Supplementary α-galactosidase reduces risk of development of flatulence and other gas-related symptoms

In this white paper, we (see names of authors at end of paper) summarize the available scientific literature on the activity of α-galactosidase and its use as a food supplement to reduce risk of development of gas-related symptoms. With this work, we aim to inform healthcare professionals such as medical doctors, dieticians, and caretakers on the use, mechanism of action, and scientific convention of α-galactosidase.

Executive Summary:

Excessive flatulence and other gas-related symptoms are experienced by approximately 10-30% of the global adult population. In irritable bowel syndrome (IBS) patients, a syndrome that affects the intestines, this can be as high as 90%.[1] Physical discomforts aside, these symptoms have extensive social consequences, such as embarrassment or anxiety, because of the sounds and smells associated with excess flatulence. Various types of hard-to-digest foods can trigger excessive flatulence and other intestinal discomforts. Amongst food constituents causing digestive challenges are gluten and lactose, as well as members of the Raffinose Family Oligosaccharides (RFOs), found in legumes. RFOs are short chains (oligomers) of sugar molecules that have been shown to lead to flatulence when they are digested by bacteria that live in the colon. As such, RFOs form a significant risk factor in the development of gas-related complaints. Digestion of RFOs in the small intestine to prevent them from reaching the colon can be achieved by ingesting a dietary supplement providing α-galactosidase. When used as a supplement, α-galactosidase reduces said risk factor by breaking down RFOs before they reach the colon, which, in turn, can provide relief in individuals who are sensitive to such food components and decrease the rate at which excessive flatulence is developed.

Why α-galactosidase?

RFOs are short chains consisting of 3-6 sugar building blocks most prominently found in legumes but also in tubers and leaves (**Figure 1**). Plants containing high levels of RFOs include legumes such as peas, soybean, chickpeas, lentils, and broccoli. Some of the most common RFO-containing foods and their RFO contents are listed in **Table 1**. Raffinose Family Oligosaccharides (RFOs) contribute to the development of flatulence and gas-related symptoms after bacterial fermentation in the colon. For this reason, researchers have investigated the possibility of breaking down RFOs before they reach the colon.[1] Supplementary α-galactosidase, an enzyme that breaks down RFOs, can do exactly that.

α-Galactosidase breaks down short chains of sugars in the small intestine. This limits bacterial fermentation of RFOs in the colon, thus lowering the risk of flatulence.

History of α-galactosidase as a supplement

Early research

As excessive flatulence can be a nuisance for individuals with decreased tolerability of certain food constituents, researchers carried out studies to discover what causes flatulence. During the 1960s, scientific interest went out mainly to perceived flatulence-causing ingredients, such as beans. To better understand the effect beans diets had on the formation of intestinal gas, scientists analyzed different types of beans and found that they caused different levels of flatulence-related symptoms.[2] After establishing this effect, the hunt was on for the specific components in the bean that cause flatulence. Researchers tried to identify such components by removing nutritional components from flatulence-causing foods one by one.[3] Finally, this experiment demonstrated that legumes from which RFOs were removed caused less flatulence. These initial findings sparked interest in a better understanding of RFOs as risk factors contributing to flatulence and how to mediate their effect.

Supplementation with α-galactosidase started around 30 years ago.

First commercial breakthrough

After the identification of RFOs as a risk factor in the development of gas-related symptoms, the next step was to devise a method to break down RFOs after ingestion. For this, supplemental use of the enzyme used by bacteria to break down RFOs in the colon, α-galactosidase, was an obvious candidate.

The first commercially available dietary supplement containing this enzyme was initially formulated as a solution.[4] Clinical trials demonstrated the efficacy of this solution in some individuals as an efficient way to reduce the risk of gastrointestinal discomfort caused by RFOs.[5]

Dosing

Individuals experiencing intestinal discomfort because of sensitivity to RFO containing foods, a dose of 300-1200 α-galactosidase units* with or after each RFO-rich meal can alleviate the effect of these risk factors. α-Galactosidase supplementation may be used more than once daily. The biological source of the enzyme used for supplementation is typically isolated and purified from a strain of the *Aspergillus niger (A. niger)* fungus.

