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BROMELAIN AS A MULTIFUNCTIONAL BIOACTIVE COMPOUND IN CANCER THERAPY

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ABSTRACT

Cancer remains a global health challenge due to the limitations of conventional therapies, including toxicity, multidrug resistance, and limited efficacy in certain tumor types. Natural compounds with multi-targeted mechanisms, such as bromelain, a proteolytic enzyme extracted from Ananas comosus (pineapple), have gained increasing attention for their therapeutic potential. Bromelain exhibits anticancer effects through apoptosis induction, cell cycle arrest, autophagy, ferroptosis, and inhibition of metastasis. Preclinical evidence demonstrates its effectiveness in breast, colorectal, lung, leukemia, and other cancers, while synergistic benefits have been observed in combination with chemotherapeutics and radiotherapy. Furthermore, nanoparticle-based delivery systems have enhanced bromelain's bioavailability and tumor-targeting capacity. Although preclinical studies strongly support bromelain's anticancer potential, clinical validation remains limited, emphasizing the need for well-structured trials to standardize dosing and confirm efficacy in humans. This review highlights bromelain's role as a promising adjunctive agent in cancer therapy and identifies directions for future research.

KEYWORDS: Ananas comosus (pineapple), bromelain, ferroptosis.

1. INTRODUCTION

Overview of Cancer and Current Treatment Challenges

Cancer remains one of the most formidable health challenges globally, characterized by uncontrolled cell proliferation and the potential to invade or spread to distant organs. Despite major advances in medical science, cancer treatment continues to face significant hurdles, including high toxicity, multidrug resistance, limited efficacy in certain tumour types, and adverse effects associated with chemotherapy and radiotherapy.[1,2] These limitations highlight an urgent

need for safer, more effective, and targeted therapies that can complement or substitute conventional treatment approaches.

Introduction to Bromelain and Its Sources (Pineapple)

Bromelain is a natural proteolytic enzyme complex primarily extracted from the fruit and stem of *Ananas comosus* (pineapple).[3] Traditionally known for its anti-inflammatory, digestive, and wound-healing properties, bromelain has garnered growing attention in biomedical research due to its wide-ranging pharmacological activities, including antithrombotic, immunomodulatory, and particularly, anticancer effects.[4,5] The therapeutic benefits of bromelain are attributed to its ability to modulate key molecular pathways involved in apoptosis, cell cycle regulation, angiogenesis, and metastasis, making it a promising candidate in oncology research.[6,7]

Importance of Exploring Natural Compounds in Cancer Therapy

The exploration of plant-derived compounds for cancer treatment is not new; many current chemotherapeutics are either directly obtained from plants or inspired by natural molecules. Natural compounds often possess multi-targeted mechanisms of action with relatively lower toxicity profiles.[8] In this context, bromelain exemplifies the potential of natural agents to enhance therapeutic outcomes while reducing side effects. As resistance to conventional drugs becomes increasingly problematic, naturally occurring bioactive compounds like bromelain offer alternative or adjunctive strategies for overcoming the limitations of existing cancer therapies [9,10]

Objective of the Review

This review aims to comprehensively evaluate the anticancer potential of bromelain derived from *Ananas comosus*, highlighting its molecular mechanisms, experimental evidence from in vitro and in vivo studies, synergistic effects with conventional chemotherapeutics, and novel delivery systems such as nanoparticles. Through this review, we intend to shed light on bromelain's role as a promising bioactive agent in cancer management and identify future research directions for its development as a complementary or standalone therapeutic intervention.[11,12]

2. Bromelain: A Bioactive Compound

Bromelain is a proteolytic enzyme complex derived primarily from the pineapple plant (*Ananas comosus*), encompassing both stem and fruit sources. It exhibits a range of therapeutic properties, including anti-inflammatory and anticancer activities, making it a compound of significant interest in pharmaceutical and nutraceutical applications.[13] The extraction, purification, and stabilization of bromelain are critical for its efficacy and commercial viability.[14]

Phytochemistry and Composition

Bromelain comprises a mixture of thiol endopeptidases and other components such as phosphatases, glucosidases, peroxidases, cellulases, glycoproteins, and carbohydrates.[15] These constituents contribute to its diverse biological activities. The enzyme complex is characterized by its proteolytic activity, which is influenced by factors like pH, temperature, and the presence of inhibitors.[15]

Table 1: Composition of Bromelain and Its Enzymatic Components.

