

Actinizyme™ and Protein Digestion

ACTINIZYME™



SCIENCE PERFECTED IN MARKET

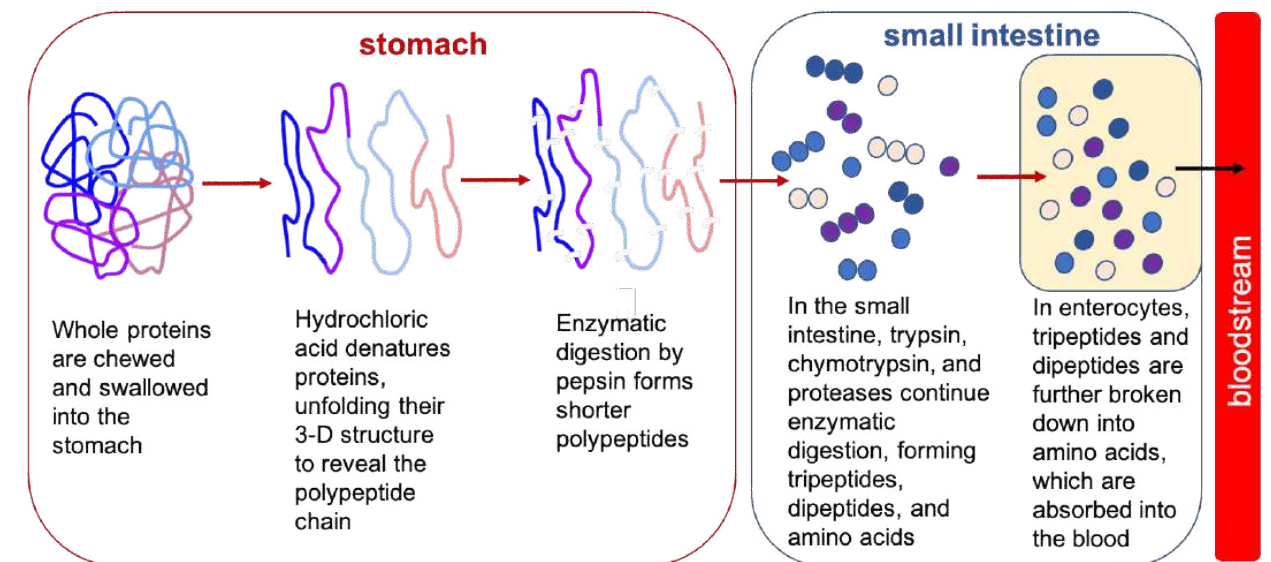

Anagenix.



Synopsis

Digestion is a process that converts nutrients from ingested food into forms that can be absorbed by the gastrointestinal tract.

Proteins are a valuable source of amino acids, which are used to build several vital compounds. The process of converting proteins into amino acids is mainly controlled by protease enzymes.



Protein intolerance is a disorder that is the result of an adverse effect of the ingestion of food proteins. It is also defined as the inability to digest or effectively break down amino acids.

Bloating and flatulence are cardinal symptoms of food intolerance, and enzymatic support is a rational approach to promote digestion and support gut comfort.

Actinizyme™, which is a whole green kiwifruit powder, contains large amounts of the highly active proteolytic enzyme, actinidin.

Together with animal proteins, actinidin is known to promote the digestion of plant proteins like gluten. Actinidin promotes the digestion of pea proteins as well, which has become a very attractive source of proteins for vegans.

Actinizyme™ is a high-quality powder ingredient derived from New Zealand Green Kiwifruit, proven to be effective in supporting digestion and supporting bowel regularity and providing occasional constipation relief.

The benefit of using the whole kiwifruit is that it provides an "entourage" effect arising from all bioactives within the fruit.



