



REVIEW

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Effect of berberine on irritable bowel syndrome: A symptom-based review

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ABSTRACT

Phytotherapeutic applications have gained a place in the symptomatic treatment of irritable bowel syndrome, one of the most common diseases globally among functional bowel diseases. This study aimed to compile evidence regarding the efficacy of berberine in relieving the symptoms of irritable bowel syndrome. In this review, the electronic databases of PubMed, Google Scholar, MEDLINE, and Web of Science were used, and current publications were searched without any language restrictions. The screening was performed by first performing a general search using the keyword "berberine and irritable bowel syndrome", followed by individual searches for each symptom. Although there are many preclinical studies investigating the effect of berberine on the gastrointestinal tract, human studies are still limited. Studies show that berberine may positively affect abdominal pain, diarrhea, inflammation, microbiota, and visceral hypersensitivity, although the mechanisms of action are not yet clear. However, available data suggest that the therapeutic use of berberine in irritable bowel syndrome may be limited to the predominant type of diarrhea and selected patients whose symptoms are evaluated individually. Evidence presented in this paper needs to be further supported by human clinical studies.

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1. Introduction

Irritable bowel syndrome (IBS) is a chronic functional bowel disease with an uncertain etiology and characterized by upper and lower gastrointestinal symptoms, such as chronic or recurrent fluctuating abdominal pain, changes in bowel habits (constipation/diarrhea), and dyspeptic complaints (meteorism, bloating, burping) (Longstreth et al., 2006). It has been reported that psychosocial factors, gut microbiota, diet, genetics, and inflammatory factors may play a role in the etiology of IBS (Soares, 2014). Recently, additional potential mechanisms of IBS, including gut microbiota alteration and low-grade inflammation/immune activation, have emerged, and the importance of gut microbiota in the etiology of the disease has been emphasized (Habtemariam, 2020; Longstreth et al., 2006).

Since there is still no diagnostic test or structural or biochemical markers specific to IBS, its diagnosis is made by excluding other

organic diseases with similar manifestations and evaluating patient symptoms according to the Rome IV criteria. According to the Bristol stool chart scores within the Rome IV diagnostic criteria, IBS is divided into four groups as "IBS with predominant diarrhea", "predominant constipation", "mixed bowel habits", and "unclassified" (IBS-D, IBS-C, IBS-M, and IBS-U, respectively) (Schmulson and Drossman, 2017). Among the functional bowel diseases, IBS is one of the most common diseases globally, with an approximate prevalence of 11.2% (Lovell and Ford, 2012; Ooi et al., 2019). Many outpatient visits, excessive examinations, unnecessary drug treatment, and the inability to obtain satisfactory results until IBS diagnosis causes a significant increase in health costs and loss of workforce (Inadomi et al., 2003; Longstreth et al., 2003).

In the symptomatic treatment of IBS, antispasmodics (otilonium bromide, mebeverine, alverine, and trimebutine) are used for abdominal pain (Clavé et al., 2011). It is known that in cases where constipation is dominant, fibrous supplements can be used in mild and moderate cases, and linaclotide and lubiprostone can relieve patients' symptoms through their effects on meteorism, abdominal pain, constipation severity, and stool consistency (Drossman et al., 2009; Chey et al., 2012). In treating diarrheal cases, the constipating side effects of bile-binding resins, such as cholestyramine,

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antidiarrheal agents (loperamide, etc.), or tricyclic antidepressants are used (Khan and Chang, 2010; Can and Yilmaz, 2015). Complementary/alternative medicine applications are also included in the treatment of IBS, and their use rate reaches 48% (Langmead et al., 2002). Other treatment modalities include acupuncture, cognitive behavioral therapy, and hypnosis (Payne and Blanchard, 1995; Webb et al., 2007; Palsson and Whitehead, 2013).

The most problematic stage in IBS management is treatment, and a step-by-step approach is recommended (Table 1) (Mansueto et al., 2015; Akyuz, 2016; Schmulson and Drossman, 2017). It is also reported that pharmacotherapeutic agents should be avoided in asymptomatic periods (Talley and Spiller, 2002).

