REVIEW

Berberis Vulgaris and Berberine: An Update Review

Mohsen Imenshahidi and Hossein Hosseinzadeh*
Department of Pharmacodynamics and Toxicology, School of Pharmacy, Mashhad University of Medical Sciences, Mashhad, Iran

Berberine is an isoquinoline alkaloid present in several plants, including Coptis sp. and Berberis sp. Berberine is a customary component in Chinese medicine, and is characterized by a diversity of pharmacological effects. An extensive search in electronic databases (PubMed, Scopus, Ovid, Wiley, ProQuest, ISI, and Science Direct) were used to identify the pharmacological and clinical studies on Berberis vulgaris and berberine, during 2008 to 2015, using ‘berberine’ and ‘Berberis vulgaris’ as search words. We found more than 1200 new article studying the properties and clinical uses of berberine and B. vulgaris, for treating tumor, diabetes, cardiovascular disease, hyperlipidemia, inflammation, bacterial and viral infections, cerebral ischemia trauma, mental disease, Alzheimer disease, osteoporosis, and so on. In this article, we have updated the pharmacological effects of B. vulgaris and its active constituent, berberine. Copyright © 2016 John Wiley & Sons, Ltd.

Keywords: Berberis vulgaris; berberine; barberry; pharmacokinetic.

INTRODUCTION

Barberry (Berberis vulgaris L.) is a well known medicinal plant in Iran and is also used as food additive (Khosrokhavar et al., 2010). Berberine is an isoquinoline alkaloid belongs to the structural class of protoberberines and present in many plants including B. vulgaris.

Previously, we reviewed the pharmacological and therapeutic effects of B. vulgaris and its active constituent, berberine (Derosa et al., 2012). But during these years, a large body of papers published about different pharmacological and therapeutic effects of berberine and B. vulgaris. Here, we have updated the last review article using most of researches during 2008–2015 about the pharmacological properties and clinical uses of berberine and B. vulgaris.

In our previous review article about B. vulgaris and its most active constituent, berberine, we presented a table that lists the applications of different parts of barberry (root, bark, leaf, and fruit) in folk medicine of Iran and other countries (Derosa et al., 2012) (Table 1).

PHARMACOKINETIC

Bioavailability

Berberine has poor intestinal absorption and oral bioavailability. In two studies in rats, oral bioavailability of berberine has reported less than 1% (0.68% (Chen et al., 2011), and 0.36% (Liu et al., 2010)). Intestinal first-pass elimination of berberine, interaction with P-glycoprotein (P-gp) pumps and high extraction and distribution in the liver are the major barriers of berberine oral bioavailability (Liu et al., 2010; Fratter, De Servi, 2015).

This poor bioavailability limits clinical use of berberine, and several strategies have been tested to improve the bioavailability of berberine. D-α-tocopheryl polyethylene glycol 1000 succinate at a concentration of 2.5% could improve area under the curve (AUC) (0–36) of berberine by 1.9 time probably via inhibition the activity of P-glycoproteins (Chen et al., 2011). Chitosan-N-AcetylCystein (Fratter, De Servi, 2015) and beta-cyclodextrin have increased the intestinal absorption of berberine because of its solubilizing effect and P-glycoprotein (P-gp) modulatory activity (Zhang et al., 2013). Lysergol (Patil et al., 2013) and sodium caprate (Lv et al., 2010; Du et al., 2011) are other compounds that have improved the oral bioavailability of berberine.

A spray dried mucoadhesive microparticle formulation of berberine has been prepared and increased the AUC of berberine by 6.98 fold (Godugu et al., 2014). An oral microemulsion formulation of berberine resulted 6.47 times greater oral bioavailability (Gui et al., 2008). Another study has used an anhydrous reverse micelle delivery system provided via lyophilization of water-in-oil emulsion which 2.4-fold increase in oral bioavailability of berberine was demonstrated (Wang et al., 2011c).
Distribution

Although berberine’s bioavailability and plasma level are very low and cannot explain its pharmacological effects, in vivo studies show that tissue distribution of berberine and its active metabolites are higher than those concentrations in the blood after oral administration (Yan et al., 2009; Tan et al., 2013). For example, in a study, oral administration of berberine (200 mg/kg) to rats has shown that berberine quickly distributes in the liver, kidneys, muscle, lungs, brain, heart, pancreas, and fat in a descending order of its amount. The distribution of berberine and its major metabolites [berberrubine (M1), thalifendine (M2), and jatrorrhizine (M4)] was also higher than those concentrations in the blood (Tan et al., 2013).

Table 1. The traditional uses of B. vulgaris (NAPALERT Database)

<table>
<thead>
<tr>
<th>System</th>
<th>Effect</th>
<th>Part of plant</th>
<th>Preparation</th>
<th>Country</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardiovascular</td>
<td>Antihypertensive</td>
<td>Stem bark</td>
<td>Decoction</td>
<td>France</td>
</tr>
<tr>
<td></td>
<td>In varicose veins</td>
<td>Dried root</td>
<td>Decoction</td>
<td>Iran</td>
</tr>
<tr>
<td>Blood</td>
<td>Blood rectifier</td>
<td>Root</td>
<td>Infusion</td>
<td>Iran</td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td>Choleretic</td>
<td>Root</td>
<td>Fluid extract</td>
<td>France</td>
</tr>
<tr>
<td></td>
<td>Cholagogue</td>
<td>Dried root</td>
<td>Infusion</td>
<td>Iran</td>
</tr>
<tr>
<td></td>
<td>Laxative</td>
<td>Dried root</td>
<td>Decoction</td>
<td>Iran</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Dried root – root bark</td>
<td>Decoction</td>
<td>Iran</td>
</tr>
<tr>
<td></td>
<td>Fruit</td>
<td>Infusion</td>
<td>Iran</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Beverage in severe</td>
<td>Dried fruit –</td>
<td>H2O extract</td>
<td>Iran</td>
</tr>
<tr>
<td></td>
<td>Diarrhea</td>
<td>Root</td>
<td>Root</td>
<td>India</td>
</tr>
<tr>
<td></td>
<td>Hepatic</td>
<td>Dried fruit</td>
<td>H2O extract</td>
<td>Iran</td>
</tr>
<tr>
<td></td>
<td></td>
<td>+ stem bark</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Stomachic</td>
<td>Fruit</td>
<td>Infusion</td>
<td>Turkey</td>
</tr>
<tr>
<td></td>
<td>Beverage in severe</td>
<td>Dried fruit</td>
<td>H2O extract</td>
<td>Iran</td>
</tr>
<tr>
<td></td>
<td>In hemorrhoids</td>
<td>Root</td>
<td>Decoction</td>
<td>Iran</td>
</tr>
<tr>
<td>Endocrine</td>
<td>Painful menstruation</td>
<td>Fruit</td>
<td>Hot H2O</td>
<td>Argentin</td>
</tr>
<tr>
<td></td>
<td>Inhibit</td>
<td>Root</td>
<td>Hot H2O</td>
<td>Afghan</td>
</tr>
<tr>
<td>Immune system</td>
<td>Antiinflammatory</td>
<td>Dried root</td>
<td>Root</td>
<td>Bulgaria</td>
</tr>
<tr>
<td></td>
<td>Rheumatoid arthritis</td>
<td>Dried root</td>
<td>Decoction</td>
<td>Iran</td>
</tr>
<tr>
<td></td>
<td></td>
<td>+ stem bark</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Antirheumatic</td>
<td>Flowers</td>
<td>Decoction</td>
<td>China</td>
</tr>
<tr>
<td></td>
<td>Gout</td>
<td></td>
<td>Decoction</td>
<td>Iran</td>
</tr>
<tr>
<td>Organisms</td>
<td>Antimicrobial</td>
<td>Root</td>
<td>Root</td>
<td>Bulgaria</td>
</tr>
<tr>
<td></td>
<td>Beverage in typhus</td>
<td>Dried root</td>
<td>H2O extract</td>
<td>Iran</td>
</tr>
<tr>
<td>Central nervous system</td>
<td>In malaria</td>
<td>Root</td>
<td>Decoction</td>
<td>Iran</td>
</tr>
<tr>
<td></td>
<td>Beverage to</td>
<td>Dried fruit</td>
<td>H2O extract</td>
<td>Iran</td>
</tr>
<tr>
<td></td>
<td>Sedative</td>
<td>Dried root</td>
<td>Root</td>
<td>Bulgaria</td>
</tr>
<tr>
<td>Respiratory</td>
<td>Whooping cough</td>
<td>Fruit</td>
<td>Decoction</td>
<td>Turkey</td>
</tr>
<tr>
<td></td>
<td>Gargle to reduce</td>
<td>Dried leaf</td>
<td>Infusion</td>
<td>Turkey</td>
</tr>
<tr>
<td></td>
<td>Blood vomiting due</td>
<td>Root</td>
<td>Root</td>
<td>India</td>
</tr>
<tr>
<td></td>
<td>to lung disorders</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Skin</td>
<td>Irrigate wounds or</td>
<td>Dried leaf</td>
<td>Infusion</td>
<td>Iran</td>
</tr>
<tr>
<td></td>
<td>In scrobutic patients</td>
<td>Dried leaf</td>
<td>Infusion</td>
<td>Iran</td>
</tr>
<tr>
<td></td>
<td>Chewed by scrobutic</td>
<td>Leaf</td>
<td>External</td>
<td>Iran</td>
</tr>
<tr>
<td></td>
<td>to harden gums</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Disinfec tant</td>
<td>Dried root</td>
<td>Decoction</td>
<td>Iran</td>
</tr>
<tr>
<td>Renal</td>
<td>Renal or urinary</td>
<td>Dried part</td>
<td>Hot H2O</td>
<td>India</td>
</tr>
<tr>
<td></td>
<td>Diuretic</td>
<td>Dried root</td>
<td>Root</td>
<td>Iran</td>
</tr>
<tr>
<td></td>
<td>Kidney inflammation</td>
<td>Dried root</td>
<td>Root</td>
<td>Bulgaria</td>
</tr>
<tr>
<td></td>
<td>Nephritis</td>
<td>Dried root</td>
<td>Decoction</td>
<td>Iran</td>
</tr>
<tr>
<td>Other</td>
<td>Astringent</td>
<td>Dried fruit</td>
<td>H2O</td>
<td>Italy</td>
</tr>
</tbody>
</table>