The Physiology of Digestion

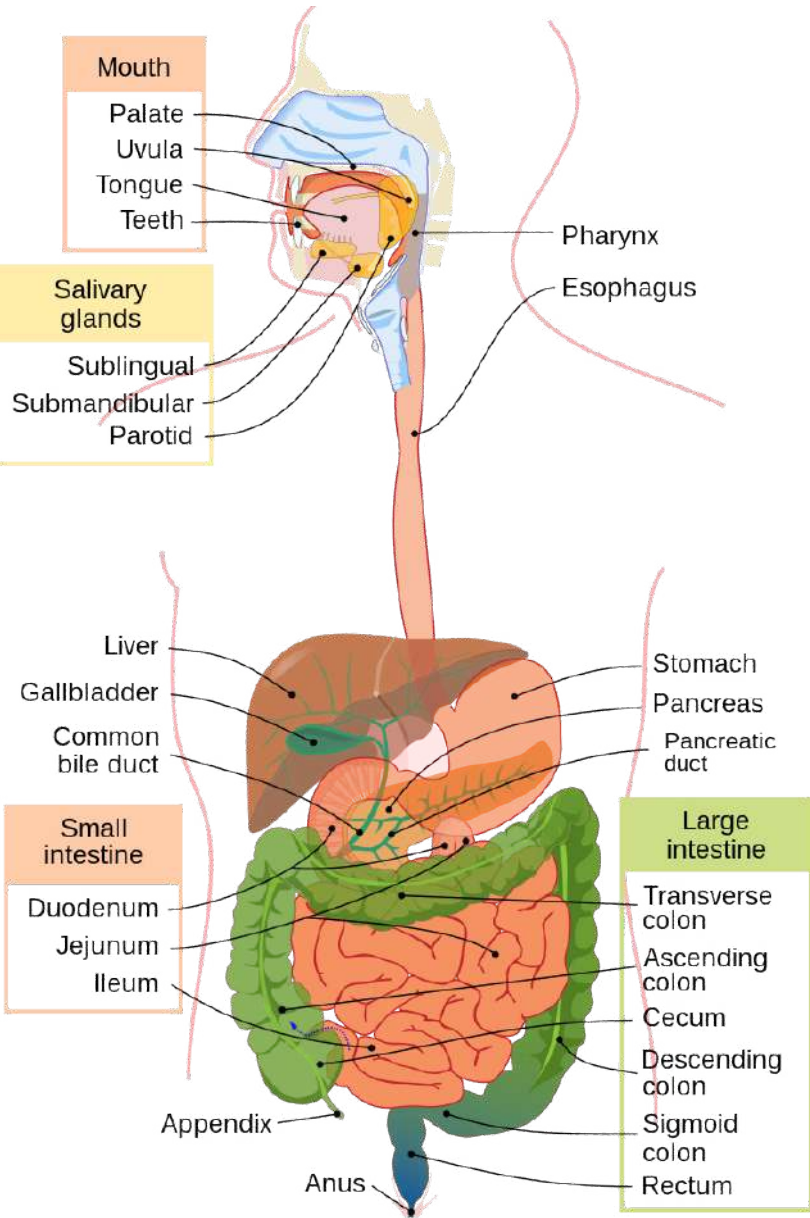


Figure 1. The digestive system
https://en.wikipedia.org/wiki/Human_digestive_system

Digestion is the process of mechanically and enzymatically breaking down food into substances for absorption into the bloodstream. Food contains three macronutrients that require digestion before they can be absorbed: fats, carbohydrates, and proteins. Through the process of digestion, these macronutrients are broken down into molecules that can traverse the intestinal epithelium and enter the bloodstream for use in the body. Digestion is a form of catabolism or breaking down of substances that involves two separate processes: mechanical digestion and chemical digestion. Mechanical digestion involves physically breaking down food substances into smaller particles to undergo chemical digestion more efficiently. The role of chemical digestion is to further degrade the molecular structure of the ingested compounds by digestive enzymes into a form that is absorbable into the bloodstream. Effective digestion involves both processes, and defects in either mechanical digestion or chemical digestion can lead to nutritional deficiencies and gastrointestinal pathologies.

Through the gastrointestinal/digestive system (Fig. 1), the nutritional substances, minerals, vitamins, and fluids, enter the body. Lipids, proteins, and complex carbohydrates are broken down into small and absorbable units (digested), principally in the small intestine. The products of digestion, including vitamins, minerals, and water, cross the mucosa and enter the lymph or the blood (absorption).

Digestion of the major food macronutrients is an orderly process involving the action of a large number of digestive enzymes. Enzymes from the salivary and the lingual glands digest carbohydrates and fats, enzymes from the stomach digest proteins, and enzymes from the exocrine glands of the pancreas digest carbohydrates, proteins, lipids, RNA, and DNA. Other enzymes that help in the digestive process are found in the luminal membranes and the cytoplasm of the cells that line the small intestine. Enzymatic action is promoted by

hydrochloric acid (HCl), which is secreted by the stomach, and bile from the liver.

The majority of chemical digestion occurs in the small intestine. Digested chyme from the stomach passes through the pylorus into the duodenum. Here, chyme will mix with secretions from both the pancreas and the duodenum. Mechanical digestion will still occur to a lesser extent. The pancreas produces many digestive enzymes, including pancreatic amylase, pancreatic lipase, trypsinogen, chymotrypsinogen, procarboxypeptidase, and proelastase¹. These enzymes are separated from the acidic environment of the stomach and function optimally in the more basic environment of the small intestine where the pH ranges from 6 to 7 due to bicarbonate secreted by the small intestinal epithelia. Importantly, the duodenum also contributes several digestive enzymes such as disaccharidases and dipeptidase. The disaccharidases include maltase, lactase, and sucrase. Maltase cleaves the glycosidic bond in maltose, producing two glucose monomers; lactase cleaves the glycosidic bond in lactose, producing glucose and galactose; and sucrase cleaves the glycosidic bond in sucrose, producing glucose and fructose. Dipeptidase cleaves the peptide bond in dipeptides. Pancreatic amylase breaks down starch into glucose. Pancreatic lipases break down dietary fats into long chain fatty acids. Pancreatic trypsin, chymotrypsin, carboxypeptidase and elastase break down a variety of peptide bonds from longer proteins, remove terminal amino acids from longer chains and remove the acidic groups from amino acids, respectively. Thus, the digestive process has converted macronutrients into forms that are absorbable into the bloodstream for bodily use.

