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REVIEW

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Pharmacotherapeutic values of berberine: A Chinese herbal medicine for the human cancer management

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Abstract

Berberine (BBR), a traditional Chinese phytomedicine extracted from various parts of Berberis plants, is an isoquinoline alkaloid used for centuries to treat diabetes, hypercholesterolemia, hypertension, and so forth. It has recently received immense attention worldwide to treat cancer due to its potent pro-apoptotic, antiproliferative, and anti-inflammatory properties. BBR efficiently induces tumor apoptosis, replicative quiescence and abrogates cell proliferation, epithelial–mesenchymal transition, tumor neovascularization, and metastasis by modulating diverse molecular and cell signaling pathways. Furthermore, BBR could also reverse drug resistance, make tumor cells sensitive to current cancer treatment and significantly minimize the harmful side effects of cytotoxic therapies. This review comprehensively analyzed the pharmacological effects of BBR against the development, growth, progression, metastasis, and therapy resistance in wide varieties of cancer. Also, it critically discusses the significant limitations behind the development of BBR into pharmaceuticals to treat cancer and the future research directions to overcome these limitations.

KEYWORDS

berberine, cancer, herbal medicine, phytomedicine

1 | BREAST CANCER

Globally in 2020, nearly 6,85,000 females lost their lives due to this main and dreadful form of cancer.[1] The primary reasons behind the high mortality of breast cancer patients are late-stage diagnosis, recurrence, and therapy resistance.[2,3] Intriguingly, berberine (BBR) can inhibit all of the above characteristics of breast cancer and improve the response of breast cancer cells to various chemo/radiotherapies via diverse mechanisms. This section discusses the pro-apoptotic, antiproliferative, antimetastatic, and chemosensitizing potential of BBR against multiple types of breast tumors.

Apoptosis is one of the potential events triggered by BBR to retard the growth of breast tumors. It promotes programmed cell death by upregulating either the extrinsic apoptotic pathway or intrinsic apoptotic pathway or both by modulating the activity of crucial proteins/molecules involved in these events. It was reported that BBR-induced double-strand breaks stimulate the release of cytochrome C and trigger caspase-9/cytochrome C mediated

apoptosis in MDA-MB-231 (in vivo) and BT549 triple-negative breast cancer (TNBC) cell lines.[4] Likewise, in MCF-7 and MDA-MB-231 breast cancer cells, BBR augmented reactive oxygen species (ROS) generation activates mitochondria-dependent apoptotic pathways.[5] Importantly, BBR triggers intrinsic apoptotic pathways specifically in MCF-7 cancer cells without causing any harm to MCF-12F, normal breast epithelial cells.[6] In the T47D human ductal breast epithelial tumor cell line, BBR induced apoptosis by reducing the amount of Cyclooxygenase-2 (COX-2) and survivin.[7] In MCF-7 and MDA-MB-231 cells, BBR promotes apoptosis in HER-2 negative breast tumors while it retard the growth in the case of HER-2 positive breast tumors by attenuating HER-2/PI3K/Akt signaling pathway and also promoting their apoptosis.[8] Furthermore, BBR could even act against dimethylbenz[a] anthracene-induced ductal carcinoma and invasive carcinoma in Sprague Dawley rats by decreasing the elevated levels of enzymatic antioxidants (Catalase and Superoxide Dismutase), nonenzymatic antioxidants (vitamin C and glutathione), pro-inflammatory cytokines (TNF-α, IL-6, and IL-1β), lipid peroxides, and NF-κB.[9]

Accumulating studies show that BBR is highly effective in treating metastatic breast cancers. It acts by suppressing the synthesis of various molecules involved in metastasis' actual events, including cell adhesion, migration, angiogenesis, EMT, and so forth. Kim et al. conducted multiple studies to investigate the antimetastatic properties of BBR on breast tumors and have come out with fascinating results. In highly metastatic MDA-MB-231 cells, BBR attenuates activator protein-1 (AP-1) DNA binding activity to achieve cell invasion through TNF-α and MMP-9.[10] Furthermore, tumor growth and metastasis were significantly reduced upon using MDA-MB-231 cells and BBR in female athymic mice xenografted. Also, on treating BBR to HCC1806 TNBC cells, downregulation of TGF-β1/SMAD3 signaling events and cell motility occurred due to the reduced expression of MMP-2.[11] In MCF-7 cells, BBR exerts its antimetastatic potential by decreasing MMP-1 and MMP-9 levels via suppression of tumor promoter (TPA)-induced PKC-α phosphorylation. Also, it inhibits tumor neovascularization in these cells by attenuation of PI3K/Akt pathway, thereby inhibiting TPA-induced vascular endothelial growth factor (VEGF) as well as VEGF-induced fibronectin.[12] Furthermore, BBR attenuates TPA-induced degradation of p53[13] and reduces the gene expression of chemokine receptors, including CCR6, CCR9, CXCR 1, and CXCR 4 in MCF-7 cells.[14]

IL-8 is a CXC chemokine that acts as the critical driver of activities underlying cancer metastasis. In extraordinarily metastatic MDA-MB-231 cells, BBR hydrochloride attenuates cell invasion via lowering the extent of IL-8 and reducing the expression of epidermal growth factor (EGF), MMP-2, basic Fibroblast Growth Factor, E-cadherin, and fibronectin. Furthermore, BBR hydrochloride activates p38 MAPK and JNK pathways and deactivates JAK2/PI3K/NF-κB/AP-1 pathways to arrest the G2/M phase of the cell cycle and induce apoptosis.[15] Likewise, BBR significantly inhibits cell invasion and growth in MCF-7 and Hs578T TNBC cells by decreasing IL-8 levels.[16] Vasodilator-stimulated phosphoprotein is an actin-associated protein that stimulates actin filament elongation and cell migration. The ability of BBR to bind to VASP and inhibit cell migration was illustrated through studies done in vitro using MDA-MB-231 cells and MCF-7 cells and in vivo using MDA-MB-231 nude mouse xenografts.[17] Ephrin B2, a potent regulator of endothelial cell behavior, is crucially involved in cell migration and angiogenesis. However, BBR attenuates ephrin B2 levels to efficiently inhibit ZR-75-30 breast tumor cells.[18]

Mounting evidence shows that BBR could sensitize breast tumor cells to wide varieties of chemotherapies and radiotherapy and thus reverse drug resistance. It radiosensitizes MCF-7 and MDA-MB-468 cells by promoting replicative quiescence and decreasing the activity of RAD51, an enzyme that repairs double-strand breaks in DNA.[19] Pan et al. conducted several studies to investigate if BBR could improve the response of various breast cancer cells to doxorubicin, the conventionally used chemotherapeutic drug. A study focusing on drug resistance was conducted on MCF-7 cells in which the cells were exposed to hypoxic conditions for 1 week to induce drug resistance. After induction, these cells were co-treated with a range of concentrations of doxorubicin and BBR. At lower concentrations, BBR augmented the response of MCF-7 cells to doxorubicin by downregulating the AMP-activated protein kinase (AMPK)/HIF-1α/P-glycoprotein pathway. Astonishingly, at higher concentrations, BBR unaided by doxorubicin induces apoptosis by suppressing the AMPK/HIF-1α pathway and thus activating p53. More interestingly, the same results obtained in in vitro studies have also been observed in in vivo studies conducted in athymic mice xenografted with drug-resistant MCF-7 cells.[20] Furthermore, Pan et al.[21] conducted another similar study in vitro and in vivo using multidrug-resistant MCF-7/MDR human breast cancer cells, which showed the same results. More importantly, BBR derivative 1,13-cycloprotoberberine also attenuates the activity of DNA topoisomerase I and II and arresting cells at the G2/M phase to retards the growth of MCF-7 and doxorubicin-resistant MCF-7/ADrR cells.[22] Doxorubicin administration induces cardiotoxicity in the majority of cancer patients. Lv et al. investigated the effect of BBR on DOX-induced cardiotoxicity and uncovered the molecular mechanism of the same in both in vitro and in vivo. For the in vitro study, MCF-7 cells and rat cardiomyocytes were cocultured together and then treated with doxorubicin and BBR. Astonishingly, BBR conferred protection against cardiotoxicity without impairing the antitumor efficacy of doxorubicin. In vivo studies were conducted by treating the male Sprague Dawley rats with either doxorubicin/BBR or both. Fascinatingly, BBR effectively inhibited the apoptosis of cardiomyocytes and improved the survival in rats challenged with doxorubicin by protecting mitochondria and inhibiting the rise in AMP/ATP ratio, AMPKα phosphorylation, and Bcl-2 expression.[23] Moreover, BBR better the growth inhibitory ability of tamoxifen in both tamoxifen-sensitive and tamoxifen-resistant MCF-7 cells via triggering apoptosis and G1 phase cell cycle arrest.[24] BBR chemosensitized the MCF-7 cells to cisplatin therapy by inducing DNA breaks and apoptosis.[25] In lapatinib-resistant BT-474^{LapR} cells, combinational treatment with lapatinib and BBR treatment induced apoptosis by suppressing

c-Myc, upregulating ROS, and reversing lapatinib resistance.[26] Apart from chemosensitizing breast cancer cells to lapatinib treatment, BBR could also effectively replace lapatinib for breast cancer treatment due to its multikinase inhibitory potential.[27] In TRAIL-resistant MDA-MB-468 TNBC cells, BBR co-treatment improves their response to TRAIL therapy by way of stimulating apoptosis via downregulating p38 MAPK pathway.[28,29]

2 | LUNG CANCER

Lung cancer is a dreadful type of cancer with a rapid mortality rate. With the global death toll reaching 1.8 million in 2020, lung cancer has been ranked first among cancer-related deaths.[30] Despite effective treatment with numerous medications, the survival rate of lung cancer patients is incredibly low.[31] Hence, there is a need to develop potent treatment alternatives for lung cancer. Extensive experiments by various research groups clearly show that BBR is highly effective in combating multiple pathological lung cancer events.

Mounting evidence illustrates that BBR may suppress lung tumors' expansion, survival, and proliferation by promoting replicative quiescence, programmed cell death, and autophagy by modulating various signaling pathways. In different nonsmall lung cancer cells, including H1299, PC9, H1650, and A549, BBR retarded cell growth, induced replicative quiescence, and promoted apoptosis by upregulating p38α MAPK pathway and augmenting the synthesis of p53 and FOXO3. FOXO3 successively elevated the amount of p21, a master effector of multiple tumor suppressor pathways in these cells.[32] Likewise, BBR hydrochloride suppressed proliferation and triggered apoptosis in A549 cells by attenuating JAK2/VEGF/NF-κB/AP-1 signaling pathways.[33] Also, BBR induced phototoxicity in A549 cells by augmenting ROS production and mitochondrial permeabilization and activating the caspase-9/caspase-3 complex.[34] Furthermore, BBR attenuated cyclin D1 expression in PG human pulmonary giant cell carcinoma and inhibited their proliferation by downregulating the AP-1 pathway and decreasing the interactions between transcription factors and CCND1 AP-1 motif.[35] In the NCI-H2452 human malignant pleural mesothelioma cell line, BBR exerted its antitumor potential by (i) suppressing cell proliferation time and dose dependently, (ii) promoting caspase-9 mediated apoptosis, and (iii) inducing protective autophagy by increasing the accrual of LC3-II (autophagy marker) and reducing the expression of p62 (autophagy marker).[36] p53 is a potent tumor suppressor protein that could effectively subject the tumor cells to apoptosis-mediated death. Katiyar et al. analyzed the impact of BBR on p53-mediated apoptosis using p53-positive (A549 cells) and p53-deficient (H1299) cells in vitro and in vivo. Fascinatingly, BBR apoptosed A549 cells more effectively than H1299 cells. However, the apoptotic potential of BBR was drastically reduced in A549 cells exposed to p53 inhibitor and A549 cells transfected with p53 antisense oligodeoxynucleotide. These findings clearly prove that BBR-mediated suppression of cell proliferation and apoptosis occurs by upregulation of p53. BBR triggered apoptosis of both H1299 and A549cells by disrupting mitochondrial membrane potential, decreasing the expression of anti-apoptotic proteins (Bcl-2, Bcl-xL), elevating the expression of pro-apoptotic proteins (Bax, Bak) and upregulating caspase-3.[37] Likewise, studies done by James et al.[38] using p53 proficient and p53 deficient lung tumor xenografts also show that p53 actively participates in tumor growth retardation by BBR.

