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REVIEW

Biological properties and clinical applications of berberine

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Abstract **Berberine, an isoquinoline alkaloid isolated from the Chinese herb *Coptis chinensis* and other *Berberis* plants, has a wide range of pharmacological properties. Berberine can be used to treat many diseases, such as cancer and digestive, metabolic, cardiovascular, and neurological diseases. Berberine has protective capacities in digestive diseases. It can inhibit toxins and bacteria, including *Helicobacter pylori*, protect the intestinal epithelial barrier from injury, and ameliorate liver injury. Berberine also inhibits the proliferation of various types of cancer cells and impedes invasion and metastasis. Recent evidence has confirmed that berberine improves the efficacy and safety of chemoradiotherapies. In addition, berberine regulates glycometabolism and lipid metabolism, improves energy expenditure, reduces body weight, and alleviates nonalcoholic fatty liver disease. Berberine also improves cardiovascular hemodynamics, suppresses ischemic arrhythmias, attenuates the development of atherosclerosis, and reduces hypertension. Berberine shows potent neuroprotective effects, including antioxidative, antiapoptotic, and anti-ischemic. Furthermore, berberine exerts protective effects against other diseases. The mechanisms of its functions have been extensively explored, but much remains to be clarified. This article summarizes the main pharmacological actions of berberine and its mechanisms in cancer and digestive, metabolic, cardiovascular, and neurological diseases.**

Keywords berberine; *Coptis chinensis*; pharmacological properties; mechanism; clinical applications

Introduction

Berberine (BBR), an isoquinoline alkaloid isolated from the Chinese herb *Coptis chinensis* and other *Berberis* plants, has a wide range of pharmacological properties; its chemical structure is represented in Fig. 1. About 2200 years ago, *C. chinensis* was widely used to treat various diseases and became an important component of Chinese medicinal compounds. *Shennong's Herbal Classic* states "*Coptis chinensis*, is mainly used to prevent or attenuate digestive system disease symptoms, such as abdominal distention and fullness, vomiting and acid regurgitation, diarrhea, jaundice, etc. Besides, it also has potential for the treatment of fever and dizziness, restless, palpitations, hematemesis and epistaxis, conjunctival congestion, toothache, and carbuncle." However, the mechanisms underlying the pharmacological effects of *C. chinensis* remain unclear. With the continuous development of modern medical technology, BBR has been discovered to be a major component of *Coptis chinensis* with multiple biological functions (Fig. 2), such as anti-inflammatory [1], anti-infective, antitumor [2], and antiarrhythmic functions and regulation of blood lipids and blood glucose [3], acting on multiple organs and systems of the body.

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Berberine and digestive diseases

Attenuating intestinal injury

Inhibiting bacteria and toxins

In 1967, Subbaiah and Amin reported that berberine sulfate has an inhibitory effect on the growth of *Entamoeba histolytica* [4]. Amin also reported the antimicrobial activity of BBR [5]. BBR shows good efficacy in controlling cholera in infant rabbit models. It arrests diarrhea symptoms, prolongs survival time, and prevents death possibly by hindering the formation of toxin by

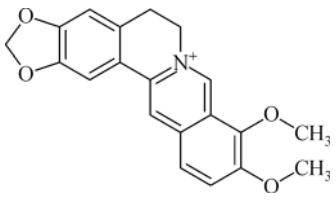

Fig. 1 Chemical structure of berberine.

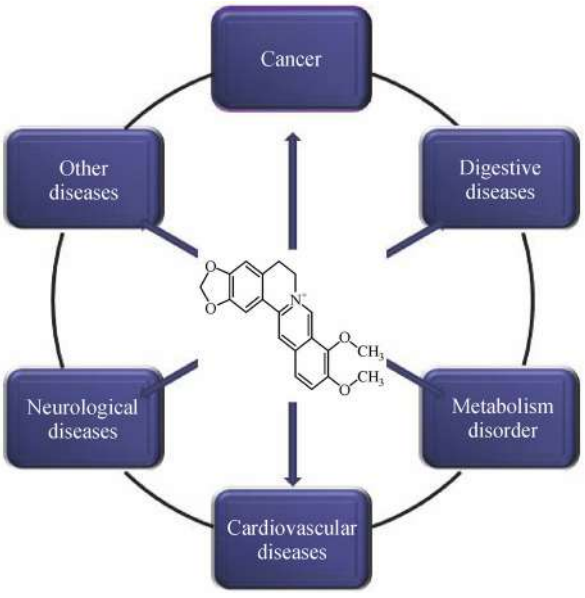

Fig. 2 Major diseases affected by berberine.

Vibrio cholerae [6]. High concentrations of BBR can suppress the growth of *Clostridium difficile* and *Bacillus cereus* by inhibiting spore outgrowth [7]. BBR enhances the antimicrobial effects of azithromycin (AZM) against *Pseudomonas aeruginosa*. The synergism of BBR and AZM not only remarkably decreases the production of virulence factors but also suppresses the inflammatory response by reducing IL-6 and IL-8 and inducing IL-10 [8]. The inflammatory response elicited by *V. cholerae* and *Escherichia coli* can be inhibited by administering BBR in a rabbit ligated intestinal loop model. Furthermore, BBR suppresses the inflammatory response to heat-labile enterotoxin and heat-stable enterotoxin [9]. Berberine is an antimicrobial drug efficient for treating *Eberthella typhosa* infection because it blocks DNA replication with low cell toxicity [10]. In addition, BBR derivatives exert bactericidal activities against methicillin-resistant *Staphylococcus aureus* and enteroinvasive *E. coli*. BBR facilitates the nuclear translocation of transcription factor EB (TFEB) and enhances TFEB-dependent bactericidal activity [11].

Inhibiting secretion and peristalsis

Berberine shows antidiarrheal pharmacological properties in infant rabbit models of cholera at least in part due to the BBR suppression of intestinal peristalsis [6]. The antidiarrheal activity of BBR is involved in the inhibition of myoelectric activity and delay of the small intestine transit partly by regulating opioid and α-adrenergic receptors [12]. In addition, BBR inhibits electrogenic ion transport in rat colonic epithelia, significantly attenuating the short circuit current responses to mast cells induced by anti-rat IgE and other agonists that stimulate chloride secretion [13]. Rabbani has demonstrated the antisecretory activity of BBR in acute diarrhea caused by enterotoxigenic *E. coli* and *V. cholerae* in a randomized controlled trial. This trial also showed that BBR is an effective and safe antisecretory drug without noted adverse effects [14].

Protecting the intestinal epithelial barrier

BBR can reduce the expression of adenosine deaminase (ADA) mRNA; as a result, the activity of ADA decreases, the adenosine signaling pathway is suppressed, and the small intestinal injury caused by indomethacin is improved by BBR treatment [15]. BBR protects the intestinal epithelial barrier from the inflammatory response by activating the AKT1/SOCS1 pathway [16]; decreasing the levels of proinflammatory cytokines TNF-α, INF-γ [17], and IL-10 [18]; reducing macrophage infiltration; and suppressing apoptosis in colonic macrophages and epithelial cells [19]. BBR also inhibits the proliferation of Th1 and Th17 cells and suppresses the phosphorylation of NF-κB to ameliorate intestinal injury and colitis [20]. It is a candidate therapeutic drug for inflammatory bowel disease [21]. BBR maintains the function of the gut–vascular barrier (GVB) by inhibiting the production of nitric oxide and inflammatory cytokines that damage the GVB and increasing the expression of tight junctions and adherent junctions; the increase in transendothelial electrical resistance enhances paracellular permeability [22,23]. BBR is associated with the activation of the Wnt/β-catenin signaling pathway [22]. BBR also augments the secretion of GLP2 to improve barrier function and intestinal permeability [24]. BBR partially reverses the distribution of tight junction proteins in membrane microdomains and attenuates intestinal epithelial tight junction damage by inhibiting the overexpression of NF-κB p65 and myosin light chain kinase [25]. The effects of berberine on intestinal injury are summarized in Fig. 3.

