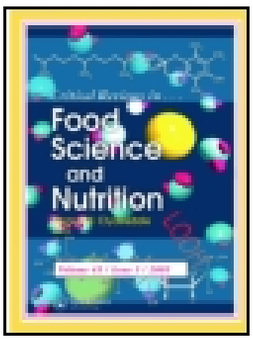

Taylor & Francis
Taylor & Francis Group

Critical Reviews in Food Science and Nutrition

ISSN: (Print) (Online) Journal homepage: https://www.tandfonline.com/loi/bfsn20

A head-to-head comparison review of biological and toxicological studies of isomaltulose, d-tagatose, and trehalose on glycemic control

Emilia Sokołowska, Anna Sadowska, Diana Sawicka, Izabela Kotulska-Bąblińska & Halina Car

To cite this article: Emilia Sokołowska, Anna Sadowska, Diana Sawicka, Izabela Kotulska-Bąblińska & Halina Car (2021): A head-to-head comparison review of biological and toxicological studies of isomaltulose, d-tagatose, and trehalose on glycemic control, Critical Reviews in Food Science and Nutrition, DOI: 10.1080/10408398.2021.1895057

To link to this article: https://doi.org/10.1080/10408398.2021.1895057

Published online: 10 Mar 2021.

CRITICAL REVIEWS IN FOOD SCIENCE AND NUTRITION
https://doi.org/10.1080/10408398.2021.1895057

Taylor & Francis
Taylor & Francis Group

REVIEW

A head-to-head comparison review of biological and toxicological studies of isomaltulose, D-tagatose, and trehalose on glycemic control

Emilia Sokołowska, Anna Sadowska, Diana Sawicka, Izabela Kotulska-Bąblińska, and Halina Car

Department of Experimental Pharmacology, Medical University of Bialystok, Bialystok, Poland

ABSTRACT

Diabetes mellitus is the most common metabolic disorder contributing to significant morbidity and mortality in humans. Different preventive and therapeutic agents, as well as various pharmacological strategies or non-pharmacological tools, improve the glycemic profile of diabetic patients. Isomaltulose, D-tagatose, and trehalose are naturally occurring, low glycemic sugars that are not synthesized by humans but widely used in food industries. Various studies have shown that these carbohydrates can regulate glucose metabolism and provide support in maintaining glucose homeostasis in patients with diabetes, but also can improve insulin response, subsequently leading to better control of hyperglycemia. In this review, we discussed the anti-hyperglycemic effects of isomaltulose, D-tagatose, and trehalose, comparing their properties with other known sweeteners, and highlighting their importance for the development of the pharmaceutical and food industries.

KEYWORDS

Isomaltulose; D-tagatose; trehalose; insulin resistance; obesity; diabetes; nutraceuticals

Introduction

Weight loss is a solution for millions of people at risk of developing full-blown diabetes and can reduce the need for continuous drug treatment. Over the last few decades, there has been a remarkable increase in obesity among both adults and children in the Western world. If the current trend continues, the number of people with diabetes in the world will double over the next 2–3 decades (Chaudhury et al. 2017). Given the medical and social consequences of this disease, it is a frightening prospect. Obesity is a profound public health challenge that affects the lives and prosperity of individuals, families, and communities globally. The World Health Organization (WHO) has calculated that almost 422 million people in 2015 (1 in 11 adults, corresponding to 8.5% of the world's adult population) have diabetes. This estimate is supposed to rise to 642 million in 2040 (1 in 10 adults), whereas type 2 diabetes (T2DM) covers 90% (International Diabetes Federation 2019; Saeedi et al. 2019).

Diabetes correlates with an increased danger of various severe complications, sometimes life-threatening and even death. It is among the top ten most common causes of adult death and indeed caused four million deaths worldwide in 2017 (International Diabetes Federation 2017). The global diabetes drugs market size, including both oral antidiabetic drugs and insulin products, was valued at USD 48,753.1 million in 2018 and is projected to reach USD 78,261.7 million by the end of 2026.

In healthy subjects, glucose levels maintain within normal limits (70–100 mg/dL) (Ramlo-Halsted and Edelman 2000) due to the adequate secretion of insulin by β cells and adequate sensitivity of peripheral tissues (skeletal muscle and liver) to its effects. Unfortunately, in millions of patients with type 2 diabetes, this precise mechanism fails. The pathogenesis of T2DM includes peripheral insulin resistance following pancreatic β-cell dysfunction, which leads to inadequate insulin secretion (Cheng and Fantus 2005) and consequently results in persistent hyperglycemia (Saltiel 2001) (Figure 1). Insulin resistance (IR) occurs in almost 20–25% of the human population. It is a fundamental factor in the initial phase of the natural history of type 2 diabetes, which occurs many years before the appearance of overt hyperglycemia (Prospective Diabetes Study UK (UKPDS) Group 1998; Ramlo-Halsted and Edelman 2000) (Figure 2). Nevertheless, this is sufficient time to develop chronic macrovascular and microvascular complications of diabetes (Cade 2008; Ramlo-Halsted and Edelman 2000) (Figure 3). In this early period, pancreatic β cells are not yet damaged and react to elevated blood glucose levels through excessive insulin secretion, leading to their hypertrophy and necrosis (Saltiel 2001; Sokolowska and Blachnio-Zabielska 2019), and further to increase in fasting insulin secretion or after loads. This classification of diabetes is based on pathogenetic mechanisms and does not identify specific subtypes. Emma Ahlqvist (Ahlqvist et al. 2018) and her colleagues used unsupervised clustering methods to create a data-based

CONTACT Emilia Sokołowska emiliasokolowska.umwb@gmail.com Department of Experimental Pharmacology, Medical University of Bialystok, Bialystok, Poland.

