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Bromelain: A Review Of Its Therapeutic Effects And Molecular Mechanisms

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Abstract: *Bromelain is a natural enzyme that can be extracted from the stem or fruit of the Ananas comosus plant and has demonstrated many therapeutic effects, including anti-inflammatory, anti-cancer, anti-allergic properties, among others. Therefore, this review is to compile a compilation of the therapeutic effects and molecular mechanisms of bromelain. The bibliographic search was carried out in the SCOPUS, PubMed and ScienceDirect databases from 2004 to 2024. The key words used were "ananas comosus", "bromelain", "therapeutic effect", "molecular mechanism". Only original articles were considered and review or observational articles were excluded. Bromelain mainly showed antidiabetic, antioxidant, anti-inflammatory and anticancer effects, in which signaling pathways such as Oxi-LDL/LPA/LPAR1/BACE1, inhibition of cytokines, stabilization of molecules due to trapping of free radicals, apoptosis, downregulation of genes related to inflammation, metastasis and angiogenesis. Bromelain showed many therapeutic effects in in vitro and in vivo trials, thus demonstrating that this natural enzyme represents a therapeutic option with a wide range of applications, backed by scientific evidence supporting its therapeutic effects.*

Keywords: *Bromelain; therapeutic effect; molecular mechanism; Ananas comosus.*

Resumen: *La bromelina es una enzima natural que se puede extraer del tallo o del fruto de la planta Ananas comosus y ha demostrado muchos efectos terapéuticos entre ellos propiedades antiinflamatorias, anticancerígenas, antialérgicas y entre otras. Por ello, de esta revisión es realizar una compilación de los efectos terapéuticos y mecanismos moleculares de la bromelina. La búsqueda bibliográfica se realizó en las bases de datos de SCOPUS, PubMed y ScienceDirect desde el 2004 hasta el 2024. Las palabras claves que se utilizaron fueron "ananas comosus", "bromelina", "efecto terapéutico", "mecanismo molecular". Se consideraron solo artículos originales y se excluyeron artículos de revisión u observacionales. La bromelina mostró principalmente efectos antidiabéticos, antioxidantes, antiinflamatorios y anticancerígenos, en los cuales estuvieron involucradas vías de señalización como la Oxi-LDL/LPA/LPAR1/BACE1, inhibición de citocinas, estabilización de las moléculas debido al atrapamiento de radicales libres, apoptosis, downregulation de genes relacionados con inflamación, con metástasis y angiogénesis. La bromelina mostró muchos efectos terapéuticos en ensayos in vitro e in vivo, demostrando así que esta enzima natural representa una opción terapéutica con una amplia gama de aplicaciones, respaldada por evidencia científica que respalda sus efectos terapéuticos.*

Palabrasclave: *Bromelina; efecto terapéutico; mecanismo molecular; Ananas comosus.*

INTRODUCTION

Daily consumption of fruits is an important part of a healthy diet; however, it has recently been displaced by the consumption of fast food, which occupies a large part of the diet. This can lead to health consequences such as heart disease, cancer, diabetes, and obesity. In response to this, there has been a shift in eating habits and support with nutritional supplements. Bromelain has been reported to promote the proper utilization of food, which could ensure an adequate daily level of micronutrients and fiber, making it a good nutritional supplement, in addition to presenting various therapeutic effects that would help alleviate certain diseases (Cervo et al., 2014).Bromelain is a natural enzyme that can be extracted from the stem or fruit of the Ananas comosus plant, with higher amounts of proteases found in the stem compared to the fruit. Methods such as centrifugation, ultrafiltration, and lyophilization are used for its isolation or purification (Parra et al., 2013). Bromelain stands out for its proteolytic activity as it helps digest proteins by breaking them down into amino acids and also strengthens the immune system by being a natural anticoagulant (Del juncal-Guzmán et al., 2021). Furthermore, it can exert its action over a wide pH range from 4.5 to 9.5 (Hadidi et al., 2020).Various studies have demonstrated that bromelain has anti-inflammatory properties associated with cancer as it inhibits cyclooxygenase-2 (COX-2) and prostaglandin E2 (PGE-2) in murine microglial cells and human monocytic leukemia cell lines (Kiani et al., 2022, Seenak et al., 2021). Additionally, it has shown therapeutic effects on allergies, osteoarthritis, sinusitis, and ulcerative colitis (Agrawal et al., 2022).Thus, the lack of awareness of the therapeutic effects of bromelain could result in this enzyme not being considered when addressing any research or pathophysiological process. Therefore, it is important to highlight the effects of this enzyme, which can be used to evaluate certain effects in future studies. Consequently, the objective of this review is to compile the therapeutic effects and molecular mechanisms of bromelain.

METHOD

Systematic searches for relevant articles were conducted in bibliographic databases such as SCOPUS, PubMed, and ScienceDirect, considering a maximum age of 20 years. The systematic search was carried out considering the following combinations of keywords: "ananas comosus", "bromelain", “therapeutic effect”, and “molecular mechanism”. Once in the databases, the article titles were examined based on the following criteria: trial or intervention, effect, and use. Then, the abstracts were analyzed based on original studies, evaluation of therapeutic effect, experimental study, and usable results.The following criteria were also taken into account to exclude information: reviews and observational studies were excluded. Bibliographic data, type of studies, age of the study, and the therapeutic effects of bromelain and molecular mechanisms to exert the mentioned effects were collected, along with the availability of the article in the database.The information collected about bromelain in the selected studies demonstrated various therapeutic effects. Due to this diversity, they were grouped into categories that presented a similarity in their therapeutic effect, also taking into consideration the presence of molecular mechanisms.

