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Effects of Berberine in the Gastrointestinal Tract — A Review of Actions and Therapeutic Implications

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Abstract: Berberine is an isoquinoline alkaloid present in several plant species, including *Coptis sp.* and *Berberis sp.* In traditional medicine, extracts of berberine are used in the treatment of diarrhea of different origins. Recent studies have shown that berberine and its derivatives have significant biological effects on gastrointestinal (GI) and other functions and may become therapeutics for the treatment of diarrhea, gastroenteritis, diabetes, hyperlipidemia, cardiovascular diseases and inflammatory conditions. This paper summarizes the current knowledge on the actions of berberine in the GI tract. Binding and target sites, activated intracellular pathways, as well as the absorption and metabolism of berberine are discussed. Effects that may be useful in future clinical treatment, like antidiarrheal, anti-inflammatory and antitumor effects are critically reviewed and potential clinical applications are presented in detail.

Keywords: Berberine; Gastrointestinal Disorders; Potential Therapeutics; Colon Cancer; Intracellular Pathways.

Introduction

Berberine is an isoquinoline alkaloid with the structure shown in Fig. 1. It is present in several plant species, which are common in the Eastern hemisphere, such as *Coptis chinensis* Franch., *Coptis japonica* Makino., *Berberis thunbergii* DC., *Hydrastis canadensis* L., and

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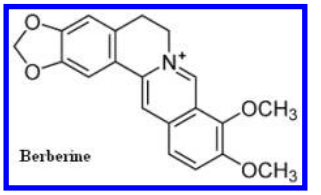

Figure 1. Structure of berberine.

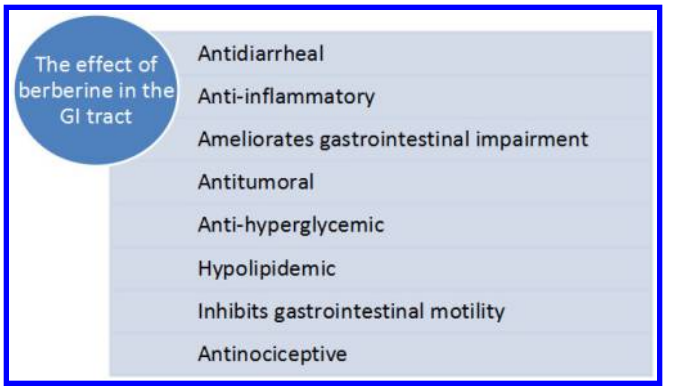

Figure 2. The effects of berberine in the GI tract.

Thalictrum lucidum Ait. It has a long history in traditional oriental medicine, where it has been used to treat diarrhea and gastroenteritis due to its antimicrobial, antimotility and antisecretory properties. Recent studies have shown that berberine and its derivatives also display a potent analgesic (Tang *et al.*, 2013), anti-inflammatory (Mo *et al.*, 2014) and anticancer activities (Tan *et al.*, 2011), and may have a potential therapeutic effect on diabetes (Hsu *et al.*, 2013), hyperlipidemia (Dong *et al.*, 2013), cardiovascular diseases (Derosa *et al.*, 2012), and CNS disorders (Bhutada *et al.*, 2011) (Fig. 2).

In this review, we discuss the pharmacological targets and intracellular mechanisms of action of berberine in the gut. We also explore potential clinical applications of berberine and its derivatives.

Anti-Diarrheal Action of Berberine

Berberine has been known principally for its antidiarrhoeal activity, which may derive from different mechanisms of action. Studies have shown that berberine decreases bacterial adherence to mucosal or epithelial surfaces (Sun *et al.*, 1988). Furthermore, berberine has a direct bactericidal effect on *V. cholera* (Khin *et al.*, 1985). It was also demonstrated that berberine is an effective and safe anti-secretory drug for diarrhea caused by microbial enterotoxins. For example, an animal study found that berberine reduces the intestinal secretion of water and electrolytes induced by the *cholera* toxin (Rabbani *et al.*, 1987).