Table 1. Step-by-step therapy for IBS symptoms

Symptom	Treatment methods	Primary treatment	Secondary treatment
Abdominal pain	Drug therapy	Antispasmodic	TCA SSRI
	Complementary therapy	Peppermint oil	Acupuncture Hypnosis Psychotherapy
Abdominal distention	Drug therapy	Antispasmodic Simethicone Activated carbon Bismuth subsalicylate Pancreatic enzyme replacement	Rifaximin Probiotics 5-HT4 agonists TCA
	Complementary therapy	Low-carb diet Fennel Chamomile	
Diarrhea	Drug therapy	Opioid agonists Bile acid sequestrants Probiotics Antibiotics	5-HT3 agonists
	Complementary therapy	Gluten-free diet FODMAP diet Fibrous foods in mild to moderate cases Laxatives (polyethylene glycol, magnesium) Mixed opioid antagonists	5-HT4 agonists Secretagogue Lubiprostone
Constipation	Drug therapy	Psyllium Calcium channel activators Guanylate cyclase C agonists	Linaclootide Prucalopride
	Complementary therapy	Fibrous supplements, senna	

TCA: Tricyclic antidepressants, SSRI: Selective serotonin reuptake inhibitors, FODMAP: The low-fermentable oligo-, di-, and monosaccharide and polyol

Active ingredients obtained from plants have been used to treat diseases since ancient times, and the transfer of herbal-derived active ingredients to modern treatment is becoming increasingly common (Kidd, 2009). With the introduction of the new complexing technique "phytosome", it is now possible to facilitate the absorption and increase the bioavailability of plant-derived active substances with long side chains and high polarity it is possible to (Scalbert and Williamson, 2000). However, the bioavailability of such substances is reduced due to their first-pass effect in the liver and intestine. Therefore, to use berberine (BBR) in treatment, it is appropriate to use the phytosome formulation developed as a drug delivery system for this chemical (Yu et al., 2017).

Berberine (C₂₀H₁₇ONO₅) is a quaternary benzyloquinoline alkaloid that can be obtained from many different plants, such as *Berberis vulgaris*, *B. aquifolium*, *Hydrastis canadensis*, *Coptis chinensis*, and it has been used in diabetes, cancer, depression, and central nervous system diseases in recent years (Kulkarni and Dhir, 2010; Liang et al., 2019; Wang et al., 2020). In addition, recent studies reported very successful results in the use of BBR in the treatment of IBS-D (Sun et al., 2014).

In this study, a review of the literature was conducted to present available evidence regarding the efficacy of BBR on IBS symptoms.

2. Materials and methods

In the research strategy of this review, the electronic databases of PubMed, Google Scholar, MEDLINE, and Web of Science were used, and all publications until August 2021 were searched without language restrictions. First, a general screening was performed with the keyword "berberine and irritable bowel syndrome", and then

each symptom was searched individually using the following keywords: "berberine and abdominal pain", "berberine and diarrhea", "berberine and visceral hypersensitivity", "berberine and microbiota", "berberine and anti-inflammatory", and "berberine and antinociceptive" berberine and motility".

3. Results and discussion

3.1. Effects of BBR on IBS symptoms

3.1.1. Abdominal pain and distention

Abdominal pain is common in IBS, and studies have shown that BBR may potentially affect visceral analgesia, particularly due to its antinociceptive effect on visceral hypersensitivity. It is considered that the analgesic effect of BBR may be related to nitric oxide and its antioxidant and anti-inflammatory activity (Hu et al., 2009; Tang et al., 2013; Kim, 2015). In the visceral pain model, BBR has been reported to reduce pain by acting on opioid receptors. BBR increased mu- and delta-opioid receptor expression in the mouse gut and rat fetal cortical neurons (Chen et al., 2015a).

