Making Sense of Digestive Enzymes

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SUMMARY: Enzymes are functional proteins essential to all living systems. In humans, enzymes act as catalysts for numerous chemical reactions including the digestion of dietary macronutrients. In the early part of the twentieth century, use of supplemental digestive enzymes was proposed as a means of compensating for the loss of enzyme activity in modern diets. As with the loss of micronutrients like vitamins and minerals from highly refined and processed foods, the loss of enzymes was thought to be an unrecognized factor contributing to poor health and disease. In the ensuing decades, research studies demonstrated supplemental enzymes can improve digestion of dietary macronutrients and reduce a variety of gastro-intestinal symptoms including gas, bloating, heartburn, nausea and abdominal discomfort. While the importance of enzymes in helping to maintain optimal health has yet to be as widely acknowledged as that of other micronutrients, research documenting their benefits continues to mount. This paper reviews the various types of enzymes, their health benefits, and use in enzyme supplements.

INTRODUCTION AND BACKGROUND

Enzymes are naturally occurring proteins that function as catalysts for the vast number of chemical reactions taking place in the human body. Enzymes enable metabolic and physiological processes to take place by reducing the amount of energy needed for a chemical reaction to occur, thereby speeding up the rate of the reaction.[1] Enzymatic activity makes life possible because vital reactions would occur millions, in some instances billions, of times more slowly if not for the catalytic activity of enzymes.[2]

Enzymes catalyze reactions by binding substrates, or chemical reactants, into a region of the enzyme called the active site. Active sites may be thought of as pockets or clefts in the enzyme into which chemical substrates fit. Since every enzyme and its active site have a unique physical conformation, enzymes have a high degree of specificity for the substrates upon which they act and the type of chemical reaction they catalyze. Enzymes are not consumed by the reactions they mediate. Once an enzyme has catalyzed a chemical reaction, it releases the altered substrate from its active site and becomes available to catalyze another reaction.[1]

In human physiology, enzymes can be broadly categorized as either digestive or metabolic in function.[3] Digestive enzymes catalyze the chemical breakdown of dietary macronutrients such as proteins, carbohydrates, and lipids within the gastrointestinal tract. Metabolic enzymes catalyze the myriad of biochemical reactions taking place in the body's cells and tissues and underlie such essential processes as energy production, synthesis and repair of cell structures, replication and repair of genetic material, and motion. While most digestive enzymes belong to a larger class of enzymes known as hydrolases, which cleave compounds by hydrolyzing a chemical bond, metabolic enzymes have wider functionality and may be broadly classified as oxidoreductases, transferases, hydrolases, lyases, isomerases, or ligases, depending on the nature of the chemical reaction they catalyze.[1]

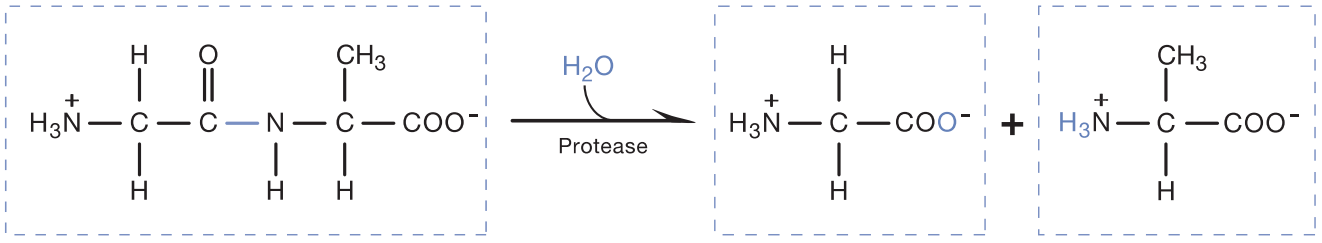
A third category of enzymes, food enzymes, can be found in raw foods like fresh fruits and vegetables. Enzymes play as vital a role in plants as they do in humans, catalyzing almost all essential biochemical reactions. When ingested as part of the diet, evidence suggests plant enzymes may contribute to the human digestive process by initiating autolysis of plant foods within the gastrointestinal tract.[4] This capacity is lost when foods are cooked, pasteurized or thermally-processed as heat alters the natural conformation of enzymes and thus destroys their catalytic ability. To compensate for the loss of enzyme activity in modern diets, supplementation with enzymes derived from animal, plant and/or microbial sources may be beneficial.

DIGESTIVE ENZYMES - Types and Activities

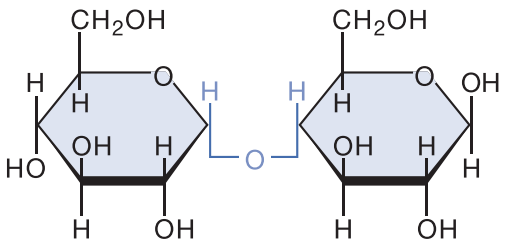
Proteases and Peptidases

Proteases catalyze the hydrolysis of proteins into smaller fragments known as peptides. Dietary protein digestion begins in the stomach where the acid-stable protease, pepsin, initiates the cleavage of peptide bonds within proteins to produce large polypeptide fragments.[5] These polypeptides enter the small intestinal tract where pancreatic and intestinal proteases and peptidases cleave peptide bonds until only small peptide units and individual amino acids remain.

