

Bromelain: A Literature Review and Discussion of its Therapeutic Applications

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Abstract

First introduced as a therapeutic compound in 1957, bromelain's actions include: (1) inhibition of platelet aggregation; (2) fibrinolytic activity; (3) anti-inflammatory action; (4) anti-tumor action; (5) modulation of cytokines and immunity; (6) skin debridement properties; (7) enhanced absorption of other drugs; (8) mucolytic properties; (9) digestive assistance; (10) enhanced wound healing; and (11) cardiovascular and circulatory improvement. Bromelain is well absorbed orally and available evidence indicates that its therapeutic effects are enhanced with higher doses. Although all of its mechanisms of action are still not completely resolved, it has been demonstrated to be a safe and effective supplement.

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Description

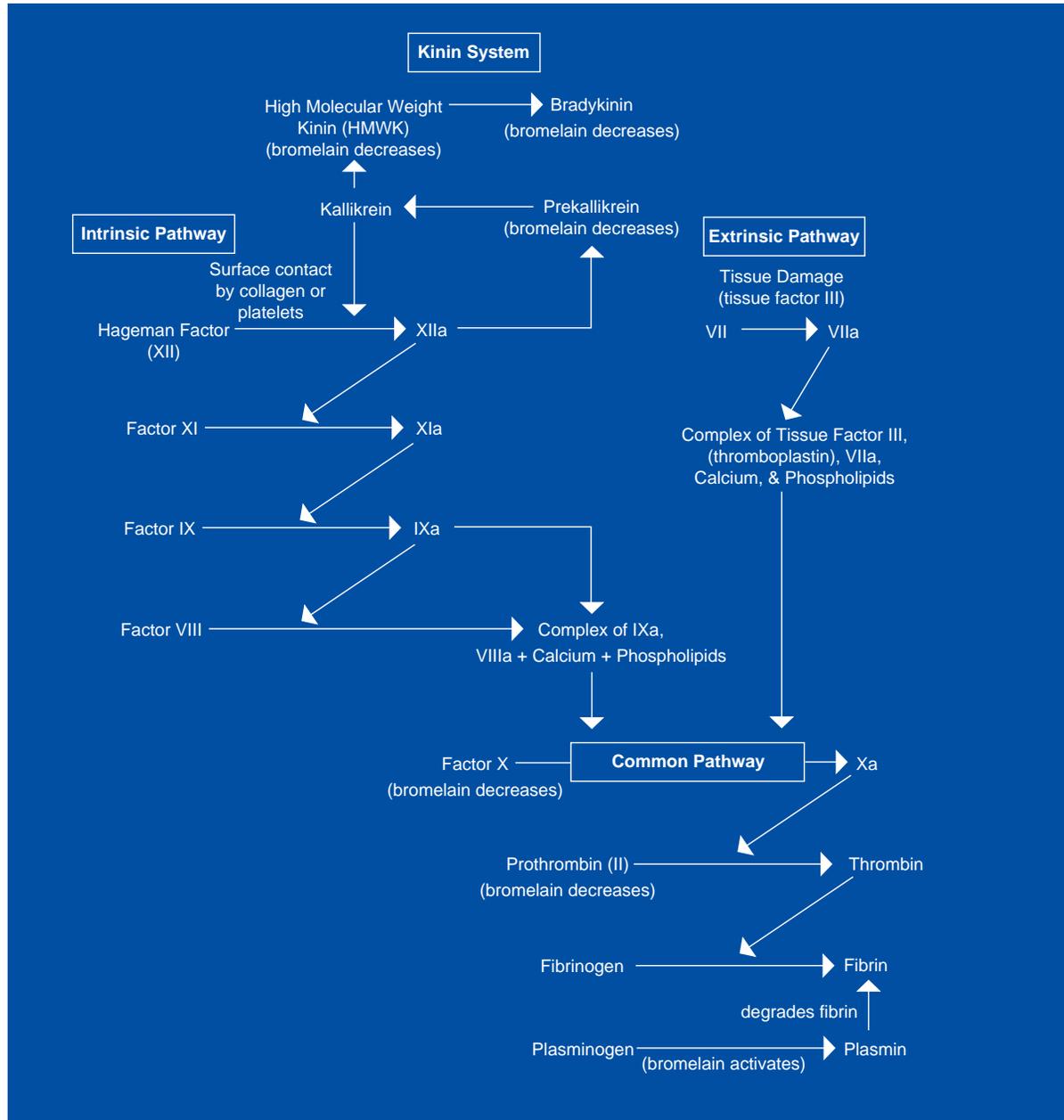
Pineapple has been used as a medicinal plant in several native cultures and bromelain has been known chemically since 1876. In 1957, bromelain was introduced as a therapeutic compound when Heinicke found it in high concentrations in pineapple stems.

Bromelain is a general name for a family of sulfhydryl proteolytic enzymes obtained from *Ananas comosus*, the pineapple plant. It is usually distinguished as either fruit bromelain or stem bromelain depending on its source, with all commercially available bromelain being derived from the stem.¹ The term bromelain will be used to refer to stem bromelain in the remainder of this article.

Bromelain's primary component is a sulfhydryl proteolytic fraction. Bromelain also contains a peroxidase, acid phosphatase, several protease inhibitors, and organically bound calcium. When the proteolytic fraction of bromelain is purified and extracted, the result is a potent proteolytic enzyme in vitro; however, this component has been shown to be physiologically inactive in vivo for many of the conditions where bromelain has a beneficial effect.² It appears that a great deal of the physiological activity of bromelain is not accounted for in its proteolytic fraction and it is likely that the beneficial effects of bromelain are due to multiple factors, not to one single factor that can be isolated.

