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REVIEW PAPER

Therapeutic Potential of Berberine in the Treatment of Glioma: Insights into Its Regulatory Mechanisms

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Abstract

Glioma is known as one of the most common primary intracranial tumors accounting for four-fifths of malignant brain tumors. There are several biological pathways that play a synergistic, pathophysiological role in glioma, including apoptosis, autophagy, oxidative stress, and cell cycle arrest. According to previous rese arches, the drugs used in the treatment of glioma have been associated with significant limitations. Therefore, improved and/or new therapeutic platforms are required. In this regard, multiple flavonoids and alkaloids have been extensively studied in the treatment of glioma. Berberine is a protoberberine alkaloid with wide range of pharmacological activities, applicable to various pathological conditions. Few studies have reported beneficial roles of berberine in glioma. Berberine exerts its pharmacological functions in glioma by controlling different molecular and cellular pathways. We reviewed the existing knowledge supporting the use of berberine in the treatment of glioma and its effects on molecular and cellular mechanisms.

Keywords Berberine · Glioma · Apoptosis · Autophagy · Cell cycle arrest

Introduction

Glioma is known as one of the most common primary intracranial tumors, which represents almost four-fifths of malignant brain tumors (da Silva et al. 2019). Gliomas are neuroectodermal in origin, arising from glial cells and glial precursor (Ostrom et al. 2017). Based on 2016 WHO update, glioma is classified by WHO as grade I-IV, while grade IV glioblastoma multiform (GBM) is known as the most common type of glioma (Howlader 2011). It has been reported that microglia, the purinergic P2X7 receptor (P2X7R) and immunocompetent cells of CNS are involved in the tumor progression and pathology of glioma. P2X7R is overexpressed in tumor cells, infiltrating microglia in glioma cells both in vitro and in vivo (Kan et al. 2019). The exosomes and miRNAs also have important roles in the pathogenesis of GBM (Saadatpour et al. 2016). In this regard, it has been shown that miR-21, miR-124, and miR-155 are involved in the pathogenesis of glioma (Guo et al. 2019; Masoudi et al. 2018). The up-regulation of NQO1 decreases reactive oxygen species (ROS) and elevates the cell proliferation in glioma cells. In addition, overexpression of PINK1 represses the ROS and cell proliferation in glioma cells (Luo et al. 2018).

Oxidative stress induces interaction of apurinic/apyrimidinic endonuclease with ectonucleotide pyrophosphatase/phosphodiesterase 2 and pyruvate kinase M2 in glioma cells (Cholia et al. 2018). Hence, modulation of the oxidative stress can be considered as a treatment strategy for glioma (Marconi et al. 2019; Wu et al. 2019). Magnetic resonance imaging (MRI) is an ideal imaging modality for the diagnosis or monitoring of CNS malignancies (Senft et al. 2011). The standard therapy of newly diagnosed GBM is the combination of radiotherapy and temozolomide (TMZ) (Stupp et al. 2009). However, in accordance with high resistance of GBM to current treatments as well as the failure of prolonging overall survival, new therapeutic approaches are needed

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(Mooney et al. 2019). In a study, authors documented that 5-ALA fluorescence-guided-surgery (5-ALA-FGS) is able to improve glioma treatment (Picart et al. 2019). In another study, redox-sensitive micelles were confirmed to be effective in the treatment of glioma (Tian et al. 2019). Moreover, it has been reported that medical plants and their active compounds such as gynostemma pentaphyllum extract, resveratrol, and berberine have also beneficial effects on glioma cells (Schild et al. 2010; Filippi-Chiela et al. 2011; Tong et al. 2019).