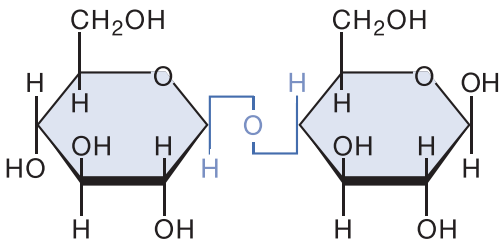
Proteases can be categorized in a number of different ways. One system classifies them according to the structure of their catalytic sites. For example, serine proteases have a serine residue in the active site, whereas cysteine proteases have a cysteine residue in the active site. A more useful system categorizes proteases according to the type of bond they cleave. Proteases that cleave an amino acid, or a small group of amino acids, from the terminal end of a peptide chain are called exopeptidases, whereas those that cleave internal bonds within a peptide chain are termed endopeptidases.



Hydrolysis site of a peptide bond to yield individual amino acids



Alpha-glycosidic bond
(can be hydrolyzed by alpha-amylase)



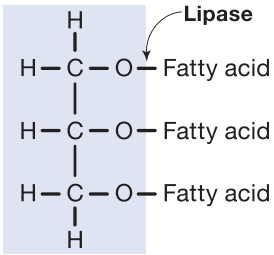
Beta-glycosidic bond
(cannot be hydrolyzed by alpha-amylase)

Carbohydrases

Carbohydrases facilitate the breakdown of dietary carbohydrates such as starches, fibers, and sugars. Carbohydrate digestion begins in the mouth where salivary amylase initiates the cleavage of alpha-glycosidic bonds between glucose units within starch molecules. This process continues while food remains in the relatively pH-neutral, fundal region of the stomach, but comes to a halt once food moves into the acidic environment of the lower stomach. In the duodenum, pancreatic amylase picks up where salivary amylase left off and resumes the hydrolysis of starch. Smaller saccharides found in the diet, and those resulting from starch digestion, are broken down into their component monosaccharides by intestinal brush border enzymes such as glucoamylase, sucrase, isomaltase, and lactase. Fibers, like starches, are polysaccharides but their internal beta-glycosidic bonds cannot be hydrolyzed by human pancreatic or intestinal enzymes (see figure above). Fibers are therefore non-digestible by humans, but they can be partially broken down by microorganisms within the gastrointestinal tract that produce the enzymes necessary to cleave the internal bonds. Supplemental fiber-digesting carbohydrases such as cellulase and hemicellulase can also effectively break the beta-glycosidic bonds in fibrous foods making them easier to digest.

Lipases

Lipases are responsible for the chemical breakdown of lipids. In the digestive tract, the primary active form of lipase is triacylglycerol lipase which cleaves ester bonds that attach fatty acids to glycerol within triglyceride molecules. Lipase is secreted at a number of stages during the digestive process. Lingual and gastric lipases are secreted in the mouth and stomach, respectively, but both act primarily in the stomach. Pancreatic lipase is secreted in pancreatic fluid and exerts its lipolytic activity in the duodenum. Of the three, pancreatic lipase is by far the most active, generating approximately 85% of the free fatty acids produced by fat digestion.[6] The pancreas also secretes phospholipase enzymes responsible for the hydrolysis of dietary phospholipids such as phosphatidylcholine, a carboxyl ester lipase that hydrolyzes cholesterol esters, and a protein co-factor for lipase called colipase. Phospholipases associated with the intestinal brush border have also been identified and are believed to contribute to the breakdown of certain fat-soluble dietary nutrients such as retinyl esters.



Triglyceride (fat) molecule consisting of three fatty acids attached to a glycerol backbone. Fatty acids are removed by lipase activity.

DIGESTIVE ENZYMES - Health Benefits

Historical Benefits

The idea of using enzymes in clinical nutrition was popularized by Edward Howell, a medical doctor and researcher who in the 1940s first proposed that food enzymes might play as important a role in human nutrition as do vitamins and minerals.[3,7] Dr. Howell noted that the diets of wild animals consist almost exclusively of raw foods, as did the diets of protohumans for millions of years before the discovery of fire. He believed that the enzymatic activity of raw foods is vital to the digestive process and spares the body from having to produce all the enzymes necessary to digest a meal.

Dr. Howell's hypothesis is supported by early animal research showing that while horses have little starch-digesting amylase activity in their saliva or upper digestive tracts, a significant percentage of the dietary starch they consume from raw oats is broken down in their stomachs. Feeding experiments using "sterilized" oats, meaning oats with inactivated enzymes, fail to reproduce these results. *In vitro* studies confirm that homogenized portions of raw foods exhibit autolytic or self-digestive activity over time, producing sugars from starch and even amino acids from proteins when these foods are allowed to incubate at temperatures and pH levels optimal for enzymatic activity.[4]

Dr. Howell believed this autolytic capacity of raw foods makes them ideal for human consumption. Cooked and processed foods force the body to rely solely on its own enzymes for digestion and divert energy away from production of metabolic enzymes. This chronic sacrifice of endogenous enzymes for digestion may lead to a state of poor health because of the body's reduced capacity to produce energy, repair tissues, and fight disease.

Howell postulated that supplementing cooked-food diets with digestive enzymes could prevent the depletion of endogenous enzymes. Supplemental enzymes, taken with meals, begin breaking foods down in the upper, fundal region of the stomach where food is held for approximately an hour before moving into the acidic, lower region of the stomach.[2] This "predigestion" simulates the autolytic breakdown of raw foods in the upper gastrointestinal tract, mimicking what Howell believed to be the natural process whereby the body conserves its endogenous enzyme supply and maintains health.

