



Pineapple

Scientific Name(s): *Ananas comosus* (L.) Merr.

Common Name(s): Bromelain, Debridase, Phlogenzym, Pineapple

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Clinical Overview

Use

Few well-controlled clinical trials have been published to support the wide range of therapeutic claims for bromelain, a crude, aqueous extract of pineapple. Evidence exists primarily for the use of bromelain in debridement of burns and as an anti-inflammatory agent.

Dosing

Two slices of pineapple contain approximately 100 mg of ascorbic acid (vitamin C). The usual dosage of bromelain is 40 mg taken 3 or 4 times daily. Pineapple products are available commercially in liquid, tablet, and capsule doseforms. Most products contain bromelain 500 mg; manufacturers suggest a dose of 500 to 1,000 mg daily.

Contraindications

Hypersensitivity to any of the components in pineapple. Cross-reaction with honeybee venom, olive tree pollen, celery, cypress pollen, bromelain, and papain have been reported.

Pregnancy/Lactation

Information regarding safety and efficacy in pregnancy and lactation is lacking. Data is lacking to support the historical use of pineapple as an emmenagogue and abortifacient.

Interactions

None well documented.

Adverse Reactions

The juice from unripe pineapples can act as a violent purgative. Bromelain ingestion is associated with a low incidence of adverse reactions, including diarrhea, menorrhagia, nausea, skin rash, and vomiting. Angular stomatitis/cheilitis can result from eating large amounts of the fruit.

Toxicology

Bromelain has very low toxicity.

Scientific Family

- Bromeliaceae

Botany

The well-known pineapple fruit is actually a complex flower head that forms around the stem. Each of the eyes on the surface is the dried base of a small flower. The pineapple is the only cultivated fruit whose main stem runs completely through it.^{1, 2} The top crown of leaves contains a bud that, when mature, indicates that the fruit is ready for cutting. The crowns from the top of the fruit are usually used for propagation because pineapples lack viable seeds; occasionally, slips from the base of the fruit or suckers are used if planting material is in short supply.³ The plant grows to a height of 1 m; the first crop is ready for harvesting approximately 18 months after planting. Because the plant is xerophytic and uses water very efficiently, pineapple may be grown in areas of relatively low rainfall (50 to 200 cm).³

History

Pineapple is native to South America and was brought to Europe by Spanish explorers. Planting began on a large scale in Hawaii in the early 19th century. Growth of the industry peaked in the 1950s, then declined slowly under the pressure of

international competition.³ Today, the bulk of the world's pineapple crop comes from Thailand, the Philippines, and Brazil. Traditional uses include the brewing of pineapple wine, production of fiber, and medicinal use as an emmenagogue, abortifacient, antiamebic, and vermifuge.

Chemistry

Pineapple is rich in citric and malic acids; citric acid concentrations in some cultivars exceed 8%.⁴ The fruit also contains moderate amounts of ascorbic acid; 2 slices of pineapple contain 100 mg of ascorbic acid.⁵ A steroidal component of the leaves possesses estrogenic activity⁴ and a variety of aromatic compounds are found in the essential oil. The residue left after juice extraction contains large quantities of vitamin A and is used as a component of livestock feed. A crude aqueous extract of pineapple known as bromelain is obtained from the stems and immature fruits; stem and fruit bromelains are chemically distinguishable from one another.⁶

Bromelain comprises a complex mixture of sulfhydryl-containing proteolytic enzymes in addition to a number of nonspecific components, such as phosphatases, glucosidases, peroxidases, cellulases, glycoproteins, and carbohydrates. The extract also contains a proteinase inhibitor consisting of iso inhibitors.⁶ Each iso inhibitor has a 2-chain structure⁷ and the amino acid sequence has been determined.⁸ In an aqueous solution, bromelain rapidly deteriorates through self-digestion.⁹ Commercial bromelain preparations are evaluated according to their proteolytic activity.

Clinical trials have assessed the effectiveness of bromelain in commercial preparations of differing complexes of proteolytic enzymes and concentrations of bromelain.

