

**LITERATURE**

- Fahey JW, Talalay P. Antioxidant functions of sulforaphane: a potent inducer of Phase II detoxification enzymes. *Food Chem Toxicol.* 1999; 37:973-979.
- Fahey JW, Zhang Y, Talalay P. Broccoli sprouts: an exceptionally rich source of inducers of enzymes that protect against chemical carcinogens. *Proc Natl Acad Sci USA.* 1997; 94:10367-10372.
- Faulkner K, Mithen R, Williamson G. Selective increase of the potential anticarcinogen 4-methylsulphinylbutyl glucosinolate in broccoli. *Carcinogenesis.* 1998; 19:605-609.
- Singletary K, MacDonald C. Inhibition of benzo[a]pyrene- and 1, 6-dinitropyrene-DNA adduct formation in human mammary epithelial cells by dibenzoylmethane and sulforaphane. *Cancer Letters.* 2000; 155:47-54.
- Zeligs MA. Diet and estrogen status: the cruciferous connection. *J Med Food.* 1998; 1:67-82.
- Zhang Y. Role of glutathione in the accumulation of anticarcinogenic isothiocyanates and their glutathione conjugates by murine hepatoma cells. *Carcinogenesis.* 2000; 21:1175-1182.
- Zhang Y, Talalay P, Cho CG, Posner GH. A major inducer of anticarcinogenic protective enzymes from broccoli: isolation and elucidation of structure. *Proc Natl Acad Sci USA.* 1992; 89:2399-2403.

## Supplemental Enzymes

**DESCRIPTION**

Enzymes are biological catalysts. Until recently, it was thought that all enzymes were protein in nature. It is now known that ribonucleic acids and other non-protein substances can have enzymatic activity, as well. Enzymes have important roles in medicine. They are used for the rapid lysis of blood clots (streptokinase, tissue plasminogen activator or TPA, urokinase) and for the treatment of Gaucher's disease (glucocerebrosidase), among other things. Enzymes are also used in the treatment of pancreatic insufficiency secondary to such disorders as cystic fibrosis and chronic alcoholic pancreatitis. Enzymes, in addition to being used therapeutically, are marketed as nutritional supplements. They are principally used as digestants. Some enzymes, in particular proteolytic enzymes, have putative anti-inflammatory and anticarcinogenic activities. The enzymes marketed for supplemental use are derived from animal, plant and fungal sources. The following describes the enzymes that are available in the nutritional supplement market place.

**ALPHA-GALACTOSIDASE**

Alpha-galactosidase is an enzyme that is derived from selected strains of the fungus *Aspergillus niger*. Alpha-galactosidase catalyzes the hydrolysis of the alpha-1→6 linkages in such carbohydrates as the disaccharide melibiose,

the trisaccharide raffinose, the tetrasaccharide stachyose and the nonsaccharide verbascose. These oligosaccharides are widely found in legumes and cruciferous vegetables, including beans, peas, broccoli, brussels sprouts and cabbage. These carbohydrates are gas productive in some. Hydrolysis of melibiose yields D-galactose and D-glucose; hydrolysis of raffinose yields D-galactose and sucrose; hydrolysis of stachyose yields D-galactose and sucrose; and verbascose yields D-galactose, D-glucose and D-fructose. The activity of alpha galactosidases is expressed in galactose units or GalU. A tablet of alpha-galactosidase typically contains 150 GalU.

**AMYLASE**

Amylases are enzymes that catalyze the hydrolysis of alpha-1, 4-glycosidic linkages of polysaccharides to yield dextrans, oligosaccharides, maltose and D-glucose. Amylases are derived from animal, fungal and plant sources. Pancreatin and pancrelipase contain amylase derived from the pancreas of animals, usually porcine pancreas. Amylase is also derived from barley malt and the fungus *Aspergillus oryzae*. There are a few different amylases. These enzymes are classified according to the manner in which the glycosidic bond is attacked. Alpha-amylases hydrolyze alpha-1, 4-glycosidic linkages, randomly yielding dextrans, oligosaccharides and monosaccharides. Alpha-amylases are endo-amylases. Exoamylases hydrolyze the alpha-1, 4-glycosidic linkage only from the non-reducing outer polysaccharide chain ends. Exoamylases include beta-amylases and glucoamylases (gamma-amylases, amyloglucosidases). Beta-amylases yield beta-limit dextrans and maltose. Gamma-amylases yield glucose. Amylases are used as digestants. Amylase activity is expressed as Dextrinizing Units or DU.