To date, eight basic proteolytically active components have been detected in the stem. The two main components have been labeled F4 and F5. The proteinase considered to be the most active fraction has been designated as F9, which comprises about 2% of the total proteins. It is estimated that 50% of the proteins in F4 and F5 are glycosylated, whereas F9 was found to be unglycosylated. The optimal pH for the F4 and F5 fractions is between 4.0 and 4.5 and for F9 close to a neutral pH.³ The entire extract of bromelain has been shown to exhibit its activity over a pH range of 4.5 to 9.8.⁴

Figure 1. Bromelain's Impact on the Kinin System & Coagulation



Since bromelain is derived from a natural source, different sources can exhibit variability in their physiological activity, even when their proteolytic activity is the same. Bromelain is not heat stable so its physiological activity can be further reduced by improper processing or storage conditions.

Absorption and Availability

Bromelain is absorbed intact through the gastrointestinal tract of animals, with up to 40% of the high molecular weight substances detected in the blood after oral administration. The highest concentration of bromelain is found in the blood 1 hour after administration; however, its proteolytic activity is rapidly deactivated,⁵ probably by the normal plasma protease controls and serum alpha2-macroglobulin.

Table 1. **Inflammatory Effects of Arachidonic Acid Metabolites**

| Metabolite | Action |
|---|--|
| PGI ₂ | vasodilation, inhibit platelet aggregation |
| PGE ₂ | vasodilation |
| Thromboxane A ₂ | vasoconstriction, platelet aggregation |
| Leukotrienes C ₄ ,D ₄ ,E ₄ | vasoconstriction, increase vascular permeability |
| Leukotriene B ₄ | chemotactic agent |

dent reduction of serum fibrinogen level is seen in rats following administration of bromelain, and at the highest concentrations of bromelain, both prothrombin time (PT) and activated partial thrombo-

plastin time (APTT) are markedly prolonged.⁸ Bromelain's fibrinolytic activity has been attributed to the enhanced conversion of plasminogen to plasmin, which limits the spread of the coagulation process by degrading fibrin.⁹

Bromelain seems to have both direct as well as indirect actions involving other enzyme systems in exerting its anti-inflammatory effect. Both etodolac and bromelain inhibit the inflammatory pain in rats in a dose-dependent manner.¹⁰ Bromelain was the most potent of nine anti-inflammatory substances tested on experimentally-induced edemas in rats;¹¹ while prednisone and bromelain have been shown to be comparable in their ability to reduce inflammation in rats.¹² Treatment with bromelain and emorfazone has been shown to decrease significantly the heat-evoked immunoreactive substance P release and subsequent edema in a rat model.¹³

Mechanism of Action

Surface contact, by collagen or platelets, activates the kinin system and the clotting cascade by stimulating the conversion of Hageman factor to an active protease (factor XIIa). Factor XIIa then activates the kinin system by converting plasma prekallikrein into kallikrein, and continues the intrinsic path of the clotting cascade by converting factor XI to its active form. Kallikrein, in an autocatalytic loop, accelerates the activation of

A variety of designations have been used to indicate the activity of bromelain; with published research varying in the designation utilized. Rorer units (R.U.), gelatin dissolving units (G.D.U.), and milk clotting units (M.C.U.) are the most commonly used measures of activity. One gram of bromelain standardized to 2000 M.C.U. would be approximately equal to 1 gram with 1200 G.D.U. of activity or 8 grams with 100,000 R.U. of activity.

Platelet Aggregation, Fibrinolysis and Anti-Inflammatory Activity

The first conclusive evidence that bromelain prevents aggregation of blood platelets was reported in 1972. Bromelain was administered orally to 20 volunteers with a history of heart attack or stroke, or with high platelet aggregation values. Bromelain decreased aggregation of blood platelets in 17 of the subjects and normalized values in 8 of the 9 subjects who previously had high aggregation values.⁶ In vitro studies have demonstrated that bromelain inhibits platelet aggregation stimulated by ADP or epinephrine, as well as by prostaglandin precursors, in a dose-dependent manner.⁷

Bromelain is an effective fibrinolytic agent in vitro and in vivo; however, its effect is more evident in purified fibrinogen solutions than in plasma. This is probably due to the antiproteases present in plasma. A dose-depen-

Hageman factor, which continues to potently activate both the kinin system and the clotting cascade. In addition, Kallikrein cleaves (HMWK) to produce bradykinin, a potent stimulator of both increased vascular permeability and pain. The activation of the clotting cascade will culminate in the conversion of fibrinogen to fibrin (see Figure 1). Fibrin then forms a protective matrix around the injured area. This matrix inhibits tissue drainage, promotes edema and blocks circulation of blood flow.

In order to determine the effects of bromelain on the plasma

kallikrein system, bradykinin levels and plasma exudation at the inflammatory site were examined in rats. Bromelain (5 and 7.5 mg/kg) caused a dose-dependent decrease of bradykinin levels at the inflammatory site and a parallel decrease of the prekallikrein levels in sera. Plasma exudation was also reduced dose dependently. Bradykinin-degrading activity in sera was elevated after treatment with bromelain, although it was unchanged in the pouch fluid.¹⁴ The levels of high molecular weight (HMW) kininogen and pre-kallikrein in rat plasma were markedly reduced after single injection of bromelain (10 mg/kg, i.v.) and gradually recovered over a 72 hour period. The level of low molecular weight (LMW) kininogen was not changed during this period.¹⁵

Bromelain-treated rats also show a reduction in Factor X and prothrombin, both of which are needed for the activation of fibrinogen to fibrin through the common

pathway of the intrinsic and extrinsic cascade.¹⁶ This indicates that bromelain's action is in part a result of inhibiting the generation of bradykinin at the inflammatory site via depletion of the plasma kallikrein system, as well as limiting the formation of fibrin by reduction of clotting cascade intermediates. These actions result in significant reduction in pain and edema, as well as enhanced circulation to the injured site.

