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The survey of antitumor effects of bromelain on neoplastic breast cells: A systematic review

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ABSTRACT

Background: Breast cancer is one of the most prevalent cancers in women worldwide. Considering the side effects of chemotherapy treatments, we investigated the anticancer effects and mechanisms of bromelain (Br) on breast cancer cells in this systematic review.
Methods: The PRISMA recommendations were followed to design this systematic review. Web of Science, PubMed, Cochrane Library, and Scopus were high-coverage databases used for searching. After considering the inclusion and exclusion criteria for the study, 18 articles were included. The desired information was gathered, entered into an Excel file, and the study outcomes were surveyed.
Results: Br revealed its anticancer effects by preventing the proliferation of cancer cells, inducing cytotoxicity, apoptosis, autophagy, and cellular oxidation in breast cancer cells. Moreover, its anti-inflammatory activity and immunomodulatory effects in the tumor environment can increase treatment outcomes. No significant side effects of this proteolytic substance have been reported, and it is a safe herbal constitution. Its combination with anticancer drugs such as cisplatin has revealed synergic effects. Besides reducing the toxicity of chemotherapy drugs, Br improves treatment outcomes.
Conclusion: Br has shown promising anticancer effects against breast cancer in in vivo and in vitro studies. However, more clinical trial studies are needed to achieve more reliable results.

Implication for health policy/practice/research/medical education:
This study demonstrated the cytotoxic effects of bromelain against breast neoplastic cells and its synergic effects with other chemotherapy drugs. Bromelain indicated anticancer properties by preventing the proliferation of cancer cells, inducing cytotoxicity, apoptosis, autophagy, and cellular oxidation in breast cancer cells. To lessen the side effects of chemotherapy, this herbal remedy may be used in cancer treatment facilities under the guidance of medical professionals.

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Introduction

Cancer is a growing disease and a significant global public health problem, which has high morbidity and mortality, among other diseases. By 2040, the disease burden worldwide will be 28.4 million cases (1). The most prevalent cancers are lung, breast, and prostate (2). Breast cancer has a significant global economic, social, clinical, and disability-adjusted life years burden (3,4). In addition to impairing people's quality of life (5), breast cancer imposes heavy medical and non-medical costs on patients, families, and communities (6). Common breast carcinoma treatments have various side effects for patients. For example, chemotherapy can cause fatigue, nausea and vomiting, dry mouth, changes in taste, decreased appetite, constipation, and hair loss (7,8). Moreover, radiotherapy-induced side effects are neutropenia, anemia, sepsis, pneumonia, and acute kidney injury (9).

Current cancer research aims to identify the risk factors, prevention, and new treatment strategies to increase survival and eliminate cancer cells. These treatments

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should have the lowest cost, effectiveness, and side effects (10). Although currently, various treatments, including biological drugs, immunomodulatory agents, and radiation therapy schemes, are available, it is necessary to find new treatment methods according to mentioned reasons.

Meanwhile, herbal treatments and phytochemicals have been welcomed by patients due to fewer side effects, cheapness, and greater accessibility (11). Bromelain (Br) is a proteolytic enzyme derived from the stem or root of pineapple (*Ananas comosus*) and contains a sulfhydryl group (12). Various cellular studies have revealed that Br possesses anti-cancerous, antioxidant, and anti-inflammatory activities and improves the death of apoptotic cells (13-16).

This study aims to systematically review the antitumor activity and the underlying mechanisms of Br on neoplastic breast cells.

Material and Methods

Data sources and search strategy

This systematic review followed Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 guidelines (http://prisma-statement.org/prismastatement/Checklist.aspx). In this regard, an extensive electronic search was undertaken on January 25, 2023 in the Web of Science (Clarivate), EMBASE, PubMed, and Scopus databases. The following search terms were used to perform the search: ((“bromelain” OR “bromelin” OR “pineapple”) AND (“mammary carcinoma cells” OR “MCF-7” OR “UFH-001” OR “4T1” OR “breast cancer cell” OR “mammary gland cells” OR “breast cancer” OR “breast neoplasms” OR “breast carcinoma” OR “breast tumors”)).

