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REVIEW

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Berberine—A potent chemosensitizer and chemoprotector to conventional cancer therapies

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Chemotherapy and radiotherapy are mainstay treatments for cancer patients. However, their clinical outcomes are highly limited by the resistance of malignant tumors to these therapies and the incurrence of serious damages in vital organs. This in turn necessitates the development of adjunct drugs that overcomes chemo/radioresistance in refractory cancers and protects vital organs from the cytotoxic effects of cancer therapies. In recent years, Berberine (BBR), a natural isoquinoline alkaloid has garnered more attention due to its potent chemosensitizing and chemoprotective properties. BBR effectively sensitizes refractory cancers to chemotherapy and radiotherapy by ameliorating the diverse events underlying therapy resistance. Furthermore, it protects the heart, liver, lungs, and kidneys from severe damages caused by these therapies. In this review, we discuss the molecular mechanisms underlying the chemo/radiosensitizing and chemo/radioprotective potential of BBR during cancer treatment. Also, we highlight the limitations that hamper the clinical application of BBR as an adjunct drug and how novel innovations have been made in recent years to circumvent these challenges.

KEYWORDS
Berberine, cancer drug resistance, chemoprotective agents, chemosensitizing agents, nutraceuticals

1 | INTRODUCTION

Despite immense advancements in diagnostic and therapeutic strategies, cancer remains the second leading cause of global mortalities (Roser & Ritchie, 2020; WHO Cancer Fact Sheet, 2018). In 2018, cancer has taken the lives of 19 million people worldwide. The major reason behind this pathetic scenario is the development of resistance in cancer patients to conventional therapies including chemotherapy and radiotherapy (Housman et al., 2014; Wang, Zhang, & Chen, 2019). Tumor cells undergo various modifications at genetic, epigenetic, proteomic, and metabolic levels to escape from the cytotoxic effects of cancer therapies. These include increased tolerance to drug-induced replicative quiescence and DNA damage, alterations in the ratio of pro-apoptotic and antiapoptotic proteins, increased cancer stemness, tumor heterogeneity, and epigenetic modifications. Hence, to overcome drug resistance, it becomes essential to administer chemosensitizers in conjunction with cancer therapies (Mokhtari et al., 2017).

Chemosensitizers are the agents that enhance the response of tumor cells to cancer therapies by modulating one or more events that promote drug resistance. Among the most potent chemosensitizers, naturally occurring herbal nutraceuticals have garnered more attention in recent years owing to their harmless nature, versatile ability to circumvent therapy resistance, potential to ameliorate the deleterious side effects of the cancer therapies, low cost, and abundant availability (Choudhari, Mandave, Deshpande, Ranjekar, & Prakash, 2020; Ranjan et al., 2019). Of all these herbal drugs, berberine (BBR), the major phytochemical constituent of *Berberis* spp. is well studied for its chemotherapeutic, chemosensitizing, and chemoprotective properties.

BBR is the isoquinoline alkaloid present in roots, bark, stems, and rhizomes of berberis such as *Berberis vulgaris*, *Mahonia aquifolium*, *Berberis aristata*, *Phellodendron amurense*, *Hydrastis canadensis*, *Coptis chinensis*, *Xanthorhiza simplicissima*, *Argemone mexicana*, *Tinospora cordifolia*, and *Eschscholzia californica* (Tang et al., 2009). It is used as folk medicine in China from 3,000 BC for the improvement of immune function, glucose metabolism, and gastrointestinal function. In malignant tumors, BBR effectively combats the cancer hallmarks including cell proliferation, selective growth, inflammation, and metastasis by regulating the signaling, epigenetic, and molecular mechanisms underlying these events (Zhang et al., 2019). It induces tumor cell apoptosis by triggering p53 mediated intrinsic apoptotic pathway and augmenting the synthesis of reactive oxygen species (ROS) (Wang, Liu, Du, Ma, & Yao, 2020a; Xu et al., 2019). Also, BBR inhibits tumor metastasis by suppressing cell migration, invasion, angiogenesis, and epithelial-mesenchymal transition (EMT) (Zhang, Jia, et al., 2019).

Mounting studies show that BBR possesses potent chemosensitizing and chemoprotective effects. It overcomes therapy resistance in refractory cancers and thereby victimizes them to the anticancer action of radiotherapy and conventional chemotherapeutic agents including doxorubicin, cisplatin, cetuximab, gemcitabine, sunitinib, and tamoxifen by modulating the cell resistance pathways, regulating the expression of proteins associated with therapy resistance, ameliorating the stresses of tumor microenvironment including hypoxia, and augmenting the cytotoxic effects of cancer therapies. Furthermore, BBR also protects the vital organs including the heart, lungs, kidneys, and liver from severe injuries caused by these cytotoxic therapies. In this review, we discuss the molecular mechanisms underlying the chemo/radiosensitizing potential of BBR on malignant tumors and its chemo/radioprotective action on normal cells. Further, we have deliberated new directions to overcome the current limitations in the clinical development of BBR as an adjunct drug to prevent therapy failure.

2 | BERBERINE CIRCUMVENTS MAJOR EVENTS UNDERLYING THERAPY RESISTANCE IN MALIGNANT TUMORS

2.1 | BBR inhibits the ability of tumor cells to evade drug-induced apoptosis

Most of the chemotherapeutic agents and radiotherapy exert their anticancer potential majorly by promoting apoptosis of tumor cells (Makin & Hickman, 2000). However, tumor cells evade therapy-induced apoptosis by down-regulating the expression of pro-apoptotic proteins (including Bax, Bad, and Bak), up-regulating the expression of anti-apoptotic proteins (including Bcl-2, Mcl-1, and Akt), activating cell survival pathways, and promoting defective initiation and implementation of apoptosis (Pommier, Sordet, Antony, Hayward, & Kohn, 2004). BBR effectively potentiate the refractory tumors to apoptosis induced by cancer therapies via diverse mechanisms. Bax/Bcl-2 ratio is the prime determinant of cell susceptibility to apoptosis and acts as a prognostic marker to determine the therapeutic response of tumor cells to cancer therapies. A decreased ratio of these proteins implies tumor resistance to apoptosis (Naseri et al., 2015). Tamoxifen- resistant MCF-7/TAM breast cancer cells express low levels of Bax and high levels of Bcl-2, indicative of apoptosis resistance. Treatment of these cells with tamoxifen alone (1 μM) does not cause significant apoptosis due to the drug's inefficacy to alter the Bax/Bcl2 ratio. However, BBR (20 μM) cotreatment for 48 hr augments the apoptotic potential of tamoxifen (1 μM) in MCF/TAM cells by increasing the Bax/Bcl-2 ratio (Wen, Wu, Fu, Zhang, & Zhou, 2016). In CNE2 human nasopharyngeal carcinoma cells, BBR pretreatment (100 μmol/L) for 3 hr circumvents radioresistance and triggers apoptosis by inhibiting the expression of Sp1 (a key contributor to radioresistance in nasopharyngeal carcinoma cells) and blocking EMT (Wang et al., 2017). Lapatinib, a novel tyrosine kinase inhibitor of HER2/EGFR is commonly used in the treatment of HER2-positive breast cancer. However, its effective use as a conventional chemotherapeutic agent is highly limited by acquired drug resistance. Zhang and colleagues intensively studied the potential of BBR to overcome lapatinib resistance using BT-474^{WT} and BT-474^{LapR} human breast cancer cells. Lapatinib resistance was developed by the continuous exposure of parental cells (WT) to 2 μM lapatinib for 12 months. BT-474^{LapR} cells developed lapatinib resistance due to a significant reduction in ROS generation via overexpression of nuclear factor erythroid 2-related factor 2 (Nrf2) levels. Both the pro-Nfr2 and anti-Nrf2 pathway of GSK-3β has been found to be activated to stabilize Nrf2 and maintain a low level of ROS in these cells. Interestingly, the treatment of BT-474^{LapR} cells with lapatinib (2 μM) in the presence of BBR (2 μM) reverses lapatinib resistance and triggers apoptosis through the suppression of the c-Myc/Nrf2 pathway and up-regulation of ROS (Zhang et al., 2016). Tumor necrosis factor (TNF)-related apoptosis-inducing ligand (TRAIL), a cytokine synthesized, and secreted by most normal cells has a fascinating ability to selectively induce apoptosis of tumor cells by binding to certain death receptors. Hence, TRAIL-based therapy has garnered more attention in recent years to treat cancer. However, the clinical applications of TRAIL are limited by primary or acquired resistance. Fascinatingly, BBR pretreatment sensitizes TRAIL-resistant MDA-MB-468 triple-negative breast cancer (TNBC) cells to TRAIL-induced apoptotic death by activating caspase-3 and poly-ADP ribose polymerase (PARP) cleavage through the down-regulation of p38 MAPK signaling pathway (Refaat, Abdelhamed, Saiki, & Sakurai, 2015; Refaat et al., 2013). Likewise, BBR triggers the apoptotic potential of TRAIL in prostate cancer cells and hepatocellular carcinoma cells by up-regulating the expression of

various apoptotic genes including GADD45A, TNFSF8, Harakiri, Casp5, and TNFRSF10B and decreasing TNERSF1B through the activation of AMPK and DR5 (TRAIL receptor) (Ke et al., 2018). Apart from these pro-apoptotic mechanisms, BBR sensitizes chemoresistant tumors to drug-induced apoptosis by modulating microRNAs (miRNAs) and other key signaling pathways as well and the details of the same are given in the corresponding sections.