After the formation of a clot, vessel repair begins with the conversion of plasminogen to plasmin, which then acts to degrade fibrin into smaller components which can be removed by monocytes and macrophages. In rats, bromelain has been shown to stimulate the conversion of plasminogen to plasmin, resulting in increased fibrinolysis. This minimizes venous stasis, facilitates drainage, increases permeability and restores the tissue's biological continuity.¹⁶

Table 2. Bromelain's Impact on Selected Mediators of Acute Inflammation

| Mediator | Action | Bromelain's Effect |
|----------------------------|--|--------------------|
| Bradykinin | vascular leakage, pain | decrease |
| Thromboxane A ₂ | vasoconstriction, platelet aggregation | decrease |
| PGE ₂ | vasodilation | slight decrease |
| PGI ₂ | vasodilation | may increase |
| IL-1 | inhibit platelet aggregation | may increase |
| PGI ₂ & PAF | leukocyte adhesion, synthesis | increase |
| TNF | acute phase responses | induced |
| PGI ₂ & PAF | fibroblast proliferation | increase |
| | collagenase synthesis | increase |
| | collagen formation | increase |
| | leukocyte adhesion, synthesis | increase |
| | acute phase responses | induced |
| | fibroblast proliferation | increase |
| | collagenase synthesis | increase |
| | collagen formation | increase |

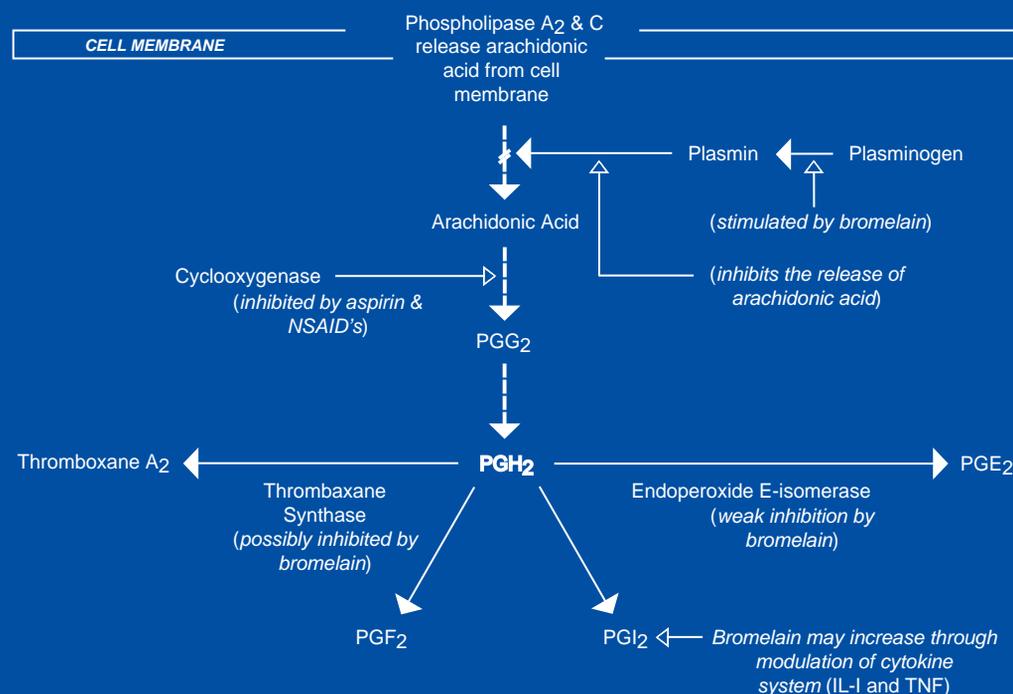


Figure 2. Bromelain's Proposed Effect on Prostaglandin Synthesis.

The therapeutic effect of bromelain may also be due to its ability to selectively modulate the biosynthesis of thromboxanes and prostacyclins; two groups of prostaglandins with opposite actions which ultimately influence activation of cyclic-3,5-adenosine (cAMP), an important cell-growth modulating compound.

The binding of epinephrine, collagen, or thrombin to platelets activates the enzymes phospholipase C and phospholipase A₂ which release arachidonic acid from membrane phospholipids (phosphatidylcholine and phosphatidylinositol). Table 1 lists the inflammatory actions of arachidonic acid metabolites.

Plasminogen, which is activated to plasmin by the oral administration of bromelain, has been shown to inhibit the release of arachidonic acid from cell membranes, resulting in decreased platelet aggregation and modulation of the series 2 prostaglandins.¹⁷ It is also hypothesized that bromelain therapy leads to a relative increase of the endogenous

prostaglandins, PGI₂ and PGE₂ over thromboxane A₂.¹⁸

Non-steroidal anti-inflammatory drugs inhibit cyclooxygenase, which is required for the synthesis of series 2 prostaglandins, resulting in a decrease in both pro and anti-inflammatory prostaglandins. Rather than blocking the arachidonic acid cascade at the enzyme cyclooxygenase, like NSAIDs, bromelain may selectively decrease thromboxane generation and change the ratio of thromboxane/prostacyclin (PGI₂) in favor of prostacyclin (see Figure 2). Bromelain, similar to NSAIDs, has been shown to inhibit PGE₂, however, its action is significantly weaker.¹⁶ Table 2 lists bromelain's impact on selected mediators of inflammation.

Antitumor

The first documented use of oral bromelain on cancer patients was in 1972. Twelve patients with ovarian and breast tumors were given 600 mg of bromelain daily for from 6

Table 3 Selected Cytokines and their physiological activities

| Cytokine | Activity |
|---------------|---|
| Interleukin-1 | <p>induces proliferation of fibroblasts</p> <p>increases leukocyte adhesion, synthesis of PGI₂ and PAF, and surface thrombogenicity</p> <p>stimulates production of collagenases and increases collagen formation</p> <p>increases acute phase responses; including fever induction, slow wave sleep, neutrophilia, hemodynamic effects, decreasing appetite and increasing synthesis of acute phase proteins</p> <p>activates resting T cells and macrophages</p> <p>stimulates ACTH and glucocorticoid release</p> <p>stimulates synthesis of IL-2 and IFN-gamma</p> <p>increases NK cell activity</p> |
| TNF-alpha | <p>induces proliferation of fibroblasts</p> <p>increases leukocyte adhesion, synthesis of PGI₂ and PAF, and surface thrombogenicity</p> <p>stimulates production of collagenases and increases collagen formation</p> <p>increases acute phase responses; including fever induction, slow wave sleep, neutrophilia, hemodynamic effects, decreasing appetite and increasing synthesis of acute phase proteins</p> <p>cytotoxic to some tumor cells</p> <p>similar actions as IL-1 on T cells and macrophages</p> <p>inhibits lipoprotein lipase</p> <p>inhibits hematopoietic stem cells</p> |
| Interleukin-6 | <p>enhances maturation of activated T and B cells</p> <p>inhibits growth of fibroblasts</p> <p>stimulates growth of hematopoietic progenitor cells</p> |
| IFN-gamma | <p>activates macrophages</p> <p>induces expression of HLA class II molecules</p> <p>antiviral activity</p> <p>activates endothelial cells</p> <p>suppresses hematopoietic progenitor cells</p> |