BBR is a good choice for combination chemotherapy in lung cancer because it can act synergistically with a wide variety of pharmacological agents to improve the therapeutic outcome, overcome drug resistance, and confer protection to normal cells. Meng et al. investigated the combinational effects of BBR and cinnamaldehyde in vitro using A549 nonsmall cell lung cancer cells and in vivo using a mice model system. In vivo studies involved urethane treatment-induced lung carcinogenesis in ICR mice and interestingly, they found that synergistic administration of BBR and cinnamaldehyde significantly attenuated the urethane-induced lung carcinogenesis in these mice by reversing urethane-induced AMPK, mTOR, AQP-1, and NF-κB expression patterns. In vitro, BBR and cinnamaldehyde together triggered A549 cell apoptosis, inhibited autophagy, cell proliferation, and wound healing, augmented the expression of AMPK, and reduced the expression of AQP-1. Taken together, the combinational therapy with BBR and cinnamaldehyde ultimately led to the starvation of the lung cancer cells due to restrictions in their acquisition of both primary and adaptive nutrients via AMPK-reduced AQP-1 expression.[39] Yuan et al. treated gefitinib-resistant H1650 and H1975 NSCLC cell line and BEAS-2B regular epithelial cell line with BBR. They determined its intracellular distribution in these cells using an ultra-performance liquid chromatography-tandem mass spectrometer. Fascinatingly, they observed a tremendously high intracellular accumulation of BBR in NSCLC cells than in BEAS-2B cells which in turn provides direct evidence on its potential to exert cytotoxic effects selectively on cancer cells.[40] DNA methyltransferase-1 (DNMT-1) is a crucial enzyme needed for DNA methylation. Any defect in DNMT-1 is associated with augmented tumor transformation and progression. In A549 and H1975 cells, BBR and metformin effectively inhibited DNMT1 gene expression by suppressing SP-1 and PDPK1 expression.[41]

Furthermore, BBR also enhanced the pharmacological effects of doxorubicin in lung tumors through the inactivation of STAT3.[42] More importantly, BBR supplementation augmented the response of lung tumor cells cultured in vitro and xenografted in vivo to radiotherapy by inducing autophagy.[43] Radiotherapy causes severe lung injury in lung cancer patients. However, BBR co-treatment along with radiotherapy in 90 nonsmall cell lung cancer patients protected the lung from radiation-induced damages and enhanced its physiological functions as well.[44]

Apart from acting as a potent pro-apoptotic, antiproliferative, and chemosensitizing drug, BBR could also serve as a promising antimetastatic drug and impede the metastatic events of lung cancer via multiple mechanisms. In highly metastatic A549 cells, BBR exerted its antimetastatic potential by decreasing the levels of ECM proteinases including MMP-2 and urokinase-plasminogen activator

(u-PA) through the regulation of Tissue inhibitor of metalloproteinase-2 and urokinase-plasminogen activator inhibitor.[45] Also, BBR attenuated the metastasis of A549 cells both in vitro and in vivo (murine A549 xenografts) by suppressing TGF-β1-induced EMT.[46] In female C57BL/6CrAlc mice whose lung parenchyma were orthotopically implanted with Lewis lung carcinoma (LLC) cells, BBR treatment dose-dependently inhibited the tumor metastasis to mediastinal lymph nodes. However, BBR did not affect the tumor growth at the primary tumor site. Synergistic administration of BBR with a chemotherapeutic drug, CPT-11 significantly retarded both the growth of a primary tumor and also its metastasis to lymph modes. Moreover, BBR also repressed the invasion of LLC cells by upregulating the levels of anti-activator protein-1 (anti-AP-1) and downregulating the expression of u-PA.[47] Apart from inhibiting the metastasis of lung cancer cells to other organs, BBR is also very effective in preventing the metastasis of different types of cancer cells to the lungs.[11,47]

3 | COLORECTAL CANCER

Colorectal carcinoma (CRC), the third major cause of cancer-related deaths, had accounted for 9,16,000 mortalities globally in 2020.[1] Despite tremendous efforts worldwide from clinicians and cancer scientists, no effective treatment is available to date to treat this dreadful disease. Diet and lifestyle greatly influence the pathogenesis of CRC. Hence, BBR supplementation would be an ideal approach to prevent the development of CRC and facilitate the pathological consequences of CRC once developed. The details of this section on the therapeutic efficacy of BBR against CRC development and progression are explained.

Accumulating evidence strongly suggests that BBR could efficiently inhibit proliferation and tumorigenesis and promote apoptosis in various CRC cell lines and colorectal carcinogenesis mouse models by modulating different proteins/signaling pathways critically involved in disease pathogenesis. In SW 620 human colonic carcinoma cells, BBR triggered the caspase-dependent apoptotic cascade and augmented cell death by upregulating JNK/p38 signaling pathways and increasing ROS generation.[48] In SW480 human colon cancer cells, BBR exerted its antitumor potential by (i) inducing G2/M phase arrest via p21 overexpression, (ii) promoting apoptosis by activating mitochondrial apoptotic events, and (iii) inhibiting neovascularization by modulating the expression of TRAIL, VEGF, and survivin.[49] In HCT 116 human CRC cells, BBR reduced cell viability and induced apoptosis by suppressing the expression of microRNA-21, an oncogenic microRNA, and augmenting the expression of ITGβ4 and PDCD4.[50] Furthermore, BBR also inhibited inflammation and thus colon tumor growth by suppressing COX-2 activity.[51] Li et al.[52] investigated the therapeutic efficacy of BBR against colorectal carcinogenesis initiated and induced in mice models by azoxymethane and dextran sulfate, respectively, and have found that BBR could significantly decrease tumor size by attenuating the expression of Ki-67, COX-2, inhibiting the phosphorylation of mTOR and p65 and promoting caspase-3 cleavage. The in vitro studies using HCT116, SW680, and LOVO colon cancer cell lines also show that BBR could suppress proliferation and trigger apoptosis via AMPK-dependent downregulation of mTOR activity AMPK independent downregulation of NF-κB. Likewise, studies done using an azoxymethane-induced rat colon tumor model[53] and 1,2-dimethyl hydrazine-induced rat colon tumor model[54] show that BBR could suppress neoplastic transformation through stimulation of an antioxidant defense system and caspase-dependent apoptosis. Apart from inducing caspase-dependent tumor apoptosis, BBR could also trigger the apoptosis of colon cancer cells in a caspase-independent manner.[55] In mouse immorto-Min colonic epithelial (IMCE) cells carrying Apc^{min} mutation and normal young adult mouse colon epithelial cells, BBR selectively induced caspase-independent apoptosis by activating apoptosis-inducing factor via consecutively augmented production of ROS, secretion of cathepsin B, and upregulation of PARP action. Likewise, BBR triggered apoptosis in HCT116 and DLD-1 colon cancer cells by inducing autophagy through the following mechanisms: (i) augmenting activating transcription factor 6 (ATF6) mediated upregulation of glucose-regulated protein 78 (GRP78), (ii) attenuating GRP78 degradation, and (iii) increased formation of autophagosome via augmented interaction between GRP78 and VPS34.[56] Huang et al. developed cell cultures from colon tissues of 1-week-old neonatal rats, induced malignancy in these cells in vitro with TGF-β, and treated them with BBR for 24 h. Interestingly, BBR upregulated the expression of DNMTs including DNMT 1, DNT3A, DNMT3B, and its corresponding downstream targets including miR-152, miR-429, and miR-29a in rat colon cells in vitro. This, in turn, provides direct evidence for the potential of BBR to treat colon cancer through the modulation of epigenetic mechanisms as well.[57]

Wnt/β-catenin signaling pathway is an oncogenic pathway implicated in various cancers. Activation of this pathway by losing its negative regulator, adenomatous polyposis coli (APC), is the hallmark pathogenic event in human CRC. Emerging studies demonstrate that BBR is highly capable of ameliorating the pathological events of CRC by downregulating the Wnt/β-catenin signaling pathway.[58–60] EGF receptor (EGFR) is a tumor promoter that is overexpressed in colonic precancerous lesions. However, BBR could down-regulate EGFR expression in IMCE cells harboring APC^{min} mutation and HT-29 cells and inhibit their growth via consecutive activation of ubiquitin ligase Cbl, its interaction with EGFR and EGFR ubiquitinylation.[61] Likewise, in dextran sulfate sodium-treated $Apc^{min/+}$ mice, BBR attenuated inflammation-induced EFGR signaling and suppressed the development of colitis-associated tumorigenesis.[62] Furthermore, BBR could combat the growth of hypoxic colon cancer cells by impeding hyperactive glucose uptake and glycolysis via inhibition of mTOR-mediated HIF-1α synthesis.[63] Arylamine N-acetyl Transferase (NAT), a detoxification-associated enzyme, is overexpressed in several cancer types, and its overexpression is reported to promote tumor survival and chemoresistance. Fascinatingly, BBR impeded NAT activity and thus reduced the viability of colo 205 colon cancer cells in a dose-dependent manner.[64]

The majority of deaths resulting from CRC occur due to the metastatic spread of cancer cells. Fortunately, accumulating studies show that BBR could act as an effective anti-metastatic drug and abrogate the metastatic events in CRC. It attenuated the migration of SW480 and HCT 116 cells and impeded their metastatic potential by activating AMPK and subsequently downregulating the integrin β1 signaling pathway.[65] Also, BBR suppressed the invasion and metastasis of CRC cells by attenuating the COX-2/PGE2-induced JAK2/STAT3 pathway.[66]

Furthermore, BBR could also disrupt the interaction between colon cancer cells and normal colon epithelial cells. Huang et al. co-cultured SW480 colon cancer cells with HCoEpiCs normal colon epithelial cells using a transwell coculture system and conditioned medium from SW480. Interestingly, SW480 cells induced EMT and promoted migration of HCoEpiCs by downregulating TGF-βII, Smad2, and p-Smad3. However, treatment of these cocultured cells with BBR reversed the SW480 induced EMT like transition and also inhibited the migration of HCoEpiCs by upregulating the expression of TGF-βII, Smad2, and p-Smad3.[67]

4 | PROSTATE CANCER

Prostate cancer, the most dreadful form of cancer that affects men above 50 accounts for nearly 1.41 million cases globally in 2020.[1] Prostate cancer shows no symptoms at the early stage, and hence, this dreadful disease is mainly diagnosed at the late phase.[68] Emerging reports show that BBR is highly effective in preventing and treating prostate cancer in men. Several research papers show that BBR could act as a promising chemopreventive and chemoprotective drug against prostate cancer. It acts selectively on prostate cancer cells and inhibits tumor proliferation and growth via induction of replicative quiescence and augmentation of apoptosis, both dose, and time-dependently.

Mantena et al. intensively studied the chemotherapeutic efficacy of BBR against DU 145 and PC3 (androgen-insensitive), LNCaP (androgen-sensitive) prostate cancer cells, and PWR-1E (nontumorigenic human prostate epithelial cells). BBR did and time-dependently inhibited the proliferation and triggered the apoptosis of DU 145, PC3, and LNCaP cells by arresting cells at the G1 phase and activating the caspase-dependent apoptotic pathway, respectively, without affecting the viability of PWR-1E cells. In DU 145 cells, BBR stopped the cell cycle by attenuating the expression of cyclins D1, cyclin D2, cyclin E, Cdk2, Cdk4, and Cdk6 proteins, enhancing the expression of Cdk inhibitory proteins (Kip1/p27 and Cip1/p21) and increased interaction between Cdk and its inhibitors. In DU 145 and LNCaP cells, BBR promoted apoptosis by increasing Bax/Bcl-2 ratio, disrupting mitochondrial membrane potential, and activating caspase-9, caspase-3, and PARP. Taken together, these study results show that BBR exerts its cytotoxic potential specifically on prostate cancer cells without causing any harm to normal prostate epithelial cells.[69] Fascinatingly, studies done by Choi have also yielded results similar to that of Mantena et al. wherein BBR selectively retarded the growth of LNCaP cells in dose (0–50 μM) and time (0–48 h) dependent manner without affecting the growth of PWR-1E cells. Furthermore, insights into the molecular mechanisms underlying the anticancer potential of BBR in vitro have shown that BBR could act more effectively against p53 expressing LNCaP cells than p53 lacking LNCaP cells in vitro. Also, BBR treatment decreased the tumor weight and volume more efficiently in LNCaP-bearing nude mice than in PC3 cells-bearing nude mice. These observations show that BBR selectively represses prostate tumor progression by inducing G_0/G_1 phase arrest and triggering apoptosis in p53 dependent manner.[70] However, in another study, BBR suppressed the proliferation of LNCaP and PC3 cells by promoting apoptosis and cell cycle both time and dose-dependently by attenuating the EGFR signaling pathway.[71] Also, BBR attenuated the migration, invasion, and EMT in these highly metastatic cells by suppressing EMT-related genes, including NODAL, bone morphogenetic protein, and Snail.[72] In PC3 cells, BBR induced dose-dependent apoptosis by augmenting ROS generation.[73] Furthermore, this phytochemical arrested PC3 cells at the G1 phase at lower doses and the G2/M stage at higher doses.[74] Taken together, all these studies show that BBR acts via diverse mechanisms to induce replicative quiescence and promote apoptosis selectively in prostate cancer cells.