Component Type	Name	Function
Protease	Thiol endopeptidases	Proteolysis of cellular proteins
Enzyme	Phosphatases	Dephosphorylation
Enzyme	Glucosidases, Peroxidases	Carbohydrate metabolism, ROS modulation
Enzyme	Cellulases	Plant Fiber degradation
Other	Glycoproteins, Carbohydrates	Stability, bioactivity

Extraction and Purification Techniques

The extraction and purification of bromelain have evolved to enhance yield, activity, and purity. Several methods have been employed:

- **Reverse Micellar Extraction (RME):** Utilizing surfactants like cetyltrimethylammonium bromide (CTAB), RME has achieved activity recoveries up to 97.56% with a purification fold of 4.54. This method leverages electrostatic interactions for selective extraction.[15]
- **High-Speed Counter-Current Chromatography (HSCCC):** When combined with reverse micellar systems, HSCCC has facilitated the purification of bromelain, yielding significant quantities with high purity levels[16]
- **Membrane Filtration Techniques:** Microfiltration and ultrafiltration have been employed to concentrate and purify bromelain. For instance, a combination of microfiltration and ultrafiltration achieved an 85% activity recovery and a 10-fold concentration of bromelain.[17]
- **Ion Exchange Chromatography:** This technique has been widely used for bromelain purification, offering high specificity and scalability. Cation exchange chromatography, in particular, has achieved up to a 10-fold purification factor.[18–20]

Bioavailability and Stability

Bromelain's therapeutic efficacy is influenced by its stability and bioavailability.

- **Stability in Gastric Conditions:** Studies have shown that bromelain maintains proteolytic activity in artificial gastric juice for up to 4 hours, indicating resilience in acidic environments.[20]
- **Enteric Nanoparticulate Formulations:** To enhance oral bioavailability and protect bromelain from gastric degradation, enteric-coated nanoparticulate formulations using polymers such as Eudragit® L100 have been developed. These formulations have demonstrated improved stability, with a shelf life extending up to two years under real-time storage conditions.[21,22]

3. Mechanisms of Action in Cancer

Proteolytic Activity and Its Impact on Tumour Cells

Bromelain's proteolytic nature enables it to degrade proteins essential for tumour cell survival and proliferation. In gastrointestinal carcinoma cell lines, bromelain treatment resulted in a concentration-dependent inhibition of cell proliferation. Specifically, half-maximal inhibitory concentration (IC_{50}) values were reported as 29 µg/mL for HT29-5F12, 34 µg/mL for HT29- 5M21, 94 µg/mL for MKN45, and 142 µg/mL for KATO-III cells.[23,24] This antiproliferative effect is attributed to bromelain's ability to disrupt cellular processes critical for tumour growth.[25]

Induction of Apoptosis

Bromelain induces apoptosis in cancer cells through both intrinsic and extrinsic pathways. In MKN45 gastric carcinoma cells, bromelain treatment led to the activation of caspases 3, 8, and 9, cleavage of poly (ADP-ribose)

polymerase (PARP), overexpression of cytochrome c, and attenuation of phospho-Akt and Bcl-2 proteins.[26,27] Similarly, in GI-101A breast cancer cells, bromelain increased the activities of caspase-9 and caspase-3, along with elevated levels of cytokeratin 18, indicating enhanced apoptotic cell death.[28]

