Bromelain Monograph

Description and Constituents

Bromelain is a general name for a family of sulfhydryl-containing proteolytic enzymes obtained from *Ananas comosus*, the pineapple plant. Although bromelain's primary constituent is a sulfhydryl proteolytic fraction, it also contains escharase (a non-proteolytic component in bromelain thought to be important in the action of topical bromelain), peroxidase, acid phosphatase, several protease inhibitors, and organically-bound calcium.[1] The beneficial effects of bromelain are due to multiple constituents apart from its proteolytic fraction.

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 2,000 m.c.u is approximately equal to 1 gram with 1,200 g.d.u. activity or 8 grams with 100,000 r.u. activity.

Pharmacokinetics

In a rat study, bromelain was absorbed intact through the gastrointestinal tract, with up to 40 percent of the high molecular weight substances detected in the blood after oral administration. The highest concentration of bromelain was found in the blood one hour after administration; however, its proteolytic activity was rapidly deactivated.[2]

Key words: bromelain, pineapple, Ananas, proteolytic, protease, anti-inflammatory, surgery, inflammation, wound, injury, intestinal pathogens, platelet aggregation, fibrinolytic, blood thinner, antibiotic, diarrhea, cancer, antimicrobial, circulation, cardiovascular, angina, prostatitis, arthritis, digestion, IBD, renal, kidney, sinusitis

Mechanisms of Action

Mechanisms for bromelain's physiological effects appear to include interactions with inflammatory, immune, cell signaling, and coagulation molecules and pathways. Bromelain also appears to have effects on cell surface antigens.

Bromelain's anti-inflammatory 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.[3-5] Experiments suggest that bromelain reduces leukocyte migration into inflamed areas and, secondary to its ability to remove cell surface molecules including the CD128 chemokine receptors, prevents firm adhesion of leukocytes to blood vessels at the site of inflammation.[6] *In vitro* evidence suggests bromelain might be a specific inhibitor of cyclooxygenase-2 (Cox-2) expression[7,8] and might induce a significant decrease of substance P concentrations.[9] Bromelain induces a significant decrease in prostaglandin E_2 concentrations *in vivo*.[9]

A variety of studies have reported an immunomodulatory effect of bromelain. *In vitro*, bromelain treatment of cells activates natural killer cells and increases the production of tumor necrosis factor-alpha, interferon gamma, interleukin-1, interleukin-2, interleukin-6, and granulocyte-macrophage-colony stimulating factor.[10-13] Bromelain treatment of cells also decreased activation of CD4(+) T cells and reduced the expression of CD25.[14] Bromelain's *in vivo* effects in these areas might not be identical to the reported *in vitro* findings, with existing evidence suggesting that bromelain might produce complex responses that might be adaptogenic in nature. In a mice study, bromelain simultaneously enhanced and

inhibited aspects of T-cell responses.[12] In a human study, bromelain supplementation increased monocytic cytotoxicity in individuals with decreased activity. It also stimulated the secretion of interleukin 1-beta from monocytes and reduced the expression of CD44.[15]

Bromelain appears to act as a signaling molecule, capable of influencing a variety of cell signaling cascades, many of which are important in cell survival. It stimulates protease-activated receptors-2 and -4;[16] up-regulates protein 53 (p53) and B-cell-lymphoma-2 associated protein (Bax); decreases expression of B-cell-lymphoma-2 gene; blocks phosphorylation of I kappa B alpha; curtails extracellular regulated protein kinase (ERK) 1 and 2, p38 mitogen-activated protein kinase (MAPK) and Akt activity; and inhibits nuclear factor-kappa B (NF-κB).[17-19] In a study on ischemia-reperfusion injury, bromelain increased phosphorylation of both Akt and foxhead box O3 (FOXO3A) – cell signaling pathways that influence cardiomyocyte survival.[20]

Evidence indicates that bromelain might influence gastrointestinal motility secondary to an adaptogenic affect on the expression of certain enzymes and signaling molecules. Laparotomy in rats results in an overexpression of inducible nitric oxide synthase (iNOS) mRNA and down-regulation of NF-κB. Bromelain counters both of these changes in the colon of the postoperative rat.[21]

Evidence has suggested bromelain counters some of the effects of certain intestinal pathogens (including *Vibrio cholera* and enterotoxic *Escherichia coli)*. An aspect of this activity appears to be related to bromelain's interaction with intestinal secretory signaling pathways, including adenosine 3':5'-cyclic monophosphate, guanosine 3':5'-cyclic monophosphate, and calcium-dependent signaling cascades. The net result is that bromelain counteracts the enterotoxin-induced increase in intestinal secretions caused by an organism like *Vibrio cholera*.[22] Other evidence suggests a different or additional mechanism of action. In *E. coli* infection, bromelain has anti-adhesion effects, temporarily (during times of active supplementation) preventing the bacteria from attaching to specific glycoprotein receptors located on the intestinal mucosa by proteolytically modifying the receptor attachment sites.[23,24] An anti-adhesion/cell surface antigen effect has also been reported *in vitro* with T cells. Bromelain removed cell surface molecules from T cells, which subsequently influenced immune cell surface adhesion properties.[25]

