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Pharmacological activities and medicinal uses of berberine: A review

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ABSTRACT

Berberine (BBR) is an isoquinoline derivative alkaloid that has been identified from a variety of plant species including Cortex phellodendron (*Huang bai*), *Hydrastis canadensis* (goldenseal), and *Rhizoma coptidis* (Huanglian). A growing body of research has demonstrated that this chemical has a wide range of biological functions, including antioxidant and anti-inflammatory, anticancer, and anti-hyperglycemic properties. BBR has been proven in studies to reduce the production of inflammatory mediators such as TNF-, IL-1, IL-6, and IL-8. Furthermore, BBR appears to boost the cellular antioxidant defense mechanism by raising the activity of CAT, SOD, and GPx while reducing OS variables such as protein carbonyl (PC) content, MDA, and NO levels. This review threw light on the pharmacological activities and medicinal uses of BBR.

Introduction

Berberine (BBR) (5,6-dihydro-9,10-dimethoxybenzo[g]-1,3-benzodioxolo [5,6-a] quinolizinium) is a nonbasic and quaternary benzylisoquinoline alkaloid, a relevant molecule in pharmacology and medicinal chemistry. Indeed, it is known as a very important natural alkaloid for the synthesis of several bioactive derivatives by means of positions for the design of new, selective, and powerful drugs (Chen *et al*., 2014).

Berberine has been detected, isolated, and quantified from various plant families and genera including Annonaceae (*Annickia, Coelocline, Rollinia, and Xylopia), Berberidaceae (Berberis, Caulophyllum, Jeffersonia, Mahonia, Nandina, and Sinopodophyllum), Menispermaceae (Tinospora), Papaveraceae (Argemone, Bocconia, Chelidonium, Corydalis, Eschscholzia, Glaucium, Hunnemannia, Macleaya, Papaver, and Sanguinaria), Ranunculaceae (Coptis, Hydrastis, and Xanthorhiza), and Rutaceae (Evodia, Phellodendron, and Zanthoxyllum)*. The genus *Berberis* is well-known as the most widely distributed natural source of BBR. The bark of B. vulgaris contains more than 8% of alkaloids, BBR being the major alkaloid (about 5%) (Arayne *et al*., 2007)

Berberine is an isoquinoline derivative alkaloid isolated from many plant species like Cortex phellodendron (*Huang bai*), *Hydrastis canadensis* (goldenseal), and *Rhizoma coptidis* (Huanglian) (Kuo *et al*., 2004). Recently, an increasing number of studies have revealed this compound has an extensive spectrum of biological functions such as antioxidant and anti-inflammatory (Li, Z., *et al*., 2014), anticancer (Sun *et al*., 2009), and anti-hyperglycemic (Mahmoud *et al*., 2017) effects. Studies have shown that BBR attenuates the output of inflammatory mediators like TNF-α, IL-1β, IL-6, and IL-8 (Lou *et al*., 2011; Zhang *et al*., 2016). In addition, BBR seems to increase the cellular antioxidant defense machinery including increasing the activity of CAT, SOD, and GPx, and decreasing OS factors like protein carbonyl (PC) content, MDA, and NO levels (Zhou and Zhou, 2011).

BBR is metabolized in the liver by oxidative demethylation, which is performed by the cytochrome P450 enzyme system (mainly by CYP2D6, CYP1A2 and CYP3A4), to yield four major phase I metabolites (demethylene berberine, berberrubine, jatrorrhizine, and thalifendine) (Liu, C.S. *et al*., 2016); these are subsequently glucuronidated via UDP-glucuronosyltransferase (UGT) to their corresponding phase II metabolites. (Guo *et al*., 2016; Liu, C.S. *et al*., 2016).

These BBR metabolites act on the same targets as BBR (e.g., AMPK and the low-density lipoprotein receptor (LDLR)) but with a lower potency (Li *et al*., 2004). Ultimately, BBR and its derivatives are excreted primarily by hepatobiliary and renal pathways. Thus, there is a need for effective strategies to improve the oral bioavailability of BBR to enable its effective use in clinical settings.

In this review, we threw the light on the pharmacological activities and medicinal uses of BBR.