Ameliorating liver injury

Animal experiments have shown that the injuries in liver-damaged mice treated with BBR are remarkably ameliorated (Fig. 4). The protective effect is due to BBR interfering with the activation of purinergic receptor P2X7

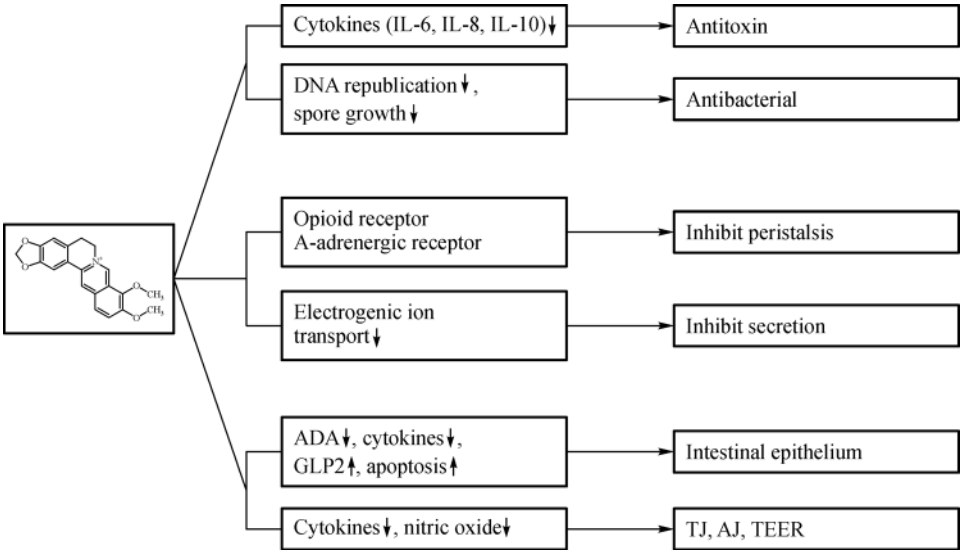

Fig. 3 Effects of berberine on intestinal injury.

and suppressing the activation of the NLRP3 inflammasome pathway [26]. Berberine inhibits the phosphorylation state of JNK1 and the production of proinflammatory cytokines in liver and adipose tissue to decrease inflammation and improve hepatic steatosis [27]. BBR attenuates the oxidative damage and hepatotoxicity caused by tert-butyl hydroperoxide by quenching free radicals and inhibiting the loss of glutathione [28]. Experiments showed that BBR significantly ameliorates acetaminophen hepatotoxicity. BBR inhibits inflammation, oxidative stress, and necrosis in injury liver [29], and it also prevents mitochondrial content and biogenesis [30]. In addition, it improves intestinal dysbacteriosis to decrease hepatotoxicity induced by dextran sulfate sodium (DSS) [31]. Hepatic steatosis is attenuated by BBR treatment in a mouse model. The mechanism shows that BBR can induce hepatocyte autophagy, activate FGF21, inhibit lipid accumulation, and increase energy expenditure [32]. The protective properties of BBR on hepatic steatosis will be further explained in the Section of "Berberine and cancer."

Inhibiting *Helicobacter pylori*

BBR exerts antibacterial effects, particularly on *Helicobacter pylori* [33] (Fig. 5). Bae found in his experiment that BBR has a potent inhibitory effect on the growth of *H. pylori* [34], which is associated with the inhibition of arylamine N-acetyltransferase activity in *H. pylori* [35]. BBR inhibits urease activity and urease maturation by targeting the urease active site sulfhydryl group to elicit anti-*H. pylori* effects [36]. Evidence from a clinical trial suggests that BBR combined with triple therapy can be an option to eradicate *H. pylori* [37]. BBR decreases hefA mRNA expression; thus, the minimum inhibitory concentrations of amoxicillin and tetracycline against some *H. pylori* strains have been reduced significantly [38]. BBR

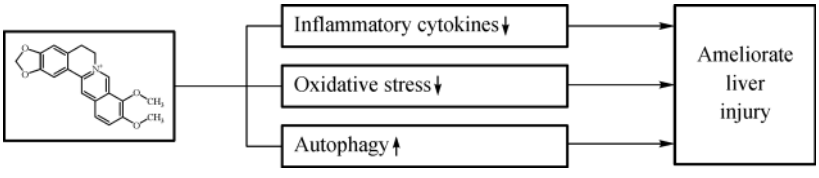

Fig. 4 Effects of berberine on liver injury.

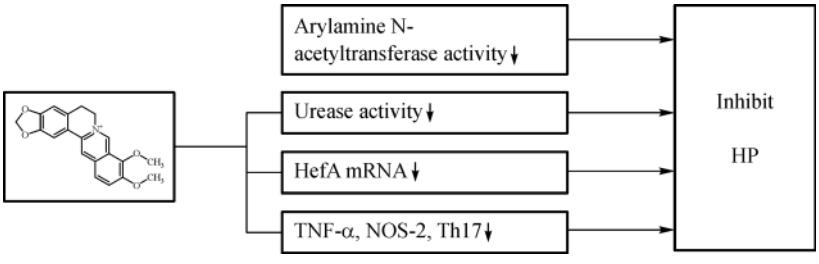

Fig. 5 Effects of berberine on *Helicobacter pylori*.

shows killing effects on multidrug-resistant *H. pylori* strains [38]. The anti-*H. pylori* effect has been further demonstrated in an open-label, randomized trial [39]. Moreover, the gastric mucosal inflammation induced by HP lipopolysaccharide (LPS) can be attenuated with BBR treatment because BBR inhibits apoptosis and suppresses the inflammatory response in epithelial cells accompanied by decreased TNF-α and NOS-2 [40]. BBR also inhibits the production of B cell-activating factor (BAFF); therefore, the BAFF-triggered Th17 response is decreased, and the inflammation in *H. pylori*-infected mice with chronic gastritis is attenuated [41].

Berberine and cancer

Anti-proliferation

Inducing cell cycle arrest

Kuo demonstrated that BBR has antitumor activities that can promote apoptosis in human leukemic HL-60 cells. BBR complexes with DNA and cell cycle arrest have been observed in BBR-induced apoptotic HL-60 cells [42]. BBR induces cell cycle arrest at the G_0/G_1 phase by upregulating proteins Cip/p21 and Kip/p27 and downregulating cyclins D1, D2, and E and cyclin-dependent kinases Cdk2, Cdk4, and Cdk6 [43,44]. With BBR treatment, the cell cycle is mainly arrested at the G_0/G_1 phase [45–48], and the cell populations at S and G_2/M are decreased [46]. In addition, BBR enhances the sensitivity of non-small cell lung cancer (NSCLC) A549 cells to ionizing radiation by inducing G_2/M arrest [49]. BBR can increase the protein expression of the cell cycle inhibitors p53 and p21 to arrest the cell cycle [47].

Inhibiting telomerase

BBR can downregulate telomerase activity, and telomerase inhibition plays an important role in the proapoptotic effect in HL-60 cells [50]. BBR can bind with various G-quadruplex DNA structures selectively and inhibit telomerase activity effectively [51]. BBR contains natural, flexible cyclic molecules that show a high affinity with the quartets of G-quadruplex structures [52]. Recently, the mechanism of BBR binding with the human telomeric G4 ($d[AG_3(T_2AG_3)_3]$) has been further elucidated by FM simulation, and results have shown that BBR has a significant potential to control the mitotic clock and proliferation of cancer cells [53].