Cell Cycle Arrest and Inhibition of Proliferation

Bromelain has been shown to arrest the cell cycle at the G_2/M phase, thereby inhibiting cancer cell proliferation. In human epidermoid carcinoma A431 and melanoma A375 cells, bromelain treatment resulted in G_2/M phase arrest, mediated by modulation of cyclin B1, phospho-cdc25C, Plk1, phospho-cdc2, and myt1. This arrest hampers the cells' ability to divide, contributing to its antiproliferative effects.[29,30]

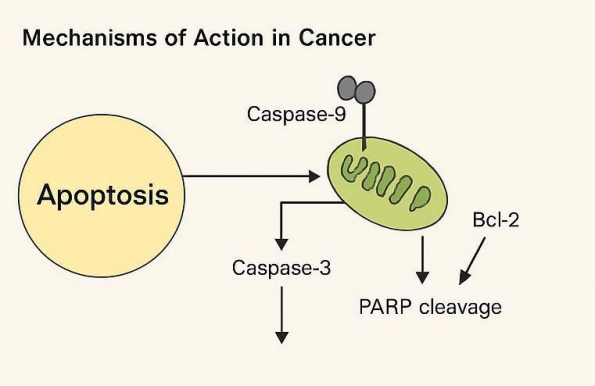

Figure 1: Mechanism of action Autophagy and Ferroptosis Induction.

Bromelain induces autophagy, a cellular degradation process, which can lead to cell death in cancer cells. In MCF-7 breast cancer cells, bromelain treatment increased autophagic activity, as evidenced by the upregulation of autophagy-related proteins like LC3BII and Beclin-1. This autophagic response was followed by apoptotic cell death, suggesting that autophagy facilitated apoptosis in these cells.[31,32] Additionally, bromelain has been implicated in inducing ferroptosis, a form of iron-dependent cell death characterized by lipid peroxidation. In colorectal cancer cells, bromelain treatment led to increased expression of ACSL-4, a key enzyme in ferroptosis, indicating its role in promoting this cell death pathway.[33,34]

Inhibition of Metastasis

Bromelain exhibits antimetastatic properties by interfering with cancer cell adhesion and migration. In glioma cells, bromelain treatment resulted in the reversible inhibition of cell migration and invasion. This effect was attributed to the proteolytic cleavage of cell surface molecules such as integrins and CD44, which are crucial for cell adhesion and motility. By disrupting these molecules, bromelain impairs the metastatic potential of cancer cells.[29,30,34]

4. In Vitro Studies on Anticancer Properties of Bromelain Breast Cancer

Bromelain exhibits potent anticancer effects against breast cancer cells. In GI-101A breast cancer cells, treatment with bromelain led to a dose-dependent increase in apoptosis, evidenced by elevated activities of caspase-9 and caspase-3, as well as increased levels of cytokeratin 18 (CK18), a marker of apoptosis. These findings were further supported by DNA fragmentation analysis and nuclear staining, confirming the induction of apoptosis in these cells (35,36). Additionally, bromelain has been shown to inhibit the proliferation of both oestrogen receptor-positive (MCF-7) and triple-negative (MDA-MB-231) breast cancer cell lines in a time- and dose-dependent manner. This antiproliferative

effect is associated with the induction of autophagy, as indicated by the upregulation of autophagy-related proteins LC3BII and beclin-1. Furthermore, bromelain treatment results in the activation of stress- related kinases such as c-Jun N-terminal kinase (JNK) and p38, while downregulating extracellular signal-regulated kinase (ERK) phosphorylation, suggesting a shift towards pro- apoptotic signalling pathways.[37,38]

In murine 4T1 breast cancer cells, bromelain has been observed to reduce cell viability in a concentration-dependent manner. When combined with radiation therapy, bromelain enhances the radiosensitivity of these cells, leading to decreased survival and proliferation. This radiosensitizing effect is attributed to the activation of apoptotic pathways, including increased activities of caspase-3 and caspase-9.[39]

Table 2: Anticancer Effects of Bromelain on Specific Cancer Types (In Vitro and In Vivo).