months to several years, with reported resolution of some of the cancerous masses and a decrease in metastasis.¹⁹ Bromelain in doses of over 1000 mg daily has been combined with chemotherapeutic agents such as 5-FU and vincristine, and has been reported to result in tumor regression.^{19,20}

Bromelain has also decreased lung metastasis of Lewis lung cancer cells implanted in mice in a dose-dependent manner. This antimetastatic potential was demonstrated by both the active and inactive bromelain, with or without proteolytic and anticoagulant properties.^{21,22}

Cytokine Induction

The successful initiation of an immune response depends on T cells and macrophages, along with the polypeptide factors they produce, called cytokines, which play a key role in communication during normal immunological response as well as infectious, inflammatory, and neoplastic disease states. Table 3 lists cytokines and their activities.

Bromelain, papain, and amylase have all been demonstrated to induce cytokine production in human peripheral blood mononuclear cells. Treatment leads to the production of tumor necrosis factor-alpha (TNF-alpha), interleukin-1-beta (IL-1 beta), and interleukin-6 (IL-6) in a time and dose-dependent manner. Interferon-alpha (IFN-alpha) and interferon-gamma (IFN-gamma), which had no effect alone, synergistically increased TNF-alpha production when applied together with the enzymes.^{23,24} The tryptic but not the autolytic fractions of papain and bromelain have a higher (10- to 40-fold) inducing capacity for TNF production than the untreated enzyme.²⁵ Trypsin alone had only a small inducing effect.

The ability to induce cytokine production may explain the antitumor effects observed after oral administration of polyenzyme preparations.

Immunity

Bromelain has been shown to remove T-cell CD44 molecules from lymphocytes and to affect T-cell activation. The highly purified bromelain protease F9 was tested on the adhesion of peripheral blood lymphocytes (PBL) to human umbilical vein endothelial cells (HUVEC). Both bromelain and protease F9 reduced the expression of CD44, but F9 was about 10 times more active than bromelain; having about 97% inhibition of CD44 expression. The results indicate that F9 selectively decreases the CD44 mediated binding of PBL to HUVEC.²⁶

Debridement

Bromelain applied topically as a cream (35% bromelain in a lipid base) can be beneficial in the elimination of burn debris and in acceleration of healing. A non-proteolytic component of bromelain is responsible for this effect. This component, referred to as escharase, has no hydrolytic enzyme activity against normal protein substrates or various glycosaminoglycan substrates and its activity varies greatly from preparation to preparation.²⁷

Topical bromelain has achieved complete debridement on experimental burns in rats in an average of 1.9 days as compared to collagenase, which required an average of 10.6 days for similar results.²⁸

Topical bromelain separates eschar at the interface with living tissue. It is hypothesized that bromelain activates collagenase in living tissue which then attacks the denatured collagen in the eschar. This produces a demarcation between living and dead tissue. With very little scraping, using a tongue depressor, all of the eschar can be removed and a bed suitable for grafting results. By using bromelain, grafting can occur as soon as 24 hours after the accident. Utilizing bromelain cream in the treatment of burns usually results in minimal or no scar tissue formation.

The applicability of topical bromelain in frostbite eschar removal was extrapolated and investigated. In the initial trial, no debridement other than that of the superficial layers of the eschar was noted. Although third degree burn injuries debrided to a graftable bed after two topical applications of bromelain, frostbite injuries remained unaffected.²⁹

Potential of Antibiotics

Antibiotic potentiation is one of the primary uses of bromelain in several foreign countries. Bromelain can modify the permeability of organs and tissues to different drugs. It prolongs sleeping time in mice administered pentobarbital³⁰ and increases spinal levels of penicillin and gentamycin in rats. In humans, bromelain has been documented to increase blood and urine levels of antibiotics¹⁶ and results in higher blood and tissue levels of tetracycline and amoxicillin when they are administered concurrently with bromelain.³¹

Treatment of 18 women with 80 mg of bromelain concurrently with amoxicillin or tetracyclin resulted in increased serum levels and concentrations of both antibiotics in uterus, ovarian tubes, and ovaries as compared with controls. This effect was not generated by indomethacin, an anti-inflammatory drug which acts as a cyclooxygenase inhibitor, which indicates that bromelain has some undetermined activity that enhances absorption and tissue distribution of antibiotics.³² A three-fold increase in the level of tetracycline in serum after oral ingestion of 540 mg of enterically-coated bromelain has also been demonstrated in a double blind test.³³

Combined bromelain and antibiotic therapy was instituted for 53 hospitalized patients with the following conditions; pneumonia, bronchitis, cutaneous staphylococcus infection, thrombophlebitis, cellulitis, pyelonephritis and perirectal and rectal abscesses. Twenty three of the patients had been on antibiotic therapy without success. Bromelain was

administered four times a day along with the following antibiotics either alone or in combination; penicillin, chloramphenicol, erythromycin or novobiacin. A control group of 56 patients was treated with antibiotics alone. Of the 23 patients who had been unsuccessfully treated with antibiotics, 22 responded favorably to the combined treatment. In every disease state studied there was a significant reduction in morbidity when the combination of bromelain and antibiotics was used as opposed to antibiotics alone. Another group of 106 cases was treated with bromelain alone, with results comparable to those obtained with antibiotic treatment.³⁴