2.2 | BBR induces cell cycle arrest

Apart from inducing apoptosis, many cancer drugs including cisplatin, tamoxifen, and doxorubicin exert their antitumor effects by inducing irreversible cell cycle arrest in malignant tumors and thereby inhibiting their proliferation. However, many tumors evade drug-induced replicative senescence and this is recognized as one of the crucial events underlying resistance (Dökümcü & Farahani, 2019). BBR retaliates these tumors by promoting cell cycle arrest at the G1 or G2/M phase and thereby renders them highly susceptible to the cytotoxic effects of radiotherapy and chemotherapy. p21 is a protein that plays a key role in triggering cell cycle arrest in cells with damaged DNA. Its mutation or loss has been reported to augment the resistance of breast tumor cells to tamoxifen therapy (Abukhdeir et al., 2008). Nevertheless, in both tamoxifen sensitive MCF-7 and tamoxifen-resistant MCF-7/TAM cells breast cancer cells, BBR cotreatment (20 μM) for 48 hr exalts the efficacy of tamoxifen (1 μM) to up-regulate p21 levels, and induce G1 phase arrest. This, in turn, suggests that BBR in combination with tamoxifen inhibits the growth of breast tumors irrespective of tamoxifen resistance (Wen et al., 2016). Furthermore, in MCF-7 and MDA-MB-468 breast cancer cells, BBR pretreatment (15 μM) for 24 hr decreases ionizing radiation-induced G2/M delay and thus increases their sensitivity to radiotherapy (Wang et al., 2012). In MG-63 osteosarcoma cells, BBR post-treatment (20 μM) for 24 hr following γ-ray irradiation (4 Gy) augments their sensitivity to radiotherapy through the induction of G2/M phase arrest (Wang et al., 2020a). Anoikis is a form of apoptosis that occurs due to the detachment of anchorage-dependent cells from the surrounding extracellular matrix. Anoikis acts as a barrier to tumor progression and metastasis by impeding the signals required for the survival of localized tumor cells. However, most of the tumor cells develop resistance to anoikis which in turn results in their survival even after detachment from the primary site and their metastasis via lymphatic and circulatory systems. Kim and colleagues evaluated the apoptotic potential of BBR in anoikis resistant MCF-7 and MDA-MB-231 cells. These cells were made anoikis resistant by being cultured on a Poly-Hema substratum. Anoikis resistant cells exhibit a low growth rate and were also found to be more invasive when compared to their respective adherent cell lines. Fascinatingly, BBR treatment (20 μM) for 72 hr inhibits the growth of anoikis resistant cells more effectively than doxorubicin by inducing cell cycle arrest at the G0/G1 phase (Kim et al., 2010). In addition to BBR, its derivative, 1,13-cycloprotoberberine also exhibits cytotoxicity against doxorubicin-resistant MCF-7/ADrR cells and reduces tumor growth by arresting them at the G2/M phase of the cell cycle (Li et al., 2013).

2.3 | BBR decreases the potential of tumors to tolerate drug induced DNA damage

Most of the conventionally used chemotherapeutic agents are highly genotoxic to tumor cells. They are designed to induce DNA damage in existing cancer cells and also prevent DNA replication during cell proliferation. However, malignant tumors are highly tolerant of chemotherapy-induced DNA damages. The flexible active sites present in the specialized polymerases of the tumor cells effectively accommodate DNA lesions, allowing replication to proceed past the lesions via translesion synthesis. Also, tumor cells effectively repair the drug-induced damages via induction of genes including RAD23B, FANCG, and FEN1 that activate DNA repair pathways. This in turn allows the tumor cells to withstand DNA damages and undergo proliferation despite chemotherapy (Salehan & Morse, 2013). However, BBR circumvents all these protective strategies of malignant tumors and victimize them to the therapeutic effects of radiotherapy and chemotherapy. Its cotreatment (13 μM) with cisplatin (3.3 μM) in MCF-7 breast cancer cells for 48 hr reduces the expression of proliferating cell nuclear antigen, an important factor involved in the DNA damage tolerance pathway and thus increases the tumor sensitivity to DNA breaks and damages induced by cisplatin. This in turn renders these breast tumor cells highly susceptible to cisplatin-mediated apoptosis (Zhao, Jing, Li, & Mao, 2016). RAD51, a central enzyme involved in the homologous repair of double-strand breaks in DNA is overexpressed in a wide variety of cancers. Due to its potential to repair radiation-induced DNA damages, RAD51 is considered as a promising therapeutic target to overcome radioresistance (King et al., 2017). Fascinatingly, BBR down-regulates RAD51 expression in various cancer cells including MCF-7 and MDA-MB-468 triple-negative breast cancer cells (Wang, Liu, & Yang, 2012), MG-63 osteosarcoma cells (Wang, Liu, Du, Ma, & Yao, 2020b), and KYSE30 and KYSE450 esophageal squamous cell carcinoma cells (Liu et al., 2011) and augments their response to radiotherapy. More importantly, during the cotreatment of KYSE30, KYSE450, and normal human fibroblast cells with BBR and ionizing rays, BBR down-regulates RAD51 activity selectively in esophageal tumor cells without affecting its expression in normal human fibroblast cells (Liu et al., 2011). This in turn shows that BBR exerts its radiosensitizing effects specifically on tumor cells.

2.4 | BBR regulates the key signaling pathways governing drug response

Various cell-signaling cascades including PI3K/Akt/mTOR, JAK/STAT, NF-κB, and MAPK are crucially involved in tumor cell proliferation, survival, and apoptosis. Constitutive activation of these pathways in malignant tumors greatly protects them from drug-induced apoptosis (Delou, Souza, Souza, & Borges, 2019). However, BBR sensitizes tumor cells to a broad spectrum of cancer therapies by regulating these signaling pathways. It suppresses the radioresistant potential of PC-3 prostate cancer cells and enhances their response to the cytotoxic effects of γ-irradiation by up-regulating MAPK/caspase-3 and

ROS pathways and inhibiting radio-resistant proteins including NF-κB, Bcl-2, ERK, and HO-1 which are expressed postradiation therapy (Hur & Kim, 2010). Furthermore, it potentiates multidrug-resistant MCF-7/MDR human breast cancer cells to doxorubicin therapy through dose-orchestrated down-regulation of AMPK signaling pathway both in vitro and in vivo (Pan et al., 2017). Signal transducer and activator of transcription 3 (STAT3) activation via feedback loop is the major signaling event underlying the resistance of tumors to radiotherapy and chemotherapy (Tan, Putoczki, Stylli, & Luwor, 2014). Nevertheless, BBR inactivates STAT3 in various tumors, which in turn remains a major reason behind its chemosensitizing efficacy. In AGS gastric cancer cells, BBR cotreatment (5 μM) for 24 hr augments their sensitivity to 5-fluorouracil (10 μM)-induced apoptosis by reducing pSTAT-3 levels (Pandey et al., 2015). In NCI-H460 and NCI-H1975 nonsmall cell lung cancer (NSCLC) cells, BBR cotreatment (30 μg/ml) for 24 hr inhibits doxorubicin-induced STAT-3 activation and thereby reverses doxorubicin resistance (Zhu et al., 2015). Nexrutine, a natural product that contains BBR as its active constituent effectively chemosensitize gemcitabine-resistant BxPC-3 and Capan-2 pancreatic cancer cells to gemcitabine treatment and inhibit their proliferation by down-regulating STAT3/NF-κB signaling pathway. More importantly, Nexrutine does not cause any harm to the nontumorigenic HPNE pancreatic cells (Gong et al., 2017). Furthermore, BBR augments the therapeutic potential of the EGFR inhibitors, erlotinib, and cetuximab in MKN45, BGC823, and SGC7901 gastric cancer cells in vitro and BGC823 cells bearing BALB/C-nu/nu mice in vivo by down-regulating EGFR/STAT3 signaling pathway (Wang et al., 2016). Irinotecan is the Food and Drug Administration approved the standard drug used in the treatment of colon cancer. However, its potential to activate the NF-κB pathway significantly reduces its ability to apoptosis cancer cells. In HCT116 colon cancer cells, BBR pretreatment inhibits the up-regulation of irinotecan induced NF-κB pathway in a dose-dependent manner and augments its apoptotic potential by decreasing the expression of NF-κB dependent antiapoptotic genes, including c-IAP1, c-IAP2, survivin, and Bcl-xL (Yu et al., 2014). This in turn suggests that BBR could be a potent adjunct drug to irinotecan in colon cancer patients.

