TECHNICAL REPORT

The use of Enzymes as Digestive Aids in Clinical Practice

Natural Health Products Directorate (NHPD)
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The objective of this report is:

1. To review and report on all primary human data with respect to fungal oral enzyme therapy as it relates to digestive purposes. Furthermore, to provide recommendations in support of safety and efficacy of specific enzymes with respect to a digestive aid purpose.

2. To provide opinion substantiated by evidence of clinical experience in support of the safety and efficacy of specific enzymes with respect to digestive purposes.

3. Provide opinion regarding a previous regulatory decision and its significance with respect to how enzymes are used in a clinical practice.

4. Provide an opinion regarding risk labeling related to the following: disease/conditions, drug/food interactions, known adverse reactions, and long-term/continuous use.

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1. Introduction

The primary human data for enzymes derived from fungal sources for digestive purposes is scarce in the scientific literature. Conversely, enzymes derived from animal sources; namely amylase, protease and lipase have a robust collection of published human studies. Specifically, pancreatic enzyme therapy (amylase, protease, lipase) has been evaluated in humans to treat steatorrhoea associated with chronic alcoholic pancreatitis, HIV and cystic fibrosis (Vecht et al. 2006; Stern et al. 2000; Brady et al. 2006; Delhaye et al. 1996; Colombo et al. 2009; Carroccio et al. 2001; Wooldridge et al. 2009; Delchier et al. 1991). Given the record of safety and efficacy of enzymes derived from animal origin, enzymes of fungal origin may be erroneously assumed to have equal or similar clinical efficacy and safety. Additionally, label claims relating to digestive benefit is of great concern in the absence of level one evidence displaying appropriate safety and efficacy.

The mandate of the present project is to "indentify and determine evidence that can be used to support safety and efficacy of fungal derived enzymes for purposes of digestion" to support the body of work completed in the NHPD issue analysis summaries (Precleared evidence for fungal enzymes (Aug 18 2008), and Minimum Evidence Requirements for Fungal Digestive Enzymes (Oct 22 2008). Individual templates for all enzymes requiring opinion accompany this document.

2. Human research using fungal sourced enzymes (amylase, protease and lipase)

After extensive review of the scientific literature there is insufficient data to declare fungal sourced enzymes as safe and efficacious for digestive purposes as monotherapy, with a few exceptions. In combination, amylase, lipase and protease derived from fungal sources have been compared in clinical efficacy/safety to animal sources of amylase, lipase and protease in the treatment of pancreogenic steatorrhoea. Specifically, fungal enzymes were evaluated for clinical efficacy in 17 adults with chronic pancreatitis and exocrine pancreatic insufficiency (M. U. Schneider et al. 1985). In this comparative analysis 'Nortase' a European product containing fungal enzymes was consumed by a test group at a combined daily dose of 10 capsules/d for a 72 hour duration. In 10 capsules, this fungal formula yielded 75, 000 U lipase as described by Desnuelle *(Rhizopus arrhizus),* 100, 000 U protease (*Aspergillus oryzae*) as described by Anson and 7,000 U amylase (Aspergillus oryzae) in accordance with FIP (M. U. Schneider et al. 1985).

The authors concluded that fungal sourced enzymes were of equal efficacy in reducing fecal fat content to that of animal sourced enzymes and "all the pancreatic enzyme preparations led to a significant reduction in total fecal fat excretion/day". No side effects were reported by the subjects in the study during the 72 hours. This is the only study found utilizing a combination of fungal derived amylase, protease and lipase in a diseased population reporting a measurable outcome related to digestion in humans.

In healthy adults without disease, pancreatic amylase, protease and lipase from animal origin has been shown to decrease bloating, gas and abdominal pain after consuming a high fat and high carbohydrate meal (Suarez et al. 1999). However fungal enzymes in healthy adults have not been evaluated.

2.1. Fungal amylase

There is insufficient level one or two evidence to declare efficacy or safety for purposes of digestion. Refer to section 3.0. for comments regarding combination with protease and lipase.