Li et al. performed a high throughput metabolomics investigation using UPLC-Q/TOF-MS/MS technique both in vitro and in vivo to elucidate the molecular targets of BBR in prostate tumors comprehensively. In vitro metabolomics study was performed by treating 22RV1 human prostate cancer cells with 10 μM BBR for 12, 24, 48, 36, 48, and 72 h. In vivo metabolomics study treated male BALB/c-nude mice bearing 22RV1 cells with BBR. Furthermore, it also investigated the growth inhibitory potential of BBR in prostate cancer cells and the tumor tissues of mice. Their study results show that BBR could effectively repress the growth of xenograft tumors in nude mice by decreasing the expression of prostate serum antigen, androgen receptor (AR), COX-2, and Bcl-2 and increasing caspase-3 expression. Moreover, in the blood and cell metabolomics analysis, BBR restored the deregulated metabolic profile to a normal state and treated prostate cancer by regulating the metabolism of purine, linoleic acid, proline, retinol, and arginine and normalizing the biosynthesis of retinoate and spermine.[75]

Hyperactivation of AR signaling is majorly responsible for the development of prostate cancer, and hence, androgen deprivation therapy is currently used for treating this dreadful disease. Prostate tumors initially respond to this treatment; later, they resume growth despite treatment and progress to castration-resistant prostate cancer (CRPC). Interestingly, BBR is highly effective in antagonizing AR and treating CRPC. It inhibits the growth of both androgen-sensitive and CRPC cells by inhibiting AR signaling through the proteasomal degradation of ARs. Apart from degrading full-length AR, BBR could also degrade several ligand-binding domains truncated AR splice variants that promote androgen-independent growth of prostate tumor cells. Furthermore, BBR could also attenuate AR expression and suppress tumor growth in nude mice bearing LNCaP xenografts.[76] In 22Rv1 prostate cancer cells, BBR significantly

reduced intracellular androgen synthesis via suppression of Aldo-keto reductase family one member C3 enzyme.[77]

Emerging studies show that BBR could radiosensitize PC3 prostate cancer cells to activate ROS and MAPK/caspase-3 and down-regulate radio-resistant proteins, including HO-1, ERK, Bcl-2, and NF-κB, and which are expressed postradiation therapy.[78] Also, BBR enabled the LNCaP and DU-145 cells to overcome hypoxia-induced radioresistance and improved their sensitivity to ionizing radiation under hypoxic conditions by repressing HIF-1α and VEGF expression.[79]

5 | PANCREATIC CANCER

Pancreatic cancer is the most aggressive cancer that begins metastasis in the early stages of its development. As per reports from Global Health Data Exchange and WHO, it accounts for 4,47,665 new cases in 2017.[80] In the majority of patients, this cancer is diagnosed only at the late refractory stage. Hence, despite the administration of powerful anticancer drugs like gemcitabine, the mortality rate of pancreatic cancer patients remains high. This pathological scenario, in turn, emphasizes the need for promising treatment alternatives for pancreatic cancer. Fortunately, evidence shows that BBR could act more effectively than conventional chemotherapeutic drugs to treat pancreatic cancer. This potent phytochemical surpassed the therapeutic potential of gemcitabine in PANC-1 and MIA PaCa-2 pancreatic ductal adenocarcinoma cells (PADCs). However, BBR and gemcitabine dose-dependently induced cell cycle arrest and apoptosis in these cells via different mechanisms. While gemcitabine inhibited cell proliferation by arresting them at S-phase, BBR induced cell cycle arrest at the G1 phase. Likewise, in contrast to the upregulation of caspase-mediated death of pancreatic cancer cells by gemcitabine, BBR augmented apoptosis by increasing the production of ROS.[81] Apart from acting against PANC-1 and MIA PaCa-2 tumor cells, BBR could impede the growth of pancreatic cancer stem cells of these PADC. Side population cells are regarded as cancer stem cells for in vitro study owing to their ability to efflux Hoechst 33342 dye. BBR reduced the side populations of PADCs as effectively as gemcitabine by decreasing the mRNA levels of stem cell-related genes, including SOX-2, POU5F1, and NONOG.[82]

Furthermore, BBR could also compete with metformin to retard the growth of PADC tumor xenografts in vivo. Unlike gemcitabine, both BBR and metformin exert their chemotherapeutic effects dose-dependently via the exact mechanisms against PDAC cells. These drugs act by downregulating mTORC1 and ERK mitogenic signaling in AMPK dependent manner at lower concentrations and in AMPK independent manner at higher concentrations.[83]

mRNA-based gene expression profiling study in untreated and BBR-treated pancreatic cancer cells shows BBR kills the pancreatic tumor cells by activating BRCA1-mediated DNA damage response, regulating G1/S and G2/M cells cycle checkpoint, and upregulating p53 signaling pathways. BBR activates these pathways by inducing DNA lesions, and DNA strand breaks via DNA intercalation and inhibition of topoisomerase activity.[84] Also, BBR retards the growth and metastasis of MIA PaCa-2 cells by arresting them at the G1 phase, promoting senescence, autophagy, increasing caspase-3 activity, and impairing migration and invasion.[85] Collectively, all these studies suggest that BBR acts pleotropically and very effectively than current chemotherapeutic agents to treat pancreatic cancer.

6 | SARCOMA

Sarcoma is a cancer that occurs due to the malignant transformation of connective tissues. Many connective tissues in our body include cartilage, muscle, bone, fat, vascular, or hematopoietic tissues. Hence, sarcoma is classified into various types based on the type of cell or tissue the tumor originates. These include osteosarcoma, chondrosarcoma, Kaposi sarcoma, fibrosarcoma, and so forth.[86] Interestingly, BBR is effective against the growth of all these types of sarcomas. In MG-63 osteosarcoma cells, BBR promotes DNA damage,[87] induces cell cycle arrest at G1 and G2/M phase, and triggers apoptosis via p-53-dependent activation of p21 and pro-apoptotic genes. p53 activity and subsequent cellular responses are activated in these cells by BBR through the induction of double-strand breaks and thus genomic lesions.[88] Also, BBR inhibits the growth of human Saos-2 and MG-63 osteosarcoma cell lines by downregulating the caspase-1/IL-1β inflammatory signaling axis.[89] Furthermore, Hsu et al.[90] found that the uptake of BBR by osteosarcoma cells could be augmented by coupling it to heparin-based nanoparticles. In HTB-94 human chondrosarcoma cells, BBR retards cell proliferation in a dose-dependent manner by inducing cell cycle arrest at the G2/M phase through the upregulation of PI3K/Akt and p38 cell signaling pathways.[91] In HT1080 fibrosarcoma cells, BBR and its phenolic derivatives, B2 and B4, acted as potent antioxidants and exerted their cytotoxic effects by increasing the gene expression of Superoxide dismutase.[92] Investigations on the individual and synergistic effects of BBR and polyethylene glycol—liposomal doxorubicin (PEG-Lip-DOX) in Meth A sarcoma transplanted BALB/c mice show that tumor growth inhibition could be achieved very effectively by BBR combinational therapy.[93]

7 | GLIOBLASTOMA

Glioblastoma is the most aggressive form of cancer that develops in the brain. The first-line treatment for glioblastoma is radiotherapy combined with a DNA alkylating agent such as temozolomide. This combinational therapy has increased patients' 2-year survival rate from 10% to 27%. However, nearly all the patients under this therapy suffer from severe adverse side effects such as leukopenia, nausea, and so forth. Furthermore, these therapies also promote disease progression and worsen the prognosis of glioblastoma patients.[94] According to WHO reports, the 5-year survival rate of patients with grade IV tumors is less than 5%. The need for promising drugs with

minimal toxicity to treat glioblastoma led to mounting investigations that explored the therapeutic efficacy of BBR against this dreadful disease. Accumulating studies show that BBR could effectively retard glioblastoma cells' growth, survival, and progression by triggering autophagy, replicative senescence, apoptosis, cell cycle arrest, ROS generation, and so forth. In T98G human glioblastoma cells, BBR dose-dependently suppressed cell proliferation by arresting them at the G1 phase via elevated expression of p27 and reduced expression of CDK2, CDK4, cyclin D, and cyclin E proteins. Also, it induced T98G cell death by increasing Bax/Bcl-2 ratio, disrupting mitochondrial membrane potential, and upregulating the expression of proteins involved in caspase-dependent apoptotic pathways, including procaspase-9, caspase-9, caspase-3, and PARP.[95] BBR activates the intrinsic apoptotic pathway in these cells in many ways, including (i) induction of stress in the endoplasmic reticulum (ER) via generation of ROS, (ii) elevation in the levels of intracellular Ca^{2+}, and (iii) mitochondrial dysfunction. More interestingly, BBR acts via the exact mechanism above to induce apoptosis of C6 rat glioma cells[96] which is given in Figure 2. This evidence, in turn, suggests that BBR exerts its cytotoxicity against glioblastoma cells by inducing cell cycle arrest and thus programmed cell death through the augmentation of ER stress and generation of ROS. Upregulation of EGFR is crucial for glioblastoma proliferation. Interestingly, BBR inhibited the growth of U87, U251, and U118 glioblastoma cells in vitro and murine U87 xenografts in vivo more effectively than temozolomide by promoting cellular senescence through the attenuation of EGFR/RAF/MEK/ERK signaling pathways. This, in turn, suggests that BBR could serve as a promising drug to treat glioblastoma.[97]

Few studies show that BBR could exert its cytotoxic effects on glioblastoma cells by inducing autophagy and targeting metabolism. In U251 and U87 cells, BBR retarded the tumor growth and metastasis by suppressing their metabolism and decreasing glycolytic capacity, altering mitochondrial dynamics, and increasing autophagy flux. It augmented autophagy in these cells by promoting the accrual of LC3B-II positive autophagosomes and subsequently reducing the p62 protein levels via downregulation of the AMPK/mTOR/ULK1 pathway.[98] Likewise, BBR retarded glioblastoma growth by inducing autophagy, reducing oxygen consumption rate, repressing mitochondrial aerobic oxidation, reducing the energy-generating potency, and decreasing metabolic activity by suppressing the activity of ERK1/2. Moreover, BBR induced oncosis-like death in these cells through ATP depletion.[99] All these observations show that BBR act in a multifaceted manner to suppress the growth and progression of glioblastoma.

8 | GASTRIC CANCER

Gastric cancer is a deadly type of cancer that accounts for 7,69,000 deaths worldwide in 2020.[1] Being the second major cause of global cancer-related death, gastric cancer has received immense attention from clinicians and cancer scientists worldwide. In most patients, gastric cancer manifests its symptoms only at the late advanced stage. Hence, chemotherapy is considered the mainstay treatment for treating this dreadful disease.[100] However, the development of drug resistance essentially limits the clinical effectiveness of chemotherapeutic drugs in gastric cancer patients. Emerging studies show that BBR could circumvent these limitations and could appear as a safe and promising drug to treat gastric cancer.

Upregulation of Survivin and STAT-3 signaling majorly contribute to chemoresistance in gastric malignancies. However, BBR treatment significantly reduced survivin expression and pSTAT-3 levels in AGS gastric cancer cells and enhanced their response to 5-fluorouracil.[101] Evodiamine is a potent chemotherapeutic drug whose clinical applications are restricted due to its potential to upregulate the synthesis of oncogenic proteins, including IL-8, VCAM-1, and ICAM-1. Nevertheless, BBR effectively counteracted the deleterious effects of evodiamine in AGS cells by downregulating the production of IL-8, ICAM-1, and VCAM-1 and significantly reducing the adhesion of evodiamine-treated AGS cells to HUVECs.[102] Also, BBR sensitizes BGC-823/DDP and SGC-7901/DDP cisplatin-resistant gastric cancer cells to cisplatin-induced apoptosis by elevating the expression of microRNA-203 and subsequently repressing the expression of Bcl-2, the anti-apoptotic protein.[103] Cetuximab, an antibody targeting EGFR, is used to treat colon and head and neck cancer. However, its combination with chemotherapy for treating EGFR overexpressing gastric cancer did not produce satisfactory results. Erlotinib is an EGFR-targeting small-molecule tyrosine kinase inhibitor. Since BBR is a potent inhibitor of EFGR in tumors, Wang et al.[104] investigated if this phytochemical could augment the therapeutic potential of erlotinib and cetuximab against gastric malignancies both in vitro and in vivo. In vitro studies were carried out by treating MKN45, BGC823, and SGC7901 gastric cancer cells with BBR and erlotinib/cetuximab. In vivo studies were carried out by treating BGC823 cells xenografted nude mice BBR and cetuximab. Fascinatingly, BBR augmented the activity of erlotinib and cetuximab in vitro and in vivo by downregulating EGFR/STAT3 signaling pathway. Taken together, this evidence strongly suggests that BBR could overcome drug resistance in gastric cancer by chemosensitizing the tumor cells to various conventionally used chemotherapeutic drugs, including cisplatin, evodiamine 5-fluorouracil, cetuximab, and erlotinib.

