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Berberine in Breast Cancer Management: Molecular Mechanisms, Therapeutic Applications, and Future Directions

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Keywords

Berberine, Breast Cancer, Triple-Negative Breast Cancer (TNBC), AMPK Pathway, PI3K/Akt/mTOR, Wnt/β-Catenin,

Abstract

Breast cancer remains one of the leading causes of cancer-related mortality among women worldwide. While conventional therapies such as surgery, chemotherapy, radiation, hormonal, targeted, and immune therapy have improved survival rates, drug resistance and recurrence remain major challenges. Berberine (BBR), a natural isoquinoline alkaloid found in various medicinal plants, has emerged as a promising candidate in integrative oncology due to its diverse pharmacological properties. This review summarizes the anticancer potential of BBR in breast cancer, particularly its ability to inhibit proliferation, induce apoptosis, regulate autophagy, suppress metastasis, and modulate key signaling pathways such as AMPK, PI3K/Akt/mTOR, Wnt/β-catenin, and MAPK/ERK. Furthermore, BBR's molecular targets—including microRNAs, p53, Ephrin-B2, and SIK3—highlight its multi-targeted mode of action. Notably, BBR demonstrates selective toxicity against cancer cells while sparing normal tissues. These findings support BBR's potential as a complementary agent to enhance the efficacy of standard therapies and overcome drug resistance. Further clinical studies are necessary to establish its safety, optimal dosing, and therapeutic integration in breast cancer management.

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1. Introduction

Breast cancer (BRCA) is the most common cancer among women and the fifth leading cause of cancer-related deaths worldwide. Recent data from (IARC)International agency for research on cancer states that in 2022, over 2.3 million new cases were reported, leading to around 685,000 deaths. An estimated 30% of breast cancer cases are attributed to modifiable risk factors, such as excess body weight, physical inactivity, and alcohol intake, and thus may be preventable [1]. The glandular and stromal (supporting) tissues are the two primary tissue types that make up the breast. Milk-producing glands (lobules) and ducts (milk passageways) are found in glandular tissues; whereas the breast's fatty and fibrous connective tissues are found in stromal tissues. Additionally, the immune system's lymphatic tissue, which eliminates waste products and cellular fluids, makes up the breast [2]. Based on molecular and clinical features, BRCA is categorized into four main types:

Luminal A: is a subtype of hormone receptor-positive breast cancer that is distinguished by the absence of HER2 over-expression, low levels of the protein Ki-67 (which indicates slower cell proliferation), and the presence of the estrogen receptor (ER) and progesterone receptor (PR). Compared to other subtypes, it usually has a better prognosis and reacts favorably to hormone therapy [3].

Luminal B: Progesterone receptor (PR) expression may be low or negative in Luminal B, a subtype of hormone receptor-positive breast cancer that is ER positive. It is more aggressive than Luminal A breast cancer and can be either HER2-positive or HER2-negative. It is distinguished by a higher rate of proliferation. Hormone therapy, chemotherapy, and, if HER2-positive, targeted anti-HER2 therapy are among the treatments that are frequently needed for luminal B tumors. Due of its more aggressive behavior, this subtype typically has a worse prognosis than Luminal A [4].

HER2-enriched: is a subtype of breast cancer that is distinguished by the HER2 (human epidermal growth factor receptor 2) protein being over expressed or amplified. Aggressive tumor growth results from this. Targeted treatments that selectively block HER2 activity, such as trastuzumab (Herceptin), are usually used to treat it. Triple-negative is a subtype of breast cancer that is distinguished by the lack of the human epidermal growth factor receptor 2 (HER2), progesterone receptor (PR), and oestrogen receptor (ER). Because of this, it cannot respond to HER2-targeted or hormone therapy. Chemotherapy is frequently the main treatment choice for TNBC because it is usually more vigorous and has a greater recurrence rate [5].

According to Globocan 2018, new breast cancer cases were estimated by 11.6% worldwide in 2018, and (breast-conserving surgery) followed by radiation therapy is the preferred surgical treatment for breast cancer. Larger tumors, situations that cannot be operated on, or personal preference often brought on by genetics or a lack of radiation access—all call for mastectomy. Axillary lymph node dissection (ALND) is utilized for late nodal illness, but sentinel lymph node (SLN) biopsy is the recommended technique for determining nodal involvement in early-stage disease. By reducing tumor size, preoperative systemic therapy can either make inoperable tumors operable or allow for breast-conserving surgery. Usually, radiation is applied following a lumpectomy or, in high-risk situations, following a mastectomy. Chemotherapy; One important treatment for breast cancer is chemotherapy, which is used both before and after surgery to reduce tumor that produce ERBB2 and hormone receptors. Given the failure of immunotherapy and endocrine therapy for triple-negative breast cancer (TNBC), it is particularly important. While anthracycline-based treatments are used for TNBC with lymph node involvement, taxane-based, nonanthracycline regimens are chosen for lower-risk instances. Furthermore, if there is still disease following surgery, capecitabine (Xeloda) is recommended for TNBC with lymph node involvement. Radiation; Following breast cancer surgery, radiation therapy is frequently utilized to eradicate any cancerous cells that may still be present but invisible. It is typically advised for patients who have a mastectomy (removing the entire breast) or a lumpectomy (removing only the tumor) for more severe, node-positive malignancy. Radiation helps patients who have a lumpectomy reduce the likelihood that the cancer would return in the same breast within 20 years [7].