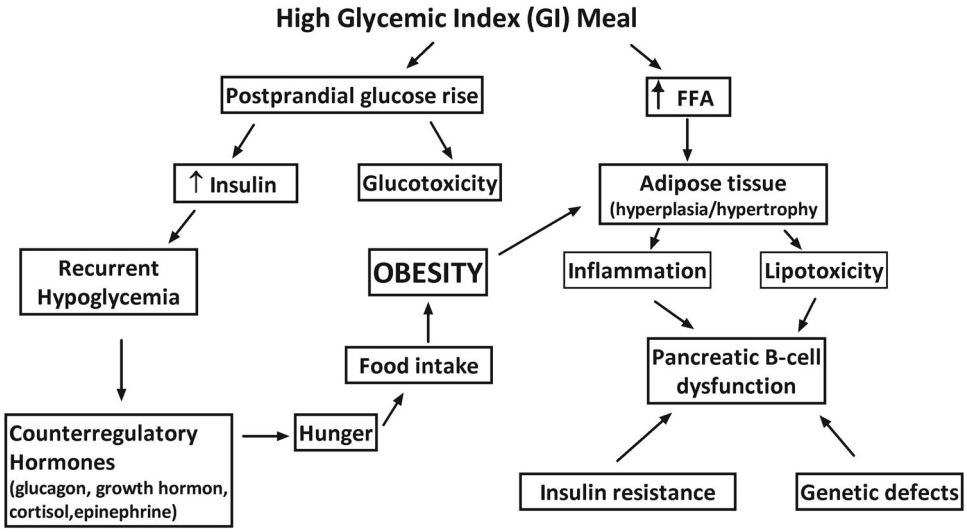

Figure 1. The influence of the consumption of a diet with a high glycemic index (GI) on the development of insulin resistance. FFA, free fatty acids. Based on: Barclay et al. 2008; Berra and Rizzo 2009; Brand-Miller et al. 2007; Cheng and Fantus 2005; Saltiel 2001.

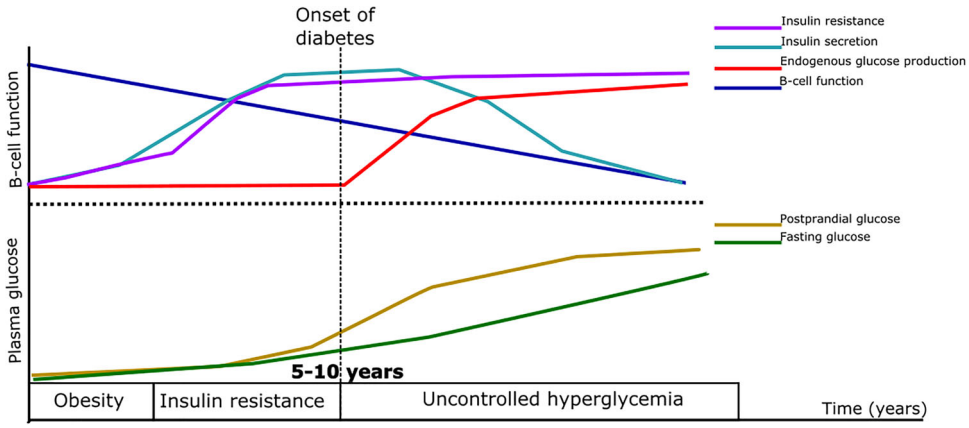

Figure 2. The natural history of type 2 diabetes. Individuals predisposed genetically and phenotypically to type 2 diabetes under the influence of environmental factors (inadequate quantitative and qualitative diet, low physical activity) present a state of energy imbalance from an early age. Increased insulin resistance with age and weight gain are associated with excessive insulin secretion. The loss of beta cells' ability to compensate for insulin hypersecretion is associated with a gradual increase in blood sugar. Failure to suppress glucose production in the liver is the principal cause of fasting hyperglycemia. Epidemiological studies indicate that type 2 diabetes mellitus is diagnosed on average after 5–10 years. It is usually preceded by a long-term prediabetes condition. Nevertheless, this is sufficient time to develop chronic macrovascular and microvascular complications of diabetes. Based on: Ramlo-Halsted and Edelman 2000; Prospective Diabetes Study UK (UKPDS) Group 1998; Sokolowska and Blachnio-Zabielska 2019.

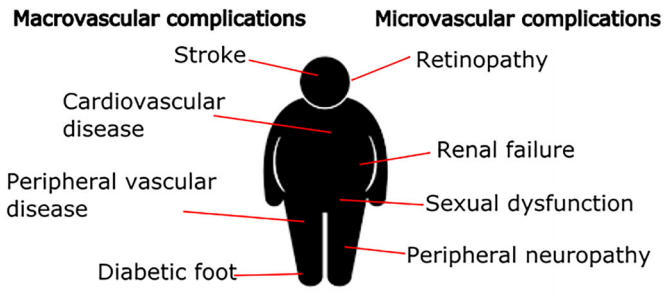

Figure 3. Macrovascular and microvascular complications of diabetes. Based on: Cade 2008; Ramlo-Halsted and Edelman 2000.

analysis for patients with diabetes. They selected six parameters, such as age at diagnosis, body mass index (BMI), glutamate decarboxylase antibodies (GADA; for identification of patients with autoimmune diabetes mellitus), glycosylated hemoglobin (HbA1c; for blood glucose control estimation), homeostatic model 2 (HOMA2)-B (for β-cell function based on C-peptide concentration estimation) and HOMA2-IR (for insulin sensitivity estimation). They identified five clusters of patients. SAID cluster determines severe autoimmune diabetes mellitus in which patients had a positive GADA score, and the mean age at diagnosis was 50-55 years. The SIDD cluster, i.e., severe diabetes with insulin deficiency, concerns GADA-negative patients with the lowest HOMA2-B score of all groups. SIRD cluster, patients with severe insulin-resistant diabetes mellitus, were 65 years old at the time of diagnosis, with higher HOMA2-B and HOMA2-IR points (reflecting incomplete compensation of insulin resistance of beta cells) and decreasing C-peptide concentration during eight years of observation (as opposed to stable concentrations observed in other clusters). The MOD cluster (diabetes mellitus associated with light obesity) includes

Table 1. Physiological properties of nutritive sweeteners.

Sugars	Glycemic classification	Energy content (kcal/g)	Relative sweetness to sucrose (100)	Relative glycaemic response (RGR)	Relative insulin response (RIR)	Status	For diabetic patients use
Monosaccharides							
Glucose	High	4	70-80	100	100	Food	No
Fructose	Very low	4	120	19	9	Food	No
D-tagatose	Very low	1.5	92	3	3	Novel	Yes
Disaccharides							
Isomaltulose	Very low	4	40-50	32	27	Novel	Yes
Lactose	Low	4	30-50	46	–	Food	No
Maltose	High	4	40-50	105	–	Food	No
Sucrose	Intermediate	4	100	68	45	Food	No
Trehalose	High	4	45	72	51	Novel	Yes
Starch hydrolysis products							
Maltodextrin	High	4	0-5	91	90	Food	No
Monosaccharide polyols							
Xylitol	Very low	2.4	100	12	11	Food	Yes*
Sorbitol	Very low	2.6	60	9	11	Food	Yes
Mannitol	Very low	1.6	70	∼0	∼0	Food	Yes
Disaccharide polyols							
Maltitol	Low	2.1	90	45	27	Food	Yes*
Isomalt	Very low	2	50	9	6	Food	Yes
Lactitol	Very low	2.4	40	5	4	Food	Yes