Howell cited many examples of raw food diets being commonly prescribed by doctors for a variety of ailments. Even before there was widespread knowledge of enzymes, raw food diets were commonly recommended based purely on empirical observations that they improved health. Raw fruits and vegetables, raw milk, and even raw butter were used to treat disorders such as constipation, indigestion, allergies, skin problems, rheumatic illness, and neurological conditions. Howell believed the health benefits of these diets derived primarily from the large quantity of enzymes people consumed. Limited modern research has been done on the benefits of raw foods, but at least one published study reported a significant reduction in weight and blood pressure in a group of persons consuming a

predominantly raw foods diet.[8] Whether this benefit can be ascribed solely to an increased consumption of food enzymes by the participants remains unclear.

Howell also described the use of supplemental enzymes for therapeutic purposes by his medical contemporaries. One doctor used a multi-enzyme preparation to bring relief to his patients suffering from joint and connective tissue diseases. Another doctor reportedly used microbial-derived enzymes to successfully treat indigestion, abdominal gas, asthma, diet-related eczema, urticaria, and a number of other conditions. These reports, while anecdotal in nature, are nevertheless thought-provoking clinical observations.

Modern use of orally administered enzymes in conventional medicine is fairly limited. More commonly employed in Europe and certain other parts of the world, enzyme use in the United States is restricted primarily to enzyme deficiency states like lactose intolerance and pancreatic insufficiency. Studies show that supplementing enzymes in these conditions can be effective in reducing symptoms and normalizing digestion. Ongoing research into the use of enzymes for gastrointestinal conditions, nutrient malabsorption, allergies, immune dysfunction, autism spectrum disorders, and as an adjunct to cancer treatment is helping to clarify the specific roles enzymes can play in treating diseases and their broader role in improving human health.

Benefits of Proteases

Proteolytic enzymes taken with meals assist in the breakdown of dietary protein and, as described earlier, may help spare the production or utilization of endogenous proteolytic enzymes. Animal studies show that supplemental proteases not only increase protein digestion, but may enhance digestion of fibrous material by degrading proteins in plant cell walls, allowing for increased exposure to microbial fibrolytic enzymes.[9] Studies on the use of oral proteolytic enzymes in humans are few in number, but one study demonstrated that enzymatic predigestion of meat proteins can reduce their allergenicity in children sensitive to these proteins.[10] This finding suggests supplemental proteases may reduce antigen translocation through the intestinal mucosa into the systemic circulation.

Specific proteases may also be helpful in reducing symptoms associated with wheat and dairy intolerances. Proteins from these foods, such as gluten and casein, are rich in proline residues that are highly resistant to hydrolysis by most digestive enzymes.[11] Intact absorption of undigested proline-rich peptides can lead to antigenic activation of T cells resulting in autoimmune damage to intestinal tissues, a pathological feature of gluten enteropathy (also known as celiac sprue or celiac disease).[11] Additionally, evidence suggests that absorption of these proline-rich peptides may exert opioid-like (exorphin) activity in the central nervous system and trigger neurological symptoms often associated with gluten enteropathy or encountered in children with autism spectrum disorders.[12] High levels of opioid-like peptides, derived in part from dietary gluten and casein, have been found in the urine of persons with autism spectrum disorders.[13] Specific endo- and exopeptidases, such as prolyl endopeptidase (PEP) and dipeptidyl peptidase-IV (DPP-IV), have been shown to cleave terminal proline-containing dipeptides *in vitro*[11,14] and may be helpful in reducing levels of bioactive prolyl peptides in the intestinal tract. DPP-IV is normally present in the intestinal brush border, but studies show its activity is abnormally low in children and adults with celiac disease[15] and that persons with autism spectrum disorders actually produce anti-DPP-IV antibodies.[16] These factors suggest supplemental peptidases may be of therapeutic value in managing disorders associated with reactivity to gluten and/or casein. Preliminary research shows that PEP reduces both the level and immunotoxicity of gluten oligopeptides in animal models.[17] And patent research on the use of enzymes in the treatment of autism spectrum disorders has shown that an enzyme preparation with DPP-IV activity can improve a variety of neurologic and digestive symptoms in autistic patients.[18] Clearly this is a promising area of research and further clinical trials are warranted.

Benefits of Carbohydrases

Carbohydrases have long been used in animal agriculture to improve the digestibility of animal feeds. Studies find that adding carbohydrases to grain-based diets usually results in increased digestible energy intake and improved animal growth.[19] In one study, an enzyme preparation containing various combinations of carbohydrases including amylase, cellulase, pectinase, and invertase was added to the feedstuffs of several groups of weaned pigs. Compared to a control group that was fed a standard diet, all the enzyme-fed pigs exhibited improved macronutrient breakdown and

SYSTEMIC USE OF PROTEOLYTIC ENZYMES

Supplemental proteases can be used for both digestive and systemic purposes. When taken between meals, proteases can exert systemic effects by being absorbed through the intestinal mucosa. Once thought to be impermeable to macromolecules like enzymes, a number of studies demonstrate that the intestinal epithelium has mechanisms whereby large molecules may cross intact into the bloodstream.[1,2,3] The predominant mechanism of entry through a normal mucosal barrier appears to be energy-dependent pinocytic uptake by enterocytes, but mechanisms involving passive diffusion through enterocytes and entry through intercellular tight junctions have also been described for a damaged, hyperpermeable mucosa.[2]