Forty eight patients with acute sinusitis were placed on standard therapy, which included antihistamines and analgesic agents, along with antibiotics if indicated. Twenty three of the patients received bromelain four times daily, while the remaining 25 received a placebo. Of the patients receiving bromelain, 83% had complete resolution of nasal mucosal inflammation compared with only 52% in the placebo group. Improvement in breathing occurred in 78% of those receiving bromelain as compared to 68% in those receiving placebo. In the patients not receiving antibiotic treatment, 85% of patients receiving bromelain had complete resolution of inflammation of the nasal mucosa and complete resolution of breathing difficulties. Only 40% of the placebo group had a similar outcome with respect to inflammation, while 53% reported resolution of breathing difficulty.³⁵

The potentiation of antibiotics and other medicines by bromelain may be due to enhanced absorption, as well as increased permeability of the diseased tissue which enhances the access of the antibiotic to the site of the infection. It is also thought that the use of bromelain may provide a similar access to specific and non-specific components of the immune system, therefore, enhancing the body's utilization of its own healing resources.

Mucolytic Properties

The topical use of the enzymes, bromelain or papain, to remove excessive cervical mucus was demonstrated in 1954. Observations following its use demonstrated that pseudo and actual space-occupying lesions could be more positively identified, and inflammatory changes of the canal and its glands could be visualized with greater accuracy.³⁶

Effects of bromelain on rabbit sputum consistency were investigated *in vitro* and *in vivo*. Of the enzymes tested, bromelain exerted the most potent lowering effect on sputum viscosity and also showed a tendency to increase the sputum volume.³⁷

In a clinical study of 124 patients hospitalized with chronic bronchitis, pneumonia or bronchopneumonia, bronchiectasis, or pulmonary abscess, those receiving bromelain orally showed a decrease in the volume and purulence of the sputum.¹⁷ These results support the effectiveness of bromelain in decreasing the viscosity of sputum so that it can be more easily cleared from the respiratory tract.

Digestive Aid

Bromelain has been used successfully as a digestive enzyme following pancreatectomy, in cases of exocrine pancreas insufficiency and in other intestinal disorders.³⁸ Because of its wide pH range, bromelain has activity in the stomach as well as the small intestine. It has also been shown to be an adequate replacement for pepsin and trypsin in cases of deficiency. The combination of ox bile, pancreatin and bromelain is effective in lowering stool fat excretion in patients with pancreatic steatorrhea. In addition, this combination resulted in a gain in weight in most cases as well as an enhanced subjective feeling of well being. Symptomatic improvement was also noted in relation to pain, flatulence and stool frequency.³⁹

Bromelain has been reported to heal gastric ulcers in experimental animals.⁴⁰ In an extensive study of the effect of bromelain on the gastric mucosa, it was found that bromelain increased the uptake of radioactive sulfur by 50% and glucosamine by 30 -90%. Increased uptake of these substances may allow the gastric mucosa to heal more rapidly under the influence of bromelain.⁴¹

In a study designed to examine the effect of bromelain on enterotoxin receptor activity in porcine small intestine, orally administered bromelain inhibited enterotoxin attachment to pig small intestine in a dose-dependent manner. Attachment was negligible after treatment. Serum biochemical analysis and histopathological examination of treated piglets showed no adverse effects with the bromelain treatment. Administration of bromelain may therefore be useful for preventing enterotoxin-induced diarrhea.⁴²

Surgical Procedures and Musculoskeletal Injuries

Bromelain also has therapeutic effects in the treatment of inflammation and soft tissue injuries. An early clinical trial on bromelain was conducted on 74 boxers with bruises on the face and haematomas of the orbits, lips, ears, chest and arms. Bromelain was given four times a day for 4 days or until all signs of bruising had disappeared. A control group of 72 boxers were given a placebo. In 58 of the boxers taking bromelain, all signs of bruising cleared completely in four days, with the remaining 16 requiring 8-10 days for complete clearance. In the control group, only 10 had complete clearance within four days, with the remainder requiring seven to fourteen days for resolution.⁴³

The edema-reducing property of bromelain was investigated in traumatically-induced hindleg edema in rats. After enteral application of bromelain a significant reduction of the edema could be observed, however,

Table 4 .

Conditions in which Bromelain has Documented Therapeutic Benefits

Angina
Arthritis
Athletic and musculoskeletal injuries
Bacterial infections
Bronchitis
Cellulitis
Cutaneous Staphylococcus infection
Debridement of Burns
Dysmenorrhea
Edema
Inflammation
Maldigestion
Pancreatic insufficiency and Steatorrhea
Platelet aggregation
Pneumonia
Pyelonephritis
Rectal abscesses
Sinusitis
Surgical traumas
Thrombophlebitis

parenteral application only resulted in a minimal therapeutic effect. Although enterally-applied enzymes are thought to be degraded in the gut, the better results were obtained after oral administration of bromelain, supporting the observation that bromelain can be absorbed by the gut without losing its biological properties.¹¹

Fifty-five pre-surgical patients were divided into two groups. Group one, consisting of 22 patients, took bromelain four times a day for 48-72 hours prior to surgery and continued for 72 hours after surgery. Group two, consisting of 33 patients, took bromelain starting on the day of surgery, with the first dose administered one hour prior to surgery. Fifty percent of group one and 42.4% of group two had complete disappearance of pain and inflammation within 72 hours. Pain and inflammation persisted past 72 hours in only one member of the group supplemented with bromelain for three days prior to surgery, as opposed to five members of the group that started supplementation one hour prior to surgery. In a separate study, supplementation of bromelain starting 48-72 hours prior to surgery reduced the average number of days for complete disappearance of pain from 3.5 to 1.5, and disappearance of inflammation from 6.9

to 2.0 days, as compared with controls receiving no bromelain.⁴⁴

Sixteen patients undergoing oral surgery were given bromelain four times a day starting 72 hours prior to surgery. At 24 hours after surgery, 75% of these patients were evaluated as having mild or no inflammation, in contrast to only 19% of a group receiving a placebo. Twenty-four hours after surgery, pain was either absent or mild in 38% of bromelain-treated patients, as opposed to 13% receiving placebo. After 72 hours, this increased to 75% of those in the bromelain group, as compared to only 38% in the placebo group.⁴⁵