Hormone therapy: In the early, late, and metastatic phases of estrogen receptor-positive breast cancer, hormonal therapy is a crucial treatment. It comprises medications such as tamoxifen (SERMs) or fulvestrant (SERDs), aromatase inhibitors (such as letrozole and anastrozole), and ovarian suppression (via LHRH agonists or radiation). These treatments delay the progression of cancer by blocking or reducing estrogen synthesis or activity. Although they are also employed, additive hormone treatments like high-dose progestin or estrogens might have negative approximately 12% of these cases are triple-negative breast cancer (TNBC). It is unknown exactly how breast tumor stops responding to tamoxifen (TAM). Recent data, however, indicates that TAM resistance is associated with elevated expression of HER2 and the epidermal growth factor receptor (EGFR) in breast cancer cells. Inhibitors that target EGFR and/or HER2 have been proven in studies to help prevent TAM resistance. However, these inhibitors' toxicity and adverse effects underscore the pressing need for less toxic treatment drugs to address TAM resistance in ER-positive breast cancer [6].

2. Treatment Options Include

For early-stage tumors, where negative margins and acceptable cosmesis can be accomplished, lumpectomy

effects including weight gain. Although they can cause resistance, new developments such as third-generation aromatase inhibitors and SERDs have improved the prognosis for metastatic breast cancer [8].

Targeted therapy: Targeted medications for triple-negative breast cancer (TNBC) focus on specific biological processes. PARP inhibitors, such as olaparib and talazoparib, are effective in BRCA-mutant TNBC because of their synthetic lethality, which stops BRCA-deficient cells from repairing their DNA. Androgen receptor (AR) antagonists, such enzalutamide, show promise in treating AR-positive TNBC by inhibiting AR signalling, which is linked to the growth and metastasis of cancers. EGFR inhibitors, including cetuximab and gefitinib, target the overexpressed EGFR in TNBC and increase the efficacy of chemotherapy, despite delivery problems. Bevacizumab and other VEGF inhibitors have shown improved outcomes in neoadjuvant settings and limit angiogenesis, which is necessary for cancer growth. These medicines offer tailored approaches for TNBC subtypes, despite ongoing challenges including as resistance and small patient groups [9].

Immune therapy: immunological cells that either damage or defend tissue are balanced by the immunological microenvironment in cancer. Type I immunity promotes tissue destruction and has been connected to better survival in malignancies like breast and melanoma. It involves CD4+ and CD8+ T cells that produce cytokines like TNF-α and IFN-γ. Better results are linked to important immune cell groups, including T cells, B cells, monocytes, and dendritic cells. By causing cellular senescence, Stat3 signaling inhibition in breast cancer may also be beneficial. On the other hand, Type II immunity, which is fuelled by CD4+ T cells that secrete IL-4, IL-6, and IL-10, suppresses cytotoxic T cells and lowers inflammation, which frequently accelerates the growth of tumors. For advanced tumors that are unresponsive to regular therapies, combining cytotoxic T cells and natural killer (NK) cells with traditional therapies including radiation, chemotherapy, and surgery shows promise. Biologic medications can also strengthen Type I immunity, which could improve the treatment of breast cancer

and lower its recurrence rate [8].

These treatments help extend survival and improve quality of life. However, drug resistance remains a major challenge, with up to 50% of patients developing tamoxifen resistance and 70% to trastuzumab within a year. Understanding the mechanisms behind this resistance is crucial for improving current treatments and developing new therapies [10].

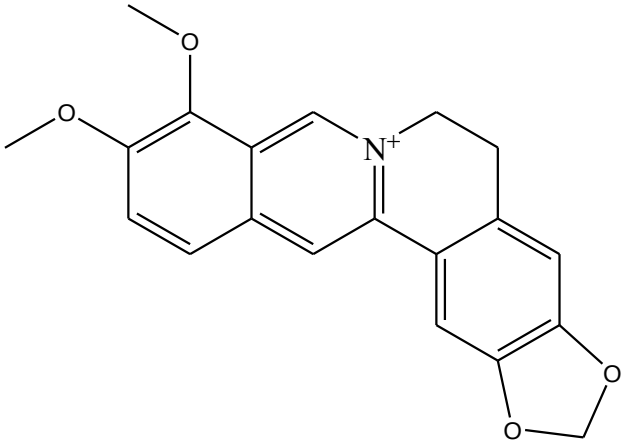
2. Overview of Berberine

Berberine (BBR) is a natural compound with a molecular weight of 336.37. It belongs to a group of chemicals called isoquinolines and is found in plants like Coptis chinensis (a Chinese herb) and certain species, such as Berberis aristata, Berberi's darwinii, and Berberis vulgaris. Later research found that BBR can also be extracted from other plants [11]. BBR has been used in traditional Chinese medicine for over a thousand years to treat various conditions, such as reducing fever, detoxifying the body, improving blood flow, and relieving dampness and cold and many others as shown in (figure 1). BBR is attracting significant attention because of its potential anticancer benefits, which are mediated through a number of biochemical pathways, particularly its ability to promote apoptosis and reduce inflammation [14]. BBR dissolves well in hot water and hot ethanol but is poorly soluble in water, ethanol, and methanol. Although its salt forms, especially phosphates and sulphates, are more soluble, it is little soluble in organic solvents. [14, 15]. BBR inhibits the growth of many tumor cells but is not harmful to human normal cells [10]. Recent studies have shown that because of its many health benefits, including lowering blood pressure, reducing oxidative stress, fighting inflammation, managing diabetes, suppressing the immune system, protecting the heart, and promoting brain health, BBR has been used extensively to treat a variety of infectious, metabolic, cardiovascular, and neurological diseases depicted in (figure 1) [12].