Study selection

The references in the mentioned databases were imported into EndNote X8 (8 November 2016, Thomson Reuters) software, and duplicate publications were removed. Two researchers independently screened all studies in terms of titles and abstracts. Based on the study’s inclusion criteria, the *in vitro* and *in vivo* publications that addressed the effects of Br on cancerous breast cells were included in the systematic review. Non-English publications and lack of access to the full text of the records were considered exclusion criteria. In the next step, the full texts of all included studies were reviewed independently by two investigators. If any conflict or disagreement occurred during the review, it was resolved by discussing the issue with other team members. A PRISMA 2020 flow diagram of the search strategy and screening results is illustrated in Figure 1.

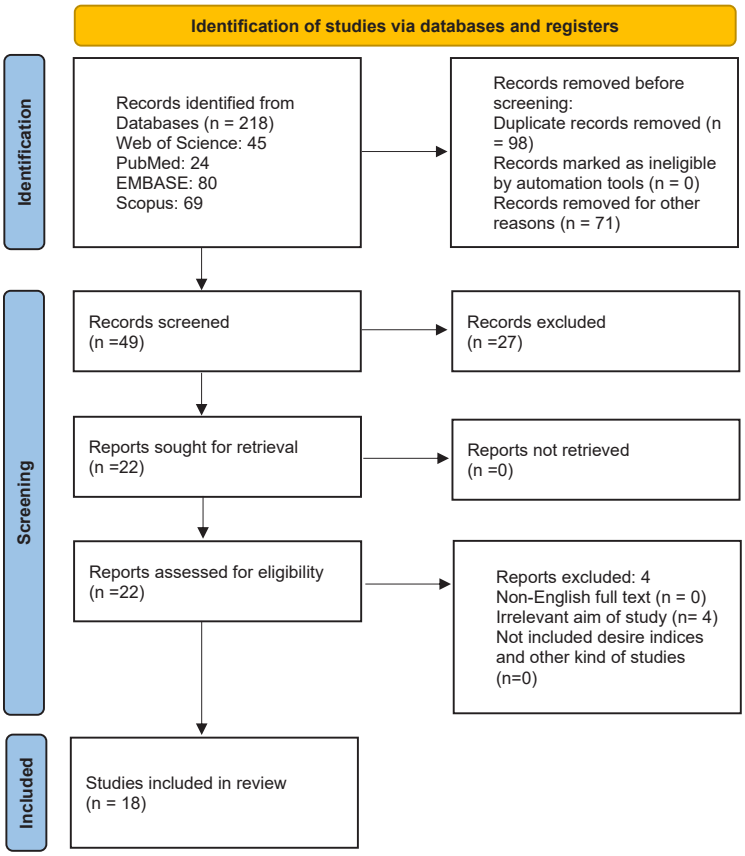

Figure 1. Flow diagram of included studies in this systematic review.

Data extraction

From the publications, the following data were extracted and registered in Excel form: lead author's name, year of publication, cell line, experimental procedure, dosage, duration of exposure, and cellular and molecular outcomes. If the extracted information was unrelated to the study's purpose, it was excluded from the study.

Results

Search results and characteristics of the included studies

The PRISMA 2020 flow diagram of the search strategy and eligible studies is illustrated in Figure 1. The initial search retrieved 218 publications. From the full title/abstract retrieved, 98 records were deleted due to duplicate titles. Seventy-one articles were removed due to lack of irrelevance, or Br studied on the other cancers. In addition, four studies were excluded for not matching the aims of this study (17-20). Finally, 18 articles were selected for the final evaluation (13,21-37) (Table 1).

Most *in vitro* and *in vivo* studies on the effects of Br on breast cancer cells were conducted on MCF-7 cells between 1994-2021. These studies investigated the antitumor activities of Br either alone or in combination with anticancer drugs at different doses. Studies have investigated various effects, including tumor growth inhibitory properties, apoptosis, autophagy, inflammation, and oxidation.

Discussion

This systematic review aimed to investigate antitumor activity and the underlying mechanism of Br on neoplastic breast cells. The pharmacological effects of Br include the ability to inhibit platelet aggregation, modulate the arachidonate cascade, inhibit the growth of malignant cells, act as an anti-inflammatory, have fibrinolytic activity, have skin debridement properties, and lessen the severe effects of SARS-CoV-2 (12).

In vitro and *in vivo* studies associated with Br revealed promising anticancer effects due to its capacity to regulate various molecular targets and signaling pathways connected to inflammation, tumor growth, and ferroptosis. Br molecularly inhibits cell division, reduces proliferation, reduces the tumor niche, prevents metastasis, modifies immune response, and promotes ferroptosis (38).