**BROMELAIN**

Bromelain refers to proteolytic enzymes which are derived from the ripe and unripe fruit, as well as the stem and leaves, of the pineapple plant, *Ananas comosus* (*Ananas sativus*).

Bromelain is comprised of several proteolytic enzymes which differ in their specificities. These enzymes hydrolyze proteins to form oligopeptides and amino acids. Bromelain is used as a digestive aid. It also has putative anti-inflammatory activity. The activity of bromelain may be expressed in bromelain units or BU. The assay is based on a 60-minute proteolytic hydrolysis of casein at pH 6.0 and 40°C. One BU is defined as that quantity of enzyme that liberates the equivalent of one microgram of L-tyrosine per hour. The bromelain proteolytic enzymes are cysteine proteinases. There are at least four distinct bromelain cysteine proteinases. The activity of bromelain may also be expressed in gelatin dissolving units (GDU) or milk clotting units (MCU). One GDU is equivalent to about 1.5 MCU.

**CELLULASE**

Cellulase is an enzyme derived from the fungi *Aspergillus niger* and *Trichoderma longbrachiatum* or other sources. Cellulose is an indigestible plant polysaccharide. It is the principal constituent of the cell wall of plants. Cellulase has cellulolytic activity, meaning that it hydrolyzes cellulose. Cellulase hydrolyzes the beta-D-1, 4-glycosidic bonds of cellulose. Cellulase derived from *Trichoderma longbrachiatum* is comprised of an enzyme complex consisting of cellulase, a glucosidase, cellobiohydrolase and a glucanase. This complex converts cellulose to beta-dextrins and ultimately to D-glucose. Cellulase is used as a digestive aid, particularly in animals, and for the management of flatulence. The activity of cellulase is expressed in cellulose units or CU.

**CHYMOTRYPSIN**

Chymotrypsin is a proteolytic enzyme that is principally derived from ox pancreas. Chymotrypsin is a serine proteinase, referring to the fact that serine and histidine residues at the active site are involved in catalysis. Trypsin, also a serine proteinase, and chymotrypsin have similar tertiary structures although very different substrate specificities. Trypsin hydrolyzes peptides at Lys/Arg residues while chymotrypsin recognizes large hydrophobic residues. Chymotrypsin is found in pancreatic preparations, such as pancreatin and pancrelipase. It is used in ophthalmology for the dissection of the zonule of the lens. It is also used as a digestant and it has putative anti-inflammatory activity.

**LACTASE**

Lactase or beta-galactosidase is an enzyme that is derived from the fungus *Kluyveromyces lactis* (formerly known as *Saccharomyces lactis*) or from the fungus *Aspergillus oryzae*. Lactase hydrolyzes the lactose beta-D-galactoside linkage, yielding D-galactose and D-glucose. Lactase may be helpful to those with lactose or milk sugar intolerance. The activity of lactase supplements is expressed in acid lactase units or ALU. A regular strength lactase caplet typically contains 4,500 ALU. Lactase derived from *Kluyveromyces lactis* is used to pretreat milk for use by those with lactose intolerance. The activity of lactase in milk is expressed in neutral lactase units or NLU. The maximum recommended dose of lactase in milk is 3,000 NLU per liter.

**PANCREATIN**

Pancreatin is a pancreatic enzyme preparation derived from hog pancreas. Pancreatin is comprised of the pancreatic enzymes trypsin, amylase and lipase. Pancreatin and pancrelipase are similar except that pancrelipase has relatively more lipase activity than does pancreatin. Trypsin hydrolyzes proteins to oligopeptides, amylase hydrolyzes starch to oligosaccharides and the disaccharide maltose, and lipase hydrolyzes triglycerides to fatty acids and glycerol. Pancrea-

tin is a digestant that is used in the treatment of pancreatic insufficiency as pancreatic enzyme replacement. A typical 500-milligram tablet of pancreatin contains 12,500 USP units of trypsin, 12,500 USP units of amylase and 1,000 USP units of lipase.

