Unique Features and Application of Non-Animal Derived Enzymes

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ABSTRACT: *Application of non-animal enzymes derived from Aspergillus and other microbial species may prove valuable in a broad range of conditions associated with digestive weaknesses such as pancreatic enzyme insufficiency, maldigestion, malabsorption, steatorrhea, lactose intolerance, celiac disease, and food sensitivities. Because of their inherent uniqueness, i.e., their ability to breakdown or hydrolyze physiologically and/or pathologically important substrates over a wide pH range, non-animal enzymes may be particularly well-suited for human use. Although these enzymes are microbially derived, modern filtration technology removes all microbial residue and allows for a clean and pure product. Their unique features and application are discussed.*

Most people will agree with the familiar adage, "You Are What You Eat," but few realize it promotes a principle that is somewhat flawed. In reality, "You Are What You *Assimilate.*" Even the healthiest of diets are without value if the body cannot properly digest and *assimilate* its nutrients. To that end, vital biological catalysts called enzymes (meaning "in yeast", since the first enzymes were discovered in yeast cells) break down protein, carbohydrates, and fats. Through this action they facilitate the digestive process and are essential to the body's absorption and full use of food.

Enzymatic activity begins in the mouth where salivary amylase, lingual lipase, and ptyalin initiate starch and fat digestion. In the stomach, hydrochloric acid activates pepsinogen to pepsin which breaks down protein, and gastric lipase begins the hydrolysis of fats. Most of digestion and absorption takes place in the small intestine and is mediated by pancreatic amylase, protease, lipase, and bile. Without proper enzyme production, the body has a harder time digesting food which may lead to a variety of chronic disorders.[1] (Table 1 lists specific enzymes and the substrate they breakdown.)

Table 1.   Specific enzymes that aid digestion and their respective substrates

Enzyme	Substrate
Amylase	Carbohydrates (starches and other polysaccharides)
Protease	Protein (large amino acid chains)
Peptidase	Peptides (smaller amino acid chains)
Lipase	Fats (triglycerides and other lipids)
Lactase	Lactose (milk sugar)
Cellulase	Cellulose (plant fiber)
Maltase	Maltose (malt sugar)
Invertase	Sucrose (table sugar)

• **Poor Digestion**

Several factors are known to contribute to the development of digestive problems. Poor eating habits, such as inadequate chewing of food, "eating on the run," or eating late in the day, can result in inadequate enzyme production. Certain dietary choices, such as excessive consumption of alcohol, refined carbohydrates and fat, as well as a high meat and cooked food diets with few raw, enzyme-rich foods may also place stress on the body's digestive capacity. In addition, problems with digestion can occur simply as a result of aging.[2] It is fairly common for elderly individuals to experience both a decrease in hydrochloric acid production as well as a general decline in digestive enzyme secretion.[2]

With an increasing aging population burdened with unhealthful diets and stressful life styles, it is likely that healthcare professionals will see more and more patients developing digestive problems. Currently, it is estimated that fifty-eight percent of the population suffers from some type of digestive disorder.[3] A lack of optimal digestive function associated with enzyme inadequacy may lead to malabsorption and a host of related conditions.

• **Naturally Occurring Digestive Enzymes**

Perhaps one largely overlooked factor that may contribute to problems with digestion may be the lack of raw, uncooked foods present in the average diet. Raw foods contain many enzymes that may help facilitate digestion. When they are eaten, mastication breaks down cell membranes allowing the release and activation of the naturally occurring enzymes present in the food. These enzymes may play a beneficial role by initiating the breakdown of the food and giving the body a head start on the digestive process.[4,5] Unfortunately, in this part of the world we tend to eat mostly cooked foods. When a food is cooked at 118° F or greater the natural enzymes are destroyed.

Even though cooking destroys these helpful, naturally occurring enzymes, it may not be reasonable to suggest that a

total raw foods diet is appropriate. For food safety reasons alone, this practice would not be advisable. Furthermore, some foods such as carrots and broccoli provide adequate nutrient value when cooked and may actually cause fewer gastrointestinal symptoms in patients who have difficulty digesting cellulose.[4-6] Inclusion of appropriate raw foods combined with enzyme replacement may be the most balanced and rational way to support those with digestive enzyme insufficiencies.

