

The Anti-Cancer Mechanisms of Berberine: A Review

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Abstract: Berberine (BBR) has been extensively studied in vivo and vitro experiments. BBR inhibits cell proliferation by regulating cell cycle and cell autophagy, and promoting cell apoptosis. BBR also inhibits cell invasion and metastasis by suppressing EMT and down-regulating the expression of metastasis-related proteins and signaling pathways. In addition, BBR inhibits cell proliferation by interacting with microRNAs and suppressing telomerase activity. BBR exerts its anti-inflammation and antioxidant properties, and also regulates tumor microenvironment. This review emphasized that BBR as a potential anti-inflammation and antioxidant agent, also as an effective immunomodulator, is expected to be widely used in clinic for cancer therapy.

Keywords: berberine, anti-tumor, traditional Chinese medicine, cancer

Introduction

Cancer is a major cluster of diseases that seriously affects human health. Therefore, development of strategies to prevent and treat cancer is critical.¹ Berberine (BBR), a small molecule isoquinoline alkaloid extracted from the rhizomes of *Coptis chinensis* and *Hydrastis canadensis*, is traditionally used to treat bacterial diarrhea.² Recent studies showed that BBR reduced lipid levels and glycemic index, and exerted anti-tumor effects.^{3–7} BBR lowered lipid levels via competitive inhibition of HMG-CoA reductase, and by interacting with the 3'-UTR of the LDL receptor (LDLR) to improve the stability of LDLR mRNA.⁸ In vivo experiment showed that BBR alleviated nonalcoholic fatty liver by activating SIRT3.⁹ In foam cells, BBR promoted cholesterol efflux by increasing ROS production, and induced autophagy by inhibiting mTOR and Akt phosphorylation.¹⁰ The mechanisms of the hypoglycemic effects of BBR have also been studied extensively. Studies showed that BBR improved insulin action through inhibition of mitochondrial and activation of AMPK.^{11,12} In liver and muscle cells, BBR restored insulin sensitivity by up-regulating InsR expression.¹³ In vitro experiments showed that BBR affected glucose uptake by down-regulating miR29-b and increasing Akt expression.¹⁴ Recent studies have shown that BBR exerted anti-tumor effects against lung cancer, cervical cancer, liver cancer, leukemia, and other malignancies.^{15–18}

BBR inhibits cancer cell proliferation through various mechanisms. Here, in this review, we discussed the effects of BBR on cell cycle, cell apoptosis, cell autophagy, ability of inhibiting cell invasion and proliferation, expression of microRNA, telomerase activity, and tumor microenvironment. Currently, BBR is widely used in basic researches and clinical trials. This review clarified the potential of BBR as an anti-cancer drug, which may speed up its clinical application and eventually benefit cancer patients.

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BBR Inhibits Cell Proliferation BBR Regulates Cell Cycle

Alterations in the cell cycle promote the development of cancer.^{19,20} Studies showed that BBR regulated cell cycle and inhibited cell proliferation in multiple cancers.^{6,21,22} BBR induced G1 phase cycle arrest in A549 lung cancer cells through inhibition of the expression of Cyclin D1 and Cyclin E1.²¹ In addition, a combination of an Hsp90 inhibitor and BBR inhibited cell growth via inhibition of CDK4 expression and modulation of cyclin D1 in colorectal cancer cells.²² In HepG2 human hepatoma cells, BBR suppressed cyclin D1 expression *in vitro* and *in vivo*.⁶ Furthermore, BBR arrested the cell cycle at G1 via reduced expression of cyclin B1 and indirect inhibition of CDC2 kinase in several cancer cells.²³ In HBT-94 chondrosarcoma cells, BBR up-regulated the expression of p53 and p21 by modulating activation of the PI3K/Akt and p38 signaling pathways, which resulted in G2/M phase arrest.²⁴ In MDA-MB-231 breast cancer cells, BBR arrested cells in S phase, which contributed to high sensitivity of cancer cells to chemotherapy.²⁵ BBR has also been shown to influence cell cycle through regulation of Rb. Specifically, BBR acted on the 3'-UTR of Rb, which resulted in inhibition of Rb mRNA degradation, stabilization of Rb translation, and inhibition of cell cycle progression.²⁶ BBR also inhibited phosphorylation of Rb protein, which prevented dissociation of the transcriptional activator E2F from Rb, and resulted in inhibition of the transition from G1 to S phase.²⁷ Together, BBR inhibits cancer cell proliferation by affecting cell cycle progression.