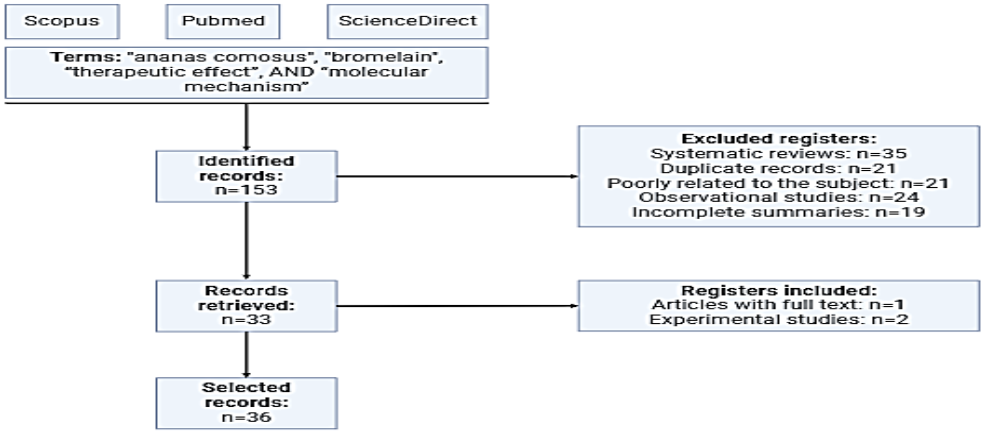

Figure 1. Flowchart of the Bibliographic Search

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RESULTS

Table 1. Therapeutic Effects and Molecular Mechanisms of Bromelain

Pharmacological effect	Test type	Sample or study model	Concentration	Mechanism of action	References
Antidiabetic	In vivo	Streptozotocin-induced type I diabetes in mice	10 mg/kg/day	Downregulation of the Oxi-LDL/LPA/LPAR1/BACE1 signalling pathway	(Abo El-Magd et al., 2021)
	In vivo	Effect of 12 weeks of bromelain on plasma fribinogen	1050 mg/day	Fibrinolytic activity, enhancing the conversion of plasminogen to plasmin	(Ley et al., 2016)
	In vivo	Therapy-controlled patients with non-proliferative diabetic retinopathy with focal edema	500 mg	Reduction of CMT (central macular thickness)	(Carnevali et al., 2023)
Antioxidant	In vitro	-	0.08 and 2mL/kg body weight	-	(Mohamad et al., 2015)
	In vitro	DPPH	2 – 10 mg/mL	Stabilisation of molecules due to free radical trapping	(Saptarini et al., 2019)
	In vivo	-	0,1%; 0,5%; 1%	-	(Bradiyya et al., 2020)
Anti-inflammatory	In vivo	Mice C57BL/6	14 mg purified bromelain from stems	Decreased production of pro-inflammatory cytokines and localisation of leukocytes at sites of inflammation.	(Hale et al., 2010)
	In vitro	Human macrophage cells U937	1, 10 y 100 µg/mL	Inhibitory effect on proinflammatory cytokines, chemokines and cyclooxygenase pathway	(Kasemsuk et al., 2018)
	In vitro	Macrophage and monocyte cells from mice RAW264.7	Bromelain extract from pineapple rhizome 100-200 µg/mL	Inhibition of inflammatory mediators and cytokines	(Insuan et al., 2021)

	In vitro	Human cellular models of stomach, intestine and chondrocytes	Patented bromelain extract (Bromeyal™)	Inhibition of IL-8, COX-2, iNOS	(Bottega et al., 2021)
	In vivo	Human Gingival Fibroblasts (HGF)	2,5 – 20 g/mL	Suppression of pro-inflammatory cytokine production IL-6 and IL-8 in HGFs	(Lu et al., 2023)
	In vivo	Exodontic patients	Bromelain extract 150 mg/day for 3 days.	-	(de la Barrera-Núñez et al., 2014)
	In vivo	Healthy males	100 mg for 4-7 days. 100 mg extract	Prevents early cytolysis	(Blasco et al., 2012)
Anti-allergic	In vitro	-	40-fold diluted pineapple extract 0,1 mg/mL of bromelain	Decrease in Cyt s 2 levels according to temperature and reaction time, inhibited by iodoacetic acid	(Kiyota et al., 2020)
	In vivo and in vitro	-	0.08 mL or 2mL/kg body weight	Negative regulation of inflammation-related genes (iNOS, NF-kB and COX2), metastasis-related genes (iCAM, VEGF and MMP9) and angeogenesis-related genes (CD26, TIMP1, HGF, MMP3, IGFBP-1 and IGFBP-2).	(Mohamad et al., 2019)
Anticancer	In vitro	Hepatocellular carcinoma cell line HepG2	25 - 125 ug/mL	Cell arrest in G0/G1 phase, decreased cell distribution in S phase, cell arrest in G2/M phase, production of apoptosis, increased p53 protein expression and downregulation of β-catenin protein.	(Murthy & Narsaiah, 2021)

	In vitro	RCC cell lines, a zebrafish model and a xenograft mouse model	0-90 ug/mL	Induction of reactive oxygen species (ROS), superoxide, autophagosomes and lysosomes Inhibition of cyclooxygenase-2 (COX-2) expression.	(Chang et al., 2019)
	In vivo	Mice	1 mg in 50% ethanol per mice	Inactivation of nuclear factor kappa B (NF-κB). Blocked phosphorylation and degradation of Iκ Bα	(Bhui et al., 2009)
Anti-dementia	In vivo	Aluminium-induced Alzheimer's disease in mice	10 mg/kg	Signalling pathway modulation TXNIP/P-IRS-1/PI3K	(Eraky et al., 2023)
Hypolipidemic	In vivo	-	20 mg/kg for 12 weeks	β-oxidation of fatty acids by regulating the expression of proteins involved in hepatic metabolic pathways.	(Hu et al., 2020)
Enzymatic debridement Wound healing activities	In vivo	Adult burn patients	-	Influence on modulation of expression of factors involved in pro- and anti-inflammatory processes, such as TNF-α, TGF-β. Activation of mesenchymal stem cells and increased anti-inflammatory activity of IL-10.	(Buta et al., 2023)
Suppression of orofacial nociception	In vivo	Induction of orofacial nociception with capsaicin, cinnamaldehyde or menthol in wild-type zebrafish lips	Administration i.p. (20 μL) at different concentrations of bromelain (0.1, 0.3 and 1.0 mg/mL)	TRPV1 channel antagonist	(Ribeiro et al., 2024)
Antioxidant Anti-inflammatory	In vivo	Progression of experimental periodontitis in Wistar rats	5 and 10 mg/kg/day	Reduction of TNF-α, IL-M-CSF6 overexpression, consequently reduction of MMP and RANKL	(Paksoy et al., 2023)