Apart from acting in synergy with conventional chemotherapeutic agents, BBR could also work individually to suppress the growth of gastric cancer cells. In SNU-5 human gastric cancer cell lines, BBR induced cytotoxicity by promoting cell cycle arrest at G2/M phase and triggering apoptosis via upregulation of p53 expression, a decrease of mitochondrial membrane potential, release of cytochrome C, and activation of caspase-3.[105] Furthermore, BBR also promoted ROS generation in SNU-5 cells and impeded their migration by reducing the expression level of MMP-1, -2, and -9.[106] In SGC-7901 gastric cancer cells, BBR inhibited cell proliferation by arresting them at the G1 phase, promoting apoptosis and establishing cross-talk between the genes and microRNAs.[107] In MGC 803 human gastric carcinoma cell line, BBR dose-dependently inhibited cell proliferation and tumorigenesis in vitro and in vivo, respectively,

by decreasing the secretion of IL-8 via inactivation of p38 MAPK, ERK1/2, and c-Jun-N-terminal kinase.[108]

9 | CERVICAL CANCER

Cervical cancer, the fourth primary type of cancer among females, has affected 6,04,000 women and led to 3,42,000 global deaths in 2020.[109] In more than 90% of cases, cervical cancer develops due to human papilloma virus (HPV) infection. Two specific HPV types, namely HPV16 and HPV18, play a significant role in developing cervical cancer.[110] Fascinatingly, BBR possesses the potential to kill both HPV 16 positive cervical cancer cells (SiHa cell lines) and HPV18 positive cervical cancer cells (HeLa cell lines) by effectively targeting both the host and viral factors crucially involved in disease pathogenesis. BBR acts on these cells by (i) selectively inhibiting constitutively expressed AP-1 in the dose and time-dependent manner and (ii) downregulating the expression of HPV oncoproteins E6 and E7. Also, in Hela cells, BBR triggers apoptosis by activating (i) intrinsic mitochondrial pathway, (ii) extrinsic death receptor pathway via activation of Fas, FasL, TNF-α, and TRAF-1, (iii) p53 expression, and (iv) MAPK pathways.[111] The uptake of BBR by these cells through membrane depolarization also led to various cytotoxic events, including modulation of HPV-18 E6-E7 viral oncoproteins, disruption of the microtubule network, and augmented p53 expression. Furthermore, in SiHa cells, BBR reversed TGF-1β mediated EMT by increasing the levels of epithelial markers including E-cadherin and decreasing the expression of mesenchymal markers including N-cadherin and Snail-1. More importantly, BBR retards tumor neovascularization both in vitro and in vivo and inhibits the metastasis of SiHa cells to lungs in xenograft mice models.[112] As observed in glioblastoma cells,[96,112] BBR triggers apoptosis of CaSki cervical cancer cells in time and dose-dependent manner by (i) increasing the ratio of p53 and Bax/Bcl-2 proteins, (ii) generating ROS and subsequently promoting ER stress and Ca^{2+} release, (iii) disrupting mitochondrial membrane potential, (iv) increasing the expression of GADD153, and (v) promoting caspase-3 activity.[113] In HeLa229 human cervical carcinoma cells, BBR inhibits cell proliferation and promotes apoptosis by upregulating p53 and downregulating Bcl-2 and COX-2 gene levels.[114] All these studies show that BBR effectively act against cervical cancer by inhibiting the growth of HPV 16 and HPV 18 oncovirus, promoting tumor apoptosis and upregulating p53 expression.

10 | SKIN CANCER

Skin, the body's external organ, has a high propensity to develop cancer due to its increased risk of exposure to various environmental carcinogens and ultraviolet radiation. Pathologically, skin cancer is classified as melanoma and nonmelanoma (squamous cell carcinoma and basal cell carcinoma). Despite affecting 2–3 million people per year globally, nonmelanoma skin cancer is easily curable and rarely results in patient death.[115] However, melanoma is a very aggressive type of skin cancer with an annual incidence and mortality rate of 20,00,000 and 55,000. Emerging evidence suggests that BBR could effectively inhibit metastatic events in melanoma cells. It reversed EMT and significantly decreased cell migration and invasion in highly metastatic B16 melanoma cells by reducing the expression of PI3K/Akt/RARα and increasing the expression of RARβ and RARγ.[116] Furthermore, BBR improved the survival of B16F-10-bearing nude mice by reducing the formation of tumor nodules and suppressing these cells' metastasis to the lungs by downregulating various signaling molecules, including CREB, ATF-2 ERK1/2, and NF-κB. In vitro, BBR dose-dependently suppressed the migration and invasion of B16F-10 cells.[117] Also, BBR attenuated melanogenesis in these cells by augmenting the phosphorylation of PI3K/Akt, ERK, and GSK-3β.[118] More importantly, BBR increased the therapeutic effects of doxorubicin in B16F-10 cells and suppressed tumor growth in vitro by reducing Kip1/p27 levels, triggering apoptosis, inducing G2/M arrest, and downregulating Akt phosphorylation. In vivo, synergistic administration of BBR and doxorubicin to murine B16F-10 cells significantly reduced the tumor volume and tumor weight.[119] In highly metastatic A375.S2 human melanoma cells, BBR inhibited migration and invasion by suppressing the expression of MMP-1 and MMP-13 through the downregulation of metastasis-associated proteins, including ROCK1, RhoA, uPA, FAK, and NF-κB. Also interestingly, BBR significantly attenuated the mobility of vemurafenib-resistant A375.S2 cells (A375.S2/PLX cells), thereby suggesting that it could act as a potent chemosensitizer.[120] Torky et al. developed a novel topical BBR formulation with improved skin penetrating characteristics by complexing BBR with sodium oleate via hydrophobic ion pairing to form BBR-oleate complex (BBR-OL) of nanometric particle size. Fascinatingly, BBR-OL exerted slow and sustained release than free BBR in vitro. Likewise, in an ex-vivo permeation study using rat skin, the BBR-OL complex exhibited superior skin penetration and deposition.[121] This evidence suggests that BBR could be a promising drug to treat melanomas.

11 | OVARIAN CANCER

Ovarian cancer is the most dreadful gynecological cancer, with a 5-year survival rate below 50%. More than 80% of ovarian cancers are diagnosed only after the metastasis of cancer cells to the abdominopelvic cavity and other distal organs. Cisplatin is the first-line drug used in the treatment of ovarian cancer. However, its clinical efficacy is highly limited due to chemoresistance.[122] Accumulating evidence shows that BBR could augment the response of ovarian cancer cells to cisplatin therapy via various mechanisms. In SKOV-3 human epithelial ovarian cancer cells, BBR improved the cytotoxic effects of cisplatin by suppressing the expression of miR-21 and stimulating the expression of PDCD4, a potent tumor suppressor.[123]

Furthermore, treatment of SKOV-3 cells with BBR alone inhibited cell growth by (i) retarding cell proliferation, (ii) inducing

TABLE 1 Mechanisms underlying pro-apoptotic effects of berberine

Cancer type	Study		Apoptotic mechanism	References
	In vitro	In vivo		
Breast	BT459, MDA-MB-231		BBR triggers caspase-9/cytochrome C mediated apoptosis by inducing double-strand breaks and thereby releasing cytochrome C.	[4]
	MCF-7, MDA-MB-231		BBR Activates mitochondria-dependent apoptotic pathway by augmenting the generation of reactive oxygen species (ROS).	[5]
	T47D		BBR-induced apoptosis by reducing the levels of Cyclooxygenase-2 (COX-2) and surviving.	[7]
	Drug-resistant MCF-7 cells	Mice xenografted with drug-resistant MCF-7 cells	BBR at higher concentrations unaided by doxorubicin induces apoptosis by suppressing AMPK/HIF-1α pathway and thus activating p53.	[20]
	Multidrug-resistant MCF-7/MDR human breast cancer cells.	Mice xenografted with multidrug-resistant MCF-7/MDR human breast cancer cells	BBR dose-dependently increased the sensitivity of these cells to doxorubicin therapy and induced cell apoptosis by downregulating AMPK signaling pathway.	[21]
	MCF-7 cells and rat cardiomyocytes	Male Sprague Dawley rats	BBR effectively inhibited the apoptosis of cardiomyocytes and improved the survival in rats challenged with doxorubicin by protecting mitochondria and inhibiting the rise in AMP/ATP ratio, AMPKα phosphorylation, and Bcl-2 expression.	[23]
	Tamoxifen-sensitive and tamoxifen-resistant MCF-7 cells		BBR enhanced the growth inhibitory potential of tamoxifen by triggering apoptosis and G1 phase cell cycle arrest.	[24]
	MCF-7 cells		BBR chemo-sensitized the cisplatin therapy by inducing DNA breaks apoptosis.	[25]
	Lapatinib-resistant BT-474^{LapR} cells		Combinational therapy with lapatinib and BBR treatment induced apoptosis by suppressing c-Myc, upregulating ROS, and reversing lapatinib resistance.	[26]
	TRAIL-resistant MDA-MB-468 TNBC cells		BBR co-treatment improves their response to TRAIL therapy by stimulating apoptosis by downregulating p38 MAPK pathway.	[28, 29]
Lung	H1299, PC9, H1650 and A549		BBR retarded cell growth, induced replicative quiescence, and promoted apoptosis by upregulating p38α MAPK pathway and augmenting the synthesis of p53 and FOXO3. FOXO3 in turn elevated the levels of p21, a	[32]

(Continues)

TABLE 1 (Continued)

Cancer type	Study		Apoptotic mechanism	References
	In vitro	In vivo		
			master effector of multiple tumor suppressor pathways.	
	A549 cells		BBR hydrochloride suppressed proliferation and triggered apoptosis by attenuating Jak2/VEGF/NF-κB/AP-1 signaling pathways.	[33]
			BBR induced photo-toxicity in by augmenting ROS production and mitochondrial permeabilization and activating caspase-9/caspase-3 complex.	[34]
	PG human pulmonary giant cell		BBR attenuated cyclin D1 expression inhibited their proliferation by downregulating AP-1 pathway and decreasing the interactions between transcription factors and CCND1 AP-1 motif.	[35]
	MPM cell line		BBR exerted its antitumour potential by (i) suppressing cell proliferation time and dose-dependently, (ii) promoting caspase-9 mediated apoptosis, and (iii) inducing protective autophagy by increasing the accrual of LC3-II (autophagy marker) and reducing the expression of p62 (autophagy marker).	[36]
	p53-positive (A549 cells) and p53-deficient (H1299) cells	tumor xenograft of these cells in athymic nude mice	BBR triggered apoptosis of both H1299 and A549cells by disrupting mitochondrial membrane potential, decreasing the activity of antiapoptotic proteins (Bcl-2, Bcl-xl), elevating the activity of pro-apoptotic proteins (Bax, Bak) and activating caspase-3.	[37]
		p53 proficient and p53 deficient lung tumor xenografts of mice model system	p53 actively participates in tumor growth retardation by BBR.	[38]
	A549 nonsmall cell lung cancer cells		BBR and cinnamaldehyde together triggered apoptosis, inhibited autophagy, cell proliferation, and wound healing, augmented the expression of AMPK, and reduced the expression of AQP-1.	[39]
	Gefitinib-resistant H1650 and H1975 NSCLC cell lines and BEAS-2B normal epithelial cell lines		High intracellular accumulation of BBR in NSCLC cells than in BEAS-2B cells which in turn provides direct evidence on its potential to exert cytotoxic effects selectively on cancer cells.	[40]
Colorectal	SW 620 human colonic carcinoma cells		BBR triggered the caspase-dependent apoptotic cascade and augmented cell death by upregulating JNK/p38 signaling pathways and increasing ROS generation.	[48]

TABLE 1 (Continued)

Cancer type	Study		Apoptotic mechanism	References
	In vitro	In vivo		
	SW480 human colon cancer cells		BBR exerted its antitumor potential by (i) inducing G2/M phase arrest via p21 overexpression, (ii) promoting apoptosis by activating mitochondrial apoptotic events, and (iii) inhibiting neovascularization by modulating the expression of TRAIL, VEGF, and surviving.	[49]
	HCT 116 human CRC cells		BBR reduced cell viability and induced apoptosis by suppressing the expression of microRNA-21, an oncogenic microRNA, and augmenting the expression of ITGβ and PDCD4.	[50]
		Mice models	BBR could significantly decrease tumor size by attenuating the expression of Ki-67, COX-2, inhibiting the phosphorylation of mTOR and p65, and promoting caspase-3 cleavage.	[52]
	HCT116, SW680, and LOVO colon cancer cell lines		BBR could suppress proliferation and trigger apoptosis of these cells via AMPK-dependent downregulation of mTOR activity and AMPK-independent downregulation of NF-κB.	[53,54]
	IMCE cells carrying Apc^{min} mutation and normal YAMC cells	Azoxymethane-induced rat colon tumor model and 1,2-dimethyl hydrazine induced rat colon tumor model	BBR selectively induced caspase-independent apoptosis by activating apoptosis-inducing factor (AIF) via consecutively augmented production of ROS, secretion of cathepsin B, and upregulation of PARP action.	[56]
	HCT116 and DLD-1 colon cancer cells		BBR triggered apoptosis by inducing autophagy through (i) augmenting ATF6 (Activating Transcription Factor 6) mediated upregulation of GRP78 (Glucose regulated protein 78) and (ii) Attenuating GRP78 degradation and (iii) increased formation of autophagosome via augmented interaction between GRP78 and VPS34.	[56]
Prostate	DU 145 and PC-3 (androgen-insensitive), LNCaP (androgen-sensitive) prostate cancer cells, and PWR-1E (nontumorigenic human prostate epithelial cells)		BBR dose and time-dependently inhibited the proliferation and triggered the apoptosis of DU 145, PC-3, and LNCaP cells by arresting cells at G1 phase and activating caspase-dependent apoptotic pathway, respectively, without affecting the viability of PWR-1E cells.	[70]