Berberine, a protoberberine alkaloid, possesses several pharmacological activities, which could be used in the treatment of different diseases such as cancer. Current evidences supported that berberine has a pivotal role in the prevention and treatment of brain-related disorders. Kim et al. (Kim et al. 2014) indicated that berberine has beneficial effects on the improvement of memory and motor dysfunction in Parkinson's disease through the modulation of apoptotic pathways. Berberine was stated to exert neuroprotective effects in an animal model of Alzheimer's disease through the regulation of amyloid precursor protein processing (Durairajan et al. 2012). In addition, Bhutada et al. (2010) found that berberine has anticonvulsant activity. Berberine also has anticancer activities against different cancers. Berberine is able to inhibit enzyme cyclooxygenase-2 activity in colon cancer (Fukuda et al. 1999). In another study, it has been reported that berberine could decrease the expression of matrix metallopeptidase (MMP)-9 and subsequently reduce the cell invasion in breast cancer cells (Kim et al. 2008). Finally, it seems that berberine exerts anti-glioma effects via modulating different cellular and molecular mechanisms, including decreasing the extracellular-signal-regulated kinase (ERK) 1/2 activity and increasing apoptosis both in vitro and in vivo (Sun et al. 2018; Eom et al. 2010). In this regard, a better insight into anti-glioma effects of berberine and involved cellular and molecular pathways could provide new milestones in the treatment of glioma. Herein, we focus on reviewing the current scenario in an attempt to provide interested readers with an updated view in this field.

Berberine in the Combination with Radiotherapy

Radiotherapy is a treatment method, which could be employed in various malignancies (Delaney et al. 2005). Radiotherapy is known as a post-surgical treatment for patients with malignant glioma (Walker et al. 1980). A systematic review indicated that the total dose delivered to glioma cells should ranges from 50 to 60 Gy, in the fraction sizes of 1.8–2.0 Gy (Laperriere et al. 2002). Different studies have indicated the beneficial effects of berberine plus radiotherapy in the treatment of cancers. In a study, it was reported that berberine increased the cytotoxicity of radiation via increasing autophagy in lung cancer (Peng et al. 2008). In another study, berberine was stated to increase the radiosensitivity of esophageal cancer cells via down-regulation of RAD51 (Liu et al. 2011). Few studies have shown the effects of berberine in combination with radiotherapy on the treatment of glioma. Yount et al. (Yount et al. 2004) reported that berberine sensitized human glioma cells in response to ionizing radiation, which can lead to the death of GBM cells. Co-administration of berberine and the low energy laser markedly decreased the LD50 of berberine. Another study also indicated the treatment effect of berberine plus laser in glioma cell line (Chen et al. 1994). Further studies are needed to evaluate the effects of berberine in combination with chemotherapy and radiotherapy in the treatment of gliomas (Fig. 1).

The Effects of Berberine on Various Molecular and Cellular Mechanisms in Glioma

Berberine and MAPKs Pathway in Glioma Cells

There are three main subfamilies of mitogen-activated protein kinases (MAPK), including the extracellular-signal-regulated kinases (ERK), MAPK14, and the c-jun N-terminal kinase or stress-activated protein kinases (JNK) (Dong et al. 2002). MAPK pathways are downstream pathways of different growth factor receptors such as epidermal growth factor (EGF) (Pece and Gutkind 2000). EGF activates both PKC-dependent and -independent pathways, thereby activating the Raf/MEK/ERK pathway (Chen and Davis 2003). It has been indicated that the Ras/Raf/MEK/ERK pathway is involved in the controlling of growth signals, cell proliferation, survival and invasion in different cancers (De Luca et al. 2012; Meier et al. 2005). Raf/MEK/ERK pathway is also implicated in the pathogenesis of glioma (See and Mukherjee 2018). In addition, ERK regulates cell proliferation in glioma cells (Jacques-Silva et al. 2004). ERK1/2 pathway regulates the BCL-2 proteins to promote cell survival in tumor cells (Balmanno and Cook 2009). In this pathway, protein kinase C (PKC) is able to activate the ERK for the migration of glioma cells (Besson et al. 2001). Lee et al. (2005) reported that the Ras/MEK/ERK pathway is involved in mediating H2O2-induced apoptosis in human glioma cells. Moreover, the activation of ERK plays an important role in the mediation of cisplatin-induced apoptosis in human glioma cells (Lee et al. 2005).