Mechanisms of interaction

Fermentation of RFOs in the GI tract

Early experiments show that RFO fermentation in the colon is an important cause of flatulence. The intestines house many bacteria and other small organisms, such as fungi, that digest components of food, including those that humans have trouble with breaking down. Together, these organisms are called the 'gut microbiome'. The contribution of the gut microbiome to general health gains more and more recognition, and a healthy microbiome is linked to reducing the risk of diseases such as obesity, type 2 diabetes, inflammatory bowel disease, Alzheimer's disease, schizophrenia, and many more.[6] In addition to their contribution to health, bacteria in the intestines can also cause undesirable effects, such as the fermentation of excess or "undigestible" food constituents. Fermentation of such constituents is typically accompanied by the production of gas. For example, in lactose-intolerant individuals, high concentrations of lactose build up in the intestines. Fermentation of the lactose by bacteria in the colon then leads to the excessive production of gas and other intestinal discomforts.[7] In unaffected individuals, human lactase breaks down lactose in the small intestine where its components are absorbed. This way, the lactose levels remain low enough to not cause any trouble. A similar process is at play in individuals that experience discomfort after the consumption of RFOs: when RFOs enter the colon, fermentation can cause intestinal discomfort and flatulence.

Table 1 - Dry-weight RFO content in common legumes and other vegetables.[13–16]

Food	*RFO content (%)*
Pigeon pea	7.7 - 8.2
Lupin	5.9
Chickpea	5.5 - 35
Peas	5.3 - 10.6
Black gram	4.3 - 7.8
Soybean	3.9 - 10.6
Lima bean	3.8
Mung bean	3.3 - 8.2
Artichoke	3.1
Scallion	3.1
Cowpea	3.0 - 7.9
Lentil	2.5 - 5.5
Garlic	2.2
Broad bean	2.2 - 2.7
Garlic spring	1.7
Parsnip	1.0
White Onion	0.9
Fennel	0.7
Chicory	0.7
Beetroot	0.5
Broccoli	0.4
Kohlrabi	0.4
Wheat flour	0.2 – 0.7

Stability and activity of α-galactosidase in the gastro-intestinal tract

After ingestion, α-galactosidase moves through the stomach into the small intestine where it shows most of its enzymatic activity. Despite the acidity of the stomach (low pH) and the more alkaline intestines (high pH), α-galactosidase stays intact after ingestion during meals.[8,9] The enzymatic activity of α-galactosidase varies in these different conditions, with the highest activity in the upper intestines.[10,11] To optimize RFO digestion by α-galactosidase, ingesting α-galactosidase during meals is recommended for 2 reasons:

1. When ingested with RFO-rich food simultaneously, α-galactosidase can immediately start breaking down RFOs in its vicinity.
2. Ingestion of a meal temporarily raises the pH of the stomach and keeps digestive agents, such as protease, busy, preserving stability of α-galactosidase.

Foods with high RFO contents include chickpeas, peas, lentils, and artichokes.

α-Galactosidase breaks down RFOs

RFOs, which include raffinose, stachyose, and verbascose, consist of 1, 2 and 3 galactose building blocks, respectively, linked together and to a sucrose (glucose & fructose) molecule with so called α-galactosyl bonds. The α-galactosidase enzyme cuts these bonds specifically, which means that any RFO can be digested into sucrose and galactose(s) by α-galactosidase (**Figure 1**). Contrary to RFOs, the remaining sucrose and galactose molecules can be easily absorbed and digested by the human body.