BBR Regulates Cell Apoptosis

Apoptosis is a gene-controlled form of cell death that plays an important role in health and disease.²⁸ BBR has been shown to promote apoptosis by activating caspases. In leukemia, BBR contributed to cell apoptosis by increasing the expression of caspase-8 and caspase-9, and inhibiting the expression of bcl-2 through activation of caspase-3.²⁹ BBR activated caspases through increased levels of cytochrome C,³⁰ activation of AMPK, and increased ROS production.^{31,32} Mitochondria are central to regulation of apoptosis.³³ A study showed that external stimulation increased the permeability of the mitochondrial membrane, which activated the caspase cascade, and resulted in apoptosis.³³ This signaling cascade was also involved in BBR-induced apoptosis in hepatoma cells.³⁴ BBR increased phosphorylation of p53 through activation of JNK/p38, which promoted the entry of the apoptotic

proteins Bax and Bim into mitochondria.³⁵ In addition, studies showed that BBR promoted apoptosis through increased acetylation of foxo1/3a and increased expression of Bim and Bax.^{36,37} In colon cancer cells, BBR promoted cell apoptosis by inducing the expression of ATF3 protein through increased p53 transcription activity.³⁸ In MDM2-overexpressing tumor cells, BBR treatment led to the degradation of MDM2, which induced cell apoptosis in acute lymphoblastic leukemia.³⁹ In conclusion, BBR contributes to cell death by inducing cell apoptosis through different mechanisms.

BBR Regulates Cell Autophagy

Autophagy is a form of programmed cell death that plays an important role in maintaining cellular homeostasis.⁴⁰ In glioblastoma, BBR targeted the AMPK/mTOR/ULK1 pathway and resulted in activation of autophagy.⁴¹ In breast cancer, BBR induced autophagic death by modulating phosphorylation of JNK and contributing to dissociation of the bcl-2/beclin-1 complex.⁴² In hepatoma cells, BBR induced autophagy by promoting the release of beclin-1 from the bcl-2/beclin-1 complex.⁴³ In addition, BBR has been shown to induce autophagy by increasing the binding capacity of GRP78 and VPS34 in cancer cells.⁴⁴ BBR also indirectly inhibited the expression of SREBP-1 through activation of AMPK, which activated the ULK1/mTOR1 signaling pathway to promote autophagy.⁴⁵ Studies have shown that autophagy-mediated drug resistance plays an important role in cancer development and that tumor cells evade apoptosis through regulation of autophagy.⁴⁶ BBR may be able to reverse drug resistance by regulating autophagy through activation of AMPK. A previous study showed that BBR promoted binding of the miR30 family with the beclin1 3'-UTR region, which resulted in the inhibition of autophagy in adipocytes.⁴⁷ From the above findings, we found that the effects of BBR on autophagy are complicated, BBR either inhibited autophagy or induced autophagy to exert its anti-tumor effects. Regulation of BBR on autophagy has been widely studied; however, additional studies are needed to further characterize the mechanisms by which BBR may regulate autophagy.

BBR Inhibits Cell Invasion and Metastasis

Patients with cancer die due to destruction of tissues and organs resulting from uncontrolled cell proliferation, and tumor cell invasion and metastasis. In breast cancer cells,