The use of BBR in folk medicine

In the Berberidaceae family, the genus *Berberis* comprises ~450–500 species, which represent the main natural source of berberine. Plants of this genus are used against inflammation, infectious diseases, diabetes, constipation, and other pathologies (Singh *et al*., 2010). The oldest evidence of using barberry fruit (*Berberis vulgaris*) as a blood purifying agent was written on the clay tablets in the library of the Assyrian emperor Assurbanipal during 650 BC (Karimov and Shakirov, 1993).

In Asia, the extensive use of the stem, stem bark, roots, and root bark of plants rich in berberine, particularly *Berberis* species, has more than

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3000 years of history. Moreover, they have been used as raw material or as an important ingredient in Ayurvedic and traditional Chinese medicine (Birdsall, 1997; Kirtikar and Basu, 1998; Gupta and Tandon, 2004; Kulkarni and Dhir, 2010).

In Ayurveda, *Berberis* species have been traditionally used for the treatment of a wide range of infections of the ear, eye, and mouth, for quick healing of wounds, curing hemorrhoids, indigestion, and dysentery, or treatment of uterine and vaginal disorders. It has also been used to reduce obesity, and as an antidote for the treatment of scorpion sting or snakebite (Dev, 2006). Berberine extracts and decoctions are traditionally used for their activities against a variety of microorganisms including bacteria, viruses, fungi, protozoa, and helminthes, in Ayurvedic, Chinese, and Middle-Eastern folk medicines (Tang *et al*., 2009; Gu *et al*., 2010).

In Yunani medicine, *Berberis asiatica* has multiple uses, such as for the treatment of asthma, eye sores, jaundice, skin pigmentation, and toothache, as well as for favoring the elimination of inflammation and swelling, and for drying ulcers (Kirtikar and Basu, 1998). Decoction of the roots, and stem barks originating from *Berberis aristata*, *B. chitria*, and *B. lycium* (Indian *Berberis* species), have been used as a domestic treatment of conjunctivitis or other ophthalmic diseases, enlarged liver and spleen, hemorrhages, jaundice, and skin diseases like ulcers (Rajasekaran and Kumar, 2009).

On the other hand, the use of decoction of Indian barberry mixed with honey has also been reported for the treatment of jaundice. Additionally, it has been reported the use of decoction of Indian barberry and *Emblic myrobalan* mixed with honey in the cure of urinary disorders as painful micturition (Kirtikar and Basu, 1998). Numerous studies dealing with its antimicrobial and antiprotozoal activities against different types of infectious organisms (Vennerstrom *et al*., 1990; Stermitz *et al*., 2000; Bahar *et al*., 2011) have been assessed so far. Moreover, it has been used to treat diarrhea (Chen *et al*., 2014) and intestinal parasites since ancient times in China (Singh and Mahajan, 2013), and the Eastern hemisphere, while in China it is also used for treating diabetes (Li *et al*., 2004).

A significant number of dietary supplements based on plants containing BBR (Kataoka *et al*., 2008) are used for reducing fever, common cold, respiratory infections, and influenza (Fabricant and Farnsworth, 2001). Another reported use for berberine-containing plants is their application as an astringent agent to lower the tone of the skin. Also, positive effects were observed on the mucous membranes of the upper respiratory tract and gastrointestinal system with effects on the associated ailments (Chen *et al*., 2014; Yu *et al*., 2016)

Furthermore, there are other genera which contain BBR. The genus Mahonia comprises of several species that contain berberine. Within them, *M. aquifolium* has been traditionally used for various skin conditions. Due to its main alkaloid (berberine), is known to be used in Asian medicine for its antimicrobial activity. *Coptidis rhizoma* (rhizomes of *Coptis chinensis*), another plant that contains berberine, is a famous herb very frequently used in traditional Chinese medicine for the elimination of toxins, "damp-heat syndromes", "purge fire", and to "clear heat in the liver" (Tang *et al*., 2009).

