Proteolytic Enzymes

Although best known as replacement therapy in pancreatic insufficiency, pancreatic extracts and other proteolytic enzymes such as papain and bromelain are also claimed to possess systemic anti-inflammatory and analgesic effects.

Proteolytic enzymes are widely marketed for the treatment of sports injuries such as ankle sprains, but most of the studies supporting this use are decades old and not up to current scientific standards. A more recent, much better designed and larger trial failed to find benefit in the treatment of ankle sprains.

Other evidence, again mostly decades old, suggests possible post-surgical benefits. More recent, though quite limited, evidence does support use in osteoarthritis and chronic musculoskeletal pain.

Common Uses

- Surgery Support [+3X]
- Osteoarthritis /Chronic Pain [+2]
- Herpes Zoster [+2]
- Minor Injuries [−2X]

(Higher numbers indicate stronger evidence; X modifier indicates contradictory results. See the Introduction for details of the rating scale.)

Surgery Support +3X

Studies of proteolytic enzymes following surgery have returned mixed results.

A double-blind, placebo-controlled study evaluated recovery from episiotomy in 160 women. Participants given 40 mg of bromelain four times daily for 3 days, beginning 4 hours after delivery, showed statistically and clinically significant decreases in edema, inflammation, and pain. However, a similar double-blind study of 158 women failed to find significant benefit.

A double-blind, placebo-controlled study that used the proteolytic enzyme product Chymoral in 204 episiotomy patients found evidence of benefit. Chymoral was also found effective for reducing inflammation in a double-blind, placebo-controlled trial involving 102 surgical removals of impacted wisdom teeth, and in a double-blind, placebo-controlled trial of 86 individuals undergoing podiatric surgery.

A controlled study of 53 individuals undergoing nasal surgery found bromelain effective at reducing bruising. Benefits were also seen in a small double-blind, placebo-controlled crossover study of individuals undergoing
dental surgery; however, no significant benefits were seen in a double-blind, placebo-controlled trial of 154 individuals undergoing facial plastic surgery.\(^6\)

In another double-blind, controlled trial, 95 patients undergoing treatment for cataracts were given 40 mg of bromelain or placebo (along with other treatments) 4 times daily for 2 days prior to surgery and for 5 days postoperatively.\(^8\) The results showed reduced pain and inflammation in the bromelain group as compared to the placebo group.

In a double-blind, placebo-controlled trial of 80 individuals, treatment with Wobenzym (a proprietary enzyme mixture containing pancreatin, papain, bromelain, trypsin, and chymotrypsin, as well as lipase, amylase, and rutin) after knee surgery significantly improved the rate of recovery, as measured by mobility and swelling.\(^2\) Another double-blind, placebo-controlled trial with 80 participants found benefit of the same enzyme combination in oral surgery.\(^10\)

**Osteoarthritis/Chronic Pain +2**

Proteolytic enzyme combinations may be helpful for osteoarthritis and other forms of chronic musculoskeletal pain, according to several small but relatively recent double-blind studies.

A 3-week, double-blind, placebo-controlled trial of 30 individuals with neck pain found that use of Wobenzyme (described above) caused small but statistically significant improvements in pain.\(^33\)

A 28-day, double-blind trial of 80 individuals with osteoarthritis of the knee compared Wobenzym (7 tablets QID) to diclofenac (50 mg bid) in a double-dummy design.\(^34\) The results showed equivalent improvement in symptoms between the two groups.

Three double-blind trials presented in abstract form evaluated proteolytic enzymes in, respectively, 73 individuals with knee arthritis, 40 individuals with shoulder arthritis, and 120 individuals with spinal pain.\(^35\) These trials compared the proprietary product Phlogenzym at a dose of 2 tabs tid (90 mg bromelain, 48 mg trypsin, and 100 mg of the flavonoid rutoside per tablet) against to diclofenac (50 mg bid in the shoulder and spine pain trials; 50 mg tid in the the knee pain trial, using a double-dummy design). Each one found statistically equivalent improvements with the enzyme combination and the drug.

A double-blind, placebo-controlled study of the oral proteolytic combination Chymoral for treatment of lumbar disc prolapse found only clinically insignificant benefits.\(^19\)

**Herpes Zoster +2**

Evidence from double-blind comparative trials suggests that proteolytic enzymes may be as effective as acyclovir for acute herpetic zoster, but placebo-controlled trials have not been performed.