In a variety of ways, BBR inhibits the growth of cancer cells. Under review, this is discussed that how BBR impacts the cell cycle, stimulates apoptosis, promotes autophagy, or cell self-digestion, and inhibits the invasion and proliferation of cancer cells. Additionally, it affects Ephrin-B2, SIK3 regulation, P53 activation, microRNA expression, and the tumor environment. BBR is currently often utilized in clinical trials and research.

BBR's capacity to stop the proliferation of cancer cells, cause cell death, and stop tumor spread makes it a promising treatment for breast cancer.

2.1. Structure of BBR



Chemical Formula	C20H18NO4+
Melting Point	145℃

3. Anticancer Approaches of BBR in Breast Cancer

As per various scholars and researchers BBR has shown encouraging anticancer effects by influencing several molecular pathways related to the progression of breast cancer. These effects include slowing down cell growth, promoting programmed cell death, decreasing the formation of new blood vessels, and altering the signaling within the tumor microenvironment. BBR appears to have the potential to counteract drug resistance and enhance the effectiveness of standard treatments. This introduction delves into the anticancer potential of BBR in breast cancer, emphasizing its mechanisms of action, therapeutic possibilities, and future avenues in integrative oncology.

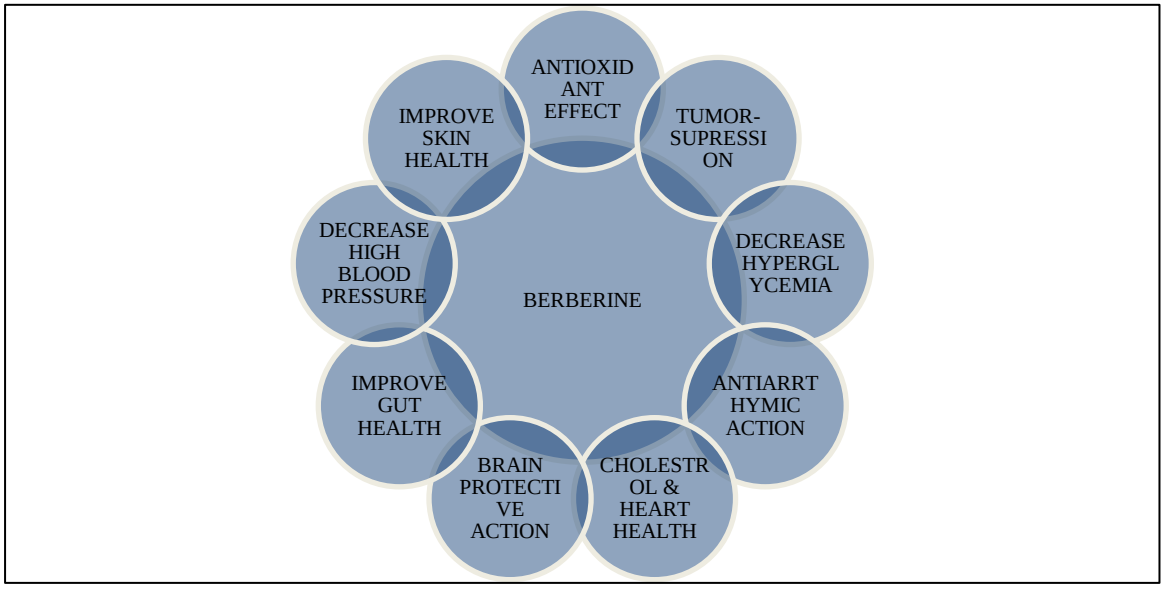


Figure 1: Multifaceted biological activities of berberine.

The diagram illustrates the diverse health benefits of Berberine, which include antioxidant effects, tumor suppression, decreased hyperglycemia, antiarrhythmic action, cholesterol and heart health, brain protective action, improved gut health, decreased high blood pressure, improved skin health, and overall antioxidant properties. These overlapping effects highlight Berberine's potential as a multifunctional therapeutic agent.

Yen-Shu Lin *et al* studied and investigated that BBR demonstrate toxic effects on triple-negative breast cancer (TNBC) cells, it did not have detrimental effects on the viability of normal human breast cells (MCF10) in an in vitro three-dimensional extracellular matrix assay. These results suggest the promise of BBR as a new candidate for TNBC therapy. The concentration of BBR used in MDA-MB-468 cancer cells was a concentration of 1 M in which it mediated a significant increase in the percentage of cells in the G1 phase and a significant decrease in the percentage of cells synthesizing DNA (S phase) and mitosis (G2/M phase), indicating cell cycle arrest [17].

Jianhao Xu *et al* examined and evaluated the effects of BBR on several animal cancer types. The stomach, liver, lung, breast, and other malignancies were among those examined. The findings demonstrated that BBR considerably decreased the weight and size of the tumors. It also inhibited the formation of blood vessels within the tumors, which can help prevent the spread of cancer. Nevertheless, BBR had no effect on the animals' body weight therefore there was no discernible weight gain or decrease. The study discovered a definite correlation between increased BBR dosages and larger tumor weight and size decreases. The strongest evidence of BBR's anti-cancer effects was seen in breast cancers, while more research is needed for colorectal and stomach cancers. No publication bias was found, meaning the results are likely reliable. In short, BBR shows promise in fighting various cancers, especially breast cancer [18].