Pharmacological activities and medicinal uses of BBR

Berberine is an isoquinoline alkaloid of the protoberberine type, which could be found in the root, rhizome, and stem bark of many plant species traditionally used for the treatment of hepatic disorders, such as *Coptis chinensis* Franch., *Coptis japonica* Makino., *Berberis thunbergii* D.C., *Thalictrum lucidum* L., barberry (*Berberis vulgaris* L.), Oregon grape (*Berberis aquifolium* Pursh), and goldenseal (*Hydrastis canadensis* L.) (Imanshahidi and Hosseinzadeh, 2008).

A series of mechanistic information of berberine have been reported, such as free radical scavenging ability, antiapoptotic and anticarcinogenic actions. The effects on antiapoptotic and free radical regulatory genes such as *Bcl-2, Bax, c-myc* and *p53*, which may be responsible for the protective properties exhibited by BBR. Berberine prevents doxorubicin-induced cardiotoxicity in mice (Zhang *et al*., 2008).

It has been reported that berberine exhibits multiple pharmacological activity, such as correcting dyslipidemias, anti-inflammatory effects, antidiabetic effects, and anticancer effects (Yu *et al*., 2005). Many experiments have shown that berberine acts to reduce the formation of ROS (Ko *et al*., 2007).

Berberine, an iso quinoline alkaloid, originally extracted from the traditional Chinese herb *Coptis chinensis* (Huanglian), is used for the treatment of bacterial infectious diseases. Recently, it has been shown to display a wide range of pharmacological activities, such as antidiarrheal, antidiabetic, antihyperlipidemic, anti-inflammatory and antitumor effects. Additionally, both animal and clinical investigations showed that berberine is beneficial in combating against reactive oxygen species (ROS) formation (Ko *et al*., 2007).

Under various physiological and pathological conditions, BBR has been found to modulate inflammation by decreasing the tumor necrosis factor-alpha (TNF-α) and interleukin (IL)-6 levels, which stimulates the matrix metalloproteinases (MMPs) production. MMPs, a family of endopeptidase enzymes, contribute to cell death by degrading tar-get tissue under inflammation states. It has been demonstrated that BBR can down-regulate the expression of MMPs (Ehteshamfar *et al*., 2020).

Under normal conditions, the body maintains a balance between the antioxidant and pro-oxidant agents (reactive oxygen species—ROS and reactive nitrogen species—RNS (Rahal *et al*., 2014). The imbalance between pro and antioxidants occurs in case of increased oxidative stress (Bhattacharyya *et al*., 2014). The oxidative stress builds up through several mechanisms: an increase in the production of reactive species, a decrease in the levels of enzymes involved in blocking the actions of pro-oxidant compounds, and/or the decrease in free radical scavengers (Pilch *et al*., 2014).

An experimental study demonstrated the effect of berberine on lipid peroxidation after inducing chemical carcinogenesis in small animals (rats). An increase in LPO (lipid peroxidation) was observed after carcinogenesis induction, but also its significant reversal after berberine administration (30 mg/kg). Berberine shows therefore at least partial antioxidant properties, due to its effect on lipid peroxidation (Thirupurasundari *et al*., 2009).

Other mechanisms involved in the antioxidant role of berberine are ROS/RNS scavenging, binding of metals leading to the transformation oxidation of certain substances, free-oxygen removal, reducing the destructiveness of superoxide ions and nitric oxide, or increasing the antioxidant effect of some endogenous substances. The antioxidant effect of berberine was comparable with that of vitamin C, a highly-potent antioxidant (Ahmed *et al*., 2015).

The increase in blood sugar leads to oxidative stress not by generating oxygen reactive species but by impairing the antioxidant mechanisms. Administration of berberine to rats with diabetes mellitus increased the SOD (superoxide dismutase) activity and decreased the MDA (malondialdehyde) level (marker of lipid peroxidation). This antioxidant effect of berberine could explain the renal function improvement in diabetic nephropathy (Liu *et al*., 2008).

The oxidative stress plays an important role in the pathogenesis of many diseases. The beneficial effect of berberine is presumed to reside mostly in its antioxidant role.