Once in the systemic circulation, proteolytic enzymes are capable of modulating a number of biochemical reactions including the activity of some inflammatory and pain mediators. This effect has been observed in both animals and humans. In one animal model of inflammation, oral administration of the proteolytic enzyme bromelain was shown to significantly reduce the presence in inflammatory exudate of PGE2, a prostanoid associated with pain, heat and fever, and substance P, a neuro-transmitter associated with pain.[4] Human studies have found that oral proteases like bromelain and trypsin can significantly reduce pain and stiffness in persons with both uncomplicated joint pain and osteoarthritis.[5,6] Reports of efficacy in inflammatory bowel disease have also appeared in the medical literature.[7]

The beneficial effects of proteases for systemic applications have been attributed to a reduction of inflammatory processes, regulation of cytokine production, induction of antiproteinases, and immunomodulatory activity.

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an increase in average daily weight gains.[20] Although some inconsistencies have been reported due to differences in product formulation, dosage level, and method of enzyme delivery, similar benefits of carbohydrase enzymes for improving feed digestibility and animal growth and performance have been demonstrated in broiler chickens and dairy cattle.[19,21-23]

Clinical studies examining the benefits of carbohydrases in humans are limited primarily to the use of lactase for lactose intolerance and alpha-galactosidase for flatulence. Lactose intolerance is caused by deficient brush border lactase activity, a condition present in most mammals including the majority of adult humans.[24] Microbial lactase preparations have been shown in placebo-controlled trials to significantly reduce breath hydrogen production and symptoms of gas and bloating in a dose-dependant manner in lactose intolerant individuals.[25-27] Interestingly, some researchers have observed that the clinical signs and symptoms of lactose maldigestion are so similar to those of irritable bowel syndrome (IBS) that they speculate the two disorders may have a common origin.[28] If this is the case, supplemental lactase may be of benefit to a significant percentage of the estimated 1-in-5 Americans afflicted with IBS.

Alpha-galactosidase is the active ingredient of Beano®, a well-known product designed to help reduce gastrointestinal symptoms associated with ingestion of foods like legumes, cruciferous vegetables, and some grains. Alpha-galactosidase, an enzyme not normally expressed in the human gastrointestinal tract, works by hydrolyzing the alpha-(1→6) galactoside linkages of digestion-resistant galactooligosaccharides such as raffinose and stachyose commonly found in flatulogenic foods. Several small human trials have been conducted to test the efficacy of this enzyme with most showing positive results. Of these studies, two double-blind, placebo-controlled trials demonstrated that supplemental alpha-galactosidase is effective at reducing symptoms of gas, bloating, and abdominal discomfort and pain.[29,30]

Carbohydrases may also be of benefit in other conditions where enzyme deficiencies are present. Studies show specific subsets of persons with chronic diarrhea and children with autism spectrum disorders may have reduced intestinal disaccharidase activity. In one study, a group of patients with chronic diarrhea demonstrated significantly lower levels of lactase, sucrase, and maltase than normal controls. The causative factors underlying the diarrhea such as infection, inflammation, and gut mucosal injury were thought to be possible contributory factors to the loss of intestinal enzyme activity.[24] In another study, more than half of a group of 36 children with autism spectrum disorders who also reported gastrointestinal symptoms were found to have low levels of glucoamylase and disaccharidase activity. Gastrointestinal endoscopy and biopsies of these children revealed chronic inflammation of the esophagus, stomach, and duodenum which may have contributed to the diminished enzyme activity.[31] Reduced disaccharidase activity may also be congenital. Sucrase-isomaltase deficiency is a relatively rare genetic disorder that manifests in infants and children as chronic diarrhea, cramping, and abdominal distension due to an inability to properly hydrolyze the disaccharide sucrose. The inability to break down isomaltose may or may not also be present. Studies utilizing fungal-derived sucrase in children with sucrase-isomaltase deficiency have reported significant clinical improvements including reduced breath hydrogen and diminished symptoms of diarrhea, gas, cramping and bloating.[32,33] While more research needs to be done, the evidence indicates that intervention with carbohydrases may prove useful in correcting the enzyme deficiencies observed in many cases of chronic diarrhea and autism spectrum disorders.

Benefits of Lipase

Supplemental lipase is frequently administered to persons with exocrine pancreatic insufficiency resulting from late-stage pancreatitis, cystic fibrosis, pancreatic resection or other disorders of the pancreas. Loss of lipase activity is potentially more serious than that of other pancreatic enzymes as its lipolytic action is not adequately compensated for by extrapancreatic enzymes. Inadequate lipolysis of triglycerides leads to excessive fecal fat loss (steatorrhea) and impaired absorption of fat-soluble nutrients such as essential fatty acids and vitamins A, D, E and K.[34] A number of published studies have demonstrated that lipase supplementation can effectively improve fat digestion and reduce steatorrhea in patients with pancreatic insufficiency. In one study, a pancreatic enzyme supplement delivering high doses of lipase normalized fat digestion in up to 63% of patients with chronic pancreatitis.[35] While porcine pancreatic enzymes (pancreatin) are considered the treatment of choice in pancreatic insufficiency, microbial enzymes have also demonstrated some efficacy. In one animal study, microbial lipase was shown to be as effective as pancreatin in correcting steatorrhea in pancreatectomised dogs.[36] One small human trial also found a trend towards reduction of fecal fat and improvement in fat absorption in a group of cystic fibrosis patients supplemented with fungal-derived lipase.[37] A recent review of lipase therapy in the journal *Pancreas* reported encouraging results from *in vitro* and animal studies using bacterial lipase from *Burkholderia plantarii*, claiming the enzyme had much better resistance against inactivation by gastric juice, bile salts, and proteolytic hydrolysis than pancreatin, and far higher lipolytic activity per unit weight than pancreatin.[34] Should bacterial lipase prove as effective in human trials, it could replace pancreatin as the treatment standard for fat malabsorption due to these advantages. The therapeutic benefit of high doses of oral lipase in such advanced types of pathology as frank pancreatic deficiency suggests that milder forms of lipid malabsorption may benefit from lower doses of a lipase-containing enzyme supplement.