Minoru Sakaguchi *et al* explored that apoptosis and proliferation are competing processes in cells, and that aberrant cell growth and apoptosis inhibition are frequently connected to tumor formation. According to studies, the nucleolus is where large concentrations of BBR (100μM) mostly collect and cause a stress response. The p53 protein, which is essential for regulating cell development and triggering cell death, is activated as a result of this reaction. Higher amounts of BBR thereby encourage apoptosis and suppress cell division. BBR essentially balances these biological mechanisms to control the growth of tumor cells [19].

Lina Zhao *et al* recently explored the effects of BBR on the behavior of the aggressive breast cancer cell line MDA-MB-231. According to their research, BBR had a number of significant effects, including reducing the cells' capacity to migrate, inhibiting specific protein activations, reducing the overproduction of important inflammatory molecules like interleukin 6 (IL-6) and tumor necrosis factor (TNF-), and suppressing the activity of NF-Kb, a protein complex that controls inflammation and immune responses in cells. BBR was a potential treatment to lessen the aggressiveness of this type of breast cancer because, to put it simply, it helped slow down the movement of cancer cells, reduced harmful signals that could promote cancer growth, and interfered with the cell machinery that controls inflammation and immune responses [20].

Cabral-Pacheco *et al* Matrix metalloproteinase's (MMPs) are essential for invasion, metastasis, and angiogenesis, among other phases of tumor development. In particular, it is known that MMP11 promotes the growth of cancer by inhibiting apoptosis. As an MMP inhibitor, BBR can control the activity of MMPs and their tissue inhibitors, which can impede the growth of cancer and cause apoptosis. This shows that by modifying MMPs, BBR may be a promising therapeutic drug for halting tumor growth [21].

Lamyae El Khalki et al studied and investigated the effectiveness of BBR against triple-negative breast cancer (TNBC), a kind of cancer that is difficult to cure, in laboratory tests. In a number of TNBC cell lines, including MDA-MB-231, MDA-MB-468, HCC1937, and others, it has been shown to eradicate cancer cells. The most BBR-sensitive of these were MDA-MB-468, BT-20, and HCC70. Furthermore, BBR possesses antiviral properties [22].

Cazzaniga *et al* Research has shown that metabolic conditions such as insulin resistance, excessive cholesterol, and chronic inflammation are associated with an increased risk of breast cancer. Cancer treatment may be successful if metabolism is targeted. BBR can enhance the prognosis of breast cancer via regulating metabolism [23].

Evgenios Agathokleous *et al* Researched that autophagy is an evolutionarily conserved cellular process that sustains internal equilibrium by degrading dysfunctional components, such as misfolded proteins and impaired organelles, thereby ensuring proper cell function [24].

Cynthia *et al* Studied and concluded that the combination of autophagy inhibitors with chemotherapy holds great potential as a promising cancer treatment approach. Several autophagy inhibitors are currently in preclinical development, showcasing the growing interest in this strategy [25].

Reza Mohammadinejad *et al* Studied that autophagy has advanced significantly, revealing its complex mechanics. Since apoptosis activation can lead to drug resistance in conditions like cancer, there has been a focus on developing compounds that change autophagy. The theory states that because cancer throws off the balance of cellular autophagy, autophagy modulators might be helpful. Because they work well and have few side effects when used sparingly, herbal medicines have attracted attention. Among them, BBR has demonstrated potential as an autophagy modulator, influencing key signalling pathways including as AMPK, MAPK, Beclin-1/Bcl-2, and mTOR. Despite the fact that BBR mostly raises autophagy levels, its effects on autophagy differ; some research indicates stimulation, while others indicate inhibition. Clinical research has looked into BBR's potential to treat metabolic syndrome, cardiovascular diseases, and other ailments [26].