	In vitro	HSC-T6 cell line	0-200 ug/mL	Suppresses HSC activation, inhibits myofibroblast activation by reducing α-SMA, Decreases activation of collagen-producing cells.	(Sayed et al., 2023)
Proteolytic	In vivo	Thioacetamide-induced liver fibrosis in male Wistar albino rats	300, 200 and 100 mg/kg body weight	Degrades ECM, decreases fibrogenic markers such as laminin and hyaluronic acid, decreases overexpression of ROS	
	In vivo	Female Wistar albino rats	10 mg/kg/body weight dissolved in 1 ml saline for 10 days.	Fibrinolytic activity by increasing the turnover of plasminogen to plasmin.	(Sahbaz et al., 2015)
Neuroprotective	In vivo	Murine model of Alzheimer's disease.	10 and 20 mg/kg body weight, i.p.	Stimulation of the cholinergic system by inhibiting AChE, promoting signal transmission and improving memory. Attenuates Aβ 1-42 aggregation by inhibiting β-secretase, reduces neuroinflammation for protection of neurons Mitigates oxidative stress by enhancing antioxidant enzyme levels and reducing nitrite and lipid peroxidation. Increases BDNF levels, promoting neurogenesis and repairing neuronal plasticity through the TrkB-related kinase B-activated signal transduction pathway.	(Kumar et al., 2022)

Healing	In vivo	Histological sections of all wounded areas	25 mg/kg/day 45 mg/kg/day	Reduction of pro-inflammatory cytokines and chemokines (IFN-gamma and TNF alpha).	(Fathi et al., 2020)
Antispasmodic	In vivo	Isolated mouse ileum in organ bath	15 mg/mL	Inhibition of membrane PAR-2, PLC and PDE4	(Borrelli et al., 2011)
Inhibitor synergistically	In vitro	SARS-CoV-2 strains cultured in Vero cells	Increased concentrations: 0, 25, 50, 100 and 250 ug/mL acetylcysteine alone 20 mg/mL	Acetylcysteine reduces disulphide bridges, altering the molecular properties of most proteins. Bromelain, alters glycosidic bonds, reducing disulphide bonds.	(Akther et al., 2021)
Antioxidants Antiproliferative	In vitro	Panel of eight human tumour cell lines: U251 (glioma), MCF-7 (breast), OVCAR-03 (ovarian), NCI-ADR/RES (ovarian expressing multi-drug resistance phenotype), NCI-H460 (lung), PC-3 (prostate), HT-29 (colon adenocarcinoma) and K-562 (chronic myeloid leukaemia).	Bromelain stock solutions CB-NP and C-NP (5 mg/ml)	Increased ROS and superoxide levels, leading to high autophagy induction in colorectal cancer cells	(Ataide et al., 2021)
Autophagy Apoptosis	In vitro	RCC cells	Stem bromelain proteases 3 units/mg protein	Autophagy and apoptosis are induced by intracellular ROS	(Tsai et al., 2021)
Hepatoprotective	In vitro	Rat livers and blood	Ananas comosus extract 600 GDU/g	Maintenance of hepatocyte integrity	(Mendes et al., 2019)
Analgesic	In vivo	-	-	Inactivation of bradykinin in inflamed tissues	
Treatment of hepatic ischaemia/reperfusion (I/R) injury.	In vitro	Female Wistar rats	0.1, 1.0 or 10 mg/kg body weight of bromelain IV	Dose-dependent modulation of bradykinin levels at inflammatory sites, fibrinolytic activity and	(Bahde et al., 2007)

				ability to inhibit platelet aggregation	
Nephroprotector	In vivo	Male Wister rats	250 mg/kg/day	-	(El-Demerdash et al., 2020)
Inhibition of testicular dysfunction	In vivo	Male Wister rats	250 mg/kg/day	-	(Jebur et al., 2020)

DPPH: 2,2-difenil-1-picrilhidracilo; HSC: Células estrelladas hepáticas; IL: Interleucina; MMP: Metaloproteinasas de matriz; RANKL: Activador del receptor del ligando del factor nuclear kappa-B; TRP: Potencial de receptor transitorio; M-CSF: factor estimulante de colonias de macrófagos; TNF-α: Factor de necrosis tumoral alfa; TGF-β: Factor de crecimiento transformante beta; ROS: Especies reactivas de oxígeno; α-SMA: α-actina del músculo liso; ECM: Matriz extracelular; AChE: Acetilcolinesterasa; BDNF; factor neurotrófico; TrKB: Tropomiosina; CCR: cáncer colorrectal avanzado, iNOS: óxido nítrico sintasas.