Inducing mitochondria-mediated apoptosis

BBR promotes the mitochondria-dependent pathway to induce apoptosis in human hepatoma HepG2 cells and human epidermoid carcinoma A431 cells. BBR stimulates the activation of caspase 8 and caspase 3 and induces the cleavage of poly ADP-ribose polymerase (PARP) and loss of mitochondrial membrane potential [54]. BBR upregulates the proapoptotic protein Bax and downregulates the suppression of the antiapoptotic proteins Bcl-2 and Bcl-x [43,54]. It can also enhance the lethal effect of the PARP inhibitor niraparib to promote apoptosis [55]. BBR significantly induces the mRNA expression of FoxO1 and FoxO3a and prevents their degradation. Therefore, BBR upregulates the transcriptional activity of FoxO, which is associated with the antiproliferation of tumors. Increasing FoxO transcription factors strongly induces the expression of the BH3-only protein Bim and activates the proapoptotic protein Bax and caspases, resulting in mitochondria-mediated apoptosis [56]. The BBR-induced overexpression of FoxO3a in apoptotic human lung adenocarcinoma cells is due to the activation of p38α MAPK [47].

Inducing p53-dependent apoptosis

BBR downregulates nucleophosmin/B23 at the mRNA and protein levels, which is related to the proapoptotic effect in HL-60 cells [50]. BBR enhances p53 activity by promoting MDM2 self-ubiquitination and degradation. In addition, BBR upregulates the expression levels of p21, PUMA, and Bax [57]. Experiments in human lung adenocarcinoma cells documented that BBR activates p53 and induces apoptosis by activating p38α MAPK [47]. BBR inhibits DAXX transcription by competitively binding to the consensus sequences of the transcription factors Sp1 and Ets1 to inhibit MDM2 expression. Consequently, p53-dependent apoptosis is induced by BBR through the suppression of MDM2 [58].

Inducing reactive oxygen species (ROS)-mediated mechanisms

Hsu has documented that BBR exerts an apoptotic effect on SW620 human colonic carcinoma cells by inducing intracellular ROS production and increasing p38 MAPK and JNK activity. BBR induces cytochrome C in the cytosol and PARP cleavage and increases the levels of FasL, c-jun, and t-BID. BBR may promote the generation of ROS in a Fas-FADD-dependent manner and activate caspase-8 and caspase-9 to induce apoptosis [59]. It also induces Ca^{2+} production, suppresses the levels of mitochondrial membrane potential, and promotes cytochrome C release and caspase 3 activity in human oral squamous cell carcinoma cancer HSC-3 cells [45]. BBR upregulates ROS generation and lipid peroxidation accompanied by suppression of the activities of superoxide dismutase and

catalase and glutathione levels through activation of the JUK pathway [56]. BBR induces oxidative stress and DNA damage, downregulates RAD51, and damages homologous recombination repair [55].

Inducing mitophagy-dependent necroptosis

MYC overexpression enhances the transcriptional activity of phosphate cytidylyltransferase 1 choline-α (PCYT1A) through the binding site, and PCYT1A increases cellular choline and its phosphorylated derivatives by regulating the choline metabolic pathway and then promotes necroptosis by activating LC3A/B and MLKL in diffuse large B cell lymphoma. BBR inhibits the proliferation of B-lymphoma cells by promoting PCYT1A mRNA degradation and inducing mitophagy-dependent necroptosis [60].

Inhibiting inflammatory cytokines

BBR inhibits the proliferation of oral cancer cells through an anti-inflammatory pathway. BBR reduces prostaglandin E_2 (PGE_2) production and inhibits COX_2 expression by inhibiting AP-1 binding in human oral epidermoid carcinoma cell lines [61]. BBR suppresses the activities of NF-κB, IKK, ERK, JNK, and AP-1 and inhibits SCC-4 cell growth through the ERK/MAPK and NF-κB pathways [62]. The anticancer cytokines IFN-β and TNF-α can be upregulated by BBR in the breast cancer cell line MCF-7 (estrogen receptor positive) [46]. BBR can modify the Cys179 residue to suppress IKK-β activity and inhibit TNF-α-induced IκBβ kinase activation, consequently suppressing the phosphorylation of p65 and promoting apoptosis [63]. BBR blocks IL-6 and TNF-α to inhibit inflammatory response-driven EGFR-ERK signaling and exerts an antitumor effect on colitis-associated colorectal cancer [64].

Other mechanisms

In glioblastoma cells, BBR induces senescence against proliferation, which is involved in the downregulation of EGFR and the inhibition of the EGFR–MEK–ERK signaling pathway [48]. However, some studies have shown that BBR has anti-aging properties, promoting AMPK activities to improve autophagic flux and restoring NAD^+ levels to prevent the development of oxidative stress-induced senescence [65]. BBR is also regarded as a novel retinoid X receptor α (RXRα) activator that binds RXRα, specifically promoting the degradation of β-catenin and inhibiting the growth of colon cancer cells via β-catenin signaling [66]. The mechanism underlying the anticancer properties of BBR in prostate cancer decreases androgen receptor (AR) transcriptional activity and promotes AR protein degradation through the disruption of AR-Hsp90 interactions [67]. BBR also regulates microRNAs to exert anticancer effects in biological processes, such as tumorigenesis, proliferation, and differentiation in various malignant diseases [68].

Anti-invasion and antimetastasis

The levels of fibronectin (FN) and VGFR are increased by TPA by activating the PI3K/AKT-dependent pathway. BBR inhibits VGFR expression to decrease TPA-induced FN and shows an antimetastatic effect on breast cancer cells [69]. BBR upregulates the expression of E-cadherin, downregulates the expression of vimentin and transcription factors Snail1 and Slug, and further inhibits the TGF-β1-induced epithelial-to-mesenchymal transition to prevent lung cancer invasion and metastasis [70].

BBR can also suppress NF-κB, IKK, ERK, and JNK and inhibit SCC-4 cell growth and metastasis by inhibiting the ERK/MAPK and NF-κB pathways [62]. BBR has potential antimigration properties in human gastric adenocarcinoma RF-1 and RF-48 cell lines. It decreases the transcriptional activity of COX_2, further regulates the gene expression of NF-κB/p65, and induces cancer apoptotic cell death [71]. BBR activates AMPK activities to suppress ERK activity and COX_2 protein expression inhibiting A375 human melanoma cell metastasis [72]. BBR also reduces the levels of matrix metalloproteinase (MMP)-1, -2, and -7, which are related to the induction of ROS, resulting in an antimigration effect in the human gastric cancer SNU-5 cell line [73]. BBR reduces the levels of MMP-2 and MMP-9, which contribute to metastasis, in SCC-4 cells [62], human gastric adenocarcinoma RF-1 and RF-48 cell lines [71], and triple negative breast cancer cells [74]. BBR also decreases the level of uPA in SCC-4 cells [62]. BBR effectively inhibits tumor proliferation and lymphatic metastasis in Lewis lung carcinoma cells by repressing AP-1 transcriptional activity and u-PA expression. In addition, BBR suppresses the migration and invasion of triple-negative breast cancer cells by inhibiting TGF-β1 and downregulating Smads [74]. BBR inhibits the intracranial invasion of nasopharyngeal carcinoma (NPC) by suppressing nasopharyngeal carcinoma cell viability and migration through NM23-H1 expression upregulation. BBR also significantly decreases the current value of I_{CRAC} in 5-8F nasopharyngeal cancer cells [75].

In addition, in NPC cells, BBR inhibits Ezrin phosphorylation mediated by Rho kinase to reduce cell motility and inhibit tumor metastasis [76]. The antitumor effects of berberine are shown in Fig. 6, Table 1, and Table 2.