Bromelain decreases thrombin-induced platelet aggregation *in vitro*.[26,27] Bromelain treatment of cells also reduces the adhesion of platelets to endothelial cells, which suggests anti-adhesion might be a component of its effects on platelet aggregation.[28] Bromelain is also an effective fibrinolytic agent *in vitro* and *in vivo*[29] by stimulating the conversion of plasminogen to plasmin, resulting in increased fibrinolysis.[5]

Clinical Indications

Clinical trials have employed a variety of preparations including bromelain alone or in combination with other nutraceutical ingredients (most commonly trypsin and rutin).

Antibiotic Potentiation

Bromelain has been documented to increase blood and urine levels of some antibiotics in humans.[30-32] Combined bromelain and antibiotic therapy was shown to be more effective than antibiotics alone in pneumonia, bronchitis, cutaneous Staphylococcus infection, thrombophlebitis, cellulitis, pyelonephritis, perirectal and rectal abscesses,[33] sinusitis,[34] and urinary tract infections.[35] A combination of bromelain, trypsin, and rutin has been used as an adjuvant therapy in combination with antibiotics for children with sepsis. Compared to antibiotics and a placebo, combining bromelain, trypsin and rutin with antibiotics resulted in earlier improvements in fever reduction and scores on the Glasgow Coma Scale, suggesting a benefit in pediatric patients with sepsis.[36]

Antidiarrheal

Bromelain supplementation helps protect animals against diarrhea caused by bacterial enterotoxins from *Escherichia coli* and *Vibrio cholerae*. It appears to exert this effect by influencing intestinal secretory signaling pathways and/or working as anti-adhesion therapy subsequent to proteolytic modification of the receptor attachment sites.[22-24]

Antimicrobial

In addition to its ability to counter some effects of certain intestinal pathogens and synergism with antibiotics, both mechanisms suggesting bromelain's benefits for specific infections, *in vitro* evidence also suggests bromelain has antihelminthic activity against the gastrointestinal nematodes *Trichuris muris* and *Heligmosomoides polygyrus*.[37,38]

In vitro evidence also suggests potential anti-Candida effects. Incubation of cells with bromelain and trypsin stimulate phagocytosis and respiratory burst killing of *Candida albicans*.[39] Pityriasis lichenoides chronica is an infectious skin disease of unknown etiology; bromelain reportedly caused complete resolution of this condition.[40]

Cancer

Several animal and human studies indicate bromelain might have some anticancer activity.[41-44] Presumably bromelain's anticancer effects are a result of its impact on immune, inflammatory, and hemostatic pathways, as well as its influence on a variety of molecules involved with cell signaling.[45] In a mouse skin cancer model, pretreatment with bromelain delayed the onset of tumorigenesis and reduced the cumulative number of tumors, tumor volume, and the average number of tumors/mouse.[17,18] In a murine model of Syngeneic sarcoma, bromelain reduced local tumor weight, but failed to produce a statistically significant reduction in lung metastasis.[46] Bromelain reportedly has *in vivo* antitumoral/antileukemic activity for the following tumor lines: P-388 leukemia, sarcoma (S-37), Ehrlich ascitic tumor, Lewis lung carcinoma, and ADC-755 mammary adenocarcinoma. In these studies, intraperitoneal administration of bromelain beginning 24 hours after tumor cell inoculation positively influenced survival.[47] In doses over 1,000 mg daily, bromelain has been combined with chemotherapeutic agents such as fluorouracil and vincristine, resulting in tumor regression.[41,44]

Cardiovascular and Circulatory Applications

Bromelain has several potential cardiovascular applications. It is reported to have effects on platelet aggregation and ischemia/reperfusion insults, and has been studied in the symptomatic management of angina pectoris and thrombosis. Bromelain decreases platelet aggregation,[26,27] is an effective fibrinolytic agent,[29] and inhibits thrombus formation.[28]

Bromelain limited myocardial injury in ischemia/reperfusion experiments, aiding functional recovery of the heart. It also increased aortic flow and reduced both the infarct size and the degree of apoptosis compared with the control animals.[48] In hepatic ischemia/reperfusion experiments bromelain treatment reduced apoptosis and endothelial cell damage, while lowering AST levels.[49] A combination of bromelain and other nutrients protected against ischemia/reperfusion injury in skeletal muscle.[50]