Glycemic classification: very low (glycemic index, GI (g eq./100g): 0-40, glycemic load, GL (g eq./day): 0-20; low (GI: >40-55, GL: >20-80), intermediate (GI: >55-70, GL: >80-120), high (GI: >70, GL: >120); GI classifies foods according to their response to postprandial glycemia (increase in blood glucose level 2 hours after a meal) produced by carbohydrates (25 or 50 g) in the consumed food compared to the reference food. GL combines the glycemic response of the diet as a whole. GL is defined as the product of the GI of a food and the amount of available carbohydrates present in the portion consumed, divided by 100 [GL = GI (glucose as a reference) × the amount of available carbohydrates (g) in a portion × 1/100]; RGR, relative glycemic response (% of that for oral glucose); RIR, relative insulin response (% of that for oral glucose). *it is safe to consume by diabetics in small amounts. Based on: Atkinson, Foster-Powell, and Brand-Miller 2008; Augustin et al. 2015; glycaemicindex.com; Meyer et al. 2000; Monro and Shaw 2008; Mortensen 2006; Salmerón et al. 1997a, 1997b.

patients with obesity but not insulin resistance. The MARD group concerned mild-aged patients with diabetes, with only minor metabolic disorders (Ahlqvist et al. 2018).

Early nonpharmacological intervention includes a low-calorie diet, weight loss, and regular physical activity (American Diabetes Association 2002). A reduction in calorie intake and weight loss of 5 to 10% have a significant impact on metabolic disorders, including diabetes and cardiovascular risk factors (Hensrud 2001; Lean et al. 2019 (DiRECT Trial)). Out of 114 patients with type 2 diabetes, those who reduced their basic body weight by 5% or more demonstrated a statistically significant reduction in glycosylated hemoglobin (HbA1c) (Wing et al. 1987). Although not all people with type 2 diabetes can achieve remission with an adequate diet and weight loss. Diabetes Remission Clinical Trial (DiRECT) study involved 298 adults with diagnosed diabetes in the last six years, BMI 27-45 kg/m2 and HbA1c >48 mmol/mol (6.5%), or >42 mmol/mol (6.0%) with glucose-lowering drugs. The long-term goal of at least 10 kg of weight loss maintained 36 (24%) of the 149 participants in the intervention group (Lean et al. 2019 (DiRECT Trial)).

None of the currently available therapies can slow or stop the progression of β-cell loss (Page and Reisman 2013). Despite the development of new antidiabetic agents, almost 60% of diabetic patients do not achieve their blood sugar targets (Saydah, Fradkin, and Cowie 2004). There is, therefore, a need for complementary intervention such as functional foods that can delay the development of diabetes and support ongoing therapies without hypoglycemia, protect or improve β-cell function, reduce cardiovascular risk factors, and regulate body weight. Pharmacological treatment usually starts with one or two oral antihyperglycemic agents. Unfortunately, as the disease progresses, when blood glucose levels remain uncontrolled, most patients need chronic treatment with exogenous insulin supported by oral diabetes therapy (Chaudhury et al. 2017). Considering that half a billion people have diabetes, there is an urgent requirement to develop and implement comprehensive policies to deal with diabetes.

Advances in biological sciences reinforce the hypothesis that nutrition modulates various body functions and can promote well-being and overcome the risk of certain civilization diseases (Hensrud 2001). Such findings initiated the ideas of functional food and nutraceuticals. Over the last 40 years, a wide range of sugar substitutes were developed and marketed. The global sweetener market is fueled by the production and consumption of diet soft drinks and low-calorie foods so that they taste like their traditional counterparts. Moreover, growing health concerns such as obesity and the increasing incidence of diabetes and cardiac arrest have encouraged consumers to change their lifestyles and adopt healthier and low-calorie diet patterns. Also, foods with a low glycemic index and a low insulin response rate contribute to a feeling of satiety and a lasting release of energy with further prolonged mental and physical productivity (Benton and Nabb 2003). Carbohydrates used in food production, such as glucose and sucrose, are rapidly digested with a high glycemic and insulin response (Table 1). However, food manufacturers modify the glycemic effect of food by replacing rapidly digested and thus highly glycemic sugars with alternative low-glycemic carbohydrates to ensure the pleasure of sweetness without the extra calories. Nevertheless, alternative sweeteners must maintain a similar organoleptic quality (sweetness), nutritional and functional properties (suitability) to sucrose. Isomaltulose, D-tagatose,

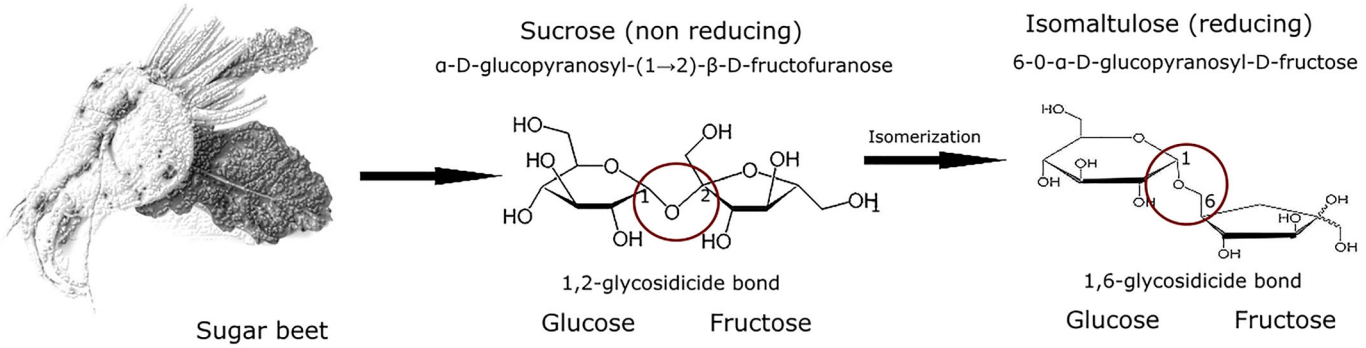

Figure 4. Origin and structure of isomaltulose. Based on: Lina, Jonker, and Kozianowski 2002; Maresch et al. 2017.

and trehalose are examples of such alternative carbohydrate components.

In this review, we will first briefly discuss the physiological properties of sugar substitutes registered as novel foods (isomaltulose, D-tagatose, trehalose) for use in groceries. Concerning clinical trial data, we then critically review the current state of knowledge about the benefits of products that not only taste the same as sugar-based goods but also offer consumer benefits, including calorie reduction, dental privileges, and decreased risk of disease in the long term through strategies such as food glycemia control. The question is whether, regardless of their properties as sweeteners, can they compete on the market realistically or have only a small niche?