In an observation study involving 59 patients with blunt injuries to the musculoskeletal system, the efficacy and tolerability of high-dose bromelain, in addition to the usual therapeutic measures, was investigated. Treatment with bromelain resulted in a clear reduction in all four parameters tested; swelling, pain at rest and during movement, and tenderness.⁴⁶

Cardiovascular and Circulatory Applications

Research has indicated that bromelain prevents aggregation of human blood platelets *in vivo* and *in vitro*, prevents or minimizes the severity of angina pectoris and transient ischemic attacks (TIA), is useful in the prevention and treatment of thrombosis and thrombophlebitis, may break down cholesterol plaques, and exerts a potent fibrinolytic activity. If administered for prolonged time periods, bromelain also exerts an anti-hypertensive effect in experimental animals.^{2,47}

Administration of 400-1000 mg/day of bromelain to 14 patients with angina pectoris resulted in the disappearance of symptoms in all patients within 4 to 90 days.⁴⁸ Similar results have been observed in patients taking between 500-700 mg/day of bromelain. After discontinuing bromelain, angina attacks reappear after a variable period of time, often

triggered by stressful experiences.²

A drastic reduction in the incidence of coronary infarct after administration of potassium and magnesium orotate along with 120-400 mg of bromelain per day has also been reported.⁴⁹

In a study involving 73 patients with acute thrombophlebitis, bromelain, in addition to analgesics, was shown to decrease all symptoms of inflammation; including, pain, edema, tenderness, skin temperature, and disability.⁵⁰

The ability of bromelain to influence these conditions may be due to its ability to breakdown fibrinous plaques. Bromelain has been shown to dissolve arteriosclerotic plaque in rabbit aorta in vivo and in vitro.² It is likely that bromelain also increases vessel wall permeability to oxygen and nutrients while increasing blood fluidity, both of which aid in these conditions.

Toxicity, Side Effects and Allergic Reactions

Bromelain is considered to have very low toxicity, with an LD₅₀ greater than 10g/kg. Toxicity tests on dogs, with increasing levels of bromelain up to 750 mg/kg administered daily, showed no toxic effects after six months. Dosages of 1.5 g/kg/day administered to rats show no carcinogenic or teratogenic effects.⁵¹

In human clinical tests, side effects have not been observed. Bromelain supplementation up to 460 mg has been shown to have no effect on heart rate or blood pressure; however, increasing doses up to 1840 mg have been shown to increase the heart rate proportionately. In some cases an increase of up to 80% of the baseline has been reported, which may be a result of bromelain's influence on IL-1 and TNF production. Maximum effects were seen at 2 hours but some residual effect remained at 24 hours. At doses above 700 mg, palpitations and subjective discomfort have been reported. Blood pressure changes have

not been demonstrated in humans at any dosage level.⁵²

The allergenic potential of proteolytic enzymes should not be underestimated, for they cause, in particular, IgE-mediated respiratory allergies of both the immediate type and the late-phase of immediate type with predominantly respiratory symptoms. Allergy to bromelain has been reported in workers of a blood-grouping laboratory, and investigation indicates that (1) bromelain is a strong sensitizer, (2) sensitization usually occurs due to inhalation and not to ingestion, (3) bromelain allergy is occupationally acquired, and adequate precautions are necessary.⁵³ The risk of sensitization to enzymes due to inhalation as a result of occupational exposure is very high (up to 50%).⁵⁴

Bromelain has been shown to cross-react with the sera in about 28% of persons with IgE allergic response to honeybee venom.⁵⁵ Bromelain, along with horseradish peroxidase and ascorbate oxidase are recognized by the IgE of sera from patients who are hypersensitive to olive tree pollen.⁵⁶

Bromelain and papain, due to their use as a meat tenderizer and to clarify beer, are considered as potential ingestive allergens and may represent an unrecognized cause of an allergic reaction following a meal. As with other food substances, a small segment of the population, particularly those with a sensitivity to pineapple, may be sensitive to oral supplementation with bromelain. As contact allergens, the enzymes play a minor role; however, it is thought that skin testing with isolated proteases like bromelain may induce systemic reactions in susceptible individuals, even at very high dilution.^{53,57}

Table 5. Considerations and Instructions for Prescribing Bromelain

1. Is there a history of occupational inhalant/skin contact with Bromelain? If yes, consider possibility of allergic reaction.
2. Does the patient have allergic reactions to bee stings, olive tree pollen or pineapple? If yes, consider possibility of allergic reaction.
3. Is there a history of heart palpitations? If yes, limit to 460 mg of bromelain per day.
4. Dose 4 times per day for best results.
5. Dosage ranges typically from 500-1000 mg/day with up to 2000 mg/day common.
6. If used pre-surgery or to minimize trauma from sporting activities, begin bromelain supplementation 72 hours prior to event.
7. Enhances effectiveness of antibiotics and absorption of glucosamine and possibly bioflavonoids, so supplement in conjunction with these substances.
8. Best results might be obtained if taken away from food, however, therapeutic efficacy has been demonstrated when bromelain is supplemented prior to or with meals.

Indications for the Use of Bromelain

There are several compelling reasons for supplementation with oral bromelain.

1. It inhibits blood platelet aggregation, favorably modulates prostaglandin formation and minimizes risk of coronary atherosclerotic disease.
2. It continues to provide a desired physiological action for as long as it is administered, with no evidence indicating that a tolerance develops.
3. It is considered to be non-toxic and lacking in side effects, so it can be used without concern in doses from 200 to 2000 mg for prolonged periods of time.
4. It is a protein and seems to be as easily metabolized as other dietary proteins.

5. It is well absorbed and seems to have greater therapeutic impact when administered orally as opposed to intravenously

6. While effective for inflammation and injury, it is even more effective if administered prior to a traumatic event, i.e. surgery or athletic competition.