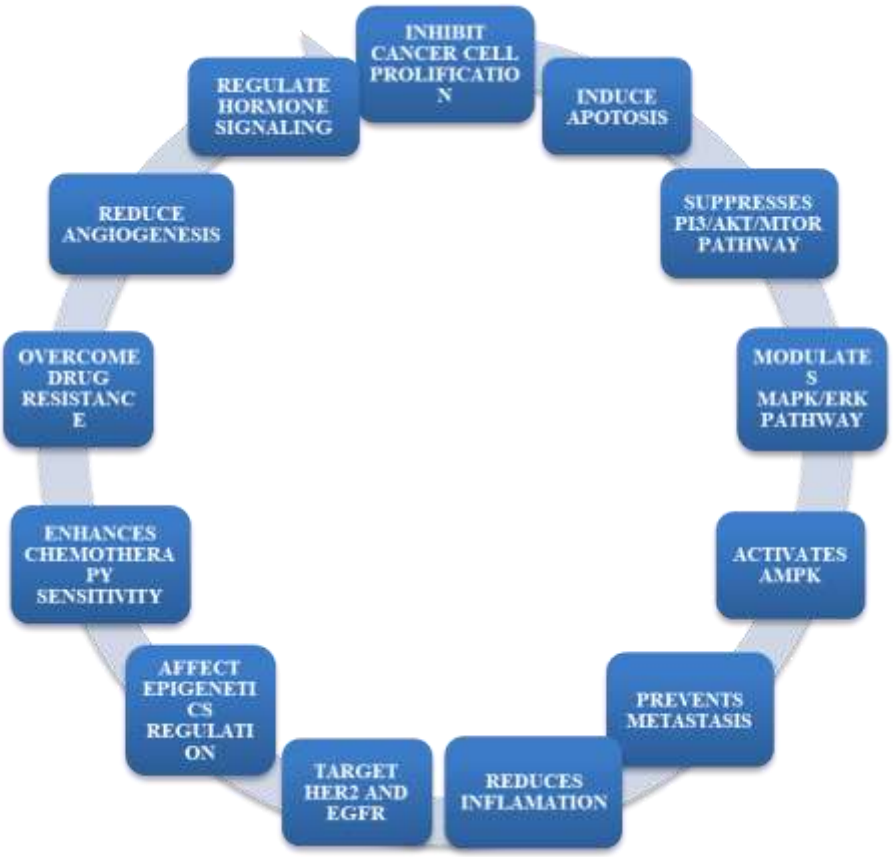


Figure 2: Anticancer mechanisms of berberine.

The diagram highlights the multifaceted anticancer activities of Berberine. These include the inhibition of cancer cell proliferation, induction of apoptosis, suppression of the PI3K/AKT/mTOR pathway, modulation of the MAPK/ERK pathway, activation of AMPK, prevention of metastasis, reduction of inflammation, targeting of HER2 and EGFR, regulation of epigenetics, enhancement of chemotherapy sensitivity, overcoming drug resistance, reduction of angiogenesis, and regulation of hormone signaling. These actions collectively contribute to Berberine's potential as a promising anticancer agent [33].

Chia-Hung Liu *et al* studied that in cancer treatment, autophagy plays a dual role. By destroying damaged cellular components, avoiding genomic instability, and preventing tumor growth, it functions as a tumor suppressor in the early stages. Nonetheless, autophagy can support cancer cell survival in established tumors by supplying nutrients and energy during stressful situations, such chemotherapy or hypoxia, which facilitates treatment resistance and tumor growth. Because of this duality, autophagy is a challenging target for cancer treatment [27].

Nalini Devarajan *et al* Investigated that the BBR was found to block autophagy in both MCF-7 breast cancer cells and their doxorubicin-resistant variant (MCF-7/ADR), specifically preventing the production of autophagosomes in the drug-resistant cells [28].

WeiFu *et al* Studied and explored the effects of BBR on breast cancer cells (MCF-7 and MDA-MB-231). BBR treatment reduced cell viability in a dose-dependent manner, with 40 μM selected for further experiments due to minimal differences between 40 μM and 60 μM doses. BBR also inhibited cell proliferation, as shown by a decrease in EdU-positive cells, and significantly increased apoptosis rates. Additionally, BBR treatment reduced cell invasion and migration, suggesting it may inhibit breast cancer cell growth and metastasis [29].

Parham Jabbarzadeh Kaboli et al investigated that BBR inhibits autophagy in breast cancer cells by targeting the PTEN/Akt/mTOR pathway and additionally modulates MAPK and Wnt/β-catenin signaling pathways [30].

Fan Zhang *et al* researched that BBR inhibits tumor metastasis by targeting key processes such as cell migration, invasion, angiogenesis, and epithelial-mesenchymal transition (EMT), effectively suppressing cancer progression [31].

Mingjiang Yao *et al* studied and research that BBR inhibits colony formation and cell migration while decreasing the viability of MDA-MB-231 cells and increasing LDH release in a dose-dependent way. It dramatically reduces the release of pro-inflammatory cytokines such as TNF-α, IL-1α, IL-1β, and IL-6. Furthermore, P2X7, NLRP3, pro-caspase-1, ASC, caspase-1 p20, IL-18, and IL-1β proteins, as well as NLRP3, Caspase-1, and ASC mRNAs, are all downregulated by BBR, which also inhibits important elements of the NLRP3 inflammatory pathway. These outcomes point to BBR's potential to reduce inflammation and the growth of cancer cells [32].

4. Molecular Targets of BBR

BBR is a multi-targeting medication that has been demonstrated to effectively treat a range of inflammatory illnesses and malignancies. Because malignancies might differ from one another or have different subtypes, it combats different cancer types by attaching to diverse molecular targets. As shown in (Figure 2), BBR has also been shown to directly bind to certain proteins and DNA sequences in breast cancer, aiding in the disease's defense [34].

4.1. Micro RNA

Satyanarayana Rachagani *et al* & Jasjit K Banwait et al Researched and discovered about 2,500 distinct microRNAs, which are tiny molecules that aid in regulating cell gene activity. According to studies, certain microRNAs can interfere with regular cell processes when they are produced in excess. Because it can result in unchecked cell growth, resistance to cell death, and the spread of malignant cells, this imbalance is intimately associated with the development and progression of tumors. Comprehending the function of microRNAs in tumor formation is essential for creating novel cancer diagnostics and therapies [35].

M. Bhaskaran *et al* studied that a class of small, single-stranded RNA molecules known as micro–RNA is essential for post-transcriptional gene control. Usually ranging in length from 21 to 25 nucleotides, these molecules work by attaching themselves to complementary sequences on messenger RNA (mRNA) transcripts. This binding causes the mRNA to either degrade or its translation into proteins to be inhibited [35].