Materials and methods

Search strategy

Studies were identified by searching the PubMed and Web of Science electronic databases, using the words: isomaltulose, palatinose, trehalose, tagatose in the following combination: diabetes, artificial sweeteners, sweetener, sugar substitute, nonnutritive sweetener, intense sweetener, diabetes, weight, obesity, obese, metabolic syndrome, cholesterol, lipids, HbA1c, glycated hemoglobin, glycemic index, glycemic load. The year of publication was not restricted. Additional studies were identified by manually searching the reference lists of relevant original and review articles. Inclusion criteria were as follows: the publication in peer-reviewed journals in English; specific consideration of sweetener intake concerning metabolic health outcomes such as food intake, weight change, diabetes, and elements of the metabolic syndrome. Articles published only in abstract form were excluded.

Isomaltulose

Physical and chemical properties. Regulatory status

Isomaltulose, also known by the trade name Palatinose™ is a reducing, functional carbohydrate composed of glucose and fructose (Dahlqvist et al. 1963), and its chemical name is 6-0-α-D-glucopyranosyl-D-fructose. It naturally occurs in honey (<1%) (Lina, Jonker, and Kozianowski 2002), and its sweetening power is about half (0.4–0.45) of that of sucrose

Table 2. Results of a clinical trial search for isomaltulose, D-tagatose, tehalose.

Search Terms	Entire Database	Search Results
Diabetes type 2 (T2DM)	7644	5114
Obesity	8524	5033
Isomaltulose	20	13
D-tagatose	2	3
Trehalose	18	30
Isomaltulose + T2DM	8	4
Isomaltulose + obesity	6	3
D-tagatose + T2DM	2	3
D-tagatose + obesity	1	0
Trehalose + T2DM	0	0
Trehalose + obesity	0	0

The website clinicaltrials.gov was searched on 10 September 2020 using the keywords: isomaltulose, tagatose and trehalose. The search criteria were as follows: (1) the period of the study was determined as from 1 January 2015 to 30 July 2020; (2) only studies with "completed" status were taken into account; (3) condition: "diabetes" or "obesity". Nine studies met the above criteria. Details of clinical trials are presented in the Table 3.

(Lina, Jonker, and Kozianowski 2002). Commercial isomaltulose is derived from sucrose by enzymatic isomerization (Figure 4) and has been used as sugar in Japan since 1985 (Lina, Jonker, and Kozianowski 2002; Maresch et al. 2017). In Asian cuisine, carbohydrates such as rice, noodles, and bread are primary food products. Moreover, Asians have a greater genetic predisposition to diabetes (Mather and Keen 1985). Hence, there is a high interest in isomaltulose in Asian countries. Tan, Tan, and Henry (2017) have shown that substituting sucrose for isomaltulose can affect glycemic control in the Asian population (Table 2, 3).

Unlike sugar alcohols, xylitol or sorbitol, isomaltulose is fully digested into glucose and fructose by α-glucosidase in the intestinal mucosa (Lina, Jonker, and Kozianowski 2002) and contributes the same caloric value as sucrose of 4 kcal/g (Mu et al. 2014) as well as a very low glycemic index (GI) of 32 (Atkinson, Foster-Powell, and Brand-Miller 2008) (Table 1). After absorption, fructose and glucose are further metabolized. However, the digestive rate of isomaltulose is four to five times slower than that of sucrose because of the strong glucose–fructose α-1,6-glycosidic bond (Mu et al. 2014; Tonouchi et al. 2011) instead of α-1,2-glycosidic as in sucrose (Figure 4), which has several impacts. Indeed, a consequence of slower hydrolysis of the isomaltulose molecule is a reduced glycemic and insulin reaction in healthy individuals and those with T2DM (not insulin-dependent), with a steady, low, and sustained growth in blood glucose levels. Kawai, Okuda, and Yamashita (1985) demonstrated that after administration of 50 g of isomaltulose or sucrose to

Table 3. Completed clinical trials on the use of isomaltulose, D-tagatose in the treatment of diabetes and obesity.

Study Title	Study Type	Conditions	Arms and Interventions	Enrollment	Outcome Measures & Results
ISOMALTULOSE					
1. The Glycaemic Effect of Isomaltulose Consumption in Healthy Participants ClinicalTrials.gov Identifier: NCT03020485 Ref. (Tan, Tan and Henry 2017)	Interventional, Randomized, Crossover Assignment Single-blinded	Diabetes Mellitus	Participants receive twice 50 g of isomaltulose (ISO) (Active Comparator) or 50 g sucrose (SUC) (Placebo Comparator) dissolved in 250 ml of water.	46 ♀♂ Chinese, Indian, Malay or Caucasian ethnic origin	Change in postprandial blood glucose for 180 minutes period Results: isomaltulose (ISO) vs. sucrose (SUC) Parameter — Results Total glucose iAUC Chinese — ISO > SUC (∼58%) Malays — ISO > SUC (∼94%) Indians — ISO > SUC (∼98%) Caucasians — ISO > SUC (∼47%) iAUC Glucose: Chinese (n = 10): 174.1 ± 69.6 vs. 109.9 ± 27.6 (p = 0.010); Malays (n = 10): 192.4 ± 82.6 vs. 98.8 ± 52.0 (p = 0.004); Indians (n = 10): 143.4 ± 60.8 vs. 72.3 ± 31.4 (p = 0.002); Caucasians (n = 10): 130.5 ± 41.3 vs. 88.4 ± 50.7 (p = 0.017)
2 Effects of Palatinose™ on Weight Management and Body Composition ClinicalTrials.gov Identifier: NCT03652207 Ref. (Lightowler et al. 2019)	Interventional, Randomized, Parallel Assignment Quadruple-blinded	Overweight Obesity Diet Modification Body Weight	Obese participants consuming an energy-reduced diet containing foods (i.e. low-fat yogurt drink, fruits drink and sweetener sachet for cereals) with 40 g/day either sucrose (SUC) (Placebo Comparator) or isomaltulose (ISO) (Active Comparator) over a period of 3 months.	64 ♀♂ Adults with BMI of 25 − 35 kg/m^2	Primary: Body weight change over a 12-week period Secondary: Body fat percentage; postprandial energy metabolism, i.e. respiratory quotient and fat oxidation measured by indirect calorimetry, BMI, waist circumference (WC). Results: isomaltulose (ISO) vs. sucrose (SUC) Parameter — Results Δ Body weight — ISO > SUC (∼52%) Δ %FFM — ISO > SUC (∼122%) Δ %FM — ISO > SUC (∼111%) Δ EI: — ISO > SUC (∼95%) Δ REE — Ns Δ postprandial RQ — ISO > SUC (∼43%) Δ FO — ISO > SUC (∼17%) Δ WC — ISO > SUC (∼57%) Primary: −3.2 ± 2.9 kg and −2.1 ± 2.6 kg for (p = 0.258). Secondary: %FFM: 2.0 ± 2.4% vs. 0.9 ± 2.6% (p = 0.127); %FM: −1.9 ± 2.5% and −0.9 ± 2.6% (p = 0.169); EI: −544 ± 470 vs. −283 ± 279 kcal/d (p = 0.022); REE: no differences; postprandial EE for ISO p = 0.011; postprandial RQ: mean iAUC2h 4.8 ± 4.1 vs. 6.9 ± 3.1 (p = 0.047); FO: 73 ± 36 vs 62 ± 32 (p = 0.05); WC: −3.3 ± 11.7 cm and −2.1 ± 7.4 cm (p = 0.666)
3 Efficacy of Palatinose™ Versus Sucrose on Flow Mediated Dilation in Healthy Subjects With Mild Hypertension ClinicalTrials.gov Identifier: NCT03986775 Ref. (de Groot, Schweitzer, and Theis 2020)	Interventional, Randomized, Crossover Assignment, Double-blinded	Overweight and Obesity	Participants receive citrus drink with 50 g of isomaltulose (ISO) (Active Comparator) or sucrose (SUC) (Placebo Comparator)	80 ♀♂ Adults with BMI of 25 − 35 kg/m^2	Primary: Brachial ultrasound FMD scan Secondary: Postprandial glycemic, insulin response. Results: isomaltulose (ISO) vs. sucrose (SUC)/ Parameter — Results ΔFMD — ISO > SUC FMD $_{T2}$ — ISO > SUC Primary: ΔFMD = −0.003% and −0.151% (p > 0.05); FMD $_{T2}$= 5.9 ± 2.9% and 5.4 ± 2.6% (p = 0.047) Secondary: not provided due to the late timing of blood sampling.
4 Formulas for Diabetes With Sucromalt & Isomaltulose on	Interventional, Randomized, Crossover	Diabetes Mellitus, Type 2	4 treatments with different types of carbohydrates	23 ♀♂ Adults with BMI of 25 − 35 kg/m^2 with T2DM	Primary: Change from baseline glycemia, insulin, Glycemic Index (GI), Glycemic Load (GL), GLP-1, GIP, hunger, fullness, desire to eat, prospective food consumption, subjective appetite at 180 minutes.