Digestion is a process that converts nutrients in ingested food into forms that can be absorbed by the gastrointestinal tract. Proper digestion requires both mechanical and chemical digestion and occurs in the oral cavity, stomach, and small intestine. Additionally, digestion requires the secretions from accessory digestive organs such as pancreas, liver and gallbladder.

Proteins from food are essential for health, but requirements vary, depending on a person's age, activity levels, body weight and other factors². Most people should aim for a maximum of 2 grams of protein per kilogram body weight per day.

The recommended dietary allowance (RDA) for protein depends on factors such as:

- Age
- Gender
- Pregnancy and breastfeeding
- Activity levels

Some people, such as elite athletes with high protein synthesis demands, may be able to eat as much as 3.5 g protein per kg of body weight daily without any side effects. However, most research indicates that eating more than 2 g per kg of body weight daily of protein for a long period of time can cause health problems.

Symptoms associated with too much protein include:

- Intestinal discomfort, bloating and indigestion
- Dehydration
- Unexplained exhaustion
- Nausea
- Irritability
- Headache
- Blood vessel disorders
- Liver and kidney injuries

Protein Digestion and Absorption

When you eat food, the body's digestive system breaks down dietary protein into individual amino acids, which are absorbed and used by cells to build other proteins and a few other macromolecules, such as DNA. Let's follow the path that proteins take down the gastrointestinal tract and into the circulatory system³.