Cancer Type	Cell Line	Effect Observed	Mechanism
Breast	GI-101A, MCF-7	Apoptosis, Autophagy	↑ Caspase-3, ↑ LC3BII
Colorectal	HT-29, HCT116	ROS generation, apoptosis	↑ AIF, PARP cleavage
Lung	A549	Inhibited proliferation, apoptosis	↑ ROS, Caspases
Leukaemia	HL-60	Cell cycle arrest, apoptosis	↓ Bcl-2, ↑ cytochrome c
In vivo	4T1 breast mouse	↓Tumour growth, ↑Radiosensitivity	↓ Ki-67, ↑ PARP-1

Colorectal Cancer

Bromelain demonstrates significant anticancer activity against colorectal cancer (CRC) cells. In vitro studies using CRC cell lines such as HT-29, HCT116, and DLD-1 have shown that bromelain treatment leads to a dose-dependent reduction in cell viability. This effect is mediated through the induction of reactive oxygen species (ROS) production, leading to oxidative stress, and the activation of autophagy pathways, as evidenced by increased formation of autophagosomes and lysosomes.[40] Furthermore, bromelain induces apoptosis in CRC cells, as indicated by the activation of caspases-3, -8, and -9, and the cleavage of poly (ADP-ribose) polymerase (PARP). These apoptotic events are associated with the upregulation of pro-apoptotic proteins such as apoptosis-inducing factor (AIF) and Endo G. [41,42] In vivo studies using zebrafish and xenograft mouse models have corroborated these findings, showing that bromelain treatment suppresses tumour growth and progression in CRC.[40,43]

Lung Cancer

Bromelain exhibits cytotoxic effects against lung cancer cells. In studies involving human lung carcinoma cell lines, bromelain treatment has been shown to inhibit cell proliferation and induce apoptosis. The mechanisms underlying these effects include the activation of caspase-dependent apoptotic pathways and the modulation of signalling pathways involved in cell survival and proliferation. Additionally, bromelain treatment leads to the generation of reactive oxygen species, contributing to oxidative stress and subsequent cell death.[44,45] These findings suggest that bromelain holds potential as a therapeutic agent in the treatment of lung cancer.

Leukaemia and Lymphoma

Bromelain has demonstrated anticancer activity against leukaemia and lymphoma cells. In vitro studies have shown that bromelain treatment leads to the inhibition of cell proliferation and the induction of apoptosis in these cancer types. The apoptotic effects are mediated through the activation of caspase-dependent pathways, including caspases-3, -8, and -9, and the modulation of mitochondrial pathways, as indicated by the release of cytochrome c and the activation of apoptosis-inducing factor (AIF).[46,47] Furthermore, bromelain treatment results in the downregulation of anti-apoptotic proteins such as Bcl-2 and MUC1, and the inhibition of survival signalling pathways, including the Akt pathway.[48]

These molecular events contribute to the induction of apoptosis and the suppression of tumour cell survival in leukaemia and lymphoma.

In Vivo Studies and Animal Models of Bromelain in Cancer Therapy Synergistic Effects with Conventional Chemotherapy

Bromelain has demonstrated potential in enhancing the efficacy of chemotherapeutic agents. In a study involving mice with 4T1 triple-negative breast cancer, the combination of bromelain and cisplatin resulted in a significant reduction in tumour size and lung metastasis compared to cisplatin alone.[48,49] This combination also modulated inflammatory markers, suggesting an anti-inflammatory role of bromelain in the tumour microenvironment.[50] Additionally, bromelain has been investigated for its synergistic effects with other chemotherapy drugs in breast cancer treatment. Studies have shown that bromelain can enhance the cytotoxic effects of chemotherapeutic agents, leading to increased apoptosis and reduced proliferation of cancer cells.[51,52]

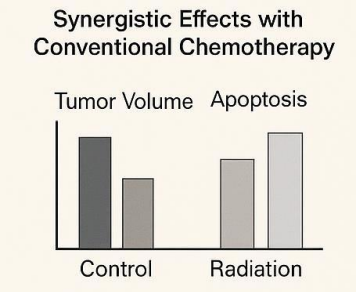

Figure 2: Synergistic Effects with Conventional Chemotherapy.