Various studies have reported Br's promising effects in treating various cancers. Kumar et al., in their review study, indicate that the cytotoxicity of monocytes in the immune system's fight against cancer is severely impaired, in addition to reducing the growth of tumors locally (39). Another review indicates that Br inhibits tumor growth and has antitumor and antiproliferative properties, as shown by the induction of p53, shifts in the reduction in cyclooxygenase-2 (COX-2) expression, induction of caspases, induction of the Bax/Bcl-2 ratio, and inhibition of the NF-B pathway by regulation of the MAPK and Akt/PKB signaling pathways (40). Pezzani et al reported that Br indicates potential anticancer effects such as apoptotic, autophagic, cytotoxic, immunomodulating, and anti-inflammatory and necrotic effects in cancer cells (41). Another review shows that Br inserts anticancer effects by two main mechanisms, including the effect on cell growth and survival pathways and angiogenesis and metastasis (42).

Apoptosis

Plant compounds, particularly Br, can boost pro-apoptotic proteins and alter apoptotic pathways, promoting cell death and apoptosis (43). Different phytochemicals and active plant compounds can induce intrinsic and extrinsic apoptosis pathways in human cancer cells and successfully treat neoplasm (44). Due to the generation of Reactive oxygen species (ROS) in breast cancer cells, Br caused apoptosis and compromised mitochondrial membrane. By increasing the expression of cell death-related pro-apoptotic proteins (P53, P21, and Bax) and decreasing the expression of antiapoptotic proteins like Bcl2, it also lessened the tumor burden (26). Another study has demonstrated that Br can cause apoptosis. This proteolytic enzyme improves the activity of caspases -3 and -9 activities at 24 hours and positively regulates the N-terminal kinases c-Jun and kinase 38 in breast cancer cells, specifically in GI-101A cells (25). By causing carcinoma cells to become arrested in the G2/M phase, Br inhibits NF-κB and triggers apoptosis. In addition, Br inhibited the NF-κB (as a proliferative marker) and reduced cancer cell proliferation (37). Br activated apoptosis by triggering the mitochondrial pathway and suppressing the expression of NF-κB and COX-2. In skin tumor studies, simultaneous downregulation of Bcl-2 and activation of p53, Bax, caspase-3, 8, and caspase nine were also reported, providing strong evidence for the potential of Br to induce apoptosis in malignant tumor cells (45).

Autophagy

In order to maintain cellular homeostasis and degrade damaged organelles and outdated proteins, autophagy is a necessary process (46). While developing new anticancer drugs targeting autophagy pathways in cancer treatment appears promising, recent findings are based on herbal remedies. Studies support plant compounds' antioxidant and anti-inflammatory effects, particularly Br, and their capacity to trigger autophagic death in cancer cells. These proteolytic compounds also appear crucial in modulating autophagy (15,16,47). In cancer, this process has a dual function because it can either inhibit tumorigenesis in cancer cells by preventing cancer cells from surviving and causing them to die. However, it also promotes tumorigenesis by encouraging cancer cell proliferation (48,49).

By activating the autophagy process, Br assisted in

Table 1. Characteristics of the selected studies of the effect of bromelain (Br) on breast cancer cell line