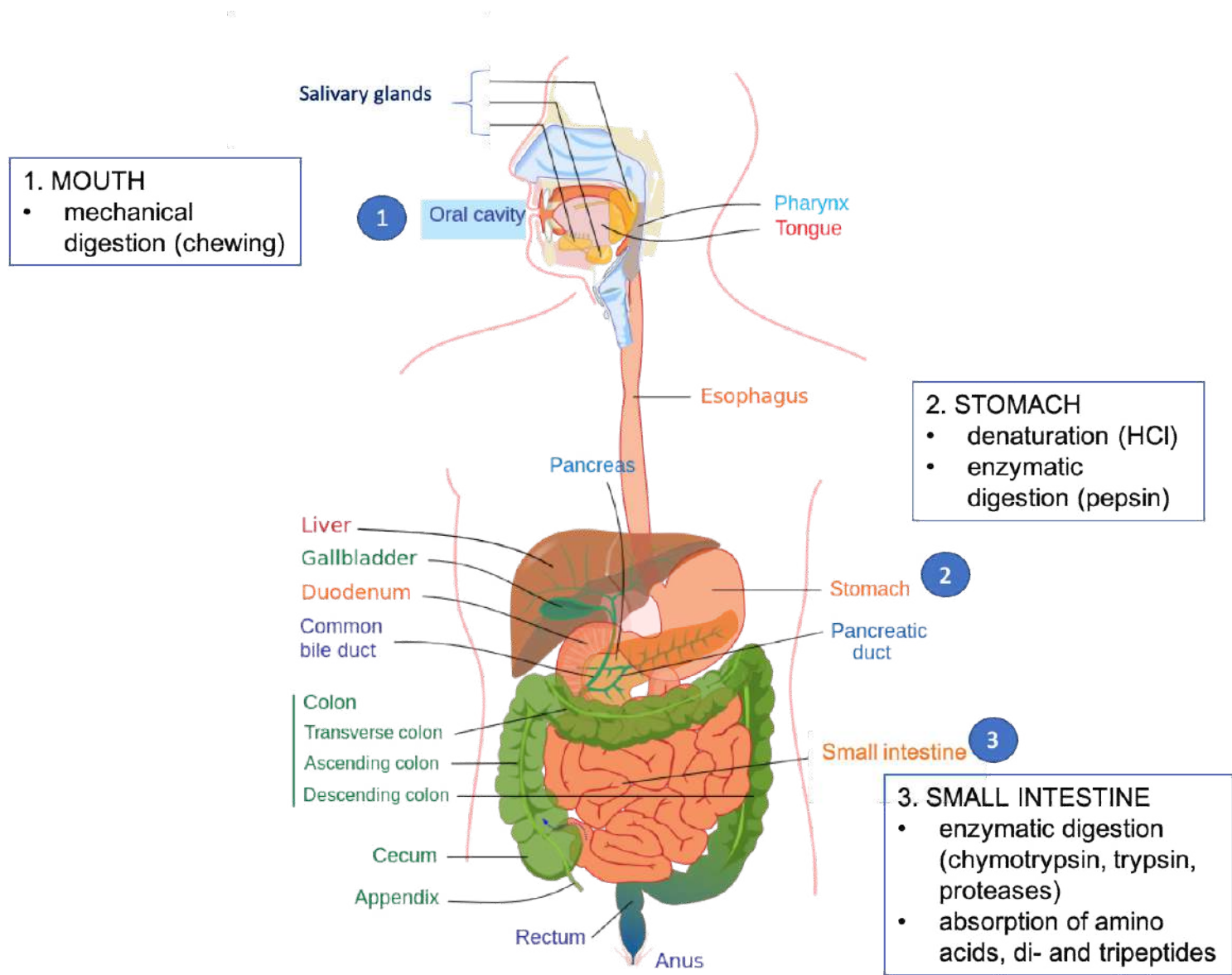


Figure 2. Protein Digestion in the human GI tract³

The first step of protein digestion is mechanical breakdown which is performed by the teeth in the mouth. From there, chewed food heads to the stomach where the acidity causes food proteins to denature, unfolding their three-dimensional structure. This is the first step of chemical digestion of proteins.

Proteins are large globular molecules, and their chemical breakdown requires time and mixing. Protein digestion in the stomach takes a longer time than carbohydrate digestion, but a shorter time than fat digestion. Eating a high-protein meal increases the amount of time required to sufficiently break down the meal in the stomach. Food remains in the stomach longer, making you feel full for longer, and potentially can lead to a feeling of overfullness, bloating and discomfort.

The two major pancreatic enzymes that digest proteins in the small intestine are chymotrypsin and trypsin. Trypsin activates other protein-digesting enzymes, all collectively called proteases, and together, these proteases break proteins down into peptides (short chains of amino acids) and to amino acids (the building blocks of proteins or polypeptides). The cells that line the small intestine release additional enzymes that also contribute to the enzymatic digestion of polypeptides.

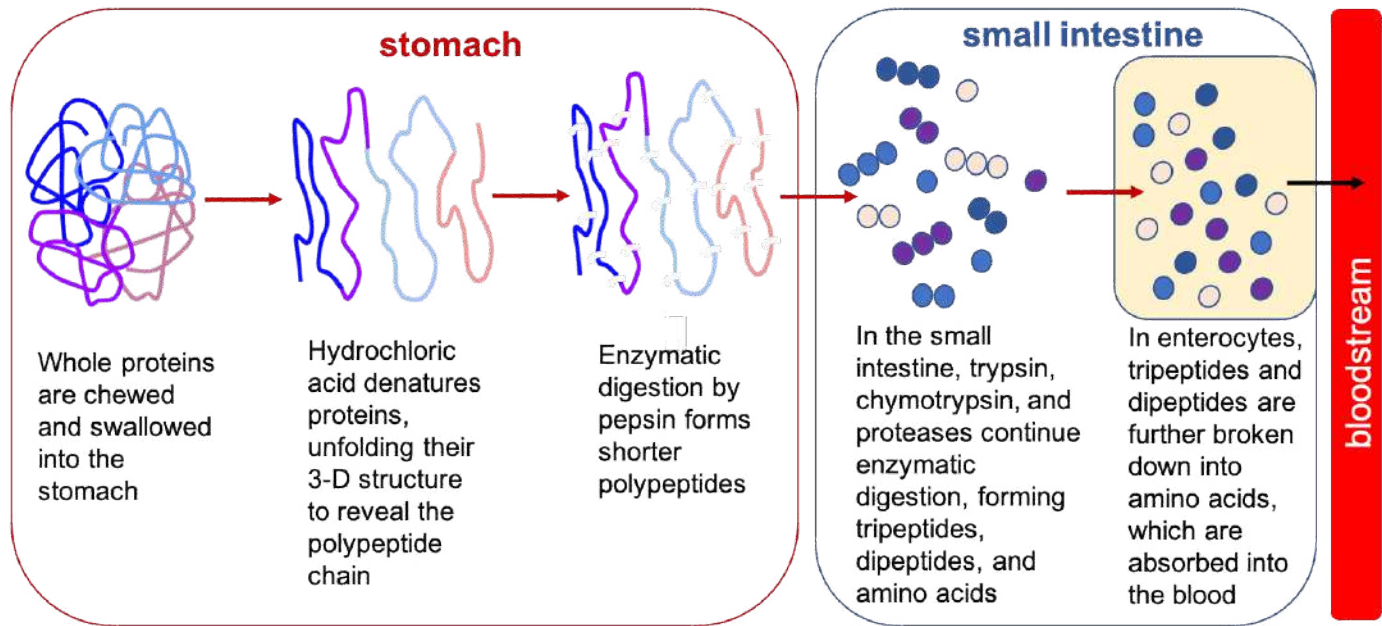


Figure 3. Summary of Protein Digestion³

patients mostly present with gastrointestinal manifestations. In non-immunological food protein intolerances, the amount of food ingested tends to be more directly related to the severity of symptoms. Excessive intestinal gas, bloating, abdominal pain, and diarrhea are common presenting symptoms. Whereas, in immunological food protein allergies, even trace amounts of the sensitized food protein can trigger an explosive reaction and may involve the skin and blood vessels. The immunological reactions occur within minutes to an hour of food protein ingestion, and symptoms can range from skin rashes, urticaria, angioedema, wheezing, to anaphylaxis, whereas non-immunological mediated reactions may occur in hours to days.