In a randomized, double-blind, placebo-controlled clinical study conducted by Chen et al. (2015b), the effect of BBR hydrochloride on clinical symptoms in IBS-D was investigated. A total of 132 patients participated in the study, and two study groups were formed, with one being orally given 200 mg BBR hydrochloride (n = 70) twice a day for eight weeks (400 mg in total) or the other being designated as the placebo (n = 62). BBR hydrochloride was shown to significantly reduce the frequency of diarrhea, abdominal pain, and the need for urgent defecation. The authors also reported that they observed an improvement trend with the use of BBR hydrochloride

in the IBS symptom, depression, anxiety, and quality of life scores (Chen et al., 2015b). However, in another clinical study, gas, and meteorism were reported as common side effects of BBR, and it was suggested that these side effects might be due to the "acarbose-

like" effects of this chemical on intestinal α -glucosidase (Di Pierro et al., 2020).

Table 2. Effects of BBR on IBS symptoms

Abdominal pain and distention			
Effects	The pathway that might play a role	Recovery outcomes	Studies
Antinociceptive	Nitric oxide	Pain threshold was significantly increased in male Sprague-Dawley rats administered BBR (50 mg/kg, i.p., once daily). Aminoguanidine reversed this effect. The BBR and BBR + aminoguanidine (nitric oxide synthetase inhibitor) groups showed reduced defecation, but aminoguanidine alone did not reduce defecation.	Tang et al. (2013)
Antinociceptive Anti-inflammatory Anti-oxidant Anti-inflammatory	Myeloperoxidase and malondialdehyde activities E-selectin Thromboxane B2	Berberine alleviated allodynia induced by CCI, a neuropathic pain model, and its anti-inflammatory and antioxidative properties contributed to the antiallodynic effect of CCI. Berberine downregulated E-selectin expression and decreased the content of TXB (2), effectively reducing the inflammatory response, thus relieving intestinal dysfunction via multiple pathways.	Kim et al. (2015) Hu et al. (2009)
Antinociceptive	Mu- and delta-opioid receptors	BBR increased mu and delta-opioid receptor expression in the mouse gut and rat fetal cortical neurons. It prolonged gastrointestinal transit and time to diarrhea reduced visceral pain. A randomized, double-blind, placebo-controlled human study (n = 132). Berberine hydrochloride 200 mg twice daily reduced the frequency of diarrhea, abdominal pain, and urgency to defecate.	Chen et al. (2015a) Chen et al. (2015b)
Diarrhea			
Inhibition of gastrointestinal motility and/or visceral hypersensitivity	Upregulation of somatostatin and glucagon-like peptide-1 and downregulation of motilin and gastrin levels Inhibition of NF- κ B Reduction of pro-inflammatory cytokine production	BBR-based nutraceuticals (twice a day, 250 mg for 90 days) reduced diarrhea by 50-70% after 30 days and by 70 to 80% after 90 days in 39 patients with functional diarrhea or diarrhea-predominant irritable bowel syndrome Reduced smooth muscle contraction and intestinal motility and delayed intestinal transit time Reduced bowel motility Reduced ileum mucosa inflammation	Di Pierro et al. (2020) Feng et al. (2013) Yu et al. (2019)
Anti-secretory	Decrease Cl(-) secretion Blockade of K+ channels	The effects of protoberberine alkaloid palmatine on active ion transport across the rat colonic epithelium were evaluated. Palmatine inhibited SK4 K(+) channels and decreased Ca(2+) activated Cl(-) secretion BBR inhibited carbachol-induced 86Rb+ efflux and K+ conductivity in the resected mucosa	Wu et al. (2008) Taylor et al. (1999)
Reducing epithelial permeability Effect on microbiota	Tight junctions Antimicrobial	It produced a dose-dependent increase in transepithelial electrical resistance in Caco-2 cells. The IC ₅₀ , minimum inhibitory concentration, minimum microbicidal concentration, and minimum microbiostatic concentration of BBR were evaluated, and the sensitivity was reported in the following order: <i>S. aureus</i> > <i>P. aeruginosa</i> S (sensitive) > <i>E. coli</i> S > <i>P. aeruginosa</i> R (resistant) > <i>E. coli</i> R > <i>B. subtilis</i> > <i>Z. ramigera</i> > <i>C. albicans</i> > <i>S. cerevisiae</i> It reduced the growth and adhesion of <i>E. coli</i> (90% reduction in adhesion). Berberine hydrochloride (100 mg, four times daily) reduced stool volume with diarrhea and stool cyclic adenosine monophosphate concentration by 77% in patients with cholera. A single oral dose of 400 mg of berberine reduced mean stool volume after treatment in patients with <i>E. coli</i> infection and cholera.	Gu et al. (2009) Čerňáková and Košťálová (2002) Sun et al. (1988) Khin et al. (1985) Rabbani et al. (1987)
Anti-inflammatory	Fecal microbiota (<i>Faecalibacterium</i> and <i>Bifidobacterium</i>) Inhibition of cytokines Stimulation of AMP-activated protein kinase Mitogen-activated protein kinase pathway Activation of the PPAR γ pathway	Partially reversed Kupfer cell hyperplasia and <i>Faecalibacterium</i> by modulating the gut microbiome composition. Inhibited IL-8 production in colonic epithelial cells Downregulated TNF, IFN- γ , KC, and IL-17 in wild-type C57BL/6 mice Significantly suppressed TNF- α elevation in colitis induced by TNBS The inhibitory effects of BBR on proinflammatory responses were eliminated by AMPK inhibition In infected macrophages, BBR deactivated ERK1/2, resulting in the time-dependent activation of p38 MAPK. Inhibited the overexpression of inducible COX-2 in the ileal mucosa	Jia et al. (2019) Zhou and Mineshita (2000) Yan et al. (2012) Zhang et al. (2011) Jeong et al. (2009) Saha et al. (2011) Feng et al. (2012)
Constipation			
Adverse events	Antidiarrheal activity	Mild to moderate constipation was the most frequently reported side effect	Yin et al. (2008), Zhang et al. (2008), Zhang et al. (2019), Chen et al. (2020)