Effects on chemoradiotherapies

Combined radiation therapy with BBR can enhance cytotoxicity in lung cancer A549 cells *in vivo* and *in*

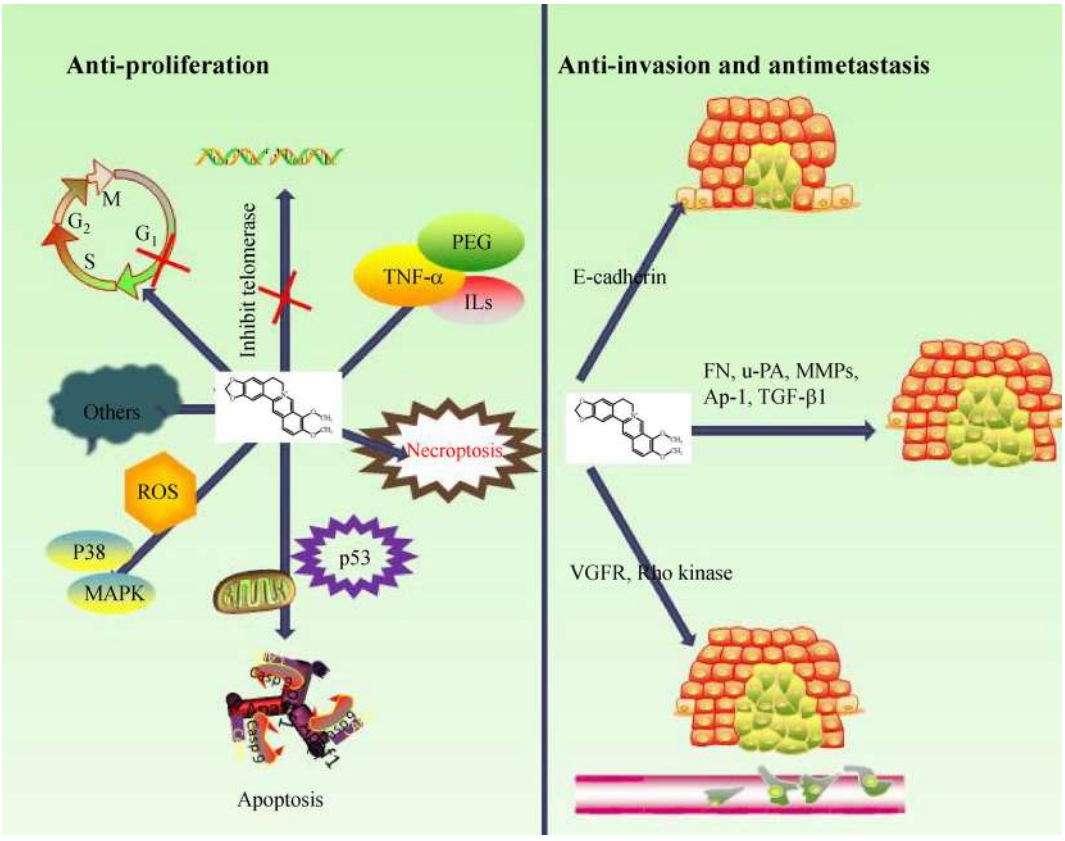

Fig. 6 Effects of berberine on cancer proliferation, invasion, and metastasis.

vitro. BBR can increase radiosensitivity via autophagy [49]. Another experiment on esophageal squamous cell carcinoma demonstrated that the underlying mechanisms are that BBR inhibits HIF-1α and VEGF expression and significantly decreases hypoxic activity. This result suggests that BBR can be used as a potential radiotherapy sensitization drug [77]. BBR cannot only enhance radiosensitivity but also increase chemosensitivity. BBR at a low dose can increase chemosensitivity to doxorubicin (DOX) in MCF-7 breast cancer cells that have been cultured under hypoxic conditions to elicit resistance. The mechanisms further indicate that BBR can suppress the protein expression of AMPK and HIF-1α. Increasing the concentration of BBR activates P53 and induces apoptosis directly [78]. BBR sensitizes human ovarian cells to the anticancer effect of cisplatin by downregulating miR-93 and inhibiting the PTEN/Akt pathway [79]. The synergistic cytotoxic effect of CPT-11 and BBR is significantly enhanced, which leads to inhibition of tumor proliferation and lymphatic metastasis in Lewis lung carcinoma cells. These results suggest that BBR represses AP-1 transcriptional activity and u-PA expression [80]. BBR possesses a significant cytotoxic effect on gefitinib-resistant NSCLC cells by inhibiting sterol regulatory element binding protein 1 activity and suppressing lipogenesis. This effect occurs because BBR strongly suppresses the activity of complex I in the mitochondrial respiratory chain, reduces ATP, and stimulates the ROS/AMPK pathway [81]. In addition, the repopulation of ovarian cancer cells triggered by the chemotherapy drug VP16 is suppressed by the inhibition of the arachidonic acid pathway through the BBR-mediated inhibition of iPLA2 and COX_2 expression. In addition, BBR decreases the PEG_2 level and suppresses the phosphorylation of FAK, which contributes to the inhibition of repopulation of ovarian cancer cells [82].

Berberine and metabolic disorder

Berberine and glycometabolism

BBR increases glucose and 2-deoxyglucose uptake in myotubes and adipocytes to enhance glucose utilization [83]. It facilitates glucose uptake in 3T3-L1 adipocytes through a mechanism that is distinct from insulin signaling and does not increase glucose transport 4 (GLUT4) expression. However, BBR increases glucose transport 1 activities, which may be associated with the increased phosphorylation of AMPK and ACC in 3T3-L1 adipocytes [84]. BBR increases the phosphorylation of the endogenous substrate AS160 to facilitate GLUT4 translocation and enhances 3-O-methyl-D-glucose transport. AMPK activity