A significant antimicrobial activity of berberine cannot fully account for its anti-diarrheal effect, especially in terms of secretory diarrhea. Indeed, studies have shown that berberine also influences the process of ion transport. Wu *et al.* (2008) found that the protoberberine alkaloid attenuates Cl− secretion through inhibition of basolateral SK4 K+ and apical CFTR channels. Moreover, Taylor *et al.* (1999) demonstrated that berberine exerts an anti-secretory effect directly upon epithelial cells and the mechanism of action may be at the level of a blockade of K+ channels. Furthermore, the expression of Na+/H+ exchanger (NHE) and AQP4 at mRNA and protein level were significantly increased in mice with experimental diarrhea and human intestinal epithelial cell lines treated with berberine (Zhang *et al.*, 2012b).

Recently, a novel mechanism has been suggested to explain the anti-diarrheal effect of berberine. It was found that berberine reinforces the tight junctions in the Caco-2 cell line, reduces epithelial permeability in the gut, and significantly increases transepithelial electrical resistance (Gu *et al.*, 2009).

Anti-Inflammatory Effect of Berberine in the GI Tract

There is a growing body of evidence indicating that berberine alleviates colitis. The compound was shown to decrease TNBS-induced colon bleeding, edema and lymphocyte infiltration in colon mucosa (Zhou and Mineshita, 2000). Animal studies also demonstrated that berberine is capable of attenuating mucosal damage and facilitating mucosal repair in DSS-induced colitis, and exerts inhibitory effects not only on mild (4-day after DSS), but also on severe colitis (7-day after DSS) (Yan *et al.*, 2012).

By now, several mechanisms underlying the anti-inflammatory action of berberine have been proposed. Berberine may improve colitis by inhibiting the growth of gram-negative intestinal bacteria, such as *E. coli, K. pneumonia* and *P. mirabilis* (Cernakova and Kostalova, 2002). Besides repressing or killing harmful gut bacteria, berberine has some positive effect on beneficial gut microbiota, such as *Bifidobacterium adolescentis* and *Lactobacillus acidophilus*. Most of the studies concentrate on the role of berberine in the inhibition of cytokine-related pathways. It was found that berberine improves TNBS-induced colitis in mice by down-regulating IFN-γ and IL-17 production and inhibiting IL-8 production in colonic epithelial cells (Zhou and Mineshita, 2000). Berberine also inhibits the expression of pro-inflammatory cytokines, such as IL-1β, IL-6, and TNF-α, and indirectly influences TLR4, NF-κB, AP-1 and MAPK-mediated pathways (Jeong *et al.*, 2009; Zhang *et al.*, 2011a; Saha *et al.*, 2011; Yan *et al.*, 2011). Other studies have revealed that berberine may play the role of a PPARγ agonist and reduce pro-inflammatory molecule levels in macrophages via PPARγ-dependent pathways (Chen *et al.*, 2008). Finally, the depletion of pro-inflammatory mediators in dendritic cells is a likely mechanism of berberine action in an IL-10 deficiency-induced mouse model of colitis (Watanabe *et al.*, 2003).

Besides regulation of the cytokine production by macrophages, berberine also regulates macrophage function by stimulating apoptosis through caspase-3 activation, as shown *in vitro* and in the DSS-induced mouse model of colitis (Yan *et al.*, 2012). Decreased

macrophage number contributes to the lowering of the levels of pro-inflammatory cytokines produced by these cells.

Some studies have shown that berberine is a potent inhibitor of inducible COX-2 generation (Feng *et al.*, 2012). As a result, berberine reduces COX-2 levels and attenuates TNBS-induced colitis *in vivo*. In terms of lipid metabolism, berberine ameliorates TNBS-induced colitis also via the inhibition of lipid peroxidation in the mouse colon, leading to reduced malonyl dialdehyde (MDA) and 4-hydroxy-2-nonenal (4-HNE) levels and restored superoxide dismutase and catalase activities (Lee *et al.*, 2010).

Berberine is presumably a strong promoter of intestinal mucosal cell survival. The compound attenuates endoplasmic reticulum stress and protects Caco-2 cells exposed to IFN-γ/TNF-α from apoptosis via the down-regulation of IRE1/XBP-1 and GRP78/BiP and the inhibition of JNK activity (Hao *et al.*, 2012).