(*continued*)

Table 3. Continued.

Study Title	Study Type	Conditions	Arms and Interventions	Enrollment	Outcome Measures & Results
Glycemic Index, Hormones & Subjective Appetite in Type 2 Diabetes ClinicalTrials.gov Identifier: NCT03829800 Ref. (Dávila et al. 2019)	Assignment, Double-blinded		(isomaltulose and sucromaltose). • ET; Ensure® Abbott Nutrition. A standard nutritional formula not specific for diabetics • GS; Glucerna® Abbott Nutrition. A formula with a patented blend of slow-digesting carbohydrates including resistant maltodextrin and sucromalt • DI; Diasip® Nutricia Advanced. A formula whose composition has isomaltulose and resistant starch • GB; Glicolab® Glucose solution (reference food)		Secondary: Age, weight, height, BMI, hip circumference, Total Cholesterol, HDL-C, LDL-C, Triacylglycerides, HbA1c. Results: Parameter — Results Peak glucose level — GB > ET > DI > GS Δ insulin $AUC_{0-180min}$ — GS < ET, DI Δ GLP-1 $AUC_{0-180min}$ — GS > ET, DI Δ GIP $AUC_{0-180min}$ — GS < ET, DI fullness — GS > ET, DI Hunger — GS < ET, DI desire to eat — GS < ET, DI Glucose maximum peak at 60 min: GB 15.03 ± 0.20 mmol/L, ET 10.80 ± 0.12 mmol/L, DI 10.17 ± 0.05 mmol/L, GS: 9.10 ± 0.06 mmol/L; $AUC0_{-180min}$ in insulin response was significantly lower in GS when compared with the other supplements ($p < 0.001$); $AUC_{0\text{-}180\,min}$ of the GLP-1 response and fullness sensation were significantly higher and for GIP response, hunger sensation, desire to eat were significantly lower in GS vs. ET and DI
5 Metabolic Response of Slow Released Carbohydrates in Diabetes Mellitus ClinicalTrials.gov Identifier: NCT01070238 Ref. (Ang and Linn 2014)	Interventional, Randomized, Crossover Assignment, Double-blinded	Type 2 Diabetes	The 3 h pre-ingestion phase- a preparation period, in which a euglycemic-hyperinsulinemic clamp that was subsequently combined with 1 g/kg b.w. of an oral 13 C-enriched isomaltulose or sucrose load. Hormonal responses and glucose kinetics were analyzed during a 4-h postprandial period.	11 ♀♂ adults with T2DM HbA1c < 8%, fasting blood glucose < 140 mg/dl	Primary: Lower postprandial glucose and insulin responses after isomaltulose ingestion than after sucrose Results: isomaltulose (ISO) vs. sucrose (SUC) Parameter — Results Mean insulin level — ISO < SUC (∼19%) Mean glucose level — ISO < SUC (∼25%) Mean C-peptide level — ISO < SUC (∼17–23%) Mean glucagon level — ISO < SUC (∼17–23%) Mean GIP level — ISO < SUC (∼12%) Mean GLP-1 level — ISO > SUC (∼64%) Absorption time — ISO > SUC (∼50%) EGP — ISO < SUC (∼40%) Systemic glucose disappearance — ISO < SUC (∼29g) Mean values: glucose concentration 5.8 ± 0.1 vs. 6.5 ± 0.1 mmol/L, insulin concentrations 371.6 ± 7.1 vs. 413.3 ± 6.5 pmol/L (both $p < 0.001$); C-peptide: 0.5 ± 0.0 vs. 0.6 ± 0.0 nmol/L, glucagon: 21.0 ± 1.1 vs. 27.3 ± 1.8 pmol/L (both $p < 0.001$); GLP-1: 20.3 ± 1.3 vs. 12.4 ± 0.9 pmol/L ($p < 0.001$); GIP: 28.1 ± 1.3 vs. 31.5 ± 2.0 pmol/L ($p < 0.001$); absorption time 216.8 ± 2.4 vs. 166.4 ± 9.6 min ($p < 0.01$); EGP: 24.0 ± 1.0 vs.40.1 ± 2.4g ($p < 0.001$); systemic glucose disappearance: 54.5 ± 0.9 vs.83.4 ± 1.7g ($p < 0.001$).
6 Energy Flux and Fat Oxidation Using Low and High Glycaemic Index Foods	Interventional, Randomized, Crossover Assignment, Double-blinded	Type 2 Diabetes Obesity PreDiabetes	Participants receive low or high GI sweetener added to the treatment meals. 30 grams of isomaltulose (ISO) (Active Comparator)	20 Healthy Chinese ♂ BMI 17 to 28 kg/m2	Primary: Glycemic response, daily blood glucose profile, substrate oxidation, energy expenditure Results: isomaltulose (ISO) vs. sucrose (SUC) Parameter — Results Δ Total glucose iAUC — ISO < SUC (∼73%)