Lead author	Year of publication	Cell line	Experimental approach	Dosage	Time of exposure	Cellular and molecular outcomes
Garbin (21)	1994	MCF-7	Crude Br proteinase-f9	25 µg/mL	Three days	IL-2 and TNFα elevated 10 and 19-fold in the PBL supernatant, respectively. It also synergizes LAK cell activity.
Eckert (22)	1999	MDA-MB-231	Oral Br-POS	3000 F.I.P. units	Ten days	Br proteinase was also found to have a growth inhibitory effect.
Paroulek (23)	2009	GI-101A	Herbal enzyme Br	1 µL-10 µL	24 h	CK18Asp396 neo-epitope levels elevated, and many apoptotic cells were seen.
Bhui (24)	2010	MCF-7	Br derived from pineapple	0–100 µg/mL	24, 48, 72, and 96 h	Br induced autophagy and retarded apoptotic cell death response to Br due to the induction of autophagy in MCF-7 cells, which is thought to be tightly regulated by the activation of JNK, p38 and ERK1=2 MAPK. Furthermore, once activated, autophagy can mediate caspase-dependent or -independent cell death.
Dhandayuthapani (25)	2012	GI-101A	Br derived from immature pineapple	5, 10, 20, 40, and 50 lg/mL	24 h	Br induced cytotoxic effects on GI-101A breast cancer cells by activating a caspase pathway (caspase-9 and caspase-3) and activated apoptotic signals.
Bhatnagar (26)	2014	MCF-7	Br from pineapple stem and Br nanoparticles	2 to 500 µg/mL	24, 48, and 72 h	Br induced apoptosis and impaired mitochondrial membrane due to ROS generation. It also reduced the tumor burden by upregulating the expression of pro-apoptotic proteins associated with cell death (P53, P21, Bax) and downregulating antiapoptotic proteins such as Bcl2.
Fouz (27)	2014	MCF-7	Commercial and recombinant Br	Br (5.125 µg/mL) and recombinant Br (6.25 µg/mL)	24, 48, 72, 96, 120, and 144 h	Br induced antiproliferative activity and affected the cytokinetics of MCF-7 cells by reducing cell viability.
Fouz (28)	2014	MCF-7	Commercial and recombinant Br	6.25 µg/mL	0, 1, 48 h	Recombinant Br produced a unique signature affecting different pathways and regulated breast cancer cells by stathmin1.
Pauzi (29)	2016	MDA-MB-231	Br + Cisplatin	0.24–9.5 µM	24 and 48 h	Br + Cisplatin induced apoptosis via the mitochondria-mediated pathway and decreased the levels of several apoptotic proteins, such as Bcl-x and HSP70. Moreover, it elevated the levels of pro-apoptotic proteins Bax.
Nasiri (30)	2017	MDA-MB-468, MDA-MB-231, and 4T1	Br + SPIONs + folic acid	27 mg /mL^{-1}	24 h	SPIONs–Br–FA inhibited growth and clonogenic potential and suppressed the immigration of FAR+ cancer cells *in vitro*. It also inhibited tumor growth *in vivo*.
Oliveira (31)	2017	MCF-7	Br-MLNC-Zn	10-100 µg/mL	24 h	It induced higher antiproliferative effect.
Mohamad (13)	2019	4T1 triple-negative	Br + Cisplatin	25 mg/kg	28 Days	Reduced tumor size and lung metastasis, alone and in combination, through downregulation of the expression of GREM1, IL-1β, IL-4, NFκB1, PTGS2, nitric oxide level, and serum IL-1β and IL-4 levels.
Raeisi (32)	2019	MCF-7	Br	0, 5- 600 µg/mL	24 h	Inhibited the growth and proliferation of MCF-7 cells in a concentration-dependent manner and showed falling in plating efficiency and survival rate in three treated human breast cancer cells.
Raeisi (33)	2019	4T1	Br	0, 5- 600 µg/mL	24 h	It inhibited the growth and proliferation and reduced the survival of the mouse 4T1 cell line.
Haiyan (34)	2020	MCF-7 and MDA-MB-231	Br extracted from the different tissues of pineapple	0, 15, and 30 µg/mL	72 h	It inhibited the growth through the upregulating of p53, Bax, and by the decreasing of the expressions of COX-2 and Bcl-2.
Karimian (35)	2020	MCF-7	Br on magnetic carbon nanoparticles	0.1, 1, 10, and 100 µg/mL	24, 48, and 72 h	It induced severe cytotoxicity at 100 µg/mL concentration, alone and in combination with magnetic carbon nanoparticles.
Raeisi (36)	2020	MCF-7	Br + cisplatin or 5-FU	0-28 µM	48 h	Br-Cisplatin combination induced concordant effects on cell proliferation impediment and apoptotic induction on MCF-7.
Mekkawy (37)	2021	MCF-7	Br +Whole body γ-irradiation	0.009-5 mg/mL	One h	Br/radiation inhibited tumor proliferation, PARP-1, Ki-67, and NF-κB and increased lipid peroxidation and ROS production in tumor tissue.

IL, Interleukin; TNFα, Tumor necrosis factor α; PBL, Blood lymphocytes; LAK, Lymphokine-activated killer cell; Bcl2, B-cell lymphoma 2; SPIONs, Superparamagnetic iron oxide nanoparticles; h, Hour; Br-MLNC-Zn, Bromelain-functionalized multiple-wall lipid-core nanocapsules; BAX, Bcl-2 Associated X-protein; CK 18, Protein cytokeratin 18; JNK, c-jun N-terminal kinase; ERK1, Extracellular signal-regulated kinase 1; GREM1, Gremlin 1; DAN Family BMP Antagonist; NFκB1, Nuclear factor κB; COX, Cyclooxygenase; PTGS2, Prostaglandin-Endoperoxide Synthase 2; MAPKs, Mitogen-activated protein kinases; PARP-1, Poly(ADP-ribose) polymerase-1; ROS, Reactive oxygen species.

decreasing cells from breast cancer tissue. Treatment of MCF-7 cells with Br increased the autophagic process and slowed their proliferation through caspase-dependent or independent cells (24).