2.5 | BBR modulates the expression of miRNAs

miRNA are the small noncoding RNAs (about 21–25 nucleotides long) that control the posttranscriptional expression of genes. By binding to the 5′-untranslated regions of mRNAs, miRNAs promote their degradation and thus inhibit protein synthesis. Mounting studies show that miRNAs play a central role in the development of drug resistance (Si, Shen, Zheng, & Fan, 2019). However, BBR sensitizes tumor cells to chemotherapy by modulating the expression of various miRNAs and associated downstream signaling events. miRNA-21 is an oncogenic miRNA whose up-regulation contributes to cisplatin resistance in ovarian cancers. BBR cotreatment (10 μM) with cisplatin (10 μM) for 24 hr reverses drug resistance in cisplatin-resistant SKOV-3 human epithelial ovarian cancer cells by suppressing miRNA-21 expression and augmenting the expression of its downstream target, programmed cell death protein 4 (PDCD4) (Liu, Fang, Shen, Xu, & Li, 2013). miRNA-93 is another miRNA that promotes cisplatin resistance via negative regulation of PTEN, an important tumor suppressor in ovarian tumors. Its expression is higher in cisplatin-resistant cancer cells when compared to their sensitive counterparts. In cisplatin-resistant A2780/DDP ovarian cancer cells, BBR cotreatment (10 μM) down-regulates the expression of miR-93 and its downstream PTEN/AKT signaling pathways, and thereby potentiate them to cisplatin-induced apoptosis and G0/G1 phase arrest (Chen, Qin, Fang, & Li, 2015). Furthermore, in cisplatin-resistant SGC-7901/DDP and BGC-823/DDP gastric cancer cells, BBR cotreatment (10 μM) for 48 hr stimulates the apoptotic potential of cisplatin via up-regulation of miRNA-203 and subsequent inhibition of antiapoptotic gene, BCL-w (You, Xie, Zhang, Zhu, & Jiang, 2016).

2.6 | BBR modulates autophagy

Autophagy is an evolutionarily conserved life process of eukaryotic cells during which the misfolded proteins and damaged or useless cellular components undergo lysosomal degradation or recycling through the formation of autophagosomes. In cancer cells, autophagy acts as a double-edged sword due to its potential to both stimulate as well as suppress tumor growth. Indeed, both up-regulation and inhibition of autophagy are reported to be associated with drug resistance (Li et al., 2019). Hence, targeting autophagy to overcome chemoresistance is a tricky task. Fascinatingly, BBR acts in a sublime manner to modulate autophagy and overcome drug resistance in malignant tumors. In some cancers, BBR induces chemosensitivity by inhibiting autophagy while in others it improves drug response in a vice versa manner. Doxorubicin-resistant MCF7/ADR breast cancer cells resist doxorubicin therapy due to the augmented features of autophagy including elevated levels of autophagosomes, increased accrual of autophagy associated protein LC3II, and decreased levels of p62, an autophagy inhibitor. However, when MCF-7/ADR cells are cotreated with BBR (100 μM) and doxorubicin (0.517 μM) for 48 hr, BBR attenuates autophagy by reducing the number of autophagosomes, decreasing LC3II levels, elevating p62 levels, suppressing the expression of multidrug resistance protein 1, and thus reverses doxorubicin resistance by regulating PTEN/Akt/mTOR signaling pathway. Likewise, in BALB/C nude female mice xenografted with MCF-7/ADR cells, BBR cotreatment (10 mg/kg) attenuates autophagy and improves their response to doxorubicin therapy (4 mg/kg) via the same aforesaid mechanism (Wang et al., 2020b). These evidences show that BBR could effectively inhibit autophagy in chemoresistant tumors and augment their sensitivity to antineoplastic drugs. However, in ACHN and 786-O human renal carcinoma cells, BBR induces sensitivity to photodynamic therapy and thus inhibits tumor growth very effectively by triggering ROS induced up-regulation of autophagy and apoptosis (Lopes et al., 2020). This in turn shows its dual ability to target autophagy in drug-resistant cells. Furthermore, BBR acts as a potent photosensitizer for phototherapy in

these renal cancer cells. It triggers the generation of ROS and other free radicals in ACHN and 786-O cells only in the presence of a light source whereas it exerts low cytotoxicity in the dark. More importantly, HK-2 human renal tubular epithelial cells derived from normal kidneys are very sensitive to photodynamic therapy when compared to renal carcinoma cells. Interestingly, BBR treatment restricts the light source only to tumor cells and protects the HK-2 cells from damages caused by photodynamic therapy. This evidence shows that BBR exerts its photosensitive effects on tumor cells and protective effect on normal cells (Lopes et al., 2020).

2.7 | BBR overcomes therapy resistance in hypoxic tumors

The inner core of growing solid tumors gets deprived of oxygen supply and turns hypoxic due to lack of blood vessels (Jing et al., 2019; Muz, de la Puente, Azab, & Azab, 2015; Petrova, Annicchiarico-Petruzzelli, Melino, & Amelio, 2018). To survive under this grave pathological milieu, hypoxic tumors undergo various adaptive changes including induction of abnormal vasculatures, increased replicative quiescence, decreased p53 expression, loss of mismatch repair, and increased epithelial to mesenchymal transition via activation of hypoxia-inducible factor-1α (HIF-1α) signaling cascades (Calzada & del Peso, 2007; Masoud & Li, 2015; Pezzuto & Carico, 2018; Warfel & El-Deiry, 2014; Xia, Jiang, & Zhong, 2018). These adaptive changes not only enable the malignant tumors to grow under a hypoxic microenvironment but also protects them from the cytotoxic effects of cancer therapies. Hypoxic tumors exhibit a highly therapy resistant phenotype and indeed improving their response to radiotherapy and chemotherapy is a great challenge. Nevertheless, BBR effectively sensitizes hypoxic tumors to conventional cancer therapies (Nalini, Selvaraj, & Kumar, 2020). ECA109 and TE13 esophageal squamous cell carcinoma cell lines cultured under low oxygen tension exhibits an increased colony-forming potential even after exposure to ionizing radiation, indicating their resistance to radiotherapy. However, BBR pretreatment (5 μM or 15 μM) for 24 hr sensitizes these hypoxic cells to radiation-induced apoptosis by decreasing HIF-1α and vascular endothelial growth factor (VEGF) expression. BBR acts by inhibiting the nuclear translocation of HIF-1α and thus retarding the downstream signaling events leading to radioresistance. Furthermore, BBR pretreatment (5 mg/kg) for 2 days improves the response of nude mice bearing ECA109 cells to the tumor inhibitory effects of radiotherapy (Yang et al., 2013). Likewise, in LNCaP and DU-145 human prostate cancer cells, BBR pretreatment (30 μM or 50 μM) for 24 hr augments their sensitivity to radiotherapy by repressing both hypoxias as well as radiation-induced HIF-1α and VEGF expression. As seen in esophageal squamous cell carcinoma cells, BBR overcomes radioresistance in these hypoxic prostate tumors by interfering with the nuclear translocation of HIF-1α and VEGF. Also, BBR pretreatment (5 or 10 mg/kg intraperitoneally) for 6 alternate days enables the murine xenografts transplanted with LNCaP cells to resist radiation-induced HIF-1α and VEGF expression and thereby potentiate them to the cytotoxic effects of radiotherapy as evidential by the significant reduction in tumor weight and volume (Zhang et al., 2014). Furthermore, BBR radiosensitizes hypoxic CNE-1 and CNE-2 nasopharyngeal cancer cells as well by attenuating hypoxia/radiation-induced up-regulation of HIF-1α and VEGF both in vitro and in vivo (Zhang et al., 2014). Apart from oxygen insufficiency, the para-necrotic regions of tumors suffer nutrition deprivation, which also renders hypoxic tumors highly radioresistant. Hence, Zeng and colleagues investigated the radiosensitizing potential of BBR in HeLa human cervical carcinoma cells under oxygen and glucose-deprived conditions. Interestingly, BBR overcomes both low glucose and hypoxia-induced radioresistance by down-regulating PI3K/HIF-1 pathway (Zeng et al., 2020). Pan and colleagues extensively studied the chemosensitizing effects of BBR in hypoxic breast tumors to doxorubicin therapy. They rendered MCF-7 cells drug-resistant by continuous exposure to hypoxia for 7 days. These drug-resistant cells were then cotreated with varied concentrations of doxorubicin and BBR. At lower concentrations (2.5, 5, and 10 μM), BBR augments the response of MCF-7 cells to doxorubicin therapy by down-regulating the AMPK/HIF-1α/P-glycoprotein pathway. However, at higher concentrations (40 μM), BBR alone (without doxorubicin) promotes apoptosis of these cells by increasing p53 levels through the down-regulation of the AMPK/HIF-1α pathway. Astonishingly, the results obtained in vitro have also been obtained in vivo in murine MCF-7 breast cancer model (Pan et al., 2017). This evidence shows that BBR overcomes hypoxia-induced radio/chemoresistance in tumors by targeting the HIF pathway.

