
Bromelain

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General Features

Bromelain refers to a group of sulfur-containing enzymes that digest protein (proteolytic enzymes or proteases). Bromelain is derived from the stem of the pineapple plant (*Ananas comosus*).¹

Experimental and clinical studies reveal that Bromelain exhibits anti-inflammatory properties, which include:

- a) Inhibition of the biosynthesis of pro-inflammatory prostaglandins and induction of prostaglandin E₁ (which tends to inhibit inflammation)
- b) Activation of proteolytic activity at sites of inflammation and fibrinolysis activity via the plasminogen-plasmin system (Bromelain stimulates the conversion of plasminogen to plasmin, which in turn activates fibrinolytic activity, dissolving fibrin-based clots and reducing swelling).^{2,3,4,5,6,7}
- c) Bromelain has also been shown to reduce plasma kininogen levels, which inhibits the production of kinins. Kinins are known to cause inflammation, swelling and pain.⁸

Human and animal studies verify that Bromelain, administered orally, is absorbed intact, from the gastrointestinal tract to the bloodstream (up to 40 percent absorption rate).^{9,10,11} The human adult intestinal epithelium has traditionally been described as non-permeable to proteins. Recently, Castell, J.V., et al, demonstrated in the American Journal of Physiology (1997) that, after oral administration of Bromelain in 19 healthy men (oral multi-dosing of 3 gms per day), plasma concentrations reached as much as 5,000 pg/mL by 48 hours. From the plasma concentration curve, it could be estimated that an average of 10.8 micrograms of Bromelain was present in plasma in the 3-to-51 hour period. The presence of undegraded Bromelain in plasma was shown unequivocally by immunoprecipitation of plasma samples with antiBromelain antibodies, followed by gel electrophoresis and immunodetection. Moreover, the enzyme retained its biological activity.¹²

Principle Active Constituents

Bromelain enzymes, which are a group of sulfur-containing proteolytic (protein digesting) enzymes.¹

Clinical Application and Mechanism of Action

1. Anti-Inflammatory Agent For Arthritis

In clinical trials, Bromelain supplementation has been shown to reduce swelling and pain in patients with rheumatoid and osteoarthritis. In one study, twenty-five patients with severe rheumatoid arthritis, three patients with osteoarthritis and one patient with gout who had residual joint swelling and impaired mobility following long-term corticosteroid therapy, were given Bromelain (20 to 40 mgs, 3-4 times daily). Twenty-eight percent of patients reported excellent improvement in regards to swelling and pain, forty-five

percent had good results, fourteen percent had fair results and fourteen percent had poor results, including the patient with gouty arthritis. Smaller amounts of steroids were required with concurrent administration of Bromelain (steroid dosing was tapered according to improvement with Bromelain). The follow-up period was 3 weeks to 13 months.¹³

In a recent double-blind clinical trial, 73 patients with gonarthrosis were randomized to receive 3 weeks of treatment with an oral enzyme preparation, containing Bromelain, trypsin and rutin (n=36) or the NSAID diclofenac (n=37). Efficacy was primarily evaluated using the Lequesne index (measuring pain and function of the affected knee). Other investigations included assessment of pain symptoms using a visual analogue scale (VAS), global assessment of efficacy and tolerability (by both patients and one physician), and various laboratory parameters. Patients were evaluated at baseline, at weekly intervals throughout the 3-week treatment period, and at 7 weeks (i.e. 4 weeks after discontinuing therapy).

The Lequesne index improved continuously in both groups: from 13.56 at baseline to 3.10 after 3 weeks (end of therapy) to 2.05 at 7 weeks (follow-up) in the enzyme group, and from 14.04 to 3.50 to 2.24 respectively, in the diclofenac group. The researchers conclude, “short-term evaluation indicates that oral enzymes may be considered an effective and safe alternative to NSAIDs, such as diclofenac in the treatment of painful gonarthrosis”.¹⁴

Singer, et al, also reported anti-inflammatory activity of oral enzymes similar to that of diclofenac in patients with progressive gonarthrosis.¹⁵

Klein, et al, demonstrated that proteolytic oral enzyme therapy was equally effective as was diclofenac in reducing pain in periartrosis of the shoulder in a clinical trial. Previously, these researchers had shown that proteolytic oral enzyme therapy was as effective as NSAIDs in reducing painful vertebral syndrome.¹⁶

2. Sports Injuries and Blunt Injuries to the Musculoskeletal System

Dating back to the 1960's Bromelain has been used (oral administration) in the treatment of sports-related injuries. In one clinical trial, fifty-eight of seventy-four boxers receiving Bromelain reported that all signs of bruising had completely healed within 4 days. Of the remaining sixteen; complete healing took 8 to 10 days. Of the seventy-two controls, only ten showed complete resolution of healing by the fourth day, the remainder taking 7 to 14 days for complete healing to occur.¹⁷

The effect of orally administered Bromelain or the reduction of swelling, bruising, healing time, and pain following various surgical procedures has been demonstrated in several clinical studies.^{6,18,19,20} In the study by Tassman, et al,¹⁸ after oral surgery, swelling decreased within 3.8 days with Bromelain, compared with 7 days for the placebo in a double-blind study. In the same study, pain duration was reduced within 5.1 days in the Bromelain group, compared with 8.1 days in the placebo group.

