Bromelain: A Potential Neutraceutical

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ABSTRACT

Bromelain is a type of proteolytic enzyme derived from either the pineapple fruit or stem and is commercially available. These two, fruit bromelain and stem bromelain have differing enzymatic components and are prepared differently. Its minimal toxicity, high effectiveness, easy accessibility, and simple procurement make it an endlessly attractive subject for researchers. The new therapeutic benefits of bromelain include promoting wound healing, enhancing drug absorption, and managing conditions such as sinusitis, bronchitis, angina pectoris, surgical trauma, and thrombophlebitis. Additionally, it has been proven to be effective in treating cardiovascular diseases, diarrhoea, and osteoarthritis. Bromelain also induces apoptotic cell death and displays anti-cancer properties. This review aims to provide an overview of Bromelain's uses and its potential applications.

Keywords: Bromelain, Bioavailability, Mechanism, Medicinal Uses, Side Effects

1. INTRODUCTION

Bromelain is a sore subject achieving recognition, which is essentially a protease enzyme derived from the fruit and stems of pineapple. It consists of a mixture of different endopeptidases and components such as phosphatase, cellulase, glycosidase, and many other protease enzymes. The pineapple itself used to be a traditional folk medicine in ancient times. Bromelain has various activities including antithrombic, anti-inflammatory, and antiedematous activities. Bromelain is also absorbed in the body without any dangerous side effects. It has many health benefits and also has therapeutic uses in the treatment of many diseases such as angina pectoris, surgical trauma, inflammation, and sinusitis. Bromelain also reduces wounds, diarrhoea, and various cardiovascular activities, it also shows anti-cancer

activities. The pineapple is also known as Ananas comous, which is one of the most famous tropical fruits in the world. The pineapple is native to South America and was acclimatized by Native Americans in the West Indies centuries before Columbus introduced it to Europe after encountering its spicy-sweet flavour on his way to the island of Guadeloupe. However, it is now recognized by people all over the world and is also known for its healing properties due to a substance present in it known as bromelain (Figure 1). It has various therapeutic uses. In 1993, a German government commission approved the use of bromelain to treat swelling and inflammation after surgery. It has also shown various beneficial effects on the digestive system, respiratory system, etc. Bromelain is also used as a dietary supplement, showing results even in cancer patients. Bromelain can be absorbed in the human intestines without degradation and without losing its biological activity [1, 2] and bromelain acts as an immunomodulator, anti-metastatic, anti-edematous, anti-thrombotic and anti-inflammatory [3, 4]. Bromelain can be isolated and purified by various methods. Bromelain works in the ph range of 4.5 to 9.5 [5]. 21st-century research is supported by the long-term use of pineapple by Native Americans, who used the juice as an anti-inflammatory, diuretic, and digestive aid. They also drank it to ease sore throats, reduce seasickness, and induce labor. According to folk medicine, its fruits were even used to terminate pregnancy by women who ate the pulp of a young, toxic pineapple [6]. Overall, bromelain appears to be a promising extract for the future development of nutraceuticals and dietetics.

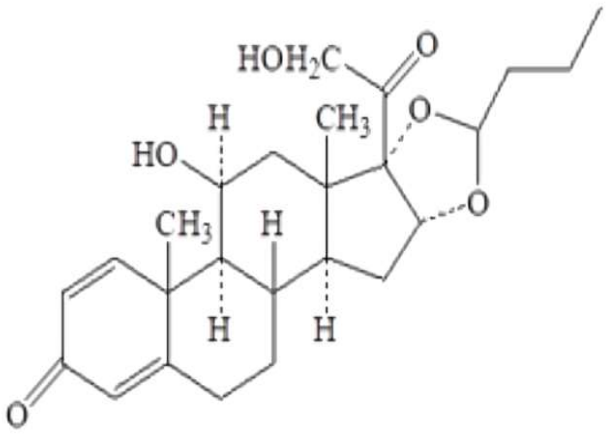

Figure 1: Structure of Bromelain

2. BACKGROUND

The first isolation of Bromelain was recorded by the Venezuelan chemist Vicente Marcano in 1891 from pineapple. In 1892 Chittenden, assisted by Joslin and Meara, fully investigated the matter and called it ‘Bromelin’. The term ‘bromelain’ was later introduced and was originally applied to any protease from any plant member of the Bromeliaceae family. It was first introduced as a therapeutic supplement in 1957. Bromelain research was first conducted in Hawaii, but more recently it has been conducted in countries in Asia, Europe, and Latin America. Germany has recently shown great interest in bromelain research; Bromelain is currently the 13th most widely used herbal medicine in Germany [7, 8]. Pineapple has a long tradition as a medicinal plant among the natives of South and Central America. However, simply eating pineapple won't give you much extra bromelain because it's most concentrated in the stem, which isn't nearly as tasty [9].