Uses and Pharmacology

It is not clear whether proteinases can be absorbed from the GI tract in a functionally intact form, although enteric coating of the tablets may help to counteract this problem.^{10, 11}

Analgesia

Clinical data

The effect of bromelain on perioperative pain, swelling, trismus, and quality of life (QOL) was assessed in a comparator double-blind, placebo-controlled randomized clinical trial (n = 45) in healthy adults undergoing surgery for removal of unilateral impacted mandibular third molar under local anesthesia. Patients were randomized to bromelain 250 mg, diclofenac sodium 25 mg, or placebo taken orally every 6 hours the morning before surgery and continuing for 4 days. Both bromelain and diclofenac significantly reduced pain leading to administration of less rescue analgesic tablets and QOL measures also improved in both treatment groups.⁵⁸

Anti-inflammatory

Animal data

Various studies have investigated the anti-edematous effects of bromelain in animal models.^{9, 10, 12} The efficacy of bromelain has been compared with the anti-inflammatory effect of prednisone, etodolac, indomethacin, acetylsalicylic acid, and oxyphenbutazone. Oral and intraperitoneal routes have been investigated. The anti-edematous action may be the result of increased tissue permeability by fibrinolysis and the reabsorption of edema fluids into the circulatory system.⁹

Clinical data

Clinical trials have employed a variety of preparations including bromelain in combination with trypsin/rutin (as Phlogenzym) compared with diclofenac or placebo. Outcomes are equivocal⁹ with older trials suggesting anti-inflammatory and analgesic effects.^{13, 14, 15}

In moderate to severe osteoarthritis during 12 weeks of administration of bromelain 800 mg daily, there was no change in total Western Ontario and McMaster Universities osteoarthritis index (WOMAC) score compared with placebo.¹⁶ A trial comparing 6 weeks of a combination of bromelain and trypsin/rutin with diclofenac 100 mg daily in osteoarthritis of the hip found no difference in total WOMAC scores, but showed the combination to be equivalent to diclofenac.¹⁷

In a review of the efficacy of bromelain on edema, bruising, pain, and healing time after surgery or trauma, a reduction in total analgesic intake and swelling after surgical correction of long bone fractures and decreased pain following dental surgery was recorded.¹⁸ Conflicting results were noted with regard to rhinoplasty surgery. In a large multicenter trial (N = 721), no effect of a combination of bromelain and trypsin/rutin was found compared with placebo in ankle ligament injury.¹⁹ No effect in managing muscle soreness after unaccustomed exercise was found for the combination preparation compared with placebo.²⁰ Bromelain was a component, along with arginine, ascorbic acid, methylsulfonylmethane, and a proprietary blend of

apple and grape polyphenols (Vinitrox), administered twice daily in a randomized, placebo-controlled trial (n = 64) that included 3 sessions of extracorporeal shockwave therapy for treatment of adults with insertional Achilles tendinopathy. Patient-rated pain scores were numerically lower at 2 and 6 months with active treatment versus placebo, but only the 6-month result was statistically significant. Ankle-hindfoot scores and patient satisfaction scores at 2 and 6 months were all significantly better with active treatment compared with placebo.**55**

Antimicrobial

Bromelain has been shown to prevent intestinal fluid secretion caused by *Vibrio cholerae* and *Escherichia coli* enterotoxins in rabbit ileum in vitro.**21** Strong antifungal activity has been documented against *Trichoderma viride*.**22** In addition, antihelminthic action has been documented.**23, 24**

Animal data

A reduced incidence of diarrhea associated with K88-positive enterotoxigenic *E. coli* was found in newly weaned piglets that received bromelain for 10 days.**25** One day after starting therapy, the piglets received a 7-day challenge with K88-positive enterotoxigenic *E. coli*. Bromelain-treated piglets had significantly lower disease scores than untreated piglets ($P < 0.05$), as well as significantly increased weight gain compared with controls ($P < 0.05$).

Clinical data

Clinical trials are lacking.