2.8 | BBR overcomes drug resistance via unique mechanisms

Apart from the aforesaid mechanisms, BBR sensitizes cancer cells to chemo/radiotherapies via unique mechanisms as well. Marverti and colleagues intensively analyzed the molecular mechanisms underlying the chemosensitizing potential of BBR in ovarian cancer cells in vitro by developing (a) highly cisplatin-resistant C13 ovarian cancer cells from parent 2008 cell line and (b) polyamine analogue cross-resistant human ovarian cancer cells. Fascinatingly, BBR cotreatment restored the sensitivity of these resistant cells to cisplatin therapy to the levels of their sensitive counterparts. This chemosensitizing potential of BBR is attributed to its potential to down-regulate the expression of folate cycle enzymes including dihydrofolate reductase and thymidylate synthase and up-regulate the expression of spermidine/spermine N1-acetyltransferase, a key enzyme in polyamine metabolism in the cisplatin-resistant cell lines (Marverti et al., 2013). Zhang and colleagues discovered novel mechanisms for BBR- induced chemosensitivity in malignant tumors. The continuous treatment of HL-60 human acute promyelocytic leukemia cells with 0.5 μM doxorubicin for 7 days induces resistance by promoting their differentiation to HL-60-N2 neutrophils. However, combination treatment with

doxorubicin and 2 μM BBR stimulates ROS generation, inhibits autophagy, and triggers apoptosis in HL-60-N2 cells. Importantly, doxorubicin together with BBR differentiates HL-60 cells to HL-60-N1phenotype. In the urethane-induced lung cancer model, doxorubicin promotes carcinogenesis by establishing an immunosuppressive tumor microenvironment and increasing the neutrophil to lymphocyte ratio. BBR cotreatment maintains neutrophil N1 phenotype, decreases neutrophil to lymphocyte ratio, and promotes the antitumor immune response of doxorubicin all of which ameliorates the incidents associated with doxorubicin-induced carcinogenesis. In H22 liver cancer allograft models injected with HL-60-N1 or HL-60-N2 cells, cotreatment with doxorubicin (10 mg/kg) and BBR (10 mg/kg) for 3 weeks maintains N1 phenotype and reduces the surface expression of CD133 and CD309 (markers whose overexpression promote resistance) on doxorubicin-derived neutrophils and thus enhances the chemosensitivity of H22 cells. Bioinformatics analysis shows that BBR impacts the regulatory influence of doxorubicin over neutrophils by controlling apoptotic events, redox process, and innate immune response. Taken together, these evidences show that BBR reverses doxorubicin resistance in tumor cells by compelling the N2-type chemoresistant neutrophils to maintain the phenotype of N1 neutrophils, reversing doxorubicin-induced immune rejection, and maintaining immune surveillance (Zhang et al., 2020).

3 | CHEMOPROTECTIVE PROPERTIES OF BERBERINE

3.1 | Hepatoprotective effects

Most of the conventional antineoplastic drugs used in cancer treatment have been proven to be highly toxic to liver cells (Grigorian & O'Brien, 2014). These drugs severely injure the hepatic tissues and thereby promote the pathogenesis of various hepatic disorders including sinusoidal obstructive syndrome, pseudocirrhosis, fatty liver, acute hepatitis, hepatic necrosis, and portal vein thrombosis (Sharma et al., 2014). Chemotherapeutic drugs cause hepatotoxicity by augmenting the activity of liver enzymes (including alanine transaminase and aspartate transaminase), increasing oxidative stress, triggering hepatic inflammation, and stimulating hepatocellular degeneration, congestion, and necrosis. However, BBR administration effectively protects the hepatocytes from injuries caused by various conventional antineoplastic drugs including doxorubicin, cyclophosphamide, and methotrexate (Table 1). Owing to its potent antioxidant effects, BBR significantly reduces the chemotherapy-induced oxidative stress in the liver by promoting the synthesis of antioxidant enzymes namely, catalase, superoxide dismutase, glutathione peroxidase, and malondialdehyde. Furthermore, BBR attenuates the elevations in liver enzymes and also protects the hepatic architecture from damages including degeneration, congestion, and necrosis (Dasari & Tchounwou, 2014; Germoush & Mahmoud, 2014; Mehrzadi et al., 2018; Zhao et al., 2012).

3.2 | Cardioprotective effects

Doxorubicin, the first-line treatment given to the majority of stage III cancer patients induces severe cardiac injury an insignificant proportion of them (Thorn et al., 2011). It damages the myocardium and causes cardiac dysfunction by increasing oxidative stress in the myocardium (evidential by elevations in serum levels of creatinine kinase, lactate dehydrogenase, aspartate aminotransferase), inducing myocardial apoptosis, promoting mitochondrial dysfunction, and increasing intracellular calcium levels (Chatterjee, Zhang, Honbo, & Karliner, 2010). Accumulating in vitro and in vivo studies show that BBR could protect the heart tissues from doxorubicin-induced cardiotoxicity. In female BALB/c mice xenografted with highly metastatic 4T1 breast cancer cells, treatment with liposomes coloaded with BBR and doxorubicin enhances tumor cell apoptosis, and attenuates cardiac injuries. This is direct proof which shows that BBR acts as a potent chemosensitizer in malignant cells and chemoprotection in normal organs (Zhang et al., 2020). Likewise, in rat cardiomyocytes cultured in vitro, BBR pretreatment (0.06, 0.25, 1.0, 4.0 μM) for 20 min renders protection from doxorubicin (1 μM) induced from acute injuries (Lv et al., 2012). BBR protects cardiac tissues from damages caused by doxorubicin by inhibiting its metabolism in the heart cytoplasm and decreasing the accrual of its secondary alcohol metabolite namely, doxorubicinol in heart tissues (Hao et al., 2015). Table 1 details the mechanisms underlying the cardioprotective effects of BBR against doxorubicin induced myocardial injuries.

3.3 | Nephroprotective effects

Cisplatin is the first-line treatment given to various end-stage cancer patients (Ozkok & Edelstein, 2014). However, in one-third of the patients under cisplatin therapy, single-dose administration of this drug leads to acute kidney injury, which in turn necessitates dose reduction or drug withdrawal (Volarevic et al., 2019). Cisplatin induces nephrotoxicity by promoting oxidative stress and inflammation, stimulating necrosis, and apoptosis in proximal tubules of the kidney (Pabla & Dong, 2008; Tsuruya et al., 2003). In fact, suppression of inflammation by attenuating pro-inflammatory cytokines or depleting T helper cells/mast cells protects the kidneys from cisplatin-induced injuries (Mohamed, 2018). Furthermore, cisplatin damages the vascular beds of the kidney by causing endothelial cell injury. Nevertheless, BBR treatment before or after cisplatin administration significantly alleviates the nephrotoxic effects of this drug in rats by (a) decreasing oxidative stress through inducible nitric oxide synthase reduction, (b) attenuating inflammation through TNF-α and cyclooxygenase-2 reduction, (c) inhibiting renal cell apoptosis through p53, active caspase 3 reductions (d) inducing autophagy through autophagy marker light chain 3B reduction, (e) repairing degeneration of tubular epithelial cells, and (f) preventing inflammatory cell infiltration, hyaline cast formation, and tubular dilation (Domitrović et al., 2013; Li et al., 2010) (Table 1). These evidences show that BBR could effectively protect the kidneys from severe damages caused by cisplatin.

TABLE 1 Chemo/radioprotective effects of berberine

Protective effects	Biological system	Protection from	Treatment	Mechanism	References
Hepatoprotection	Mice of either gender	Doxorubicin	BBR pretreatment (ip; 60 mg/kg) 1 hr before ip administration of doxorubicin (2.5 mg/kg) for 7 alternate days	• ↓ mice mortality • Restore body weight • ↓ elevated serum levels of alanine transaminase, aspartate transaminase • ↓ vascular congestion, hepatocellular degeneration, necrosis, fibrosis, and inflammatory cell filtration in liver	(Zhao, Zhang, Tong, Chen, & Luo, 2012)
	Male Sprague Dawley rats weighing 250–300 g	Doxorubicin	Intragastrical administration of BBR (5, 10, and 20 mg/kg) for 10 consecutive days and single ip injection of DOX (20 mg/kg) on 8th day	• ↓ elevated serum levels of alanine transaminase, aspartate transaminaase, blood urea nitrogen, total cholesterol • Restore antioxidant levels (catalase, superoxide dismutase, glutathione peroxidase, and malondialdehyde) • Protects hepatic architecture from damages including congestion and necrosis	(Chen et al., 2016)
	White male albino rats	Cyclophosphamide	Single ip administration of cyclophosphamide (200 mg/kg) and treatment with BBR (orally at a dose of 50 mg/kg) for 11 consecutive days	• ↓ oxidative stress, inflammation • ↓ elevated levels of alanine transaminase, alkaline phosphatase, and total bilirubin	(Germoush & Mahmoud, 2014)
	Male Wistar rats	Methotrexate	BBR pretreatment (100 mg/kg) for 10 consecutive days and ip administration of methotrexate (20 mg/kg) on 9th day	• ↓ oxidative stress • ↓ elevated levels of alanine transaminase, aspartate transaminase, and hepatic malondialdehyde	(Mehrzadi et al., 2018)
	Male Wistar rats	Methotrexate	Oral BBR administration (25 and 50 mg/kg) for 7 days before or after methrotrexate injection	• BBR up-regulates Nrf2/HO-1 pathway and PPARγ in hepatocytes which in turn lead to: • ↓ oxidative stress • ↓ Bax expression and apoptosis • Restores of cell morphology to normalcy	(Mahmoud, Hozayen, & Ramadan, 2017)