Bloating and flatulence are cardinal symptoms of food intolerance. Enzymatic support is a rational approach to promote digestion and support gut comfort.

Proteases: Multifunctional Enzymes in Life and Disease

Proteases likely arose at the earliest stages of protein evolution as simple destructive enzymes necessary for protein catabolism and the generation of amino acids in primitive organisms⁵. For many years, studies on proteases focused on their original roles as blunt aggressors for protein demolition. However, the realization that, beyond these nonspecific degradative functions, proteases act as sharp scissors and catalyze highly targeted and specific reactions of proteolytic processing, producing new protein products, inaugurated a new era in protease research. Thus, proteases regulate the fate, localization and activity of many proteins, modulate protein-protein interactions, create new bioactive molecules, contribute to the processing of cellular information, and generate, transduce, and amplify molecular signals. As a direct result of these multiple actions, proteases influence DNA replication and transcription, cell proliferation and differentiation, tissue morphogenesis and remodeling,

angiogenesis, neurogenesis, ovulation, fertilization, inflammation, immunity, etc. Accordingly, many proteases are a major focus of attention for the pharmaceutical industry as potential drug targets or as diagnostic and prognostic biomarkers⁵.

Our interest is proteases from edible plants which can supplement our own digestive proteases by providing additional protease specificity and activity to improve digestion and reduce protein-based food intolerance.



Kiwifruit

Kiwifruit are enjoyable to eat. They are also a good source of minerals, dietary fiber, and they are a most effective laxative. Their outstanding nutritional quality is their very high content of vitamin C⁶. There is very little, if any, loss of nutritional quality during long-term storage or ripening even if the overall appeal and quality of the fruit deteriorates. They have rapidly become popular amongst consumers, there are novel and new cultivars coming on the market, they are available in a range of colors and flavors, and they can mostly be stored for remarkably long periods of time under refrigerated and controlled atmospheric conditions.

Internally, the fruit are very attractive with dark seeds in a green to dark-green flesh (*Actinidia deliciosa*) or flesh which ranges from green to lime-green to a clear golden-yellow (*A. chinensis*). In both species there may also be attractive red pigmentation in the inner pericarp. The external appearance and the fruit flesh of some species change color during ripening.



Actinidin

Kiwifruit, and in particular, the green Hayward variety, contain large amounts of the highly active proteolytic enzyme actinidin, which is somewhat similar to the proteases found in other fruits such as pineapple, figs, or papaya.

Dietary Fibers

Kiwifruit contain about 2-3% dietary fiber due to pectins and other oligosaccharides and polysaccharides that are not broken down and absorbed in the small intestine. A 100 g serving of kiwifruit will therefore supply about 10% of the recommended daily requirement.

Laxatives

Kiwifruit are famous for promoting gentle laxative benefits. Individuals vary in their response. Consumption of large numbers of fresh fruit could have an excessively vigorous purgative effect and the laxative effect can limit the number of kiwifruit some people are able to eat in any one day. Fresh kiwifruit or dried kiwifruit products are often used to maintain regularity of bowel movements, especially for older and sedentary people such as hospital patients who lack the mobility required to support proper gut motility. Clinical data supports the daily consumption of kiwifruit and kiwifruit powders to increase numbers of complete spontaneous bowel movements in healthy people suffering from occasional constipation.



Actinidin

Actinidin is a plant protease obtained from kiwifruit with a molecular weight of 23.5 kDa and contains 220 amino acids. Actinidin represents up to 40% of the soluble protein in green kiwifruit. The enzyme was first described in 1959 but thus far, actinidin has only been sporadically assessed for applications in the dietary industry.

Effect on Dairy Proteins

Actinidin has been used to hydrolyze proteins in Whey Protein Isolate (WPI) and Milk Protein Concentrate (MPC) to reduce immunoreactivity of lactoglobulin and casein. The allergenic nature of milk proteins limits their use in food products for some parts of the population. Allergenicity is due to the presence of epitopes: specific amino acid sequences in the primary and secondary structures of proteins/peptides which trigger immune responses. Proteolysis can disrupt linear and conformational peptide epitopes and is one of the approaches to reduce antigenicity of milk allergens⁷.

Actinidin is also able to substantially reduce the antigenicity of casein and lactoglobulin in a time and temperature manner. The results of a study published by Kaur et al.⁸ indicate that milk protein hydrolysates obtained by actinidin had reduced levels of antigenicity due to modifications of protein conformation or cleavage and masking of conformational and linear epitopes of the tested antigens. It could therefore be used in applications where reduction of allergenicity is required.

Kaur et al. also evaluated the effects of actinidin on various milk proteins⁹ showing that actinidin appears to prefer whey proteins over caseins as its substrates, making it an attractive candidate for high whey proteins consumers like athletes.