Berberine and alkaloid isolated from BA have a property of inhibition significantly carcinogenesis induced by 20-methylcholanthrene (200 microg/0.1mL/mouse) of N-trisodiethylamine (NDEA-0.02% NDEA in distilled water, 2.5 mL/animal by gavage, first day a week for 20 weeks) in a dose dependent manner in small animals. Berberine dose of 0.5, 2.5 or 5.0 mg/kg reduces significant level of tumor in animal after an injection of 20-methylcholanthrene and increased their life span compared with the control. Berberine dose of 10, 25 or 50 mg/kg was administered

simultaneously with NDEA, the markers of liver injury were reduced significantly compared with animal treated with NDEA only, which resulted in all values being elevated. Methanolic extract of stems of BA is also showing promising results against breast and colon cancer cell lines. Infective Hepatitis is the highly contagious disease that attacks hepatocytes of liver. Hepatitis 'A' (Known as Infectious Hepatitis) is an acute infection caused by Hepatitis 'A' Virus (HAV) and RNA virus. The Route of infection of 'HAV' is fecal-oral route. Symptoms appear 2 to 6 weeks after the initial infection and usually symptoms are less than two months. BA has Berberine, Aromoline, Palmatine, oxyacanthine. Berberine have properties of cholegogue, hepatostimulant and astringent and are useful in treating anorexia, dysentery and hepatitis. BA definitely reduces the duration of symptoms of Hepatitis. The hepatoprotective effect of BBR was demonstrated on laboratory animals (mice), in which hepatotoxicity was induced by doxorubicin. Pretreatment with berberine significantly reduced both functional hepatic tests and histological damage (inflammatory cellular infiltrate, hepatocyte necrosis (Zhao *et al*., 2012).

The mechanism by which berberine reduces hepatotoxicity was also studied on CCl4 (carbon tetrachloride)-induced hepatotoxicity. Berberine lowers the oxidative and nitrosamine stress, and modulates the inflammatory response in the liver, with favorable effects on the changes occurring in the liver. Berberine prevents the decrease in SOD activity and the increase in lipid peroxidation and contributes to the reduction in TNF-α, COX-2, and iNOS (inducible nitric oxide synthase) levels. The decrease in transaminase levels supports the hypothesis according to which berberine helps maintain the integrity of the hepatocellular membrane (Domitrović *et al*., 2011)

Berberine is reported to inhibit cholesterol and triglyceride synthesis in human hepatoma cell line (HepG2) cells and primary hepatocytes. BBR shows increased glucose consumption in a dose dependent manner. In vivo models of animals also confirmed BBR's beneficial role in preventing or treating NAFLD. Intraperitoneal injection of BBR compound chemical for 3 weeks has been studied to alleviate hyperlipidemia and fatty liver in obese and diabetes mice (Yin *et al*, 2008). In hyperlipidemic hamsters with BBR strongly reduce fat storage in liver. As for mice with high fat diet (HFD) induced fatty liver, sixteen weeks BBR supplement could alleviate hepatic steatosis and decrease liver lipid content by 14%45. BBR prevents development of obesity and insulin resistance in HFD-fed rats. BBR has been shown to reduce liver necrosis both in nonalcoholic steatosis and in steatosis due to hepatitis C infection. Ethanolic root extract of BA shows antifungal activity. The extract of BA (aqueous, alcoholic and powdered root in distilled water) shows a wide range of antibacterial activity against Gram-positive bacteria. The extract was also tested for antibacterial activity against Gram-negative bacteria; the antibacterial activity was limited against *E. coli, S.* Typhimurium, *S. dysenteriae* type 1 and *V. cholera*, the best activity being against *V. cholera*. The Gram-negative bacteria reported here and causing diarrhea and dysentery are susceptible to the extract of BA (Sharma *et al*., 2002).

Berberine exerted anti-depressant like effect in various behavioral paradigms of despair possibility by modulating brain biogenic amines. Further, nitric oxide pathway or sigma receptors are involved in mediating its antidepressant like activity in mouse forced swim test. Dried and Powdered root extracted with water and methanol and crude extract was administered to normal and alloxan induced diabetic albino rat. The result shows that BA roots contain potent and orally effective antidiabetic components which either triggers the formation of insulin or shows insulin like effect. Antidiabetic activity was screened in albino Wistar rat by inducing diabetes by alloxan Geand streptozocin. Diabetic rats were treated with ethanolic extract of BA. The results conclude that ethanolic extract possesses antidiabetic activity. Berberine may be associated with promoting regeneration and functional recovery of β-cells. Many studies demonstrated that berberine lowers blood sugar, through the following mechanisms:

Inhibition of mitochondrial glucose oxidation and stimulation of glycolysis, and subsequently increased glucose metabolization (Yin *et al*., 2008). Decreased ATP level through the inhibition of mitochondrial function in the liver, which may be the probable explanation of gluconeogenesis inhibition by berberine (Xia *et al*., 2011).