- **Enzyme Replacement**

In addition to consuming adequate levels of raw foods, a common approach to supporting the patient with digestive enzyme inadequacy is oral enzyme replacement. This entails providing enzyme supplements, whether they be animal or non-animal derived, in the quantity necessary to maintain adequate digestive capacity and facilitate absorption of essential nutrients. Oral enzyme replacement has proven to be helpful over many years of use.[7-11] In addition to the well known benefits associated with enzyme replacement, it has been suggested that oral supplementation with enzymes may have a sparing effect on the body's own digestive enzymes.[5,12]

Much like the enterohepatic circulation of bile, research has demonstrated the existence of enteropancreatic circulation of endogenous and/or exogenous digestive enzymes.[12] To elaborate, enzymes are secreted by the pancreas into the lumen of the intestine to participate in the digestion of protein, carbohydrates and fats. A portion of the enzymes are then absorbed intact across the intestinal wall and transported through the blood back to the pancreas. They are then taken up intact by pancreatic secretory cells and reserved for re-secretion in response to the next meal. This is called enteropancreatic circulation of digestive enzymes. It is suggested that oral enzyme supplementation may allow conservation of the body's own digestive enzymes by contributing to the pool of enzymes available for recirculation.[12] Further study must be conducted to confirm this concept and to determine whether this might reduce the level of modern day functional stress on the pancreas, might support organ regeneration, or may have any demonstrable health benefits.

The mainstay of the enzyme replacement approach has been the use of pancreatic enzyme supplements that provide proteases, amylases, and lipases derived from porcine (pork) pancreas. Despite their proven record of success, enzyme replacement with pancreatic enzyme supplements is associated with the following inherent limitations:

1. Pancreatic enzymes are susceptible to being destroyed by gastric acid and pepsin.[9,13] A pH sensitive enteric coating designed to dissolve above a pH of 5.5 to 6.0 has been applied to various forms of pancreatic enzymes in an attempt to protect them through the hostile environment of the stomach; yet, in clinical studies the coated supplements were even less effective than those uncoated.[8,10,11] The enteric coated supplements usually remained intact in the stomach but often failed to dissolve in the small intestine due to hyperacidity in the duodenum.[8,11]

2. Products with an extremely high level of pancreatic enzyme potency must be initially provided in the form of uncoated tablets to assure efficacy.[11] This is so the potency of the residual enzymes – that have not been destroyed in the stomach and have reached the small intestine – will be adequate to provide a digestive benefit.

3. The activity of pancreatic enzymes are dependent on the existence of specific pH levels in the small intestine that may be lacking in those with impaired health.[8,11]

4. They are not suitable for use by vegetarians.

- **Advantages of Non-Animal Derived Enzymes**

Oral supplementation with non-animal derived enzymes, such as microbial enzymes — those manufactured by a fermentation process of *Aspergillus,* for example — is associated with a number of inherent uniquenesses. They offer effective digestive support that works synergistically with, or as an alternative to, animal-derived enzymes and are free of some of the inherent limitations of conventional pancreatic enzyme supplements.[5] They provide a broad spectrum of digestive enzymes — protease, lipase, amylase, lactase, maltase, invertase, and even cellulase for aiding cellulose hydrolysis. One of the most functionally valuable attributes related to microbial enzymes is that they appear to possess unusually high stability and activity throughout a wide range of pH conditions (from a pH of 2-10).[8] This enables them to be more consistently active and functional for a longer distance as they are transported through the digestive tract.

It is important to note that these enzymes, although microbially derived, contain no microbial residue. Modern filtration technology allows for a clean and pure product, consisting strictly of enzymes.

- **Digestive Enzymes:**
  Assessment & Clinical Applications

Insufficient amounts of digestive enzymes can cause or exacerbate abnormal digestive conditions, such as maldigestion, food allergies or sensitivities, intestinal fermentation, putrefaction and peroxidation, and the phenomenon known as intestinal hyperpermiability, or "leaky gut." Some research suggests that microbial enzymes may support healthy digestion. They have been the subject of various studies evaluating their effects on lactose intolerance, pancreatic exocrine deficiency, steatorrhea, celiac disease and a variety of other digestive disorders.[5,8,9,14-16] Following is a simple overview of the primary symptom complex associated with digestive weakness, available assessment tools to target intestinal hyperpermiability, and the more common clinical applications of microbial enzymes related to digestive disorders:

Primary Symptom Complex[17-18]

- Indigestion and fullness lasts 2-4 hours after eating
- Bloating
- Excessive passage of gas
- Abdominal cramps, aches
- Difficulty gaining weight
- Roughage and fiber causes constipation
- Alternating constipation and diarrhea
- Undigested food and mucus in the stool

Laboratory Assessment of Digestion

The Complete Digestive Stool Analysis (CDSA) directly measures the pancreatic enzyme chymotrypsin and shows indicators of poor protein and fat digestion (valerate, iso-butyrate, triglycerides, fecal fat, cholesterol).[19] This profile also evaluates metabolic markers reflective of malabsorptive syndromes and cultures for normal and pathogenic bacterial species along with yeasts. Additional add-ons to the CDSA include extensive assays for parasites and amoeba, both of which are common causes of digestive symptoms.[20]