(Continues)

TABLE 1 (Continued)

Cancer type	Study		Apoptotic mechanism	References
	In vitro	In vivo		
	LNCaP cells, PWR-1E cells	LNCaP-bearing nude mice and PC3 cells-bearing nude mice	BBR selectively repress prostate tumor progression by inducing G_0/G_1 phase arrest and triggering apoptosis in p53 dependent manner.	[70]
	LNCaP and PC-3 cells		BBR suppressed the proliferation of LNCaP and PC-3 cells by promoting apoptosis and/or cell cycle both time and dose-dependently by attenuating EGFR signaling pathway.	[71]
	PC-3 cells		BBR-induced dose-dependent apoptosis by augmenting ROS generation as well.	[73]
	prostate cancer cells	Male BALB/c-nude mice	BBR could effectively repress the growth of xenograft tumors in nude mice by decreasing the expression of prostate serum antigen, androgen receptor, COX-2, and Bcl-2 and increasing caspase-3 expression.	[75]
	Nude mice bearing LNCaP xenografts		BBR could also attenuate AR (androgen receptor) expression and suppress tumor growth.	[76]
	PC3 prostate cancer cell		BBR could radio-sensitize by activating ROS and MAPK/caspase-3 and downregulating radio-resistant proteins including HO-1, ERK, Bcl-2, and NF-κB, and which are expressed postradiation therapy.	[78]
Pancreatic	PANC-1 and MIA-PaCa2		BBR dose-dependently induced cell cycle arrest at G1 phase and augmented apoptosis by increasing the production of ROS.	[81]
	PDAC cells		BBR down-regulate mTORC1 and ERK mitogenic signaling in AMPK-dependent manner at lower concentrations and in an AMPK-independent manner at higher concentrations.	[83]
Sarcoma	MG-63 osteosarcoma cells		BBR induces cell cycle arrest at G1 and G2/M phase, and triggers apoptosis via p-53-dependent activation of p21 and pro-apoptotic genes.	[88]
	Saos-2 and MG-63 osteosarcoma cell lines		BBR inhibits the growth by downregulating caspase-1/IL-1β inflammatory signaling axis.	[89]
Glioblastoma	T98G human glioblastoma cells		BBR induced cell death by increasing Bax/Bcl-2 ratio, disrupting mitochondrial membrane potential, and upregulating the expression of proteins involved in caspase-dependent apoptotic pathways including procaspase-9, caspase-9, caspase-3, and PARP.	[95]

TABLE 1 (Continued)

Cancer type	Study		Apoptotic mechanism	References
	In vitro	In vivo		
	C6 rat glioma cells		BBR activates apoptotic pathway in these cells in many ways including (i) induction of stress in endoplasmic reticulum (ER) via generation of ROS (ii) elevation in the levels of intracellular Ca^{2+} and (iii) mitochondrial dysfunction.	[96]
	U87, U251 and U118 glioblastoma cells	Murine U87 xenografts	BBR inhibited the growth by promoting cellular senescence through the attenuation of EGFR/RAF/MEK/ERK signaling pathways.	[97]
Gastric	BGC-823/DDP and SGC-7901/DDP cisplatin-resistant gastric cancer cells		BBR induce apoptosis by elevating the expression of microRNA-203 and subsequently repressing the expression of bcl-w, the antiapoptotic protein.	[103]
	SNU-5 human gastric cancer cell lines		BBR induced cytotoxicity by promoting cell cycle arrest at G2/M phase and triggering apoptosis via upregulation of p53 expression, decrease of mitochondrial membrane potential, release of cytochrome C, and activation of caspase-3.	[105]
	SGC-7901 gastric cancer cells		BBR inhibited cell proliferation by arresting them at G1 phase, promoting apoptosis, and also establishing cross-talk between the genes and microRNAs.	[107]
	MGC 803 human gastric carcinoma cell line		BBR dose-dependently inhibited cell proliferation and tumorigenesis by decreasing the secretion of IL-8 via inactivation of p38 MAPK, ERK1/2, and c-Jun-N-terminal kinase.	[108]
Cervical	SiHa cell lines and HeLa cell lines		BBR acts on these cells by (i) selectively inhibiting constitutively expressed AP-1 in dose and time-dependent manner and (ii) downregulating the expression of HPV oncoproteins E6 and E7.	[111]
	Hela cells		BBR triggers apoptosis by activating (i) intrinsic mitochondrial pathway, (ii) extrinsic death receptor pathway via activation of Fas, FasL, and TNF-α and TRAF-1, (iii) p53 expression, and (iv) MAPK pathways. BBR modulate HPV-18 E6-E7 viral oncoproteins, disruption of microtubule network, and augmented p53 expression.	[111]

(Continues)

TABLE 1 (Continued)

Cancer type	Study		Apoptotic mechanism	References
	In vitro	In vivo		
	HeLa229 human cervical carcinoma cells		BBR inhibits cell proliferation and promotes apoptosis by upregulating p53 and downregulating Bcl-2 and Cox-2 gene levels.	[114]
	CaSki cervical cancer cells		BBR triggers apoptosis time and dose-dependently by (i) increasing the ratio of p53 and Bax/Bcl-2 proteins, (ii) generating ROS and subsequently promoting ER stress and Ca^{2+} release, (iii) disrupting mitochondrial membrane potential, (iv) increasing the expression of GADD153, and (v) promoting caspase-3 activity.	[113]
Skin	B16F10 cells	Murine B16F10 cells	BBR increased the therapeutic effects of doxorubicin and suppressed tumor growth in vitro by reducing Kip1/p27 levels, triggering apoptosis, inducing G2/M arrest, and downregulating Akt phosphorylation.	[119]
Ovarian	SKOV-3 human epithelial ovarian cancer cells		BBR inhibited cell growth by (i) retarding cell proliferation, (ii) inducing apoptosis through the upregulation of BCL-2 and survivin and downregulation of BAX, and (iii) demethylating the hMLH1 promoter and promoting the gene expression of hMLH1.	[124]
	A2780/DDP cisplatin-resistant ovarian tumor cells		BBR enhanced the apoptotic potential of cisplatin by repressing miR-93 expression and its associated PTEN/Akt pathways.	[125]

TABLE 2 Antimetastatic mechanisms of berberine in various cancers

Cancer type	Study		Antimetastatic mechanism	References
	In vitro	In vivo		
Breast	MDA-MB-231		BBR abrogates TNF-α induced MMP-9 mediated cell invasion by attenuating Activator protein-1 (AP-1) DNA binding activity.	[10]
			BBR hydrochloride attenuates cell invasion by decreasing the level of IL-8 and suppressing the expression of epidermal growth factor (EGF), MMP-2, basic Fibroblast Growth Factor, E-cadherin, and fibronectin. Furthermore, BBR hydrochloride arrests these cells at G2/M phase of cell cycle and induces programmed death by activating p38 MAPK and JNK pathways and deactivating deactivating JAK-2/PI3K/NF-κB/AP-1 pathways.	[15]
	Mice xenografted with MDA-MB-231 cells		BBR led to significant reduction in tumor growth and its metastasis to lungs.	[11]
	HCC1806 TNBC cells		BBR downregulated TGF-β1/SMAD3 signaling events and cell motility by decreasing the expression of MMP-2.	[11]
	MCF-7 cells		BBR exerts its antimetastatic potential by decreasing MMP-1 and MMP-9 levels via suppression of Tumor promoter (TPA)-induced PKC-α phosphorylation.	[12]
			BBR inhibits tumor neovascularization in these cells by inhibiting TPA-induced vascular endothelial growth factor (VEGF) and fibronectin as well as VEGF-induced fibronectin through the attenuation of PI3K/Akt pathway.	[12]
			BBR attenuates TPA-induced degradation of p53 and reduces the gene expression of chemokine receptors including CCR6, CCR9, CXCR 1, and CXCR 4.	[14]
	MCF-7 and Hs578T TNBC cells		BBR significantly inhibits cell invasion and growth by decreasing IL-8 levels.	[16]
	MDA-MB-231 cells and MCF-7 cells	MDA-MB-231 nude mouse xenografts	BBR could bind to VASP (Vasodilator-stimulated phosphoprotein) and inhibit cell migration.	[17]
	ZR-75-30 breast tumor cells		BBR efficiently inhibits the proliferation and migration by attenuating ephrin B2 levels.	[18]
Lung	A549 cells		BBR exerted its antimetastatic potential by decreasing the levels of ECM proteinases including MMP-2 and urokinase-plasminogen activator (u-PA) through the regulation of Tissue inhibitor of metalloproteinase-2 and urokinase-plasminogen activator inhibitor.	[45]
	A549 cells	Murine A549 xenografts	BBR attenuated the metastasis by suppressing TGF-β1-induced EMT.	[46]
		C57BL/6CrAlc mice whose lung parenchyma were orthotopically implanted with Lewis Lung carcinoma cells	BBR treatment dose-dependently inhibited the tumor metastasis to medisatinal lymph nodes. BBR also repressed the invasion of LLC cells by upregulating the levels of Anti-activator protein-1 (anti-AP-1) and downregulating the expression of u-PA.	[47]

(Continues)

TABLE 2 (Continued)

Cancer type	Study		Antimetastatic mechanism	References
	In vitro	In vivo		
Colorectal	SW480 and HCT 116 cells		BBR attenuated migration and impeded their metastatic potential by activating AMPK and subsequently downregulating integrin β1 signaling pathway.	[65]
	CRC cells		BBR suppressed the invasion and metastasis by attenuating COX-2/PGE2-induced JAK2/STAT3 pathway.	[66]
	SW480 and normal HCoEpiCs		BBR could also disrupt the interaction between colon cancer cells and adjacent normal colon epithelial cells.	[67]
			BBR reversed the SW480-induced EMT-like transition and also inhibited the migration of HCoEpiCs by upregulating the expression of TGF-βII, Smad2, and p-Smad3.	[67]
Prostate	LNCaP and PC-3 cells		BBR attenuated the migration, invasion, and EMT in these highly metastatic cells by suppressing EMT-related genes including NODAL, bone morphogenetic protein 7, and Snail.	[72]
	LNCaP and DU-145 cells		BBR enabled the cells to overcome hypoxia-induced radio-resistance and improved their sensitivity to ionizing radiation under hypoxic conditions by repressing HIF-1α and VEGF expression.	[79]
Pancreatic	MIA PaCa2 cells		BBR retards the growth and metastasis by arresting them at G1 phase, promoting senescence, autophagy, increasing caspase-3 activity, and impairing migration and invasion.	[85]
Glioblastoma	U251 and U87 cells		BBR retarded the tumor growth and metastasis by suppressing their metabolism and thereby decreasing glycolytic capacity, altering mitochondrial dynamics, and increasing autophagy flux.	[98]
Gastric	SNU-5 human gastric cancer cell lines		BBR also promoted ROS generation in SNU-5 cells and impeded their migration by reducing the expression level of MMP-1, -2, and -9.	[106]
Cervical	SiHa cells	SiHa cells to lungs in xenograft mice models	BBR reversed TGF-1β mediated EMT by increasing the levels of epithelial markers including E-cadherin and decreasing the expression of mesenchymal markers including N-cadherin and Snail-1.	[111]
Skin	B16 melanoma cells		BBR reversed EMT and significantly decreased cell migration and invasion in highly metastatic B16 melanoma cells by decreasing the expression of PI3K/AKT/RARα and increasing the expression of RARβ and RARγ.	[116]
	B16F-10 cells	B16F-10 bearing nude mice	BBR improved the survival by reducing the formation of tumor nodules and also suppressed the metastasis of these cells to lungs by downregulating various signaling molecules including CREB, ATF-2, ERK1/2, and NF-κB.	[117]
	A375.S2 human melanoma cells		BBR inhibited migration and invasion by suppressing the expression of MMP-1 and MMP-13 through the downregulation of metastasis-associated proteins including ROCK1, RhoA, uPA, FAK, and NF-κB.	[120]

apoptosis through the upregulation of Bcl-2 and survivin and downregulation of BAX, and (iii) demethylating the hMLH1 promoter and promoting the gene expression of hMLH1.[124] In A2780/DDP cisplatin-resistant ovarian tumor cells, BBR enhanced the apoptotic potential of cisplatin by repressing miR-93 expression (an important miRNA involved in the development of cisplatin resistance in ovarian carcinoma cells) and its associated PTEN/Akt pathways.[125] Furthermore, BBR also improved the response of ovarian cancer cells to niraparib, a PARP inhibitor, by inducing oxidative DNA damage and attenuating homologous recombination repair.[126] Apart from sensitizing ovarian tumors to chemotherapy, BBR could even prevent the recurrence of ovarian cancer by suppressing chemotherapy-induced repopulation of tumor cells. Zhao et al. cocultured the surviving ovarian cancer cells in the microenvironment of VP16 drug-treated dying cells by using a transwell system. Interestingly, BBR treatment inhibited the VP16-induced AA pathway and FAK phosphorylation by downregulating the caspase-3/iPLA$_2$/AA/COX-2/PGE$_2$ pathway, suppressing the repopulation of ovarian cancer cells.[127] Mechanisms underlying pro-apoptotic and antimetastatic mechanisms of BBR in various cancers are given in Tables 1 and 2, respectively.