(Continues)

TABLE 1 (Continued)

Protective effects	Biological system	Protection from	Treatment	Mechanism	References
Cardioprotection	Male adult Sprague–Dawley rats weighing 200–250 g	Doxorubicin	BBR pretreatment (5, 10, and 20 mg/kg) orally for 10 consecutive days and ip administration of single dose of doxorubicin (20 mg/kg) on 8th day	• ↓ free radical injury, intracellular Ca^{2+} elevation and mitochondrial dysfunction in cardiac tissues • ↓ serum creatine kinase and its isoenzyme, malondialdehyde • ↑ levels of superoxide dismutase and catalase in cardiomyocytes	(Xiong et al., 2018)
	Male Sprague Dawley rats	Doxorubicin	Intragastrical administration of BBR (50, 100, and 200 mg/kg) for 14 consecutive days with intravenous injection of doxorubicin (4 mg/kg) for 7 alternate days	• ↓ lactate dehydrogenase, creatine kinase enzymes and isoenzymes, aspartate aminotransferase	(Hao, Yu, Gu, Xing, & Xue, 2015)
	Neonatal rat cardiomyocyte culture	Doxorubicin	BBR pretreatment (0.06, 0.25, 1.0, 4.0 μM) for 20 min before exposure to 1 μM doxorubicin for required period of time	• ↓ caspase-3 and −9 levels • ↓ phosphorylation of AMPKα and p53 • ↓ cytochrome C and Bax levels • ↑ Bcl-2 activity	(Lv et al., 2012)
	Male adult Sprague–Dawley rats		Single ip injection of doxorubicin (20 mg/kg) immediately followed by intragastrical administration of BBR (30, 60, and 120 mg/kg) and then once a day for three consecutive days	• ↑ survival and stroke volume • ↓ myocardial injury • ↓ caspase-3 levels, phosphorylation of AMPKα and p53; • ↓ elevation of AMP/ATP ratio • ↑ Bcl-2 activity	
	Mice of either gender	Doxorubicin	BBR pretreatment (ip; 60 mg/kg) 1 hr before ip administration of doxorubicin (2.5 mg/kg) for 7 alternate days	• ↓ mice mortality • Restore body weight • ↓ lactate dehydrogenase • ↓ QRS duration • ↓ myocardial injury	(Zhao et al., 2011)
	Male adult Sprague–Dawley rats weighing 200–250 g	Doxorubicin	Intraperitoneal doxorubicin injection (20 mg/kg) on three alternate days and BBR treatment (10 and 20 mg/kg) by oral administration daily for 10 days	• BBR inhibits SIRT1 induced p66shc expression which in turn results in the following changes in myocardium: • ↑ levels catalase, superoxide dismutase, glutathione peroxidase • ↓ levels of malondialdehyde • Improved electrocardiogram	(Wu, Zhang, Wu, Shan, & Xiong, 2019)

TABLE 1 (Continued)

Protective effects	Biological system	Protection from	Treatment	Mechanism	References
				• Restored morphology in mycoytes • ↓ oxidative stress and mitochondrial damage	
	H9c2 cardiomyocytes	Evodiamine	Pretreatment with BBR (0, 2.5, 5, 10, 20, and 40 μM) for 24 hr followed by treatment with 10 μM evodiamine for 24 hr	• ↓ extrinsic apoptosis via Nrf2 dependent and ROS independent pathways	(Guan et al., 2020)
Nephroprotection	Female adult Wistar albino rats (140–160 g)	Cisplatin	ip injection of single dose of cisplatin (8 mg/kg) followed by BBR treatment (1 mg/kg/day) for 30 days	• ↓ oxidative stress, inflammation and apoptosis • Repaired degeneration of tubular epithelial cells, inflammatory cell infiltration, hyaline cast formation, and tubular dilation.	(Mohamed, 2018)
	BALB/cN mice	Cisplatin	BBR treatment (1, 2 and 3 mg/kg) orally for two consecutive days, 48 hr after single ip injection of cisplatin (13 mg/kg)	• ↓ elevated levels of blood urea nitrogen, creatinine, NF-κB, TNF-α, COX-2, iNOS, p53, active caspase-3, and autophagy marker light chain 3B • Restored morphology of kidneys	(Domitrović et al., 2013)
	Male Wistar rats	Cisplatin	BBR pretreatment (100 mg/kg; orally) for 7 consecutive days and single cisplatin injection (7.5 mg/kg; intraperitoneally) on 7th day	• ↑ antioxidant potential and ↓ oxidative stress in renal tissues by increasing glutathione, superoxide dismutase, glutathione peroxidase, and catalase activities • ↓ elevated levels of blood urea nitrogen, creatinine, malondialdehyde, nitric oxide, protein carbonyl levels, and myeloperoxidase activity	(Allameh et al., 2020)
Radioprotection	Cervical cancer patients (n = 42), seminoma patients (n = 21) and lymphoma patients (n = 21)	Radiotherapy	Treatment with BBR (300 mg) for three times daily from 3 to 5 week of radiotherapy	• ↓ nauseating symptoms	(Li et al., 2010)
	NSCLC patients (n = 90)	Radiotherapy	Radiotherapy in the presence of BBR (20 mg/kg/day) for 6 weeks	• ↓ lung injury • ↑ pulmonary function • ↓ plasma ICAM-1 and TGF-β1	(Liu et al., 2008)
	Nude mice xenografted with SMMC-7721 hepatocellular carcinoma cells	Radiotherapy	Treatment with BBR preloaded into folic acid conjugated Janus gold mesoporous silica	• ↓ intestinal mucosal injury by decreasing elevations in intestinal fatty acid binding	(Li et al., 2019)

(Continues)

TABLE 1 (Continued)

Protective effects	Biological system	Protection from	Treatment	Mechanism	References
			nanoparticles (25 mg/kg for 3 days) followed by irradiation with 1 Gy/min of X-rays for 5 and 10 min after 24 hr of postinjections	protein and diamine oxidase	
	HHL-5 normal liver cells	Radiotherapy	Exposure to X-rays for 2 hr followed by treatment with varied doses of BBR 24 hr	• ↓ radiation-induced apoptosis, cell cycle arrest, oxidative stress • ↑ Nrf2 signaling pathway	(You, Cao, & Lin, 2019)

3.4 | Radioprotective effects

Radiotherapy not only harms the cancer cells but also injures the normal cells in the vicinity of malignant tumors (Mohan et al., 2019). However, BBR, while sensitizing the tumor cells to the cytotoxic effects of radiotherapy also protects the neighboring normal cells from radiation-induced acute injuries. When HuH7, HepG2 human hepatoma cells, and HHL-5 normal liver cells exposed to X-rays for 2 hr were treated with different doses of BBR for 24 hr, BBR enhances the potential of radiation to reduce cell viability, induce apoptosis and G0/G1 phase arrest, promote oxidative stress, and downregulate Nrf2 signaling pathway only in hepatoma cells. Whereas in HHL-5 cells, BBR ameliorates these radiotherapy exacerbated cytotoxic events thereby proving its radioprotective effects (You et al., 2019). Li and colleagues developed BBR nanocarriers wherein BBR was preloaded into folic acid conjugated Janus gold mesoporous silica nanoparticles using a modified sol–gel technique. This nanocarrier with high BBR loading potential was designed to retain BBR in tumor cells for a longer period of time, thereby enhancing its bioavailability and increasing its therapeutic efficacy. Interestingly, BBR nanocarrier accumulates more in SMMC-7721, human hepatocellular carcinoma cells and accumulates very less in HL-7702, normal human liver cells. This nanocarrier (2.5 μg/ml) effectively sensitizes SMMC-7721 to radiotherapy and protects HL-7702 cells from the cytotoxic effects of radiotherapy. Furthermore, in nude xenografts bearing SMMC-7721 cells, intravenous administration of BBR nanocarriers (25 mg/kg for 3 days) not only increased the radiation (1 Gy/min of X-rays for 5 min)-induced tumor cell death but also protects the intestinal mucosa from radiation-induced injuries (Li, Wang, et al., 2019). In lymphoma and cervical cancer patients receiving abdomen radiotherapy, treatment with BBR (300 mg) for 3 times daily from 3 to 5 week of radiotherapy significantly minimizes the incidence and the severity of acute radiation intestinal syndrome including fatigue, nausea, colitis, vomiting, and diarrhea (Li et al., 2010). Likewise, in NSCLC patients receiving radiation therapy (2 Gy/day) to a total 60–70 Gy, treatment with BBR (20 mg/kg/day) for 6 weeks reduces the radiation-induced lung injury, improves the pulmonary function, and decreases the levels of radiation exacerbated inflammatory markers namely, ICAM-1 and TGF-β (Liu et al., 2008). These evidences show that BBR could act as a potent radioprotector in cancer patients.