At last, the amelioration of the splanchnic ischemia was also reported as the possible mechanism of berberine anti-inflammatory action (Cho *et al.*, 2004).

Inhibition of GI Motility

Berberine significantly reduces smooth muscle contractility and intestinal motility, and delays intestinal transit time, as evidenced in rodents based on intestinal myoelectric activity and upper GI transit studies (Feng *et al.*, 2013; Gu *et al.*, 2013). The inhibitory action of berberine could potentially be explained by the up-regulation of somatostatin and glucagon-like peptide-1 (GLP-1) and down-regulation of motilin and gastrin levels. Some reports demonstrate that the endogenous opioid system (EOS) is also involved in the regulation of GI motility. An *in vitro* study showed that antagonizing EOS by the non-selective opioid receptor antagonist naloxone (NAL) blocks the inhibitory effect of berberine on rat intestinal myoelectric activity (Cosola *et al.*, 2006; Feng *et al.*, 2013).

Berberine Ameliorates Impaired GI Function

Lipopolysaccharide (LPS) found in the outer membrane of gram-negative bacteria has been recognized as the major initiator of sepsis. LPS released by *E. coli* can injure the microcirculation and vascular endothelial cells and promote the excessive secretion of immune-associated cytokines (Kim *et al.*, 2012; Lee *et al.*, 2013). Studies have suggested that berberine effectively reduces the inflammatory response stimulated by LPS through the inhibition of E-selectin expression, the decrease of the TXB2 content (Hu *et al.*, 2009), the inhibition of TNF-α, IFN-γ and NO release and the up-regulation of IL-10 in mice (Li *et al.*, 2006). Furthermore, berberine prevents intestinal mucosal injury caused by LPS-mediated endotoxemia in the rat and enhances intestinal mucosal recovery, possibly through increased intestinal glutamine transport and enhanced glutaminase activity (Niu *et al.*, 2011). The preventive effect of berberine in the rat model of LPS-induced intestinal injury may also result from the attenuation of the intestinal oxidative damage through the elevation of the activities of SOD and GSH-Px, reduction of the levels of MDA

and NO, and the suppression of the expression of TLR4 and NF-κB in the ileum (Zhang *et al.*, 2011b). As a result, berberine attenuates intestinal injury and decreases mortality in animals exposed to LPS.

Furthermore, berberine was able to antagonize the TNFα-mediated barrier defects in the cell model and in the rat colon. Berberine prevented TNFα-induced claudin-1 disassembly and up-regulation of claudin-2. Moreover, the effects of berberine were mimicked by genistein plus BAY11-7082, indicating that they are mediated via the tyrosine kinase, pAkt and NFκB, pathways. Berberine was therefore suggested as a therapeutic approach against barrier breakdown in intestinal injury (Amasheh *et al.*, 2010).

In the model of indomethacin-induced lethal enteropathy, berberine was shown to increase the number of COX-2 expressing cells in the lamina propria and the production of PGE2 by isolated lamina propria mononuclear cells (Watanabe-Fukuda *et al.*, 2009). This suggests that berberine may be an efficient treatment option for the adverse effect of NSAIDs in the small intestine.

Anticancer Action of Berberine in the Colon

Several mechanisms underlying the antitumor activity of berberine in different types of carcinoma have been identified. These include stimulating caspase-dependent apoptosis and caspase-independent cell death through the activation of apoptosis inducing factor (Wang *et al.*, 2002, 2012) suppressing cancer cell growth and proliferation through the induction of cell cycle arrest (Yan *et al.*, 2011), and inhibiting metastasis by down-regulating matrix metalloproteinases and the activity of the AP-1 transcription factor (Fukuda *et al.*, 1999; Tillhon *et al.*, 2012). Signaling pathways and proteins regulated by berberine and involved in its anticancer activity include, among others, p53, MAPK, and NF-kB (Sun *et al.*, 2009).