3. BIOCHEMICAL PROPERTIES

Bromelain has a wide range of enzymatic activities such as a pH range of 5.5 to 8.0. [10]. Different protein fractions were obtained using different biochemical techniques such as sodium dodecyl sulfate-polyacrylamide gel electrophoresis‖ (SDS-PAGE), isoelectric focusing (IEF), and multicathode PAGE [11, 12].

4. BIOAVAILABILITY AND ADSORPTION

Bromelain is generally absorbed in the body through the gastrointestinal tract. Bromelain concentration was found to be highest one hour after its administration. There are reports that 40% is absorbed from the gut, also in an experimental study it has a half-life of 6-9 hours. Bromelain was also detected in the blood of rats after oral administration [13]. Bromelain can be consumed in remarkable amounts; approximately 12 g/day can be consumed without any dangerous side effects [14]. In a study by Castell et al. [14], bromelain was found to retain its proteolytic activity in plasma and was also found to be associated with alpha 2-macroglobulin and alpha 1-antichymotrypsin, two blood antiproteinases. In a recent study, it was shown that 3.66 mg/ml of bromelain was stable in artificial gastric juice after 4 hours of reaction, and also 2.44 mg/ml of bromelain remained in artificial blood after 4 hours of reaction [15].

5. MECHANISM OF ACTION

Bromelain is a protease enzyme derived from the stems of pineapples that is composed of a mixture of different thiol endopeptidases and other components like phosphatase, glucosidase, peroxidase, cellulase, escharase, and several protease inhibitors. It selectively inhibits the biosynthesis of proinflammatory prostaglandins and also has analgesic properties, as well as anticancerous and pro-apoptotic effects. The mechanism of action of bromelain is shown in Figure 2. Bromelain holds potential therapeutic effects as a treatment of conditions including angina pectoris, bronchitis, sinusitis, surgical trauma, and osteoarthritis. It is considered as a safe food supplement.