4 | BERBERINE PREVENTS TUMOR RELAPSE

Besides therapy resistance, another major obstacle for the successful treatment of cancer patients is cancer recurrence. In the majority of cases, cancer stem cells (CSC) have been reported to be the key contributor to tumor relapse. CSCs are the small subpopulation of cells in tumors with self-renewal, self-differentiation, and tumorigenic properties. They are highly resistant to chemo- and radiation- therapies and hence, CSCs are considered as high-interest targets to prevent therapy failure and cancer recurrence (Phi et al., 2018). Fascinatingly, BBR effectively eliminates and sensitizes CSC in various tumors. In CSC-derived from SAS and OECM-1 oral squamous carcinoma cells, BBR treatment inhibits cell survival and reduces their stem cell characteristic including self-renewal potential, anchorage-independent growth ability, invasive effects, and aldehyde dehydrogenase activity in a dose-dependent manner by decreasing the activity of miRNA-21. More importantly, BBR improves the response of these CSC to cisplatin and 5-fluorouracil. Also, its treatment in immunocompromised mice xenografted with CSC of SAS/OECM-1 cells reduces tumor growth dose-dependently without affecting the body weight. These evidences show that BBR acts independently and also in conjunction with conventional chemotherapies to prevent the recurrence of oral cancer (Lin et al., 2017). In breast cancers, tumor relapse majorly occurs due to the development of chemoresistance in CSC through the augmented expression of cell membrane ATP-binding cassette (ABC) transporters and the resistance of proteins involved in the intrinsic apoptosis pathway. Hence, Ma and colleagues developed targeting BBR liposomes with the potential to enter resistant membrane and regulate mitochondrial proteins of breast CSCs. They treated human breast CSC and murine cancer stem xenografts with these BBR liposomes. Fascinatingly, BBR liposomes crossed the

membrane of CSC, inhibited ABC transporters (ABCC1, ABCC2, ABCC3, ABCG2), and selectively accumulated in mitochondria. This in turn led to increased Bax and decreased Bcl-2 activity, the opening of mitochondrial permeability transition pores, increased cytochrome C release into the cytosol, activation of caspase-9/caspase-3 cascades, and ultimately apoptosis of breast CSCs (Ma et al., 2013). Park and colleagues investigated the inhibitory effects of BBR on the CSC of PANC-1 and MIA PaCa-2 pancreatic ductal adenocarcinoma cells by analyzing the side population cells. Interestingly, BBR treatment (15 μM) for 72 hr attenuates the growth of these side population cells more effectively than gemcitabine (10 nM) by down-regulating the expression of major stem cell-associated genes including NANOG, SOX2, and POU5F1 (Park, Sung, & Chung, 2014). Likewise, BBR decreases the side population cells of MCF-7 breast cancer cells in a dose-dependent manner by down-regulating ABCG2, a CSC marker (Kim et al., 2008). Besides targeting CSC, BBR prevents tumor relapse by inhibiting chemotherapy exacerbated repopulation of adjacent surviving tumor cells as well. VP 16 is an anticancer drug that stimulates the repopulation of ovarian cancer cells by increasing prostaglandin E_2 (PGE_2) levels through the activation of the arachidonic acid (AA) pathway. Zhao and colleagues cocultured the surviving SKOV-3 ovarian cancer cells in the microenvironment of VP16 drug-treated dying cells using a transwell system. During this coculture, the untreated SKOV-3 cells in the vicinity of VP16 drug-treated cells showed a remarkable increase in their viability and proliferation, indicative of tumor cell repopulation. However, BBR cotreatment (5 μmol/L) with VP16 for 10 days inhibits tumor cell repopulation by blocking VP16 induced activation of caspase-3/$iPLA_2$/AA/COX-2/PGE_2 pathway and FAK phosphorylation (Zhao et al., 2017). Taken together, these studies show that BBR prevents tumor relapse by abrogating or sensitizing CSC and inhibiting drug exacerbated repopulation of tumor cells.

5 | CLINICAL TRIALS

Apart from mounting in vitro and in vivo studies, few clinical studies have also been carried out to investigate the potential of BBR to prevent tumor relapse and ameliorate radiation-induced injuries. Chen and colleagues clinically evaluated the potential of BBR to prevent cancer recurrence in colorectal adenoma patients who have undergone complete polypectomy. In the randomized controlled double-blinded multicentric study on 924 colorectal adenoma patients after polypectomy, one set of patients (n = 462) received 300 mg BBR tablets twice a day while the other set (n = 462) received placebo treatment during the 2-year follow-up. BBR tablets were prepared by extracting BBR from an alkaline solution and crystallizing the extracts with hydrochloric acid. After affirming the purity of 97% or greater, the crystallized BBR extracts were then made into tablets with sodium starch glycolate, magnesium stearate, and maize starch as major auxiliary ingredients. Each tablet contained 100 mg BBR. Interestingly, BBR treatment significantly reduced the risk of relapse of colorectal adenoma. More importantly, almost all the patients under study tolerated BBR during the long-term administration (Chen et al., 2020). In another randomized, double-blinded study on 90 NSCLC patients receiving radiotherapy (2 Gy/day to a total of 60–70 Gy), oral administration of 20 mg/kg BBR (obtained from Beijing Medicinal Material Company, China) daily to 42 patients for 6 weeks remarkably reduced the radiation-induced lung injury, improved pulmonary function, and decreased the plasma levels of soluble intracellular adhesion

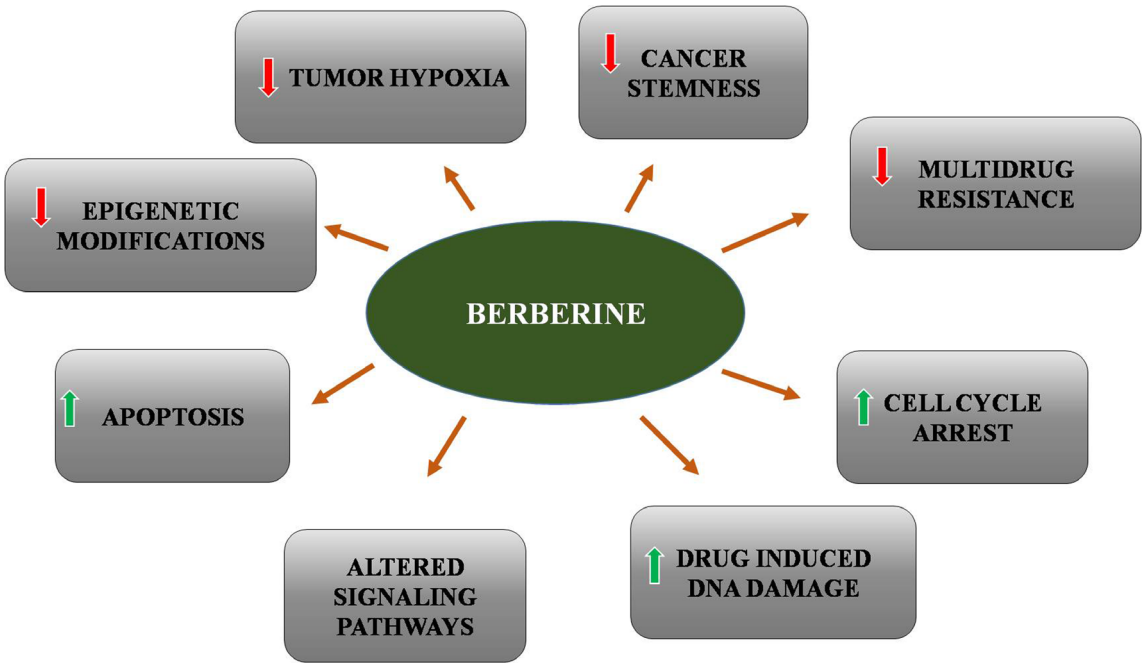

FIGURE 1 Berberine ameliorates major events that cause cancer therapy resistance [Colour figure can be viewed at wileyonlinelibrary.com]