Benefits of Multi-Enzyme Preparations

A large number of studies examining the effects of broad-spectrum enzyme supplementation in human subjects have been conducted in Germany, France, Italy, and Russia. Most of these published studies have not yet been translated. Several studies conducted in the United States and Great Britain, however, suggest that multi-enzyme preparations can improve digestion and mitigate a variety of gastro-intestinal symptoms. One interesting, unpublished experiment conducted by an enzyme manufacturer examined the effects of a microbial, multi-enzyme preparation on carbohydrate and protein digestion in a dynamic, multi-compartmented gastrointestinal model that simulates the physiological conditions within the human stomach and small intestinal tract.[38] Four test meals were introduced into the apparatus under varying conditions: two meals, one with enzymes and one without, under conditions of optimal digestion; two meals, one with enzymes and one without, under conditions of significantly reduced gastric and pancreatic secretion (to simulate impaired digestion). Under conditions of optimal digestion, the enzyme supplement was shown to significantly improve carbohydrate digestion and slightly improve protein digestion. Under conditions of impaired digestion the enzyme supplement significantly improved both carbohydrate and protein digestion. In addition to improving digestion, the enzyme supplement was shown to be active in both the gastric and intestinal regions of the apparatus.

Human studies have also been conducted using multi-enzyme combinations. In an open trial involving 16 nursing home patients on enteral tube feeding, a multi-enzyme supplement consisting of bromelain and microbial-derived protease, amylase, cellulase, lactase, and lipase was administered along with the feeding solution for 15 days.[39] During the test period, total serum protein was shown to increase significantly reflecting improved digestibility of the enteral formula and enhanced nutritional status of the patients. Serum lymphocyte counts were also found to be significantly higher suggesting an

improvement in immune function. These positive changes reversed when the enzyme supplement was withdrawn. In a double-blind, placebo-controlled human trial, an enzyme supplement containing proteases, carbohydrases, and lipase derived from both pancreatic and microbial sources was administered with meals to a group of hospital patients reporting gastrointestinal symptoms. At 8 weeks, global improvement scores were significantly higher in the enzyme group than in the placebo group. Symptoms reduced by the enzyme preparation included abdominal pain, nausea, vomiting, heartburn, bloating, flatulence, and loss of appetite.[40]

ENZYME DERIVATION

Digestive enzymes can be derived from animal, plant or microbial sources. Animal source enzymes, commonly known as "pancreatin", are typically derived from porcine or bovine pancreas and include lipase, amylase, and the protease trypsin. Porcine pancreatin is the standard treatment for pancreatic insufficiency in conventional western medical practice. Plant-based enzymes include the widely used proteases bromelain, from pineapple, and papain, from papaya. Other plant-derived enzymes, such as actinidain from kiwi and ficain from fig, have been identified and characterized but are typically not used in digestive enzyme preparations. Microbial-based digestive enzymes most commonly derive from the fungal organisms *Aspergillus oryzae* and *Aspergillus niger*. These organisms produce a wide variety of enzymes including proteases, peptidases, carbohydrases, and lipase. Some bacteria also produce commercially used enzymes. For example, a non-pathogenic strain of enterobacteria known as Serratia E15 is the source of an acid-stable proteolytic enzyme known as Serratia peptidase (also known as serratiopeptidase or serrapeptase).

ENZYME NOMENCLATURE

As described earlier, enzymes may be placed into one of 6 broad classes depending on their functional activity: oxidoreductases, transferases, hydrolases, lyases, isomerases, and ligases. Each of these classes is further divided into subclasses and sub-subclasses. Every enzyme has a particular 4-number Enzyme Commission (EC) designation assigned to it by an organization called the Nomenclature Committee of the International Union of Biochemistry and Molecular Biology (NC-IUBMB).[1,41] The first number in an EC designation defines the major class to which the enzyme belongs. For example, all EC 1 enzymes are oxidoreductases, all EC 2 enzymes are transferases, all EC 3 enzymes are hydrolases, and so forth. Numbers that follow refer to the subclass, sub-subclass and, finally, the order in which the enzyme was added to the list. For example, the enzyme alpha-amylase has an EC number 3.2.1.1. This means the enzyme belongs to the major class of hydrolases (EC 3), a subclass of hydrolases known as glycosylases (EC 3.2), a subclass of glycosylases known as glycosidases (EC 3.2.1), and was the first enzyme to be added to this class (EC 3.2.1.1).[41] While EC numbers are not commonly used within the nutritional supplement industry and are rarely found on product labels or in the lay health literature, they can be very helpful in making a positive identification of an enzyme.