**PANCRELIPASE**

Pancrelipase is a standardized preparation of porcine pancreas that principally contains the pancreatic enzymes lipase, trypsin and amylase. Pancrelipase is similar to pancreatin except that it has relatively more lipase activity than pancreatin. Lipase hydrolyzes triglycerides to fatty acids and glycerol. Amylase hydrolyzes starch to oligosaccharides and the disaccharide maltose, and trypsin hydrolyzes proteins to oligopeptides. Pancrelipase is a digestant. It is used in the treatment of steatorrhea secondary to pancreatic insufficiency such as occurs in cystic fibrosis or in chronic alcoholic pancreatitis. A typical capsule of pancrelipase contains 4,500 USP (United States Pharmacopoeia) units of lipase, 25,000 USP units of trypsin and 20,000 USP units of amylase.

**PAPAIN**

Papain is a mixture of proteolytic enzymes derived from the juice of the unripe fruit of the tropical plant *Caroica papaya*, commonly known as papaya. Papain hydrolyzes proteins to form oligopeptides and amino acids. Papain also contains the proteolytic enzyme chymopapain which differs from papain in electrophoretic mobility, solubility and substrate specificity. The molecular weight of chymopapain is approximately 27,000 daltons. Papain is used as a digestive aid. It is also used as a meat tenderizer. Papain has putative anti-inflammatory activity. The activity of papain is expressed in papain units or PU. The assay of papain activity is based on the hydrolysis of casein.

**PEPSIN**

Pepsin is a proteolytic enzyme which is secreted by the stomach where it hydrolyzes proteins to polypeptides and oligopeptides. Pepsin that is derived from animal tissue is sometimes used in combination with dilute hydrochloric acid or betaine hydrochloride as an adjunct in the management of gastric hypochlorhydria.

**TRYPSIN**

Trypsin is a proteolytic enzyme which is principally derived from porcine pancreas. It is a serine proteinase, referring to the fact that serine and histidine residues at the active site are involved in catalytic activity. Chymotrypsin, also a serine proteinase, and trypsin have similar tertiary structures, although very different substrate specificities. Trypsin hydrolyzes peptides at Lys/Arg residues, while chymotrypsin recognizes large hydrophobic residues. Trypsin is found in pancreatic preparations, such as pancreatin and pancrelipase;

it has been used for the debridement of wounds. It is used as a digestant and it has putative anti-inflammatory activity.

#### SUPEROXIDE DISMUTASE

Superoxide dismutases are enzymes that play major roles in the protection of cells against oxidative damage. The two major forms of superoxide dismutase (SOD) in humans are the mitochondrial manganese SOD and the cytosolic copper/zinc SOD. A copper/zinc SOD, isolated from beef liver, has been used intra-articularly for degenerative joint disorders as an anti-inflammatory agent. SOD is also marketed as a nutritional supplement. Oral SOD has putative anti-inflammatory activity.

#### WOBEMUGOS/WOBENZYME

Wobe-Mugos and Wobenzyme are proprietary enzyme preparations that have putative anti-inflammatory and anticarcinogenic activities. Wobe-Mugos contains the proteolytic enzymes papain, trypsin and chymotrypsin. The papain is derived from the fruit of the papaya plant. Trypsin and chymotrypsin are derived from bovine pancreas. Wobenzyme contains pancreatin, papain, bromelain, trypsin and chymotrypsin. Pancreatin, which contains amylase, trypsin and lipase, is derived from porcine pancreas. Bromelain is derived from the pineapple plant. The activity of the proteolytic enzymes in Wobe-Mugos and Wobenzyme is expressed in FIP units. The FIP unit is the measurement of enzyme activity according to the test methods of the Federation Internationale Pharmaceutique. Wobe-Mugos (papain, trypsin and chymotrypsin) is an orphan drug for the treatment of multiple myeloma.