The loss of mitochondrial trans-membrane has a potential and crucial role in the apoptosis process (26). By preventing the activation of MAPK-regulated NF-κB, which starts the mitochondrial death pathway when skin tumors are initiated, Br reduces COX-2 expression (45). Combination of Br with cisplatin in the treatment of MDA-MB-231 cells caused a loss of mitochondrial membrane potential, which revealed that the mitochondrial pathway was entailed in the apoptosis induced by combination treatment (29).

ROS production

ROS like hydrogen peroxide, hydroxyl radical, superoxide radical, and singlet oxygen are well known to be cytotoxic and have been linked to the etiology of various human diseases, including cancer (50). Br induced apoptosis and compromised the mitochondrial membrane because of ROS production. Some active plant compounds may induce the cytotoxicity and apoptosis of cancer cells. The production of ROS, which results in oxidative stress, is one of the therapeutic approaches that may be effective in harming cancer cells (51). So, this mechanism was the focus of some efforts to develop novel active components for cancer medications. However, some plant compounds may strengthen antioxidant defence by activating cellular antioxidant enzymes or enhancing radical scavenging (51).

Studies indicate that Br can potentially kill tumor cells *in vitro* and *in vivo* by stimulating the production of ROS. Br elevated ROS generation in Ehrlich ascites carcinoma cells, leading to oxidative stress in cancerous cells. This cytotoxic situation causes cell death in breast cancer cells (26). Another study revealed that Br increased ROS content and lipid peroxidation in MCF-7 cells, eventually leading to mitochondrial membrane depolarization (37). A decrease in intracellular glutathione and the production of ROS as a result of Br were followed by the depolarization of the mitochondrial membrane. When ROS are produced, the mitochondrial membrane may depolarize and apoptosis may be induced simultaneously. So, ROS were the mediators of Br's depolarization of the mitochondrial membrane (52). According to another study, caspases can cleave p53 and produce two cytosolic fragments that travel to the mitochondria and cause the membrane to become depolarized (53). ROS production and lipid peroxidation are crucial in autophagy and cell apoptosis in cancer tumors, which inhibits their growth (54).

Anti-inflammatory effect

The primary uses of Br in the medical field are associated with its anti-inflammatory effects. It reduces edema and inflammation in animals by histamine and pro-inflammatory cytokine. By preventing the synthesis of bradykinin and serotonin at the level of inflammatory tissue, Br reduces vasodilation, elevated capillary permeability, reduced leukocyte migration, and local pain (41). Br alone and combined with cisplatin treatment demonstrated a reduction of tumor nitric oxide levels, tumor inflammatory gene expression, and serum IL-1 and IL-4 levels. So, it inserts an antitumor effect by modulating the tumor's environmental inflammation (13). Br also reduces prostaglandin E2 (PGE-2), tumour necrosis factor α (TNFα) levels, and the expressions of COX-2 and Bcl-2 in a tumor environment (22,24,40,53).

Immunomodulatory effect

Br induces immunomodulatory properties and causes immune cytotoxicity of blood lymphocytes and monocytes in mammary carcinoma cells (22,40). Additionally, Br has been shown to increase impaired monocyte cytotoxicity against tumor cells and significantly slow down local tumor growth (23). Another study also reported that after Br application, the concentrations of interleukin-2 (IL-2) and TNF-α elevated in the peripheral blood lymphocytes against MCF-7 breast cancer cells and inhibited tumor growth (21). The pro-inflammatory mediators induced by leukocyte migration and the hyaluronan receptor CD44 were reduced by Br (54). Br and its combination with cisplatin have significantly reduced the levels of pro-inflammatory IL-1β and immunosuppression IL-4 cytokines (13). In addition, Br inhibited interferon gamma and PMA-induced IL-2, IL-4 mRNA accumulation, and the extracellular protease Br suggests a novel function for inhibitors of intracellular signal transduction pathways in T cell signal transduction (55). The extracellular domains of the surface molecules CD45RA, CD44, CD6, CD7, CD8, E2/MIC2, and Leu 8/LAM1 were removed by Br's action, which improved T cell activation via CD2. The expansion of Br in monocytes and granulocytes, along with the extension of the surface molecules, reinforced the enzyme's benefits for increasing immune cell adhesion and activation (61).