C.-X. QIN *et al* studied that TSLNC8 is significantly elevated in breast cancer tissues and cell lines. It's up regulation inhibits breast cancer cell proliferation and the G1-to-S phase transition. TSLNC8 directly binds to miR-214-3p, and increased miR-214-3p levels can counteract TSLNC8's suppressive effects. Additionally, miR-214-3p directly targets the 3'-UTR of FOXP2, indicating that FOXP2 is a downstream target [36].

L.-C. HAN *et al* investigated the Dual-Luciferase reporter assay demonstrated that miR-214-3p directly regulates survivin by decreasing its mRNA expression. Cells transfected with miR-214-3p mimics showed significantly reduced hRluc/Luc fluorescence ratios and decreased survivin mRNA levels over time, while miR-214-3p prevent increased survivin expression. Functionally, miR-214-3p mimics inhibited the proliferation of MCF-7 breast cancer cells, whereas its inhibitors promoted proliferation ($p<0.05$) [37].

ZhaoYin *et al* Researched and shown that by suppressing the expression of miR-19a/92a, BBR reduces the viability of multiple myeloma (MM) cells. Targeting its seed region with t-anti-miR-19a/92a dramatically inhibits MM cell proliferation, migration, and colony formation since miR-19a/92a is associated with seven different forms of hematological malignancies. These results shed light on the anti-MM properties of some traditional Chinese herbal remedies and imply that the miR-19a/92a cluster may be a therapeutic target for MM [38].

4.2. SIK3 [salt-induce kinase 3]

Lavanya Ponnusamy *et al* Studied In breast cancer tissues, SIK3 expression is significantly unregulated and is associated with advanced stages, poor survival, and tumor growth. Increased SIK3 mRNA levels in breast cancer tissues, particularly in luminal A,

luminal B, and HER2-positive subtypes, are confirmed by data from the TCGA and Zhao datasets. SIK3 levels are also greater in breast cancer tissues, according to protein expression analysis from the UALCAN database. SIK3 expression is higher in luminal-type breast cancer cell lines than in basal-like and normal cells, according to Western blot analysis. SIK3 deletion using CRISPR/Cas9 dramatically slows the development of cancer cells while having no effect on healthy cells. These results imply that SIK3 enhances the proliferation and survival of breast cancer cells [39].

S Charoenfuprasert *et al* investigated that SIK3 overexpression has been shown to influence the cell cycle and promote the development and proliferation of breast cancer cells. This implies that SIK3 regulates processes that regulate cell division, hence playing a critical role in the advancement of cancer [40].

Dalal Alotaibi *et al* studied that prostratin inhibits SIK3 expression and phosphorylation, a key factor in high salt-induced cancer cell proliferation. These findings suggest that prostratin selectively targets breast tumors with minimal impact on normal breast epithelium, making it a promising candidate for cancer treatment [41].

4.3. P53 ACTIVATION

Jian Liu *et al* examined that in p53-null leukemic cells (jurkat and U937), BBR induces autophagy by increasing LC3 II and ATG5 and lowering p62; 3-MA prevents this action. Both transcriptionally and post transcriptionally, it suppresses MDM2, and overexpression of MDM2 reverses the autophagy and apoptosis brought on by BBR. Additionally, BBR stimulates MDM2 self-ubiquitination, which is reliant on its E3 ligase function. In vitro, MDM2 overexpression counteracts the effects of BBR, which increases doxorubicin-induced apoptosis and autophagy. BBR increases doxorubicin sensitivity in vivo, lowering peripheral leucocytes and raising leukemia mice survival to 70%. These results imply that BBR increases chemotherapeutic sensitivity by inducing autophagy and down regulating MDM2 [42].

Ali Yousif Babiker *et al* & Guoyuan Ma et al studied that p53 is a crucial tumor suppressor gene and plays a significant role in regulating apoptosis in different type of cancer cells. This gene's protein acts as a transcription factor that controls when the cell cycle begins. Therefore, p53 plays a crucial role in determining whether a cell divides or not. The p53 protein plays a role in starting apoptosis when a cell is irreparably damaged. For example, by controlling Apaf-1, which initiates the activation of the caspase 3 signaling pathway, p53 can induce cell death and decrease BCL2 through BAX, increasing the BAX/BCL2 ratio [43, 44].

4.4. Ephrin-B2

Weina Ma *et al* Studied the Eph receptor family, which is the biggest class of transmembrane receptor tyrosine kinesis. Through bidirectional signaling, this family interacts with ephrin ligands to control cellular responses. The membrane-bound protein ephrin-B2 is involved in the invasion, migration, and survival of cancer cells. Its cytoplasmic domain mediates its signaling, which includes interactions with signaling molecules and regulates mechanisms such as the internalization of VEGFR2, which in turn triggers downstream pathways like MAPK and PI3K/AKT. By targeting ephrin-B2 and suppressing the expression of MMP-2 and MMP-9, BBR prevented cell division and metastasis [45].

Farnaz Barneh *et al* studied and investigated how different pre-clustered ephrin-B2-Fc concentrations affected MDA-MB-231 breast cancer cells. It showed that the EPHB4 receptor inhibits tumor growth in triple-negative breast cancer (TNBC) cells in a dose-dependent manner. After six days, when the cells were in a post-confluent condition, the inhibition was noticed [46]. Iason Psilopatis et al Research has shown that whereas BBR selectively targets ephrin-B2 to reduce BC cell growth and migration, ephrin-B2-Fc therapy appears to only have EPHB4-mediated anti-BC effects [47].

