Bio-gen Extracts

BROMELAIN
EC 3.4.22.32

Bromelain is the collective term for enzymes (principally proteolytic enzymes) derived from the ripe and unripe fruit, as well as the stem and leaves, of the pineapple plant, *Ananas comosus*, a member of the Bromeliaceae family. Commercial bromelain is typically stem bromelain. Bromelain is mainly comprised of cysteine proteases, with smaller amounts of acid phosphatase, peroxidase, amylase and cellulase. Bromelain contains at least four distinct cysteine proteases.

The principal stem protease is called stem bromelain or stem bromelain protease. Two additional proteases found in the stem are called ananain and comosain. Fruit bromelain is the name given to the principal protease found in the fruit. Stem protease is a basic glycoprotein with a molecular weight of 28,000 daltons

Pineapple has been used as a folk medicine by the natives of the tropics for centuries.

It has been used as a digestive aid, as a cleansing agent to improve the texture of the skin, and to promote the healing of wounds. It is used commercially in certain cosmetics and as a meat tenderizer and dietary supplement.

Bromelain may have digestant activity and there is research suggesting that it may have wound healing, anti-inflammatory, antidiarrheal and anticarcinogenic effects

The most commonly used measures of activity are MCU or GDU. One GDU is equivalent to about 1.5 MCU.

Pineapple workers often have their fingerprints almost completely obliterated due to the proteolytic action of bromelain

RESEARCH REVIEW

Bromelain has been shown to speed healing time and reduce pain following various surgical procedures, including oral surgical procedures and episiotomy. It has also been used with significant positive results in the treatment of various athletic injuries. In one open case observation study, high-dose bromelain was administered to 59 patients with blunt injuries to the musculoskeletal system. A clear reduction in swelling, pain at rest and during movement and in tenderness was reported. Positive bromelain studies related to oral surgery and episiotomy have been double-blind and placebo-controlled. Positive effects have been attributed by some to anti-inflammatory activity, rather than to an analgesic effect.

Bromelain has been used with some success as a substitute for trypsin and pepsin in cases of pancreatic insufficiency and post-pancreatectomy.

In vitro and *in vivo* studies show some bromelain-induced inhibition of platelet aggregation, and some positive bromelain-related effects have been reported in patients with thromboses and angina. In one double-blind study of 73 patients with acute thrombophlebitis, bromelain, used with analgesics, reduced pain, edema, redness, tenderness, elevated skin temperature and disability. The effective doses ranged between 60-160 milligrams daily of 1,200 MCU bromelain.

Bromelain's reported mucolytic activity has prompted some use of it in respiratory tract diseases. It has shown some benefit in chronic bronchitis and, in a double-blind study, in acute sinusitis.

Bromelain's reported efficacy (in combination with papain) in easing dysmenorrhea symptoms has been attributed to a smooth-muscle-relaxant effect since it has been observed to decrease spasms of contracted cervixes in these patients. Some hypothesize that muscle-relaxing effects of bromelain on the uterus are due to modulation of various prostaglandins.

In animal models, bromelain has shown significant antidiarrheal activity. In these experiments, bromelain inhibited activity of enterotoxigenic *Escherichia coli* and *Vibrio cholerae*. It significantly reduced heat-stable and heat-labile

BROMELAIN
EC 3.4.22.32

ACTIONS AND PHARMACOLOGY

Bromelain may have digestant activity and has putative anti-inflammatory, immunomodulatory, antidiarrheal, anticarcinogenic and wound healing actions.

MECHANISM OF ACTION

Bromelain's digestant activity is based on its ability to hydrolyze proteins to oligopeptides and amino acids. Bromelain's proteolytic enzymes are cysteine proteases. Cysteine proteases cleave peptide bonds by nucleophilic attack via active-site cysteine residues. Other members of the cysteine protease family, include calpains and caspases.

The mechanism of the putative anti-inflammatory activity is not well understood. It may be accounted for, in part, by activation of plasmin production from plasminogen and reduction of kinin, via inhibition of the conversion of kininogen to kinin. Other possibilities, include proteolytic degradation of circulating immune complexes and inhibition of signaling by extracellular regulated kinase (ERK)-2 and $p21^{ras}$. It is speculated that the possible protective effect of bromelain in murine EAE (experimental allergic encephalomyelitis), the animal model of multiple sclerosis, is due to proteolytic cleavage of accessory molecules involved in the interaction of T lymphocytes and antigen presenting cells, thus increasing the activation threshold of the autoreactive T lymphocytes.