Table 1 Antiproliferation effect of berberine

Origin	Cell line	Effect of berberine	Mechanism	Experiment model	Year	Authors
Human leukemia	HL-60	Antiproliferation, induces apoptosis and cell cycle arrest	Complexes with DNA	*In vitro*	1995	Kuo *et al*. [42]
Human leukemia	HL-60	Antiproliferation, induces apoptosis	Downregulates nucleophosmin/B23 and telomerase activity	*In vitro*	1999	Wu *et al*. [50]
Human leukemia	U937	Antiproliferation	Inhibits telomerase activity	*In vitro*	1999	Wu *et al*. [50]
Oral cancer	OC2, KB	Antiproliferation	Reduces AP-1 expression, inhibits COX-2 protein	*In vitro* and *in vivo*	2004	Kuo *et al*. [61]
Human breast cancer	MCF-7	Antiproliferation, induces apoptosis and G_0/G_1 arrest	Upregulates interferon-β and TNF-α	*In vitro*	2005	Kang *et al*. [46]
Human hepatoma	HepG2	Antiproliferation, induces apoptosis	Activates caspases 8, caspases 3 and PARP	*In vitro*	2006	Hwang [54]
Human epidermoid carcinoma	A431	Antiproliferation, induces G_1 arrest and apoptosis	Upregulates Cip/p21 and Kip/p27 protein, disrupts mitochondrial membrane potential, activates caspase 3 and PARP	*In vitro*	2006	Mantena *et al*. [44]
Human oral squamous carcinoma cancer	HSC-3	Antiproliferation, induces cell cycle arrest and apoptosis	Induces ROS and Ca 21 production, suppresses the levels of mitochondrial membrane potential (MMP)	*In vitro*	2007	Lin *et al*. [45]
Human colonic carcinoma	SW620	Antiproliferation, induces apoptosis	Generates reactive oxygen species and activates JNK/p38 MAPK and FasL	*In vitro*	2007	Hsu *et al*. [59]
Non-small cell lung cancer	A549	Induce autophagy, enhances radio-sensitivity	Induces autophagy	*In vitro* and *in vivo*	2008	Peng *et al*. [49]
Human leukemia	Jurkat	Antiproliferation, induces apoptosis	Modifies cysteine 179 of IκBα kinase, suppresses nuclear factor-κB–regulated antiapoptotic gene products	*In vitro*	2008	Pandey *et al*. [63]
Acute lymphoblastic leukemia	EU-1, Sup-B13	Antiproliferation, induces apoptosis	Downregulates DAXX expression and promotes MDM2 degradation	*In vitro*	2010	Zhang *et al.* [57]
Prostate cancer	LNCaP	Antiproliferation	Suppresses androgen receptor	*In vitro* and *in vivo*	2011	Li *et al*. [67]
Human breast cancer	MCF7, T47D	Antiproliferation	Suppresses TPA-induced VEGF and fibronectin	*In vitro*	2013	Kim *et al*. [69]
Esophageal squamous cell carcinoma	ECA109, TE13	Induces autophagy, enhances radio-sensitivity	Decreases hypoxic activity	*In vitro* and *in vivo* (ECA109)	2013	Yang *et al*. [77]
Human neuroblastoma	SK-N-SH, NB-1691	Antiproliferation, induces apoptosis	Inhibits the transcription of DAXX	*In vitro*	2013	Li *et al*. [58]
Human lung adenocarcinoma	A549	Induces apoptosis and G_0/G_1 arrest	Induces FOXO3a and p53, activates p38α MAPK	*In vitro*	2014	Zheng *et al.* [47]
Human ovarian	A2780	Sensitizes the effect of cisplatin	Downregulates miR-93 and inhibits the PTEN/Akt pathway	*In vitro*	2015	Chen *et al.* [79]
Human glioblastoma	U87, U251	Antiproliferation, induce senescence	Downregulates EGFR and inhibits the EGFR–MEK–ERK signaling pathway	*In vitro* and *in vivo* (U87)	2015	Liu *et al.* [48]
Colon cancer	KM12C	Antiproliferation	Binds RXRα to suppress β-catenin signaling	*In vitro* and *in vivo*	2017	Ruan *et al*. [66]
Diffuse large B cell lymphoma	HEK-293T	Antiproliferation, impedes mitophagy-dependent necroptosis, induces mitophagy-dependent necroptosis	Accelerates PCYT1A mRNA degradation and inhibits the MYC-driven aberration of choline metabolism	*In vitro* and *in vivo*	2017	Xiong *et al.* [60]
Ovarian cancer	A2780, HO8910	Antiproliferation, increases sensitivity to PARP inhibition, homologous recombination repair	Induces oxidative DNA damage and impairs homologous recombination repair	*In vitro* and *in vivo* (A2780)	2017	Hou *et al*. [55]
Breast cancer cell	MCF-7	Reverses resistance to doxorubincin	Inhibits AMPK-HIF-1α	*In vitro* and *in vivo*	2017	Pan *et al*. [78]

(*Continued*)

Origin	Cell line	Effect of berberine	Mechanism	Experiment model	Year	Authors
Colon intestinal	IMCE	Antitumorigenesis	Block IL-6 and TNF-α, inhibits EGFR-ERK signaling	*In vitro* and *in vivo*	2017	Li *et al.* [64]
Ovarian cancer	SKOV3	Antiproliferation	Suppresses the arachidonic acid metabolic pathway and phosphorylation of FAK	*In vitro*	2017	Zhao *et al.* [82]
Gefitinib-resistant non-small cell lung cancer	H1975	Antiproliferation, suppression of lipogenesis	Induces reactive oxygen species generation and activates the AMPK pathway	*In vitro*	2018	Fan *et al.* [81]

Table 2 Anti-invasive and antimetastatic effects of berberine

Origin	Cell line	Effect of berberine	Mechanism	Experiment model	Year	Authors
Lewis lung carcinoma	Lewis lung carcinoma	Antiproliferation, antimetastasis	Represses AP-1 transcriptional activity and u-PA expression	*In vitro* and *in vivo*	2001	Mitani *et al*. [80]
Human gastric adenocarcinoma	RF-1, RF-48	Antimetastasis	Decreases the expression of COX-2, MMP-2, and MMP-9	*In vitro*	2006	Yu *et al*. [71]
Human gastric cancer	SNU-5	Antimetastasis	Downregulates the expression of matrix metalloproteinases-1, -2, and -7	*In vitro*	2006	Lin *et al*. [73]
Nasopharyngeal carcinoma	5-8F	Anti-invasion	Downregulates NM23-H1 expression	*In vitro* and *in vivo*	2008	Liu *et al*. [75]
Human tongue squamous cancer	SCC-4	Antimetastasis, anti-invasion	Inhibits FAK, IKK, NF-κB, u-PA and MMP-2 and MMP-9	*In vitro*	2009	Ho *et al.* [62]
Nasopharyngeal carcinoma	5-8F	Antimetastasis	Inhibits Ezrin phosphorylation	*In vitro* and *in vivo*	2009	Tang *et al*. [76]
Human melanoma	A375	Antimetastasis	Reduces ERK activity and COX-2, induces AMPK activation	*In vitro*	2012	Kim *et al*. [72]
Non-small cell lung cancer	A549	Antiproliferation, antimetastasis	Inhibits TGF-β1-induced epithelial-to-mesenchymal transition	*In vitro* and *in vivo*	2014	Qi *et al*. [70]
Triple-negative breast cancer	MDA-MB231	Anti-invasion	Downregulates TGF-β1	*In vitro* and *in vivo*	2018	Kim *et al.* [74]

is stimulated by BBR, and the intracellular energy status in skeletal muscle is reduced [85]. BBR also regulates the expression of metabolic genes, leading to the suppression of lipogenesis and induction of energy expenditure in adipose tissue and muscle [86]. BBR activates protein kinase C (PKC) to increase insulin receptor (InsR) gene expression. It effectively upregulates the transcription of the InsR-dependent PKC/AMPK pathway and improves glucose consumption and insulin sensitivity in a type 2 diabetes mellitus rodent model [87]. A clinical trial also demonstrated that InsR expression is elevated and glucose is lowered in patients with type 2 diabetes mellitus, especially those with liver disease and those treated with BBR [88]. In addition, BBR can improve insulin sensitivity in adipocytes by inhibiting proinflammatory responses in macrophages. BBR not only downregulates LPS- and TNF-induced proinflammatory responses by inhibiting the MAPK pathway but also suppresses ROS generation by stimulating AMPK activities in macrophages [89]. BBR inhibits aerobic respiration, leading to a reduction in oxygen consumption and the induction of the AMP/ATP ratio, thereby increasing AMPK activity [83]. BBR inhibits mitochondrial respiration in L6 myotubes by inhibiting the mitochondrial respiratory complex I [90]. Although BBR inhibits oxygen consumption in the mitochondria, it does not induce extra cell toxicity through

enhancing anaerobic respiration to compensate for the inhibition of aerobic respiration [83]. BBR activates SIRT1 by increasing the NAD^+/NADH ratio and the expression of nicotinamide phosphoribosyltransferase. SIRT1 plays an indispensable role in the preventive effects of BBR on diet-induced insulin resistance. The effect of BBR on improving insulin sensitivity is partly due to BBR reverting mitochondrial dysfunction and improving hyperglycemia in skeletal muscle through activation of SIRT1-dependent mitochondrial biogenesis [91]. Wang has shown that the oral administration of BBR can downregulate blood lipid and glucose levels through promoting the production of the short chain fatty acid (SCFA) butyrate by the gut microbiota. This result suggests that BBR lowers ATP and NADH levels to regulate the energy metabolism network in the intestinal microbiota to upregulate PTB/BUT enzymes and increase butyrate production [92]. BBR suppresses basal autophagy in mature adipocytes of mice fed a high-fat diet by targeting BECN1. The inhibition of autophagy decreases fatty acid oxidation and increases insulin sensitivity [93]. BBR decreases the expression of peroxisome proliferator-activated receptor γ (PPARγ) and fatty acid transferase and then inhibits fatty acid uptake, eventually improving free fatty acid-induced insulin resistance in L6 myotubes [94].