NAPALERT, Natural Products Alert.
Metabolism

Some studies show that oxidative demethylation and glucuronidation are the major metabolic pathways of berberine in rats. The major circulating metabolites of berberine are M1 and M2 (via demethylation), M3 (via demethylation) (Fig. 1), and their corresponding glucuronides, with M2-glucuronide approximately 24-fold higher than M1-glucuronide. Several CYP enzymes are involved in formation of M1 and M2. The glucuronidation of M2 is much faster than M1. Both M1 and M2 can be glucuronidated by UGT2B1 and UGT1A1 while M2 glucuronidation is favored by UGT1A1 (Liu et al., 2009).

In vivo studies about the CYPs mediate metabolism of berberine shows that CYP2D6 is the primary human CYP producing berberine’s metabolites, followed by CYP1A2, 3A4, 2E1, and CYP2C19 (Guo et al., 2011a; Li et al., 2011b). Chen et al. have shown that CYP2D6 and CYP1A2 were responsible for 75.25% and 23.32% of the berberine metabolite M1, and responsible for 46.89% and 8.67% of M2 (thalifendine or berberrubine) (Chen et al., 2013b). Therefore, CYP2D subfamily plays a major role in berberine metabolism, and CYP2D6 pharmacogenetics and drug-drug interactions should be considered when berberine is used.

Excretion

In a study in rat, the excretion profiles of berberine and its metabolites after oral administration of administration 200 mg/kg has been evaluated. The results indicate that total recovered rate of berberine is 22.83% and major route of excretion of berberine is fecal (9.2 × 10^-6% in bile (24 h), 0.0939% in urine (48 h) and 22.74% in feces (48 h)). The major metabolites of berberine [thalifendine (M1) and berberrubine (M2)], mostly exert via bile and urine (Fig. 2) (Ma et al., 2013b).

Effect of berberine on cytochromes P450 and P-glycoproteins

Many in vitro and animal studies have reported interactions between berberine and cytochromes P450 (CYPs) or P-gp, but little is known about whether berberine alters CYP activities in humans, especially after repeated regular doses and are this possible alternations clinically important or not?

One study shows that Berberine has no influence on the activities of CYP3A4, CYP1A2, and CYP2C19 but can inhibit the activity of CYP2E1 and CYP2D6 (Chen et al., 2013a). On the other hand, a study has demonstrated the activity of CYP3A4 and CYP1A2 could be
induced by berberine in HepG2 cell, which was confirmed by the increase of its mRNA and protein expression (Cui et al., 2014). Totally, it seems that the effect of berberine on CYPs activity is dose-dependent. Lower doses of berberine appear to have a low risk of drug-drug interactions related to change in CYP enzyme activity. However, high doses of berberine may suppress CYPs activity and cause drug–drug interactions. For example, repeated administration of the three low doses of oral berberine for 14 days (10, 30, 100 mg/kg, i.g., daily) to C57BL/6 mice did not affect the expression of 20 dominant CYPs in mice livers. However, highest dose of berberine (300 mg/kg), caused 67.6% and 87.4%, decrease in mRNA of CYP3A11 and CYP3A25, respectively, whereas the mRNA of CYP1A2 increased 43.2%, and activities of CYP2D22 and CYP3A11 decreased 32.4% and 67.9%, respectively. CYP 2B10, CYP2A4, and CYP2C9 were not altered at mRNA and enzyme activity levels (Guo et al., 2011b). In humans, A two-phase randomized-crossover clinical study in healthy male subjects showed that repeated administration of berberine (300 mg, three times a day, p.o.) decreases the activities of CYP2D6, 2C9, and CYP3A4 (Guo et al., 2012). The inhibition of intestinal P-gp is another drug–drug interaction that should be considered in administration of berberine. In animal studies; berberine caused a dose-dependent increase in bioavailability of digoxin and cyclosporine A by inhibition of intestinal P-gp (Qiu et al., 2009).

INTERACTION WITH OTHER DRUGS

Metformin. Co-administration of 10 mg/kg berberine and 2 mg/kg metformin at a single intravenous dose in rats, have increased the initial plasma concentration and AUC of metformin and have decreased volume of distribution and systemic clearance of metformin in rats, suggesting that berberine inhibits disposition of metformin through OCT1 and OCT2. Berberine inhibits the transport activity of OCT1 and OCT2 and has a significant potential of drug–drug interactions with metformin (Kwon et al., 2015). Regarding common use of berberine in diabetic patients, this drug–drug interaction is very important.

Ketoconazole. Oral co-administration of 60 mg/kg berberine with 10 mg/kg Ketoconazole increased the AUC for Ketoconazole to 215% compared with those administered Ketoconazole alone in male rats. AUC for berberine enhanced to 173% compared with those administered berberine alone. These pharmacokinetic interactions may have some role in the synergism reported for berberine and ketoconazole (Zhou et al., 2012).

Digoxin. Berberine increases bioavailability of Digoxin probably via its inhibitory effect on intestinal P-gp. Administration of berberine (30,100 mg/kg) to rats increases the AUC of Digoxin by 33% and 70%, respectively (Ju et al., 2011).

Cyclosporine A. Cyclosporine A and cyclosporine A bioavailability. Berberine is a CYP3A4 inhibitor and a P-gp transporter substrate (Colombo et al., 2014). Interaction studies have shown that coadministration of cyclosporine A with berberine significantly increases the blood concentration of cyclosporine A (Wu et al., 2005; Xin et al., 2006; Qiu et al., 2009). For example, in a clinical trial, on 52 renal-transplant recipients, co-administration of cyclosporine A and 0.2 g berberine three times daily for 3 months, has increased the trough blood concentrations of cyclosporine A by 89.9%. (Wu et al., 2005). Berberine also increases the emptying time of stomach and small intestine which might be another reason for the increase in cyclosporine A bioavailability. (Xin et al., 2006). In view of these findings, concomitant administration of berberine is not reasonable during cyclosporine A treatment.

Toxicology

Generally, berberine shows very low toxicity and side effects (Pang et al., 2015). The administration method is a significant factor which can affect acute toxicity of berberine. In mice, the LD50 of intravenous injection and intraperitoneal injection are, respectively, 9.0 and 57.6 g/kg, and intragastric administration caused no LD50 (Kheir et al., 2010). In human, some clinical studies that evaluated the safety of berberine, reported only mild gastrointestinal reactions, including diarrhea and constipation (Zhang et al., 2008c; Zhang et al., 2010; Pang et al., 2015). But some other clinical studies indicated different adverse effects including transient elevation in serum bilirubin level (Linn et al., 2012), distribution of sex-hormone synthesis pathway (Lao-Ong et al., 2013), suppression of both cellular and humoral immune functions (Mahmoudi et al., 2016), and prothrombotic effects (Holy et al., 2009).

CENTRAL NERVOUS SYSTEM EFFECTS

Autoimmune encephalomyelitis and multiple sclerosis

Berberine has been proposed as a potential therapeutic agent for multiple sclerosis (MS). In experimental autoimmune encephalomyelitis (EAE), an established model of MS, berberine has ameliorated clinical severity and pathological parameters of EAE. It has reduced the permeability of blood–brain barrier and has inhibited the activity of MMP-9 in the CSF and brain of EAE mice (Ma et al., 2010). Inhibition of differentiation of Th17 cells through direct actions on the Janus Kinase (JAK)/Signal Transducer and Activator of Transcription (STAT) pathway is a mechanism that has been proposed for this effect (Qin et al., 2010). Berberine also inhibits gelatinase activity and reduces laminin degradation which provides further support that berberine can be a potential therapeutic agent for MS (Jiang et al., 2013).

Anticonvulsant

Temporal lobe epilepsy is a long lasting neurological disorder that is resistant to available drugs. A study has shown that berberine pretreatment can attenuate spontaneous recurrent seizures in intrahippocampal kainate (4 μg)-induced temporal lobe epilepsy in rats. Regarding that in this study, berberine has also reduced the nitrite level and lipid peroxidation, it has been suggested that
Berberine’s effect is due to its effectiveness in lessening of oxidative stress (Mojarrad and Roghani, 2014). In another study, we showed that B. integrerrima, which contains berberine as main constituent, has anticonvulsant activity in pentylentetrazole-induced seizures and therefore, may be useful in petit mal epilepsy (Hosseinzadeh et al., 2013).