#### ACTIONS AND PHARMACOLOGY

##### ACTIONS

Alpha-galactosidase, amylase, bromelain, cellulase, chymotrypsin, lactase, pancreatin, pancrelipase, papain and pepsin have digestant activities. Bromelain, chymotrypsin, papain, and trypsin have putative anti-inflammatory activity. Superoxide dismutase has putative anti-inflammatory activity. Wobe-Mugos and Wobenzyme have putative anti-inflammatory and anticarcinogenic activities.

##### MECHANISM OF ACTION

Alpha-galactosidase hydrolyzes melibiose to D-galactose, and D-glucose; raffinose to D-galactose and sucrose; stachyose to D-galactose; and sucrose and verbascose to D-galactose, D-glucose and D-fructose. Amylase hydrolyzes starch to oligosaccharides and maltose. Bromelain hydrolyzes proteins to oligopeptides and amino acids. Cellulase hydrolyzes cellulose to D-glucose. Chymotrypsin hydrolyzes proteins to oligopeptides. Lactase hydrolyzes lactose to D-galactose and D-glucose. Pancreatin and pancrelipase hydrolyze triglycerides to fatty acids and glycerol, proteins to oligopeptides and starch to oligosaccharides and maltose.

Papain hydrolyzes proteins to oligopeptides and amino acids. Pepsin hydrolyzes proteins to polypeptides and oligopeptides. Trypsin hydrolyzes proteins to oligopeptides.

The mechanism of the putative anti-inflammatory activity of the proteolytic enzymes bromelain, chymotrypsin, papain and trypsin is not well understood. It is believed that a fraction of these proteolytic enzymes is absorbed, probably via the enteropancreatic circulation. It is speculated that the putative anti-inflammatory activity of these enzymes may be accounted for, in part, by their activation of plasmin production from plasminogen and by their reduction of kinin via inhibition of the conversion of kininogen to kinin. Degradation of circulating immune complexes may be another possible mechanism.

The putative anti-inflammatory and anticarcinogenic activities of Wobe-Mugos and Wobenzyme are also open to speculation. Possibilities include a decrease of circulating immune complexes, disruption of adhesion molecules on tumor and endothelial cells, degradation of cytokines and cytokine receptors and possible immunomodulatory effects. Bromelain is speculated to play a role in differentiation of malignant cells.

The mechanism of the putative anti-inflammatory activity of superoxide dismutase is unknown.

#### PHARMACOKINETICS

The fungal- and plant-derived enzymes appear more resistant to inactivation and denaturation by stomach acid than are the animal-derived enzymes. Pancreatin and pancrelipase require enteric coating to prevent denaturation and inactivation by stomach acid. In the small intestine, a fraction of the enzymes may be absorbed via the enteropancreatic circulation. Much is unknown regarding the pharmacokinetics of oral enzymes in humans.

#### INDICATIONS AND USAGE

Supplemental enzymes (alpha-galactosidase, chymotrypsin, lactase, pancreatin, pancrelipase, papain and pepsin) are used as digestive aids in some circumstances. Some (bromelain, superoxide dismutase, chymotrypsin, papain and trypsin) are said to have some anti-inflammatory activity. There is some evidence that Wobe-Mugos and Wobenzyme may have some anti-inflammatory and anticarcinogenic activities.

#### RESEARCH SUMMARY

Supplemental enzymes have been used for some time as digestive aids with various degrees of efficacy. Those with digestive disorders, however, should not use digestive enzymes unless they are approved by their physicians. Pancreatin is used pharmaceutically in some with pancreatic insufficiency secondary to such disorders as cystic fibrosis and chronic alcoholic pancreatitis. It is used in this context as

pancreatic enzyme replacement therapy. Pancrelipase is used in the treatment of steatorrhea secondary to pancreatic insufficiency related, again, to such disorders as cystic fibrosis and chronic alcoholic pancreatitis.