DISCUSSION

Bromelain has shown many therapeutic effects in various pathologies both in in vitro and in vivo trials (Table 1). Among these effects are its antidiabetic properties, as bromelain has significantly decreased fasting blood glucose in rats initially administered streptozotocin, a drug commonly used to induce diabetes in mice by producing toxicity in pancreatic β-cells, thereby causing decreased insulin and increased blood glucose (Ghasemi & Jeddi, 2023). One of the mechanisms attributed to reducing diabetes is the downregulation of the Oxi-LDL/LPA/LPAR1/BACE1 signaling pathway, in which many proteins involved in that signaling are elevated in diabetic mice and bromelain has reduced the levels of these proteins and consequently also glucose (Abo El-Magd et al., 2021). Additionally, oral administration of bromelain plus curcugreen has shown a protective role in patients with diabetic retinopathy and focal edema as it improves central macular thickness and baseline vascular perfusion in the deep capillary plexus over time compared to the control group (Carnevali et al., 2023). On the other hand, it has been investigated whether bromelain reduces plasma fibrinogen and other cardiovascular disease risk factors in diabetic patients, finding that bromelain does not influence these parameters as it did not show a statistically significant difference when compared with placebo (Ley et al., 2016).Cancer is a complex disease that represents a significant public health burden worldwide. Despite advances in understanding its mechanisms and therapeutic approaches, the need for effective and safe strategies to prevent and treat cancer remains a priority (OMS, 2022). In this context, bromelain, an enzyme derived from pineapple, has been studied for its anticancer potential. This work discusses four studies investigating the effect of bromelain on different types of cancer, focusing on its ability to inhibit proliferation, induce apoptosis, and suppress metastasis. Through various experimental models and methodological approaches, these studies provide evidence of the anticancer effects of bromelain in several types of cancer, including skin cancer, colorectal cancer, liver cancer, and breast cancer.

Firstly, the studies reveal that bromelain exerts its anticancer effect through multiple mechanisms. This includes the induction of apoptosis, or programmed cell death, in cancer cells, as well as the inhibition of cell proliferation and metastasis. Additionally, bromelain shows the ability to modulate various cellular signaling pathways associated with carcinogenesis, such as the NF-kappa B, MAPK, and Wnt/β-catenin pathways. A common finding in the studies is bromelain's ability to reduce the expression of inflammatory and tumor-promoting proteins, such as COX-2 and β-catenin, while increasing the expression of proteins associated with tumor suppression, such as p53 and Bax. This ability to regulate gene expression and cellular activity suggests significant therapeutic potential for bromelain in cancer treatment (Mohamad et al., 2019, Murthy & Narsaiah, 2021, Bhui et al., 2009). Furthermore, bromelain is observed to induce the production of reactive oxygen species (ROS), contributing to selective cell death in cancer cells (Chang et al., 2019). This effect is associated with the activation of processes such as autophagy, which also contributes to the suppression of tumor growth and metastasis. It is important to note that these studies use a variety of experimental models, ranging from cell cultures to animal models, which reinforces the validity and relevance of the findings. However, more research, especially clinical studies in humans, is needed to validate the efficacy and safety of bromelain as a therapeutic agent against cancer.From the studies reviewed for antioxidant capacity, the first study by Mohamad and collaborators investigates the effect of pineapple vinegar on acetaminophen-induced liver injury in mice. It is observed that pineapple vinegar shows significant antioxidant capacity, which correlates with an improvement in glutathione (GSH) levels and a decrease in lipid peroxidation in the liver. Additionally, gallic acid is identified as one of the main active compounds in pineapple vinegar, along with other phenolic compounds. These compounds are associated with the antioxidant capacity of pineapple vinegar and its hepatoprotective effect (Mohamad et al., 2015). On the other hand, the second study by Saptarini and collaborators also focuses on antioxidant activity but centers on plant extracts in general, including bromelain, as antioxidant agents. The ability of plant-derived antioxidant agents to protect against induced free radicals and reduce oxidative stress is highlighted. The DPPH method is used to evaluate the antioxidant activity of these extracts (Saptarini et al., 2019). Comparing both studies, it is observed that both pineapple vinegar and plant extracts show significant antioxidant activity. Both studies emphasize the importance of