**Antidepressant**

Berberine inhibits the immobility period in mice in both tail-suspension and forced swim tests and following its acute administration has resulted in increased levels of dopamine (31%), norepinephrine (31%), and serotonin (47%) in the whole brain of mice. The antidepressant-like effect of berberine in forced swim test has been inhibited by pretreatment with l-arginine or sildenafil. Therefore, it can be concluded that berberine exerts antidepressant-like effect in mice possibly via modulating brain biogenic amines (serotonin, norepinephrine, and dopamine) and nitric oxide pathway (Kulkarni and Dhir, 2008). In another study, it has been shown that berberine is a substrate and also an inhibitor of OCT2 and OCT3, and its inhibition on OCT2-mediated and OCT3-mediated NE and 5-HT uptake may contribute to the increased monoamine concentration in mouse brain (Sun et al., 2014).

**Neuroprotective**

Berberine has shown neuroprotective effects in several brain injury models (Zhou et al., 2008; Benaissa et al., 2009; Abdel Moneim, 2015). In a chronic brain injury model of rats (administration of aluminum trichloride), berberine administration 4h following the aluminum administration significantly prevents rats from the impairment of learning and memory function and hippocampal neuron injury, while significantly inhibits the decreasing of ChAT and SOD activities, the increasing of AchE activities, MDA contents, and MAO-B activities, as well as the expression of MAO-B mRNA and protein (Liu et al., 2008a; Zhang et al., 2009).

In a middle cerebral artery occlusion model of ischemic injury, berberine has improved neurological outcome and reduced ischemia/reperfusion (I/R)-induced cerebral infarction 48h after occlusion of middle cerebral artery via inhibition of reactive oxygen species generation, and subsequent release of pro-apoptotic factor cytochrome c and apoptosis-inducing factors in mitochondria (Zhou et al., 2008). Berberine shows anti-apoptotic effects against ischemia by decreasing HIF-1α, caspase 9, caspase 3, and increasing Bcl-2/Bax ratio (Zhang et al., 2012a) and by the increased phosphor-activation of Akt (higher p-Akt to total Akt), (Hu et al., 2012a; Kim et al., 2014b; Simoes Pires et al., 2014; Zhang et al., 2014d). Berberine can inhibit the degradation of retinoblastoma mRNA through its function on the poly (A) tail which avoids cells entering in the apoptotic process (Chai et al., 2014). However, pro-apoptosis by berberine under hypoxia also has been reported (Cui et al., 2009), and it seems that berberine regulates neuronal apoptosis in cerebral ischemia, which might be dependent on the degree of cell injury (Zhang et al., 2012a).

Berberine activates neurons by blocking K+ current and lowering the threshold of the action potential. In a neonatal rat model of degenerating brain disease induced by MK-801, berberine has shown neuroprotective effects on damaged neurons probably via blocking K+ current and lowering the threshold of the action potential (Lee et al., 2010a) adenosine monophosphate (AMP)-activated protein kinase (AMPK) activation in BV-2 microglia (Lu et al., 2010), reducing the production of tumor necrosis factor-α, interleukin-1β, and prostaglandin E2 from activated microglia (Nam et al., 2010; Chen et al., 2014a), inhibition of the excessive production of glutamate (Campisi et al., 2011; Lin et al., 2013), reducing matrix metalloproteinase-9 activity (Hong et al., 2012), decreasing nitric oxide (NO) production in oligodendroglial cells (Nadjafi et al., 2014a), increasing heme oxygenase-1 mRNA and protein expression (Chen et al., 2012), and attenuation of intracellular Ca2+ overload (Nadjafi et al., 2014b) are other mechanisms proposed for neuroprotective and anti-neuroinflammatory effects of berberine.

**Parkinson**

There is controversy about the effect of berberine on Parkinson, and it seems to be related to the model of Parkinson and type of cells used in different studies. In 6-hydroxydopamine-lesioned model of Parkinson’s disease in rat, treated with l-DOPA (10 mg/kg) and/or berberine (5 and 15 mg/kg) once daily for 21 days, berberine leads to the degeneration of dopaminergic neurons in the substantia nigra (Shin et al., 2013). Berberine also, aggravates 6-hydroxydopamine-induced cytotoxicity in PC12 cells and enhances the degeneration of dopaminergic cell death. It also decreased dopamine levels in substantia nigra (Kwon et al., 2009). On the other hand, pretreatment of SH-SY5Y cells with berberine significantly reduces 6-hydroxydopamine-induced generation of reactive oxygen species, caspase-3 activation, and subsequent cell death. Furthermore, berberine induces p38 and PI3K/Akt activation, which are involved in Nrf2 expression and neuroprotection (Bae, Lee, Kim, et al., 2013).

In a model of Parkinson’s disease in mice, induced by 1-methyl-4-phenyl-1, 2,3,6-tetrahydropyridine/probenecid treatment, berberine enhanced coordination and motor balance by preventing dopaminergic neuronal damage. Berberine also improved short-term memory by reducing apoptosis in the hippocampus. Berberine showed maximal potency at 50 mg/kg. Based on these data, berberine may serve as a potential therapeutic agent for the alleviation of motor dysfunction and memory impairment in patients with Parkinson’s disease (Kim et al., 2014a).

**Drug dependence**

Berberine inhibits the rewarding effects of drugs of abuse such as cocaine, morphine, and nicotine (Bhutada, Mundhada, Bansod, et al., 2011). **Cocaine.** Berberine can be effective for inhibiting the behavioral and reinforcing effects of cocaine possibly via modulating the central dopaminergic system. A study in male Sprague-Dawley rats shows that
administration of berberine (200 mg/kg, p.o.) 30 min before the daily injections of cocaine significantly reduces the cocaine-induced dopamine biosynthesis and locomotor activity via inhibition of tyrosine hydroxylase expression (Lee et al., 2009).

**Ethanol.** Administration of berberine (2.5, 5, and 10 mg/kg, i.p.) reduces locomotor stimulant effect of acute ethanol and reduces ethanol-induced rewarding effects in mice (Pa et al., 2010). In another study, using the ethanol withdrawal-induced hyperexcitability method in mice, administration of berberine in higher doses (10 and 20 mg/kg, i.p.) dose-dependently attenuated ethanol withdrawal-induced hyperexcitability signs (Bhutada et al., 2011).

**Morphine.** Recently, we reported that aqueous extract of *B. vulgaris* can reduce morphine withdrawal syndrome, using conditioned place preference method. In our study, administration of aqueous extract of barberry (200 mg/kg) inhibited the acquisition and reinstatement of morphine-induced conditioned place preference (Imenshahidi et al., 2014). Berberine also significantly reduces morphine withdrawal behaviors following discontinuation of repeated morphine administration in rats, possibly through decreasing hippocampal brain-derived neurotrophic factor mRNA expression and blocking the increase in hypothalamic CRF expression and TH expression in the locus coeruleus (Lee et al., 2012).

**Huntington disease**

Using transgenic mouse model expressing the Huntington disease (HD) protein, berberine can alleviate motor dysfunction and prolong the survival of transgenic N171-82Q HD mice and promote the degradation of mutant huntingtin by increasing autophagic function. Berberine can also reduce the accumulation of mutant huntingtin in cultured cells. It seems that berberine can be tested on HD patients to further evaluate its effects in treatment of HD patients (Jiang et al., 2015).

**Analgesic effects**

*B. vulgaris* hydroethanolic extract has shown antinociceptive effects in different animal models of pain such as, acetic acid-induced writhing test (for chronic pain) and tail-flick test (for acute pain) but is less effective than morphine. Berberine in dose of 20 mg/kg, has also shown antiallodynic effect comparable with that of amitryptiline 10 mg/kg in allodynia induced by chronic constriction injury of the sciatic nerve in rats, a neuropathic pain model, probably via its antioxidative and anti-inflammatory properties (Kim, 2015).

**CARDIOVASCULAR EFFECTS**

Cardiovascular effects of berberine have been studied extensively during recent years and many new properties have been attributed to this active ingredient of *B. vulgaris* including antiatherosclerosis, antimyocyte proliferation, cardiotoxic, and antiarythmia effects.

**Atherosclerosis**

Many studies have reported anti-atherosclerosis effect of berberine and several mechanisms have suggested explaining this property of berberine. Lee et al. have suggested that berberine inhibits the formation of foam cells by macrophages via enhancing LXRalphA-ABCA1-dependent cholesterol efflux (Lee et al., 2010b). Berberine can also effectively reduce intracellular superoxide levels in lipopolysaccharide-stimulated macrophages via selective inhibition of gp91 phox expression and enhancement of SOD activity. The intracellular superoxide level is an important source of oxidative stress in the developing atheroma (Sarna et al., 2010).