Inhibition of DPP 4 (dipeptidyl peptidase-4), a ubiquitous serine protease responsible for cleaving certain peptides, such as the incretins GLP1 (glucagon-like peptide-1) and GIP (gastric inhibitory polypeptide); their role is to raise the insulin level in the context of hyperglycemia. The DPP4 inhibition will prolong the duration of action for these peptides, therefore improving overall glucose tolerance. Berberine has a beneficial effect in improving insulin resistance and glucose utilization in tissues by lowering the lipid (especially triglyceride) and plasma free fatty acids levels (Chen *et al*., 2011). The effect of berberine (1,500 mg day) on glucose metabolism was also demonstrated in a pilot study enrolling 84 patients with type 2 diabetes mellitus. The effect, including on HbA1c, was comparable to that of metformin (1,500 mg/day), one of the most widely used hypoglycemic drugs. In addition, berberine has a favorable influence on the lipid profile, unlike metformin, which has barely any effect (Yin *et al*., 2008).

Berberine can provide cardio-protection in ischemic conditions by playing various roles at different levels: modulation of AMPK (AMP—activated kinase) activity, AKT (protein kinase B) phosphorylation, modulation of the JAK/STAT (Janus kinase/signal transducers and activators of transcription) pathway and of GSK3β (glycogen synthase kinase 3β (Chang *et al*., 2016). AMPK is an important enzyme playing an essential role in cellular metabolism and offering protection in ischemic conditions by adjusting the carbohydrate and lipid metabolism, the function of cell organelles (mitochondria, endoplasmic reticulum) and the apoptosis (Zaha *et al*., 2016).

Berberine activates the PI3K (phosphoinositide 3-kinase)/AKT pathway which is considered a compensatory mechanism limiting the pro-inflammatory processes and apoptotic events in the presence of aggressive factors. The activation of this pathway is associated with a reduction of the ischemic injury through the modulation of the TLR4 (toll-like receptor 4)-mediated signal transduction (Hua *et al*., 2007). The beneficial effect of berberine in cardiac failure was demonstrated in a study on 51 patients diagnosed with NYHA (New York Heart Association) III/IV cardiac failure with low left ventricular ejection fraction (LVEF) and premature ventricular contractions and/or ventricular tachycardia. These patients received tablets containing 1.2 g berberine/day, together with conventional therapy (diuretics, ACEI—angiotensin-converting-enzyme inhibitors, digoxin, nitrates) for 2 weeks. An increase in LVEF was observed in all patients after this period, but also a decrease in the frequency and complexity of premature ventricular contractions. The magnitude of the beneficial effect was in direct proportion with the plasma concentration of berberine (Zeng, 1999).

The immunomodulatory effect of berberine was demonstrated in many experimental and clinical contexts. In an experimental autoimmune myocarditis model, berberine contributed to mitigate the cardiac damage by: limiting the rise in anticardiac myosin antibodies, modulating the activity of certain STATs and blocking Th1 and Th2 cell differentiation, which play an important role in the pathogenesis of myocarditis (Liu, X. *et al*., 2016). Experimental autoimmune neuritis is an experimental animal model equivalent to the Guillain-Barre syndrome in humans. This neurologic syndrome is characterized by autoimmune injury of the peripheral nervous system. The beneficial effect of berberine on this animal model resided in its influence on cellular and humoral immunity through the inhibition of lymphocyte proliferation (especially CD4), and the decrease in pro-inflammatory cytokines (IL-6 and TNF α) (Li, H., *et al*., 2014).