Mechanisms, by which berberine suppresses cancer in the GI tract, still need to be fully elucidated. Wang *et al.* (2012) reported that berberine activates apoptosis-inducing factor (AIF), leading to caspase-independent cell death and showed that there is a link between berberine-induced ROS generation and AIF activation in colon tumor cells. Of note, they also demonstrated that normal colon epithelial cells are less susceptible to berberine-induced cell death, suggesting specific mechanisms of inhibition of colon tumor cell growth in presence of the compound. Another study showed that the antitumor action of berberine in colon cancer is attributed to its antioxidant and anti-lipid-peroxidative properties (Thirupurasundari *et al.*, 2009). In line, Hsu *et al.* reported that berberine effectively inhibits COX-2 expression in SW620 human colon cancer cells in a dose- and time-dependent manner, thus modifying the redox balance of the JNK and/or p38 pathways and stimulating apoptosis (Fukuda *et al.*, 1999; Hsu *et al.*, 2007).

Several studies suggest that berberine displays a potent antiproliferative effect on colon cancer cells. This action may result from down-regulating β-catenin mRNA expression and blocking of the Wnt/β-catenin signaling pathways (Wu *et al.*, 2012) or from inducing G1/S and G2/M cell cycle arrest (Chidambara Murthy *et al.*, 2012; Wang *et al.*, 2013).

Simultaneously, berberine may up-regulate Sesn2, which mediates the inhibition of the PI3K–mTOR complex (mTORC)1-axis (Budanov and Karin, 2008).

Berberine activates AMPK, which inhibits migration-promoting signaling by decreasing integrin b1 protein levels, thus displaying a potent antimetastatic action. Berberine has also been shown to exhibit an anti-cachectic effect in a colon cancer-bearing mouse model through IL-6, a key molecule in cancer-induced cachexia (Iizuka *et al.*, 2002).

Finally, berberine may be of great significance in colon cancer chemoprevention. One study showed that berberine treatment up-regulates the multi-drug resistant transporter (pgp-170) expression in two oral (KB, OC2), two gastric (SC-M1, NUGC-3) and two colon (COLO 205, CT 26) cancer cell lines (Lin *et al.*, 1999). This leads to a reduced response to Paclitaxel in cancer cells.

Anti-Metabolic Action of Berberine

For a long time, it has been thought that berberine is poorly absorbed through the gut wall because of the low plasma concentrations found after its administration (Pan *et al.*, 2002). Therefore, the clinical relevance of the compound was questioned and mainly referred to in terms of local action in the intestine. However, more recent studies have shown that the absorption of berberine changes significantly in pathological conditions, which alter the intestinal environment, as well as with some co-administered compounds. These include LPS, which was shown to enhance the intestinal absorption of alkaloids from *Rhizoma coptidis* in rats through decreased intestinal efflux and intestinal metabolism (Ma *et al.*, 2012). Another modulator, sodium caprate, significantly improves the absorption of berberine in the small intestine by stimulating mucosal-to-serosal transport in different areas of the small bowel. Consequently, a strong hypoglycemic effect of berberine co-administered orally with sodium caprate vs. berberine alone was reported (Lv *et al.*, 2010). Finally, although it seems that there is no direct effect of the intestinal flora on the metabolic stability of berberine and its derivatives, it may play a significant role in the enterohepatic circulation of berberine metabolites (Zuo *et al.*, 2006). These observations open a wider perspective on berberine in the gut and underline the need to consider metabolism and absorption in the intestine as an important element of berberine pharmacokinetics.

Inhibition of Glucose Absorption in the GI Tract

The direct hypoglycemic effect of berberine involves well-described post-absorption actions, including stimulating insulin secretion or release, increasing insulin receptor expression (Zhang *et al.*, 2010), insulin-sensitizing (Wang *et al.*, 2011), protecting pancreatic islets (Chueh and Lin, 2011) and β-cells (Shen *et al.*, 2012), stimulating glycolysis, promoting the utilization and transformation of glucose (Li *et al.*, 2012), up-regulating AMP-activated protein kinase (Hardie, 2011) and glucose transporter (Cok *et al.*, 2011), and down-regulating mitochondrial respiratory complex I (Turner *et al.*, 2008).