The mechanism of bromelain's putative immunomodulatory activity is likewise poorly understood. Bromelain has been shown to increase CD2-mediated T cell activation, to enhance antigen-independent binding to monocytes and to increase interferon (IFN)-gamma-dependent, tumor necrosis factor (TNF)-alpha, interleukin(IL)-1 beta, and interleukin(IL)-6 production in peripheral blood monocytes. These effects are thought to be due to bromelain's proteolytic activity at cell surfaces, whereby it either removes surface molecules or reveals ones that already exist on cell membranes, thereby altering receptor-ligand interactions. Recent studies have reported that bromelain proteolytically blocks activation of extracellular regulated kinase(ERK)-2 in T cells, resulting in inhibition of T cell signal transduction.

Bromelain has been found to reduce the incidence of enterotoxigenic *Escherichia coli* diarrhea in piglets. This effect is thought to be due to inactivation of enterotoxigenic *E. coli* receptors in the small intestine via proteolytic cleavage of the glycoprotein receptor.

The putative anticarcinogenic activity of bromelain is open to speculation. Possibilities include disruption of adhesion molecules on tumor and endothelial cells via its proteolytic activity and inhibition of signaling by ERK-2 and $p21^{ras}$. It has also been speculated that bromelain may play a role in the differentiation of enterotoxin-induced secretion, among other effects.

RESEARCH REVIEW

In the realm of immunity, bromelain is being tested for possible effects in T cell-mediated autoimmune diseases, including multiple sclerosis, type 1 diabetes and rheumatoid arthritis. In combination with trypsin and the flavonoid rutin, bromelain has been reported to protect against experimental allergic encephalomyelitis. This research is ongoing.

Bromelain has recently shown an ability to decrease lung metastases of Lewis lung cancer cells in mice. In another recent study, oral bromelain was administered to 16 breast cancer patients for ten days. The results of this study suggested that bromelain stimulated deficient monocyte cytotoxicity of mammary tumor patients. More research is needed.

malignant cells. Certain cysteine proteases (e.g., caspases) are involved in apoptosis. Were bromelain to enter cancer cells, one may speculate that it could induce apoptosis. On the other hand, bromelain entering normal cells does not appear to be desirable.

The putative wound healing activity of bromelain may be accounted for by its possible anti-inflammatory activity.

PHARMACOKINETICS

The pharmacokinetics of bromelain in humans are mostly unknown. Bromelain is active under a wide pH range (between pH3-10) and may not be inactivated by stomach acid. The putative anti-inflammatory, immunomodulatory and anticarcinogenic actions of bromelain most likely require that it gets absorbed from the intestine. It is conceivable that unabsorbed bromelain may mediate some of these possible effects via a signal transduction mechanism. However, this is entirely speculative. There is some evidence from tissue culture studies that bromelain may be able to enter cells and some bromelain may be absorbed via the enteropancreatic circulation. Research is very much needed on the pharmacokinetics of bromelain.

INDICATIONS AND USAGE

There is some evidence that bromelain may be useful in speeding the healing time of some injuries and surgical wounds, that it is a digestive aid in some conditions, that it inhibits platelet aggregation and is helpful in some with thromboses and angina, that it has positive effects in some respiratory tract diseases, dysmenorrhea and some forms of diarrhea. It has also exhibited some immune-enhancing and anticancer effects.

CONTRAINDICATIONS

Bromelain is contraindicated in those hypersensitive to any component of a bromelain-containing product.

PRECAUTIONS

Bromelain supplements should be avoided by pregnant women and nursing mothers.

The use of bromelain for the treatment of any disorder must be medically supervised. The use of bromelain for the treatment of diarrhea caused by enteropathogenic *E. coli*, cancer or any inflammatory disorder is experimental.

Those on anticoagulants or antithrombotic agents should exercise caution in the use of bromelain. Bromelain may have blood-thinning activity in some.

ADVERSE REACTIONS

Gastrointestinal symptoms such as nausea and vomiting, diarrhea and cramping have been reported. There are occasional reports of metrorrhagia and menorrhagia

DRUG INTERACTIONS

Antibiotics (amoxicillin, tetracycline): Concomitant use of bromelain and amoxicillin or tetracycline have been reported to increase the serum levels of these antibiotics.

Anticoagulants (e.g., warfarin): Bromelain may enhance the anticoagulant activity of such drugs as warfarin.

Antithrombotic agents (e.g., aspirin): Bromelain may enhance the antithrombotic activity of such drugs as aspirin.

OVERDOSAGE

There are no reports of bromelain overdosage in the literature.

DOSAGE AND ADMINISTRATION

Bromelain is available as a single ingredient product or in combination with other supplementary enzymes (see Supplementary Enzymes). Dosage ranges from 500-2,000 GDUs (gelatin digestion units) taken one to three times daily.