7. It seems to enhance the absorption of and improve the action of other substances when they are administered in combination.

8. Because of its impact on the cytokine system, particularly IL-1 and TNF, which stimulate fever and acute phase response, and its demonstrated ability to increase the heart rate, bromelain may assist in generating an acute-stage healing response.

Bromelain has a wide range of conditions for which it has well documented therapeutic efficacy (see Table 4).

Dosage and Prescription Instructions

Available research does not demonstrate an enhanced efficacy of bromelain when it is administered between meals. It is generally recommended that bromelain be taken away from food unless it is being used as a digestive aid, because it is believed that otherwise, it will tend to act as a digestive enzyme and its therapeutic benefit may be diminished. While this may in fact be the case, the clinical studies conducted on bromelain have not followed this protocol.

Bromelain has shown therapeutic benefits in doses as small as 160 mg/day; however, it is thought that, for most conditions, best results occur starting at a dose of 750-1000 mg/day. Most research on bromelain has been done utilizing divided doses, usually four per day, and findings indicate that results are dose-dependent. See table 5 for a summary of prescription instructions.

Conclusion

Bromelain has been used for a variety of clinical applications for more than 35 years. Although its mechanisms of action has not been completely resolved, bromelain has demonstrated a beneficial effect on the kinin system, the coagulation cascade, the cytokine system, and prostaglandin synthesis. Bromelain is believed to enhance the absorption of flavonoids and has been shown to increase absorption of glucosamine, so bromelain supplementation should be considered when these nutrients are given. It may also enhance absorption and utilization of many other substances; however, to date research in this area has focused primarily on antibiotics. Bromelain has been shown to exert a beneficial ef-

fect at doses as low as 160 mg/day, however, there is a general consensus among researchers that the best results occur when bromelain is given in doses above 500 mg per day and that results improve in a dose-dependent manner with higher levels of bromelain supplementation. Bromelain has been demonstrated to be well absorbed after an oral dose and has been shown to be safe at high doses for prolonged periods of time. For the conditions discussed in this review, bromelain has shown itself to be an effective supplement.

References

1. Rowan AD, Buttle DJ, Barrett AJ. The cysteine proteinases of the pineapple plant. *Biochem J* 1990;266:869-875.
2. Taussig SJ, Nieper HA. Bromelain: its use in prevention and treatment of cardiovascular disease, present status. *J IAPM* 1979;6:139-151.
3. Harrach T, Eckert K, Schulze-Forster K, et al. Isolation and partial characterization of basic proteinases from stem bromelain. *J Protein Chem* 1995;14:41-52.
4. Jeung A. *Encyclopedia of Common Natural Ingredients Used in Foods, Drugs, and Cosmetics*. New York, NY: John Wiley & Sons;1980:74-76.
5. White RR, Crawley FE, Vellini M, et al. Bioavailability of 125I bromelain after oral administration to rats. *Biopharm Drug Dispos* 1988;9:397-403.
6. Heinicke RM, Van der Wal M, Yokoyama MM. Effect of bromelain on human platelet aggregation. *Experientia* 1972;28:844-845.
7. Morita AH, Uchida DA, Taussig SJ. Chromatographic fractionation and characterization of the active platelet aggregation inhibitory factor from bromelain. *Arch Inter Phar Ther* 1979;239:340-350.
8. Livio M, Bertoni MP, De Gaetano G, et al. Effect of bromelain on fibrinogen level, prothrombin complex factors and platelet aggregation in the rat - A preliminary report. *Drugs Expt Clin Res* 1978;4:49-53.
9. De-Giuli M, Pirotta F. Bromelain: interaction with some protease inhibitors and rabbit specific antiserum. *Drugs Exp Clin Res* 1978;4:21-23.