Puglisi et al. also investigated the role of actinidin in the hydrolysis of cream milk proteins. The results indicate that actinidin retains the ability to degrade the casein fractions in the presence of cream fat up to 5%¹⁰.

These activities of actinidin indicate the use in solubilizing milk proteins, thereby improving the functionality of milk proteins (such a solubility, heat stability, foaming stability and overrun) in different foods.

ACTINIZYME™



Effect on Other Food Proteins – Soy, Meat, Cereals/Grains

Chalabi et al. investigated the proteolytic activities of kiwifruit actinidin on different fibrous and globular proteins¹¹. They investigated the proteolytic activity and substrate specificity of actinidin on native proteins. Herein, the proteolytic activity of actinidin was compared to papain on several different fibrous and globular proteins under neutral, acidic and basic conditions.

The researchers found that actinidin has narrow substrate specificity, with the highest enzymatic activity for the collagen and fibrinogen substrates. Collagen is a major fibrous component of extracellular connective tissue such as skin, tendon, blood vessels and bones. Most of the previous studies showed that the triple helix of collagen is resistant to many proteolytic enzymes including pepsin, trypsin and papain and only it is sensitive to cleavage by collagenases. Despite the resistance of collagen to many proteases, actinidin showed a good collagenolytic effect on this substrate.

Actinidin's suitable specificity makes it a useful enzyme for targeting specific applications.

Further studies have found actinidin enhances protein digestion in the stomach and small intestine using an in vitro digestion model. Two in vitro studies^{12,13} reported the effect of actinidin on the digestion of several proteins derived from soy, meat, milk and cereal under stimulated gastric conditions or followed by stimulated intestinal conditions. They treated the substrates with actinidin after treatment with pepsin and gastric pH (stimulating gastric digestion) or with pancreatin at small intestinal pH. They found that under stimulated gastric conditions, kiwifruit extract containing actinidin enhanced the digestion of some food proteins, including caseins, soy protein, and beef muscle.

Moreover, the effect of actinidin on the digestion of food proteins was determined in vivo in animals. In rats and pigs, actinidin was found to enhance the gastric digestibility of beef muscle protein, gelatin, soy protein and gluten and increase the rate of stomach emptying^{14,15,16}.

Together with animal proteins, actinidin is known to promote the digestion of plant proteins like gluten, again reducing its allergenicity¹⁷. Kaur et al. has also published a paper showing that actinidin promotes the digestion of pea proteins, which has become a very attractive source of proteins for vegans¹⁸.

An Effective Digestive Aid

For many years the economics of production of actinidin were not considered favorable. However, ongoing research into methods of extraction and possible use of actinidin has contributed to improved production and an increase in demand for the enzyme¹⁹.

Actinidin is also an effective aid for the relief and prevention of indigestion and constipation²⁰. Unlike most conventional indigestion remedies, actinidin boosts the protein-digestive activity of the stomach rather than altering the pH. It is thought that many of the disruptive events that cause the digestive system to malfunction do so by disrupting the natural release of specific enzymes essential for normal digestion. Actinidin can help supplement the body in situations where its own natural enzyme mechanism is malfunctioning. Taken prior to meals, actinidin helps to prepare, activate, and accelerate natural digestive reactions. In doing this, it helps to establish the body's own biological balance thus ensuring proper functioning digestion and eliminating the symptoms of indigestion.

Actinidin has been proposed as a digestive aid, and in vitro and in vivo experimental trials support enhanced protein digestion in the stomach and small intestine.

Actinizyme™ Nature's Digestive Support

Actinizyme is a high-quality powder ingredient derived from New Zealand Green Kiwifruit, proven to be effective in supporting digestion and bowel regularity and providing occasional constipation relief.

The benefit of using the whole kiwifruit is providing an “entourage” effect arising from all bioactives within the fruit and kiwi is well-regarded for its nutrient adequacy.

EFSA (European Food Safety Authority) has recently approved that the “consumption of 2 whole kiwifruit (*Actinidia deliciosa* var. Hayward) contributes to the maintenance of normal defecation.”²¹