In addition, BBR can inhibit hepatic gluconeogenesis to increase glucose utilization in peripheral tissues. BBR restricts fatty acid oxidation to decrease acetyl CoA contents and limits pyruvate transport into mitochondria through mitochondrial pyruvate carrier 1 (MPC1). BBR preserves the acetylation of MPC1 and blocks gluconeogenesis [95]. BBR exerts a glucose-lowering effect on hepatocytes, which neither affects insulin secretion nor depends on insulin concentration [96]. However, BBR can restore the diminished insulin secretion in INS-1E cells and in islets from diabetic db/db mice by increasing AMPK phosphorylation and uncoupling protein-2 (UCP2) expression. Activation of AMPK and UCP2 attenuates oxidative stress and inhibits mitochondrial ROS production in HG-treated rat islets [97]. Moreover, BBR supplementation can normalize the levels of leptin and adiponectin, which contributes to reversing lipid and glucose homeostasis [91]. The effects of berberine on glycometabolism are summarized in Fig. 7.

BBR ameliorates insulin resistance caused by complications in type 2 diabetes mellitus. BBR alleviates mesenteric artery endothelial dysfunction and enhances vascular vasodilation. BBR increases phosphorylated IRs and activates the IR-Akt-eNOS cascade in type 2 diabetes mellitus rodent models [98,99]. BBR also alleviates cerebral arterial contractility by inhibiting Ca_L (L-type Ca^{2+}) channel function and Ca^{2+} release from the RyRs in cerebral vascular smooth cells (VSMCs) under hyperglycemic conditions in the rat model of streptozotocin-induced diabetes [100]. Oxidative stress and glial fibrillary acidic protein-immunoreactive astrocytes are ameliorated in the hippocampus of diabetic rats because of the beneficial effects of BBR on the reduction of superoxide dismutase (SOD) activity and lipid peroxidation and the regulation of the NO system. BBR exerts a protective effect on central nervous system disorders induced by diabetes mellitus [101].

Berberine and lipid metabolism

BBR is an effective cholesterol-lowering drug that has been tested in a clinical trial. It reduces serum cholesterol, triglyceride, and low-density lipoprotein cholesterol (LDL-c) without affecting serum high-density lipoprotein cholesterol (HDL-c) levels. According to the experimental results in hepatoma cells, BBR upregulates low-density lipoprotein receptor (LDLR) expression by directly

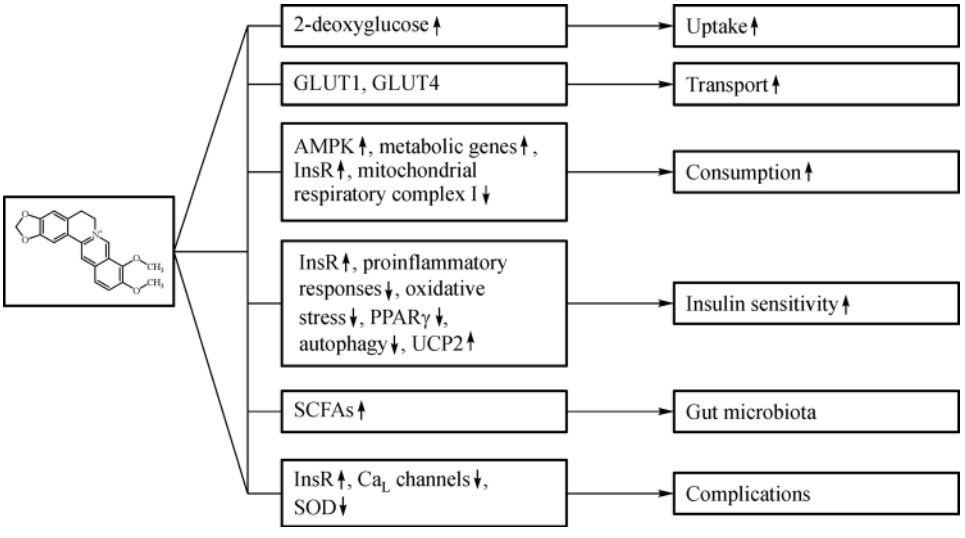

Fig. 7 Effects of berberine on glycometabolism.

stimulating the ERK signaling pathway to stabilize LDLR mRNA; as a result, LDL-c homeostasis is improved. The mechanism has no relation to the activation of SREBP or the activity of HMGCoA reductase [102]. Therefore, BBR is a nutraceutical considered as an alternative therapy to reduce LDL-c levels in statin-tolerant patients to avoid the statin-associated muscular adverse reaction [103]. BBR also increases the mRNA levels of Luc-UTR transcript and endogenous LDLR mRNA through the LDLR 3′ UTR region in the livers of Alb-Luc-UTR mice [104]. BBR can increase the phosphorylation levels of hepatic AMPK and ACC in obese db/db mice to promote fatty acid oxidation, eventually ameliorating hyperlipidemia [105]. BBR exerts an antilipolytic effect mainly by reducing the inhibition of phosphodiesterase by 3T3-L1 adipocytes, leading to the attenuation of cAMP-induced lipolysis [106]. BBR regulates the expression of metabolic genes, suppresses lipogenesis, and induces energy expenditure by activating AMPK activity in adipose tissue and muscle. As a result, body weight is reduced and triglyceride level is decreased [86]. Experiments suggest that BBR can lower blood cholesterol levels, which are associated with the inhibition of intestinal absorption, and decrease cholesterol micellarization and cholesterol uptake by enterocytes. In addition, BBR reduces cholesterol esterification and secretion by inhibiting ACAT2 expression and decreases permeability through Caco-2 monolayers [107]. BBR can modulate cholesterol metabolism and bile acid homeostasis to exert a lipid-lowering effect. It suppresses bile salt hydrolase activity and increases the levels of taurocholic acid in the intestine, which activates the intestinal FXR pathway and reduces the expression of the Cd36 gene, thereby reducing the uptake of long-chain fatty acids in the liver. Consequently, obesity is prevented, and triglyceride accumulation is ameliorated [108].

Berberine and obesity

BBR reduces body weight and increases energy expenditure without a significant effect on food intake in db/db mice [86]. Except for the previously described mechanisms by which BBR mediates lipid metabolism, the antiadipogenic and anti-inflammatory effects of BBR on 3T3-L1 adipocytes contribute to the reduction in adipocytes. BBR inhibits the expression of adipogenic enzymes (fatty acid synthase, acetyl-CoA carboxylase, acyl-CoA synthase, and lipoprotein lipase) and transcription factors (SREBP-1c, C/EBP-α, and PPAR-γ), thereby decreasing the production of adipocytes and the secretion of leptin. BBR downregulates proinflammatory markers, including TNF-α, IL-6, C-reactive protein, and haptoglobin [109]. BBR strongly increases the expression of UCP1 and other classical BAT marker genes to facilitate energy expenditure and thermogenic activities in the BAT of obese db/db mice. The transcription of UCP1 is increased by BBR treatment through AMPK activation and PGC-1α recruitment. In addition, BBR contributes to a robust defense against obesity by inducing energy expenditure and adaptive thermogenesis *in vivo* [110]. BBR mitigates body weight gain by shifting the structure of the gut microbiota and reducing microbial diversity in high-fat diet-induced obesity rats. BBR markedly increases SCFA-producing bacteria, including *Allobaculum*, *Bacteroides*, *Blautia*, *Butyricoccus*, and *Phascolarctobacterium*, which contribute to the amelioration of metabolic abnormalities [111].