Other laboratory tests include breath tests for lactose intolerance and for overgrowth of bacteria in the upper gut. Patients may not be aware of the relationship of food intake to their symptoms, so testing confirms this relationship and helps distinguish between lactose intolerance and more general malabsorptive syndromes.[21]

Bacterial overgrowth is particularly an issue in patients who have taken medication to decrease production of gastric HCl or frequent antibiotic therapy, particularly the elderly whose production of HCl may already be suboptimal. This can be a significant factor that can impact nutrient absorption along with the creation of maldigestive-type symptoms. Bacterial production of hydrogen and methane are determined after a carbohydrate challenge. Excessive levels of these gases reflect overgrowth of bacteria in the upper gut.[22-24] Enzyme replacement can be an important support for patients challenged by this condition.

The capacity of the gut to permit absorption of nutrients while excluding pathogens and food antigens is largely dependent on the integrity of the gut lining. This quality, termed "intestinal permeability", can be determined easily by a simple lab study. Two test substances, lactulose and mannitol, are taken by mouth and their clearance through the body measured over time. Values of absorptive capacity and gut 'leakiness' to macromolecules are thus determined.[25] This measurement represents an evaluation of the body's ability to absorb nutrients and to maintain the barrier function of the gut, assisting with appropriate distinction between self and non-self for the mucosal immune system of the gut.[26]

Lactose Intolerance

The most widely recognized enzyme deficiency is lactose intolerance. It is relatively ethno-specific, affecting nearly 75% of African-Americans, Jews, Native Americans, and Hispanic-Americans. It is estimated that 90% of Asian-Americans are lactose intolerant as well.

Individuals who are lactose intolerant do not produce the enzyme lactase, which is responsible for breaking down sugars in dairy products. As a result, these sugars pass through the digestive system undigested often resulting in diarrhea, flatulence, bloating, cramping, and abdominal pain.

Prehydrolyzed milk, which has been treated with an enzyme derived from the *Kluyveromyces lactis* yeast, is used with great success by individuals with lactase insufficiency.[14] In addition, lactose maldigestion has been shown to improve in preschool children by the direct addition of lactase derived from the *Aspirgillus oryzae* to milk at mealtime.[15]

Fat Malabsorption

Fat malabsorption is characterized by an abnormal fecal secretion of fat (steatorrhea) which can lead to impaired nutrition by limiting the absorption of essential fats, fat-soluble vitamins, other vitamins, proteins, carbohydrates, minerals, and water. Fat malabsorption may be the result of several factors including inadequate digestive enzymes and bile salt secretion, diarrhea, infection, and mucosal cell abnormality.[27] Clinically, fat malab-sorption is most often associated with pancreatic exocrine deficiency, Crohn's disease, giardiasis and cryptos-poridiosis, lactose intolerance, and gliadin sensitivity.[27]

Oral supplementation of porcine-derived pancreatic enzymes is commonly recommended for those patients with maldigestion and malabsorption due to pancreatic insufficiency.[7-11] Interestingly, animal studies suggest that an acid-stable lipase derived from *Aspergillus* may be more effective than conventional pancreatic replacement in helping to improve fat malabsorption in subjects with pancreatic exocrine deficiency. [8,9,16]

In a placebo-controlled, randomized, cross-over study by Farndon, et al, an enzyme preparation from *Aspergillus oryzae* was studied to compare the effectiveness of conventional pancreatic enzyme therapy with that of acid stable microbial lipase in animals (dogs) with total pancreatic exocrine insufficiency.[8] Lipase from *A. oryzae*, with a potency of 4,800 LU's (lipase units) was compared against 60,000 LU's of lipase from pancreatin. The lipase from *A. oryzae* is stable at a wide range of pH from 2-10. It digests dietary fat beginning in the stomach and continuing in the small intestine. It is water soluble, heat stable, and non-toxic.

Significant improvements were seen in the form of reductions in both fecal fat and stool volume, with no significant difference between the microbial lipase and the pancreatin treated animals. The most striking finding was that 4,800 LU's of acid-stable lipase from *A. oryzae* was as effective as 60,000 LU's, or 12.5 times that amount, of conventional pancreatin.[8]

In another cross-over study, the effectiveness of acid-stable microbial lipase, enteric coated pancreatin, and conventional pancreatin were compared in 17 human patients experiencing chronic pancreatitis, exocrine pancreatic insufficiency and severe steatorrhea.[9] All three treatment protocols resulted in significant improvement with all patients becoming virtually symptom-free on each of the three treatment protocols. Similar to the study mentioned above, the results showed that 75,000 LU's per day of acid-stable microbial lipase was largely as effective as greater amounts of lipase from enteric coated pancreatin (100,000 LU's per day) and conventional pancreatin (360,000 LU's per day).[9] Its stability and activity throughout a wide range of pH conditions may have contributed to its significant effectiveness as seen in these two studies.