BBR: Berberine, IBS: Irritable bowel syndrome, CCI: Chronic constriction injury, TXB (2): Thromboxane B2, NF- κ B: Nuclear Factor kappa B, TNF: Tumor necrosis factor, IFN- γ : Interferon gamma, IL-17: Interleukin 17

3.1.2. Diarrhea

Many studies have shown that BBR can prevent diarrhea with different mechanisms of action. In addition to its antimicrobial effect, studies show that it plays a role in ion transport, especially in secretory diarrhea. BBR strengthens tight junctions in the Caco-2 cell line, reducing intestinal epithelial permeability and significantly increasing transepithelial electrical resistance. It also reduces epithelial permeability in the intestine (Khin et al., 1985; Rabbani et al., 1987; Sun et al., 1988; Taylor et al., 1999; Wu et al., 2008; Gu et al., 2009).

In a retrospective clinical study conducted by Di Pierro et al. (2020), 39 patients with functional diarrhea or IBS-D that used a BBR-based nutraceutical (twice a day, 250 mg for 90 days) were evaluated. It was reported that after 30 days of BBR use, diarrhea was reduced by 50-70%, and this rate of decrease reached 70 to 80% at the end of 90 days. The study results confirmed the antidiarrheal properties of BBR and provided evidence for its use in some functional intestinal diseases characterized by the frequent defecation of mushy and/or watery stool (Di Pierro et al., 2020).

3.1.2.1. Gastrointestinal motility and/or visceral hypersensitivity

BBR has been shown to significantly reduce smooth muscle contraction and intestinal motility and delay intestinal transit time. The inhibitory effect of BBR has been potentially explained by the upregulation of somatostatin and glucagon-like peptide-1 and the downregulation of motilin and gastrin levels (Feng et al., 2013).

In a mouse study conducted to demonstrate the mechanism of action of BBR, mice with IBS and intestinal inflammation were orally administered BBR, which was shown to reduce intestinal mucosal inflammation by inducing nuclear factor kappa-B (NF- κ B). BBR was reported to decrease the expression of pro-inflammatory cytokines [interleukin (IL)-1 β , IL-6, interferon- γ , and tumor necrosis factor- α] and promote the expression of anti-inflammatory cytokines (IL-10 and transforming growth factor- β). It was also noted to improve terminal ileum tissue inflammation and reduce intestinal motility (Yu et al., 2019).