Recently, in an open case observation study involving patients with blunt injuries to the

musculoskeletal system, the efficacy and tolerability of high-dose Bromelain was investigated by an orthopedic surgeon. In addition to usual therapeutic measures, 59 patients were treated with Bromelain preparations for one to three weeks based upon healing response. Treatment with Bromelain resulted in clear reduction of swelling, pain at rest and during movement, and tenderness to palpation. The addition of Bromelain to the treatment regime accelerated the rate of healing compared to the usual rate of healing observed for blunt injuries to the musculoskeletal system. The tolerability of the Bromelain preparation was very good, and patient compliance was correspondingly high.²¹

Experimental Investigations Demonstrating The Anti-inflammatory Properties of Bromelain
Recent reviews have confirmed the analgesic, anti-inflammatory and edema-reducing properties of Bromelain and other proteolytic enzyme combinations.^{1,16}

As reported by Kleef, et al, Bromelain-treated lymphocytes from healthy human donors displayed a 60 percent to 90 percent reduction in cell surface adhesion compared to untreated lymphocytes in vitro. The selective modulation of cell adhesion molecules may help explain some of the clinical effects observed after Bromelain treatment in patients suffering from chronic inflammatory disease, HIV and cancer.²²

Over the past few years, a number of studies have demonstrated the effects of oral enzymes, including Bromelain, on suppressing the synthesis of pro-inflammatory cytokines^{14,34} and adhesion molecules,^{22,35} the latter are expressed on the surface of cells, enabling cell-cell interactions, which are fundamental processes of the inflammatory reaction.^{36,37}

In summary, oral enzyme therapy reduces various parameters of inflammation and pain by affecting the release of mediators of inflammation, modulation of adhesion molecules, reduction of immune complexes, activation of fibrinolysis and direct influences on nociceptors.^{14,16}

3. Digestive Aid

Bromelain in combination with other digestive enzymes and ox bile has been reported to help digest food⁴¹, but is not generally used alone for this purpose.

Dosage

Anti-inflammatory: 250-750 mg, three times daily on an empty stomach. Bromelain is often standardized to 2,000 milk clotting units (MCU) which is 1333.3 Gelatin Dissolving Units (GDU)^{38,47}

Adverse Side Effects and Toxicity

Currently, NSAIDs are first-line therapy in osteoarthritis. However, endoscopic studies have shown that lesions of the gastric mucosa developed in 14 to 31 percent of patients receiving long-term treatment with NSAIDs.^{23,24,25,26} In particular, the elderly may be seven times more likely to have silent ulcers from NSAID use.^{24,25,27,28} Other potential adverse effects of NSAIDs include cardiac, renal, hepatic and central nervous system damage.¹⁴ From an economic

standpoint, the treatment of gastrointestinal adverse effects from NSAIDs has been calculated to add 45 percent to the cost of arthritis care.^{29,30}

By comparison, therapy with oral enzymes is not associated with severe gastrointestinal irritation, erosion, ulcerations, and related risks^{14,1} and is generally well tolerated.^{14, 21,31,32,33}

Determination of pepsinogen A and C, which are indicators of the function and morphological condition of the gastric mucosa, confirmed good gastric tolerability with administration of oral enzymes, including Bromelain.¹⁴

Unpublished data from trials of up to 4 years duration in patients with various clinical conditions (i.e. rheumatoid arthritis, multiple sclerosis) suggest that oral enzyme therapy, including Bromelain, is very well tolerated over longer periods.¹⁴

In regards to toxicity, animal studies have shown no toxic effects with Bromelain doses up to 10 grams per kilogram as no LD₅₀ (50 percent lethal dose) exists for Bromelain doses in this range.³⁸

Drug-Nutrient Interactions

1. Anticoagulant Medications (warfarin, coumadin etc) - In regards to potential adverse drug-nutrient interactions, studies using Bromelain on isolated human platelets in vitro revealed that Bromelain prevented thrombin-induced platelet aggregation, whereas papain enzyme was less active in preventing platelet aggregation. There is strong biological plausibility that Bromelain may further potentiate the anti-clotting influence of warfarin and coumadin, potentially increasing risk of a bleeding disorder. As well, animal studies and reports with humans indicate that Bromelain treatment can reduce thrombus formation via its thrombolytic action. To date there are no published reports of bleeding disorders occurring in humans using Bromelain supplementation. However, until more information is available, it is advisable to use caution and proper patient monitoring (prothrombin time, INR), when recommending Bromelain to patients on warfarin or anticoagulant therapy.^{39,40}
2. Antibiotics – Bromelain has been shown to increase the amount of antibiotics in the blood and urine with concurrent orally administration.^{42,43,44,45,46}

Pregnancy and Lactation

During pregnancy and lactation, the only supplements that are considered safe include standard prenatal vitamin and mineral supplements. All other supplements or dose alterations may pose a threat to the developing fetus and there is generally insufficient evidence at this time to determine an absolute level of safety for most dietary supplements other than a prenatal supplement. Any supplementation practices beyond a prenatal supplement should involve the cooperation of the attending physician (e.g., magnesium and the treatment of preeclampsia.)

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