phenolic compounds and other natural antioxidants in protecting against oxidative damage and associated diseases.In the study by Kiyota and collaborators, an innovative approach to reducing levels of Cit s 2, an allergen present in oranges, using pineapple extract and its protease bromelain is presented. The importance of this work lies in the need to find solutions to reduce the presence of allergens in common foods, such as oranges, which could benefit people with food allergies. The notable finding that treatment with diluted pineapple extract and bromelain helps reduce residual levels of Cit s 2 below a safe limit is promising. This suggests that this technique could be a viable strategy for producing orange juice with reduced allergen content, potentially benefiting people with food allergies related to Cit s 2. However, it is mentioned that treatment with bromelain may introduce the risk of ingesting pineapple allergens. This implies the need to carefully evaluate the potential risks and benefits of this approach, especially for people with pineapple allergies (Kiyota et al., 2020).According to the reviewed studies, bromelain has protective activity. The first study reveals the improvement of rats with Alzheimer's disease induced by AlCl3 and D-galactose after consuming bromelain in low doses (10 mg/kg body weight), high doses (20 mg/kg body weight), in combination with donepezil (10.2 mg/kg body weight), and also treated with donepezil (2 mg/kg body weight). All these treatments reversed the effect of the disease (improvements in behavioral parameters, biochemical estimation, cortical staining). This study confirms the neuroprotective activity of this treatment (Kumar et al., 2022). A second study also administered AlCl3 to rats, inducing serious liver problems such as increased Al in liver tissue, changes in hematological parameters, increased concentrations of TBARS and H2O2, decreased enzymatic and non-enzymatic antioxidants and proteins, and altered bilirubin levels. Bromelain alone reduced lipid peroxidation and improved antioxidant status; as a supplement before intoxication, it managed to restore enzymatic and non-enzymatic antioxidants (Mendes et al., 2019). The studies analyzed and reviewed regarding antidemence properties reveal that bromelain has the ability to reduce dementia in patients with neurodegenerative diseases such as Alzheimer's. According to Eraky and researchers in an in vivo study in rats on the ameliorative effect of bromelain on Alzheimer's disease, which was induced by aluminum (AlCl3), improvements were found in exploratory activity, cognitive and spatial functions (dementia), and reduced levels of anxiety and depression (Eraky et al., 2023). In another similar study where bromelain was administered intraperitoneally for 30 consecutive days at low doses of 10 mg/kg body weight and high doses of 20 mg/kg, donepezil 2 mg/kg, and the combination of bromelain + donepezil (10 and 2 mg/kg), it was demonstrated that they could significantly reduce the effects of AlCl3 and D-galactose, which produced cognitive impairment and other neurodegenerative effects in the rats. The use of bromelain alone and in combination with donepezil stood out for preventing spatial learning and memory deficits, reducing cognitive impairment, dementia, oxidative damage, and increasing synaptic plasticity (Kumar et al., 2022). Both studies demonstrate the neuroprotective activity of bromelain alone or in combination with other drugs such as donepezil (Eraky et al., 2023).On the other hand, bromelain also showed hypolipidemic effects as described in the research conducted by Dave and collaborators, where the hypolipidemic capacity of bromelain obtained from the stem, which is also used against overweight individuals, is evaluated. This study reveals that bromelain at the cellular level has the ability to irreversibly inhibit the differentiation between 3T3-L1 type adipocytes by reducing the expression of the adipogenic gene at the genetic level and also inducing lipolysis and apoptosis in adipocytes (Dave et al., 2012). From a molecular point of view, the addition of bromelain halted adipose tissue formation by negatively affecting the regulation of C/EBPα and PPARγ genes, regardless of the expression of the C/EBPβ gene. Additionally, bromelain also decreased mRNA levels of various proteins essential for lipid metabolism, such as ap2, FAS, LPL, CD36, and ACC (Dave et al., 2012). This study reveals the great potential of bromelain in reducing elevated lipid levels and achieving a hypolipidemic effect in vivo (Hu et al., 2020).Bromelain is a mixture of proteolytic enzymes present in all tissues of pineapple (Ananas comosus). It is known as an efficient debridement agent in the treatment of burns and tissue regeneration. In the first phase of wound healing, bromelain's proteases hydrolyze fibrin, a clot deposited on the wound. They also digest damaged components of the extracellular matrix such as collagen, elastin, and laminin through proteolysis. This digestion induces the release of growth and angiogenic factors in the matrix, as well as the activation of

bioactive chemokines and cytokines, and the processing of cell-to-cell and matrix-to-cell adhesion molecules. Bromelain contains a non-proteolytic enzyme called escharase, which does not have analytical activity against normal proteins and efficiently cleaves glycosaminoglycan substrate and removes eschars (Bayat et al., 2019).Bromelain has the ability to clean necrotic tissue from the wound and form a protective barrier against microorganisms. However, because it is an enzyme, it has usage limitations in the industry as it is easily denatured and degraded, besides being unstable in some formulations. Bromelain directly affects pain mediators such as bradykinin, reduces swelling and bruising, and shortens the healing period after trauma and surgical procedures. Additionally, bromelain reduces plasma kininogen, thus inhibiting the production of kinin, known as an agent that induces inflammation, pain, and swelling (Bayat et al., 2019).The pharmacological effect of a proteolytic compound refers to its ability to break down proteins. This can be useful in treating certain conditions, such as inflammation and blood clotting. On the other hand, an antispasmodic is a drug that acts to reduce or prevent involuntary muscle spasms. These spasms can occur in various parts of the body, such as the muscles of the gastrointestinal tract, uterus, or smooth muscles in other areas (Visse & Nagase, 2003). Both types of pharmacological effects can be beneficial in treating certain medical conditions. For example, a drug that has both proteolytic and antispasmodic effects could be useful in treating gastrointestinal disorders involving inflammation and muscle spasms, such as irritable bowel syndrome. It is important to note that while these pharmacological effects can be useful in treating certain conditions, these drugs should always be used under the supervision and prescription of a healthcare professional as they may have side effects and contraindications (Laskowski, s.f.).In addition to the aforementioned pharmacological effects, the analgesic effect is also noteworthy. In the literature review, a systematic review and meta-analysis were found evaluating the effects of bromelain, a cysteine protease isolated from pineapple, in patients undergoing third molar surgery. Six randomized clinical trials meeting the eligibility criteria were identified. The results show that bromelain has a positive effect on improving physical appearance, social isolation, and sleep quality during the first postoperative week. Additionally, differences were found in pain intensity both during the first 24 hours and 7 days after surgery, indicating that bromelain can reduce postoperative pain. However, there was no evidence that bromelain was effective in reducing trismus and facial swelling (Mendes et al., 2019).

This is complemented by another study indicating that bromelain, a protease enzyme found in pineapple, has shown antinociceptive effects, that is, the ability to reduce pain perception or response to harmful stimuli. This study investigated how bromelain alleviates nociception in the orofacial region of adult zebrafish, focusing on TRP (transient receptor potential) channels. It was found that bromelain reduced nociceptive responses caused by TRP channel activators, and inhibition of certain TRP channel subtypes prevented this antinociceptive effect. These results support the therapeutic potential of bromelain as a pain suppressor in the orofacial region, suggesting that its action is related to the modulation of TRP channels (Parra et al., 2013).

CONCLUSION

In this review, the therapeutic effects and molecular mechanisms of bromelain, a proteolytic enzyme primarily extracted from pineapple, were analyzed. It was found that this enzyme exhibits various properties, notably its antioxidant, anticancer, anti-inflammatory, antidiabetic, neuroprotective, wound healing, hepatoprotective, hypolipidemic, and proteolytic capabilities. Therefore, our review highlights the versatility of bromelain in treating various medical conditions. Additionally, the presented molecular mechanisms suggest that bromelain primarily exerts its beneficial effects through the modulation of inflammatory pathways, enhancement of the immune response, and interference with specific pathological processes. It is concluded that bromelain represents a therapeutic option with a wide range of applications, supported by scientific evidence that backs its therapeutic effects.