Radioprotection and Radiosensitization

Bromelain exhibits dual roles in radiotherapy by sensitizing tumour cells to radiation while protecting normal cells. In vitro and in vivo studies have demonstrated that bromelain pretreatment enhances the radiosensitivity of Ehrlich ascites carcinoma cells, leading to increased tumour cell death.[53,54] Simultaneously, bromelain offers radioprotective effects to normal tissues, reducing radiation-induced damage.[55] Further research using tumour- bearing mice models has shown that bromelain's radiosensitizing effect is mediated through the inhibition of proliferation markers like Ki-67 and the activation of apoptotic pathways involving PARP-1.[56]

Toxicological Studies and Safety Profile

Preclinical studies have consistently reported the low toxicity profile of bromelain. In animal models, the lethal dose (LD50) of bromelain is greater than 10 g/kg, indicating a wide safety margin.[57] Long-term administration in dogs at doses up to 750 mg/kg daily for six months showed no adverse effects.[58] Moreover, no carcinogenic or teratogenic effects were observed in rats at dosages of 1500 mg/kg per day.[59] Clinical evaluations have also supported bromelain's safety. In a study involving patients with inoperable pseudomyxoma peritonei, treatment with a combination of bromelain and N-acetylcysteine (BromAc®) did not result in liver or kidney toxicity. While some inflammatory responses were noted, key blood parameters remained within normal ranges, underscoring bromelain's tolerability in therapeutic settings.[60]

6. Therapeutic Applications and Delivery Systems Nanoparticle Formulations for Targeted Delivery

To improve the specificity and efficacy of bromelain in cancer therapy, researchers have explored nanoparticle-based delivery systems. One such approach involves the use of superparamagnetic iron oxide nanoparticles (SPIONs)

conjugated with bromelain and folic acid (SPIONs–Br–FA). This formulation has demonstrated enhanced targeting of tumour cells, leading to reduced tumour burden and increased survival in 4T1 breast cancer-bearing mice.[48,55]

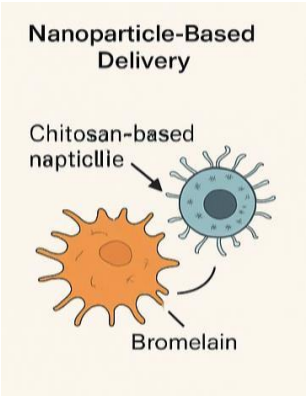

Figure 3: Nanoparticle based Bromelain delivery.

Another strategy employs lactobionic acid-modified chitosan nanoparticles to deliver bromelain alongside doxorubicin. This combination not only facilitates deeper penetration into tumour tissues but also enhances the accumulation of the chemotherapeutic agent at the tumour site, thereby improving its antitumor efficacy.[52,59]

Combination Therapies with Chemotherapeutic Agents

Bromelain has shown promise in augmenting the effects of conventional chemotherapeutic drugs. In vitro studies have revealed that bromelain, when combined with agents like 5- fluorouracil (5-FU), irinotecan, and oxaliplatin, exhibits synergistic cytotoxic effects against colorectal cancer cells. This synergy results in enhanced apoptosis and reduced cell viability compared to treatments with chemotherapeutic agents alone.[61,62]

Furthermore, the combination of bromelain with N-acetylcysteine (NAC) has been investigated for its potential to potentiate the efficacy of various chemotherapeutic agents, including cisplatin and paclitaxel. This combination has been shown to inhibit the growth and proliferation of gastrointestinal cancer cells more effectively than either agent alone.[63,64]