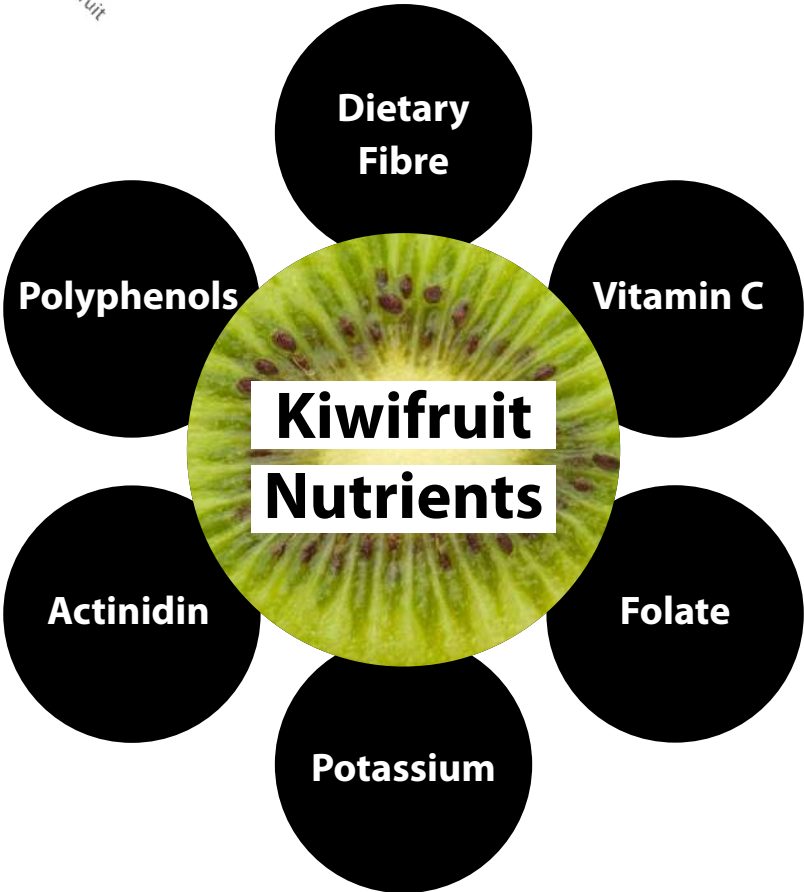
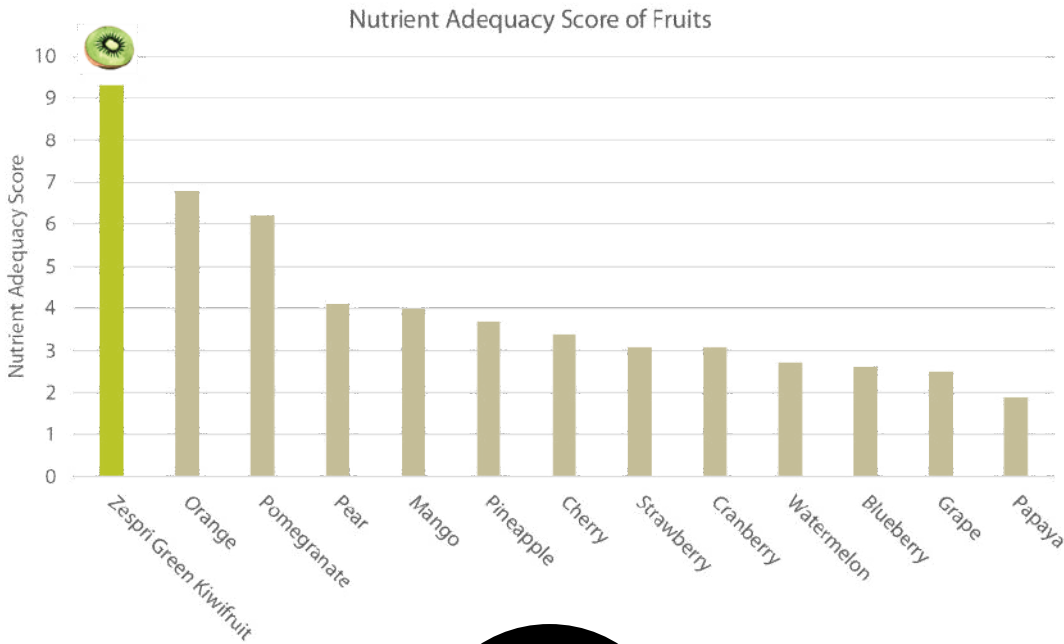
600 mg of Actinizyme™ is **functionally equivalent** in terms of digestive health properties and the maintenance of normal defecation, to 2 whole green kiwifruit.

- Actinizyme is freeze-dried, green kiwifruit (*Actinidia deliciosa* var. Hayward).
- In 2 clinical trials, 600 mg of Actinizyme resulted in a statistically significant increase in stool frequency of 0.6 – 1.4 stools/week^{22,23}
- EFSA concluded that a cause-and-effect relationship has been established between the consumption of 2 whole green kiwifruit and the maintenance of normal defecation.

- EFSA considered the evidence from 6 clinical trials which showed that ≥2 whole green kiwifruit increased stool frequency by 0.5 – 2 stools/wk.
- The magnitude of effect of 2 whole green kiwifruit on stool frequency is equivalent to that shown with 600 mg of Actinizyme in several clinical studies.



Kiwifruit - Packed full of Goodness



Actinizyme® - clinically proven for occasional constipation relief

The first clinical was conducted in New Zealand with 29 participants and published in 2015.

The second clinical was performed in North America with 83 participants and is publication pending.