**One enzymatic unit (1 U) represents the amount of α-galactosidase that breaks down one micromole of RFO per minute.*

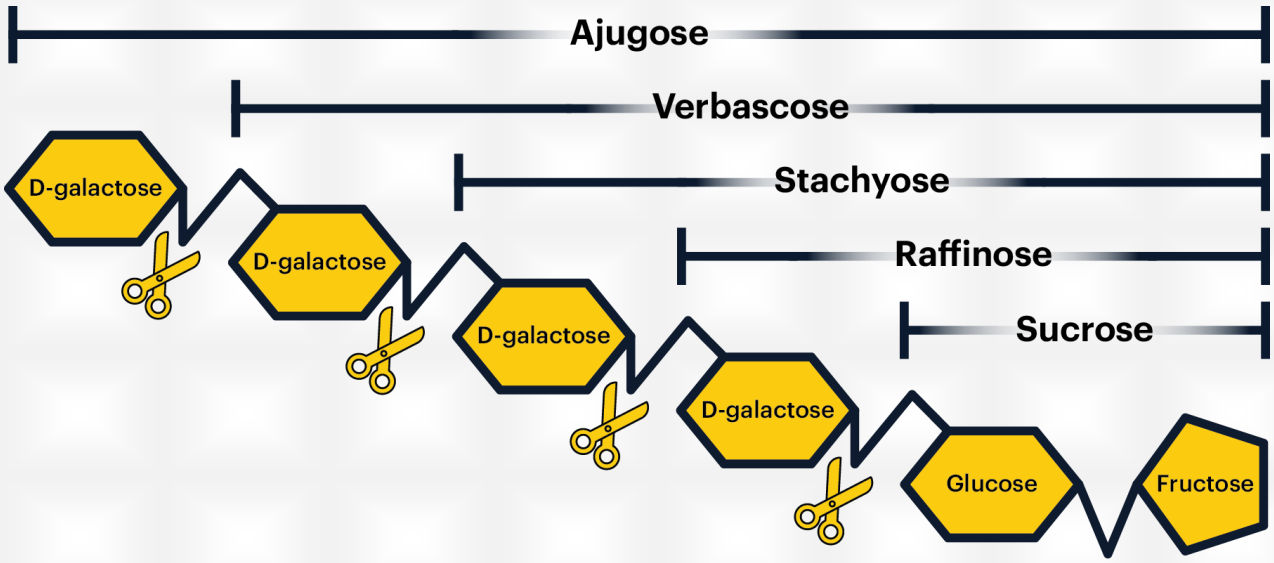

Figure 1 - *Members of the RFO family and sucrose. All α-galactosyl bonds that can be hydrolyzed by α-galactosidase are indicated by scissors.*

Supplemental α-galactosidase breaks down RFOs before they reach the colon

The primary purpose of α-galactosidase supplementation is to reduce the number of RFOs reaching the colon. α-Galactosidase breaks down RFOs into smaller sugar molecules, such as galactoses and sucrose (**Figure 1**). Invertase subsequently breaks down sucrose into glucose and fructose. The small intestines absorb free galactose, glucose, and fructose quickly, which makes these nutrients unavailable for bacterial fermentation in the colon. This leads to reduced fermentation and therefore a reduction in excessive gas production.

α-Galactosidase in other biological contexts

α-Galactosidase is a commonly occurring protein that is present in many animal, fungal and bacterial species. Bacteria use it to break down polysaccharides, as does *A. niger*, a strain of which is the industrial source for most α-galactosidase supplements.

Although humans can make α-galactosidase, it is not present in the intestinal lumen. Human α-galactosidase has a role in the lysosome, an organelle of the cell. A lysosomal deficiency in α-galactosidase is the hallmark of the X-linked Fabry Disease.[12] Fabry Disease is a lysosomal storage disease leading to renal, cardiac and neurological complications. The body does not absorb supplemental α-galactosidase into the bloodstream and therefore supplemental use of the enzyme does *not* contribute to treatment of symptoms of Fabry Disease.