Pepsin, in combination with dilute hydrochloric acid has been used as an adjunctive treatment of gastric hypochlorhydria. Papain is used as a digestant. Lactase is effective in some with milk sugar (lactose) intolerance, and cellulase has reportedly been of benefit in some with flatulence. Amylases have been used as digestants, as has chymotrypsin and bromelain. Alpha-galactosidase is used to manage flatulence in those who develop "gas" from the consumption of certain foods, such as beans. Superoxide dismutase, used intra-articularly, has reportedly shown some anti-inflammatory effects in animals, but clinical studies are lacking.

More studies have been done on bromelain, Wobe-Mugos and Wobenzyme. Bromelain is a major constituent of Wobenzyme, which also includes pancreatin, papain, trypsin and chymotrypsin. Wobe-Mugos contains papain, trypsin and chymotrypsin. These enzyme preparations have demonstrated some anti-inflammatory and anticarcinogenic activity. Wobe-Mugos is an orphan drug for use in the treatment of multiple myeloma.

Wobe-Mugos and Wobenzyme have shown an ability to clear circulating immune complexes from the body, in both animal and human experiments. These antibody/antigen complexes have been implicated in some inflammatory processes, including those related to rheumatoid arthritis and some other autoimmune diseases. Antigen-induced experimental arthritis in rabbits was inhibited by these enzyme preparations in one experiment. Wobenzyme reportedly improved the condition of patients with chronic polyarthritis in another study. No side effects were noted. Recently, significant pain reduction was associated with use of these proteolytic enzyme preparations in subjects with osteoarthritis of the knee and peri-arthritis of the shoulder.

Long-term rectal administration of Wobe-Mugos has been reported to inhibit growth of solid tumors and development of experimental metastases in mice inoculated with B16 melanoma cells. In another recent study, Wobe-Mugos significantly increased survival time in mice with Lewis lung carcinoma. In a recent randomized trial, Wobe-Mugos was said to significantly reduce the acute sequelae of radiation in head and neck cancers.

There is a report in which Wobe-Mugos was tested in comparison with acyclovir in subjects with herpes zoster. The enzyme preparation was said to be as efficacious as acyclovir in alleviating pain. Effects on skin lesions were largely equal. More study is needed.

## CONTRAINDICATIONS, PRECAUTIONS, ADVERSE REACTIONS

### CONTRAINDICATIONS

Supplemental enzymes are contraindicated in those hypersensitive to any component of an enzyme-containing preparation.

### PRECAUTIONS

The use of digestive enzymes for the treatment of pancreatic insufficiency requires medical supervision.

Those who wish to use supplemental enzymes for any indication should first discuss their use with their physicians.

Pregnant women and nursing mothers should avoid supplemental enzymes unless prescribed by their physicians.

Galactosemics should avoid the use of alpha-galactosidase. D-galactose is one of the substances formed via the action of alpha-galactosidase.

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

### ADVERSE REACTIONS

*Alpha-galactosidase:* Gastrointestinal symptoms such as cramping and diarrhea have been reported. Allergic-type reactions, including rash and pruritis, have also been reported.

*Amylase:* Allergic-type reactions, including rash and pruritis, have been reported.

*Bromelain:* Gastrointestinal symptoms such as nausea and vomiting, diarrhea and cramping, have been reported. Metrorrhagia and menorrhagia have been occasionally reported. Hypersensitivity reactions have been reported, including rashes and exacerbation of asthma.

*Pancreatin:* The most frequently reported adverse reactions are gastrointestinal and include diarrhea, abdominal pain, nausea and vomiting. Hyperuricemia has been reported with the use of pancreatin products.

*Pancrelipase:* The most frequently reported adverse reactions are gastrointestinal and include diarrhea, abdominal pain, nausea and vomiting, constipation, melena and perianal irritation. Hyperuricemia and hyperuricosuria have been reported with the use of pancrelipase products, primarily with non-enteric coated formulations. Cases of fibrosing colonopathy have been reported primarily in cystic fibrosis patients.

*Wobe-Mugos/Wobenzyme:* The most frequently reported adverse reactions are gastrointestinal and include diarrhea, abdominal pain, nausea and vomiting. There is a report of an anaphylactic reaction in a woman receiving intramuscular injections of Wobe-Mugos. There is a report of circulatory