	ClinicalTrials.gov Identifier: NCT03031886 Ref. (Henry et al. 2017)			or sucrose (SUC) (Placebo Comparator) to dinner and breakfast and 20 grams to lunch and snack.		Δ MAGE ISO < SUC (∼60%) Δ RQ (10 h) ISO < SUC (∼8%) Δ iFat oxidation breakfast ISO > SUC (∼28%) Δ iFat oxidation lunch ISO > SUC (∼192%) Δ iFat oxidation snack ISO > SUC (∼50%) iAUC glucose: 502.5 ± 231.4 vs. 872.6 ± 493.1 mmol/L (p = 0.002) ; MAGE: 1.67 ± 0.53 vs. 2.68 ± 1.13 mmol/L (p < 0.001); RQ (10 h): 0.064 ± 0.030 vs. 0.070 ± 0.041 (p = 0,014); i Fat oxidation (g/min): breakfast −0.015 ± 0.021 vs. −0.021 ± 0.025 (p = 0.026), lunch −0.014 ± 0.015 vs. −0.041 ± 0.027 (p < 0.001), snack 0.003 ± 0.009 vs. 0.002 ± 0.011 (p = 0.013)
7	Clinical Trial for Liquid Food (Inslow) ClinicalTrials.gov Identifier: NCT02641743 Ref. (Liu et al. 2016)	Interventional, Randomized, Crossover Assignment Single-blinded	Diabetes	Each participant was requested to consume one of is energetic test meals (200 kcal per serving 200 ml) Inflow at 7:00 AM; carbohydrate adjusted liquid food using isomaltulose (ISO) as the major carbohydrate (>50%) or standard balanced formula (SUC) Inslow: 56% ISO, 23% dextrin, 15% fiber. The standard balanced meal included 85% dextrin as the main carbohydrate, together with sugar and fiber.	36 ♀♂ older adults with T2DM	Primary: plasma glucose concentration Secondary: plasma insulin and free fatty acid concentration Results: isomaltulose (ISO) vs. sucrose (SUC) Parameter — Results Δ Postprandial glucose — ISO < SUC (p < 0.0001) Δ Peak of insulin — 60 min vs 30 min Δ Insulinogenic index — ISO > SUC (p < 0.0001) Δ plasma FFA — Ns
D-TAGATOSE						
1	Naturlose (D-Tagatose) Efficacy Evaluation Trial ClinicalTrials.gov Identifier: NCT00955747 Ref. (Ensor et al. 2015)	Interventional, Randomized, Parallel Assignment, Quadruple-blind	Type 2 Diabetes	Placebo Comparator: Sugar Substitute Splenda (SPL) 1.5 g dissolved in 125 ml of water three times per day. Experimental: 15 g Tagatose (TAG) dissolved in 125 ml of water three times a day for 12 months.	494 ♀♂ adult, older adult with T2DM,BMI ≤45kg/m2	Primary: Change in Hemoglobin A1C (HbA1c) level from baseline Secondary: Changes in BMI, fasting blood glucose, insulin, blood lipids Results: D-Tagatose (TAG) vs. Splenda (SPL) Parameter — Results Δ HbA1c decline — TAG > SPL (p < 0.0001) Δ BMI — Ns Δ fasting blood glucose reduction — TAG > SPL(p = 0.0079) Δ Insulin concentration — Ns Δ blood cholesterol reduction — TAG > SPL(p = 0.0157) Δ LDL reduction — TAG > SPL(p = 0.0057) Δ HDL — Ns Δ Triglyceride reduction — TAG < SPL(p = 0.0048)
2	A Clinical Study to Evaluate the Effect of Naturlose (Tagatose) ClinicalTrials.gov Identifier: NCT00961662 Ref. (Ensor et al. 2014)	Interventional, Randomized, Parallel Assignment, Single-blind, multicenter	Type 2 Diabetes	The subjects were randomized in one of the 3 arms receiving 2.5, 5 or 7.5 g of D-tagatose (TAG) three times daily, immediately prior to meals for 6 months.	161 ♀♂ adult, older adult with T2DM,BMI ≤ 45 kg/m2	Primary: Change from baseline HbA1c after six months of treatment in patients with type 2 diabetes mellitus Secondary: For 6 month: plasma glucose concentrations and plasma lipids, decrease of ≥0.5% in HbA1c level at each visit; decrease of fasting plasma glucose, body weight loss;

(*continued*)

Table 3. Continued.

Study Title	Study Type	Conditions	Arms and Interventions	Enrollment	Outcome Measures & Results		
				after 8 months: decrease of ≥1% in HbA1c level			
				Results:			
				Parameter	TAG 2.5g	TAG 5g	TAG 7.5g
				≥0.5 HbA1c decrease (%)	(19%) 7.6 ± 0.66%	(15%) 7.4 ± 0.63%	(25%), 7.3 ± 0.60%
				(after 6 months)	vs. 7.6 ± 1.01%,	vs. 7.3 ± 0.85%,	vs. 7.1 ± 0.75%;
				Fasting glucose	130.4 ± 28.8 mg/dL vs.	129.5 ± 24.0 mg/dL	136.7 ± 22.8 mg/dL
				(after 6 months)	136.3 ± 31.9 mg/dL;	vs. 131.2 ± 26.3 mg/ dL	vs. 123.1 ± 17.1 mg/dL;
				Triglyceride	162 ± 89.8 mg/dL vs.	181 ± 92.7 mg/dL	179 ± 99.8 mg/dL
				(after 3 months)	179 ± 93.4 mg/dL	vs. 218 ± 149 mg/dL,	vs. 165 ± 74.7 mg/dL
				Body weight	Ns	165.4 ± 33.0 lbs	167.4 ± 33.0 lbs
				(after 6 months)		vs. 161.7 ± 27.5 lbs	vs. 160.6 ± 29.3 lbs

The values in brackets are the differences between the test sugar (ISO, isomaltulose; TAG, D-tagatose) and the reference sugar (SUC, sucrose). BMI, body mass index; EI, energy intake; FFA, free fatty acids; FFM, free fat mass; FM, fat mass; FMD, flow-mediated dilation; FO, fat oxidation; iAUC, incremental area under the curve; ns, non-significant; MAGE, mean amplitude of glycaemic excursion; REE, resting energy expenditure; RQ, respiratory quotient; WC, waist circumference; Δ, changes from baseline values.

healthy volunteers, the maximum increase in glucose concentration after 60 min was 110.9 mg/dL vs. 143.3 mg/dL, respectively. Isomaltulose, apart from its influence on glycemia and insulin, has desired properties used in the manufacturing of energy drinks and due to its bulking properties in bakery products. Isomaltulose is classified as "generally recognized as safe" (GRAS) in the USA and has been approved following a premarket safety estimation as a dietary component following the Novel Food Regulation in the European Union (EU) in 2005 (Holub et al. 2010) (classified as novel food), as well as in Australia and New Zealand in 2007. Unlike sucrose, isomaltulose is hardly used by plaque bacteria and is therefore not cariogenic (Jonker, Lina, and Kozianowski 2002).