Encapsulation and Stabilization Techniques

To address the challenges associated with the stability and bioavailability of bromelain, various encapsulation techniques have been developed. For instance, encapsulating bromelain in chitosan nanoparticles has been shown to protect the enzyme from degradation, thereby enhancing its stability and therapeutic efficacy.[65]

Additionally, microencapsulation using sodium alginate and positively charged amino acids has been explored to achieve controlled release and improved stability of bromelain in gastrointestinal environments. This approach aims to protect bromelain from denaturation during oral administration, thereby preserving its therapeutic activity.[66,67]

Table 3: Encapsulation Techniques for Bromelain and Their Benefits

Method	Material Used	Benefit
Chitosan nanoparticles	Chitosan	Protection from GI degradation
Hydrogel beads	Sodium alginate + amino acids	Temperature & pH stability
Enteric nano formulation	Eudragit® L100	Targeted intestinal release

Another innovative method involves the use of hydrogel beads for bromelain encapsulation. This technique provides protection against temperature variations and enhances the enzyme's stability, making it suitable for various biomedical applications.[68,69]

7. Clinical Studies and Human Trials

Efficacy and Safety in Cancer Treatment

Clinical investigations into bromelain's role in cancer therapy have primarily focused on its supportive benefits rather than direct anticancer effects. Notably, bromelain has been utilized in enzymatic debridement for chronic wounds and deep burn injuries, demonstrating potential safety and efficacy in these contexts.[70,71]

Additionally, its anti-inflammatory and analgesic properties have been explored in treating conditions like osteoarthritis and rheumatoid arthritis, which could be beneficial in managing cancer-related symptoms.[72]

In the realm of oncology, bromelain's application has extended to alleviating postoperative complications. For instance, a randomized controlled trial assessed the effects of bromelain combined with alpha-lipoic acid on early complications following breast-conserving surgery.[73]

Clinical Outcomes

The study found a significant reduction in breast edema and seroma formation in patients receiving the combination therapy compared to those who did not.[74] Furthermore, bromelain has been investigated for its potential to enhance the efficacy of chemotherapeutic agents. Preclinical studies suggest that bromelain may sensitize cancer cells to the cytotoxic effects of chemotherapy, thereby improving treatment outcomes.[75,76] However, these findings are primarily based on laboratory studies, and more extensive clinical trials are necessary to confirm these effects in humans.[77]

Potential Side Effects and Limitations

While bromelain is generally considered safe, some side effects have been reported in clinical settings. These include gastrointestinal symptoms such as diarrhoea, nausea, and vomiting, as well as allergic reactions and an increased risk of bleeding, particularly in individuals taking anticoagulant medications like warfarin and clopidogrel.[78,79] Additionally, there have been sporadic reports of allergic reactions and asthma symptoms related to occupational exposure to bromelain.[80]

It is important to note that while bromelain has shown promise in preclinical studies, its effectiveness in cancer treatment has not been conclusively demonstrated in human trials.[81,82] Therefore, while it may offer supportive benefits, bromelain should not be considered a standalone treatment for cancer. Patients should consult healthcare professionals before incorporating bromelain into their treatment regimen, especially if they are taking other medications or have underlying health conditions.[83]

Table 4: Reported Side Effects and Clinical Safety of Bromelain.

Observation	Reported in Study	Outcome
GI disturbances	Clinical therapy (BromAc®)	Nausea, vomiting, mild inflammation
Haemorrhagic risk	Patients on warfarin/clopidogrel	Increased bleeding tendency
Long-term safety	Dog models, rat studies	No carcinogenic/teratogenic effects

8. Future Perspectives and Research Directions Challenges in Clinical Translation

One significant hurdle in the clinical application of bromelain is the variability in its composition. Different extraction methods and sources can lead to inconsistencies in the enzyme's activity and concentration, making it difficult to standardize dosing and ensure reproducible therapeutic effects.[84,85]