BBR inhibited cell proliferation and metastasis by targeting ephrin-B2 and inhibiting the expression of MMP-2 and MMP-9.⁴⁸ In addition, BBR inhibited the expression of MMP-2 and MMP-9 via downregulation of TGF- β 1.⁴⁹ In melanoma, BBR inhibited the EMT through downregulation of RAR α and upregulation of RAR β , which resulted in inhibition of the PI3K/Akt signaling pathway.⁵⁰ In triple-negative breast cancer cells, BBR inhibited cell proliferation by down-regulating IL8 expression through inhibiting the EGFR/MEK/ERK signaling pathway.⁵¹ In addition, BBR has been shown to inhibit the COX-2/PGE2-JAK2/STAT3 signaling pathway, which resulted in reduced expression of MMP2 and MMP9.⁵² Angiogenesis plays a key role in cancer progression and metastasis.⁵³ In vitro and in vivo studies showed that BBR inhibited the expression of VEGF mRNA in tumor cells,⁵⁴ induced phosphorylation of eEF2,⁵⁵ down-regulated the activity of HIF-1 α , which resulted in reduced expression of VEGF,⁵⁶ and inhibited the PI3K/AKT signaling pathway.⁵⁷ In SW480 colorectal cancer cells, BBR inhibited proliferation and migration by down-regulating expression of GRP78.⁵⁸ In addition, BBR inhibited tumor metastasis by reducing the expression of the transcription factor snail-1.¹⁶ In all, BBR inhibits cell invasion and metastasis by affecting the expression of tumor-related signaling pathways and proteins.

BBR Regulates Tumor Microenvironment

Tumor cells secrete cytokines to alter the surrounding tumor microenvironment, which promotes tumor cell proliferation and metastasis.⁵⁹⁻⁶¹ In osteosarcoma, BBR altered the inflammatory microenvironment by down-regulating the caspase-1/IL-1 β signaling pathway, which resulted in cell apoptosis.⁶² In autoimmune diseases, BBR suppressed the Th17 response through direct interaction with T cells and DC cells.⁶³ BBR has been shown to improve osteoarthritis through inhibition of IL-1 β signaling, and inhibition of cartilage damage.⁶⁴ In all, BBR regulates tumor microenvironment by affecting inflammatory response and immune molecules.

BBR's Antiinflammatory Properties

In inflammatory macrophages, BBR induced Nrf2 activation in an AMPK-dependent manner and inhibited inflammation.⁶⁵ BBR reduced oxidized low-density lipoprotein (ox-LDL)-induced inflammation by regulating the AMPK/mTOR signaling pathway.⁶⁶ In hepatic fibrosis,

BBR inhibited the inflammation induced by thioacetamide treatment.⁶⁷ In skeletal progenitor cells, BBR exerted its anti-inflammatory activities by activating the AMPK α -SIRT-1-PGC-1 α signaling pathway and inhibiting the mitogen-activated protein kinase 4 (MKK4)-SAPK/JNK-C-JUN.⁶⁸ A study showed that BBR treatment down-regulated TNF α , IL-1 β and IL-6, which suppressed the seizure-like behavior in Zebrafish.⁶⁹ In adjuvant arthritis in mice, BBR significantly alleviated joint destruction and inflammatory cell infiltration by regulating the AMPK/NF- κ B pathway.⁷⁰ Together, BBR inhibits inflammation by regulating different signaling pathways and cytokines.

BBR's Antioxidant Activities

In thioacetamide-induced liver fibrosis, BBR suppressed hepatic fibrosis by elevating hepatic antioxidant enzymes.⁶⁷ In spiral ganglion cells, BBR exerted antioxidant effects via mediating the generation of reactive oxygen species.⁷¹ In experimental varicocele, BBR as an antioxidant agent, promoted testicular antioxidant potential, promoted spermatogenesis, and upregulated the sperm quality.⁷² A study showed that BBR protected PC-12 cells from oxidative injury by inhibiting ROS via PI3K/AKT/mTOR signaling pathways.⁷³ In the pentylentetrazole-induced kindling model of epilepsy in rats, BBR exerted antioxidant properties and anti-epileptogenic effects by up-regulating superoxide dismutase levels.⁷⁴ In the intestinal tissue of mice, BBR treatment enhanced the antioxidant status by increasing the activities of catalase and glutathione peroxidase enzymes.⁷⁵ These findings demonstrated that BBR exerts antioxidant properties through various mechanisms, and BBR might be the potential antioxidant agent.

BBR Acts as an Effective Candidate for Tumor Immunotherapy

Immunotherapy for the treatment of tumors has received increased attention. BBR has been shown to exert positive effects on tumor immunotherapy. A study showed that BBR acted as a dopamine D1- and D2-like receptor antagonist to inhibit secretion of IFN- γ , TNF- α , IL-6, and IL-1 β from LPS-stimulated lymphocytes.⁷⁶ BBR also improved autoimmune neuropathy by down-regulating TNF- α and IL-1 levels, and by inhibiting proliferation of CD4+ T cells.⁷⁷ Moreover, BBR inhibited the phosphorylation of STAT1, which resulted in inhibition of IFN- γ -induced IDO1 expression.⁷⁸ These

results indicated that BBR is a potential therapeutic candidate for tumor immunotherapy.