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REFERENCES

1. Abo El-Magd, N. F., Ramadan, N. M., & Eraky, S. M. (2021). The ameliorative effect of bromelain on STZ-induced type 1 diabetes in rats through Oxi-LDL/LPA/LPAR1 pathway. Life Sci 285, 119982. https://doi.org/10.1016/j.lfs.2021.119982
2. Agrawal, P., Nikhade, P., Patel, A., Mankar, N., & Sedani, S. (2022). Bromelain: A Potent Phytomedicine. Cureus, 14(8), e27876. https://doi.org/10.7759/cureus.27876
3. Akhter, J., Quéromès, G., Pillai, K., Kepenekian, V., Badar, S., Mekkawy, A. H., Frobert, E., Valle, S. J., & Morris, D. L. (2021). The Combination of Bromelain and Acetylcysteine (BromAc) Synergistically Inactivates SARS-CoV-2. Viruses, 13(3), 425. https://doi.org/10.3390/v13030425
4. Ataide, J. A., Cefali, L. C., Figueiredo, M. C., Braga, L. E. de O., Ruiz, A. L. T. G., Foglio, M. A., Oliveira-Nascimento, L., & Mazzola, P. G. (2021). In vitro performance of free and encapsulated bromelain. Sci Rep 11(1), 10195. https://doi.org/10.1038/s41598-021-89376-0
5. Badriyya, E., Pratiwi, A., Dillasamola, D., Aldi, Y., & Husni, E. (2020). Topical Anti-Inflammatory Activity of Bromelain. Pharmacogn J 12(6s), 1586-1593. https://doi.org/10.5530/pj.2020.12.217
6. Bahde, R., Palmes, D., Minin, E., Stratmann, U., Diller, R., Haier, J., & Spiegel, H.-U. (2007). Bromelain ameliorates hepatic microcirculation after warm ischemia. J Surg Res 139(1), 88-96. https://doi.org/10.1016/j.jss.2006.10.004
7. Bayat, S., Amiri, N., Pishavar, E., Kalalinia, F., Movaffagh, J., & Hashemi, M. (2019). Bromelain-loaded chitosan nanofibers prepared by electrospinning method for burn wound healing in animal models. Life Sci 229, 57-66. https://doi.org/10.1016/j.lfs.2019.05.028
8. Bhui, K., Prasad, S., George, J., & Shukla, Y. (2009). Bromelain inhibits COX-2 expression by blocking the activation of MAPK regulated NF-kappa B against skin tumor-initiation triggering mitochondrial death pathway. Cancer Lett 282(2), 167-176. https://doi.org/10.1016/j.canlet.2009.03.003
9. Blasco R, R., Rubio A, J. A., Anguera V, A., Ayllón S, A., Ramos C, D. J., & Jiménez D, J. F. (2012). Suplementación con bromelia en el daño muscular producido durante el ejercicio físico excéntrico. Estudio Bromesport. Arch Med Deporte Rev Fed Esp Med Deporte Confed Iberoam Med Deporte 29(150 (Julio / Agosto)), 769-783.
10. Borrelli, F., Capasso, R., Severino, B., Fiorino, F., Aviello, G., De Rosa, G., Mazzella, M., Romano, B., Capasso, F., Fasolino, I., & Izzo, A. A. (2011). Inhibitory effects of bromelain, a cysteine protease derived from pineapple stem (Ananas comosus), on intestinal motility in mice. Neurogastroenterol Motil 23(8), 745-e331. https://doi.org/10.1111/j.1365-2982.2011.01735.x
11. Bottega, R., Persico, I., De Seta, F., Romano, F., & Di Lorenzo, G. (2021). Anti-inflammatory properties of a proprietary bromelain extract (BromeyalTM) after in vitro simulated gastrointestinal digestion. Int J Immunopathol Pharmacol 35, 20587384211034686. https://doi.org/10.1177/20587384211034686
12. Buta, M., Annand, D., Findeisen, S., Hickey, S., Sheridan, R., Friedstat, J., Schulz, J., Bojovic, B., & Goverman, J. (2023). 555 Pain Management During Bromelain-Based Enzymatic Debridement in a U.S. Adult Burn Center. J Burn Care Res Off Publ Am Burn Assoc 44(Suppl 2), S110. https://doi.org/10.1093/jbcr/irad045.151
13. Carnevali, A., Vaccaro, S., Borselli, M., Bousyf, S., Lamonica, L., Randazzo, G., Giannaccare, G., & Scorcia, V. (2023). Anatomical and Functional Effects of an Oral Supplementation of Bromelain and Curcugreen in Patients with Focal Diabetic Macular Edema. J Clin Med 12(23), 7318. https://doi.org/10.3390/jcm12237318
14. Cervo, M. M. C., Llido, L. O., Barrios, E. B., & Panlasigui, L. N. (2014). Effects of Canned Pineapple Consumption on Nutritional Status, Immunomodulation, and Physical Health of Selected School Children. J Nutr Metab 2014, 861659. https://doi.org/10.1155/2014/861659
15. Chang, T.-C., Wei, P.-L., Makondi, P. T., Chen, W.-T., Huang, C.-Y., & Chang, Y.-J. (2019). Bromelain inhibits the ability of colorectal cancer cells to proliferate via activation of ROS production and autophagy. PloS One 14(1), e0210274. https://doi.org/10.1371/journal.pone.0210274
16. Dave, S., Kaur, N. J., Nanduri, R., Dkhar, H. K., Kumar, A., & Gupta, P. (2012). Inhibition of adipogenesis and induction of apoptosis and lipolysis by stem bromelain in 3T3-L1 adipocytes. PloS One 7(1), e30831. https://doi.org/10.1371/journal.pone.0030831
17. de la Barrera-Núñez, M.-C., Yáñez-Vico, R.-M., Batista-Cruzado, A., Heurtebise-Saavedra, J.-M., Castillo-de Oyagüe, R., & Torres-Lagares, D. (2014). Prospective double-blind clinical trial evaluating the effectiveness of Bromelain in the third molar extraction postoperative period. Med Oral Patol Oral Cirugia Bucal 19(2), e157-162. https://doi.org/10.4317/medoral.19105
18. Del juncal-Guzmán, D., Hernández-Maldonado, L. M., Sánchez-Burgos, J. A., González-Aguilar, G. A., Ruiz-Valdiviezo, V. M., Tovar, J., & Sáyago-Ayerdi, S. G. (2021). In vitro gastrointestinal digestion and colonic fermentation of phenolic compounds in UV-C irradiated pineapple (Ananas comosus) snack-bars. LWT 138, 110636. https://doi.org/10.1016/j.lwt.2020.110636
19. El-Demerdash, F. M., Baghdadi, H. H., Ghanem, N. F., & Mhanna, A. B. A. (2020). Nephroprotective role of bromelain against oxidative injury induced by aluminium in rats. Environ Toxicol Pharmacol 80, 103509. https://doi.org/10.1016/j.etap.2020.103509
20. Eraky, S. M., Ramadan, N. M., & Abo El-Magd, N. F. (2023). Ameliorative effects of bromelain on aluminum-induced Alzheimer's disease in rats through modulation of TXNIP pathway. Int J Biol Macromol 227, 1119-1131. https://doi.org/10.1016/j.ijbiomac.2022.11.291
21. Fathi, A. N., Sakhaie, M. H., Babaei, S., Babaei, S., Slimabad, F., & Babaei, S. (2020). Use of bromelain in cutaneous wound healing in streptozocin-induced diabetic rats: An experimental model. J Wound Care 29(9), 488-495. https://doi.org/10.12968/jowc.2020.29.9.488