4.5. LSD1

Guan-Jun Yang *et al* Studied that the enzyme LSD1 (lysine-specific demethylase 1A) alters gene activity by removing methyl groups from histone and non-histone proteins. It contributes to both activation and repression of genes. Many malignancies have hyperactive LSD1, which encourages tumor growth and unfavorable results. LSD1 inhibition is being investigated as a possible cancer therapy. LSD1+8a is a variation that affects the formation of brain cells. A protein called LSD1 plays two roles in breast cancer. By interacting with proteins like estrogen receptors and HDACs, it can encourage the growth, metastasis, and resistance to chemotherapy of cancer. It can, however, function as a tumor suppressor in some situations, such as when it forms the LSD1/NuRD complex, which slows the spread of cancer. Basically, depending on how it interacts, LSD1 can either aid or impede breast cancer [48].

Jingxin Feng *et al* Investigated and found that a protein known as LSD1 has been shown to be more active in breast cancer than in healthy breast tissue. Lack of estrogen receptors, lymph node metastases, and more advanced cancer are all associated with elevated LSD1 levels. Additionally, survival rates were poorer for patients with elevated LSD1 levels. Increasing LSD1 in breast cells caused them to move more, change form, and behave like cancer cells in lab tests. This occurred because they acquired markers that facilitate movement and lost markers that hold cells together. Conversely, aggressive cancer cells became less mobile and invasive when LSD1 was decreased. To put it briefly, LSD1 increases the aggressiveness and propensity for spread of breast cancer, which may make it a target for future therapies [49].

5. Signalling Pathways Regulated by BBR in Breast Cancer

5.1. AMPK Signaling Pathway

D. Grahame Hardie *et al* studied that AMP-activated protein kinase a cellular energy sensor, plays a crucial role in maintaining energy balance and controlling drug resistance in breast cancer [50].

Yue Pan et al found that hypoxia increases the resistance of breast cancer cells (MCF-7) to the chemotherapeutic medication DOX by activating AMPK to make up for the oxygen lost by mitochondrial respiration. When exposed to DOX, MCF-7 cells under hypoxia (low oxygen) fared better than those in normoxia (normal oxygen) (8.4%–60.1% greater vitality). Additionally, hypoxia decreased the quantity of DOX within the cells. The activation of the AMPK system, which raises the levels of proteins like p-AMPK, HIF-1α, and P-gp in low oxygen environments, is connected to this resistance [51].

Yue Pan *et al* Studied the Low-dose BBR (10 μM) activates AMPK, reducing HIF-1α and P-gp expression. This decreases drug efflux, enhancing doxorubicin (DOX) sensitivity in resistant breast cancer cells. Since these effects are reversed by inhibiting AMPK or stabilizing HIF-1α, the AMPK-HIF-1α-P-gp pathway is essential. High-dose BBR (80 μM) causes mitochondrial apoptosis via upregulating p53 and activating AMPK. Since p53 and cell death are unaffected by stabilizing HIF-1α, this happens independently of HIF-1α. Drug-resistant cells are immediately killed by high-dose BBR through the activation of the AMPK-p53 pathway [52].

5.2. PI3K/AKT/mTOR Pathway

Krisida Cerma *et al* studied that one important signaling mechanism that frequently contributes to treatment failure in breast cancer, particularly hormone receptor-positive (HR+) forms, is the PI3K/AKT/mTOR pathway. Resistance to endocrine therapy and anti-HER2 therapies may result from dysregulation of this system brought on by mutations in PIK3CA or AKT or loss of PTEN. In order to combat this, specific medications such as PI3K inhibitor Alpelisib and mTOR inhibitor Everolimus have been authorized for the treatment of HR+/HER2-negative metastatic breast cancer, especially where PI3K mutations or endocrine resistance are present. The PI3K/AKT/mTOR pathway controls the survival, growth, and metabolism of cells. Activated by RTKs and GPCRs, PI3K converts PIP2 to PIP3, activating AKT and mTOR. PTEN negatively regulates this process. In cancer, mutations in PIK3CA, AKT, or PTEN loss lead to uncontrolled growth, especially in HR+ (~40%) and HER2+ (~25%) breast cancer, with PTEN loss common in TNBC. Targeted inhibitors like Everolimus (mTOR) and Alpelisib (PI3K) treat HR+ metastatic BC. Mutation testing via PCR, NGS, or liquid biopsy aids in therapy selection [53].

Miriam Martini *et al* investigated that changes in the PI3K/AKT/mTOR pathway are essential for cancer, which makes PI3K inhibitors a potentially effective treatment strategy. However, because of a number of complicating variables, it is still unclear how PI3K mutations and therapy response are related. Resistance may result from additional genetic changes, such as KRAS mutations or PTEN loss, present in tumors without identified PI3K mutations. Furthermore, PI3K/mTOR inhibitor effectiveness may be restricted by ERK signaling activity. Although combination treatments, such as MEK and PI3K inhibitors, have had some effectiveness, toxicity is still a problem. The predictive significance of PI3K mutations requires more thorough genetic investigation, and focusing on class II PI3Ks may present novel therapeutic options [54].