TABLE 2 Chemo/radiosensitizing potential of BBR in various cancers

Cancer type	Biological system	Therapy	Events associated with chemo/radiosensitization	Underlying mechanism	References
Breast cancer	In vitro—MCF-7 and tamoxifen-resistant MCF-7/TAM cells	Tamoxifen	Induce G1 phase arrest Induce apoptosis	↑ p21 expression ↑ Bcl-2/Bax ratio	(Wen et al., 2016)
	In vitro—MCF-7/MDR cells In vivo—MCF-7/MDR cells bearing 8 week old female BALB/c nu/nu mice	Doxorubicin	Induce apoptosis	↓ AMPK/HIF-1α/P-glycoprotein pathway	(Pan, Shao, et al., 2017)
	In vitro—hypoxia induced doxorubicin resistant MCF-7 cells In vivo – MCF-7/hypoxia bearing 8 week old female BALB/c nu/nu mice	Doxorubicin	Reverse hypoxia induced drug resistance	↓ AMPK/HIF-1α/P-glycoprotein pathway	(Pan, Zhang, et al., 2017)
	In vitro—doxorubicin resistant MCF7/ADR cells In vivo—BALB/C nude female mice xenografted with MCF-7/ADR cells	Doxorubicin	Inhibit autophagy	Regulation of PTEN/Akt/mTOR signaling pathway	(Wang et al., 2019)
	In vitro—doxorubicin resistant MCF-7/ADrR cells	Doxorubicin	Induce G2/M arrest		(Li et al., 2013)
	In vitro—MCF-7 and MDA-MB-468 cells	Radiotherapy	Prolongs the persistence of double strand breaks in DNA Induce cell cycle arrest	↓ RAD 51	(Wang et al., 2012)
	In vitro—MCF-7 cells	Cisplatin	Augments the potential of cisplatin to induce DNA breaks and damages	↑ expression of proliferating cell nuclear antigen	(Zhao et al., 2016)
	In vitro—Lapatinib resistant BT-474^{LapR} cells	Lapatinib	Induce oxidative stress	↓ c-Myc/Nrf2 pathway ↑ ROS	(Zhang et al., 2016)
	In vitro—TRAIL-resistant MDA-MB-468 TNBC cells	TRAIL	Induce apoptosis	↓ p38 MAPK signaling pathway	(Refaat et al., 2013; Refaat et al., 2015)
	In vitro—Anoikis resistant MCF-7 and MDA-MB-231 cells		Induce cell cycle arrest at G0/G1 phase		(Kim et al., 2010)
	In vitro – T47D and MDA-MB-231 cells	Doxorubicin	Induce necrosis and cell cycle arrest	↑ cellular internalization and half-life	(Khan et al., 2019)
Prostate cancer	In vitro—PC-3 cells	Radiotherapy	Induce apoptosis	↑ MAPK/caspase-3 and ROS pathways ↓ radio-resistant proteins including Bcl-2, NF-κB, HO-1, and ERK	(Hur & Kim, 2010)

TABLE 2 (Continued)

Cancer type	Biological system	Therapy	Events associated with chemo/ radiosensitization	Underlying mechanism	References
	In vitro—LNCaP and DU-145 cells In vivo—murine xenografts transplanted with LNCaP cells	Radiotherapy	Reverse hypoxia-induced radioresistance	↓ hypoxia/radiation induced-HIF-1α and VEGF expression	(Zhang, Yang,
	In vitro—LNCaP, C42, C42-EV, and C42-DN cells	TRAIL	Induce apoptosis	↑ AMPK and DR5	(Ke et al., 2018)
Gastric cancer	In vitro—AGS cells	5-fluorouracil	Induce apoptosis	↓ survivin and STAT-3 pathways	(Pandey et al., 2015)
	In vitro—cisplatin resistant SGC-7901/ DDP and BGC-823/ DDP cells	Cisplatin	Induce apoptosis	↑ miRNA-203 ↓ bcl-w.	(You et al., 2016)
	In vitro—SGC7901 and BGC823 cells In vivo—female 5-week-old BALB/ C-nu/nu nude mice bearing BGC823 cells	Erlotinib and Cetuximab	Induce apoptosis	↓ EGFR/STAT3 signaling pathway	(Wang et al., 2016)
Ovarian cancer	In vitro—cisplatin resistant SKOV3 cells	Cisplatin	Induce apoptosis	↓ miR-21 ↑ PDCD4	(Liu et al., 2013)
	In vitro—cisplatin sensitive A2780 cells and cisplatin resistant A2780/DDP cells	Cisplatin	Induce apoptosis Induce G0/G1 phase arrest	↓ miR-93 and its downstream PTEN/ AKT signaling pathways	(Chen et al., 2015)
	In vitro—highly cisplatin resistant C13 cells and polyamine analogue cross-resistant human ovarian cancer cells	Cisplatin	Inhibit tumor growth	↓ expression of folate cycle enzymes ↑ expression of spermidine/spermine N1-acetyltransferase	(Marverti et al., 2013)
Esophageal cancer	In vitro—ECA109 and T13 esophageal squamous cell carcinoma cells In vivo—murine xenograft transplanted with ECA109 cells	Radiotherapy	Reverse hypoxia-induced radioresistance	↓ HIF-1α and VEGF	(Yang et al., 2013)
	In vitro—KYSE30 and KYSE450 cells	Radiotherapy	Prolongs the persistence of double strand breaks in DNA	↓ RAD51	(Liu et al., 2011)
Nasopharyngeal cancer	In vitro—CNE-1 and CNE-2 cells In vivo—male nude mice transplanted with CNE-2 cells	Radiotherapy	Reverse hypoxia-induced radioresistance	↓ hypoxia/radiation induced HIF-1α and VEGF expression	(Zhang, Zhang, et al., 2014)
	In vitro—CNE2 cells	Radiotherapy	Induce apoptosis	↓ Sp1 expression ↓ EMT	(Wang et al., 2017)
Hepatocellular carcinoma	In vitro—Huh7 and HepG2 hepatoma cells	Radiotherapy	Induce apoptosis, G0/G1 phase arrest, and oxidative stress	↓ Nrf2 signaling associated proteins including Nrf2, HO-1 and NQO-1	(You et al., 2019)
	In vitro—Huh7 cells	TRAIL	Induce apoptosis	↓ AMPK and DR5	(Ke et al., 2018)

(Continues)

TABLE 2 (Continued)

Cancer type	Biological system	Therapy	Events associated with chemo/ radiosensitization	Underlying mechanism	References
Lung cancer	In vitro—NCI-H460 and NCI-H1975 cells	Doxorubicin	Induce apoptosis and inhibit cell proliferation	↓ doxorubicin-induced STAT3 activation	(Zhu et al., 2015)
Oral cancer	In vitro—CSC derived from SAS and OECM-1 oral squamous carcinoma cells	Cisplatin/5-fluorouracil	Decrease cell viability		(Lin et al., 2017)
Cervical cancer	In vitro—HeLa cells	Radiotherapy	Ameliorate hypoxia and low glucose induced resistance	↓ PI3K/HIF-1 pathway	(Zeng et al., 2020)
Pancreatic cancer	In vitro—gemcitabine resistant BxPC-3 and Capan-2 pancreatic cancer cells	Gemcitabine	Inhibit cell proliferation	↓ STAT3/NF-κB signaling pathway	(Gong et al., 2017)
Colon cancer	In vitro—HCT 116 cells	Irinotecan	Induce apoptosis	↓ expression of NF-κB dependent antiapoptotic genes, including c-IAP1, c-IAP2, survivin, and Bcl-xl	(Yu et al., 2014)
Osteosarcoma	In vitro—MG63 cells	Radiotherapy	Inhibit EMT Induce apoptosis, tumor invasion, and G2/M phase arrest	↓ RAD51	(Zhu et al., 2014)
Leukemia	In vitro—HL-60 cells In vivo—urethane-induced lung carcinogenesis model	Doxorubicin	Maintain neutrophil N1 phenotype, reduce neutrophil to lymphocyte ratio, promote antitumor immune response of doxorubicin, stimulate ROS generation, inhibit autophagy, and induce apoptosis	Regulatory influence of doxorubicin over neutrophils by controlling apoptotic events, redox process and innate immune response	(Zhang et al., 2020)
Renal carcinoma	In vitro—ACHN and 786-O cells	Photodynamic therapy	Induce autophagy and apoptosis	↓ ROS	(Lopes et al., 2020)

molecule-1 and TGF-β1 (Liu et al., 2008). Likewise, treatment of lymphoma or seminoma patients (n = 18) and cervical cancer patients (n = 21) receiving abdominal or pelvic radiotherapy with 300 mg BBR tablets (obtained from Sanchine-Sunnyhope Pharmaceutical, China) thrice a day significantly reduces the incidence as well as the severity of radiation-induced acute intestinal syndromes (Li et al., 2010). Very importantly, in all these studies BBR did not cause any adverse events in study participants. These investigations show that BBR is a safe and ideal candidate for long term use as an adjunct therapy in cancer patients.

6 | RECENT ADVANCES

Despite the meritorious potential of BBR to combat chemo/radioresistance and tumor relapse and protect normal cells and organs from cytotoxic cancer therapies, its clinical applications are limited due to poor oral bioavailability, low aqueous solubility, scarce intestinal absorption, and rapid intestinal and hepatic efflux (Liu, Zheng, Zhang, & Long, 2016). However, with the advent of the nanocarrier system, various advancements have been made in recent years to overcome these challenges and improve BBR's bioavailability, solubility, and absorption. Currently, these nanocarriers are even more modified and developed with the potential to accommodate both BBR and anticancer drugs. These nanocarriers display features of improved half-life, increased cellular internalization, significantly high plasma drug concentration, and sequential release of both chemo drug and natural drug specifically on the tumor sites for a longer period of time. Kabari and colleagues developed layer-by-layer lipid nanoparticles using hyaluronic acid and lactoferrin (self-tumor targeting polymers)

