Int. J. Plant Bas. Pharm. (2022) 2(2), 190-195

INTERNATIONAL JOURNAL OF PLANT BASED PHARMACEUTICALS

https://ijpbp.com

REVIEW

OPEN ACCESS

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

Ibrahim Bashan[a,*]

[a] *Mersin University, Medical Faculty of Mersin University, Department of Medical Education, 33343, Mersin, Turkey*

ARTICLE INFO

Article History:

Received: 08 March 2022
Revised: 16 April 2022
Accepted: 19 April 2022
Available online: 20 April 2022

Edited by: B. Tepe

Keywords:
Diarrhea
Abdominal pain
Motility
Phytotherapy

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.

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,

* Corresponding author:
E-mail address: ibashan@yahoo.com (I. Bashan)
e-ISSN: 2791-7509
doi: https://doi.org/10.55484/ijpbp.1084455

Please cite this article as: Bashan, I., 2022. Effect of berberine on irritable bowel syndrome: A symptom-based review. International Journal of Plant Based Pharmaceuticals, 2(2), 190-195, https://doi.org/10.55484/ijpbp.1084455.

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	Rifaximin
		Simethicone	Probiotics
		Activated carbon	5-HT4 agonists
		Bismuth subsalicylate	TCA
		Pancreatic enzyme replacement	
	Complementary therapy	Low-carb diet	
		Fennel Chamomile	
Diarrhea	Drug therapy	Opioid agonists	5-HT3 agonists
		Bile acid sequestrants	
		Probiotics	
		Antibiotics	
	Complementary therapy	Gluten-free diet	
		FODMAP diet	
		Fibrous foods in mild to moderate cases	5-HT4 agonists
		Laxatives (polyethylene glycol, magnesium)	Secretagogue
		Mixed opioid antagonists	Lubiprostone
Constipation	Drug therapy	Psyllium	Linaclotide
		Calcium channel activators	Prucalopride
		Guanylate cyclase C agonists	
	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 ($C_{20}H_{17}ONO_5$) is a quaternary benzylisoquinoline 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	Myeloperoxidase and malondialdehyde activities	Berberine alleviated allodynia induced by CCI, a neuropathic pain model, and its anti-inflammatory and antioxidative properties contributed to the antiallodynic effect of CCI.	Kim et al. (2015)
Anti-inflammatory	E-selectin Thromboxane B2	Berberine downregulated E-selectin expression and decreased the content of TXB (2), effectively reducing the inflammatory response, thus relieving intestinal dysfunction via multiple pathways.	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.	Chen et al. (2015a)
		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. (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	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	Di Pierro et al. (2020)
	Inhibition of NF-κB	Reduced smooth muscle contraction and intestinal motility and delayed intestinal transit time	Feng et al. (2013)
	Reduction of pro-inflammatory cytokine production	Reduced bowel motility Reduced ileum mucosa inflammation	Yu et al. (2019)
Anti-secretory	Decrease Cl(-) secretion	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	Wu et al. (2008)
	Blockade of K+ channels	BBR inhibited carbachol-induced 86Rb+ efflux and K+ conductivity in the resected mucosa	Taylor et al. (1999)
Reducing epithelial permeability	Tight junctions	It produced a dose-dependent increase in transepithelial electrical resistance in Caco-2 cells.	Gu et al. (2009)
Effect on microbiota	Antimicrobial	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: *S. aureus* > *P. aeruginosa* S (sensitive) > *E. coli* S > *P. aeruginosa* R (resistant) > *E. coli* R > *B. subtilis* > *Z. ramigera* > *C. albicans* > *S. cerevisiae*	Čerňáková and Košťálová (2002)
		It reduced the growth and adhesion of *E. coli* (90% reduction in adhesion).	Sun et al. (1988)
		Berberine hydrochloride (100 mg, four times daily) reduced stool volume with diarrhea and stool cyclic adenosine monophosphate concentration by 77% in patients with cholera.	Khin et al. (1985)
		A single oral dose of 400 mg of berberine reduced mean stool volume after treatment in patients with *E. coli* infection and cholera.	Rabbani et al. (1987)
	Fecal microbiota (*Faecalibacterium* and *Bifidobacterium*)	Partially reversed Kupfer cell hyperplasia and *Faecalibacterium* by modulating the gut microbiome composition.	Jia et al. (2019)
Anti-inflammatory	Inhibition of cytokines	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	Zhou and Mineshita (2000) Yan et al. (2012) Zhang et al. (2011)
	Stimulation of AMP-activated protein kinase	The inhibitory effects of BBR on proinflammatory responses were eliminated by AMPK inhibition	Jeong et al. (2009)
	Mitogen-activated protein kinase pathway	In infected macrophages, BBR deactivated ERK1/2, resulting in the time-dependent activation of p38 MAPK.	Saha et al. (2011)
	Activation of the PPARγ pathway	Inhibited the overexpression of inducible COX-2 in the ileal mucosa	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:İrritable bowel syndrome, CCI: Chronic constriction injury, TXB (2): Thromboxane B2, NF-κB: 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-κB). BBR was reported to decrease the expression of pro-inflammatory cytokines [interleukin (IL)-1β, 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-1β, IL-6, and TNF) and may indirectly affect inflammatory pathways mediated by MAPK, AP-1, TLR4, and NF-κB (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.