Few studies have addressed the presence of potential links between berberine and MAPKs. Indeed, available evidences still are not conclusive. Berberine decreases tumor growth and suppresses p-ERK1/2 and Ki-67 expression in glioma

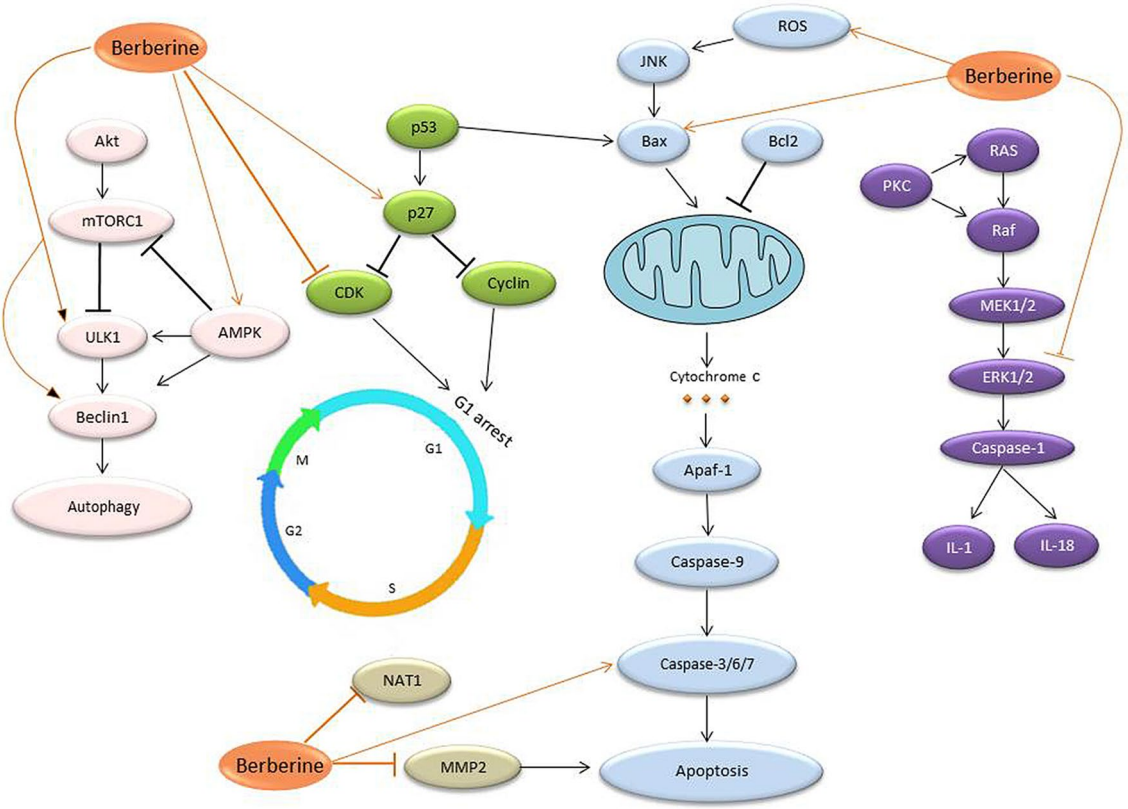

Fig. 1 Schematic representation of the beneficial effects of berberine on different signaling pathways in glioma cells. *AMPK* 5′ AMP-activated protein kinase; *Apaf-1* apoptotic protease activating factor-1; *Bcl-2* B-cell lymphoma 2; *Bax* B-cell lymphoma 2-associated X; *ERK* extracellular-signal-regulated kinase; *IL-1β* interleukin-1β; *IL-18* interleukin-18; *JNK* c-Jun N-terminal kinases; *ULK1* Unc-51-like autophagy activating kinase 1

cells (Sun et al. 2018). In another study, berberine significantly inhibited the Caspase-1-Mediated IL-1β and IL-18 releasing via inhibition of ERK1/2 signaling in glioma cells (Tong et al. 2019). Berberine greatly reduces the epidermal growth factor receptor (EGFR). Downregulation of EGFR resulted in inhibiting the RAF-MEK-ERK signaling pathway, but AKT phosphorylation was not changed (Liu et al. 2015). More studies are also needed to evaluate the effects of berberine on different proteins of the MAPKs pathway in gliomas.