The induction of human serum paraoxonase 1 (PON1) by berberine explains another mechanism of protection against atherosclerosis (Cheng et al., 2011). PON1 is associated with high-density lipoprotein (HDL) and can inhibit the oxidative modification of low-density lipoprotein (LDL), implying that PON1 may prevent atherosclerosis (Cheng et al., 2011). Berberine reduces matrix metalloproteinase-9 (MMP-9) and extracellular matrix metalloproteinase inducer expression by inhibiting the activation of p38 pathway in PMA-induced macrophages (Huang et al., 2011) and reducing the activity of NF-kappaB in oxLDL-induced macrophages (Wang et al., 2009a; Huang et al., 2012). This suggests a potential role for berberine as a therapeutic agent for stabilizing atherosclerotic plaque because overproduction of MMPs by monocytes/macrophages leads to degradation of extracellular matrix and atherosclerotic plaque rupture (Huang et al., 2011). Berberine also inhibits human aortic smooth muscle cell, possibly by down-regulating urokinase-type plasminogen activator MMP-2 and MMP-9; and interrupting activator protein-1 and NF-kappa B mediated signaling pathways (Liu et al., 2014). Berberine can also inhibit the expression of LOX-1 through ET-1 receptors (Guan et al., 2010; Chi et al., 2014a) and promote the expression of scavenger receptor class B type I in macrophage-derived foam cells (Guan et al., 2010). Inducing autophagy through activation of the AMPK/mTOR signaling pathway (Fan et al., 2015), inhibition of the expression and production of TNF-alpha, MCP-1, and IL-6, via PPAR receptors (Chen et al., 2008; Pham et al., 2011; Chi et al., 2014b) and inhibition of cholesterol accumulation in human macrophages by impairment of macrophage cytosis (Zimetti et al., 2015) are other mechanisms proposed for anti-atherosclerotic effects of berberine (Table 2).

On the other hand, there is one report that indicates berberine can promote the development of atherosclerosis and foam cell formation. The foam cell formation is mediated through induction of scavenger receptor A expression in macrophages, and increasing the uptake of modified LDL (Li et al., 2009b).

**Endothelial dysfunction**

Berberine has a beneficial effect on endothelial function by increasing NO. NO plays a pivotal role in the regulation of endothelial progenitor cells (EPC) function and mobilization (Xu et al., 2009a) which contribute in...
<table>
<thead>
<tr>
<th>Mechanism</th>
<th>Pharmacologic effect</th>
<th>Therapeutic potential</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inhibits gelatinase activity</td>
<td>Treatment of MS</td>
<td>Antidepressant</td>
<td>(Jiang et al., 2013)</td>
</tr>
<tr>
<td>Reduces laminin degradation</td>
<td>Treatment of MS</td>
<td>Anti-hypertension</td>
<td>(Jiang et al., 2013)</td>
</tr>
<tr>
<td>Inhibition of organic cation transporter 2 (OCT2) and 3 (OCT3), decreasing</td>
<td>Inhibition of 5-HT and NE uptake</td>
<td>Anti-Atherosclerosis effect</td>
<td></td>
</tr>
<tr>
<td>caspase 9, caspase 3 and increasing Bcl-2/Bax ratio</td>
<td>Anti-apoptotic effects in brain</td>
<td>Neuroprotective effects</td>
<td>(Zhang et al., 2012a)</td>
</tr>
<tr>
<td>Reduction of tyrosine hydroxylase expression</td>
<td>Inhibition of dopamine biosynthesis</td>
<td>Anti-Atherosclerosis effect</td>
<td></td>
</tr>
<tr>
<td>Decrease in hippocampal BDNF mRNA expression</td>
<td>Ameliorating depression-like and anxiety-like behaviors</td>
<td>Anti-Atherosclerosis effect</td>
<td></td>
</tr>
<tr>
<td>Enhancing LXRApha-ABCA1-dependent cholesterol efflux</td>
<td>Inhibition of formation of foam cells by macrophages</td>
<td>Anti-osteoarthritis</td>
<td></td>
</tr>
<tr>
<td>Inhibition of gp91 super (phox) expression</td>
<td>Reduction of intracellular superoxide in macrophages</td>
<td>Anti-Atherosclerosis effect</td>
<td></td>
</tr>
<tr>
<td>Induction of human serum paraoxonase 1</td>
<td>Inhibition of oxidative modification of LDL</td>
<td>Protection against myocardial ischemia</td>
<td>(Yu et al., 2009)</td>
</tr>
<tr>
<td>Increasing NO production via PI3K/AKT/eNOS pathway</td>
<td>Up-regulation of endothelial progenitor cells mobilization and function</td>
<td>Anti-arrhythmic effect</td>
<td>(Xu et al., 2008; Xu et al., 2009a)</td>
</tr>
<tr>
<td>AMPK-dependent Rafl activation</td>
<td>Up-regulation of LDLR expression</td>
<td>Attenuation of left ventricular remodeling after MI.</td>
<td>(Zhang et al., 2014c)</td>
</tr>
<tr>
<td>Activating AMPK and PI3K-Akt-eNOS signaling</td>
<td>Anti-apoptotic effect in cardiomyocytes</td>
<td>Anti-osteoarthritis</td>
<td>(Lee et al., 2015)</td>
</tr>
<tr>
<td>Inhibition of p38 MAPK</td>
<td>Promoting autophagy</td>
<td>Anti-diabetes</td>
<td>(Zhang et al., 2012b)</td>
</tr>
<tr>
<td>Suppression of transient receptor potential vanilloid 4</td>
<td>Direct vasorelaxation and reducing vascular stiffness</td>
<td>Anti-hypertension</td>
<td>(Wang et al., 2015a)</td>
</tr>
<tr>
<td>Expression of Na+ /H+ exchanger</td>
<td>Enhancing the absorption of Na+ and water</td>
<td>Anti-arrhythmia</td>
<td>(Zhang et al., 2012)</td>
</tr>
<tr>
<td>Activation of Runx2 by p38 MAPK</td>
<td>Promotion of osteoblast differentiation</td>
<td>Anti-arrhythmia</td>
<td>(Lee et al., 2008)</td>
</tr>
<tr>
<td>Suppressing p38 MAPK activity</td>
<td>Suppression of chondrocyte apoptosis</td>
<td>Anti-diabetes</td>
<td>(Zhou et al., 2015)</td>
</tr>
</tbody>
</table>

5-HT, serotonin; AMPK, AMP-activated protein kinase; BDNF, brain-derived neurotrophic factor; LDL, low-density lipoprotein; LDLR, low-density lipoprotein receptor; MAPK, mitogen activated protein kinase; MI, myocardial infarction; MS, multiple sclerosis; NE, norepinephrine; NO, nitric oxide.

improvement of endothelial function (Xu et al., 2008). A clinical study has demonstrated that Berberine-induced up-regulation of the number and function of circulating EPCs in healthy subjects is related to NO production (Xu et al., 2009a). Mechanistically, it has been shown that improvement of the proliferative activity of EPCs by berberine is via the PI3K/AKT/eNOS signaling pathway (Xiao et al., 2014).

Elevated circulating endothelial microparticles are associated with endothelial dysfunction (Wang et al., 2009b). Berberine therapy (1.2 g/d) in healthy subjects for 1 month has reduced circulating CD31+/CD42– microparticles and upregulated endothelial function (Wang et al., 2009b). Another clinical study in healthy subjects also showed that berberine treatment significantly reduces circulating CD31+/CD42– MPs through reducing oxidative stress (Cheng et al., 2013).

Berberine has shown anti-inflammatory effects in vascular endothelial cells. These anti-inflammatory effects exert by inhibition of the TNF-alpha-induced expression of ICAM1, and the activation of NF kappaB in cultured human aortic endothelial cells (Liu et al., 2015b).

### Anti-arrhythmic effect

Berberine has shown anti-arrhythmic effect in stretch-induced arrhythmias after myocardial infarction in rats by reducing the incidence of premature ventricular beats and inhibiting the occurrence of ventricular tachycardia (Cao et al., 2012). In diabetic rats, also berberine produces anti-arrhythmic effects. The effects of berberine on IK1/Kir2.1 may be an important mechanism for this anti-arrhythmic effect (Yu et al., 2009; Wang et al., 2011b). Whole-cell patch-clamp in streptozotocin-induced diabetic rats were subjected to heart ischemia by the occlusion of left anterior descending coronary artery has shown that oral administration of berberine (100 mg/kg), recovers depressed I(to) and I(Ca) currents and significantly shortens the prolonged QTc interval (Cao et al., 2012). In addition, berberine also suppresses the current of hyperpolarization-activated cyclic nucleotide-gated four channels that may contribute to pacemaker currents (Ifs) and its antiarrhythmic action (Chen et al., 2014b).
Hypercholesterolemia

Berberine has been identified as a novel cholesterol-lowering drug acting through different mechanisms including up-regulation of low-density lipoprotein receptor expression via AMPK-dependent Raf-1 activation (Kong et al., 2008; Li et al., 2014b), down-regulation of PCSK9 through sterol regulatory element binding protein-2 activation (Cameron et al., 2008; Li et al., 2009a; Jia et al., 2014), and reducing the inhibition of PDE (Zhou et al., 2011). The mechanism of berberine differs from that of statins and combination of berberine (90 mg/kg/day, oral) with simvastatin (6 mg/kg/day, oral) in hyperlipidemic rats, reduce serum LDL cholesterol and serum triglyceride more effective than that of the simvastatin or berberine monotherapy. Therefore, combination therapy using simvastatin and berberine can be a new regimen for hypercholesterolemia (Kong et al., 2008).