Regulatory background

In the USA, *A. niger* is a GRAS (Generally Recognised As Safe) species authorized by the Food and Drug Administration (FDA). GRAS is a FDA-regulated label which is awarded to any substance considered safe for use in the production of substances used in the food industry. Likewise, *A. Niger* has been approved as safe by the European Food Safety Authority (EFSA) in the production of the aforementioned substances. In Europe, a health claim for the reduction of risk in the development of excessive flatulence invoked by α-galactosidase supplementation is pending, while awaiting an assessment by the European Food Safety Authority (EFSA).

Fermentation of 5 grams of raffinose produces 300 ml of flatus.

Scientific and clinical evidence

Evaluation methods

The reduction of the risk of excessive flatulence and/or other gas-related symptoms has been the subject of several clinical studies. Most of these studies are randomized controlled clinical trials, which means that a) the effect of α-galactosidase is compared to a control treatment (usually a placebo) and b) that the groups receiving α-galactosidase or placebo are comparable with respect to personal characteristics such as age, sex and symptom status.

Clinical effect of α-galactosidase is assessed by measurement of gas production. In the studies included, gas production is monitored in one or more of the following ways:

(1) Measurement of physical passing of gas.
(2) Assessment using questionnaires.
(3) Estimation of gas production using MRI.
(4) Assessment of breath hydrogen.

Supplementation of 300-1200 units of α-galactosidase during RFO-rich meals reduces the risk of developing gas-related symptoms.

On top of this, evaluation of α-galactosidase in other research settings has provided more detailed insights of properties such as activity and stability. Such experiments include measurement of enzyme activity and stability, physiological effect (flatulence, breath volume and content, body weight etc.) in animals and determination of the raffinose and stachyose content of the intestines.

Pertinent evidence

Supplemental α-galactosidase is shown to be *stable* in stomach conditions, and optimally *active* in conditions of the small intestine.[19] This would enable breakdown of RFOs before these are fermented in the colon, thereby contributing to gas-related symptoms. A number of randomized, controlled trials study such effect of supplemental α-galactosidase on the risk of gas-related symptoms in humans. Out of a total of nine trials in the past thirty years (between 1994 and 2021), five report regular supplemental use of at least 300 units of α-galactosidase taken with meals. Four of these studies report that periodic supplementation with α-galactosidase reduces the severity of gas related symptoms such as flatulence and bloating.[1,20–22] One of the latter studies shows effectiveness of high doses of α-galactosidase when the use of an RFO-rich diet is not established in the study protocol.[23] Single dosing of α-galactosidase was studied in two trials. Single dosing after a RFO-rich meal may provide a benefit to sensitive individuals but the effect was shown to be less consistent [24,25]. Finally, doses below 300 units of α-galactosidase do not result in a consistent desired effect.[5]

In animals, the digestion of RFO increases between 2.7 to 4 fold in animals when administering α-galactosidase as a supplement.[9,26,27] Correspondingly, diets with higher levels of RFO are shown to increase the production of gas in humans and rats.[3,18] Fermentation of 5 grams of raffinose may result in up to 300 ml of flatus.[17]

Combined, the pertinent evidence from clinical studies shows clinical efficacy of α-galactosidase supplementation to reduce the risk on the development of flatulence and other gas-related symptoms after consumption of an RFO-rich meal. In these studies a dose of 300-1200 units of α-galactosidase ingested per RFO-rich meal was used.

Currently ongoing research

The clinical efficacy of α-galactosidase is currently the subject of study in one clinical trial (NCT05520411), where the effect of a combination of enzymes is evaluated in individuals with high risk of gas-related symptoms.

Key takeaways

- α-Galactosidase has a history of almost 30 years of use as a food supplement.
- RFOs, such as raffinose and stachyose, are a risk factor in the development of excessive gas production and other gas-related symptoms.
- A dose 300-1200 α-galactosidase units with or after each meal can significantly reduce these risk factors.
- Supplementary α-galactosidase breaks down RFOs before they reach the colon.
- With appropriate dosing before or during meals, α-galactosidase is clinically shown to reduce the risk of formation of excessive gas.**

Authors and contribution

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***EFSA health claim currently awaiting approval*

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