5.3. Wnt/Beta-Catenin Pathway

Noah Lieb *et al* investigated how the Wnt/β-catenin system controls cell behavior and gene expression. In the absence of the Wnt ligand, β-catenin is phosphorylated by a destruction complex consisting of Axin, APC, CK1, and GSK3β, designating it for degradation. This keeps β-catenin levels low and gene activity low. Wnt inhibits the degradation of β-catenin via binding to the Frizzled receptor and LRP6 to form a signalosome. As a result, genes important in cell growth and development are activated; β-catenin can accumulate, reach the nucleus, and activate TCF/LEF transcription factors. Axin mutations are one example of a pathway defect that can result in excessive β-catenin and breast cancer [55].

H Ruan *et al* studied that BBR inhibits the β-catenin signaling system, which is frequently hyperactive in prostate cancer. According to this study, BBR functions by triggering the activation of a protein known as RXRα, which aids in reducing the negative effects of β-catenin. Unlike other known RXRα-binding molecules, BBR attaches to a distinct location on RXRα. BBR's special binding enables it to halt the growth of cancer cells and cause cell cycle arrest in colon cancer cells. Furthermore, BBR strengthens the bond between RXRα and β-catenin, which breaks down β-catenin and further prevents the progression of cancer. Additionally, the study discovered that BBR enhances the anti-cancer benefits of 9-cis-RA, a different chemical. This could lead to the usage of lower dosages of each medication, which would lessen side effects [56].

Hongkun Li et *al* Studied the exploration of BBR influence on the Wnt/β-catenin signaling pathway offers new insights for the development of targeted therapies, paving the way for more personalized and effective breast cancer treatments in the future [57].

5.4. MAPK /ERK Signaling Pathway

Qiang Zhang et al investigated the development and spread of breast cancer is significantly influenced by the mitogen-activated protein kinase (MAPK) signaling pathways. The study discovered that by blocking the mTOR/p70S6K and MAPK signaling pathways, BBR caused cytostatic autophagy in BGC-823 cells. In particular, the mTOR/p70S6K signaling pathway was more strongly inhibited when BGC-823 cells were pretreated with MAPK inhibitors (PD98059, SP600125, and SB203580), as seen by decreased phosphorylation of mTOR and p70S6K. This suggests that the mTOR/p70S6K pathway is regulated by upstream MAPK signaling in BBR-induced autophagy.

Furthermore, pretreatment with the autophagy inhibitor 3-MA partially reversed the changes in phosphorylation of ERK, JNK, and p38 (components of the MAPK pathway) induced by BBR. This indicates that BBR-induced autophagy exerts negative feedback on the MAPK signaling pathway, contributing to enhanced BBR-induced cell death in BGC-823 cells. These findings highlight the crosstalk between MAPK signaling and autophagy in mediating BBR's effects [58].

Sangmin Kim *et al* observed that BBR suppresses MEK and ERK phosphorylation and down-regulates the production of the EGFR protein in a dose-dependent manner. This implies that the ERK signaling pathway, which is a component of the IL-8-related processes, may be inhibited by BBR in order to limit cell invasiveness and growth in triple-negative breast cancer (TNBC) [59].

5.5. Wnt-Beta-Catenin Pathway

Arabi Mahanujam *et al* Additional research is necessary to understand the function that the Wnt/β-catenin pathway plays in the development and progression of BC. Wnt signaling abnormalities are linked to increased metastasis, tumorigenicity, and resistance to treatment, especially in HER2 and TNBC subtypes. Developing focused therapy therapies requires an understanding of the unique patterns of Wnt pathway dysregulation found in BC subtypes and cell lines. In order to improve treatment results for BC patients, future research should concentrate on examining the role of β-catenin and other Wnt pathway components in BC progression and medication resistance. It's also worthwhile to investigate targeted medicines that concentrate on γ-catenin [60].

C.XIAO *et al* UCA1 silencing inhibits the Wnt/β-catenin signaling pathway by increasing the expression of its negative regulators (p-GSK-3β and GSK-3β) and reducing β-catenin protein levels, leading to decreased transcription of downstream genes like cyclin D1 and MMP-7. This suggests UCA1 plays a role in promoting Wnt/β-catenin activation in breast cancer [61].

Conclusion

Berberine shows promise in treating breast cancer due to its ability to inhibit cancer cell growth, induce cell death, and reduce tumor spread. According to studies, it could reduce adverse effects and increase the efficacy of conventional treatments like chemotherapy. To completely comprehend its mechanics and safety in humans, more research is necessary. Future strategies should concentrate on developing BBR-based medications or combination therapy, investigating the best dosages, and conducting clinical trials to validate its advantages. Furthermore, examining its potential to prevent cancer recurrence may lead to novel approaches to the long-term treatment of breast cancer. All things considered, BBR has promise as a supplemental therapy; however, more research is necessary to fully realize its therapeutic potential. Clinical studies to find the ideal dosage and treatment regimens, more human studies are required. Combination therapy involving BBR alongside existing treatments like immunotherapy and chemotherapy shows promise for improved outcomes. Researchers are also exploring nano-delivery systems to enhance BBR's effectiveness and absorption. Additionally, future studies may focus on personalized medicine, investigating how BBR interacts with different types of breast cancer to develop tailored treatments.

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Author Contributions

N.S. Conceptualized the study, **T.M.** Prepared the manuscript draft.

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Conflicts of Interest

No conflicts of interest are disclosed by the authors.

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