In a randomized study on 50 mice with IBS and intestinal inflammation, the effect of BBR on visceral hypersensitivity was investigated. The authors reported that the group given BBR had improved visceral hypersensitivity compared to the placebo group, and it was suggested that this might have been mediated by nitric oxide (Tang et al., 2013).

3.1.2.2. Microbiota

Symbiont and pathobiont compositions show a balanced distribution in the microbiota of healthy individuals (Round and Mazmanian, 2009). Healthy nutrition and probiotics can positively affect the colon microbiota (Delzenne and Bindels, 2019). Studies have shown that one of the most important effects of BBR is its ability to alter gut microbiota composition. Similar to probiotics, including *Bifidobacterium adolescentis* and *Lactobacillus acidophilus*, it has been reported that BBR can induce cell death in harmful intestinal bacteria while increasing the composition of beneficial bacteria (Čerňáková and Košťálová, 2002). In addition, in another study investigating the effects of the IBS-D gut microbiome on the liver, it was emphasized that IBS-D was not only a functional bowel disease but could also cause inflammation in the liver. It has also been found that BBR can partially reverse Kupffer cell hyperplasia

and inflammation in the liver by modulating the gut microbiome composition (Jia et al., 2019).

3.1.2.3. Anti-inflammatory effects

Many studies show that BBR can positively affect colitis (Zhou and Mineshita, 2000; Yan et al., 2012) and must provide evidence that the anti-inflammatory mechanism of action is mainly through inhibiting cytokine pathways. Zhou and Mineshita (2000) reported that BBR inhibited IL-8 production in colonic epithelial cells by suppressing IFN- γ and IL-17 production (Zhou and Mineshita, 2000). In addition, different studies have demonstrated that BBR inhibits the expression of proinflammatory cytokines (IL-1 β , IL-6, and TNF) and may indirectly affect inflammatory pathways mediated by MAPK, AP-1, TLR4, and NF- κ B (Jeong et al., 2009; Saha et al., 2011; Zhang et al., 2011; Yan et al., 2012). Moreover, BBR is a potent inhibitor of inducible COX-2, reducing COX-2 levels and attenuating colitis *in vivo* (Feng et al., 2012).

3.1.3. Constipation

The antidiarrheic effects of BBR have limited use in IBS cases with the predominant type of diarrhea (Sun et al., 2014). In clinical studies on BBR in different patient populations, mild to moderate constipation is the most frequently reported side effect (Yin et al., 2008). In a clinical study in which 116 patients with type 2 diabetes with dyslipidemia were randomized to the BBR and placebo groups, five participants in the BBR group (1.0 g daily) experienced mild to moderate constipation (Zhang et al., 2008). In another study that systematically evaluated the efficacy and safety of BBR for the treatment of hyperlipidemia, the rate of constipation was reported to be higher in the BBR group than in the control group (Zhang et al., 2019). Similarly, in another clinical research investigating the clinical potential and safety of BBR in the prevention of colorectal adenoma recurrence, constipation was determined to be the most common adverse event (1% in the BBR group and <0.5% in the placebo group) (Chen et al., 2020) (Table 2).

Although there are many preclinical studies investigating the effect of BBR on the gastrointestinal tract, human studies are still limited. Current studies have shown that BBR may positively affect abdominal pain, diarrhea, inflammation, microbiota, and visceral hypersensitivity. However, the mechanisms of action of this chemical have not yet been clarified. BBR has a wide spectrum of effects on the gastrointestinal tract, and in this review, its effect on IBS was evaluated by considering each symptom separately. Studies show that the use of BBR in IBS may be limited only to the predominant type of diarrhea, and constipation appears as a side effect. Although many preclinical studies report that BBR reduces abdominal pain, another symptom of IBS, and has an antinociceptive effect, it should be used with caution, especially in patients with distention.

4. Conclusions

Existing studies provide evidence for the use of BBR as a drug in IBS-D and show that it can be beneficial when used in selected patients. However, the evidence presented in this paper needs to be supported by further human studies to evaluate the efficacy and side-effect profile at different doses, examine the interaction with other drugs, and investigate the effects on other comorbidities.

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Conflict of interest

The author declares that there is no conflict of interest regarding the publication of this paper.

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Supplementary File

None.

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