Actinizyme® and Actinidin

Actinizyme® contains the kiwifruit-unique protease called actinidin which was highlighted in this monograph. Actinidin strongly enhances the digestion of:

- Dairy proteins: casein, whey
- Animal meat proteins (beef, chicken, and fish)
- Collagen
- Plant proteins including:
 - Wheat gluten
 - Pea
 - Almond
 - Soy
 - Rice
 - Hemp
 - Tofu
 - Quinoa



Health Benefits of Enhanced Protein Digestion with Actinizyme®

Together with promoting digestive support, proteins are more effectively broken into amino acids, which in return promotes more rapid absorption.

The more rapidly available amino acids can be utilized for:

- Building: proteins are an important building block for bones, muscle, cartilage, hair, skin, and nails.
- Repairing: proteins are used to build and repair tissues.
- Oxygenating: red blood cells need protein to carry oxygen through the body.
- Digesting: enzymes are proteins and they help to digest food and make new cells and chemicals.
- Regulating: proteins are used in hormone regulation. Many hormones are proteins too.

**Reduces
Bloating
and
Discomfort**

Actinizyme® a holistic solution for digestive health and wellbeing

Enhances protein digestion

Supports bowel regularity by gently facilitating laxation

Supports digestive comfort

Improves stool form

Increases Quality of Life parameters in constipated persons

SynbioGUT – The Synbiotic Solution for Digestive Discomfort

Synbiotics are defined by the ISAPP as:

“A mixture, comprising live microorganisms and substrate(s) selectively utilized by host microorganisms that confers a health benefit on the host”

At Anagenix we have developed a turnkey synbiotic solution with IFF strains and our kiwifruit powder which promotes digestion and supports bowel regularity. We are currently working with several probiotic companies to deliver further turnkey solutions.

Actinizyme® made from non-GMO New Zealand green kiwifruit is a holistic and functional food ingredient that is clinically proven to promote bowel regulatory and contains enzymes promoting the digestion of proteins. The whole fruit concept provides the “entourage” effect of several biological compounds such as:

- Enzymes
 - Actinidin: a proteolytic enzyme promoting protein digestion
- Dietary Fibers
 - Complex kiwifruit pectin
 - Hemicellulose
 - Cellulose
- Phytochemical
 - Polyphenolic compounds
- Vitamins
 - Vitamin C
 - Vitamin E
- Minerals
 - Potassium

How Actinizyme can help providing a better environment for probiotics

- Food for prebiotic growth: kiwifruit pectin is a highly methoxylated pectin which is gently fermented through the colon promoting bacterial diversity and increase in SCFAs.
- Increases mucus: Actinizyme improves gut leucine and mucus synthesis and mucus secretion, which creates a favorable environment for anaerobic bacteria like *F. prausnitzii* and *A. muciniphila*.
- Reduce inflammation: antioxidants in Actinizyme like Vitamin C and Vitamin E and polyphenolic compounds (e.g. epicatechin), neutralize reactive oxygen species to reduce inflammation.

Our Turnkey Solution – HOWARU Green

- Actinizyme® green kiwifruit powder 600mg
- *Bifidobacterium lactis* HN019 1B CFU

The medicinal rationale behind this synbiotic is based on the synergistic effect of Actinizyme on indigestion and bowel regularity together with the beneficiary effect of HN019 in improving bowel movements. Actinizyme also has the ability to support the growth of HN019 by up to 193% (Table 1).

***Bifidobacterium lactis* HN019 promotes digestive comfort and helps to relieve occasional constipation²⁴.**

Actinizyme is proven to relieve constipation and promotes the digestion of proteins to prevent indigestion and flatulence.

Other Actinizyme Synbiotic Concepts Starting with a Low Dose of 25 mg per Billion cfu of Probiotics

In addition to HN019, Actinizyme has been shown in vitro to support the growth of other commercial probiotic strains, including *Lactobacillus* and *Bacillus* species (Table 1). Growth can be achieved with 25 mg of Actinizyme per billion cfu of probiotic.

Table 1: Probiotic strains that grow on Actinizyme and their potential health benefits

Probiotic	% growth with Actinizyme ¹	Potential health benefits
<i>Bifidobacterium lactis</i> HN019	193%	Gastrointestinal and immune health - improves intestinal transit time and reduces GI symptoms
<i>Lactobacillus rhamnosus</i> HN001	136%	Women’s (maternal) health including immunity for mum and baby, postnatal mental health, vaginal health and protection against gestational diabetes
<i>Bifidobacterium lactis</i> BB12	16%	One of the most clinically studied strains for constipation. Also evidence to support oral health, immune health and healthy cholesterol levels
<i>Bacillus coagulans</i> SC208	12%	Supports gastrointestinal and immune health

Unique Value Proposition

Actinizyme contains actinidin which enhances the digestion of proteins.

Actinizyme contains soluble and insoluble fibers promoting bowel regularity.

Actinizyme supports the growth of commercially available probiotics with a low dose of 25 mg per billion cfu.

Stability reports proves the shelf-life of this synbiotic.

The convenient dosage of 600 mg of Actinizyme makes it perfect to design several finished dosage forms.

¹ As shown in in vitro assays. Report available upon request.



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