Acknowledgments

None.

Conflict of interest

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

CRediT authorship contribution statement

Ibrahim Bashan: Data analysis, Manuscript writing

ORCID Numbers of the Authors

I. Bashan: 0000-0002-0034-2727

Supplementary File

None.

References

Akyuz, F., 2016. İrritabl Barsak Sendromu. *Güncel Gastroenteroloji Dergisi*; 20(4), 415-420.

Can, G., Yılmaz, B., 2015. İrritabl bağırsak sendromunun tanı ve tedavisinde yaklaşımlar. *Güncel Gastroenteroloji Dergisi*, 19(3), 181-191.

Čerňáková, M., Košťálová, D., 2002. Antimicrobial activity of berberine—A constituent ofMahonia aquifolium. *Folia Microbiologica*, 47(4), 375-378.

Chen, C., Lu, M., Pan, Q., Fichna, J., Zheng, L., Wang, K., Kreis, M., 2015a. Berberine improves intestinal motility and visceral pain in the mouse models mimicking diarrhea-predominant irritable bowel syndrome (IBS-D) symptoms in an opioid-receptor dependent manner. *PLoS One*, 10(12), e0145556.

Chen, C., Tao, C., Liu, Z., Lu, M., Pan, Q., 2015b. A randomized clinical trial of berberine hydrochloride in patients with diarrhea-predominant irritable bowel syndrome. *Phytotherapy Research*, 29(11), 1822-1827.

Chen, Y.X., Gao, Q.Y., Zou, T.H., Wang, B.M., Liu, S.D., Sheng, J.Q., Fang, J.Y., 2020. Berberine versus placebo for the prevention of recurrence of colorectal adenoma: a multicentre, double-blinded, randomised controlled study. *The Lancet Gastroenterology & Hepatology*, 5(3), 267-275.

Chey, W.D., Lembo, A.J., Lavins, B.J., Shiff, S.J., Kurtz, C.B., Currie, M.G., Johnston, J.M., 2012. Linaclotide for irritable bowel syndrome with constipation: a 26-week, randomized, double-blind, placebo-controlled trial to evaluate efficacy and safety. *Official Journal of the American College of Gastroenterology | ACG*, 107(11), 1702-1712.

Clavé, P., Acalovschi, M., Triantafillidis, J.K., Uspensky, Y.P., Kalayci, C., Shee, V., OBIS Study Investigators., 2011. Randomised clinical trial: otilonium bromide improves frequency of abdominal pain, severity of distention and time to relapse in patients with irritable bowel syndrome. *Alimentary Pharmacology & Therapeutics*, 34(4), 432-442.

Delzenne, N.M, Bindels, B., 2019. Food for thought about manipulating gut bacteria. *Nature*, 577(7788), 32-34.