10. Inoue K, Motonaga A, Dainaka J, et al. Effect of etodolac on prostaglandin E2 biosynthesis, active oxygen generation and bradykinin formation. *Prostaglandins Leukot Essent Fatty Acids* 1994;51:457-462.
11. Uhlig G, Seifert J. The effect of proteolytic enzymes (traumanase) on posttraumatic edema. *Fortschr Med* 1981;99:554-556.
12. Vellini M, Desideri D, Milanese A, et al. Possible involvement of eicosanoids in the pharmacological action of bromelain. *Arzneimittelforschung* 1986;36:110-112.
13. Yonehara N, Shibutani T, Inoki R. Contribution of substance P to heat-induced edema in rat paw. *J Pharmacol Exp Ther* 1987;242:1071-1076.
14. Kumakura S, Yamashita M, Tsurufuji S. Effect of bromelain on kaolin-induced inflammation in rats. *Eur J Pharmacol* 1988;150:295-301.
15. Uchida Y, Katori M. Independent consumption of high and low molecular weight kininogens in vivo. *Adv Exp Med Biol* 1986;198:113-118.
16. Taussig SJ, Batkin S. Bromelain, the enzyme complex of pineapple (*Ananas comosus*) and its clinical application. An update. *J Ethnopharmacol* 1988;22:191-203.
17. Schafer A, Adelman B. Plasmin inhibition of platelet function and of arachidonic acid metabolism. *J Clin Invest* 1985;75:456-461.
18. Felton GE. Fibrinolytic and antithrombotic action of bromelain may eliminate thrombosis in heart patients. *Med Hypotheses* 1980;6:1123-1133.
19. Gerard G. Anti-cancer therapy with bromelain. *Agress* 1972;3:261-274.
20. Nieper HA. A program for the treatment of cancer. *Krebs* 1974;6:124-127.
21. Taussig SJ, Szekerczes J, Batkin S. Inhibition of tumor growth in vitro by bromelain, an extract of the pineapple plant (*Ananas comosus*). *Planta Med* 1985;6:538-539.
22. Batkin S, Taussig SJ, Szekerezes J. Antimetastatic effect of bromelain with or without its proteolytic and anticoagulant activity. *J Cancer Res Clin Oncol* 1988;114:507.
23. Desser L, Rehberger A, Paukovits W. Proteolytic enzymes and amylase induce cytokine production in human peripheral blood mononuclear cells in vitro. *Cancer Biother* 1994;9:253-263.
24. Desser L, Rehberger A. Induction of tumor necrosis factor in human peripheral-blood mononuclear cells by proteolytic enzymes. *Oncology* 1990;47:475-477.
25. Desser L, Rehberger A, Kokron E, et al. Cytokine synthesis in human peripheral blood mononuclear cells after oral administration of polyenzyme preparations. *Oncology* 1993;50:403-407.
26. Munzig E, Eckert K, Harrach T, et al. Bromelain protease F9 reduces the CD44 mediated adhesion of human peripheral blood lymphocytes to human umbilical vein endothelial cells. *FEBS Lett* 1995;351:215-218.
27. Houck JC, Chang CM, Klein G. Isolation of an effective debriding agent from the stems of pineapple plants. *Int J Tissue React* 1983;5:125-134.
28. Klaue P, Dilbert G, Hinke G, et al. Tierexperimentelle untersuchungen zur enzymatischen lokalbehandlung subdermaler verbrennungen mit bromelain. *Therapiewoche* 1979;29:796-799.
29. Ahle NW, Hamlet MP. Enzymatic frostbite eschar debridement by bromelain. *Ann Emerg Med* 1987;16:1063-1065.
30. Moss JN, Frazier CV, Martin GJ. Bromelains, the pharmacology of the enzymes. *Arch Int Pharmacodyn* 1963;145:168.
31. Tinozzi S, Venegoni A. Effect of bromelain on serum and tissue levels of amoxycillin. *Drugs Expt Clin Res* 1978;4:39-44.
32. Luerti M, Vignali ML. Influence of bromelain on penetration of antibiotics in uterus, salpinx and ovary. *Drugs Expt Clin Res* 1978;4:45-48.
33. Renzinni G, Varengo M. The absorption of tetracyclin in combination with bromelain by oral application. *Arzneim-Forsch* 1972;22:410-412.
34. Neubauer RA. A plant protease for potentiation of and possible replacement of antibiotics. *Exp Med Surg* 1961;19:143-160
35. Ryan RE. A double-blind clinical evaluation of bromelains in the treatment of acute sinusitis. *Headache* 1967;7:13-17.
36. Hunter RG, Henry GW, Heinicke RM. The action of papain and bromelain on the uterus. *Am J Ob Gyn* 1957;73:867-873.
37. Suzuki K, Niho T, Yamada H, et al. [Experimental study of the effects of bromelain on the sputum consistency in rabbits]. *Nippon Yakurigaku Zasshi* 1983;81:211-216.

38. Knill-Jones RP, Pearce H, Batten J, et al. Comparative trial of Nutrizym in chronic pancreatic insufficiency. *Brit Med J* 1970;4:21.
39. Balakrishnan V, Hareendran A, Sukumaran Nair C. Double-blind cross-over trial of an enzyme preparation in pancreatic steatorrhea. *J Asso Phys Ind* 1981;29:207-209.
40. Seligman B. Bromelain—an anti-inflammatory agent—thrombophlebitis. No toxicity. *Angiology* 1962;13:508-510.
41. Felton G. Does Kinin released by pineapple stem bromelain stimulate production of prostaglandin E1-like compound. *Haw Med J* 1976;2:39-47.
42. Mynott TL, Luke RK, Chandler DS. Oral administration of protease inhibits enterotoxigenic Escherichia coli receptor activity in piglet small intestine. *Gut* 1996;38:28-32.
43. Blonstein JL. Control of swelling in boxing injuries. *Practitioner* 1960;185:78.
44. Tassman GC, Zafran JN, Zayon GM. Evaluation of a plant proteolytic enzyme for the control of inflammation and pain. *J Dent Med* 1964;19:73-77.
45. Tassman GC, Zafran JN, Zayon GM. A double-blind crossover study of a plant proteolytic enzyme in oral surgery. *J Dent Med* 1965;20:51-54.
46. Masson M. Bromelain in blunt injuries of the locomotor system. A study of observed applications in general practice. *Fortschr Med* 1995;113:303-306.
47. Giacca S. Clinical experiments with bromelain in peripheral venous diseases and chronic bronchitic states. *Minerva Med* 1965;56:Suppl.104.
48. Nieper HA. Effect of bromelain on coronary heart disease and angina pectoris. *Acta Med Empirica* 1978;5:274-278.
49. Nieper HA. Decrease of the incidence of coronary heart infarct by Mg- and K-orotate and bromelain. *Acta Med Empirica* 1977;12:614-618.
50. Seligman B. Oral bromelains as adjuncts in the treatment of acute thrombophlebitis. *Angiology* 1969;20:22-26.
51. Taussig SJ, Yokoyama MM, Chinen N, et al. Bromelain: A proteolytic enzyme and its clinical application. *HirJ Med Sci* 1975;24:185-193.
52. Gutfreund A, Taussig S, Morris A. Effect of oral bromelain on blood pressure and heart rate of hypertensive patients. *Haw Med Jour* 1978;37:143-146.
53. Gailhofer G, Wilders-Truschnig M, Smolle J, Ludvan M. Asthma caused by bromelain: an occupational allergy. *Clin Allergy* 1988;18:445-450.
54. Chida T. A study on dose-response relationship of occupational allergy in a pharmaceutical plant. *Sangyo Igaku* 1986;28:77-86.
55. Tretter V, Altmann F, Kubelka V, et al. Fucose alpha 1,3-linked to the core region of glycoprotein N-glycans creates an important epitope for IgE from honeybee venom allergic individuals. *Int Arch Allergy Immunol* 1993;102:259-266.
56. Batanero E, Villalba M, Monsalve RI, et al. Cross-reactivity between the major allergen from olive pollen and unrelated glycoproteins: evidence of an epitope in the glycan moiety of the allergen. *J Allergy Clin Immunol* 1996;97:1264-1271.
57. Wuthrich B. Proteolytic enzymes: potential allergens for the skin and respiratory tract? *Hautarzt* 1985;36:123-125.