Influence on metabolic parameters

A 12-week, cross-over, intervention study in twenty-three people with impaired glucose tolerance shows that regular isomaltulose intake has a significant beneficial effect on parameters related to metabolic syndrome, such as impairments of glucose tolerance and early insulin secretion in response to an oral glucose load, an accumulation of visceral fat and a dyslipidemic profile (Oizumi et al. 2007). In a long-term (5 weeks) model of metabolic syndrome, feeding of adult male rats with a diet containing 39.6% isomaltulose showed a favorable effect in all metabolic syndrome factors (reduced visceral fat mass, improved glucose tolerance, significant improvements in fasting blood glucose, insulin, leptin, and serum triglyceride levels, decreased fat mass and an increased lean body mass). Moreover, isomaltulose inhibits the rise in blood pressure and further signs of progress of diabetic nephropathy in an obese diabetic rat model (Suzuki et al. 2017). Furthermore, in healthy and obese patients, isomaltulose consumption inhibits an increase in insulin resistance and blood pressure, but likewise, may exert beneficial effects on endothelial function and cardiovascular health (Arai et al. 2007; de Groot, Schweitzer, and Theis 2020). However, in a 12-week, randomized, double-blind study, isomaltulose (50 g/day) did not reduce glycosylated hemoglobin (HbA1c) (sucrose: 7.39 ± 0.78%; isomaltulose: 7.24 ± 0.76%, $p = 0.844$) in patients with type 2 diabetes in free-living conditions, but lowered triglycerides (sucrose: 179 ± 49 mg/dL; isomaltulose: 144 ± 52 mg/dL, $p = 0.016$) (Brunner et al. 2012). To highlight, the normal HbA1c level is below 5.7% (Chaudhury et al. 2017).

Ang and Linn (2014), in a randomized, double-blind cross-over study using a stable (13) C-enriched isomaltulose, or sucrose assessed the effects of their bolus administration on postprandial glucose metabolism in 11 adults with type 2 diabetes. Unlike sucrose, isomaltulose reduced blood glucose rise and enhanced insulin release. On the other hand, the amount of oral and endogenous glucose introduced into the systemic circulation 4 h after isomaltulose intake was lower. Therefore, after the ingestion of isomaltulose (1 g/kg b.w.), 29 g less glucose had to be removed from the systemic circulation (Ang and Linn 2014).

Table 4. List of patent applications for isomaltulose, D-tagatose, trehalose.

Application	Patent Number (publication date)
ISOMALTULOSE	
Food Additive/ingredient	SG11202000810T(A) (2020-02-27); PL1677618(T3) (2011-10-31); PL1858348(T3) (2016-08-31); DE102011012205(A1) (2012-08-02); ZA200501009(B) (2006-10-25); DE102008037185(A1) (2009-03-12); WO9508926(A1) (1995-04-06); WO2006119991(A1) (2006-11-16)
Quality improvement	PL2931057(T3) (2020-02-28); NZ581366(A) (2012-06-29); ZA200506219(B) (2006-12-27); US2006096587 (A1) (2006-05-11); US20060096587(A1) (2006-05-11)
Nutritional supplement/Functional food	US2010004194(A1) (2010-01-07); PL2592950(T3) (2018-09-28); US2011009358(A1) (2011-01-13); EP2272521(A1) (2011-01-12); US2006188627(A1) (2006-08-24)
Flavor modification/enhancement	EA200870429(A1) (2009-04-28); US2008175974(A1) (2008-07-24); WO2004008870(A1) (2004-01-29); DE102008050591(A1) (2010-04-15)
D-TAGATOSE	
Food Additive/ingredient	PL2494872(T3) (2015-03-31); JP2017136079(A) (2017-08-10); CN106107899(A) (2016-11-16); KR20040007524(A) (2004-01-24); JP2012143243(A) (2012-08-02); US2012128852(A1) (2012-05-24); US478672 (A) (1988-11-22); US6475540(B1) (2002-11-05); WO9722263(A1) (1997-06-26)
Quality improvement	KR20190048946(A) (2019-05-09); US2005214426(A1) (2005-09-29); US6432464(B1) (2002-08-13)
Nutritional supplement /Functional food/Prebiotic	US2019117721(A1) (2019-04-25); PL2837292(T3) (2018-03-30); KR101475620(B1) (2014-12-22); US19980075694P (2001-04-25); US7202219(B1) (2007-04-10); EP1056358(A1) (2000-12-06); EP1173186(A4) (2000-04-04)
Flavor modification/enhancement	KR20010033864(A) (2001-04-25); US2005214426(A1) (2005-09-29); US2006159801(A1) (2006-07-20); DE10307445(A1) (2004-10-21); WO1999034689(A1) (1999-07-15)
TREHALOSE	
Food Additive/ingredient	CN109673702 (2019-04-26); CN109645088(A) (2019-04-19); CN108835182(A) (2018-11-20); CN108835172(A) (2018-11-20); CN107136153(A) (2017-09-08); JPH07322810A (1995-12-12); EP1032276A4 (2004-05-19); WO0189313(A1) (2001-11-29); MX2007002052(A) (2007-07-16); US6620791(B1) (2003-09-16); WO0189313(A1) (2001-11-29)
Preservation	DE102008027686(A1) (2009-12-17); EP0983727(A2) (2000-03-08); CN108684807(A) (2018-10-23); CN105767170(A) (2016-07-20); DE102008027686(A1) (2009-12-17); EP0983727(A2) (2000-03-08); US6005100(A) (1999-12-21); US5026566(A) (1991-06-25)
Quality improvement	KR20040051747(A) (2004-06-19); KR101798767(B1) (2017-11-16); CN107455743(A) (2017-12-12); WO2004098321(A1) (2004-11-18); US2006096587(A1) (2006-05-11);
Nutritional supplement/Functional food	CN110584116(A) (2019-12-20); CN109673879(A) (2019-04-26); GB2353934(A) (2001-03-14); CN106538682(A) (2017-03-29); KR20110034732(A) (2011-04-06); ZA200506219(B) (2006-12-27); US2006188627(A1) (2006-08-24); EP1500335(A1) (2005-01-26); GB2356788(A) (2001-06-06); GB2353934(A) (2001-03-14); EP0619951(A2) (1994-10-19);
Flavor modification/enhancement	CN109258783(A) (2019-01-25); WO2005079516(A2) (2005-09-01); WO2004107883(A1) (2004-12-16)

The website worldwide.espacenet.com was searched on 16 September 2020 using the keywords: isomaltulose, tagatose and trehalose. The search criteria were: A21, A22, A23 according to CPC classification (Cooperative Patent Classification).