Di Pierro, F., Bertuccioli, A., Giuberti, R., Saponara, M., Ivaldi, L., 2020. Role of a berberine-based nutritional supplement in reducing diarrhea in subjects with functional gastrointestinal disorders. *Minerva Gastroenterologica e Dietologica*, 66(1), 29-34.

Drossman, D.A., Chey, W.D., Johanson, J.F., Fass, R., Scott, C., Panas, R., Ueno, R., 2009. Clinical trial: lubiprostone in patients with constipation-associated irritable bowel syndrome–results of two randomized, placebo-controlled studies. *Alimentary Pharmacology & Therapeutics*, 29(3), 329-341.

Feng, A.W., Gao, W., Zhou, G.R., Yu, R., Li, N., Huang, X.L., Li, J.S., 2012. Berberine ameliorates COX-2 expression in rat small intestinal mucosa partially through PPARγ pathway during acute endotoxemia. *International Immunopharmacology*, 12(1), 182-188.

Feng, Y., Li, Y., Chen, C., Lin, X., Yang, Y., Cai, H., Jia, Y., 2013. Inhibiting roles of berberine in gut movement of rodents are related to activation of the endogenous opioid system. *Phytotherapy Research*, 27(10), 1564-1571.

Gu, L., Li, N., Li, Q., Zhang, Q., Wang, C., Zhu, W., Li, J. (2009). The effect of berberine *in vitro* on tight junctions in human Caco-2 intestinal epithelial cells. *Fitoterapia*, 80(4), 241-248.

Habtemariam, S., 2020. Berberine pharmacology and the gut microbiota: A hidden therapeutic link. *Pharmacological Research*, 155, 104722.

Hu, Y., Chen, X., Duan, H., Hu, Y., Mu, X., 2009. Chinese herbal medicinal ingredients inhibit secretion of IL-6, IL-8, E-selectin and TXB2 in LPS-induced rat intestinal microvascular endothelial cells. *Immunopharmacology and Immunotoxicology*, 31(4), 550-555.

Inadomi, J.M., Fennerty, M.B., Bjorkman, D., 2003. The economic impact of irritable bowel syndrome. *Alimentary Pharmacology & Therapeutics*, 18(7), 671-682.

Jeong, H.W., Hsu, K.C., Lee, J.W., Ham, M., Huh, J.Y., Shin, H.J., Kim, J.B., 2009. Berberine suppresses proinflammatory responses through AMPK activation in macrophages. *American Journal of Physiology-Endocrinology and Metabolism*, 296(4), E955-E964.

Jia, Q., Zhang, L., Zhang, J., Pei, F., Zhu, S., Sun, Q., Duan, L., 2019. Fecal microbiota of diarrhea-predominant irritable bowel syndrome patients causes hepatic inflammation of germ-free rats and berberine reverses it partially. *BioMed Research International*, 2019, 4530203.

Khan, S., Chang, L., 2010. Diagnosis and management of IBS. *Nature Reviews Gastroenterology & Hepatology*, 7(10), 565-581.

Khin, M.U., Myo, K., Nyunt, N.W., Aye, K., Tin, U., 1985. Clinical trial of berberine in acute watery diarrhoea. *British Medical Journal (Clinical Research Ed.)*, 291(6509), 1601-1605.

Kidd, P.M., 2009. Bioavailability and activity of phytosome complexes from botanical polyphenols: the silymarin, curcumin, green tea, and grape seed extracts. *Alternative Medicine Review*, 14(3), 226-246.

Kim, H.J., 2015. Berberine ameliorates allodynia induced by chronic constriction injury of the sciatic nerve in rats. *Journal of Medicinal Food*, 18(8), 909-915.

Kulkarni, S.K., Dhir, A., 2010. Berberine: a plant alkaloid with therapeutic potential for central nervous system disorders. *Phytotherapy Research: An International Journal Devoted to Pharmacological and Toxicological Evaluation of Natural Product Derivatives*, 24(3), 317-324.

Langmead, L., Chitnis, M., Rampton, D.S., 2002. Use of complementary therapies by patients with IBD may indicate psychosocial distress. *Inflammatory Bowel Diseases*, 8(3), 174-179.