2.2. Fungal protease

Proteases from *Aspergillus oryzae, Aspergillus niger/ Rhizopus niveus* were evaluated in an open label study to determine if the addition of proteases to whey protein concentrate (WPC) could increase protein absorption over a WPC control group not treated with protease. The product 'Aminogen' (Triaroco Industries) was added to 50 grams of WPC (measuring 42.5 grams of protein) following an overnight fast (Oben et al. 2008). Doses in the two trial groups were: 2.5 grams of protease (125 SAP *Aspergillus niger or Rhizopus niveus,* 62,000 HUT *Aspergillus oryzae*) or 5 grams of protease (250 SAP Aspergillus niger or *Rhizopus niveus* and 250,000 HUT *Aspergillus oryzae*). Blood samples were collected at 0 hr, 0.5 hr, 1 hr, 2 hr, 3 hr, 3.5 hr and 4 hr for amino acid and C-reactive protein analysis. The results revealed a postprandial total serum amino acid level 2.2 and 3.5 times above the control group (Oben et al. 2008). Refer to protease template for further data.

2.3. Fungal lipase

The therapeutic potential of an acid- resistant fungal lipase prepared from *Aspergillus niger* was administered with a fatty meal to 10 adults with steatorrhoea from cystic fibrosis. This fungal lipase was also compared in 10 other subjects with steatorrhoea against two conventional lipase products from animal origin (Zentler-Munro et al. 1992).

The fungal lipase had no effect on fecal weight or on the coefficient of fat absorption, while the animal derived lipases decreased fecal fat excretion (Zentler-Munro et al. 1992). The authors suggested that the fungal lipase administered passed intact through the gastric acid, but had limited lipolytic effect in the duodenum. Some explanations may be due inhibition via bile of the fungal lipase or the lack of combined protease promotes binding of bile acids to undigested proteins and reduces the solubility of the products of fat digestion in bile acid micelles. The four capsule dose of fungal lipase was suggested to be equivalent in enzymatic activity to the animal based lipase (Zentler-Munro et al. 1992). The authors suggested that a reason other than dose influenced the lack of efficacy.

3. Other enzymes

3.1. Bromelain and papain

Historically, the term "proteolytic" has been used when describing both bromelain and papain. Both substances have a long history of laboratory use due to their ability to cleave a variety of proteins at variety of amino acid sequences (e.g. immunoglubulins, T-cell receptors) used in scientific research related to immunobiology (Ratia et al. 2008; Yang et al. 2010; Siniakov et al. 1979; Richard M Epand & Raquel F Epand 2002).

Both bromelain and papain in combination have substantial evidence for uses completely unrelated to digestion. Refer to enzyme templates for other uses beyond digestion. Level one data for bromelain or papain for digestive purpose is limited. This well known limitation is illustrated in a comment almost 20 years ago suggesting that bromelain is ineffective as a proteolytic enzyme in the duodenum (Zentler-Munro et al. 1992). *"The pineapple produces an acid-resistant protease-bromelains-but inclusion of this enzyme in pancreatic enzyme supplements has not been shown convincingly to improve protein absorption, and this enzyme is no longer in use"* (Zentler-Munro et al. 1992). No dosage of bromelain or papain can be declared safe or effective for digestive purposes using level one and two data.

Papain has been used to treat a rare condition called phytobezoars. A phytobezoar is a plant fibre concretion that is found in the gastrointestinal tract. Phytobezoars usually occur in patients who have undergone gastric surgery and have delayed gastric emptying (E. L. Baker et al. 2007). However, this is a rare indication for any consumers of digestive enzyme products and is merely included here for completeness. Optimal dosages and enzyme activity are unknown due to the rarity of this indication (Zarling & Moeller 1981; Dugan et al. 1972; E. L. Baker et al. 2007).

3.2. Cellulase, Hemicellulase, Glucoamylase, Maltase, Pectinase, Xylanase

There is insufficient level one and two evidence to declare efficacy or safety for purposes of digestion. These enzymes are not routinely prescribed by experts in natural medicine (ex: Naturopathic Doctors), and they are not presented as therapeutic options in the curricula of naturopathic medical schools. Indeed it is not clear what therapeutic goal has caused these enzymes to be added to enzyme formulas.