Atherogenesis is a consequence of high blood lipid levels and is associated with inflammatory changes in the vascular wall. Berberine interferes with this process by up-regulating the expression of SIRT1 (silent information regulator T1) and by inhibiting the expression of PPARγ (peroxisome proliferator-activated receptor-γ). SIRT1 is a NAD-dependent deacetylase. The SIRT1 enzyme has many targets (PPARγ, p53), all playing

different roles in atherogenesis (Chi *et al*., 2014).

The chronic kidney damage occurring in time in patients with HT (hypertension) and DM (diabetes mellitus) is well known; it is mainly due to atherosclerosis of the renal artery, caused by inflammation and oxidative stress. The protective effect of berberine on kidneys was studied on 69 patients suffering from both HT and DM, with blood pressure and blood sugar levels controlled with conventional medication. The patients received 300 mg berberine/day for 24 months, with 2-week interruptions every 5 months. The authors recorded lower CRP (C-reactive protein), MDA and SOD levels after treatment, but without significant changes in creatinine, arterial pressure, or glycaemia levels. These results support the renal protective effect of berberine through its anti-inflammatory and antioxidant effects (Dai *et al*., 2015). Another animal study tested the renoprotective effect of berberine after administration of $HgCl_2$ (mercury chloride). This substance induces hepato-renal damage by increasing the oxidative stress (increases lipid peroxidation and NO levels and lowers glutathione and SOD levels as well as the activity of other protective enzymes). Administration of $HgCl_2$ increased the AST (aspartate aminotransferase), ALT (alanine aminotransferase), and ALP (alkaline phosphatase) levels, compared to the control group. However, pretreatment with berberine lowered these enzymes significantly. In addition, both urea and creatinine levels were significantly increased in the HgCl2 group vs. the control group, and again pretreatment with berberine prevented these changes. Additionally, the authors recorded higher pro-oxidant and lower antioxidant levels in the intervention group. These data support the hepatic and renal protective effects of berberine. Other studies performed on animal models with CCl_4–induced hepatotoxicity demonstrated the same effect (Othman *et al*., 2014). In addition, berberine can lower the nephrotoxicity caused by cisplatine. In an animal study, berberine was administered in progressive doses of 1, 2, 3 mg/kg, orally, for 2 successive days, starting 2 days after cisplatine administration. After the last doses of berberine, the animals were sacrificed, and the kidneys were examined by the pathologist. The results showed significant histological improvement and a reduction in NF-kB (nuclear factor kappa-light-chain-enhancer of activated B cells), TNF α, COX2 an iNOS levels, all of which support the anti-inflammatory effect of berberine (Domitrović *et al*., 2011)

Several studies have demonstrated the efficacy of BBR against fibrotic diseases in vivo, including pulmonary fibrosis, (Chitra *et al*., 2015) myocardial fibrosis, (Zhang *et al*., 2014) renal fibrosis, (Wang *et al*., 2016) and adipose tissue fibrosis, (Xu *et al*., 2021) and multifaceted causal relationships illustrate the efficacy of BBR against liver fibrosis. (Wang *et al*., 2016; Bansod *et al*., 2021). As a multifunctional drug used in traditional Chinese medicine, berberine (BBR) can be used to treat various liver diseases (Yang *et al*., 2021).

BBR is a potential anti-liver fibrosis agent. In fibrotic mouse models, we found that BBR alleviates liver fibrosis by inducing ferrous-ion redox reactions to activate reactive oxygen species (ROS)-mediated ferroptosis in hepatic stellate cells, which suggests a possible strategy for the treatment of liver fibrosis (Yi *et al*., 2021). Similar effects of BBR in carbon tetrachloride (CCl4)-induced liver fibrosis models were also demonstrated by other team recently (Bansod *et al*., 2021).

The activity of BBR against these multifactorial chronic diseases may be attributable to its multitargeted mode of action. (Zhang *et al*., 2011). Inflammation and oxidative stress are key drivers of liver fibrosis, and it has been clearly demonstrated that BBR has anti-inflammatory and anti-oxidative activities. (Zhou *et al*., 2008). It is therefore that the activity of BBR against liver fibrosis has been explored in many studies during recent years. (Zhang *et al*., 2008; Zhang *et al*., 2016).