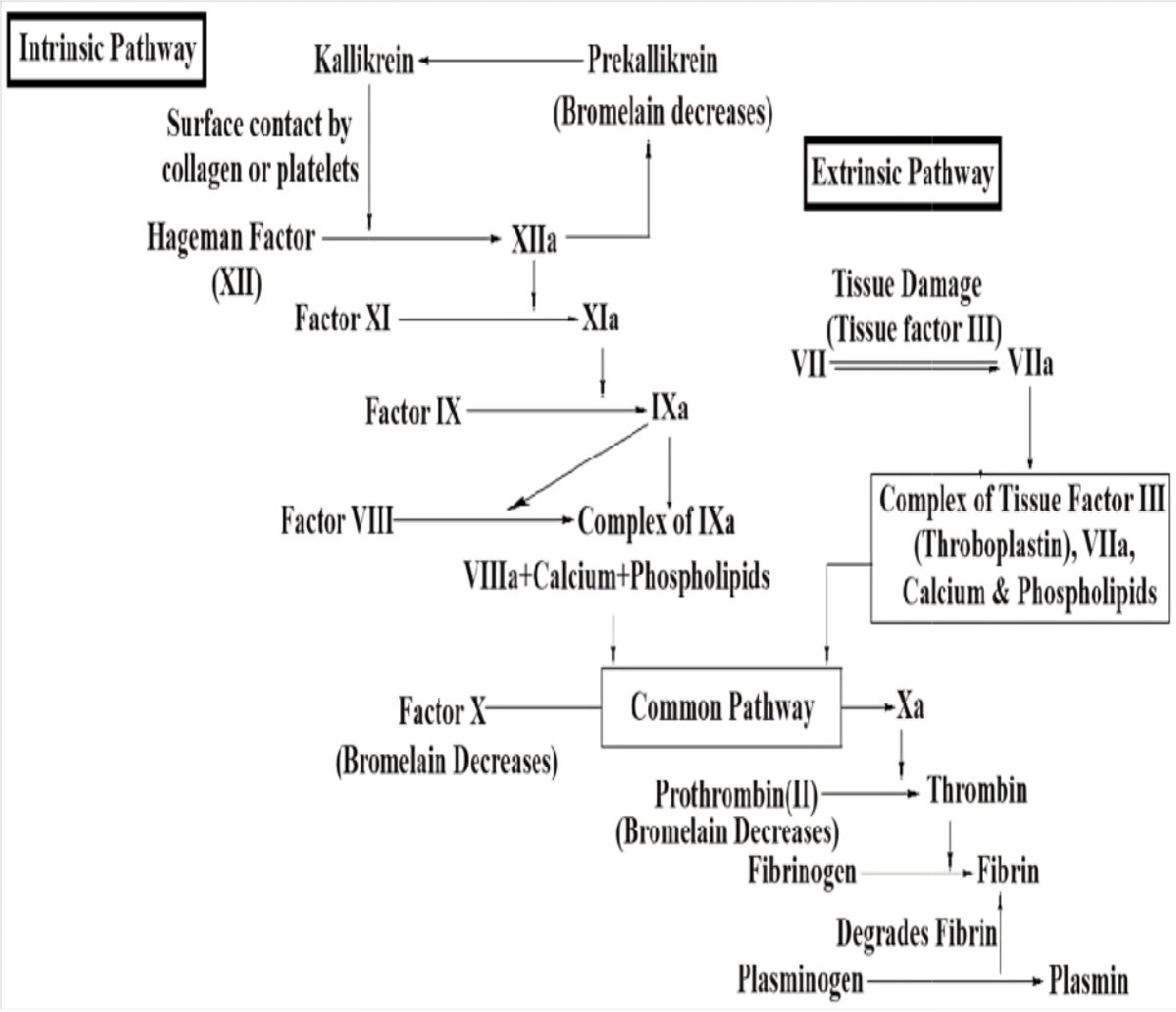

Figure 2: Mechanism of action [16, 17]

Although we know that pineapple has been native to the Americas for centuries, the bioactive plant essence Bromelain was not isolated in chemical form until the late 19th century. In 1957, it was launched as a therapeutic supplement. Bromelain is also known as a proteolytic enzyme, which means it digests proteins. There are eight different chemicals in it that help digest protein [18]. While inflammation helps the body heal when injured, excessive swelling can lead to health complications and accelerate aging. By breaking down fibrin, bromelain is said to help prevent blood clotting and improve circulation. Similarly, supplement manufacturers claim that this enzyme activity thins the blood, prevents plaque build-up in the arteries, and slows the coagulation (or clumping) of platelets [19]. This is why Native Americans used parts of another pineapple plant to dress and treat wounds. Bromelain also slows the build-up of kinins, another byproduct of inflammation, and prostaglandins, hormone-like compounds found throughout the body. Prostaglandins, associated with swelling and clotting at sites of injury, can contribute to disease if their presence is excessive. In a five-year study of more than 200 people, bromelain was found to be effective in slowing the growth of inflammatory prostaglandins [20].