Clinical Evidence Gap

Additionally, while bromelain has demonstrated anticancer properties in vitro and in animal models, there is a lack of comprehensive clinical trials confirming its efficacy and safety in humans. This gap underscores the need for well-designed studies to validate its therapeutic potential.[86,87]

Innovative Delivery Strategies

To enhance the therapeutic efficacy of bromelain, researchers are exploring advanced delivery systems. For instance, bromelain-conjugated and lactobionic acid-modified chitosan nanoparticles have been developed to improve targeted delivery to tumour sites. These nanoparticles facilitate better accumulation in tumours and enhance the cytotoxic effects of chemotherapeutic agents like doxorubicin.[88,89]

Another approach involves the use of pH-sensitive bromelain nanoparticles, which release the enzyme in the acidic microenvironment of tumours, thereby increasing its anticancer activity while minimizing effects on healthy tissues.[90,91]

Potential for Personalized Cancer Therapy

The integration of bromelain into personalized cancer therapy is an emerging area of interest. Given its ability to modulate various biological pathways, including inflammation and immune responses, bromelain could be tailored to individual patient profiles to enhance treatment outcomes. However, more research is needed to understand its interactions with specific genetic and molecular characteristics of different cancers.[92,93]

Exploration of Other Phytochemicals in Pineapple for Cancer Therapy

Beyond bromelain, pineapple contains other bioactive compounds with potential anticancer properties. Phytochemicals such as caffeic acid, ferulic acid, and synaptic acid have been identified in pineapple and shown to exhibit inhibitory effects on heat shock protein 90 (Hsp90), a molecular chaperone involved in cancer progression.[94,95] These findings suggest that a combination of these compounds could offer a multifaceted approach to cancer therapy. [96,97]

Furthermore, studies have indicated that pineapple vinegar, rich in various phytochemicals, may delay cancer progression, highlighting the potential of whole-food approaches in cancer prevention and treatment.[98–100]

9. CONCLUSION

Summary of Key Findings

Bromelain, a proteolytic enzyme extracted from pineapple stems, has demonstrated a range of pharmacological activities in preclinical studies, including anti-inflammatory, immunomodulatory, and anticancer effects. In vitro and animal model research has shown that bromelain can induce apoptosis, inhibit tumour cell proliferation, and modulate immune responses, suggesting its potential as an adjunct in cancer therapy.

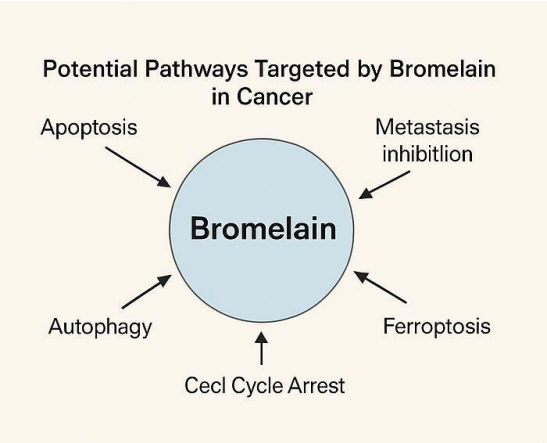

Figure 4: Targeted pathways by Bromelain

Clinical Implications and Potential for Bromelain in Cancer Therapy

The integration of bromelain into cancer treatment regimens offers promising avenues, particularly in enhancing the efficacy of chemotherapeutic agents and mitigating associated side effects. Studies have indicated that bromelain may sensitize cancer cells to chemotherapy and reduce inflammation-related complications. Its role in modulating immune responses further underscores its potential utility in comprehensive cancer care.

Need for Further Research

Despite encouraging preclinical data, the translation of bromelain's anticancer properties into clinical practice remains limited. There is a pressing need for well-designed clinical trials to evaluate its safety, optimal dosing, and therapeutic efficacy in humans. Future research should also focus on standardizing bromelain preparations to ensure consistency and reproducibility in clinical outcomes.

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