12 | OTHER CANCERS

Apart from acting against the cancers above, BBR could also effectively inhibit the growth of other major types of cancer, including leukemia, hepatocellular carcinoma, oral cancer retinoblastoma, esophageal cancer, and endometrial cancer. In promyelocytic leukemia cells, BBR inhibits tumor growth by inducing mitochondria-dependent apoptosis, ROS-dependent apoptosis, cell cycle arrest, and inhibiting the activity of NAT.[128] In lymphocytic, lymphoblastic, myelomonocytic, and acute myeloid leukemia cells, BBR exerts its chemotherapeutic potential majorly by activating programmed cell death.[129–132] Likewise, BBR employs apoptosis as an essential tool to impede the growth of various oral cancer cells.[133] BBR suppresses the metastatic events in retinoblastoma cells, including cell invasion and migration, by downregulating p38 and PI3K/Akt signaling pathways.[134] Similarly, treatment of endometrial cancer cells, AN3 CA, and HEC-1-A with BBR significantly reduced tumor growth and suppressed their invasive and migratory potential by regulating the miR-101/COX-2 axis.[135] Also, in the tail vein injection-induced lung metastasis model, BBR treatment dramatically decreased the tumor nodule formation in the lungs without exerting any toxicity in the lungs.

13 | CONCLUSIONS AND FUTURE PERSPECTIVES

Chemotherapy and radiotherapy are conventionally used to treat cancer patients. However, an alarming rise in cancer-related mortalities in recent years despite these therapies strongly suggests a need for the development of adjunct/alternative medicines to treat this dreadful disease. The significant factors that limit the therapeutic outcome of conventional chemo/radiotherapies in cancer patients are the development of therapy resistance, harmful side effects including cardiotoxicity, nephrotoxicity, and so forth, and cancer relapse after therapy. Furthermore, conventional cancer therapies, including targeted therapies, do not deal with the life-threatening events of cancer, including EMT, tumor neovascularization, tumor hypoxia, and so forth. Hence, alternative/adjunct drugs to be developed for treating cancer should possess the potential to overcome the limitations of current therapies, including drug resistance, harmful side effects, and cancer relapse. The present review has put forth numerous pieces of evidence that strongly suggests that BBR could act as a promising alternative/adjunct medicine to treat cancer. Emerging studies show that BBR

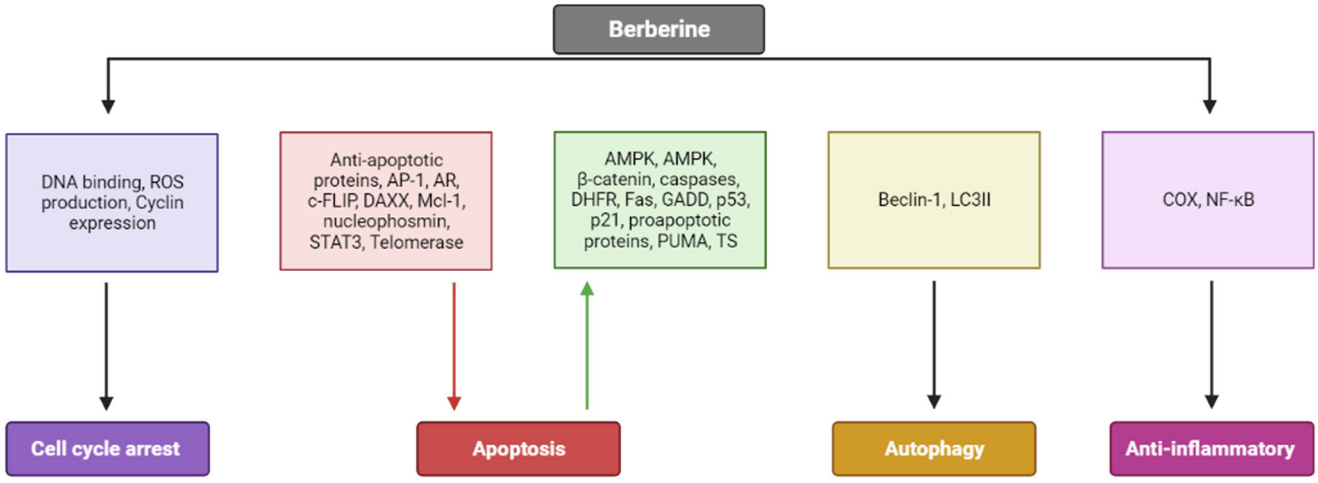

FIGURE 1 The diverse effects of BBR on cell cycle arrest, apoptosis, autophagy and anti-inflammation. This multipotent molecule can be directed to do specific function by changing the underlying pathway or target of interest. For example, the direct interaction of BBR with NF-kB initiates anti-inflammatory mechanisms in cells. BBR, berberine.

could work very effectively than conventional chemotherapeutic drugs and inhibit the growth of wide varieties of cancer cells by promoting apoptosis, inducing cell cycle arrest, triggering autophagy, and augmenting replicative senescence through the modulation of diverse signaling pathways (Figure 1). Moreover, BBR acts very effectively against metastatic cancers and circumvents the important events preceding metastasis, including EMT, tumor angiogenesis, and tumor hypoxia. Significantly, BBR has improved the response of various cancer cells to conventionally used chemotherapeutic drugs, including doxorubicin, tamoxifen, cisplatin, sunitinib, irinotecan, temozolomide, and so forth, and also radiotherapy.

Furthermore, BBR, a very safe drug which causes no serious side effects even during prolonged use and acts selectively on tumor cells without harming the normal cells. On top of exerting these chemoprotective effects, BBR could also circumvent the harmful side effects caused by cytotoxic therapies. Taken together, from the present review, it is evident that BBR possesses enormous potential to (i) promote apoptosis, autophagy, and replicative senescence, (ii) inhibit EMT, tumor angiogenesis, tumor hypoxia, (iii) sensitize

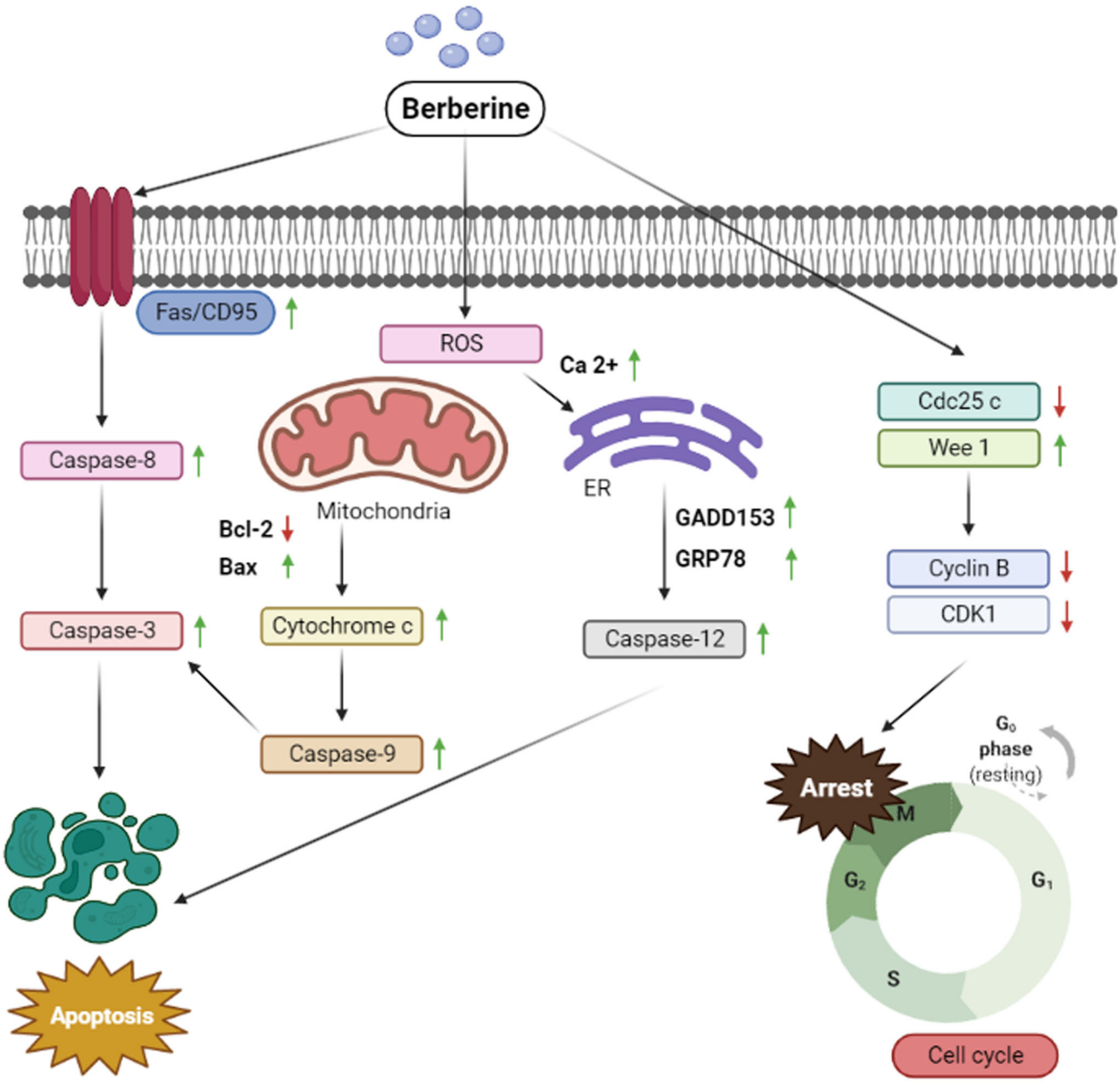

FIGURE 2 BBR induced programmed cell death and cell cycle arrest in cells through Fas/CD95 receptor. Treatment of BBR resulted in notable DNA damage via ROS production, ER stress, and release of Ca^{2+}. The impairment of mitochondria caused by the imbalance between Bax/Bcl-2 also induced the release of cytochrome c followed by activation of caspase-9 and -3 and finally apoptosis. BBR, berberine; ER, endoplasmic reticulum; ROS, reactive oxygen species.

drug-resistant cancer cells to conventional therapies, (iv) act very effectively than conventional therapies, (iv) protect the body from harmful side effects of conventional therapies, and (v) act selectively on tumor cells without harming the normal cells. All these chemotherapeutic properties of BBR show that this Chinese herbal medicine could be considered an essential, safe, and pharmacologically active alternative/adjunct drug to treat cancer.

Nevertheless, the poor oral bioavailability and poor aqueous solubility of BBR, along with its low intestinal absorption and rapid intestinal and hepatic efflux, essentially hampers its development into pharmaceuticals to treat cancer patients. Fortunately, emerging research has shown that these limitations could be effectively overcome by developing oral delivery systems of BBR, including solid lipid nanoparticles, nanostructured lipid carriers, liposomes, gold nanoparticles, silver nanoparticles, self-nano emulsifying system, and so forth. Hence, more research on the design and development of potent BBR drug delivery systems is needed to improve its oral bioavailability, prolonged existence, and sustained release from the intestine and liver. Another major limitation behind the clinical application of BBR is the lack of clinical trials to validate the results of extensively done in vitro and in vivo studies. More clinical trials on the chemotherapeutic and chemosensitizing potential of novel BBR formulations in wide varieties of cancer patients will continue in deed open new avenues to transform BBR from bench-side research to bedside treatments.

Furthermore, very little research has been done to date to assess the potential of BBR to combat cancer relapse and the growth of cancer stem cells. Cancer stem cells, the small subpopulation of cells in tumor with self-renewal, self-differentiation, and tumorigenic properties, play a crucial role in cancer recurrence and metastasis. Moreover, they are highly resistant to chemo- and radiation-therapies. Hence, cancer stem cells are considered a high-interest target to improve cancer patients' survival and quality of life. Therefore, detailed investigations on the inhibitory effects of BBR against the growth of cancer stem cells and cancer relapse are very much needed to prove the applications of BBR as a therapeutic agent.

In conclusion, the strong, versatile, and diverse potential of BBR to impede the hallmark events of cancer, overcome therapy resistance, and minimize their harmful side effects are well documented. Hence, BBR holds more potential to clinically emerge as a promising anti-neoplastic drug to treat various cancers. However, (i) development of oral delivery systems of BBR with improved bioavailability and sustained release, (ii) clinical evaluation of the chemotherapeutic and chemosensitizing potential of BBR in wide varieties of cancer patients, and (iii) in-depth research on its potential to prevent cancer relapse and combat the growth of cancer stem cells is highly needed to affirm its practical application in clinical practice to treat cancer.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

DATA AVAILABILITY STATEMENT

Data sharing is not applicable as no new data is generated, or the article describes entirely theoretical research.