Berberine and MMPs Pathways in Glioma Cells

Known as zinc-dependent endopeptidases family, MMPs are involved in the progression of cancer via increasing the cancer cell growth, migration, invasion, metastasis, and angiogenesis (Egeblad and Werb 2002). MT1-MMP has an important role in the pathophysiology of human malignant gliomas (Forsyth et al. 1999). In a study, it was reported that MMP-2 is localized in vasculature cells and tumor cells of malignant astrocytomas as well (Sawaya et al. 1996). MMP-2 inhibition significantly decreases tumor cell invasion, migration, and tumor growth in glioma cells (Badiga et al. 2011). In addition, these MMPs could be utilized as prognosis factors in the treatment of glioma (Thorns et al. 2003). Inhibition of MMPs can be a strategy for controlling cancer cells. Nyormoi et al. (2003) indicated that the inhibitor of MMP-2/MMP-9 led to inducing of apoptosis in cancer cells. Moreover, inhibition of MMPs can sensitize glioma cells to TMZ (Ulasov et al. 2013). It has been reported that berberine has beneficial effects on MMPs in cancer. Berberine also prevents the cell migration through inhibition of MMP-1, -2, and -9 in gastric cancer (Lin et al. 2008a). In another study, it was documented that MMP-1 and MMP-9 could be inhibited by berberine in human breast cancer (Kim et al. 2012). Berberine enhances the anti-glioma effects of As2O3-; therefore, the treatment with As2O3 and berberine synergistically decreased the activation of PKC alpha and epsilon and triggered actin cytoskeleton rearrangements. Also, the levels of jun and myc, and MT1-MMP, and MMP-2 reduced (Lin et al. 2008b).

Berberine and Autophagy Pathway in Glioma Cells

Autophagy is a process of protein recycling, which initiates with sequestering of cytoplasmic organelles in the membrane of vacuole, a process named autophagosome (Mizushima 2007). PtdIns3K-Akt-mTORC1 is a very important signaling pathway which is related to autophagy (Wu et al. 2009). TOR acts as the main regulator of autophagy. In addition, AMPK inhibits mTORC1 activity (Kang et al. 2011), which leads to suppressing ULK1 (Kang et al. 2011). ULK1 induces the Beclin-1 phosphorylation, which can result in autophagy (Russell et al. 2013). The autophagy process act as a tumor suppressor in the early stage of tumor development (Kondo et al. 2005). It has been showed that the mTOR, AKT and Ki-67/MIB-1 expression increased in glioma cells with a rise in grade of malignancy (Annovazzi et al. 2009). Autophagy could be used as a therapeutic target in the treatment of several cancers (Kondo et al. 2005); therefore, the induction of autophagy can promote the radiosensitivity in glioma cells (Palumbo et al. 2012). TMZ is able to exert its anti-glioma effects via inducing autophagy (Fan and Weiss 2011). This chemotherapy agent induces autophagy through ATM-AMPK-ULK1 signaling pathways in glioma cells (Zou et al. 2014). It has been shown that berberine induces autophagy in various cancers (Wang et al. 2010; Yu et al. 2014). A study has reported that berberine dephosphorylated mTOR, leading to the induction of autophagy. Berberine activates AMPK, which negatively regulates the mTOR and enhances the autophagy. In addition, berberine treatment elevated the p-Beclin-1 Ser93 in GBM cells. Berberine increased phosphorylated ULK1, a downstream target of mTOR. These signaling pathways lead to induction of autophagy in GBM cells (Wang et al. 2016).

Berberine and Cell Cycle Arrest in Glioma Cells

In different phases of the cell cycle (G1, S/DNA synthesis, G2, M/mitosis) during development, DNA is duplicated and the chromosomes are distributed into two daughter cells (Pardee 1989). Insulin-like growth factor-binding protein (IGFBP)-3 inhibits the cell proliferation via stimulation of cell cycle arrest. The expression of IGFBP-3 leads to G1 arrest, whereby the levels of the cell cycle-regulated proteins including cyclin D1, cyclin D3, cyclin A, cyclin E, and cyclin-dependent kinase (CDK) 2 and CDK4 may be decreased (Kim et al. 2010). The acetylation of p53 is also involved in the cell cycle arrest (Li et al. 2012). It has been shown that the induction of G1 arrest could contribute to control of cancer (Pardee 1989). Berberine promotes the cell cycle arrest in different cancers by decreasing cyclin D1, cyclin D3, cyclin A, cyclin E, and cyclin-dependent kinase (CDK) 2 and CDK4 (Lin et al. 2006; Mantena et al. 2006). In addition, berberine induces the G1 arrest through an increase in the expression of P27 and a decrease in the cyclin-dependent kinase (CDK) 2, CDK4, cyclin E proteins, and cyclin D (Eom et al. 2010).