6. THERAPEUTIC AND CLINICAL USES

6.1.Cancer

In several animal and human researches imply Bromelain might have some anti-metastatic potential. In doses over 1,000 mg daily, Bromelain has been combined with chemotherapeutic agents which includes five-FU and vincristine, resulting in tumour regression. Recent studies have shown that Bromelain has the potential to alter key pathways that aid malignancy. Presumably, the anti-cancerous interest of Bromelain is because of its direct impact on most cancer cells and their microenvironment, in addition to at the modulation of immune, anti-inflammatory, and hemostatic systems. [1]. Most of the in vitro and in vivo studies on the anticancer interest of Bromelain are focused on the mouse and human cells, both cancerous and regular, handled with Bromelain arrangements. In a test conducted with the aid of Beez et al chemically caused mouse pores and skin papillomas were handled with Bromelain and they observed that it reduced tumor formation, tumour volume and brought on apoptotic cell death [25]. In one take look associated with Bromelain treatment of gastric carcinoma Kato III cell traces, a substantial reduction of cellular boom has been discovered [26]. Even as in any other have a look at Bromelain reduced the invasive ability of glioblastoma cells and reduced de novo protein synthesis [27]. Bromelain is determined to boost the expression of p53 and Bax in mouse skin, the activators of apoptosis [25]. Bromelain additionally decreases the hobby of mobile survival regulators such as Akt and Erk, therefore selling apoptotic cell demise in tumors. Unique research has tested the role of NFκB, Cox-2, and PGE2 as promoters of cancer development. Evidence shows that the signalling and over-expression of NF-κB plays a vital part in many types of cancers [28, 29]. Cox-2, a a couple of goal genes of NF-κB, enables the conversion of arachidonic acid into PGE2 and as a consequence promotes tumor angiogenesis and progression [30, 31]. It's far taken into consideration that inhibiting NF-κB, Cox-2, and PGE2 activity has the capacity as a treatment of cancer. Bromelain turned located to down-adjust NF-κB and Cox-2 expression in mouse papillomas [25] and in models of skin tumourigenesis [32]. Bromelain has additionally been proven to inhibit bacterial endotoxin (LPS)-brought about NF-κB hobby in addition to the expression of PGE2 and Cox-2 in human monocytic leukemia and murine microglial mobile traces [33, 34]. Bromelain markedly has in vivo antitumoural interest for the subsequent cellular lines: P388 leukemia, sarcoma (S-37), Ehrlich ascetic tumor, Lewis lung carcinoma, and ADC-755 mammary adenocarcinoma. In those researches, intraperitoneal administration of Bromelain after 24 hours of tumor cellular inoculation led to tumor regression [25].

6.2.Surgery

Management of Bromelain before a surgical treatment can lessen the average wide variety of days for the entire disappearance of aches and put up-surgical operation irritation [35, 36]. Trials suggest that Bromelain is probably powerful in reducing swelling, bruising, and pain in ladies having episiotomy [37]. In recent times, Bromelain has been used for treating acute irritation and sports injuries [38].

6.3.Sinusitis

Nowadays, Bromelain has been recommended as a complementary remedy for sinusitis. Preliminary research recommends that it can help reduce congestion, enhance breathing and

suppress coughing. It's permitted to use the fee E as a complementary treatment for nasal and sinus swelling and irritation after ear, nostril, and throat surgery. An overview of 3 small but properly designed formerly posted studies discovered that it may help relieve sinusitis signs [38].

6.4.Osteoarthritis

Osteoarthritis is the maximum not unusual form of arthritis in Western countries; in the United States of America. Occurrence of osteoarthritis stages from 3.2 to 33% depending on the joint [39]. An aggregate of Bromelain, trypsin, and rutin become as compared to Diclofenac in 103 patients with osteoarthritis of the knee. After six weeks, each treatment ended with a good sized and similar discount within the pain and inflammation [40]. Bromelain is a food supplement that could provide an alternative remedy to the nonsteroidal drug (NSAIDs) [41]. It plays a crucial role in the pathogenesis of arthritis [42]. Bromelain has analgesic residences that are thought to be the result of its direct impact on pain mediators such as bradykinin [43, 44]. The earliest reported studies investigating bromelain were a series of case reviews on 28 patients, with slight or intense rheumatoid or osteoarthritis [45].

6.5.Ulcers

Bromelain has been stated to heal gastric ulcers in experimental animals. In an extensive examination of the effect of bromelain on the gastric mucosa, bromelain accelerated the uptake of radioactive sulfur through 50 percent and glucosamine via 30-90 percent. Extended uptake of those substances may additionally allow the gastric mucosa to heal extra swiftly [45].

6.6.Immunity

Bromelain can set off cytokine manufacturing in human peripheral blood mononuclear cells. Treatment results in the activation of herbal killer cells and the production of tumor necrosis thing-alpha, interleukin-1-beta, and interleukin-6 in a time- and dose-based manner. Bromelain has also been proven to cast off T-cellular CD44 adhesion molecules from lymphocytes and to affect T-cell activation [45].

6.7.Blood Coagulation and Fibrinolysis

Bromelain is thought to impact Blood coagulation with the aid of increasing the serum fibrinolytic ability and by inhibiting the synthesis of fibrin, a protein worried in blood clotting [46]. In rats, the reduction of serum fibrinogen stage by bromelain is dose Biotechnology studies International 3 dependent. At a higher concentration of bromelain, each prothrombin time (PT) and activated partial thromboplastin time (APTT) are markedly extended [47]. In-vitro and in-vivo research have cautioned that bromelain is an effective fibrinolytic agent as it stimulates the conversion of plasminogen to plasmin, resulting in extended fibrinolysis with the aid of degrading fibrin [48, 49].