3.3. Pepsin

There is insufficient level one and two evidence to declare efficacy or safety of pepsin for purposes of digestion. Pepsin has been used in the product 'Spasmocanulase' distributed by Novartis pharmaceuticals, however due to the presence of multiple agents in the product it is unknown if the antispasmodic effects are related to pepsin. (Mohamed et al. 2002).

3.4. Beta- glucanase

In a recent study, beta-glucanase from *Tricoderma reesei* was mixed with oat bran to study the effects of viscosity on post-prandial insulin, glucose and several hormones known to influence satiety. Blood samples from those consuming a liquid meal treated with beta-glucanase displayed increased insulin, increased plasma glucose and changes in hormones related to satiety. Dosage used in study was 0.2 grams = 140,000 BU (Juvonen et al. 2009).

3.5. Phytase

Phytase has been studied in humans as an enzyme to increase iron absorption. High doses of phytic acid found in plant material are known to inhibit iron absorption *in vivo*. Phytase from *Aspergillus niger* has been added to food products to increase the bioavailability of iron in adults and infants (Sandberg et al. 1996)(R F Hurrell et al. 1998; Davidsson et al. 1997; Sandberg et al. 1996; Zhang et al. 2007; Thacher et al. 2009; Troesch et al. 2009).

3.6. Invertase/sacrosidase

Invertase/sacrosidase is limited to use in congenital sucrase-isomaltase deficiency (CSID) (Lücke et al. 2009; Treem et al. 1993; Treem et al. 1999). Refer to section 5.0. regarding safety of products containing invertase/sacrosidase.

3.7. Alpha-galactosidase

Fungal sources of alpha-galactosidase and lactase have the highest level of clinical efficacy and safety established for the purposes of digestion of all the enzymes requiring an opinion (Ganiats et al. 1994; Levine & Weisman 2004; Di Stefano et al. 2007). Higher dose and chronic use of alpha-galactosidase from *Aspergillus niger* poses a few concerns related to diabetes and genetic galactosemia. Fabry's disease is not an indication for use of oral alpha-galactosidase as treatment of Fabry's is with intravenous route of delivery (Whybra et al. 2009; Mehta et al. 2009). For further details regarding dose and safety, refer to the alpha-galactosidase template.

3.8. Lactase

The use of lactase in infant formulas and in adults to treat lactase deficiency is well established. Level one data most often cites *Aspergillus oryzae* as the fungal source of lactase (Portincasa et al. 2008;

Medow et al. 1990; Lin et al. 1993; Sanders et al. 1992; Barillas & Solomons 1987; DiPalma & Collins 1989; Tan-Dy & Ohlsson 2005; Vaillancourt et al. 2009). For further details regarding dose and safety refer to the lactase template.

4. Recommendations for fungal enzyme efficacy

No label claim for digestive purposes should be accepted based on level three to level five evidence. The enzymes with level one data where a label claim is acceptable include: 1. Fungal protease; 2. Fungal amylase, lipase and protease in combination; 3. Fungal alpha-galactosidase; 4. Fungal lactase. Specific label claims for the use of invertase/sacrosidase as monotherapy for the treatment of CSID is warranted. However, the product Sucraid would most likely be prescribed by a physician after diagnosis of CSID. In practice, phytase is rarely if ever prescribed orally as a treatment to increase the bioavailability of various metals. Given phytase's ability to increase absorption of iron and zinc, those products containing the dose of phytase to cause such increase would be contraindicated in those with certain genetic blood disorders (e.g. thalassemia, hemochromatosis). Refer to phytase template for doses used to achieve increased bioavailability of iron and zinc.

Comparatively, the health claim "May aid digestion" is no more acceptable than "Stomachic" or "Digestive tonic". These health claims are vague and leave room for misinterpretation. In the absence of level one or two data, marketing/efficacy claims such as "May help arthritis" or "May help cancer" would be equally unacceptable. Replacing a specific pathology-based claim with a vague physiology-based claim does not diminish potential harm. In addition, there is a danger that consumers may interpret a physiology-based claim as in implied endorsement that a product is safe for chronic, long-term use.