In general, the mechanism of Br in preventing the growth and destroying the cells of cancer cells is illustrated in Figure 2.

Synergistic response with other chemotherapy drugs

Br delivery in combination with other molecules is frequently investigated to obtain a synergistic effect. Although Br by itself has demonstrated cytotoxic and apoptotic effects in cancer cell lines, other studies have been developed combining this enzyme with other substances or extracts. For example, studies on breast cancer were mainly investigated with the combination of Br and cisplatin. Therefore, an efficient method to inhibit

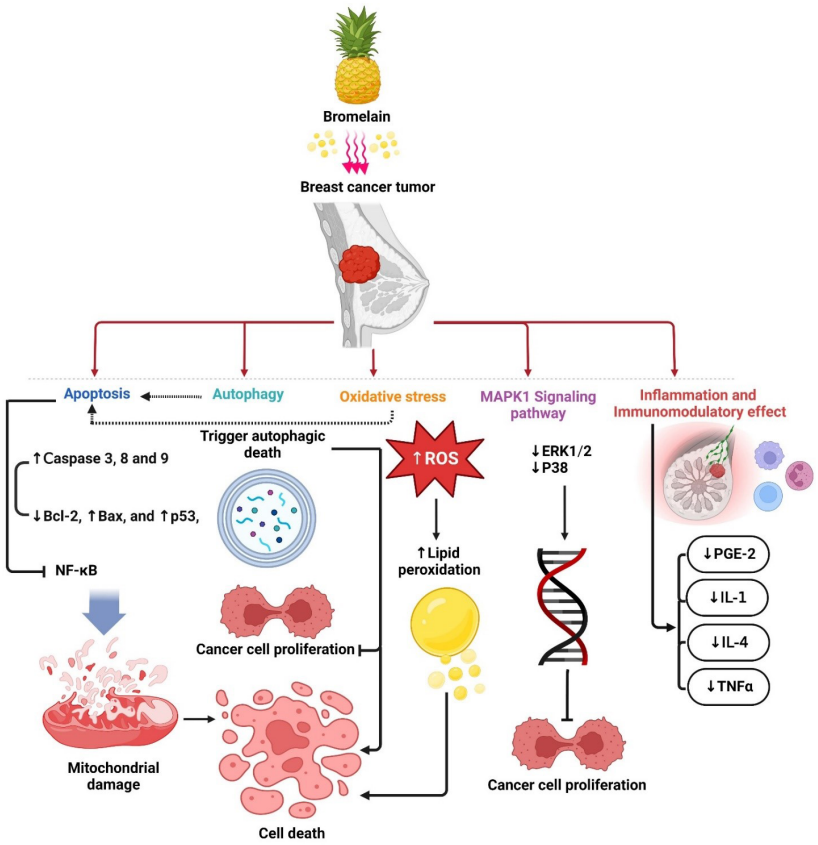

Figure 2: Effects of bromelain on breast cancer cells. Bcl2; B-cell lymphoma 2, BAX; Bcl-2 Associated X-protein, NFκB; Nuclear factor κB, ERK; Extracellular signal-regulated kinase, PGE-2; prostaglandin E2, IL; Interleukin, TNFα; Tumor necrosis factor α.

cancer cell growth that develops resistance to cisplatin is to combine cisplatin with additional anticancer drugs that work differently from cisplatin. The effectiveness of the treatment process could be maintained or even increased while using this strategy to reduce the severity of the side effects related to each individual agent (29). Some studies have shown that combining anticancer drugs with Br can increase the anticancer effects of drugs such as cisplatin and increase the apoptotic effects of Br in breast cancer cells. For example, Br with cisplatin combination against MDAMB-231 cells enhanced apoptosis synergistically (29). Another study showed that Br + cisplatin administration in mice for 28 days enhanced the antitumor activity of cisplatin on breast cancer (4T1) cells by downregulating the expression of tumor inflammatory genes and modifying the environmental tumor inflammation (13). On MCF-7 cells, a single treatment with Br had more antiproliferative effects than combination therapy. Moreover, on MCF-7 cells, the Br + cisplatin combination had a synergistic effect. In addition, when compared to cisplatin alone, Br + cisplatin had a synergic effect on inducing cell apoptosis in MCF-7 cells (36).