ENZYME ACTIVITY UNITS

Measuring enzyme activity is a somewhat complex task as each enzyme requires a special assay that must be performed according to standardized specifications. Fortunately, such assays have been developed and described in two monographs: the Food Chemical Codex (FCC)[42] and the United States Pharmacopoeia (USP).[43] These documents represent a compendium of standards that help ensure the quality and safety of foods, drugs, and, increasingly, nutritional supplements. Responsible voices within the nutritional supplement industry have long called for standardized reporting of enzyme activities based on FCC and USP standards. This not only helps ensure the quality and consistency of enzyme products, but assists consumers in making an informed decision about which type of enzyme product to buy.

The most recent edition of the FCC (FCC V) lists some forty enzymes, the methods by which the potencies of these enzymes are assayed, and the units that should be used to describe their activity. Some of the more common digestive enzymes and their units are listed in the following table.

Enzyme Name	Potency Unit
Alpha-Amylase (fungal source)	DU (dextrinizing unit)
Alpha-Amylase (bacterial source)	BAU (bacterial amylase unit)
Cellulase (unspecified source)	CU (cellulase unit)
Alpha-Galactosidase (fungal source)	GalU (galactosidase unit)
Beta-Glucanase (microbial source)	BGU (beta-glucanase unit)
Glucoamylase (amyloglucosidase) (fungal source)	Glucoamylase unit[1]
Hemicellulase (fungal source)	HCU (hemicellulase unit)
Invertase (sucrase) (fungal source)	INVU[2] (invertase unit)
Lactase (beta-galactosidase)	ALU[3] (acid lactase unit) (fungal source)
Lipase (fungal source)	FIP[4] (Fungi Lipase-International)
Lysozyme (animal or microbial source)	Lysozyme unit
Phytase (unspecified source)	FTU (phytase, or "fytase", unit)
Protease (plant source)	PU (papain unit)
Protease (bacterial source)	PC (bacterial protease unit)
Protease (acid) (fungal source)	SAP (spectrophotometric acid protease unit)
Protease (neutral/alkaline)(fungal source)	HUT (hemoglobin unit on the tyrosine basis)
Pullulanase (bacterial source)	PU (pullulanase unit)

1 The unit AGU (amyloglucosidase unit) is often used in the nutritional industry
2 The unit SU (Sumner unit) is also frequently used
3 The unit NLU (neutral lactase unit) is used for lactase assayed in a neutral medium
4 The unit LU (lipase unit) may also be used depending on the type of lipase assay performed

Enzymes derived from porcine (or sometimes bovine) pancreas – i.e. pancreatin – are described in both the USP and FCC. Pancreatin is typically a blend of amylase, lipase, and protease, whose activities are simply listed as USP Units. According to the latest edition of the USP (USP 31), each milligram of pancreatin should contain no less than 25 USP Units of amylase activity, 2.0 USP Units of lipase activity, and 25 USP Units of protease activity. More concentrated preparations are labeled as a whole number multiple – for example, 2X, 4X, 8X – of these minimum activities.

ENZYMES - Frequently Asked Questions

Who should take digestive enzymes?

Digestive enzymes are suitable for anyone who consumes moderate amounts of cooked and/or processed foods in their diets as these foods are devoid of their own endogenous enzymes. Enzymes can also be used by anyone who wants to maximize digestion and nutrient absorption and may be especially helpful for persons who feel they have digestive difficulties or need support breaking down specific dietary components such as dairy, wheat, legumes or high-fiber foods.

Can children take enzymes?

Yes, but smaller doses should be used. One half of an adult dose can be used for children under the age of 12. For children under 5, consult with your healthcare practitioner.

What type of enzymes should I use?
For most people, a broad-spectrum enzyme supplement designed to break down multiple components of the diet, such as proteins, carbohydrates, and fats, would be suitable. If you feel you have difficulty with one particular class of foods you may want to look for an enzyme product designed to maximally digest that food. For example, an individual who has difficulty digesting legumes should look for a supplement that contains a higher content of the enzyme alpha-galactosidase, the carbohydrase known to break down problematic carbohydrates in legumes. Similarly, a person with difficulty digesting fatty foods might benefit more from an enzyme preparation with a high content of lipase, while someone with lactose intolerance would be best served by a high-lactase product.

Persons with particular dietary restrictions should also choose an appropriate enzyme supplement. For example, vegetarians may wish to avoid animal-source enzymes such as pancreatin, while persons with allergies or sensitivities to particular plants or microbial organisms should not use enzymes derived from those sources.

What should I look for when reading the enzyme activities listed on the label of a digestive enzyme supplement?
Enzyme activities, where applicable, should be reported in unit amounts specified by the Food Chemical Codex (FCC) for plant and microbial enzymes or the US Pharmacopoeia (USP) for animal-source enzymes. Milligram amounts are appropriate for most vitamins and minerals, but do not give sufficient information about the potencies of enzymes. FCC and USP units are widely recognized as the highest standard for accurately labeling enzyme activities. The presence of FCC or USP units on a label helps ensure that the enzymes have been tested for activity levels set forth by the US Pharmacopoeia and are recognized by the American food industry. Enzyme products that do not report activity in terms of FCC and/or USP units cannot be easily assessed, or compared, for potency and efficacy.