Liang, Y., Xu, X., Yin, M., Zhang, Y., Huang, L., Chen, R., Ni, J., 2019. Effects of berberine on blood glucose in patients with type 2 diabetes mellitus: a systematic literature review and a meta-analysis. *Endocrine Journal*, 66(1), 51-63.

Longstreth, G.F., Thompson, W.G., Chey, W.D., Houghton, L.A., Mearin, F., Spiller, R.C., 2006. Functional bowel disorders. *Gastroenterology*, 130(5), 1480-1491.

Longstreth, G.F., Wilson, A., Knight, K., Wong, J., Chiou, C.F., Barghout, V., Ofman, J.J., 2003. Irritable bowel syndrome, health care use, and costs: a US managed care perspective. *The American Journal of Gastroenterology*, 98(3), 600-607.

Lovell, R.M., & Ford, A.C., 2012. Global prevalence of and risk factors for irritable bowel syndrome: a meta-analysis. *Clinical Gastroenterology and Hepatology*, 10(7), 712-721.

Mansueto, P., Seidita, A., D'Alcamo, A., Carroccio, A., 2015. Role of FODMAPs in patients with irritable bowel syndrome. *Nutrition in Clinical Practice*, 30(5), 665-682.

Ooi, S.L., Correa, D., Pak, S.C., 2019. Probiotics, prebiotics, and low FODMAP diet for irritable bowel syndrome–What is the current evidence?. *Complementary Therapies in Medicine*, 43, 73-80.

Palsson, O.S., Whitehead, W.E., 2013. Psychological treatments in functional gastrointestinal disorders: a primer for the gastroenterologist. *Clinical Gastroenterology and Hepatology*, 11(3), 208-216.

Payne, A., Blanchard, E.B., 1995. A controlled comparison of cognitive therapy and self-help support groups in the treatment of irritable bowel syndrome. *Journal of Consulting and Clinical Psychology*, 63(5), 779-786.

Rabbani, G.H., Butler, T., Knight, J., Sanyal, S.C., Alam, K., 1987. Randomized controlled trial of berberine sulfate therapy for diarrhea due to enterotoxigenic *Escherichia coli* and *Vibrio cholerae*. *Journal of Infectious Diseases*, 155(5), 979-984.

Round, J.L., Mazmanian, S.K., 2009. The gut microbiota shapes intestinal immune responses during health and disease. *Nature Reviews Immunology*, 9(5), 313-323.

Saha, P., Bhattacharjee, S., Sarkar, A., Manna, A., Majumder, S., Chatterjee, M., 2011. Berberine chloride mediates its anti-leishmanial activity via differential regulation of the mitogen activated protein kinase pathway in macrophages. *PLoS One*, 6(4), e18467.

Scalbert, A., Williamson, G., 2000. Dietary intake and bioavailability of polyphenols. *The Journal of Nutrition*, 130(8), 2073S-2085S.

Schmulson, M.J., Drossman, D.A., 2017. What is new in Rome IV. *Journal of Neurogastroenterology and Motility*, 23(2), 151-163.

Soares, R.L., 2014. Irritable bowel syndrome: a clinical review. *World Journal of Gastroenterology: WJG*, 20(34), 12144-12160.

Sun, D., Abraham, S.N., Beachey, E.H., 1988. Influence of berberine sulfate on synthesis and expression of Pap fimbrial adhesin in uropathogenic *Escherichia coli*. *Antimicrobial Agents and Chemotherapy*, 32(8), 1274-1277.

Sun, S., Wang, K., Lei, H., Li, L., Tu, M., Zeng, S., Jiang, H., 2014. Inhibition of organic cation transporter 2 and 3 may be involved in the mechanism of the antidepressant-like action of berberine. *Progress in Neuro-Psychopharmacology and Biological Psychiatry*, 49, 1-6.

Talley, N.J., Spiller, R., 2002. Irritable bowel syndrome: a little understood organic bowel disease?. *The Lancet*, 360(9332), 555-564.