Bioavailability and delivery system

Br is absorbed through the gut epithelium and has a high bioavailability. It can bind to two anti-proteinases in the blood in its active form (57). New strategies have been provided in recent years to improve the antitumor effects of Br from the bench to the bedside. Enhancing the bioavailability of Br as a bioactive compound using novel pharmaceutical nanoformulations is the most promising strategy (41,58). Administration of Br in different studies may be alone or in conjunction with other molecules. However, one of the best administration methods was nanoparticle formulation, which can be effectively used as a new approach for cancer chemotherapy (41).

In order to fight cancer, it is necessary to develop nano-delivery systems with improved protease activity or sustained Br release (38). Br, as a proteolytic enzyme, increases binding affinity and changes the surface area of the particles. Br acts as a surface moderator in chitosan nanoparticles modified with lactobionic acid to increase their penetration of tumor cells (59). Studies have demonstrated that Br nanoparticles inhibit the proliferation of MCF-7 BC cells. These nanoparticles increase their lifespan, reduce cell proliferation, boost apoptosis, and improve chemosensitivity to inhibit cancer cell growth. Br nanoparticles and pineapple nanoemulsion were more likely to be delivered by breast cancerous cells (26,39).

Moreover, a study showed that Br combined with nanoparticles (magnetic carbon nanoparticles) was significantly reduced. Additionally, the slow delivery of synthesized magnetic carbon nanoparticles significantly treated cancer (35). Br nanocapsules also have a more substantial antiproliferative effect than Br solution (31). So, Br can be delivered to the desired organ for treating and preventing cancer using various nanostructured materials.

Toxicity and side effects

The body thoroughly absorbs Br after oral administration. It has no significant side effects, not even after prolonged use (57). Even Br lessens the side effects caused by radiotherapy and chemotherapy used in cancer treatment. Br offers encouraging results as a clinical treatment for breast cancer and mucin-producing peritoneal tumors in people (38).

The toxicity profile of Br has been reported to have almost no toxic effects in clinical and preclinical studies (12). On ovarian and colon cancer cell lines, Br exhibits remarkable anticancer properties, but it is toxic to healthy cell lines. Therefore, it is imperative to create a safe, targetable delivery system in order to minimize Br's adverse effects on healthy cell lines while maximizing their toxic effects on tumor sites (60). The lethal dose (LD50) in mice is greater than 10 g/kg (61). In another study, no significant changes were reported in blood coagulation parameters after administration Br at doses up to 3000 FIP units per day (62).

In general, the cytotoxic effects of Br depend on its dosage (25). So, the side effects should be investigated with different doses, and the best limit of its consumption and effective dose should be investigated. More clinical studies are needed to obtain reliable results about the toxic effects of Br on the body and normal cells.

Limitations of the study

One of the limitations of the studies on the anticancer effects of Br against breast cancer is the failure to investigate the efficacy of Br for difficulty index specifically and highlighted indications, contraindications, side effects, and toxicity. In addition, although there were many preclinical studies on the anticancer effects of Br, more clinical studies are needed to obtain reliable results in this field.

Conclusion

Br showed promising anticancer effects against breast cancer *in vivo* and *in vitro* studies. Br revealed its anticancer effects through anti-inflammatory activity, immunomodulatory effect, preventing the proliferation of cancer cells, inducing cytotoxicity, apoptosis, autophagy, and cellular oxidation in breast cancer cells. Although minor side effects of this proteolytic substance have been reported and it is a safe herbal constitution, more clinical studies are needed to obtain reliable results from it. Its combination with anticancer drugs such as cisplatin revealed a synergic effect. Besides reducing the toxicity of chemotherapy drugs, Br improves treatment outcomes. The results of this research can be of interest to doctors in treating breast cancer so that they can minimize the side effects of chemotherapy drugs by using herbal treatments.

Authors' contributions

All authors progressed the concept of this study. ER and MRK wrote the protocol. SHS and CMS collated the data for the study. The first draft of the manuscript was written by MRK and thoroughly revised by all authors.

Conflict of interests

The authors declare there are no conflicts of interest.

Ethical considerations

Authors have carefully monitored ethical issues such as text plagiarism, duplicated publication, misconduct, data fabrication, and falsification.

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