When should I take enzyme supplements?
For digestive purposes, enzymes are best taken at the beginning or in the middle of a meal. Encapsulated enzymes can be swallowed whole or the capsule can be pulled apart and the contents mixed with liquid or food. Digestive enzymes should not be mixed with extremely hot foods or beverages to avoid inactivation of the enzymes. Proteolytic enzyme supplements being used to achieve a systemic effect, such as modulating inflammation, should be taken between meals so that the enzymes do not expend their activity on food digestion, but are instead absorbed intact into the bloodstream.

Can a broad-spectrum digestive enzyme supplement be used for systemic benefits?
Proteases are the only enzymes that have been shown to exert systemic effects in the body. While other enzymes such as carbohydrases and lipase may be absorbed from the intestinal tract into the bloodstream, there is no scientific data describing the type of effects, if any, they have once in the systemic circulation.

How much of a digestive enzyme supplement should I take?
Individuals respond differently to digestive enzymes so it is best to start by following the package directions and adjusting the dose either upward or downward to achieve the best clinical response. The dosage should also roughly correspond to the amount of food being eaten, so more enzymes should be taken with a heavy meal, less with a lighter meal.

What can I expect when starting digestive enzyme supplementation and how will I know it is working?
Some individuals may notice a slight increase in bowel movement frequency and gas when beginning digestive enzyme supplementation. These symptoms are generally temporary and may last for a few days as the gastrointestinal tract adjusts to the presence of exogenous digestive enzymes. Improvements in digestion and gastrointestinal function may be seen immediately upon taking an enzyme supplement or may take several days to several weeks to become noticeable.

Can digestive enzymes help with food allergies or intolerances?
Preliminary research suggests supplemental digestive enzymes may be helpful for certain types of food-related allergy symptoms. As described earlier, predigestion of meat proteins with proteolytic enzymes has been shown to reduce their allergenicity in sensitive children. Similarly, some doctors report that carbohydrases are helpful in reducing allergies or sensitivities to certain plant foods, although clinical studies supporting this observation are currently lacking. Plant foods contain thousands of different proteins, many of which are potentially allergenic.[44] Carbohydrases like cellulase, hemicellulase, and beta-glucanase that break down the fibrous components of plant cells may help expose allergenic proteins making them more vulnerable to degradation by endogenous or supplemental proteolytic enzymes. Carbohydrase products have also been developed that claim to modify phenolic compounds in plant foods in such a way as to facilitate their metabolism by persons with phenol sensitivities. While much research remains to be done to demonstrate the efficacy of enzymes in reducing or neutralizing offending substances in foods, preliminary evidence suggests this approach may hold promise for those suffering from food sensitivities and/or allergies.

I have candida, can digestive enzymes help with that?
Candida albicans is a fungal organism that resides in the gastrointestinal tract of most humans.[45] While the pathogenicity of intestinal candidal colonization remains controversial, the belief that this yeast may provoke both digestive and systemic symptoms persists. Persons with health problems believed to be related to candidiasis may theoretically benefit from supplemental enzymes as yeast cell walls are known to be susceptible to enzymatic hydrolysis. Beta-glucanase is a type of carbohydrase enzyme that breaks the bonds of beta-glucan, a component of yeast cell walls. Enzyme preparations with beta-glucanase activity are routinely used in laboratory settings to lyse fungal cell walls for a variety of experimental procedures, and *in vitro* research has demonstrated the ability of beta-glucanase to reduce the viability of candidal organisms in their own protective biofilms.[46] Lysozyme is another enzyme shown to have anti-candidal activity. Isolates of candidal organisms derived from the oral cavity of HIV-infected individuals have been shown to rapidly lose viability when exposed to lysozyme.[47] While clinical studies have yet to be done demonstrating the ability to reduce candida levels in the intestinal tract and/or mitigate symptoms believed to be candida-related, enzyme preparations containing beta-glucanase and lysozyme may prove to be an effective adjunct to anti-candidal regimens.

Do chewable enzymes work as well as tablets or encapsulated enzymes?
The efficacy of an enzyme product depends on the types and potencies of the enzymes it contains. Chewable enzymes may contain the same types of enzymes found in non-chewable tablets or encapsulated products, but they are typically lower in potency in order to minimize possible irritation to the oral mucosa and also to accommodate other ingredients like flavors and sweeteners. Chewable enzymes are often a good choice for children and persons who have difficulty swallowing pills. Because of the lower potency, however, adults taking chewable enzymes may need to take more of the product to achieve optimal digestive benefits.

Can enzymes be taken with betaine hydrochloride?
Betaine hydrochloride, or betaine HCl, is often used to increase acidity in the stomach and thereby improve gastric protein digestion. It may also be used as a source of betaine (trimethylglycine) which acts as a methyl donor for important biochemical reactions in the body. It is

unclear to what extent betaine HCl reduces gastric pH, but, depending on how much is taken, it may possess sufficient acidity to deactivate pH-sensitive enzymes such as those contained in pancreatin. Fungal enzymes have a much wider pH tolerance[36,48] and thus their efficacy should not be adversely affected by the presence of betaine HCl.

Can people have adverse reactions to enzymes?

There are no reports of serious adverse effects with oral enzyme supplementation when used according to package directions. Some individuals may experience respiratory sensitivity to enzymes derived from Aspergillus organisms and should thus avoid inhalation of the powder when mixing capsule contents with foods or beverages.

Do enzymes interact with any drugs?