Generally, from a clinical perspective, enzymes are prescribed for occasional use and short duration, unless the enzyme/s is being used to treat a diagnosed deficiency or disease (e.g. CSID, lactase deficiency) under medical supervision. If an enzyme/s has met the criteria for level one or two data, the duration of use should be clearly labeled "For occasional use", "For long-term use consult a healthcare provider" on the product.

In clinical use, bromelain is rarely if ever prescribed to treat patients with digestive concerns. As described in the submitted template, bromelain's use in the literature and in clinical practice is predominantly as an anti- inflammatory, most notably for the treatment of pain/inflammation associated with osteoarthritis. Based on the lack of evidence for any measurable outcome related to digestive purposes, no digestive health claim is warranted for bromelain.

5. Recommendations for fungal enzyme safety

It could be argued that the historical use of digestive enzymes in the supplement market has a strong safety record with minimal reported side effects. However, this safety record may be an artifact of the questionable use of cellulase, hemicellulase, pectinase, phytase and invertase in many products. Colloquially known as "fairy dusting", the addition of these enzymes may increase the apparent safety profile, but fails to meet any efficacy standard.

To any reasonable level of accuracy, the safety of most enzymes in oral form for digestive purposes is unknown in long term use. Research conducted for the purposes of digestion varies from 24-72 hours (refer to enzyme templates) with some research on non-digestive purposes extending up to 7.5 weeks (Braun et al. 2005). Theoretically in healthy adults, chronic use of digestive enzymes may down regulate endogenous enzyme production.

Oral enzymes have not been shown to be safe in pregnancy or breast feeding. As many enzymes can liberate free glucose from complex polysaccharides, there are always theoretical risks in pregnancy.

Additionally, almost all enzymes evaluated in this project had some occupational allergy risk (specifically, a host of IgE mediated reactions - refer to templates). A universal label warning for all enzyme products is warranted. These include: 1. A warning for the potential of allergic reaction and to stop usage if this occurs. 2. Clear labeling that the product has not been evaluated in pregnancy or breast feeding and may not be safe. 3. The product is for occasional use with food, and chronic use should be supervised by a healthcare provider.

The insufficient data from level one evidence and the mixed side effects observed in clinical practice prevent the accurate recommending of which enzymes and which doses may interact with medication, food or other natural health care products. There is potential risk of additive or inhibitory effects when combining some multi-vitamins that contain digestive enzymes with other enzyme products (e.g. Wobenzym). Furthermore, most published level one data have subjects discontinue medication during the trial period.

From a clinical perspective, the following scenarios are of greatest concern when working with patients suffering from digestive disorders: 1. Papain or bromelain use at any dose in those with gastric lesions. 2. Any enzyme capable of hydrolysis of complex polysaccharides used in those with diabetes or those with impaired fasting glucose 3. Use of digestive enzyme products along with Wobenzym or other poly-enzyme 'anti-inflammatory' products.

With respect to the enzymes requiring an opinion, no clear evidence of anti-coagulant effects or fibrinolytic effects were found with enzyme research relating to digestion. Outside of research relating to digestion, it appears that there is some concern regarding increased bleeding risk with chronic use of bromelain (Gläser & Hilberg 2006)(Heinicke et al. 1972) and to a lesser degree papain (Hellebrekers et al. 2000). Additionally, the concern regarding bromelain increasing the absorption of certain antibiotics has been discussed in the literature. (Renzini & Varengo 1972; Maurer 2001; Komiya 1986).

Given the magnitude of risk, and the potential to do harm, label warnings on products containing bromelain or papain are justified. The dose at which bromelain can cause harm is difficult to predict with any degree of accuracy. The individual variability in self prescribed dosing along with individual doses of prescribed medications (e.g. aspirin, clopidogrel) make a prediction on interaction virtually impossible. To solve this, it is recommended that a label warning indicating possible "blood thinning" effects should be implemented irrespective of dose. Such label warnings should include "If you are on blood thinning medication consult a healthcare provider before using this product".

Based on clinical experience, fungal protease enzymes (section 2, 2.2.) alone or in combination with fungal amylase and fungal lipase appear safe for self-care when used occasionally for relief of symptoms.

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