The crucial step in the hypoglycemic action of berberine is the absorption through the gut wall. Berberine is poorly absorbed in the digestive tract and its main transporter is glycoprotein P(P-GP) (Pan *et al.*, 2002). It was reported that P-GP, encoded by the *mdr1* gene in humans and *mdr1a* and *mdr1b* genes in rodents, plays an important role in the integrity of the intestinal barrier and protects the body from many exogenous toxins and therapeutic drugs. Therefore, P-GP becomes a critical factor in limiting oral drug bioavailability in the intestine (Takano *et al.*, 2006). The hypoglycemic effect of berberine described above is therefore limited by P-GP. In the absence of functional P-GP in the intestine, an increased absorption of considerable important drugs, including berberine, resulting in dramatically increased drug exposures *in vivo*, has been noted (Yu *et al.*, 2010).

It has been observed that berberine inhibits the expression of disaccharidases, such as maltase and sucrase both, in Caco-2 cells and the rat digestive tract, with the most significant effect found in the duodenum (Pan *et al.*, 2003; Liu *et al.*, 2010; Deng *et al.*, 2012). This results in less glucose being formed from carbohydrate digestion, which leads to the reduction of blood glucose levels.

Berberine is also believed to be involved in the regulation of endocrine pancreatic secretion. The key mediator here is the product of the enteroendocrine L cells of the gut, GLP-1, which is secreted into the blood stream in response to nutrient ingestion and significantly contributes to the overall insulin response to oral glucose (Doyle and Egan, 2007; Deacon, 2004). Berberine treatment significantly increases GLP-1 levels in blood, ileum, and colon in the diabetic rat, thus elevating insulin secretion and improving the function of β-cells in the pancreas. Furthermore, berberine may significantly increase the number of L cells in ileum (Lu *et al.*, 2009).

Interestingly, there is a striking overlap between the above-mentioned hypoglycemic actions of berberine that needs to be mentioned. Berberine inhibits α-glucosidase activity in the upper small intestine and in this way, delays the carbohydrate digestion and increases its content in chyme entering the lower small intestine. The most abundant population of endocrine L cells is located here, which may be stimulated physiologically (by carbohydrates) and pharmacologically (by berberine).

Hypolipidemic Action of Berberine

Cholesterol homeostasis is affected by numerous factors that influence absorption, synthesis, clearance and excretion, and related metabolic pathways. Berberine interferes with several of them, displaying a clear cholesterol-lowering effect, which was evidenced in animal models and human subjects. Those mechanisms include lowering intestinal cholesterol absorption (Wang *et al.*, 2010), increasing LDL-receptor expression in the liver, promoting bile formation and secretion (Briand *et al.*, 2013) and interacting with micelles through hydrophilic and hydrophobic binding sites to form alkaloid–bile salt agglomerates (Megyesi and Biczok, 2007). Finally, berberine exerts an anti-obesity effect by inhibiting fecal microbes. This inhibitory effect may be associated with a decrease in intestinal calorie intake and *de novo* lipogenesis (Zhang *et al.*, 2012a).

Other Actions of Berberine in the GI Tract

Despite several years of attempts, the pharmacological target for berberine remains unknown. Recently, it has been reported that berberine concentration-dependently inhibits myoelectrical activity and GI transit in an opioid receptor-dependent manner (Feng *et al.*, 2013). However, studies on Jatrorrhizine, a protoberberine alkaloid isolated from the medicinal plants *Berberis aristata* and *Coptis chinensis*, showed that it increases the contractility of the gastric antral and ileum smooth muscles in rat. Jatrorrhizine dose-dependently offset postoperative ileus-induced delayed gastric emptying and intestinal transit in rats, an action mediated via the cholinergic pathway (Zhang *et al.*, 2012). Interestingly, yet another study showed that berberine induces bidirectional regulation (Chen *et al.*, 2013). When the jejunum is in low contractile states, berberine induces contractions via the cholinergic system. On the contrary, if the jejunum is in high contractile states, relaxations stimulated by berberine relate to the adrenergic system and nitric oxide-dependent mechanism.

Berberine has a potent antinociceptive effect, which prevents the progression of visceral hypersensitivity to colorectal distension and is possibly mediated by NO (Tang *et al.*, 2013). This underlines the therapeutic potential of berberine for the treatment of patients with gastric and intestinal dysfunction, like in IBS.