In rabbits feeding with high fat diet, berberine reduced the serum total cholesterol, low-density lipoprotein cholesterol, and triglycerides levels, and aortic atherosclerosis, which the mechanisms were associated with the inhibition of iNOS activity and down-regulation of PPARγ mRNA level (Luo et al., 2012). Berberine also promotes CPT I A mRNA expression through stimulating PPARα (Shi et al., 2008; Wang et al., 2011a). Berberine elevates expressions of insulin-induced gene 2 (Chang et al., 2009; Luo et al., 2011), vitamin D receptor (Luo et al., 2011) low-density lipoprotein receptor, and scavenger receptor class-B type 1 genes in liver of high-fat diet rats that can inhibit the cholesterol synthesis of liver (Jin et al., 2010). The low dose of berberine (28 mg/kg) is more effective in countering hyperlipidemia than high dose in rabbits (112 mg/kg) (Chang et al., 2009; Jin et al., 2010; Luo et al., 2011).

In male Sprague-Dawley rats which fed by cornstarch-casein-sucrose-based high-cholesterol (2%, w/w) and high-fat (27.5%) diet, berberine reduced plasma triglycerides levels by 31% but had no effect on both T-C and non-HDL-C (Jia et al., 2008). Although the bioavailability of oral berberine is much lower than that of intraperitoneal administration, it had a stronger lipid-lowering effect, indicating that the gastrointestinal tract is important for the hypolipidemic effect of berberine (Gu et al., 2015). A part of this effect is through inhibiting the intestinal absorption and further by decreasing enterocyte cholesterol uptake and secretion and interfering with intraluminal cholesterol micellarization (Wang et al., 2014a). Berberine has also benefit effects on HDL-C. In non-obese diabetic mice, oral administration of 50, 150, or 500 mg of berberine/kg over 14 weeks, have increased HDL-C levels (Chueh and Lin, 2011).

Clinical studies also show that berberine is effective and safe to mildly improve lipid profile. In a clinical study in 228 subjects with primary hypercholesterolemia, berberine showed more effective than ezetimibe in reducing LDL cholesterol (31.7% vs. 25.4%, p < 0.001) and better tolerated (Pisciotta et al., 2012).

In a double-blind and placebo-controlled design, 144 subjects were enrolled and received 500 mg berberine b.i.d., for 3 months. Berberine reduced the body weight, body mass index, total cholesterol, triglycerides, and LDL cholesterol and increased HDL cholesterol compared with placebo (Derosa et al., 2013).

Cardioprotective effect on ischemia-reperfusion injury

Berberine has protective effect in ischemia reperfusion injury of the heart (Zeng et al., 2003). Recent studies have revised the mechanisms of this protective effect. Berberine significantly decreases AMPK protein concentration, and the ratio of adenosine diphosphate/adenosine triphosphate (ATP) and AMP/ATP in the myocardial of ischemic areas and increased AMPK protein concentration, and the ratio of AMP/ATP and adenosine diphosphate/ATP in the non-ischemia areas (Chang et al., 2012). In cultured neonatal rat cardiomyocytes, berberine shows antiapoptotic effect and improves cardiac functional recovery following myocardial I/R via activating AMPK and PI3K-Akt-eNOS signaling (Yu et al., 2009; Yu et al., 2015). Berberine regulates high mobility group box 1 and toll-like receptor to protect myocardial ischemia (Zhang et al., 2014a).

Promoting autophagy through inhibition of p38 mitogen activated protein kinase (MAPK) and activation of phospho-Akt signaling pathway (Zhang et al., 2014c) and up-regulating Notch1/Hex1-PTEN/Akt signaling (Li et al., 2014a; Yu et al., 2015), are another mechanism that attenuate left ventricular remodeling and cardiac dysfunction after myocardial infarction.

In a clinical study undertaken on 130 acute coronary syndrome patients undergoing percutaneous coronary intervention, berberine (300 mg, three times a day, for 30 days) in addition to standard therapy, has shown benefit effects via reducing circulating inflammatory markers including MMP-9, intercellular adhesion molecule-1, vascular cell adhesion molecule-1, interleukin-6, C-reactive protein, and monocyte chemoattractant protein (Meng et al., 2012).

Cardiotoxic

Berberine exerts positive inotropic effects and has been used in the treatment of congestive heart failure (Salehi, 2009). The high dose of berberine (63 mg/kg) can decrease left ventricular end-diastolic pressure, improve [-dp/dt(max)], decurtate left ventricular relax time constant quantity and decrease [Ca2+]i level in diastole heart failure rat models (Zhang et al., 2008b). Berberine also decreases plasma brain natriuretic peptide in rats with chronic congestive heart failure (Li et al., 2009c).

Cardiotoxic and protective effect of berberine were also exerted in cardiac dysfunction induced by hyperglycemia/hypercholesterolemia through alleviating cardiac lipid accumulation and promoting glucose transport (Dong et al., 2011).

Hypertension

In traditional medicine, B. vulgaris has been used in hypertension and arrhythmia ( Fatehi-Hassanabad et al., 2005). Several pharmacological studies demonstrated this effect of B. vulgaris and berberine (Fatehi-Hassanabad et al., 2005; Guo et al., 2015; Liu et al., 2015a; Wang et al., 2015a). Different mechanisms proposed for this effect including α1-adrenoceptor antagonism, ACE-inhibition (Salar et al., 2010) and...
directly release of NO/cGMP, inhibition of intracellular Ca\(^{2+}\) release from caffeine-sensitive pools, blocking of L-type calcium channels and the potentiation of acetylcholine (Derosa et al., 2012).

A recent work has suggested that berberine could inhibit the activities of RAS and pre-inflammatory cytokines IL-6, IL-17, and IL-23, which are involved in the pathophysiolog of hypertension (Guo et al., 2015). Berberine induces direct vascular relaxation and lowers vascular stiffness through suppression of transient receptor potential vanilloid 4 (Wang et al., 2015a). Berberine also reduces endothelium-dependent contractions through activating AMPK, which reduces endoplasmic reticulum stress and down-regulates cyclooxygenase-2 (COX-2) in spontaneously hypertensive rats carotid arteries (Liu et al., 2015a). The cardiovascular effects of berberine were cited in Table 3.

**IMMUNE SYSTEM EFFECTS**

**Anti-inflammatory and immunosuppressive effects**

Berberine reduces the production and mRNA expression of thymic stromal lymphopoietin (TSLP) in human mast cell line-1 cells and inhibits the production of TSLP in primary mast cells and activation of caspase-1 in human mast cell line-1 cells. Regarding the role of TSLP in allergic diseases such as atopic dermatitis, asthma, and chronic obstructive pulmonary disease, berberine can help to treat these diseases (Moon et al., 2011). Berberine also suppresses IgE production by human B cells and may consider as a treatment for IgE-mediated food allergy (Yang et al., 2014).

Berberine possess anti-inflammatory effects trough different mechanisms. Berberine reduces the leukocyte-endothelium adhesion and vascular cell adhesion molecule-1 expression in lung and decreases the number of adhered THP-1 cells and vascular cell adhesion molecule-1 expression at both RNA and protein levels (Wu et al., 2012).

Berberine attenuates lipopolysaccharide-induced expression of inflammatory genes (inducible nitric oxide synthase [iNOS], COX-2, interleukin [IL]-6), and the generation of nitric oxide and reactive oxygen species, but enhances the transcription of Nrf2-targeted antioxidative genes (nicotinamide adenine dinucleotide phosphate quinone oxidoreductase-1 [NQO-1], heme oxygenase-1), as well as the nuclear localization and phosphorylation of Nrf2 protein. Berberine-induced activation of Nrf2 is AMPK-dependent (Jeong et al., 2009; Lee et al., 2013; Mo et al., 2014). Berberine effectively reduces Src expression and activity and inhibits TLR-mediated cell motility in macrophages (Cheng et al., 2015). It is also a potent natural inhibitor of phospholipase A (2) (Chandra et al., 2011).

Berberine significantly inhibits splenocyte proliferation, IL-2, TNF-α, and IFN-γ secretion. Berberine has also inhibitory effects on the Th17 response via a direct effect on T cells and an indirect action via dendritic cells. Therefore, berberine may act as a potential immunosuppressive drug (Ma et al., 2013a; Yang et al., 2013).

The ethanolic extract of barberry is able to decrease the formalin and acetic acid injection-induced inflammation in foot and peritoneum and also can ameliorate an external body-induced chronic inflammation as well. In addition, the reduction of late phase of chronic pain in parallel with chronic inflammation suppression is considerable (Kiasalari et al., 2011).

**ENDOCRINE EFFECTS**

**Contraceptive**

Berberine can inhibit in vitro development of zygotes of mice and receiving of berberine by mated female mice decreases the proportions of recovered blastocysts and full-term fetuses (Tsuno and Kato, 2011). This berberine-induced inhibition of the development of mouse zygotes is reversible (Sugimoto et al., 2012).

**Polycystic ovary syndrome**

Insulin resistance and hyperinsulinemia play an important role in the pathogenesis of polycystic ovary syndrome (PCOS), which is characterized by ovulatory dysfunction, hyperandrogenism, and presence of polycystic ovaries on pelvic scanning. Insulin resistance is significantly associated with the long-term risks of metabolic syndrome and cardiovascular disease. Berberine reduces insulin resistance similar to metformin (Li et al., 2013c). Some studies have evaluated the effect of berberine on insulin resistance in women with PCOS (Wei et al., 2012; Li et al., 2013b; Li et al., 2013c).