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REFERENCES

[1] WHO Cancer Fact Sheet; **2020**. https://www.who.int/news-room/fact-sheets/detail/cancer (accessed: February 2022).
[2] M. M. Rivera-franco, E. Leon-rodriguez, *Breast Cancer: Basic Clin. Res.* **2018**, 12.
[3] A. M. Gonzalez-Angulo, F. Morales-Vasquez, G. N. Hortobagyi, *Adv. Exp. Med. Biol.* **2007**, *608*, 1.
[4] Y. Zhao, Z. Jing, J. Lv, Z. Zhang, J. Lin, X. Cao, Z. Zhao, P. Liu, W. Mao, *Biomed. Pharmacother.* **2017**, *95*, 18.
[5] J. Xie, Y. Xu, X. Huang, Y. Chen, J. Fu, M. Xi, L. Wang, *Tumor Biol.* **2015**, *36*, 1279.
[6] J. B. Patil, J. Kim, G. K. Jayaprakasha, *Eur. J. Pharmacol.* **2010**, *645*, 70.
[7] Y. Pazhang, S. Ahmadian, N. Javadifar, M. Shafiezadeh, *Tumor Biol.* **2012**, *33*, 207.
[8] H. P. Kuo, T. C. Chuang, M. H. Yeh, S. C. Hsu, T. D. Way, P. Y. Chen, S. S. Wang, Y. H. Chang, M. C. Kao, J. Y. Liu, *J. Agric. Food Chem.* **2011**, *59*, 8216.
[9] K. C. Karnam, M. Ellutla, L. N. Bodduluru, E. R. Kasala, S. K. Uppulapu, M. Kalyankumarraju, M. Lahkar, *Biomed. Pharmacother.* **2017**, *92*, 207.
[10] S. Kim, J. H. Choi, J. B. Kim, S. J. Nam, J. H. Yang, J. H. Kim, J. E. Lee, *Molecules* **2008**, *13*, 2975.
[11] S. Kim, J. Lee, D. You, Y. Jeong, M. Jeon, J. Yu, S. W. Kim, S. J. Nam, J. E. Lee, *Cell. Physiol. Biochem.* **2018**, *45*, 795.
[12] S. Kim, S. J. Oh, J. Lee, J. Han, M. Jeon, T. Jung, S. K. Lee, S. Y. Bae, J. Kim, W. H. Gil, S. W. Kim, J. E. Lee, S. J. Nam, *Cell. Physiol. Biochem.* **2013**, *32*, 1541.
[13] S. Kim, J. Han, N. Y. Kim, S. K. Lee, D. H. Cho, M. Y. Choi, J. S. Kim, J. H. Kim, J. H. Choe, S. J. Nam, *Oncol. Rep.* **2012**, *27*, 210.
[14] N. Ahmadiankia, H. K. Moghaddam, M. A. Mishan, A. R. Bahrami, H. Naderi-Meshkin, H. R. Bidkhori, M. Moghaddam, S. J. Mirfeyzi, *Iran. J. Basic Med. Sci.* **2016**, *19*, 125.
[15] X. Li, S. J. Zhao, H. L. Shi, S. P. Qiu, J. Q. Xie, H. Wu, B. B. Zhang, Z. T. Wang, J. Y. Yuan, X. J. Wu, *Oncol. Rep.* **2014**, *32*, 2777.
[16] S. Kim, D. You, Y. Jeong, J. Yu, S. W. Kim, S. J. Nam, J. E. Lee, *Phytomedicine* **2018**, *50*, 43.
[17] K. Su, P. Hu, X. Wang, C. Kuang, Q. Xiang, F. Yang, J. Xiang, S. Zhu, L. Wei, J. Zhang, *Oncotarget* **2016**, *7*, 45849.
[18] W. Ma, M. Zhu, D. Zhang, L. Yang, T. Yang, X. Li, Y. Zhang, *Phytomedicine* **2017**, *25*, 45.
[19] J. Wang, Q. Liu, Q. Yang, *Int. J. Mol. Med.* **2012**, *30*, 1166.
[20] Y. Pan, D. Shao, Y. Zhao, F. Zhang, X. Zheng, Y. Tan, K. He, J. Li, L. Chen, *Int. J. Biol. Sci.* **2017**, *13*, 794.
[21] Y. Pan, F. Zhang, Y. Zhao, D. Shao, X. Zheng, Y. Chen, K. He, J. Li, L. Chen, *J. Cancer* **2017**, *8*, 1679.
[22] Y. B. Li, W. L. Zhao, Y. X. Wang, C. X. Zhang, J. D. Jiang, C. W. Bi, S. Tang, R. X. Chen, R. G. Shao, D. Q. Song, *Eur. J. Med. Chem.* **2013**, *68*, 463.
[23] X. Lv, X. Yu, Y. Wang, F. Wang, H. Li, Y. Wang, D. Lu, R. Qi, H. Wang, *PLoS One* **2012**, *7*(10), 1.

[24] C. Wen, L. Wu, L. Fu, X. Zhang, H. Zhou, *Mol. Med. Rep.* **2016**, *14*, 2250.
[25] Y. Zhao, Z. Jing, Y. Li, W. Mao, *Oncol. Rep.* **2016**, *36*, 567.
[26] R. Zhang, H. Qiao, S. Chen, X. Chen, K. Dou, L. Wei, J. Zhang, *Cancer Biol. Ther.* **2016**, *17*, 925.
[27] P. Jabbarzadeh Kaboli, M. P. Y. Leong, P. Ismail, K. H. Ling, *Pharmacol. Rep.* **2019**, *71*, 13.
[28] A. Refaat, S. Abdelhamed, I. Saiki, H. Sakurai, *Oncol. Lett.* **2015**, *10*, 1907.
[29] A. Refaat, S. Abdelhamed, H. Yagita, H. Inoue, S. Yokoyama, Y. Hayakawa, I. Saiki, *Oncol. Lett.* **2013**, *6*(3), 84.
[30] WHO. https://www.who.int/news-room/fact-sheets/detail/cancer (accessed: February 2022).
[31] C. Zappa, S. A. Mousa, *Transl. Lung Cancer Res.* **2016**, *5*, 288.
[32] F. Zheng, Q. Tang, J. Wu, S. Zhao, Z. Liang, L. Li, W. Wu, S. Hann, *J. Exp. Clin. Cancer Res.* **2014**, *33*, 36.
[33] J. Li, F. Liu, S. Jiang, J. Liu, X. Chen, S. Zhang, H. Zhao, *Oncol. Lett.* **2018**, *15*, 7409.
[34] R. Bhattacharyya, B. Saha, M. Tyagi, S. K. Bandyopadhyay, B. S. Patro, S. Chattopadhyay, *Free Radical Res.* **2017**, *51*, 723.
[35] Y. Luo, Y. Hao, T. Shi, W. Deng, N. Li, *Acta Pharmacol. Sin.* **2008**, *29*, 628.
[36] Z. Yao, Y. Wan, B. Li, C. Zhai, F. Yao, Y. Kang, Q. Liu, D. Lin, *Oncol. Rep.* **2018**, *40*, 3603.
[37] S. K. Katiyar, S. M. Meeran, N. Katiyar, S. Akhtar, *Mol. Carcinog.* **2009**, *48*, 24.
[38] M. A. James, H. Fu, Y. Liu, D. R. Chen, M. You, *Mol. Carcinog.* **2011**, *50*, 1.
[39] M. Meng, S. Geng, Z. Du, J. Yao, Y. Zheng, Z. Li, Z. Zhang, J. Li, Y. Duan, G. Du, *Oncotarget* **2017**, *8*, 76385.
[40] Z. W. Yuan, E. L. H. Leung, X. X. Fan, H. Zhou, W. Z. Ma, L. Liu, Y. Xie, *Talanta* **2015**, *144*, 20.
[41] F. Zheng, J. Wu, Q. Tang, Q. Xiao, W. Wu, S. S. Hann, *J. Cell. Mol. Med.* **2018**, *22*, 600.
[42] T. Zhu, L. L. Li, G. F. Xiao, Q. Z. Luo, Q. Z. Liu, K. T. Yao, G. H. Xiao, *Am. J. Chin. Med. (Gard. City. N. Y).* **2015**, *43*, 1487.
[43] P. Peng, W. H. Kuo, H. C. Tseng, F. P. Chou, *Int. J. Radiation Oncol. Biol. Phys.* **2008**, *70*, 529.
[44] Y. Liu, H. Yu, C. Zhang, Y. Cheng, L. Hu, X. Meng, Y. Zhao, *Eur. J. Cancer* **2008**, *44*, 2425.
[45] P. L. Peng, Y. S. Hsieh, C. J. Wang, J. L. Hsu, F. P. Chou, *Toxicol. Appl. Pharmacol.* **2006**, *214*, 8.
[46] H. Qi, L. Xin, X. Xu, X. Ji, L. Fan, *J. Transl. Med.* **2014**, *12*, 22.
[47] N. Mitani, K. Murakami, T. Yamaura, T. Ikeda, I. Saiki, *Cancer Lett.* **2001**, *165*, 35.
[48] W. H. Hsu, Y. S. Hsieh, H. C. Kuo, C. Y. Teng, H. I. Huang, C. J. Wang, S. F. Yang, Y. S. Liou, W. H. Kuo, *Arch. Toxicol.* **2007**, *81*, 719.
[49] K. N. Chidambara Murthy, G. K. Jayaprakasha, B. S. Patil, *Eur. J. Pharmacol.* **2012**, *688*, 14.
[50] Y. Lü, B. Han, H. Yu, Z. Cui, Z. Li, J. Wang, *Oncol. Lett.* **2018**, *15*, 5971.
[51] K. Fukuda, Y. Hibiya, M. Mutoh, M. Koshiji, S. Akao, H. Fujiwara, *J. Ethnopharmacol.* **1999**, *66*, 227.
[52] W. Li, B. Hua, S. M. Saud, H. Lin, W. Hou, M. S. Matter, L. Jia, N. H. Colburn, M. R. Young, *Mol. Carcinog.* **2015**, *54*, 1096.
[53] C. J. Thirupurasundari, R. Padmini, S. N. Devaraj, *Chem. Biol. Interact.* **2009**, *177*, 190.
[54] A. E. Ghareeb, F. Moawed, D. A. Ghareeb, E. I. Kandil, *Asian Pac. J. Cancer Prev.* **2018**, *19*, 1685.
[55] L. Wang, L. Liu, Y. Shi, H. Cao, R. Chaturvedi, M. W. Calcutt, T. Hu, X. Ren, K. T. Wilson, D. B. Polk, F. Yan, *PLoS One* **2012**, *7*, e36418.
[56] X. La, L. Zhang, Z. Li, P. Yang, Y. Wang, *Oncotarget* **2017**, *8*, 20909.
[57] C. Huang, H. Liu, X. L. Gong, L. Y. Wu, B. Wen, *Oncol. Rep.* **2017**, *37*, 1637.
[58] K. F. Albring, J. Weidemüller, S. Mittag, J. Weiske, K. Friedrich, M. C. Geroni, P. Lombardi, O. Huber, *BioFactors* **2013**, *39*, 652.
[59] H. Ruan, Y. Y. Zhan, J. Hou, B. Xu, B. Chen, Y. Tian, D. Wu, Y. Zhao, Y. Zhang, X. Chen, P. Mi, L. Zhang, S. Zhang, X. Wang, H. Cao, W. Zhang, H. Wang, H. Li, Y. Su, X. K. Zhang, T. Hu, *Oncogene* **2017**, *36*(50), 6906.
[60] K. Wu, Q. Yang, Y. Mu, L. Zhou, Y. Liu, Q. Zhou, B. He, *Int. J. Oncol.* **2012**, *41*, 292.
[61] L. Wang, H. Cao, N. Lu, L. Liu, B. Wang, T. Hu, D. A. Israel, R. M. Peek, Jr., D. B. Polk, F. Yan, *PLoS One* **2013**, *8*, e56666.
[62] D. Li, Y. Zhang, K. Liu, Y. Zhao, B. Xu, L. Xu, L. Tan, Y. Tian, C. Li, W. Zhang, H. Cao, Y.y Zhan, T. Hu, *Lab. Invest.* **2017**, *97*, 1343.
[63] L. Mao, Q. Chen, K. Gong, X. Xu, Y. Xie, W. Zhang, H. Cao, T. Hu, X. Hong, Y. Y. Zhan, *Oncol. Rep.* **2018**, *39*, 2436.
[64] J. G. Chung, G. W. Chen, C. F. Hung, J. H. Lee, C. C. Ho, H. C. Ho, H. L. Chang, W. C. Lin, J. G. Lin, *Am. J. Chin. Med. (Gard. City. N. Y).* **2000**, *28*, 227.
[65] J. J. Park, S. M. Seo, E. J. Kim, Y. J. Lee, Y. G. Ko, J. Ha, M. Lee, *Biochem. Biophys. Res. Commun.* **2012**, *426*, 461.
[66] X. Liu, Q. Ji, N. Ye, H. Sui, L. Zhou, H. Zhu, Z. Fan, J. Cai, Q. Li, *PLoS One* **2015**, *10*(5), e0123478.
[67] C. Huang, L. Tao, X. Wang, Z. Pang, *J. Cell. Physiol.* **2019**, *234*, 11679.
[68] S. W. Leslie, L. E. Siref, *Cancer, Prostate*, StatPearls Publishing, **2018**.
[69] S. K. Mantena, S. D. Sharma, S. K. Katiyar, *Mol. Cancer Ther.* **2006**, *5*, 296.
[70] M. S. Choi, *Int. J. Oncol.* **2009**, *34*, 1221.
[71] Z. H. Huang, H. F. Zheng, W. L. Wang, Y. Wang, L. F. Zhong, J. L. Wu, Q. X. Li, *Mol. Med. Rep.* **2015**, *11*, 2125.
[72] C. H. Liu, W. C. Tang, P. Sia, C. C. Huang, P. M. Yang, M. H. Wu, I. L. Lai, K. H. Lee, *Int. J. Med. Sci.* **2015**, *12*, 63.
[73] S. M. Meeran, S. Katiyar, S. K. Katiyar, *Toxicol. Appl. Pharmacol.* **2008**, *229*, 33.
[74] W. Lu, S. Du, J. Wang, *Mol. Med. Rep.* **2015**, *11*, 3920.
[75] X. Li, A. Zhang, H. Sun, Z. Liu, T. Zhang, S. Qiu, L. Liu, X. Wang, *Oncotarget* **2017**, *8*, 65022.
[76] J. Li, B. Cao, X. Liu, X. Fu, Z. Xiong, L. Chen, O. Sartor, Y. Dong, H. Zhang, *Mol. Cancer Ther.* **2011**, *10*, 1346.
[77] Y. Tian, L. Zhao, Y. Wang, H. Zhang, D. Xu, X. Zhao, Y. Li, J. Li, *Asian J. Androl.* **2016**, *18*(4), 607.
[78] J. M. Hur, D. Kim, *Toxicol. Res.* **2013**, *26*, 109.
[79] Q. Zhang, C. Zhang, X. Yang, B. Yang, J. Wang, Y. Kang, Z. Wang, D. Li, G. Huang, Z. Ma, X. Sun, J. Cai, G. Tao, S. Dai, W. Mao, J. Ma, *Diagn. Pathol.* **2014**, *27*, 9.
[80] G. Lippi, C. Mattiuzzi, *Arch. Med. Sci.* **2020**, *16*, 820.
[81] S. H. Park, J. H. Sung, E. J. Kim, N. Chung, *Braz. J. Med. Biol. Res.* **2015**, *48*, 111.
[82] S. H. Park, J. H. Sung, N. Chung, *Mol. Cell. Biochem.* **2014**, *394*, 209.
[83] M. Ming, J. Sinnett-Smith, J. Wang, H. P. Soares, S. H. Young, G. Eibl, E. Rozengurt, *PLoS One* **2014**, *9*, 1.
[84] L. Pinto-Garcia, T. Efferth, A. Torres, J. Hoheisel, M. Youns, *Planta Med.* **2010**, *76*, 1155.
[85] A. Agnarelli, M. Natali, M. Garcia-Gil, R. Pesi, M. G. Tozzi, C. Ippolito, N. Bernardini, R. Vignali, R. Batistoni, A. M. Bianucci, S. Marracci, *Sci. Rep.* **2018**, *8*, 10599.
[86] J. W. Potter, K. B. Jones, J. J. Barrott, *Crit. Rev. Oncol. Hematol.* **2018**, *126*, 1.
[87] Y. Zhu, N. Ma, H. X. Li, L. Tian, Y. F. Ba, B. Hao, *Mol. Med. Rep.* **2014**, *10*, 1734.
[88] Z. Liu, Q. Liu, B. Xu, J. Wu, C. Guo, F. Zhu, Q. Yang, G. Gao, Y. Gong, C. Shao, *Mutat. Res. Fundam. Mol. Mech. Mutagen.* **2009**, *662*, 75.
[89] J. Hao, X. Jin, B. Cao, W. Wenbo, *Oncol. Rep.* **2017**, *37*(2), 729.