Side-Effects of Berberine

There are only a few reports on the side-effects of berberine in the GI tract, including mildly upset stomach after oral administration. Moreover, berberine has low acute toxicity: the LD50 in rats is 205 mg/kg when given intraperitoneally (Kulkarni *et al.*, 1972). Presently, berberine is abundantly used in Chinese medicine in tablets and capsules at doses of 0.2–1.0 g/day for the treatment of various diseases and only mild constipation, especially in type 2 diabetes mellitus patients, was reported (Yin *et al.*, 2008).

Of note, berberine can be used during pregnancy or labor. In line, one study showed that Chinese Goldthread Rhizome and berberine did not induce neonatal jaundice in newly born rats; moreover, no influence on the activity of glucose-6-phosphate dehydrogenase in mice red blood cells was observed (Yang and Wang, 2008).

Conclusions

Berberine has a wide spectrum of effects in the GI tract, as evidenced by results gathered in a series of basic and pre-clinical studies discussed in this review and summarized in Table 1. These include a potent anti-diarrheal, anti-inflammatory, antitumor and anti-nociceptive action, to name just a few. Despite the fact that the targets and mechanisms of action remain unknown and require further investigations, berberine has potential to be widely used in clinics in the therapy of irritable bowel syndrome (IBS), intestinal injury or metabolic diseases. The data presented above warrants interest in berberine as potential drug for GI diseases and encourages further studies.

Table 1. A Summary of the Effects of Berberine in the GI Tract

Effect in the GI Tract	Mechanism of Berberine Action	Study Details	Authors
Anti-diarrheal	Bactericidal to *V. cholera* and *E. coli*	Berberine (300 μg/ml) produced inhibitory effect on *E. coli* CI6 bacteria growth (loss of adherence ability by 90%).	Sun D
		In the study on a group of 185 cholera patients (male:female 108:77, age 30–40 years), berberine hydrochloride tablets (100 mg, four times a day) reduced the volume of diarrhoeal stools by one liter. One dose of berberine reduced cyclic adenosine monophosphate concentration in stools by 77% 24 h after administration.	Khin MU
	Inhibits intestinal secretion	Intragastric administration of berberine (80 mg/kg, twice daily) reduced diarrhea symptoms in sennoside A-induced mouse model of diarrhea and significantly increased the expression levels of NHE3 (Na^+/H^+ exchanger3) and AQP4 (Aquaporin4).	Zhang Y
		Preincubation with a protoberberine alkaloid palmatine (1.0–300 μm), inhibited carbachol-evoked I_{SC} in male Wistar rat colonic mucosa ($n = 8$–23).	Wu DZ
		Berberine reduced (100 μM, $n = 5$) or virtually abolished (500 μM, $n = 5$) carbachol stimulated inward short circuit current response in human colonic mucosa. Pretreatment of T84 intestinal epithelial cell line monolayers with berberine for 15 min attenuated (100 μM) or significantly inhibited (500 μM) responses to forskolin ($n = 5$–8).	Taylor CT
	Reduces gutepithelial permeability	Incubation with berberine (50 μM) fully prevented the TNF-α induced barrier defects in human colon carcinoma cell line HT-29/B6 ($n = 8$) and colon specimens of male Wistar rats ($n = 7$)	Amasheh M
		Caco-2 cells incubated with berberine (25-100 μM) for 2–72 h produced a dose-dependent increase in transepithelial electrical resistance.	Gu L
	Reduces smooth muscle contractility and intestinal motility	Berberine (10^{-6}–10^{-4} mol/kg, *i.p.*) decreased upper GI transit in a concentration-dependent manner in mice ($n = 8$).	Feng Y

(*Continued*)

Table 1. (*Continued*)