Research indicates bromelain prevents or minimizes the severity of angina pectoris. After discontinuing bromelain, angina attacks reappear after a variable period of time.[51,52] A drastic reduction in the incidence of coronary infarct after administration of potassium and magnesium orotate along with 120-400 mg bromelain per day has been reported.[53] In a study involving 73 patients with acute thrombophlebitis, bromelain plus analgesics was shown to decrease symptoms of inflammation, including pain, edema, tenderness, skin temperature, and disability.[54]

Digestive Aid

Bromelain has been used successfully as a digestive enzyme following pancreatectomy, in cases of exocrine pancreas insufficiency, and in other intestinal disorders.[55] The combination of ox bile, pancreatin, and bromelain is effective in lowering stool fat excretion in patients with pancreatic steatorrhea, resulting in symptomatic improvements in pain, flatulence, and stool frequency.[56] A combination of bromelain with enzymes derived from *Aspergillus niger* improved protein utilization in elderly nursing home patients.[57] In a pilot study, bromelain, in combination with sodium alginate, sodium bicarbonate, and essential oils, significantly improved dyspeptic symptoms.[58] In rats, bromelain given post-colonic surgery (laparotomy) countered the surgery-induced decrease in intestinal motility, improved defecation, and increased stool weight and water content.[21]

Inflammatory Bowel Disease

Daily treatment with oral bromelain, beginning at age five weeks, decreased the incidence and severity of spontaneous colitis in mice bred to have an increased incidence of this condition. Bromelain also significantly decreased the clinical and histological severity of colonic inflammation in mice with established colitis.[59] *In vitro* evidence suggests that bromelain might reduce the inflammatory molecules generated by biopsy-obtained colonic cells obtained from patients with inflammatory bowel disease. Treating these colonic cells with bromelain decreased the secretion of a variety of proinflammatory molecules including colony-stimulating factor and interferon-gamma.[60] Case reports detailing the successful use of bromelain in the treatment of mild ulcerative colitis have been published. Two patients who were not responding to conventional medical therapy took bromelain in

addition to their usual drug regimen. The addition of bromelain was reported to result in rapid improvement of symptoms, which was confirmed by endoscopy.[61]

Multiple Sclerosis

In individuals with relapsing multiple sclerosis, bromelain given in combination with trypsin and rutoside did not have an observed treatment effect compared to placebo.[62]

Musculoskeletal Injuries

In animals, bromelain promotes healing post acute injury.[63] Human studies suggest similar benefits. Bromelain has been shown to speed healing from bruises and hematomas.[64] In blunt injuries to the musculoskeletal system resulting in strains and torn ligaments, bromelain produced a reduction in swelling, pain at rest and during movement, and tenderness.[65] However, in one study, the combination of bromelain, trypsin, and rutin was reported to be no more effective than placebo for the treatment of patients with acute ankle sprains.[66] An enzyme preparation that included bromelain, in combination with dietary counseling and acupuncture, promoted healing of rotator cuff tendinitis.[67]

Bromelain has yielded mixed results for countering exercise-induced pain. Bromelain, in combination with papain and fungal-derived protease enzymes, might reduce the damaging effects of unaccustomed exercise and accelerate recovery of muscle tissue.[68] A combination of bromelain, papain, trypsin, pancreatic enzymes, and other proteolytic substances attenuated soft tissue injury and soreness resulting from intense exercise.[69] In a negative study, ingestion of bromelain had no effect on elbow flexor pain, loss of range of motion, or loss of concentric peak torque as a result of an unaccustomed exercise regimen.[70]

Osteoarthritis

Mixed results have been reported for bromelain in osteoarthritis. In an open-labeled study, one month of bromelain resulted in significant decrease in pain and stiffness in patients with knee osteoarthritis.[71] A combination of bromelain, trypsin, and rutin was compared to diclofenac in 103 patients with osteoarthritis of the knee. After six weeks, both treatments resulted in significant and similar reductions in pain and inflammation.[72] In another six-week trial, diclofenac or a combination of bromelain, trypsin, and rutin in persons with osteoarthritis of the hip reduced pain and joint stiffness equally well.[73] In another study, bromelain given to individuals with knee osteoarthritis for 12 weeks resulted in no improvement compared to the placebo group.[74]

Prostatitis

In an open-labeled study of 17 men with category III chronic prostatitis (nonbacterial chronic prostatitis and prostatodynia), one month of treatment with a combination of bromelain, papain, and quercetin resulted in an improvement of at least 25 percent in symptom score in 14 of 17.[75]

Renal Disease

Administration of bromelain, trypsin, rutin, and vitamin E slowed the progression of renal disease and decreased urinary protein and the severity of tubular fibrosis in a rat model of kidney disease.[76]