Berberine and nonalcoholic fatty liver disease (NAFLD)

The antihyperlipidemic effect of BBR also improves nonalcoholic fatty liver disease. BBR ameliorates hyperlipidemia and removes excess hepatic fat accumulation by stimulating AMPK activities, and it also improves liver function [105]. BBR suppresses inflammatory signaling and adipose tissue inflammatory responses by reducing the phosphorylation of JUK1 and inflammatory cytokines, including IL-1β, IL-6, and/or TNF-α, in C57BL/6J mice fed a high-fat diet, thereby improving hepatic steatosis [27]. BBR exerts a protective effect on the liver following cholesterol overloading partly by inhibiting hepatic autophagic flux. BBR not only decreases hepatic cholesterol levels and suppresses cholesterol trafficking toward the plasma membrane by decreasing sterol carrier protein 2 but also mitigates the COX_2-mediated production of prostaglandin metabolites, thereby modulating Akt/mTOR activity [112]. The effects of berberine on lipid metabolism, obesity, and NAFLD are summarized in Fig. 8.

Berberine and cardiovascular diseases

Berberine and heart failure

BBR exhibits hemodynamic improvement in patients with refractory congestive heart failure. BBR has strong positive inotropic and peripheral resistance-lowering effects. It reduces the left ventricular systolic dimension and induces the left ventricular ejection fraction to decrease ventricular pressure. The ventricular filling pressures are decreased by BBR by reducing systemic and pulmonary venous pressures [113]. BBR increases the indices of inotropism. BBR can modify the contractile states of the myocardium with no changes in heart rate [113]. Fbxo32, an antihypertrophic E3 ligase, can be upregulated by BBR to ameliorate pathological hypertrophic remodeling and prevent the development of heart failure in cardiac-deficient Pak1 mice under pressure overload [114]. BBR features muscarinic agonist-like properties, decreases the spontaneous contraction rate, and exerts chronotropic activity in cardiomyocytes of

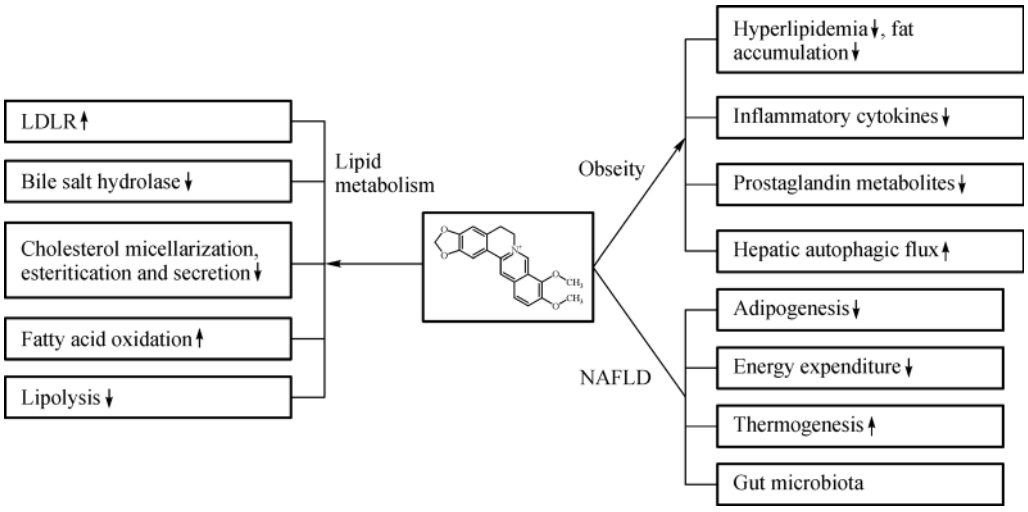

Fig. 8 Effects of berberine on lipid metabolism, obesity, and nonalcoholic fatty liver disease.

neonatal mouse cardiomyocytes by activating cardiac M_2 muscarinic cholinergic receptors [115].

Berberine and arrhythmias

BBR effectively suppresses ischemic ventricular tachyarrhythmias, including ventricular premature contractions (VPCs), paired VPCs, VPCs with R on T, and ventricular tachycardias caused by ligating the left anterior descending coronary artery, in canine models [116]. BBR exerts antiarrhythmic effects on action potential duration (APD) and ionic currents of ventricular myocytes. BBR prolongs APD in ventricular myocytes, and the underlying mechanism is that BBR at concentrations of 0.3–30 μmol/L can selectively block the rapid current (I_{Kr}) in the outward delayed rectifier potassium current (I_K). At concentrations higher than 10 μmol/L, BBR exerts an inhibitory effect on the transient outward (I_{to1}) current [117]. Experiments in *Xenopus* oocytes have documented that BBR not only inhibits I_K and inward rectifier potassium current (I_{K1}) in a concentration-dependent manner but also produces a voltage-dependent block of HERG channels; as a result, depolarization is significantly increased, and APD is prolonged [118]. In addition, BBR can upregulate Kir2.1 channel protein expression, restore I_{K1} potassium current and current density [119], recover the diminished I_{to} and I_{Ca} current densities, restore the prolonged QTc interval [120], and stabilize resting membrane potential [119] to show antiarrhythmic effects in a rat model of diabetes mellitus with myocardial infarction.

Berberine and atherosclerosis

BBR has antihypercholesterolemic efficacy. It reduces the levels of total cholesterol, triglycerides, and LDL cholesterol; increases HDL cholesterol [121]; and improves the leptin-to-adiponectin ratio [122] in patients with a risk of cardiovascular disease. Clinical evidence suggests that BBR–silymarin association exerts a strong effect on the improvement of lipid and glucose metabolism and possibly promotes cardiovascular health. Silymarin not only increases BBR oral bioavailability but also reduces gastrointestinal discomfort [123]. BBR exerts protective pharmacological properties against hyperglycemia-induced cellular injury and endothelial dysfunction. It can ameliorate hyperglycemia-induced endothelial injury and enhance endothelium-dependent vasodilatations by activating the AMPK signaling pathway and inducing eNO production [124]. BBR is potentially efficacious in reducing cardiometabolic disease risk and improving cardiovascular diseases. It regulates lipid profile and blood pressure, improves hypercholesterolemia and hypertension, inhibits the inflammation of vascular endothelium, and enhances endothelial function [125–127]. The beneficial effects of BBR can attenuate the development of atherosclerosis. Given its protective effect on cardiovascular disease and lipid metabolism, BBR is considered a potentially beneficial complement to menopausal women to relieve their discomfort and improve quality of life [128].

Berberine and ischemic heart disease

BBR shows protective properties against myocardial ischemia/reperfusion injury through antioxidative and anti-inflammatory effects. It attenuates apoptosis, increases SOD level, decreases infarct size, and diminishes serum creatine kinase and lactate dehydrogenase levels, which are associated with activation of SIRT1 signaling [129]. Experiments in rat H9c2 myocytes confirmed that BBR can ameliorate hypoxia/reoxygenation injury by decreasing the level of autophagy. It downregulates the expression

of the autophagy-related proteins SIRT1, BNIP3, and Beclin-1 and inhibits AMPK-mTOR pathway activities [130]. BBR also ameliorates the increase in cardiac output of ischemic ventricular disease [116].

Berberine and hypertension

BBR demonstrates relaxant and anticonstrictive effects on the isolated thoracic aortas of rats in a dose-dependent manner. BBR exerts hypotensive effect partly by inhibiting angiotensin-converting enzyme activities and inducing the release of NO and cGMP production directly in vascular tissues [131,132]. BBR significantly reduces the expression of oxidized LDL (oxLDL) and TNF-α-induced lectin-like oxLDL receptor 1 and inhibits oxidative stress by reducing intracellular ROS levels to protect endothelial cells and improve endothelium-mediated vasodilatation [133]. A clinical trial proved that BBR can effectively decrease the mean 24-h systolic and 24-h pulse pressures in patients [134]. BBR can improve vascular stiffness and antivascular aging to decrease the mean BP and pulse BP through the blockade of transient receptor potential vanilloid 4 channels, reduction in intracellular Ca^{2+} levels in VSMCs, and induction of vasorelaxation [135]. In addition, BBR can alleviate the effect of norepinephrine (NE) to improve pulmonary arterial hypertension by suppressing protein phosphatase 2A signaling pathways [136].