6.8.Wound Healing

Bromelain also has wound debridement traits. Bromelain implemented topically as a cream (35% bromelain in a lipid base) can be beneficial in the elimination of burn debris and in the

acceleration of the recovery method. A non-proteolytic component of bromelain is liable for this effect. This issue, referred to as escharase, has no hydrolytic enzyme pastime towards ordinary protein substrates or numerous glycosaminoglycan substrates and its interest varies substantially from education to practice [49].

6.9.Cardiovascular and Circulatory Applications

Some studies indicate bromelain prevents or minimizes the severity of angina pectoris. A drastic discount in the occurrence of coronary infarct after the management of potassium and magnesium rotation along with one hundred twenty-four hundred mg bromelain in keeping with the day has been mentioned. In a have a look concerning 73 patients with acute thrombophlebitis, bromelain, similar to analgesics, was proven to lower signs of infection inclusive of pain, edema, tenderness, skin temperature, and disability [49].

6.10. Respiratory Diseases

Bromelain also relieves in respiratory problems. In a clinical study of 124 sufferers hospitalized with continual bronchitis, pneumonia, bronchopneumonia, bronchiectasis, or pulmonary abscess, the ones receiving bromelain orally showed a decrease inside the quantity and purulence of the sputum [49].

6.11. In Diarrhea and Digestive Aid

Proof has recommended that bromelain counteracts some of the consequences of certain intestinal pathogens like Vibrio cholera and Escherichia coli, whose enterotoxin causes diarrhea in animals. Bromelain seems to exhibit this impact through interacting with intestinal secretary signaling pathways, together with adenosine three: five -cyclic monophosphatase, guanosine 3: 5 -cyclic monophosphatase, and calcium-structured signaling cascades [50]. Other research suggests a distinctive mechanism of action. In E. coli infection, an energetic supplementation with bromelain leads to a few anti-adhesion outcomes which save the bacteria from attaching to unique glycoprotein receptors placed at the intestinal mucosa using proteolytically modifying the receptor attachment sites [51, 52]. Melain has been used successfully as a digestive enzyme following pancreatectomy, in instances of exocrine pancreas insufficiency and other intestinal disorders. The combination of ox bile, pancreatin, and bromelain is effective in decreasing stool fat excretion in patients with pancreatic steatorrhea, resulting in symptomatic improvements in pain, flatulence, and stool frequency [51, 52].

6.12. In the Case of Peyronie’s Disease

Peyronie's disorder, named after the French healthcare professional who first recognized it in the 18th century, is characterized by the aid of an intense curvature of the erect penis caused by plaque or a tough lump that forms on the appendage. Peyronie's disease impacts more than 1 percent of person men between the while of 45 and 60. And in extreme instances, the condition causes a wonderful ache at some stage in erection, making sexual hobby not possible. There is no known cure, but treatment alternatives encompass three sorts of surgery. however, none of the surgical alternatives has been confirmed to be continuously successful and might increase the threat of impotence or similar deformation of the penis. The motive of Peyronie's ailment is unwell-known, but the cause it tends to occur in older men is that as we

age, the variety of enzymes in our frame starts to dissipate. It is why we tend to lose our hearing, eyesight and memory as we become older. It's also why a few men can enjoy a build-up of scar tissue of their penises, leading to Peyronie's ailment [53]. There truly aren't enough enzymes to break down all of the plaque and foreign substances that flow into the blood stream PDI]. The important thing to Bromelain's ability as a natural treatment for Peyronie's ailment is its impact on collagen the number one fabric in scar tissue. Of all the protein-digesting enzymes, bromelain is most effective at stimulating collagenase, the enzyme that breaks down collagen by way of dissolving the peptide bonds that preserve their proteins together. Taking bromelain may also slow or reverse the tissue construct-up that causes Peyronie's one more cause in no way to underestimate the strength of pineapple [54].