[90] H. K. Hsu, K. H. Hsu, Y. M. Cheng, H. Y. Suen, S. F. Peng, *Molecules* **2018**, *23*, 3121.
[91] S. H. Eo, J. H. Kim, S. J. Kim, *Oncol. Res.* **2014**, *22*, 147.
[92] V. Pongkittiphan, W. Chavasiri, R. Supabphol, *Asian Pac. J. Cancer Prev.* **2015**, *16*, 5371.
[93] J. Yahuafai, T. Asai, N. Oku, P. Siripong, *Biol. Pharm. Bull.* **2018**, *41*(7), 1103.
[94] C. Fernandes, A. Costa, L. Osório, R. C. Lago, P. Linhares, B. Carvalho, C. Caeiro, *Glioblastoma [Internet]*, Codon Publications, **2017**.
[95] K. S. Eom, J. M. Hong, M. J. Youn, H. S. So, R. Park, J. M. Kim, T. Y. Kim, *Biol. Pharm. Bull.* **2008**, *31*, 558.
[96] T. C. Chen, K. C. Lai, J. S. Yang, C. L. Liao, T. C. Hsia, G. W. Chen, J. J. Lin, H. J. Lin, T. H. Chiu, Y. J. Tang, J. G. Chung, *Int. J. Oncol.* **2009**, *34*, 1681.
[97] Q. Liu, X. Xu, M. Zhao, Z. Wei, X. Li, X. Zhang, Z. Liu, Y. Gong, C. Shao, *Mol. Cancer Ther.* **2015**, *14*, 355.
[98] J. Wang, Q. Qi, Z. Feng, X. Zhang, B. Huang, A. Chen, L. Prestegarden, X. Li, J. Wang, *Oncotarget* **2016**, *7*, 66944.
[99] Y. Sun, J. Yu, X. Liu, C. Zhang, J. Cao, G. Li, X. Liu, Y. Chen, H. Huang, *Biomed. Pharmacother.* **2018**, *102*, 699.
[100] A. D. Wagner, N. L. Syn, M. Moehler, W. Grothe, W. P. Yong, B. C. Tai, J. Ho, S. Unverzagt, *Cochrane Database Syst. Rev.* **2017**, *8*(8), CD004064.
[101] A. Pandey, K. Vishnoi, S. Mahata, S. C. Tripathi, S. P. Misra, V. Misra, R. Mehrotra, M. Dwivedi, A. C. Bharti, *Nutr. Cancer* **2015**, *67*(8), 1295.
[102] H. L. Shi, X. J. Wu, Y. Liu, J. Q. Xie, *Life Sci.* **2013**, *93*, 830.
[103] H. Y. You, X. M. Xie, W. J. Zhang, H. L. Zhu, F. Z. Jiang, *In Vitro Cell. Dev. Biol. Anim.* **2016**, *52*(8), 857.
[104] J. Wang, S. Yang, X. Cai, J. Dong, Z. Chen, R. Wang, S. Zhang, H. Cao, D. Lu, T. Jin, Y. Nie, J. Hao, D. Fan, *Oncotarget* **2016**, *7*, 76076.
[105] J. P. Lin, J. S. Yang, J. H. Lee, W. T. Hsieh, J. G. Chung, *World J. Gastroenterol.* **2006**, *12*, 21.
[106] J. P. Lin, J. S. Yang, C. C. Wu, S. S. Lin, W. T. Hsieh, M. L. Lin, F. S. Yu, C. S. Yu, G. W. Chen, Y. H. Chang, J. G. Chung, *In Vivo* **2008**, *22*, 223.
[107] Y. Yang, N. Zhang, K. Li, J. Chen, L. Qiu, J. Zhang, *Drug Des. Devel. Ther.* **2018**, *12*, 393.
[108] H. L. Li, H. Wu, B. B. Zhang, H. L. Shi, X. J. Wu, *Mol. Med. Rep.* **2016**, *14*, 1430.
[109] WHO. https://www.who.int/news-room/fact-sheets/detail/cervical-cancer (accessed: February 2022).
[110] R. Faridi, A. Zahra, K. Khan, M. Idrees, *Virol. J.* **2011**, *8*, 269.
[111] B. Lu, M. Hu, K. Liu, J. Peng, *Toxicol. In Vitro* **2010**, *24*(6), 1482.
[112] S. C. Chu, C. C. Yu, L. S. Hsu, K. S. Chen, M. Y. Su, P. N. Chen, *Mol. Pharmacol.* **2014**, *86*, 609.
[113] J. P. Lin, J. S. Yang, N. W. Chang, T. H. Chiu, C. C. Su, K. W. Lu, Y. T. Ho, C. C. Yeh, M. D. Mei-dueyang, H. J. Lin, J. G. Chung, *Anticancer Res.* **2007**, *27*, 3379.
[114] H. Y. Wang, H. Z. Yu, S. M. Huang, Y. L. Zheng, *Mol. Med. Rep.* **2016**, *14*, 3855.
[115] A. Fahradyan, A. Howell, E. Wolfswinkel, M. Tsuha, P. Sheth, A. Wong, *Healthcare* **2017**, *5*, 82.
[116] Y. Kou, L. Li, H. Li, Y. Tan, B. Li, K. Wang, B. Du, *Biochem. Biophys. Res. Commun.* **2016**, *479*(2), 290.
[117] T. P. Hamsa, G. Kuttan, *Phytother. Res.* **2012**, *26*, 568.
[118] Y. C. Song, Y. Lee, H. M. Kim, M. Y. Hyun, Y. Y. Lim, K. Y. Song, B. J. Kim, *Int. J. Mol. Med.* **2015**, *35*, 1011.
[119] A. Mittal, S. Tabasum, R. P. Singh, *Phytomedicine* **2014**, *21*, 340.
[120] J. F. Liu, K. Lai, S. F. Peng, P. Maraming, Y. P. Huang, A. C. Huang, F. S. Chueh, W. W. Huang, J. G. Chung, *Molecules* **2018**, *23*, 2019.
[121] A. S. Torky, M. S. Freag, M. M. A. Nasra, O. Y. Abdallah, *Int. J. Pharm.* **2018**, *549*, 76.
[122] S. Kim, Y. Han, S. I. Kim, H. S. Kim, S. J. Kim, Y. S. Song, *NPJ Precis. Oncol.* **2018**, *2*, 20.
[123] S. Liu, Y. Fang, H. Shen, W. Xu, H. Li, *Acta Biochim. Biophys. Sin. (Shanghai)* **2013**, *45*, 756.
[124] P. Jin, C. Zhang, N. Li, *Anti-Cancer Agents Med. Chem.* **2015**, *15*, 511.
[125] Q. Chen, R. Qin, Y. Fang, H. Li, *Cell. Physiol. Biochem.* **2015**, *36*, 956.
[126] D. Hou, G. Xu, C. Zhang, B. Li, J. Qin, X. Hao, Q. Liu, X. Zhang, J. Liu, J. Wei, Y. Gong, Z. Liu, C. Shao, *Cell Death Dis.* **2017**, *8*, e3070.
[127] Y. Zhao, L. Cui, Y. Pan, D. Shao, X. Zheng, F. Zhang, H. Zhang, K. He, L. Chen, *Cell. Prolif.* **2017**, *50*, e12393.
[128] C. C. Lin, S. T. Kao, G. W. Chen, J. G. Chung, *Anticancer Res.* **2005**, *25*, 4149.
[129] C. C. Lin, S. Y. Lin, J. G. Chung, J. P. Lin, G. W. Chen, S. T. Kao, *Anticancer Res.* **2006**, *26*, 1097.
[130] J. Liu, Z. Chen, Y. Cui, H. Wei, Z. Zhu, F. Mao, Y. Wang, Y. Liu, *Aging* **2020**, *12*, 3298.
[131] S. Ravera, F. Ghiotto, C. Tenca, E. Gugiatti, S. Santamaria, B. Ledda, A. Ibatici, G. Cutrona, A. N. Mazzarello, D. Bagnara, M. Cardillo, D. Zarcone, Z. Darzynkiewicz, E. Ciccone, F. Fais, S. Bruno, *Sci. Rep.* **2020**, *10*, 16519.
[132] J. Li, L. Yang, R. Shen, L. Gong, Z. Tian, H. Qiu, Z. Shi, L. Gao, H. Sun, G. J. Zhang, *Nanobiotechnology* **2018**, *16*, 76.
[133] C. C. Lin, J. S. Yang, J. T. Chen, S. Fan, F. S. Yu, J. L. Yang, C. C. Lu, M. C. Kao, A. C. Huang, H. F. Lu, J. G. Chung, *Anticancer Res.* **2007**, *27*, 371.
[134] Y. Wang, J. Yuan, L. Yang, P. Wang, X. Wang, Y. Wu, K. Chen, R. Ma, Y. Zhong, X. Guo, Y. Gong, M. Gui, Y. Jin, *Adv. Clin. Exp. Med.* **2018**, *27*(7), 899.
[135] Y. Wang, S. Zhang, *Biomed. Pharmacother.* **2018**, *103*, 1287.

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