Burns

Escharase is a nonproteolytic component in bromelain thought to be important in the action of topical bromelain.**11** Topical preparations typically contain 35% of a bromelain-derived enzyme mixture extracted from pineapple stems in a lipid base (Debridase).**9**

Animal data

Topical application of pineapple-derived enzymes has been shown to separate burned tissue or eschar from living tissue in animal models.**9, 10, 26, 27** Complete debridement of experimental burns in rats was achieved in 2 days, with no damage to adjacent tissues.**9, 26**

In pigs with experimentally-induced circumferential burns, topical application of Debridase relieved burn-induced compartment syndrome within 30 minutes and did not cause any adverse local or systemic effects or affect healthy, unburned tissue.**27**

Clinical data

A prospective, noncomparative clinical study examined the efficacy of Debridase in 130 patients with deep second- and third-degree burns. The topical bromelain preparation was applied for 4 hours under an occlusive dressing. Application of the preparation was repeated as necessary, with the majority (72.6%) of patients requiring only 1 application. Percentage of debridement was 89% (standard deviation [SD] = 21%) for a single application, 77% (SD = 27%) for 2 applications, and 62% (SD = 27%) for 3 applications.**28** Topical bromelain has also been studied for eschar removal in frostbite.**9**

Ear, nose, throat/acute sinusitis

In a clinical trial (N = 116), decreased symptom duration was demonstrated in children with acute sinusitis with oral bromelain administration over standard therapy.**29** Similar results were reported in a clinical trial (N = 48) evaluating bromelain against standard therapy in acute sinusitis.**10**

Immunomodulation

Because bromelain modulates immune responses, the possibility of clinical use has been suggested. In vitro studies**30, 31, 32** have shown that bromelain modulates T- and B-cell immune responses**30** blocks activation of extracellular regulated kinase-2 T cells**31** and activates murine macrophages and natural killer cells.**32** In vivo, mice treated with bromelain had increased B-cells and reduced interleukin-2, indicating an enhanced antibody response.**30**

Clinical data

Bromelain has been investigated for use in pityriasis lichenoides chronica, an uncommon rash of unknown origin. In a small study (N = 8), complete clinical response was reported following 3 months of oral bromelain therapy. No adverse reactions were reported. Anti-inflammatory, immunomodulatory, and antiviral actions of bromelain may have been responsible for the effect.**33**

Malignant disease

Bromelain's cancer fighting ability may be due to several mechanisms including antiproliferative, anti-inflammatory, and immune-modulating activity.⁵⁶ Pineapple juice reduces the mutagenic activity of carcinogens in the Ames Salmonella typhimurium assay by approximately 50%. In vitro studies have demonstrated concentration-dependent inhibition of tumor-cell proliferation by bromelain.⁹ However, a study investigating the effects of pineapple on the growth of HepG2 human liver cancer cells in vitro found no antiproliferative activity.³⁴ Bromelain reversibly reduced glioma cell adhesion, migration, and invasion without affecting cell viability in vitro.

Animal data

Bromelain also reduced local tumor weight but did not reduce lung colonization in a murine tumor growth model.^{35, 36} Mouse melanoma cells, preincubated in vitro with bromelain, reduced lung metastatic tumor weight. However, no survival benefit was found.⁹

Clinical data

Ingestion of pineapple resulted in the inhibition of endogenous nitrosation in human volunteers, suggesting that the ascorbic acid content of the fruit can limit the formation of potentially toxic digestive by-products.³⁷ Anecdotal reports of the beneficial effects of high-dose oral bromelain therapy in cancer patients have been published.³⁸ Bromelain also has been used in combination with chemotherapeutic agents, such as fluorouracil and vincristine.^{9, 10}

Bromelain stimulated monocytic cytotoxicity in breast cancer patients in vitro. Sixteen breast cancer patients and healthy volunteers received oral bromelain 3,000 mg/day for 10 days. Cytotoxic activity also increased. Bromelain was less effective in stimulating the cytotoxicity of monocytes from healthy donors.³⁹

Other uses

Bowel preparation

Patients (n = 126) undergoing colonoscopy were randomly assigned to 1 of 3 preprocedural bowel preparation regimens: polyethylene glycol 4 L, polyethylene glycol 2 L, or polyethylene glycol 2 L plus 1 L of pineapple juice. The regimen that included pineapple juice produced significantly better cleansing of the transverse and right side of the colon.⁵⁷