Effect in the GI Tract	Mechanism of Berberine Action	Study Details	Authors
	Unknown	In the study on a group of 165 adult patients with acute diarrhea due to *E. coli* and cholera, 400 mg of berberine in a single oral dose reduced the mean stool volume during three consecutive 8-h periods after treatment.	Rabbani GH
Anti-inflammatory	Antibacterial against gram negative bacteria	Berberine inhibited growth of *P. aeruginosa* and *E. coli*.	Cernakova M
	Regulates cytokine levels	Histological lesions, morphological damage and myeloperoxidase activity were reduced after oral administration of berberine (7.5 and 15 mg/kg/day) in TNBS-induced colitis in male Sprague-Dawley rats ($n = 5$). Berberine (10^{-5} M) reduced IL-8 production in rectal mucosa ($n = 5$).	Zhou H
		Berberine (100 mg/kg/day, p.o.) administered during the 3-day recovery after 4-day DSS treatment or 2-, 4-, and 6-day recovery after 7-day DSS treatment in wild-type C57BL/6 mice ($n > 5$) down-regulated DSS-induced TNF, IFN-γ, KC and IL-17.	Yan F
	Improves intestinal mucosal cell survival	Berberine (20 μM, 2 h) reversed apoptosis in Caco-2 cells incubated with IFN-γ (2.5 ng/mL) and TNF-α (50 ng/mL) for 24 h.	Hao X
	Inhibits lipid peroxidation	Orally administered berberine (10 or 20 mg, once a day from 3 days before TNBS treatment to the day before sacrifice) in male C3H/HeN and C3H/HeJ mice ($n = 3$) inhibited lipid peroxidation in liposomes.	Lee IA
	Ameliorates splanchnic ischemia	Extract from *Coptidis rhizoma* (containing 20.8% berberine) at the dose of 62.5 and 125 mg/kg body wt./day administered for 10 or 30 consecutive days protected against renal dysfunction in rat model of renal ischemia.	Cho EJ
Amelioration of intestinal impairment in endotoxemia and enteropathy	Reduces inflammatory response	Berberine (10, 50 and 100 μg/ml) down regulated E-selectin expression and decreased the content of TXB_2 in the intestinal microvascular endothelial cells (RIMECs) challenged with 1 μg/mL LPS.	Hu Y

Table 1. (*Continued*)

Effect in the GI Tract	Mechanism of Berberine Action	Study Details	Authors
	Inhibits TNF-α, IFN-γ and NO release and up-regulates IL-10	Significant reduction in plasma TNF-α, IFN-γ and NO levels, and augmentation in IL-10 secretion after berberine (50 mg/kg, p.o., once a day for 5 days) administered in mice ($n = 30$) challenged with LPS.	Li F
	Increases intestinal glutamine transport and glutaminase activity	Berberine (50 mg/kg, p.o., once a day for 5 days) reversed the effect of LPS on ileal and jejunal glutaminase activity in male Sprague-Dawley rats ($n = 6$).	Niu L
	Prevents sepsis and its complications	Berberine (30 or 120 mg/kg, p.o., for 2 weeks) attenuated intestinal oxidative damage by elevating the activities of SOD and GSH-Px, reducing the levels of MDA and NO, and suppressing the expression of TLR4 and NF-κB in ileum in male Sprague-Dawley rats ($n = 12$).	Zhang Q
	Increases the number of COX-2 expressing cells	Indomethacin-induced increase in ADA mRNA expression was attenuated in the small intestine of female BALB/c mice ($n = 5$) fed with chow containing berberine at twice the concentration corresponding to that in 2% Orengedokuto (includes 0.0703% berberine). Berberine was administered from the first indomethacin injection until the end of the experiment.	Watanabe-Fukuda Y
Antitumoral	Stimulates caspase-independent cell death	Treatment with berberine (50 and 100 μM) resulted in a significant stimulation of the mouse immorto-Min colonic epithelial (IMCE) cell death.	Wang L
	Displays anti-oxidant and anti-lipid-peroxidative properties	Berberine (30 mg/kg, treatment for 60 days) significantly enhanced the antioxidant status in azoxymethane-induced colon cancer rats ($n = 6$).	Thirupurasundari CJ
	Induces apoptosis	SW620 colon cancer cells incubated with berberine (50 μM) for 24 h displayed a marked loss of viability proving berberine elicit apoptosis.	Fukuda K
	Inhibits cell proliferation and reduces metastatic potential	Incubation of HT-29 cells and IMCE cells carrying the *APC* mutation for 24 h with berberine (50 μM) resulted in a decrease of total EGFR and inhibition of proliferation.	Wang L

(*Continued*)

Table 1. (*Continued*)