Leaky Gut and Food Allergies

While it was once held that the intestinal mucosa was an impenetrable barrier, it has been clearly demonstrated in human and animal studies that large molecular weight material is in fact absorbed intact, passing into the bloodstream after oral adminis-tration.[28-34] Some of the intact macromolecules shown to be absorbed include lactalbumin, ovalbumin, globulin proteins, ferritin, plant and animal enzymes such as bromelain and chymotrypsinogen, and even whole viruses.[33-40]

This phenomenon known as intestinal hyperpermeability, or leaky gut, is believed to play a role in the pathogenesis of a number of conditions, including inflammatory bowel disease, immune dysfunction, certain inflammatory disorders (e.g., arthritis), eczema, and food allergies.[28-32]

Proteins, and even smaller polypeptides, when absorbed intact can have significant effects in specific target tissues. For example, it is known that orally administered peptide hormones such as thytropin releasing hormone and luteinizing hormone are biologically active and manifest pharmacological effects in target tissues.[41-42] It has been extrapolated that, in patients with increased intestinal permeability, incomplete digestion of dietary protein allows macromolecular antigens to leak across the intestinal wall into the bloodstream. When absorbed they may trigger the body's defenses against exposure to what it perceives as foreign protein or polypeptide invaders, producing the symptoms of allergy.

Enzymes administered orally at meals may improve the digestion of dietary protein and, as a result, decrease the quantity of antigenic macromolecules leaking into circulation. Additionally, protease enzymes from *Aspergillus oryzae* appear to be absorbed intact following oral administration. It has been proposed that once in the bloodstream they may hydrolyze any previously

absorbed antigenic dietary proteins they encounter, potentially decreasing an allergic response.[30,32] Further research is needed to determine the role of enzymes in supporting patients with food allergies, but utilizing a variety of highly potent, acid-stable proteases, such as those derived from *Aspergillus oryzae* and non-animal derived peptidases may provide valuable protein and polypeptide digestive support.

Celiac Disease

The gliadin (carbohydrate) fraction of gluten found in wheat and other grains is known to be the cause of intestinal damage in celiac disease. Some research indicates that the amylytic enzymes derived from *Aspergillus* species can be used *in vitro* to remove the gliadin, markedly reducing its toxicity to Celiac disease patients.[16]

- **Proper Application of Non-Animal Derived Digestive Enzymes**

Since saliva is replete with amylase, the carbohydrate-digesting enzyme, proper chewing of food is an important first step in ideal digestion. But considerable evidence suggests that more can be done than just chewing our food thoroughly. Oral supplementation of digestive enzymes taken at mealtime may further assist digestion.

During the first portion of a meal, the food that is eaten is relatively free of stomach acids and endogenous enzyme activity. This predigestion phase is when food enzymes have the greatest opportunity to work. Like naturally occurring food enzymes, supplemental microbial enzymes–if taken just before eating–will have time to mix with the meal to help initiate the digestive process. As the pH level in the stomach plummets, most enzymes become inactivated. However, just because an enzyme loses its shape doesn't mean that it's forever useless. When inactivated enzymes enter the intestinal tract they encounter a more favorable pH environment, one that will allow at least some enzymes to resume activity. This seems to be particularly true of microbial enzymes derived from *Aspergillus* species. As previously mentioned, these enzymes appear to be remarkably stable, even when subjected to a highly acidic environment.

- **Other Guidelines for Optimal Digestion**

Other suggestions that may help improve digestion include relaxation. Taking several deep abdominal breathes prior to beginning each meal can be very effective. The next step is to chew more thoroughly to help liberate plant enzymes which help to predigest the food eaten. This may also have a sparing effect on the body's own digestive enzymes. Eating several small meals throughout the day rather than one or two large meals may also improve digestion considerably and is less likely to result in malabsorption if enzyme levels are low or borderline. For patients with compromised digestion (the most common signs being gas, bloating, fluid retention, diarrhea, constipation, and gastritis), natural enzyme supplementation may provide further support by helping to breakdown carbohydrates, fats, and proteins, allowing the body to absorb nutrients more effectively.

- **A Note of Precaution**

Oral administration of digestive enzymes are generally without adverse effects in most individuals, however, they are not intended for use in patients with gastric or duodenal ulcer. If any burning sensation or gastric irritation occurs after the use of any digestive enzyme, the patient should discontinue its use, take an antacid, and contact their health care practitioner.

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