BBR's Other Functions Effects of BBR on microRNA

MicroRNA is a class of single-stranded RNA involved in post-transcriptional regulation.⁷⁹ More than 2500 microRNAs have been identified, and over-expression of many microRNAs has been shown to be closely related to onset and development of tumors.⁸⁰⁻⁸² In endometrial cancer cells and multiple myeloma cells, BBR inhibited cancer invasion and metastasis by interacting with microRNAs.⁸³⁻⁸⁵ In hepatoma cells, BBR mediated the transcriptional activation of p21 and GADD45α by up-regulating the expression of miR-23a.⁸⁶ In colon cancer cells, BBR down-regulated miR-429 and inhibited E-cadherin expression.⁸⁷ Together, BBR inhibits cancer invasion and metastasis by regulating the expression of microRNAs or interacting with them. Although studies have shown that BBR inhibited cancer development by

interacting with microRNAs, the interaction sites and mechanisms associated with these inhibitory effects need to be further explored.

BBR Regulates Telomerase Activity

Telomerase activity is inhibited in normal cells, and abnormal activation of telomerase results in immortalization in tumor cells.⁸⁸ BBR inhibited binding of AP-2 to the hTERT promoter, which resulted in reduced expression of hTERT and reversal of tumor cell immortalization.⁸⁹ Another study showed that BBR stabilized the structure of the endogenous telomere G-quadruplex,⁹⁰ which resulted in inhibition of binding of hTR to this complex and inhibition of telomerase activity.⁹¹ Together, BBR affects cell proliferation by inhibiting telomerase activity.

Discussion and Conclusion

The traditional Chinese medicine BBR has been shown to affect cell cycle, cell apoptosis, cell autophagy, and the tumor microenvironment. BBR has also been shown to