7. SIDE EFFECTS OF BROMELAIN

7.1.Allergy

Bromelain now and again causes aspect results, one among them that's observed amongst bromelain customers is, mild to excessive sorts of allergic reactions. These are skin allergies and additionally digestive allergies (noted above). Pores and skin allergies encompass hives, pores and skin rash, itching and swelling of pores and skin. Other than that, someone may also suffer from respiration issues and tightness in throat. human beings that have hypersensitive reactions from carrot, fennel, celery, rye, papaya, birch or cypress pollen, positive grass or latex, may additionally suffer with bromelain side outcomes which are much like the same old facet outcomes they revel in [55, 56].

7.2.Digestive Troubles

These are the maximum common bromelain side results which are experienced with the aid of humans with an overdose of bromelain. Those aspect effects are nausea, vomiting, diarrhea, palpitation, indigestion, lack of appetite, headache, muscle pain, dizziness, drowsiness, and lethargy. Ladies can enjoy uterine bleeding and heavy menstruation as nicely. It is also counselled that human beings with peptic ulcers ought to now not to consume bromelain in any form. Also, people with another digestive sickness have to consult the fitness care issuer before using bromelain [55, 56].

7.3.Different Outcome

Bromelain is theoretically stated to increase blood flow. So, human beings that are suffering from blood disorders or bleeding disorders and taking remedies for the same must not use bromelain, to keep away from any bromelain aspect consequences. They are advised to use bromelain most effectively after medical intervention and strict medical supervision. Bromelain needs to also no longer be taken to a few weeks previous to any dental operations and surgical procedures. It is safe now not to apply bromelain whilst pregnant and nursing. Also, humans which might be suffering with liver disease and kidney disorder need to keep away from it [55, 56].

8. DISCUSSION

Bromelain is a combination of enzymes derived from pineapple. Its effects are particularly a product of its proteolytic hobby, which stimulates fibrinolysis by growing plasmin, but it additionally has been shown to prevent kinin production and to inhibit platelet aggregation [58]. Bromelain is used for aches; muscle discomfort, burns, and many other situations, however, there may be no top clinical proof to help those uses. In conjunction with giving a few foremost health benefits such as dietetic and neutraceuticals, it gives a few slight facet outcomes too. As reviewed it allows in many health-related troubles inclusive of irritation, in submit-surgical operation trauma, in case of wound recuperation, and majorly in cancer treatment. Its slight side consequences are rashes, gastric issues, allergic reactions. There are still miles to obtain within the research of Bromelain. We need to dig in more approximately it to find available information about its more tricky mechanism how it acts and its utilization in specific ailments. Normal, it could be stated as a widely known product used now and is in masses of use [58].

9. HERB DRUG INTERACTIONS

Human beings taking "blood-thinners" (anticoagulant or anti-platelet medication), which include aspirin, warfarin (Coumadin), heparin, clopidogrel (Plavix), non-steroidal medicinal drugs consisting of ibuprofen (Motrin, Advil), naproxen (Naprosyn, Aleve) need to most effective use bromelain below a doctor's supervision. It should additionally be used with caution with the aid of human beings taking herbs and dietary supplements which are ideal to growth the chance of bleeding, together with ginkgo biloba and garlic. Research endorses bromelain may additionally grow the absorption of different medications, such as:

- Amoxicillin, tetracycline, and different antibiotics
- Chemotherapy pills which include 5-fluorouracil and vincristine
- "ACE inhibitor" blood strain medicines consisting of captopril (Capoten) and lisinopril (Zestril)
- Medicines that reason drowsiness, inclusive of benzodiazepines lorazepam (Ativan) or diazepam (Valium), some antidepressants, narcotics which includes codeine and barbiturates such as Phenobarbital [57].

10. SUMMARY

Bromelain has wide range of blessings. It has first-rate therapeutic impact and also may be utilized in numerous diseases and have amazing use with less dangerous aspect effects. It could be a first-rate dietary complement of twenty first century. It is also visible that bromelain is nicely absorbed inside the frame and additionally does no longer have hazardous threatening impact. Bromelain has been identified as a secure and a success form of healing agent and is being utilized by people worldwide for some ailments, including bronchitis, sinusitis, arthritis, and infection. Various findings from conventional and clinical reviews indicate that bromelain may be a powerful anticancer healing agent. From the in-vitro and in-vivo information that is presently to be had, bromelain demonstrates immunomodulatory and anti-neoplastic consequences, similar to anti-microbial outcomes .as the paper reviewed it has important nutritional, neutraceuticals, and dietetic costs with a lot of effectiveness. Bromelain will outshine many in the end.

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