For example, in a prospective study in 150 infertile women with PCOS undergoing in vitro fertilization treatment, patients were randomized to receive berberine, metformin, or placebo tablets for 3 months before ovarian stimulation. In the berberine and metformin groups, greater reductions in total testosterone, fasting glucose, and fasting insulin, free androgen index and increases in sex hormone-binding globulin, were observed in comparison with placebo group. Three months of treatment with metformin or berberine before the in vitro fertilization cycle increased the pregnancy rate and reduced the incidence of ovarian hyperstimulation syndrome. Totally, berberine had a more pronounced therapeutic property and achieved more live births with fewer side effects than metformin (An et al., 2014). In an in vitro model of insulin resistant ovary, using dexamethasone to induce insulin resistance, berberine could alleviate the degree of insulin resistance and the androgen synthesis, indicating that that this compound has favorable therapeutic effect for the treatment of polycystic ovaries (Wang et al., 2010).

**Antiabortion**

Traditional Chinese medicinal herbs containing berberine have been historically used to prevent miscarriage. In a study in mouse pronuclear embryos, berberine significantly increased the cell numbers of mouse blastocysts and decreased apoptotic cell rates in vitro. Berberine significantly increased miRNA-21 and Bcl-2 transcription and protein levels and significantly

---

**Copyright © 2016 John Wiley & Sons, Ltd.**

<table>
<thead>
<tr>
<th>Therapeutic effect</th>
<th>Kind of study</th>
<th>Mechanism</th>
<th>Dose (or concentration)</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anti-Atherosclerosis</td>
<td>Cell culture</td>
<td>Enhancing cholesterol efflux</td>
<td>5, 10, and 20 μM for 6–24 h</td>
<td>Lee et al., 2010b</td>
</tr>
<tr>
<td></td>
<td>Cell culture</td>
<td>Inhibition of gp91 superoxide expression</td>
<td>1.3 and 10 μM</td>
<td>Sarna et al., 2010b</td>
</tr>
<tr>
<td></td>
<td>Cell culture</td>
<td>Inhibition of matrix metalloproteinase-2 expression</td>
<td>1–50 μM</td>
<td>Huang et al., 2012</td>
</tr>
<tr>
<td></td>
<td>Cell culture</td>
<td>Induction of human serum paraoxonase 1</td>
<td></td>
<td>Cheng et al., 2011</td>
</tr>
<tr>
<td></td>
<td>Cell culture</td>
<td>Inhibition of matrix metalloproteinase-9 expression</td>
<td>5–50 μM</td>
<td>Huang et al., 2011</td>
</tr>
<tr>
<td></td>
<td>Cell culture</td>
<td>Reducing the activity of NF-κB in oxLDL-induced macrophages</td>
<td>1–50 μM</td>
<td>Huang et al., 2012</td>
</tr>
<tr>
<td></td>
<td>Cell culture</td>
<td>Improvement of endothelial function</td>
<td>20 μM</td>
<td>Xiao et al., 2014</td>
</tr>
<tr>
<td></td>
<td>Human</td>
<td>Anti-arrhythmic</td>
<td>1.2 g/d</td>
<td>Wang et al., 2009b</td>
</tr>
<tr>
<td></td>
<td>Animal</td>
<td>Hypercholesterolemia</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Animal</td>
<td>Promoting CPT I A mRNA expression</td>
<td>60 and 300 mg/kg</td>
<td>Wang et al., 2011a</td>
</tr>
<tr>
<td></td>
<td>Animal</td>
<td>Elevating expression of insulin-induced gene 2</td>
<td>28 and 112 mg/kg</td>
<td>Luo et al., 2011</td>
</tr>
<tr>
<td></td>
<td>Animal</td>
<td>Increasing expression of scavenger receptor class-B type 1 gene</td>
<td>28 and 112 mg/kg</td>
<td>Jin et al., 2010</td>
</tr>
<tr>
<td></td>
<td>Animal</td>
<td>Inhibiting the intestinal absorption of cholesterol</td>
<td>150 mg/kg</td>
<td>Wang et al., 2014a</td>
</tr>
<tr>
<td></td>
<td>Animal</td>
<td>Ischemia-reperfusion injury</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Animal</td>
<td>Activating AMPK and PI3K-Akt-eNOS signaling</td>
<td>200 mg/kg/d</td>
<td>Yu et al., 2015</td>
</tr>
<tr>
<td></td>
<td>Animal</td>
<td>Regulation of high mobility group box 1 and toll-like receptor</td>
<td>30 and 60 mg/kg/d</td>
<td>Zhang et al., 2014a</td>
</tr>
<tr>
<td></td>
<td>Animal</td>
<td>Promoting autophagy through inhibition of p38 MAPK</td>
<td>10 and 50 mg/kg/d</td>
<td>Zhang et al., 2014c</td>
</tr>
<tr>
<td></td>
<td>Animal</td>
<td>Up-regulating Notch1/Hes1-PTEN/Akt signaling</td>
<td>200 mg/kg/d</td>
<td>Yu et al., 2015</td>
</tr>
<tr>
<td></td>
<td>Human</td>
<td>Reducing circulating inflammatory markers</td>
<td>300 mg, t.i.d.</td>
<td>Guo et al., 2015</td>
</tr>
<tr>
<td></td>
<td>Human</td>
<td>Direct vascular relaxation through suppression of TRPV4</td>
<td>20–100 μM</td>
<td>Wang et al., 2015a</td>
</tr>
</tbody>
</table>

ADP, adenosine diphosphate; AMPK, AMP-activated protein kinase; EPC, endothelial progenitor cells; MAPK, mitogen activated protein kinase; RAS, renin-angiotensin system.
decreased caspase-3 and chromosome ten transcription and protein levels. It can be concluded that berberine has anti-apoptotic and pro-growth effects in mouse blastocysts (Zhang et al., 2015a).

**Diabetes**

In China, in 1986, a hypoglycemic effect was accidentally found when berberine was used to diabetic patients with diarrhea (Pang et al., 2015). Moreover, berberine has positive effects in treating diabetic nephropathy, diabetic neuropathy, and diabetic cardiomyopathy (Pang et al., 2015). During 2009–2015, more than 110 clinical trials and animal studies have evaluated and demonstrated antidiabetic effect of berberine. Many mechanisms such as increasing insulin sensitivity, modulating gut microbiota, activating the adenosine AMPK pathway, promoting intestinal gluconic acid-like protein-1 secretion, stimulating glycogenolysis in peripheral tissue cells, inhibiting gluconeogenesis in liver, increasing glucone transporter, and upregulating hepatic low-density lipoprotein receptor mRNA expression have been proposed for antidiabetic activity of berberine (Vuddanda et al., 2010; Xiao et al., 2011; Derosa et al., 2012). Regarding there are more than ten review articles about berberine and diabetes (Cicero and Tartagni, 2012; Dong et al., 2012; Pang et al., 2015), we refer the readers to those papers.

**Obesity**

Many studies suggest that berberine has an anti-obesity effect in animals and cell culture via inhibition of adipogenesis (Liu et al., 2008b; Hwang et al., 2009; Zhang et al., 2014d). Promotion of AMPK activity (Kim et al., 2009), decrease in the expression of PPARγ and C/EBPα, and increase in expression of GATA-2 and GATA-3 both at the gene and protein levels (Hu, 2010), inhibition of of IκB kinase β (ser 181)(Shang et al., 2010), increasing mitochondrial SirT3 activity (Teodorov et al., 2013), inhibition of proinflammatory IL-6 and TNF-alpha protein release (Spatuzza et al., 2014) and regulating gut microbes (Xie et al., 2011) have proposed as mechanisms of anti-obesity effect of berberine in in vitro and in vivo studies. In a pilot study in obese human subjects, administration of 500 mg berberine orally t.i.d. for 12 weeks produced a mild weight loss (average 5 lb/subject) in obese human subjects. Tests of cardiovascular, hematological, liver, and kidney function following berberine treatment showed no detrimental side effects to this natural compound. Collectively, this study has showed that berberine has a moderate weight loss effect (Hu et al., 2012b)

**GASTROINTESTINAL TRACT**

**Liver**

**Liver fibrosis.** The proliferation of hepatic stellate cells has important role in the development of fibrosis during liver injury. 48 h incubation of rat hepatic stellate cells with berberine has inhibited the proliferation of these cells and induced cell cycle arrest in G1 phase. Therefore, berberine can prevent hepatic fibrosis by inhibition of hepatic stellate cell proliferation (Sun et al., 2009). Another study has shown that berberine can prevent experimental liver fibrosis through regulation of lipid peroxidation and anti-oxidant system (Zhang et al., 2008a).