Berberine and other cardiovascular diseases

BBR can dramatically attenuate the impairment of cardiac function and pathophysiological severity and decrease anticardiac myosin antibody levels to ameliorate myosin-induced myocardial injury in experimental autoimmune myocarditis rats. BBR exerts a protective effect by suppressing Th17 and Th1 cell differentiation and reversing the increased response of Th17/Th1 cells through blocking p-STAT1, p-STAT3, and p-STAT4 activities [137]. BBR ameliorates the cardiotoxicity caused by anthracycline DOX by upregulating Sirt3 and Sirt1 protein expression to restore the increase in mitochondrial-mediated apoptosis and oxidative stress, promote mitophagy, and induce mitochondrial biogenesis [138]. The effects of berberine on cardiovascular diseases are summarized in Fig. 9.

Berberine and neurological diseases

BBR has potent neuroprotective properties. At low concentrations, BBR significantly attenuates 6-OHDA-induced cytotoxicity to protect PC12 cells and zebrafish from further damage through the activation of hormetic mechanisms, which are activated by the induction of PI3K/AKT/Bcl-2 cell survival and Nrf2/HO-1 antioxidative signaling pathways. However, the neuroprotective activities of BBR at high concentrations are minimal [139]. BBR effectively protects spiral ganglion cells from damage through its antiapoptotic and antioxidative properties. At low concentrations, BBR can decrease apoptosis induced by *Cytomegalovirus* in cultured spiral ganglion cells by suppressing NMDAR1/Nox3; therefore, mitochondrial ROS generation is significantly reduced [140]. BBR also shows a protective effect on ischemia-reperfusion injury of the brains of mice subjected to transient middle cerebral artery occlusion. The underlying pathogenesis has been elucidated: BBR impedes the release of HMGB1 and inhibits NF-κB nuclear translocation, consequently suppressing HMGB1/TLR4/NF-κB signaling [141]. BBR has protective abilities against ischemic brain damage in rats partly by blocking outward potassium current (I_A) and delaying rectifier potassium current (I_K) in acutely isolated CA1 pyramidal neurons from rat hippocampi [142]. BBR demonstrates potential antidepressant-like actions. BBR is a substrate and an inhibitor of organic cation transporter 2 and transporter 3, which are low-affinity and high-capacity transporters (uptake-2), respectively. Studies on transfected MDCK cells have documented that BBR can increase serotonin/NE/dopamine (5-HT/NE/DA) levels by inhibiting OCT2- and OCT3-mediated 5-HT and NE uptake, leading to enhanced monoamine neurotransmission in mouse brains [143]. BBR enhances 5-HT_2 receptor activation partly by influencing the BDNF-eEF2 pathway in the hippocampus and CREB signaling in the frontal cortex [144]. In stress mouse models, BBR inhibits the proinflammatory cytokines IL-6 and TNF-α, decreases the activation of microglia, and inhibits the NF-κB pathway in the hippocampus to show antidepressant-like effects [145].

Berberine and other diseases

BBR exerts protective effects on kidney tissues against aldosterone-induced podocyte injury. It can suppress aldosterone-induced oxidative stress and endoplasmic reticulum stress and improve the podocyte injury and extensive fusion of foot processes [146]. BBR relieves edema and pain in monoarthritic rats by selectively decreasing JAK3 phosphorylation through binding to the kinase domain of JAK3, consequently suppressing inflammation in the synovial tissues of rat joints [147]. BBR promotes osteoblast differentiation to accelerate osteogenesis by activating Runx2 and increasing COX_2 expression [148]. Studies have confirmed that BBR can suppress the propagation of ZIKV in both murine and human testes [149].

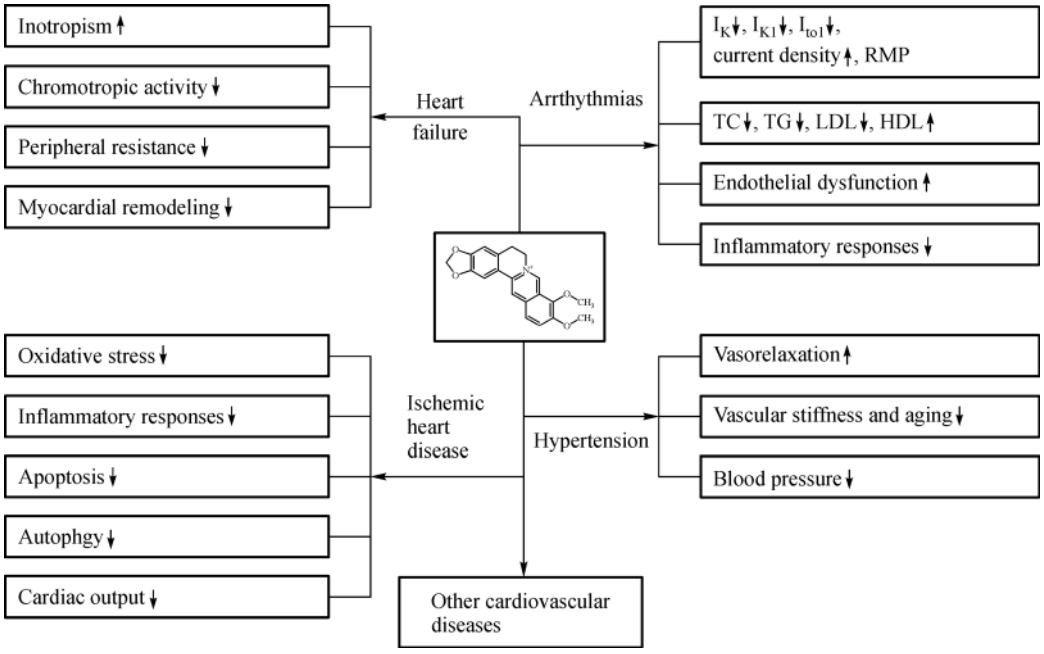

Fig. 9 Effects of berberine on cardiovascular diseases.

Conclusions

Cancer and cardiovascular, metabolic, and neurological diseases are chronic illnesses that require long-term, ongoing management. In the course of medical treatment, many challenges emerge, such as resistance, adverse drug reactions, and serious concomitant symptoms. BBR is a safe and effective natural product that is used in various diseases and pathological conditions; thus, it is a potential choice for long-term treatment and management. Recently, a serious challenge in anticancer therapy is multidrug resistance (MDR), and overcoming MDR is a major goal that requires enormous efforts to achieve. BBR not only inhibits the proliferation, invasion, and metastasis of cancer but also enhances the effects of chemoradiotherapies. It is a promising drug with few adverse reactions, which may offer an exciting therapeutic option to solve the problem. In addition, the cancer risk in diabetic patients increases slightly, and cancer mortality increases. Therefore, BBR stands out for its wide range of pharmacological effects that are beneficial to cancer and metabolic disorders. Furthermore, BBR is expected to be appropriate for patients suffering from more than one disease, considering the strong association among metabolic, cardiovascular, and neurological diseases. In this article, we explained the properties of BBR and its mechanisms, and most data were obtained from preclinical experiments; the clinical trials have not been extensively carried out. Therefore, evidence from clinical investigations is insufficient, and further clinical research should be conducted in the future.

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Compliance with ethics guidelines

Danyang Song, Jianyu Hao, and Daiming Fan declare that they have no conflict of interest. This manuscript is a review article and does not involve a research protocol requiring approval by the relevant institutional review board or ethics committee.

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