Esophageal meat impaction

An in vitro experiment suggests fresh (or frozen/thawed), but not processed, pineapple juice is effective at 4.5 hours in moving impacted esophageal meat bolus.⁴⁰ Caution is advised when using proteolytic enzymes for this purpose because of the risk of complications, such as hemorrhagic pulmonary edema or aspiration pneumonia.⁴¹

Multiple sclerosis

In a large, multicenter clinical trial, bromelain with trypsin/rutin had no effect on neurological symptoms over placebo.⁴²

Nutrition

Positive nutritional effects have been shown in bedridden, tube-fed, nursing home patients who received a supplementary digestive aid containing bromelain plus an extract of *Aspergillus niger*. Total protein concentration improved significantly with the supplement ($P < 0.02$), which was reversed after withdrawal.⁴³

Sepsis

Phlogenzym (an oral enzyme formulation of rutoside, bromelain, and trypsin) showed efficacy as an adjuvant for early improvement in children with sepsis in a double-blind, randomized, controlled trial (N = 60). Fever, hemodynamic support, results from the Glasgow Coma Scale, and oral feeding improved 1 to 2 days earlier for the Phlogenzym-treated patients compared with placebo.⁴⁴

Ulcerative colitis

Case reports detailing the successful use of bromelain in the treatment of mild ulcerative colitis have been published.⁴⁵ Patients took bromelain in addition to their usual drug regimen and experienced rapid improvement of symptoms, confirmed by endoscopy.

Other animal or in vitro experiments have reported diuretic⁴⁶ and glycemic and cholesterol activity⁴⁷ renal-protective action⁴⁸ and inhibition of platelet aggregation.^{9, 49}

Dosing

Two slices of pineapple contain approximately 100 mg of ascorbic acid (vitamin C), approximately the recommended daily adult intake. Commercially available bromelain supplements contain predominately stem bromelain, as compared with fruit bromelain⁵⁰

The usual dosage of bromelain is 40 mg 3 or 4 times daily. However, because bromelain is regarded as being relatively nontoxic, doses of up to 2,000 mg/day have been used.⁹ Most commercial products contain bromelain 500 mg; manufacturers suggest a dosage regimen of 500 to 1,000 mg daily.

Confusion may arise with bromelain dosage because bromelain activity is defined in a number of ways, including roser units, gelatin-dissolving units, milk-clotting units⁵¹ and Fédération Internationale Pharmaceutique standards.⁹

Pregnancy / Lactation

Information regarding safety and efficacy in pregnancy and lactation is lacking. Clinical evidence to support the traditional use of pineapple as an emmenagogue and abortifacient is limited. Previously, bromelain/trypsin (as Kimotab) was investigated for use in breast engorgement during lactation.⁵²

Interactions

None well documented.

Adverse Reactions

Repeated exposure of pineapple cutters to bromelain can result in the obliteration of fingerprints, and the hooked margins of the leaves can cause painful mechanical injury.

Ethyl acrylate, an aromatic component of the juice, can produce dermal sensitization. Allergy to pineapple has been documented. Cross-reactivity studies with bromelain indicate an immunoglobulin E (IgE)-mediated reaction, and cross-reaction with honeybee venom, olive tree pollen, celery, cypress pollen, and papain has been reported. Sensitization to enzymes may follow inhalation (through occupational or other exposure; some reviews show up to 50% occurrence) or ingestion (rare). An unusual case report describes delayed allergic contact cheilitis caused by a bromelain-containing mouthwash.^{10, 53, 54}

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Toxicology

Bromelain has very low toxicity. Lethal intraperitoneal doses (LD₅₀) of bromelain have been determined as 37 and 85 mg/kg in mice and rats, respectively. No immediate toxic effects were observed. These doses far exceed those normally administered to humans. No effects in human clinical tests were documented with bromelain supplementation up to 460 mg; however, doses of up to 1,840 mg increased heart rate.^{9, 10}

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