Respiratory Conditions

In a murine model of acute asthma, bromelain decreased airway reactivity and sensitivity to irritants, decreased markers of lung inflammation including infiltration by eosinophils and leukocytes, and moderated aspects of local airway immunity (reducing CD19+ B cells and CD4+ and CD8+ T lymphocytes).[77,78]

Several studies conducted in the 1960s reported a benefit of bromelain for sinusitis.[34,79,80] For example, in patients with sinusitis who were not receiving antibiotic treatment, 85 percent of patients receiving bromelain had complete resolution of inflammation of the nasal mucosa and complete resolution of breathing difficulties, while in the placebo group only 40 percent had a complete resolution of inflammation and only 53 percent reported resolution of breathing difficulty.[34] In a more recent study in children with acute sinusitis, treatment with bromelain shortened the duration of symptoms and speeded recovery compared with usual care.[81]

Rheumatoid Arthritis

Two animal studies suggested a benefit of proteolytic enzymes in adjuvant-induced arthritis (a model of rheumatoid arthritis). In these studies, rats were administered cyclosporin, a mixture of proteolytic enzymes (bromelain, trypsin, rutin), or cyclosporin plus enzymes. While both cyclosporin and enzymes reduced inflammation and destructive arthritis-associated changes, the best results

occurred in the rats given cyclosporin and proteolytic enzymes.[82,83]

One uncontrolled study conducted in humans in the 1960s suggested that bromelain might be of benefit in rheumatoid arthritis. Bromelain was given for 3-13 months to 29 subjects with arthritic joint swelling. Twenty-five of these subjects had rheumatoid arthritis, two had osteoarthritis, one had both rheumatoid and osteoarthritis, and one had gout. All subjects had residual joint swelling despite long-term corticosteroid therapy. Addition of bromelain reportedly resulted in significant to complete decrease in soft tissue swelling in 21 subjects.[84]

In studies of bromelain's anti-inflammatory potential for rheumatoid arthritis, it has been reported to be as or more effective and better tolerated than naproxen (Aleve®), piroxicam (Feldene®), ketoprofen (Oruvail®), indomethacin (Indocin®), etodolac (Lodine®), and diclofenac (Voltaren®).[85,86]

Surgery

Administration of bromelain pre-surgery can reduce the average number of days for complete disappearance of pain and inflammation post-surgery.[87,88] Bromelain has been reported to reduce post-operative swelling and edema.[89] Two trials indicate bromelain might be effective in reducing swelling, bruising, and pain in women having episiotomy.[90,91]

Wound Debridement

Bromelain applied topically as a cream (35% bromelain in a lipid base) can be beneficial for elimination of necrotic tissue and acceleration of healing. A non-proteolytic component, escharase, is responsible for this effect. It has no hydrolytic enzyme activity against normal protein substrates or various glycosaminoglycan substrates and varies greatly from preparation to preparation.[92] Topical application of this preparation has been shown to separate burned or necrotic tissue (eschar) from living tissue in animal[93-96] and human studies.[97-99] Limited evidence also suggests a similar debridement benefit in frostbite.[100] In these instances this topical preparation is an effective, selective and safe method of removing necrotic skin from healthy tissue. Debridement accomplished in this manner is accompanied by minor to moderate pain, which is generally treated by providing an analgesic medication.[97]

Drug Interactions

Bromelain has been documented to increase blood and urine levels of some antibiotics in humans.[30-32] Because of its anti-platelet aggregation[26,27] and fibrinolytic[29] effects, bromelain may theoretically potentiate the effect of blood thinners. However, it has historically been used pre-surgery to speed healing.[89-91]

Side Effects and Toxicity

Bromelain is considered to have very low toxicity, with an LD_{50} greater than 10 g/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 showed no carcinogenic or teratogenic effects.[101]

In human clinical tests, side effects are generally not observed; however, caution is advised if administering bromelain to individuals with hypertension, since one report indicated individuals with pre-existing hypertension might experience tachycardia following high doses of bromelain.[102]

Anti-bromelain antibody titers (IgG) have been detected in both serum and stool after long-term oral therapy in mice. Repeated exposure is required for development of anti-bromelain antibodies. Proteolytic activity appears to be a prerequisite for this response. These results indicate that bromelain can trigger systemic and mucosal immunoglobulin responses; however, the clinical relevance of this has yet to be determined.[103,104]

Bromelain, as well as other proteolytic enzymes, can cause IgE-mediated respiratory allergies of both the immediate type and the late-phase of immediate type.[105]

Information regarding safety in pregnancy and lactation is lacking.

Dosage

Bromelain has demonstrated therapeutic benefits in doses as small as 160 mg per day; however, it is thought for most conditions the best results occur at doses of 750-1,000 mg daily. Most research on bromelain has been performed utilizing four divided daily doses. Findings suggest that results are generally dose-dependent.

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