22. Ghasemi, A., & Jeddi, S. (2023). Streptozotocin as a tool for induction of rat models of diabetes: A practical guide. EXCLI J 22, 274-294. https://doi.org/10.17179/excli2022-5720
23. Hadidi, M., Amoli, P. I., Jelyani, A. Z., Hasiri, Z., Rouhafza, A., Ibarz, A., Khaksar, F. B., & Tabrizi, S. T. (2020). Polysaccharides from pineapple core as a canning by-product: Extraction optimization, chemical structure, antioxidant and functional properties. Int J Biol Macromol 163, 2357-2364. https://doi.org/10.1016/j.ijbiomac.2020.09.092
24. Hale, L. P., Chichlowski, M., Trinh, C. T., & Greer, P. K. (2010). Dietary supplementation with fresh pineapple juice decreases inflammation and colonic neoplasia in IL-10-deficient mice with colitis. Inflamm Bowel Dis 16(12), 2012-2021. https://doi.org/10.1002/ibd.21320
25. Hu, P.-A., Chen, C.-H., Guo, B.-C., Kou, Y. R., & Lee, T.-S. (2020). Bromelain Confers Protection Against the Non-Alcoholic Fatty Liver Disease in Male C57BL/6 Mice. Nutrients 12(5), 1458. https://doi.org/10.3390/nu12051458
26. Insuan, O., Janchai, P., Thongchuai, B., Chaiwongsa, R., Khamchun, S., Saoin, S., Insuan, W., Pothacharoen, P., Apiwatanapiwat, W., Boondaeng, A., & Vaithanomsat, P. (2021). Anti-Inflammatory Effect of Pineapple Rhizome Bromelain through Downregulation of the NF-κB- and MAPKs-Signaling Pathways in Lipopolysaccharide (LPS)-Stimulated RAW264.7 Cells. Curr Issues Mol Biol 43(1), 93-106. https://doi.org/10.3390/cimb43010008
27. Jebur, A. B., El-Demerdash, F. M., & Kang, W. (2020). Bromelain from Ananas comosus stem attenuates oxidative toxicity and testicular dysfunction caused by aluminum in rats. J Trace Elem Med Biol 62, 126631. https://doi.org/10.1016/j.jtemb.2020.126631
28. Kasemsuk, T., Vivithanaporn, P., & Unchern, S. (2018). Anti-inflammatory effects of bromelain in lps-induced human U937 macrophages. Chiang Mai J Sci 45, 299-307.
29. Kiani, M., Zabihi, E., Nafarzadeh, S., Nouri, H. R., Bijani, A., & Seyedmajidi, M. (2022). Anti-Cancer Effect of Bromelain and Its Combination with Cisplatin on HN5 Cell Line (Squamous Cell Carcinoma). J Dent 23(3), 257-265. https://doi.org/10.30476/DENTJODS.2021.89577.1478
30. Kiyota, K., Yoshimitsu, M., Kajimura, K., & Yamano, T. (2020). Reduction of Orange Allergen Cit s 2 Levels in Fresh Orange Juice with Pineapple Bromelain Enzymatic Treatment. Shokuhin Eiseigaku Zasshi. J Food Hyg Soc Jpn 61(1), 17-21. https://doi.org/10.3358/shokueishi.61.17
31. Kumar, R., Kumar, R., Sharma, N., Khurana, N., Singh, S. K., Satija, S., Mehta, M., & Vyas, M. (2022). Pharmacological evaluation of bromelain in mouse model of Alzheimer's disease. Neurotoxicology, 90, 19-34. https://doi.org/10.1016/j.neuro.2022.02.009
32. Ley, C. M., Ni, Q., Liao, X., Gao, H.-L., & Robinson, N. (2016). Bromelain and cardiovascular risk factors in diabetes: An exploratory randomized, placebo controlled, double blind clinical trial. Chin J Integr Med 22(10), 728-737. https://doi.org/10.1007/s11655-016-2521-2
33. Lu, H.-C., Ng, M. Y., Liao, Y.-W., Maekawa, S., Lin, T., & Yu, C.-C. (2023). Bromelain inhibits the inflammation and senescence effect in diabetic periodontitis: A preliminary in vitro study. J Dent Sci 18(2), 659-665. https://doi.org/10.1016/j.jds.2022.09.018
34. Mendes, M.-L.-T., do Nascimento-Júnior, E.-M., Reinheimer, D.-M., & Martins-Filho, P.-R.-S. (2019). Efficacy of proteolytic enzyme bromelain on health outcomes after third molar surgery. Systematic review and meta-analysis of randomized clinical trials. Med Oral Patol Oral Cirugia Bucal 24(1), e61-e69. https://doi.org/10.4317/medoral.22731
35. Mohamad, N. E., Abu, N., Yeap, S. K., Lim, K. L., Romli, M. F., Sharifuddin, S. A., Long, K., & Alitheen, N. B. (2019). Apoptosis and metastasis inhibitory potential of pineapple vinegar against mouse mammary gland cells in vitro and in vivo. Nutr Metab 16, 49. https://doi.org/10.1186/s12986-019-0380-5
36. Mohamad, N. E., Yeap, S. K., Lim, K. L., Yusof, H. M., Beh, B. K., Tan, S. W., Ho, W. Y., Sharifuddin, S. A., Jamaluddin, A., Long, K., Nik Abd Rahman, N. M. A., & Alitheen, N. B. (2015). Antioxidant effects of pineapple vinegar in reversing of paracetamol-induced liver damage in mice. Chin Med 10, 3. https://doi.org/10.1186/s13020-015-0030-4
37. Murthy, S. S., & Narsaiah, T. B. (2021). Cytotoxic Effect of Bromelain on HepG2 Hepatocellular Carcinoma Cell Line. Appl Biochem Biotechnol 193(6), 1873-1897. https://doi.org/10.1007/s12010-021-03505-z
38. Organización Mundial de la Salud (OMS). (2022). Cáncer. https://www.who.int/es/news-room/fact-sheets/detail/cancer
39. Paksoy, T., Ustaoğlu, G., Şehirli, A. Ö., Ünsal, R. B. K., Sayıner, S., Orhan, K., Aycı, N. B., Çetinel, Ş., Aksoy, U., & Öğünç, A. V. (2023). Effect of bromelain on periodontal destruction and alveolar bone in rats with experimental periodontitis. Int Immunopharmacol 121, 110446. https://doi.org/10.1016/j.intimp.2023.110446
40. Parra, A. Q., Clavijo, D., & Martinez, M. C. P. (2013). Cinética de la bromelina obtenida a partir de la piña perolera (Ananas Comosus) de Lebrija-Santander. BISTUA Rev Fac Cienc Basic, 10(2), Article 2. https://doi.org/10.24054/01204211.v2.n2.2012.84
41. Ribeiro, S. R. L., Santos, S. A. A. R., Rodrigues, A. L. O. de S., de Sena, G. M., Vieira-Neto, A. E., & Campos, A. R. (2024). Bromelain regulates TRP channels to induce orofacial nociception relief in adult zebrafish. Biochem Biophys Rep 37, 101598. https://doi.org/10.1016/j.bbrep.2023.101598
42. Sahbaz, A., Aynioglu, O., Isik, H., Ozmen, U., Cengil, O., Gun, B. D., & Gungorduk, K. (2015). Bromelain: A natural proteolytic for intra-abdominal adhesion prevention. Int J Surg 14, 7-11. https://doi.org/10.1016/j.ijsu.2014.12.024