**Nonalcoholic Fatty liver disease.** The Nonalcoholic Fatty liver disease (NAFLD) is one of the most prevalent causes of liver enzymes enhancement and has a close relationship with obesity, dyslipidemia, type II diabetes, and hypertension (Kashkooli et al., 2015). Berberine can alleviate fatty liver in db/db and ob/ob mice (Chang et al., 2010), rat (Zhan et al., 2010), and human (Kashkooli et al., 2015). Proposed mechanisms include reversing the methylation state of genes involved in lipid metabolism (Chang et al., 2010), lowering blood lipid level and improving hepatic anti-oxidative capability (Zhan et al., 2010), down-regulation of uncoupling protein-2 mRNA and protein expressions in hepatic tissue (Yang et al., 2011), improving insulin resistance of NAFLD by up-regulating mRNA and protein levels of IRS-2, a key molecule in the insulin signaling pathway (Xing et al., 2011), up-regulating the mRNA expression of leptin receptor (Yin et al., 2009), down-regulation of the LXRalpha/FAS signaling pathway of hepatocytes (Han et al., 2015) and restoring the expression of L-type Pyruvate Kinase gene (Zhang et al., 2015b).

**Carbon tetrachloride induced liver toxicity.** Berberine has hepatoprotective effects against Carbon tetrachloride (CCl4)-induced hepatotoxicity (Feng et al., 2010). The hepatoprotective mechanisms of berberine may be related to the attenuation of oxidative/nitrosative stress and free radical scavenging, as well as to the inhibition of TNF-α, inducible nitric oxide synthase, and cyclooxygenase-2 (Domitrovic et al., 2011). In a clinical trial on 184 patients with NAFLD, administration of berberine (0.5 g t.i.d) has been resulted in a significant reduction of NAFLD and related metabolic disorders (Yan et al., 2015).

Berberis vulgaris L. root, stem, and fruit extracts also have protective effect against the CCl4-induced oxidative damage via modulation on detoxification enzymes and antioxidant and free radical scavenger effects (Fallah Huseini et al., 2010; Eidi et al., 2011; Fallah Huseini et al., 2012).

**Anti-diarrhea**

Berberine has been widely used for treating of gastroenteritis and diarrhea patients in China for a long time (Zhang et al., 2012b). Previously, we reviewed antidiarrheal effects of berberine (Derosa et al., 2012). During recent years several studies indicated that berberine has various pharmacological effects, including inhibition of intestinal fluid accumulation and ion secretion (Alzamora et al., 2011), anti-inflammatory (Amasheh et al., 2010), anti-microbial (Gu et al., 2011), anti-inhibition of smooth muscle contraction (Li et al., 2011a), each of which may contribute to the anti-diarrhea effect. For example, it has been shown that berberine reduces epithelial gut permeability via reinforcing tight junctions (Gu et al., 2009) and ameliorates pro-inflammatory cytokines involve in intestinal permeability in CCl4-induced diarrhea model.
epithelia tight junction damaging (Li, et al., 2010b; Cao et al., 2013). Several studies have also demonstrated effects of berberine on ion exchange and water transfer including inhibition of cAMP-activated potassium current [I K (cAMP)] (Yin et al., 2010), inhibitory effect on colonic Cl⁻ secretion (Alzamora et al., 2011), enhancing the absorption of Na⁺ and water via the expression of Na⁺/H⁺ exchanger (Zhang et al., 2012b).

**Inflammatory diseases of gut**

Berberine prevents damage to the intestinal mucosal barrier in early phase of sepsis (Amasheh et al., 2010). In animal models of endotoxemia, berberine protects gut damage through different mechanisms including attenuation of disruption of tight junctions in intestinal epithelium (Gu et al., 2011), suppressing the increased TNF-alpha, reducing enterocyte apoptosis (Li et al., 2011a), IL-1beta, and nitrite oxide (NO) (Zhang et al., 2011), attenuating the disruption of tight junctions in intestinal epithelium (Li et al., 2012a). TNF-alpha, reducing enterocyte apoptosis (Li et al., 2011a), IL-1beta, and nitrite oxide (NO) (Zhang et al., 2011), attenuating the absorption of Na⁺ and water via the expression of Na⁺/H⁺ exchanger (Zhang et al., 2012b).

**SKIN EFFECTS**

Berberine has proposed as an anti-skin aging agent due to its inhibitory effect on basal and UV-induced matrix metalloproteinase-1 and matrix metalloproteinase-9 expressions in human dermal fibroblasts and normal human keratinocytes, respectively (Kim and Chung, 2008a; Kim et al., 2008b). Berberine has inhibitory effects on subcutaneous preadipocytes differentiation and facilitates lipolysis in adipocytes and therefore, is expected to be useful for slimming and related skin troubles such as skin swelling, cellulite, and so on (Yashiki et al., 2010).

As we mentioned in the previous review article, *B. vulgaris* L. has shown antilipogenic effect in the sebaceous glands of hamster (Derosa et al., 2012). In 2012, in a clinical study in adolescents aged 12–17 years with moderate to severe acne vulgaris, oral capsules containing aqueous extract of dried barberry (600 mg daily for 4 weeks, n = 25) significantly reduced the mean number of non-inflamed, inflamed, and total lesions as well as mean Michaelson’s acne severity score. It seems that oral aqueous extract of barberry is a safe, well-tolerated, and effective in adolescents with moderate to severe acne vulgaris (Fouladi, 2012). In another study on patient with mild-to-moderate acne, *B. vulgaris* fruit juice was effective against acne lesions (Johnson and Rafikhah, 2014).

**ANTIMICROBIAL EFFECTS**

**Antibacterial effects**

Berberine is widely used as an anti-infective in traditional medicine (Boberek et al., 2010). Berberine has been shown to exhibit antibacterial activity against a variety of bacteria, including *Streptococcus agalactiae* (MIC = 78 μg/mL) (Peng et al., 2015), *Actinobacillus pleuropneumoniae* (MIC = 0.3125 mg/mL) (Kang et al., 2015), different strains of *Staphylococcus* (MIC = from 16 to 512 micro g/mL) (Wojtyczka et al., 2014) and, *Shigella dysenteriae* (Kong et al., 2010). Berberine also effectively prevents the formation of *E. epidermidis* biofilm on the surface of the titanium disk and is a potential agent for the treatment of perioperative infection (Wang et al., 2009c; Wang et al., 2009d).

There are several studies about possible berberine mechanism(s) of antibacterial actions. A number of studies demonstrate that berberine is a DNA ligand, able to bind both single-stranded and double-stranded DNA *in vitro* (Bae, Lee, Kim, et al., 2013; Chi et al., 2014a; Chi et al., 2014b; Liu et al., 2014). Therefore, binding of berberine to DNA in bacteria can lead to DNA damage. A Recent study indicates that the primary mechanism of antibacterial action of berberine is due to inhibition of the cell division protein FtsZ (Boberek et al., 2010). Berberine has a synergistic effect with some common antibiotics especially with linezolid, cefoxitin, and erythromycin (Wojtyczka et al., 2014). This suggests the potential use of berberine in combinations with other antibiotics as an efficient therapeutic tool for antibiotic-resistant bacterial infections.

**Antiparasitic effects**

Several studies show that berberine via its antioxidant activity exerts beneficial effects on *Schistosoma mansoni*-induced organ toxicity in splenic (Al-Quraishy et al., 2013), hepatic (Dkhil, 2014), renal and testicular tissues of mice (Dkhil et al., 2014).

A similar protective effect has been shown in *Plasmodium chabaudi*-induced spleen injury (mice malaria) (Dkhil et al., 2015).

*B. vulgaris* methanolic extract and berberine alone have demonstrated good scolicidal activities against protoscoleces of hydatid cysts in low concentration and short exposure time on *in vitro* model. But *in vivo* efficacy of *B. vulgaris* and berberine has not been evaluated (Mahmoudvand et al., 2014b).

Berberine also has a promising anti-leishmanial effect, with IC50 = 7.1 μM in *L. donovani* promastigotes (Saha et al., 2009), and IC50 values varying from 2.1 to 26.6 μg/mL in *L. major* and *L. tropica* promastigotes (Mahmoudvand et al., 2014a). Berberine exerts an apoptosis-like death (Saha et al., 2009) and modulates macrophage effector responses via the MAPK pathway (Saha et al., 2011).

The ethanolic extract of *B. vulgaris* fruits, also exhibits an effective leishmanicidal activity against *L. tropica* on *in vitro* model (IC50 = 4.83 μg/mL) (Mahmoudvand et al., 2014c). A lotion prepared from root bark extract of *B. vulgaris* has shown good
suppression effects (90% recovery) in mice infected with cutaneous leishmaniasis. *(L. major)* (Salehabadi et al., 2014).

**Antiviral**

Berberine has shown antiviral properties against herpes simplex virus types 1 and 2 (HSV-1, 2) in Vero cells (Chin et al., 2010; Dkhil and Al-Quraishy, 2014). Berberine at 150 μg/mL provided 76.5% inhibition of plaque of HSV-1 and 80% inhibition against HSV-2 (Dkhil et al., 2014). Berberine strongly inhibits the growth of two H1N1 strains (PR/8/34 or WS/33) of the influenza A virus. Berberine does not prevent the expression of key viral proteins, but can reduce the growth of the virus by inducing the formation of viral protein aggregates within the host cell cytoplasm (Cecil, 2011; Cecil et al., 2011). An in vivo influenza virus model in mice also has shown that berberine reduced mouse mortality from 90% to 55% and decreased virus titers in the lungs on day 2 postinfection (Wu et al., 2011). Berberine also suppresses the replication of respiratory syncytial virus in epithelial cells, probably via inhibition of RSV-mediated early p38 MAPK activation (Shin et al., 2015).