Effect in the GI Tract	Mechanism of Berberine Action	Study Details	Authors
		Berberine (10 and 20 μM) inhibited cell proliferation by 20% after a 24 h treatment and reduced the migration of SW480 and HCT116 cells.	Budanov AV
	Displays anticachectic action	Berberine (0.2 and 0.4% of the diet) significantly prevented weight loss and decrease in adipose tissues and gastrocnemius muscle in male mice (n = at least 5) bearing colon 26/clone 20 carcinoma cells.	Iizuka N
	Targets multiple pathways to induce cell death	Up to 85 and 86% of SW480 colon cancer cells were arrested on G_0/G_1 after 24 and 48 h treatment, respectively, with berberine (25 μM). A relative increase of 30% in MMP was observed after treatment with 50 μM berberine for 24 h. Treatment with berberine at 25 μM resulted in elevated expression of Bax/Bcl2.	Chidambara Murthy KN
Anti-hyperglycemic	Decreases disaccharidase activity	Berberine (100 and 200 mg/kg, p.o., once daily for 5 weeks) significantly decreased disaccharidase activity in intestinal regions of STZ-induced hyperglycemic male Sprague-Dawley rats (n = 6).	Liu L
		Huanglian Wan extract (0.75 and 1.5 g/kg, p.o. administration for 33 days) decreased the activity of disaccharidases (maltase, sucrase and lactase) in duodenum, jejunum and ileum of STZ-induced hyperglycemic male Sprague-Dawley rats (n = 8).	Deng YX
	Promotes the release of GCG	Berberine (120 mg/kg per day, p.o. for 5 weeks) significantly increased GLP-1 (7–36) amide levels in blood, ileum, and colon in STZ-induced hyperglycemic male Sprague-Dawley rats (n = 7).	Deacon CF
Hypolipidemic	Inhibits cholesterol absorption	Male Golden Syrian hamsters (n = 15) fed on diet enriched with 0.17% berberine for 4 weeks displayed reduced fractional cholesterol absorption by 10% as compared with control.	Wang Y
	Influences gut microflora	Berberine (100 mg/kg, once daily for 18 weeks) significantly modified the gut microbiota in high-fat diet (HFD)-fed rats (120 samples).	Zhang X

Table 1. (*Continued*)

Effect in the GI Tract	Mechanism of Berberine Action	Study Details	Authors
		Berberine (200 mg/kg, p.o., for 6 weeks) significantly reduced proportions of Firmicutes and Bacteroidetes to total fecal bacteria in male C57BL/6J mice fed on the high-fat diet ($n = 6$).	Xie W
Inhibition of GI motility	Inhibits myoelectrical activity and GI transit in opioid receptor-dependent manner	Berberine (10^{-6}–10^{-4} mol/kg at 5 ml/kg, *i.p.* in male BALB/c mice, $n = 8$ and 10^{-6}–10^{-4} mol/kg in adult Sprague-Dawley rats, $n = 8$) inhibited GI motility.	Feng Y
		Berberine sulfate (0.2, 2.0 and 20.0 mg/kg, *i.p*) significantly inhibited myoelectric activity and transit of the rat small intestine. The effect was partially mediated by opioid and alpha-adrenergic receptors.	Eaker EY
	Increases contractility of gastric antrum and ileum smooth muscles via cholinergic pathways	Jatrorrhizine hydrochloride (protoberberine alkaloids, 0.1, 0.3 and 1.0 mg/kg, p.o.) increased gastric emptying and accelerated intestinal transit in rat model of postoperative ileus ($n = 10$).	Zhang B
	Influences nitrergic pathways in a bi-directional manner	Berberine (5–30 μmol/l) exerted stimulatory effects on the contractility of rat jejunal segment in low contractile states ($n = 6$), and inhibitory effects in high contractile states ($n = 6$), relating to cholinergic system, adrenergic system and nitric oxide relaxing mechanism	Chen DP
Antinociceptive	Influences colonic hypersensitivity	Berberine (50 mg/kg, *i.p.*, once daily) significantly increased the nociceptive threshold in male Sprague-Dawley rats ($n = 8$). Aminoguanidine reversed the effect of berberine.	Tang QL

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