43. Saptarini, N. M., Rahayu, D., & Herawati, I. E. (2019). Antioxidant Activity of Crude Bromelain of Pineapple (Ananas comosus (L.) Merr) Crown from Subang District, Indonesia. J Pharm Bioallied Sci 11(Suppl 4), S551-S555. https://doi.org/10.4103/jpbs.JPBS_200_19
44. Sayed, A. A., Soliman, A. M., Marzouk, M., Mohammed, F. F., & Desouky, S. (2023). Bromelain mitigates liver fibrosis via targeting hepatic stellate cells in vitro and in vivo. Tissue Cell, 82, 102118. https://doi.org/10.1016/j.tice.2023.102118
45. Seenak, P., Kumphune, S., Malakul, W., Chotima, R., & Nernpermpisooth, N. (2021). Pineapple consumption reduced cardiac oxidative stress and inflammation in high cholesterol diet-fed rats. Nutr Metab 18(1), 36. https://doi.org/10.1186/s12986-021-00566-z
46. Tsai, K.-Y., Wei, P.-L., Azarkan, M., M'Rabet, N., Makondi, P. T., Chen, H.-A., Huang, C.-Y., & Chang, Y.-J. (2023). Cytotoxic properties of unfractionated and fractionated bromelain alone or in combination with chemotherapeutic agents in colorectal cancer cells. PloS One 18(6), e0285970. https://doi.org/10.1371/journal.pone.0285970
47. Laskowski Jr, M. Qasim al-Din and the origins of the experimental approach to the pharmacology of the mind. Drug Disc Tod, 8(18), 822-828
48. Visse, R., & Nagase, H. (2003). Matrix metalloproteinases and tissue inhibitors of metalloproteinases: Structure, function, and biochemistry. Circ Res 92(8), 827-839. https://doi.org/10.1161/01.RES.0000070112.80711.3D