effects on glucose tolerance or serum lipids, compared with controls. In another study, brewer's yeast improved glucose tolerance and had beneficial effects on lipids in Chinese adults. More study is needed.

CONTRAINDICATIONS, PRECAUTIONS, ADVERSE REACTIONS

CONTRAINDICATIONS

Brewer's yeast is contraindicated in those hypersensitive to any component of a brewer's yeast containing-product. It is also contraindicated in those taking monoamine oxidase inhibitors.

PRECAUTIONS

Pregnant women and nursing mothers should avoid brewer's yeast supplements pending long-term safety studies.

ADVERSE REACTIONS

Brewer's yeast is generally well tolerated. Occasional allergic reactions have been reported. Some may develop flatulence when taking brewer's yeast. Some do not like the bitter taste.

INTERACTIONS

DRUGS

Monoamine oxidase (MAO) inhibitors: including phenelzine sulfate, tranylcypromine sulfate and pargyline HCl. Concomitant use of brewer's yeast and MAO inhibitors may cause hypertension.

OVERDOSAGE

No reports of overdosage.

DOSAGE AND ADMINISTRATION

Brewer's yeast is available as flakes, powder, tablets and capsules. These preparations are prepared from dried, crushed cells of *Saccharomyces cerevisiae.* Dosage is variable. Some marketed chromium and selenium preparations are derived from chromium-rich and selenium-rich baker's yeast, respectively. (See Chromium and Selenium.)

LITERATURE

See Chromium, Selenium, Yeast Beta-Glucan and Nucleic Acids/Nucleotides.

Also:

Clark LC, Combs GF Jr, Turnball BW, et al. Effects of selenium supplementation for cancer prevention in patients with carcinoma of the skin. A randomized controlled trial. Nutritional Prevention of Cancer Study Group. *JAMA.* 1996; 276:1957-1963.

Guan X, Matte JJ, Ku PK, et al. High chromium yeast supplementation improves glucose tolerance in pigs by decreasing hepatic extraction of insulin. *J Nutr.* 2000; 130:1274-1279.

Li YC. Effects of brewer's yeast on glucose tolerance and serum lipids in Chinese adults. *Biol Trace Elem Res.* 1994; 41:341-347.

Bromelain

DESCRIPTION

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, as well.

The activity of bromelain may be expressed in six different ways: Rorer units, FIP units, BTU (bromelain tyrosine units), CDU (casein digestion units), GDU (gelatin digestion units) or MCU (milk clotting units).

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

An interesting aside, is that pineapple workers often have their fingerprints almost completely obliterated due to the proteolytic action of bromelain.

ACTIONS AND PHARMACOLOGY

ACTIONS

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 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.

RESEARCH SUMMARY

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 enterotoxin-induced secretion, among other effects.

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.

CONTRAINDICATIONS, PRECAUTIONS, ADVERSE REACTIONS

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.

INTERACTIONS

DRUGS

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.

LITERATURE

Batkin S, Taussig SJ, Szekerezes J. Antimetastatic effect of bromelain with or without its proteolytic and anticoagulant activity. *J Cancer Res Clin Oncol.* 1988; 114:507-508.

Bock U, Kolac C, Borchard G, et al. Transport of proteolytic enzymes across Caco-2 cell monolayers. *Pharm Res.* 1998; 15:1393-1400.

Chandler DS, Mynott TL. Bromelain protects piglets from diarrhea caused by oral challenge with K88 positive enterotoxigenic Escherichia coli. *Gut.* 1998; 43:196-202.

Eckert K, Grabowska E, Strange R, et al. Effects of oral bromelain administration on the Impaired immunocytotoxicity of mononuclear cells from mammary tumor patients. *Oncol Rep.* 1999; 6:1191-1199.

Kumakura S, Yamashita M, Tsurufuji S. Effect of bromelain on kaolin-induced inflammation in rats. *Eur J Pharmacol.* 1988; 150:295-301.

Masson M. [Bromelain in blunt injuries of the locomotor system. A study of observed applications in general practice]. [Article in German]. *Fortschr Med.* 1995; 113:303-306.

Metzig C, Grabowska E, Eckert K, et al. Bromelain proteases reduce human platelet aggregation in vitro, adhesion to bovine endothelial cells and thrombus formation in rat vessels in vivo. *In Vivo.* 1999; 13:7-12.

Munzig E, Eckert K, Harrach T, et al. Bromelain protease F9 reduces the CD44 mediated adhesion of human peripheral blood lymphocytes to human umbilical vein endothelial cells. *FEBS Lett.* 1994; 351:215-218.

Mynott TL, Guandalini S, Raimondi F, Fasano A. Bromelain prevents secretion caused by Vibrio cholerae and Escherichia coli enterotoxins in rabbit ileum in vitro. *Gastroenterology.* 1997; 113:175-184.

Mynott TL, Ladhams A, Scarmato P, Engwerda CR. Bromelain from pineapple stems, proteolytically blocks activation of extracellular regulated kinase-2 in T cells. *J Immunol.* 1999; 163:2568-2575.