The fundamental feature of liver fibrosis is the abnormal activation of HSCs, and BBR has been shown to be a potential treatment for thioacetamide (TAA)-, CCl4-, ethanol- and high cholesterol-induced liver fibrosis models; in these contexts, it likely acts by suppressing HSC activation and downregulating alpha-smooth muscle actin (α-SMA) and transforming growth factor-β1 (TGF-β1) levels. (Sun *et al*., 2009; Domitrović *et al*., 2013; Li, J., *et al*., 2014; Eissa *et al*., 2018; Bansod *et al*., 2021).

Previous studies have indicated that the direct beneficial effects of BBR involving modulation of the expression of multiple genes involved in HSC activation, cholangiocyte proliferation and liver fibrosis are linked to the downregulation of two important ribonucleotide molecules that promote liver fibrosis progression: microRNA34a and long noncoding RNA H19 (Wang *et al*., 2021).

Another commonly reported mechanism is the induction of HSC (Hematopoietic stem cells) cycle arrest in G1 phase, which inhibits HSC activation and prevents liver fibrosis (Zhou *et al*., 2021). In addition, BBR has been revealed to have direct antifibrotic activity in bile duct ligation-induced liver fibrosis, due to its suppression of HSCs activation, and (partly) due to its inhibition of the AMPK signalling pathway (Wang *et al*., 2016). However, other studies have found that BBR exerts hepatoprotective effects and prevents liver fibrosis by activating the AMPK signalling pathway (Li, J. *et al*., 2014; Wang *et al*., 2016; Bansod *et al*., 2021). BBR was also shown to activate the AMP-activated protein kinase (AMPK) pathway and inhibit macrophage polarization and TGF-β1/Smad3 signalling, thereby alleviating tissue fibrosis (Xu *et al*., 2021).

Endoplasmic Reticulum stress (ER stress) may be another target of BBR treatment, and it has indeed been confirmed that a reduction in ER stress was the most logical explanation for the fact that BBR hinders the progression of hepatic steatosis to fibrosis. (Zhang *et al*., 2016). Moreover, BBR was shown to directly relieve liver injury-induced hepatic metabolic disorders by decreasing ER stress in hepatocytes (Yang *et al*., 2021), and the inhibition of Akt/FoxO1 signalling-mediated reduction of oxidative ER stress has been associated with BBR treatment of liver fibrosis. (Bansod *et al*., 2021). In other work, Zhang *et al*. (2008) reported that BBR prevents hepatic fibrosis by regulating the antioxidant system and lipid peroxidation in multiple hepatotoxic factor-induced fibrosis models, which was reflected by improved liver function, an increased antioxidant index and a decrease in fibrosis markers (Zhang *et al*., 2008; Bansod *et al*., 2021).

BBR-mediated normalization of liver function, suppression of inflammation, amelioration of ECM deposition and prevention of fibrosis correlate with NF-κB- and PPARγ-regulation (Cao *et al*., 2018). Many anticancer agents, such as methotrexate, (Sadeghian *et al*., 2018) doxorubicin (Zhao *et al*., 2012) and cyclophosphamide, (Germoush and Mahmoud, 2014) are hepatotoxic (and thus cause hepatitis, steatohepatitis, liver cell necrosis, liver fibrosis or cirrhosis), and it is imperative to identify ways to limit this hepatotoxicity. It is therefore encouraging that anticancer drug-induced liver histopathological changes, including fibrosis, are significantly decreased by BBR treatment in animal studies (Zhao *et al*., 2012; Germoush and Mahmoud, 2014).

Orally administered BBR displayed therapeutic effects in cirrhotic patients in a 1982 Japanese clinical study, with these effects being due to BBR inhibiting intestinal bacterial tyrosine decarboxylase (Watanabe *et al*., 1982). Moreover, some randomized, placebo-controlled trials have found that BBR has positive effects in hyperlipidemic patients with virus hepatitis related cirrhosis (Riccioni *et al*., 2018).

Conclusion

This review highlighted the positive pharmacological activities and the promising medicinal uses of BBR.

Conflict of interest

The authors declare that they have no conflict of interest.

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