A double-blind trial of 192 individuals with acute herpes zoster compared the effect of a proprietary proteolytic enzyme mixture to that of acyclovir.\(^18\) Each enzyme capsule contained 30 mg trypsin, 30 mg chymotrypsin, and 75 mg papain, as well as 30 mg thymus extract (a purported immune stimulant); the acyclovir tablets contained 200 mg of the drug. Participants were given 4 capsules five times daily until the disappearance of symptoms (maximum 14 days) and their pain was assessed at intervals. Statistically equivalent pain relief was demonstrated in both groups, but the acyclovir group had more side effects (primarily mild gastrointestinal disturbance). Equivalent benefits were also seen in another double-blind trial.\(^15\)

**Minor Injuries -2X**

A double-blind, placebo-controlled study of 44 individuals with sports-related ankle injuries found that treatment with proteolytic enzymes resulted in faster healing and reduced the time away from training by about 50%.\(^11\) Three other small double-blind studies involving a total of about 80 athletes found that treatment with various proteolytic enzyme combinations significantly improved the rate of healing of bruises and other mild athletic injuries as compared to placebo.\(^12,13,14\)
However, a very large (n=721) recent double-blind, placebo-controlled trial of proteolytic enzymes for the treatment of ankle sprain failed to find benefit with bromelain, trypsin, or rutoside, separately or in combination.  

Small studies of proteolytic enzymes conducted more than 30 years ago reported benefits for other types of minor injuries. For example, a double-blind trial of 100 individuals given a subcutaneous injection of their own blood to simulate bruising found that treatment with a proteolytic enzyme combination significantly speeded hematoma resolution. A double-blind, placebo-controlled trial involving 71 individuals with finger fractures found that treatment with a trypsin-chymotrypsin combination produced a significant improvement in recovery rate. Finally, in a controlled study, 74 boxers with facial and/or upper body bruises were given bromelain until all signs of bruising had disappeared; another 72 boxers were given placebo. Fifty-eight of the group taking bromelain lost all signs of bruising within 4 days, compared to only 10 of the group taking placebo.

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**Other Proposed Uses**

One double-blind, placebo-controlled trial from the early 1960s found proteolytic enzymes helpful for symptoms of postpartum breast engorgement.

A study reported in 2002 tested combination therapy with bromelain and ibuprofen for enhancing recovery from heavy exercise by decreasing delayed-onset muscle soreness, but found no benefits.

Another 2002 study failed to find proteolytic enzymes helpful for reducing side effects of adjuvant pelvic irradiation.

Proteolytic enzymes have also been proposed as a treatment for food allergies on the assumption that they enhance breakdown of allergenic proteins. Some alternative medicine practitioners advocate the unproved theory that exogenous allergens contribute to autoimmune disease, and on this basis proteolytic enzymes have been recommended for rheumatoid arthritis, lupus, and other autoimmune diseases.

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**Mechanism of Action**

Proteolytic enzymes appear to be absorbed whole to a certain extent and to produce anti-inflammatory, antiedema, immunomodulatory, and fibrinolytic effects.

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**Dosage**

Recommended dosages vary with the form of proteolytic enzymes used. See the Appendix for U.S. brand names of clinically tested products.

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**Safety Issues**

In clinical trials, use of oral proteolytic enzyme combinations has been associated with relatively few and mild side-effects, consisting primarily of gastrointestinal distress and allergic exanthema.
Bromelain is the best studied proteolytic enzyme. In rat studies, no toxic effects were seen at oral doses as high as 10 g/kg. A 6-month study conducted in dogs with increasing daily levels of bromelain up to 750 mg/kg showed no toxic effects. Rat studies have found no carcinogenicity with bromelain in doses up to 1.5 g/kg/day. However, bromelain has been reported to cause both immediate-type and late-phase IgE-mediated reactions. Sensitization usually occurs by inhalation and may be occupationally acquired. Symptoms may occur hours after exposure and may be refractory to antihistamine and steroid treatments. Cross-allergenicity with bromelain has been reported for wheat flour, rye flour, kiwi fruit, perennial ryegrass, grass pollen, and birch pollen. In addition, one study that investigated the effects of bromelain in 20 hypertensive patients found a concentration-dependent increase in both heart rate and systolic blood pressure. Caution may be warranted with high doses of bromelain in hypertensive patients.

One study of 47 patients with various disorders leading to edema and inflammation found no significant effects of oral bromelain (40 mg 4 times daily for 1 week) on bleeding, coagulation, and prothrombin time. Maximum safe dosages in individuals with severe hepatic or renal disease are not known.

**Safety in Young Children and Pregnant or Lactating Women**

Maximum safe dosages for pregnant or lactating women, or young children, have not been established.

**Drug Interactions**

Papain might potentiate anticoagulant and antiplatelet agents. Pancreatin may interfere with folate absorption (see the Folate article).

**References [+]**


Last reviewed April 2005 by EBSCO CAM Review Board