Berberine and Apoptosis Pathways in Glioma Cells

Apoptosis contributes to tumor pathogenesis by different pathways (Wong 2011). There is an inverse relationship between cell apoptosis and tumor progression (Symonds et al. 1994). The changes in the ratio of pro- and anti-apoptotic proteins are involved in cell death. There are two general classes of apoptosis pathways, including intrinsic and extrinsic ones (Fulda and Debatin 2006). Caspases are important parts of apoptosis pathways (Leist et al. 1997). Thus, the change in caspases activities affects apoptosis and carcinogenesis in different cancers (Ghavami et al. 2009). Death receptors and their ligands have important roles in the external apoptosis pathway, including TNF, TNFR1, TNFR1-associated death domain protein (TRADD), and TNFR-associated factor (TRAFs). In addition, FAS (CD95) and FASL ligand (CD95L) are members of the extrinsic pathway (Ashkenazi 2008). Additionally, intrinsic pathways are related to non-receptor proteins, which stimulate apoptosis through intracellular signals that influence different targets within the cell or mitochondria. These proteins mainly includes the B-cell lymphoma protein 2 (Bcl-2) family proteins and cytochrome c (Wu and Bratton 2013). Various malignant glioma cells also express apoptotic proteins in intrinsic and extrinsic pathways (Song et al. 2003). It has been reported that apoptotic proteins are appropriate targets in controlling cancers (Wu and Bratton 2013).

Berberine increases the ROS and intracellular Ca (2+) and also induces ER stress. In addition, this natural compound markedly increases apoptosis by induction of a higher ratio of Bax/Bcl-2 proteins, the activation of caspase-3 and -9, and the cleavage of the poly(ADP-ribose) polymerase (PARP) (Eom et al. 2010). Berberine treatment markedly increases the apoptosis via induction of a higher ratio of the Bax/Bcl-2 proteins, mitochondrial membrane potential disruption, and activation of procaspase-9, caspase-3, caspase-9, and poly (ADP-ribose) polymerase (PARP). Berberine inhibits the glioma cell proliferation through promoting G1 arrest and apoptosis (Eom et al. 2008). Berberine increases the production of ROS and Ca2 + in glioma cells. Berberine inhibits Bcl-2 but increases Bax. The caspase-8, -9, and -3 were activated by berberine in glioma cells (Chen et al. 2009).

Berberine and Arylamine N-acetyltransferases in Glioma Cells

There are two related genes on chromosome 8, which have an important role in encoding the human arylamine

N-acetyltransferases (NAT1 and NAT2). NATs are known as polymorphic drug-metabolizing enzymes (Sim et al. 2014). NAT1 and NAT2 from this family are expressed in different tissues in the body (Windmill et al. 2000). These enzymes add an acetyl group from the O to the N group of arylacetohydroxates, which leads to the activation of arylamine carcinogens (Kabir and Rehman 2018). NAT1 is involved in cancer cell growth, since it is over€expressed in several cancers, leading to an increase in the resistance to chemotherapy (Butcher and Minchin 2012). Therefore, human arylamine N-acetyltransferases can be a drug target (Butcher and Minchin 2012). It has been reported that berberine inhibits the expression of NAT in cancer (LIN et al. 2005; Chung et al. 1999). In addition, berberine suppresses NAT1 in GBM cells (Wang et al. 2002). Further studies are needed to estimate the effects of berberine on NATs in gliomas.

Conclusions

Increasing evidence shows that berberine has pharmacological effects on tumor growth, cell proliferation, glycolytic capacity, migration, invasion, G1 arrest, NAT1, apoptosis, and autophagy signaling in glioma cells. In addition, berberine in combination with radiotherapy has beneficial effects on gliomas. Therefore, berberine could be used as an adjuvant therapy in the treatment of glioma. Further clinical and pre-clinical studies are needed to assess the therapeutic effects of berberine in the treatment of glioma.

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Compliance with Ethical Standards

Competing interest All authors declare that they have no conflicts of interest.

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