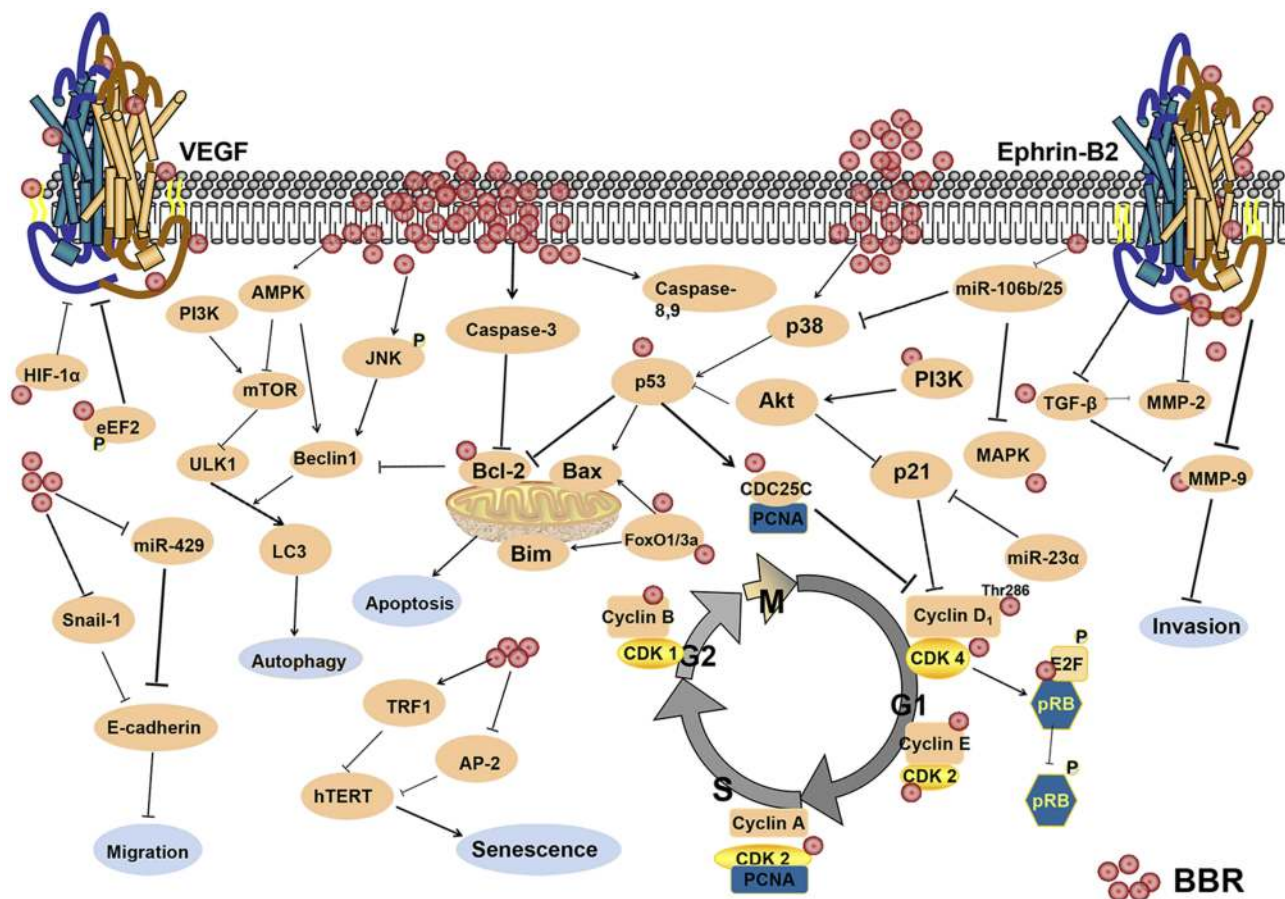


Figure 1 The anti-cancer mechanisms of berberine.

exert anti-inflammatory and antioxidant effects. Tumor immunotherapy is a hotspot for tumor therapy in recent years, immune-suppressants such as PD-1/PD-L1 suppressants have emerged one after another. However, it is difficult to be widely used in clinic due to their high prices. BBR as an effective immunomodulator and a kind of cheap Chinese traditional drug, is expected to be widely used in clinical practice as an ideal drug for immunotherapy.

As studies showed, BBR exerted its role on autophagy through different mechanisms. In several cancer cells, BBR inhibited cell proliferation by inducing autophagy and also reversed drug resistance by regulating cell autophagy.^{45,46} However, in mature adipocytes, BBR maintained the cellular homeostasis by inhibiting autophagy.⁴⁷ Studies showed that autophagy plays an important role in maintaining a stable intracellular environment.^{92,93} We inferred that autophagy plays different roles in cells. On the one hand, tumor cells evaded apoptosis through decreasing autophagy level; therefore, BBR treatment up-regulated autophagy and led to cancer cell death. On the other hand, BBR treatment lowered the original high level of autophagy in mature adipocytes to contribute to maintenance of a stable intracellular environment. Regulation of BBR on autophagy is complicated; therefore, studies are needed to make further progress on regulation of BBR on autophagy.

Although BBR exerts beneficial effects that may aid in the treatment of tumors, the efficacy of BBR is limited by poor solubility in water, rapid metabolism, and low absorption rate in intestines. Therefore, development of formulations that improve absorption of BBR in the intestines may have great potential for treatment of cancer. Xiao et al successfully designed nanoparticles that significantly increased the bioavailability of BBR, which demonstrated that nanotechnology may be a promising strategy for improving the pharmacokinetics of BBR.⁹⁴ Clinical trials mainly focused on the function of BBR on lowering lipid levels and regulating blood sugar. However, nowadays, anti-tumor effects of BBR are being investigated in a number of clinical trials.

In this review, we discussed the anti-tumor mechanisms of BBR (Figure 1), and its potential as an anti-cancer drug. BBR has been shown to inhibit cell proliferation and angiogenesis through modulating cell cycle, cell apoptosis, cell autophagy, and the tumor microenvironment. This review emphasized that BBR as a potential anti-inflammation and antioxidant agent, also as an effective immunomodulator, is expected to achieve clinical application for cancer therapy.

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Disclosure

The authors report no conflicts of interest in this work.

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