Rowan AD, Butte DJ, Barrett AJ. The cysteine proteinases of the pineapple plant. *Biochem J.* 1990; 266:869-875.

Targoni OS, Tary-Lehmann M, Lehmann PV. Prevention of murine EAE by oral hydrolytic enzyme treatment. *J Autoimmun.* 1999; 12:191-198.

Taussig SJ, Batkin S. Bromelain, the enzyme complex of pineapple (*Ananas comosus*) and its clinical application. *J Ethnopharmcol.* 1988; 22:191-203.

Bromine (Bromide)

DESCRIPTION

Bromine belongs to the halogen group of elements. Its atomic number is 35 and its symbol is Br. Bromine is a readily volatile, dark-reddish-brown liquid with a strong, disagreeable odor (*bromos* in Greek means stench) and an irritating effect on the eyes and throat. It is the only non-metallic element that is liquid under ordinary conditions. Many of the compounds of bromine are salts or bromides. Halogen comes from the Greek word meaning salt-producer. Bromine occurs in the form of salts in sea and ocean water, mineral springs and natural salt deposits.

Bromine is not considered an essential nutrient for humans. A bromine-deficiency state has been reported in goats. Goats fed diets low in bromide were found to have depressed growth, fertility and life expectancy. Also observed in these animals were decreased red-blood-cell count, increased milk fat and a greater number of spontaneous abortions. Dietary bromide has also been found to alleviate growth retardation caused by hyperthyroidism in mice and chicks and to substitute for part of the chloride requirement for chicks. Insomnia in some hemodialysis patients has been associated with bromide deficiency.

Bromide is the fifth most abundant inorganic anion in human plasma and tissues, following chloride, bicarbonate, phosphate and sulfate. In plasma, it is present at a concentration of 20-150 micromolar.

Bromine may play a role in the respiratory burst of eosinophils. Eosinophils play a central role in host defenses against helminthic parasites and other large invading metazoan pathogens, and possibly against some cancers. This is in contrast to neutrophils, which primarily ingest and kill relatively small microbes Eosinophil peroxidase catalyzes the oxidation of bromide to hypobromous acid and hypobromite, which may participate in the killing role of eosinophils. There is some evidence that this may occur by oxidative damage to proteins through bromination of tyrosine residues. Brominating oxidants may also participate in allergen-induced asthma.

Daily dietary intake of bromide is about 2 to 8 milligrams. Fish, grains and nuts are rich sources of bromide.

Potassium bromide had been used as a sedative drug in the United States and is still occasionally used as a sedative and anticonvulsant in Europe. Prolonged intake of potassium bromide can lead to bromide intoxication or bromism. Bromo-Seltzer does not contain bromine. Bromides are used in some homeopathic remedies such as kali bromatum.

The terms bromine and bromide are sometimes used interchangeably. Bromine is usually found as its bromide form.

ACTIONS AND PHARMACOLOGY

ACTIONS

None known for dietary bromine.

INDICATIONS AND USAGE

There are no indications for the supplemental use of bromine (bromide).

RESEARCH SUMMARY

An association has been made between insomnia experienced by some hemodialysis patients and bromide deficiency. This warrants followup.

CONTRAINDICATIONS, PRECAUTIONS, ADVERSE REACTIONS

CONTRAINDICATIONS

Supplemental bromide is not recommended for anyone.

PRECAUTIONS

Given our present state of knowledge regarding bromine, supplemental bromide is not recommended for anyone.

ADVERSE REACTIONS

Use of potassium bromide as a sedative drug may give rise to bromide intoxication or bromism. Symptoms include nausea, vomiting, slurred speech, memory impairment, drowsiness, irritability, ataxia, tremors, hallucinations, mania, delirium, psychoses, stupor and coma. Skin rashes of various types may occur, and toxic epidermal necrolysis has been reported.

OVERDOSAGE

Death after acute bromide poisoning is rare since vomiting follows the ingestion of large doses of potassium bromide. Ingestion of large doses of potassium bromide can lead to severe central nervous system depression, including coma.

DOSAGE AND ADMINISTRATION

No recommended dosage. Bromine as bromide may be found in colloidal or liquid mineral preparations and in some homeopathic remedies.

LITERATURE

Nielsen FH. Other trace elements. In: Ziegler EE, Filer LL Jr, eds. *Present Knowledge in Nutrition.* 7th ed. Washington, DC: ILSI Press; 1996:353-377.

Nielsen FH. Ultratrace minerals. In: Shils ME, Olson JA, Shike M, Ross AC, eds. *Modern Nutrition in Health and Disease.* 9th ed. Baltimore MD: Williams and Wilkins; 1999:283-303.

Thomas EL, Bozeman PM, Jefferson MM, King CC. Oxidation of bromide by the human leukocyte enzymes myeloperoxidase and eosinophil peroxidase. *J Biol Chem.* 1995; 270;2906-2913.