**Antifungal**

Berberine has shown antifungal activity against *Candida albicans* (MIC = 34.52 μg/mL) (Zhao et al., 2010), *Microsporum canis* (Xiao et al., 2015) and *B. cinerea* (Parvu et al., 2010). *B. vulgaris* bark extract also has significant antifungal activity against *B. cinerea*, and its effect is stronger than that of pure berberine (Parvu et al., 2010). There are some studies about synergistic effects of berberine and fluconazole against fluconazole-resistant *C. albicans*. (Xu et al., 2009b; Li et al., 2013a). In this synergism effect, berberine plays a major antifungal role, while fluconazole plays a role in increasing the intracellular berberine concentration (Li et al., 2013a). Endogenous ROS augmentation and mitochondrial aerobic respiration shift contribute to the synergistic action of fluconazole plus berberine against fluconazole-resistant *C. albicans* (Xu et al., 2009b).

**MUSCULOSKELETAL EFFECTS**

**Osteoporosis**

Berberine inhibits osteoclastogenesis and bone resorption through amelioration of RANKL-mediated osteoclast formation and survival (Hu et al., 2008). In a cell culture system, the strongest inhibitory effect has been exhibited at the concentration of 10 μmol/L (Wei et al., 2009). On the other hand, in osteoblastic cells; berberine enhances osteoblast differentiation through activation of Runx2 by p38 MAPK (Lee et al., 2008). Taken together, berberine may have a therapeutic potential for treatment of osteoporosis.

Berberine has prevented glucocorticoid-induced osteoporosis in rats by inhibiting bone resorption and improving bone formation (Xu et al., 2010).

**Osteoarthritis**

Several studies suggest a protective role for berberine in the development of osteoarthritis. In an IL-1β-induced rat osteoarthritis model, berberine has shown an anticitabatic effect and in IL-1β-induced rat articular chondrocytes, berberine has decreased IL-1β-induced NO production and glycosaminoglycan release (Hu et al., 2011a). Berberine also ameliorates cartilage degeneration by promoting matrix production of chondrocytes, partly via activation of Akt (Zhao et al., 2014). Berberine suppresses chondrocyte apoptosis and ameliorates cartilage degeneration via activating AMPK signaling and suppressing p38 MAPK activity (Zhou et al., 2015).

**Rheumatoid arthritis**

Berberine proposed to have therapeutic potentials in the treatment of rheumatoid arthritis (Wang et al., 2011d). Berberine selectively induces apoptosis in dendritic cells (Hu et al., 2011b) and exerts antiproliferative effects against activated rheumatoid arthritis fibroblast-like synoviocytes which play a key role in the initiation and progression of rheumatoid arthritis (Wang et al., 2011d). In rats with bovine type II collagen-induced arthritis, an animal model for rheumatoid arthritis, berberine decreases arthritic scores and suppresses collagen–specific immune responses (Wang et al., 2014b).

**RENAL EFFECTS**

**Urolithiasis**

*B. vulgaris* is a widely used plant for the treatment of urolithiasis (Bashir et al., 2010). Animal studies rationalize its medicinal use for the treatment of urolithiasis. For example, the aqueous-methanolic extract of *B. vulgaris* root bark, inhibited deposition of calcium oxalate crystal in renal tubules and protected against related changes including polyuria, impaired renal function, and the development of oxidative stress in kidneys of rats were undergone a model of calcium oxalate urolithiasis (developed in male Wistar rats by adding 0.75% ethylene glycol in drinking water) (Bashir et al., 2010). In same animal model of calcium oxalate urolithiasis, berberine has also shown antiurolithic property through a combination of antioxidant, diuretic, urinary alkalizing, and hypocalciuric effects (Bashir, Gilani, Siddiqui, et al., 2010).

**Renal ischemia/reperfusion**

Ischemia/reperfusion injury plays a crucial role in renal transplantation. Berberine pretreatment has been shown to attenuate ischemia/reperfusion injury by suppression of mitochondrial stress and endoplasmic reticulum stress pathways (Yu et al., 2013). Berberine has also an ameliorative effect on pulmonary and hepatic injuries following renal ischemia/reperfusion in rats (Gholampour et al., 2014; Gholampour et al., 2015).
PREVENTION OF ADVERSE DRUG REACTIONS

Cisplatin-induced kidney damage

In a study in mice, berberine has shown nephroprotective activity against Cisplatin-induced renal injury through the inhibition of oxidative/nitrosative stress, apoptosis, inflammation, and autophagy (Domitrovic et al., 2013).

Isoniazid-induced hepatotoxicity

Concurrent administration of berberine and isoniazid in rats protects against isoniazid-induced oxidative stress and inflammation leading to liver injury. This protective effect can be related to its ability to up-regulate PPAR and suppression of NF-kB, iNOS, and release of the pro-inflammatory cytokines (Mahmoud et al., 2014).

Acute radiation intestinal syndrome in abdomen radiotherapy

Radiation-induced acute intestinal symptoms are the most relevant complication of abdominal and pelvic radiation. In a clinical trial on 36 patients, pretreatment with berberine ameliorated the incidence and severity of radiation-induced acute intestinal symptoms in patients with abdominal/pelvic radiotherapy (Li et al., 2010a).

Bleomycin induced pulmonary toxicity

Berberine administration exhibited the beneficial effects against bleomycin-induced lung injury and fibrosis in rats through activating Nrf2 and suppressing NF-kappaB dependent inflammatory and TGF-beta1 mediated fibrotic events (Chitra et al., 2013).

Weight gain associated with antipsychotics

Weight gain is a common adverse effect of second generation antipsychotics such as clozapine and risperidone. Increased peripheral adipogenesis via the sterol regulatory element binding factor-1 pathway is one critical mechanism proposed for antipsychotic drug-induced weight gain. In a cell culture study, berberine diminished the induction of adipogenesis and downregulated mRNA and protein expression levels of sterol regulatory element binding factor-1-related proteins (Hu et al., 2010). In a rat model of olanzapine-induced weight gain, 2 weeks administration of metformin and berberine significantly reduced the white fat accumulation and olanzapine-induced weight gain (Hu et al., 2014).

Doxorubicin-induced cardiotoxicity

Pretreatment with berberine has significantly attenuated doxorubicin-induced cardiotoxicity in mice (Zhao et al., 2011). Another study in rat has shown that berberine attenuates doxorubicin-induced cardiomyocyte apoptosis via inhibiting an increase in the AMP/ATP ratio and AMPKα phosphorylation, protecting mitochondria as well as elevating Bel-2 expression (Lv et al., 2012).

Berberine also has inhibited the metabolism of doxorubicin in the cytoplasm of rat heart and decreased the accumulation of doxorubicinol (a metabolite of doxorubicin) in heart (Hao et al., 2015). On the other hand, berberine has sensitized A549, HeLa, and HepG2 cells to the anticancer effects of doxorubicin (Tong et al., 2012). Therefore, it seems that berberine decreases cardiotoxicity and increases anticancer effects of doxorubicin.

Gastric damage induced by nonsteroidal anti-inflammatory drugs

The protective effect of berberine on gastric damage induced by nonsteroidal anti-inflammatory drugs has evaluated in rats and demonstrated that berberine exerts protective effect on gastric damage induced by nonsteroidal anti-inflammatory drugs and the increase of PGE2 and COX-1, as well as decrease of NO and COX-2 are probable mechanisms (Wang et al., 2012).

CONCLUSION

The pharmacological properties of berberine and \textit{B. vulgaris} propose them as natural drugs for clinical use in different diseases and pathological conditions including diabetes, cancers, cardiovascular disease, hyperlipidemia, hypertension, diarrhea, inflammation, bacterial and viral infections, cerebral ischemia, mental disease, Alzheimer, osteoporosis, and etc. Cancer comprises most numbers of published articles followed by diabetes, cardiovascular, central nervous system, gastrointestinal, antimicrobial, pharmacokinetic, musculoskeletal, and prevention of adverse drug reactions. Regarding toxicity, berberine seems to be almost safe in customary doses but there are not enough clinical documents about berberine and \textit{B. vulgaris} safeties. Interaction with other drugs is another aspect must be considered in clinical use of berberine. Metformin, ketoconazole, digoxin, and cyclosporine are among most studied drug interactions of berberine. The inhibition of intestinal P-gp and CYPs are two major mechanisms in drug–drug interaction of berberine and other drugs. The effect of berberine on CYPs activity is dose-dependent. Lower doses of berberine appear to have a low risk of drug–drug interactions, but high doses of berberine may suppress CYPs activity and cause drug–drug interactions. Regarding common use of berberine in diabetic patients, this drug–drug interaction is very important. In future, more reliable clinical trials are needed to evaluate the efficacy of berberine in treating different pathological conditions. Poor bioavailability of berberine (less than 1%) limits clinical use of berberine and several strategies have been tested to improve the bioavailability of berberine.


Hu Y Effects of Berberine and its combinations on adipogenesis. 3484268 Ph.D., South Dakota State University, Ann Arbor, 2010.


Liu Y, Lou SY, He YM. 2008b. Effects of berberine on cell proliferation, peroxisome proliferation activated receptor gamma,


alpha in peripheral blood mononuclear cells (PBMCs) of human subjects. *Front Pharmocol Biol* 5: 240.