Tang, Q.L., Lai, M.L., Zhong, Y.F., Wang, A.M., Su, J.K., Zhang, M.Q., 2013. Antinociceptive effect of berberine on visceral hypersensitivity in rats. *World Journal of Gastroenterology: WJG*, 19(28), 4582-4589.

Taylor, C.T., Winter, D.C., Skelly, M.M., O'Donoghue, D.P., O'Sullivan, G.C., Harvey, B.J., Baird, A.W., 1999. Berberine inhibits ion transport in human colonic epithelia. *European Journal of Pharmacology*, 368(1), 111-118.

Wang, Z.C., Wang, J., Chen, H., Tang, J., Bian, A.W., Liu, T., Yang, F., 2020. Synthesis and anticancer activity of novel 9, 13-disubstituted berberine derivatives. *Bioorganic & Medicinal Chemistry Letters*, 30(2), 126821.

Webb, A.N., Kukuruzovic, R., Catto-Smith, A.G., Sawyer, S.M., 2007. Hypnotherapy for treatment of irritable bowel syndrome. *Cochrane Database of Systematic Reviews*, (4), CD005110.

Wu, D.Z., Yuan, J.Y., Shi, H.L., Hu, Z.B., 2008. Palmatine, a protoberberine alkaloid, inhibits both Ca^{2+}-and cAMP-activated Cl^- secretion in isolated rat distal colon. *British Journal of Pharmacology*, 153(6), 1203-1213.

Yan, F., Wang, L., Shi, Y., Cao, H., Liu, L., Washington, M.K., Polk, D.B., 2012. Berberine promotes recovery of colitis and inhibits inflammatory responses in colonic

macrophages and epithelial cells in DSS-treated mice. *American Journal of Physiology-Gastrointestinal and Liver Physiology*, 302(5), G504-G514.
Yin, J., Xing, H., Ye, J., 2008. Efficacy of berberine in patients with type 2 diabetes mellitus. *Metabolism*, 57(5), 712-717.
Yu, F., Ao, M., Zheng, X., Li, N., Xia, J., Li, Y., Chen, X.D., 2017. PEG–lipid–PLGA hybrid nanoparticles loaded with berberine–phospholipid complex to facilitate the oral delivery efficiency. *Drug Delivery*, 24(1), 825-833.
Yu, Z.C., Cen, Y.X., Wu, B.H., Wei, C., Xiong, F., Li, D.F., Yao, J., 2019. Berberine prevents stress-induced gut inflammation and visceral hypersensitivity and reduces intestinal motility in rats. *World Journal of Gastroenterology*, 25(29), 3956-3971.
Zhang, L.S., Zhang, J.H., Feng, R., Jin, X.Y., Yang, F.W., Ji, Z.C., Li, X.M., 2019. Efficacy and safety of berberine alone or combined with statins for the treatment of hyperlipidemia: a systematic review and meta-analysis of randomized controlled clinical trials. *The American Journal of Chinese Medicine*, 47(04), 751-767.
Zhang, M., Long, Y., Sun, Y., Wang, Y., Li, Q., Wu, H., Mei, Q., 2011. Evidence for the complementary and synergistic effects of the three-alkaloid combination regimen containing berberine, hypaconitine and skimmianine on the ulcerative colitis rats induced by trinitrobenzene-sulfonic acid. *European Journal of Pharmacology*, 651(1-3), 187-196.
Zhang, Y., Li, X., Zou, D., Liu, W., Yang, J., Zhu, N., Ning, G., 2008. Treatment of type 2 diabetes and dyslipidemia with the natural plant alkaloid berberine. *The Journal of Clinical Endocrinology & Metabolism*, 93(7), 2559-2565.
Zhou, H., Mineshita, S., 2000. The effect of berberine chloride on experimental colitis in rats *in vivo* and *in vitro*. *Journal of Pharmacology and Experimental Therapeutics*, 294(3), 822-829.

Reviewed by:

Jelena POPOVIC-DJORDJEVIC: University of Belgrade, Belgrade, SERBIA
Mir Babak BAHADORI: University of Tehran, Tehran, IRAN