for targeted dual delivery of BBR and rapamycin into lung cancer cells. Fascinatingly, this nanoparticle is designed for the speedy release of BBR followed by the controlled release of rapamycin in order to sensitize lung tumors to the antineoplastic action of rapamycin. These nanoparticles exert powerful cytotoxicity against A549 lung cancer cells due to their increased cellular internalization via CD44 receptor overexpressed in malignant tumors. Also, this nanoparticle exerts superior therapeutic effects over the free drugs in murine xenografts bearing A549 cells by reducing the average number of microscopic lung foci by 88.09% and VEGF levels by 3.1-fold when compared to the positive control mice (Kabary, Helmy, Elkhodairy, Fang, & Elzoghby, 2018). Likewise, hydrophilic albumin nanoparticles modified using a nano-in-nano strategy to incorporate and sequentially release etoposide and BBR show a remarkable increase in cellular internalization and thus exert potent cytotoxicity against A549 lung cancer cells. Also, mice treated with these dual-targeted nanoparticles display 10-fold increase in caspase-3 levels and 4-fold decrease in VEGF level when compared to positive control mice (Elgohary, Helmy, Mortada, & Elzoghby, 2018). Furthermore, poly (lactic-co-glycolic acid) nanoparticles designed to codeliver both BBR and doxorubicin using conjugation/encapsulation technology exerts improved anticancer potential in vitro, low toxicity on normal human peripheral blood mononuclear cells, and high pharmacokinetics in vivo. While inhibiting the proliferation of MDA-MB-231 and T47D breast cancer cells in vitro by inducing apoptosis, cell cycle arrest, and necrosis, this nanoparticle exerts a 14-fold increase in half-life in Sprague Dawley rats and significantly high plasma drug concentration (Khan, Joshi, Nakhate, Kumar, & Gupta, 2019). In female BALB/c mice xenografted with highly metastatic 4T1 breast cancer cells, liposomes coloaded with BBR and doxorubicin enhances tumor cell apoptosis and also attenuates cardiac injuries (Zhang et al., 2019c). Li and colleagues developed polyethyleneimine-cholesterol nanocarrier coloaded with BBR and miRNA-122. This nanocarrier increases the stability of BBR during delivery and enhances the delivery potential of miRNA-122 in malignant tumors. The intracellular codelivery of miRNA-122 and BBR by this nanocarrier in CAL-27 oral squamous cell carcinoma cells significantly inhibits their migration and invasion (Li et al., 2018). Lipid coated mesoporous silica nanoparticles is a novel pH and temperature-responsive dual drug delivery system that improves the biocompatibility and efficacy of drugs pair and maintain optimal drug profile even at the high temperature and low pH of tumor microenvironment. Codelivery of BBR and evodiamine using this nanocarrier into tumor cells inhibits their migration and invasion in vitro and retards cancer growth in murine tumor xenografts. Also, this nanocarrier causes decreased systemic toxicity than the individual free drugs (Feng et al., 2018). On top of these nanocarriers, hyaluronic acid conjugated Janus nanocarrier coloaded with BBR and doxorubicin display collective features of aforesaid nanocarriers including pH-responsive and CD44 receptor mediated drug delivery into tumor cells, significantly high biocompatibility, intracellular accumulation, and good safety profile. Very importantly, this Janus nanocarrier effectively inhibits chemotherapy-induced cancer recurrence both in vitro and in vivo. During the treatment of HepG2 and H22 hepatocellular carcinoma cells and H22 xenografted male ICR mice with this Janus nanocarrier, BBR significantly retards the doxorubicin exacerbated tumor cell re-population by down-regulating caspase-3/iPLA2/COX-2 pathway. Furthermore, as expected, this nanocarrier protects the HL-7702 normal human embryonic liver cells from drug-induced cytotoxicity (Zhang et al., 2019). Taken together, these studies strongly suggest that the nanocarriers with dual drug delivery systems overcome current limitations in the clinical applications of BBR and hold a good prospective for development into pharmaceuticals to overcome drug resistance and tumor relapse.

7 | DISCUSSION AND CONCLUSION

Chemoresistance and tumor relapse are the prime contributors to therapy failure and increased patient mortality. Hence, strategies to circumvent these events are crucially needed to save the lives of cancer patients. However, overcoming chemo/radioresistance in malignant tumors is not an easy task due to the following reasons. First of all, malignant tumors evade the pharmacological effects of cancer therapies by simultaneously adopting various drug-resistant mechanisms. For example, MCF-7 breast cancer cells show resistance to doxorubicin therapy by evading drug-induced apoptosis and cell cycle arrest, inhibiting autophagy, turning hypoxic, and also becoming anoikis resistant. Furthermore, a given cancer cell exhibit different drug-resistant mechanism against different therapies. For example, SGC-7901 gastric cancer cells show resistance to cisplatin therapy by down-regulating miRNA-203 whereas it resists the anticancer effects of cetuximab and erlotinib by up-regulating EGFR/STAT3 pathway. To add more complications, certain molecules (e.g., ROS), pathways (e.g., AMPK pathway), and events (e.g., autophagy) improves drug sensitivity in few cancer types and promote resistance in other cancer types. Above all, CSCs and hypoxic tumors aggressively resist cancer therapies due to their modified phenotype and protective tumor microenvironment. Additionally, besides tumor cells, radiotherapy and chemotherapeutic agents themselves elicit the expression of proteins or activate signaling events that hamper their therapeutic potential against the cancer cells. Doxorubicin induces drug resistance in NCI-H460 and NCI-H1975 lung cancer cells by activating STAT-3 pathways. Irinotecan promotes cell proliferation in HCT116 colon cancer cells by augmenting the NF-κB pathway. In hypoxic tumors, radiotherapy itself promote angiogenesis and other pathological events by inducing the expression of HIF-1α and VEGF. All these evidences show that sensitizing tumor cells to conventional cancer therapies is a complex and challenging task. Hence, the adjunct drugs that are developed to overcome therapy resistance should be empowered with the potential to combat all the chemo/radioresistant events induced by tumor cells, CSCs, and cancer therapies.

This review clearly shows that BBR is a highly ideal drug to reverse therapy resistance induced by tumor cells, radiotherapy, and chemotherapeutic agents. It acts against wide varieties of chemo/radioresistant tumor cells and sensitizes them to cancer treatment by inhibiting their potential to escape from therapy-induced apoptosis

and DNA damages, promoting cell cycle arrest, regulating key signaling pathways governing drug response, modulating miRNA expression, regulating autophagy, and inhibiting inflammation. BBR accomplishes these events majorly by targeting the crucial molecules/pathways associated with therapy resistance including Bax, Bcl2, ROS, STAT3, Nrf2, RAD51, p21, miRNA-21, survivin, NF-κB, AMPK, and MAPK (Figure 1). Doxorubicin, cisplatin, and radiotherapy are the first line therapies routinely given to patients with moderate and advanced cancers. As shown in Table 2, BBR effectively sensitizes various chemo/radioresistant tumors to these therapies via diverse mechanisms suggestive of its potential for routine clinical applications in cancer patients. Furthermore, BBR effectively down-regulates HIF-1α, the key player of pathogenicity and resistance in hypoxic tumors, and thus reverses chemo/radioresistance in these tumors. Also, BBR acts in a duplicitous manner to circumvent the pathways and events that act as a double-edged sword in therapy resistance. More importantly, BBR down-regulates the radiotherapy, irinotecan, evodiamine, and doxorubicin-induced therapy resistance pathways including HIF-1α, NF-κB, IL-8, and STAT-3, respectively, and ameliorates the events associated with drug-induced immunosuppression. At the same time, BBR also protects the heart, liver, lung, kidney, and neighboring cells of the tumor microenvironment from the serious damages caused by cancer therapies. On top of exerting these chemosensitizing and chemoprotective action, BBR prevents cancer recurrence as well by targeting CSC and drug exacerbated repopulation of tumor cells. Currently, BBR has entered the clinical trial in cancer patients and has proven its efficacy to prevent cancer recurrence in colorectal adenoma patients after polypectomy. Furthermore, it protects the lymphoma and cervical cancer patients receiving abdomen radiotherapy from acute radiation intestinal syndrome and NSCLC patients from radiation-induced lung injuries. All these evidences show that BBR holds enormous potential to serve as an adjunct drug in cancer patients. But still, its clinical development is limited due to its scarce bioavailability, poor aqueous solubility, and low intestinal absorption. Nevertheless, recent investigations show that these challenges could be easily circumvented by administering BBR via dual drug delivery system-based nanocarriers empowered with features of the synchronized release of BBR with an anticancer drug, increased half-life, high cellular internalization, and powerful chemosensitizing effects specifically on tumor cells.

To conclude, the robust and versatile role of BBR to ameliorate the major events underlying drug resistance and cancer recurrence is well documented. Furthermore, BBR repairs the organ damages caused by cytotoxic therapies and restores their morphology and function. Hence, BBR could be regarded as a safe and promising adjunct drug to treat cancer. However, more clinical investigations on the chemosensitizing and chemoprotective efficacy of BBR coloaded into dual drug nano delivery systems are highly warranted to develop this nutraceutical into pharmaceuticals to prevent therapy failure and tumor relapse.

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CONFLICT OF INTEREST

The authors declare no conflicts of interest.

AUTHOR CONTRIBUTIONS

Nalini Devarajan, Selvaraj Jayaraman, Ponnulakshmi Rajagopal, and Senthil Kumar Ganesan have contributed to framing review topics, collecting study materials, preparing the manuscript, proofreading, etc. Jaideep Mahendra, Purushothaman Venkatratnam and Hema Palaniappan have written the chemoprotective properties of the berberine.

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