepatic steatosis, and improvement of antioxidant defenses through increased glutathione (GSH) and superoxide dismutase (SOD) levels [27].

Neuroprotective effect of berberine: The rising prevalence of neurological disorders highlights the need for novel therapeutic agents, and BBR has emerged as a promising candidate. In a rat model of paclitaxel (PTX)-induced peripheral neuropathic pain. **Singh *et al.*** investigated the neuroprotective role of BBR. Their findings revealed that BBR administration prolonged tail-flick and cold allodynia latency times, while lowering histopathological damage scores. Furthermore, BBR reduced lipid peroxidation and increased SOD and GSH levels in the sciatic nerve. The Nrf2 signaling pathway was mostly responsible for these protective benefits [28].

Nephroprotective effect of berberine: BBR has strong protective action against nephrotoxicity brought on by methotrexate (MTX). By raising SOD and GSH levels, it improves antioxidant capacity while significantly reducing serum creatinine, urea, uric acid, and kidney weight. Furthermore, BBR raises serum albumin levels, this effect is mostly due to Nrf2 signaling pathway activation [29].

Lung-protective effect of berberine: BBR also exhibits protective properties in lipopolysaccharide (LPS)-induced acute lung injury. Treatment with BBR reduces inflammatory mediators such as IL-6 and IL-8, decreases reactive oxygen species (ROS) generation, alleviates pulmonary edema, limits neutrophil infiltration, and mitigates endoplasmic reticulum (ER) stress [30].

Antidiabetic effect of berberine: Diabetes is a long-term metabolic disorder with a steadily increasing global prevalence and projections suggest a sharp rise in affected individuals by 2030. Berberine (BBR), a natural bioactive compound, has shown strong potential in both the prevention and management of this condition. Its preventive properties against oxidative imbalance and mitochondrial malfunction in diabetic neuropathy are demonstrated by experimental studies. By primarily activating the Nrf2 signaling pathway,

BBR treatment was observed to decrease neuronal damage and neuroinflammation [(31)].

Antitumor effect of berberine: Ni and associates looked at how berberine (BBR) affected K1 cells from papillary thyroid carcinoma that were subjected to high glucose levels. According to their findings, BBR dramatically reduced the growth of these HG-induced cancer cells. This effect was partially ascribed to the Nrf2 signaling pathway being activated [(32)].

Berberine and covid 19 disease: Two independent studies have highlighted the therapeutic potential of berberine (BBR) in COVID-19 management. Evidence suggests that BBR primarily targets the NF-κB and MAPK signaling pathways, both of which play a central role in regulating cytokine storms. BBR significantly reduced the production of proinflammatory cytokines and chemokines such IL-1, IL-6, and IL-8 in human lung epithelial cells infected with SARS-CoV-2 [(33)]. Furthermore, BBR treatment at a daily dose of 900 mg for 14 days significantly decreased blood levels of TNF-α, IL-6, and C-reactive protein (CRP) in COVID-19 patients who presented with diarrhea, according to clinical results [(21)].

Funding: No funding.
Conflict of interest: The authors had nothing to declare.

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