Some forms of proteolytic enzymes have been shown to reduce platelet aggregation[49] and so may theoretically potentiate the effects of anticoagulant medications such as Coumadin®. Proteolytic enzymes with DPP-IV activity may in theory interfere with DPP-IV-inhibiting drugs. Carbohydrases may increase the intestinal availability and absorption of glucose and could potentially interfere with the efficacy of oral hypoglycemic drugs or insulin.[50] While none of these effects have ever been reported in the medical literature, as a safety precaution, persons taking anticoagulants, anti-DPP-IV medications, oral hypoglycemic agents or insulin should consult with their healthcare providers before using an enzyme supplement.

Are there any contraindications to taking digestive enzymes?

There is a general perception that proteolytic enzymes may exacerbate preexisting damage to the esophageal, gastric or duodenal mucosa, but there are scant data in the medical literature to support this notion. One study from the mid-1980s found that bromelain could induce mucosal hemorrhage in the stomachs of rats whose gastric veins had been ligated in order to produce gastric congestion,[51] but it is entirely unclear whether these results can be extrapolated to humans under normal, or even most abnormal, physiological circumstances. In contradistinction, many practitioners have observed that proteolytic enzymes can be safely taken by persons with documented gastrointestinal lesions. As a precaution, however, persons with gastritis, active ulcer, gastroesophageal reflux disorder or known damage to the gastrointestinal mucosa may wish to consult with a healthcare provider before using supplements containing proteolytic enzymes. Persons with diabetes or a condition known as galactosemia should consult with a doctor before using an enzyme product as carbohydrases may increase the intestinal production and absorption of glucose and galactose.[52] Pregnant or nursing women should consult with a healthcare provider before using supplemental enzymes.

Persons with allergies should avoid enzymes derived from the food or substances to which they are allergic. The following chart should help clarify which types of enzymes to avoid.

If you are allergic or sensitive to:	Avoid this type of enzyme:
Pork	Pancreatin
Pineapple	Bromelain
Papaya	Papain
Figs	Ficain
Kiwi	Actinidain
Latex	Bromelain, Papain, Actinidain, Ficain
Aspergillus organisms	Fungal-derived enzymes
Saccharomyces organisms	Fungal-derived enzymes

Will enzymes with dipeptidyl peptidase-IV activity enable me to consume gluten-containing foods?

Dipeptidyl peptidase-IV (DPP-IV) has been shown *in vitro* to break down gluten peptides and may therefore be useful to persons with mild sensitivities to foods like wheat, rye or barley. It is unlikely, however, that an enzyme supplement with DPP-IV activity would be able to neutralize *all* the bioactive peptides found in a gluten-containing meal. Thus persons with frank gluten enteropathy, or celiac disease, should continue to avoid all foods known to contain gluten.

Can persons with glucose dysregulation, or taking anti-DPP-IV medication, use enzyme products that provide DPP-IV activity?

DPP-IV is an enzyme with multiple functionality in the body. In addition to being a brush border digestive enzyme, DPP-IV can also be found in the bloodstream and various tissues of the body.[53] One of the main activities of DPP-IV in the bloodstream is to deactivate two hormones known as glucagon-like peptide 1 (GLP-1) and glucose-dependent insulinotrophic peptide (GIP). These gut-derived hormones, also known as incretins, both potentiate insulin secretion by the pancreas and thus play an important role in blood glucose regulation. Persons with type 2 diabetes have been shown to have an impaired incretin response to glucose[54] and new types of antidiabetic drugs have recently been developed that either increase incretin activity in the body or inhibit DPP-IV inactivation of the incretins. Although it has never been reported in the medical literature or by physicians who utilize DPP-IV in clinical practice, supplementation with DPP-IV for digestive purposes may theoretically suppress incretin activity or interfere with anti-DPP-IV medications. As a precaution, persons with known disorders of glucose metabolism or those taking DPP-IV inhibitors should consult with a healthcare practitioner before using an enzyme product with DPP-IV activity.

Can digestive enzymes be used with probiotics?

The enzyme lysozyme is known to have a lytic effect on bacterial cell walls, but its impact, if any, on probiotic supplements is not known. Probiotic bacteria naturally synthesize and secrete a variety of digestive enzymes suggesting they are capable of surviving in an enzyme-rich environment. It may be prudent, however, to try and take the two products apart from each other wherever possible.

How should enzymes be stored?

Enzymes should be stored in a cool, dry place (59°F-85°F) away from direct light.

CONCLUSION

Extensive research on enzyme use in both animals and humans along with an understanding of human physiology provide a compelling case for supplementing with digestive enzymes. Throughout humankind's evolutionary history, protohumans subsisted primarily on raw plant and animal foods. These types of foods contain an abundance of enzymes which may play as important a role in human health as vitamins and minerals. Modern diets contain dramatically less enzyme activity due to cooking and heavy processing of foods and many prominent doctors and researchers over the last century have maintained that this loss of dietary enzymes may be a significant contributing factor to the degenerative diseases and poor health often experienced with aging. Compounding the problem, it is now clear that certain health conditions, including normal aging, can significantly reduce the capacity to synthesize and secrete enzymes.[55] Supplementing with digestive enzymes can compensate for reduced enzyme intake and the gradual decline in enzyme production with aging. The addition of enzymes to diets not only aids food digestion, but may help spare endogenous enzymes to perform important metabolic functions. Research over the last half century in both animals and humans confirms that supplemental enzymes can enhance macronutrient and micronutrient bioavailability and reduce the incidence and severity of gastrointestinal symptoms associated with poor or incomplete digestion.

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