Isomaltulose prolongs intestinal glucose absorption, whereby influences the secretion of gut peptides glucose-dependent insulinotropic polypeptide (GIP) and glucagon-like peptide 1 (GLP-1). GLP-1 causes a decrease in insulin resistance and attenuates postprandial hyperglycemia by reducing oral glucose appearance and inhibiting endogenous glucose production (EGP) (Ang and Linn 2014; Keyhani-Nejad et al. 2015) (Table 3), but also improves glycemia via enhancing pancreatic beta-cell functions. The rate of nutrients entry and interaction with the small intestine stimulates the release of intestinal peptides (O'Donovan et al. 2004), which is the principal mechanism for regulating gastric emptying, satiety, and insulin secretion (Ang and Linn 2014; Keyhani-Nejad et al. 2015). After 12 weeks of isomaltulose intake (40 g/day) was observed a significant reduction in energy consumption in comparison to patients taking sucrose ($p = 0.022$) (Lightowler et al. 2019). Furthermore, a randomized, double-blind, cross-over study showed lower postprandial appetite and better metabolic profile after isomaltulose, maltodextrin or sucromalt consumption (Dávila et al. 2019). Hira et al. (2011) and Keyhani-Nejad et al. (2016) have shown that the concentration of GLP-1 in rat blood increases significantly as a result of isomaltulose bypassing the upper intestine K cells producing GIP and interaction with ileum light, where GLP-1-producing cells (L-cells) are most abundant. Similarly act acarbose (100 mg) (α-glucosidase inhibitor), which delays sucrose uptake from the jejunum to the ileum (Seifarth et al. 1998).

Several clinical trials have confirmed reduced plasma glucose levels, body weight, waist circumference after isomaltulose administration and hence lower insulin secretion, indicating elevated fat oxidation, as shown by respiratory quotient measurements (Arai et al. 2007; Henry et al. 2017; Lightowler et al. 2019; Liu et al. 2016) (Tables 2 and 3). Similarly, König et al. (2012), in a double-blind, randomized, cross-over study, described lower glycemic and insulin reactions and increased fat oxidation after isomaltulose intake (50 g) in overweight, insulin-resistant individuals at rest and during physical activity.

The consumption of Inslow, a liquid feeding formula (Meiji Dairy Products, Tokyo, Japan), prepared by partially replacing dextrin with 56% isomaltulose, reduces postprandial hyperglycemia, inhibits hyperinsulinemia, and improves insulin sensitivity in individuals with type 2 diabetes (Liu et al. 2016) (Table 3). An interventional, four-week cross-over trial conducted by Holub et al. (2010) showed that enriching the daily diet with 50 g of isomaltulose (instead of high GI products) is well tolerated with no signs of gastrointestinal distress (Lina, Jonker, and Kozianowski 2002) and contributes to the improvement of carbohydrate metabolism as a result of its lower and prolonged glycemic response. There were no adverse influences on blood lipids (total cholesterol, low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), and apo). Cardiovascular risk markers (oxidized LDL) and NEFA (nonesterified fatty acids) levels remained stable for both

sucrose and isomaltulose, while carbohydrate metabolism parameters such as blood glucose levels and insulin resistance were significantly lower.

Isomaltulose regulates insulin resistance in patients with NAFLD (nonalcoholic liver diseases) by modifying bile acids, fatty acids, and glycine/serine metabolism. It significantly affects various metabolites, in particular taurodeoxycholic acid, arachidonic acid, and betaine (Kawaguchi et al. 2018). That is important because the development of insulin resistance can be caused by various factors such as amino acids, fatty acids, and biliary acid metabolism (Legry et al. 2017; Park et al. 2020; Postic and Girard 2008). In the blood serum in the group of isomaltulose patients, there was a significant decrease in L-arginine concentration and an increase in L-ornithine concentration. Changes in the metabolism of both amino acids may contribute to an improvement in insulin resistance. L-arginine inhibits the gene expression of the insulin-1 receptor substrate (IRS-1), phosphatidylinositol 3-kinase (PI3K), and Akt (protein B kinase) in the insulin signaling pathway and leads to increased insulin resistance (Kawaguchi et al. 2018; Liang et al. 2017). L-ornithine regulates insulin-like growth factor-1, an insulin-like protein binding complex 3 in muscle tissue, which also increases insulin resistance (Zając et al. 2010). Furthermore, 22-week feeding of mice with isomaltulose prevented steatosis of the liver (48.5%) compared to sucrose, and improved glucose tolerance without differences in body composition and food intake. Moreover, sucrose increased the expression of suppressor of cytokine signaling 2 (Socs2) in the liver 2.3 times, which is involved in the growth hormone signaling pathway and participates in NAFLD development (Keyhani-Nejad et al. 2015).

Toxicity

The gastrointestinal tolerance of isomaltulose is comparable to sucrose (Holub et al. 2010; Lina, Jonker, and Kozianowski 2002). The administration of isomaltulose at dietary levels up to 10% (7.0 and 8.1 g of isomaltulose/kg body weight/day) for 13 consecutive weeks for 20 male and 20 female Wistar rats was well tolerated without any abnormalities in condition, growth, food, and water consumption, ophthalmoscopy, hematology, clinical chemistry, urinalysis, organ weights, macroscopic and histopathological findings, and results of immunotoxicity and neurotoxicity screens (Jonker, Lina, and Kozianowski 2002). According to the Ames test, isomaltulose seems to be a nonmutagenic sugar without embryotoxic or teratogenic effects in rat fetuses (Lina, Smits-van Prooije, and Waalkens 1997) nor maternal toxicity at levels up to 7 g/kg body weight/day (Lina, Jonker, and Kozianowski 2002). In summary, isomaltulose is a promising sugar for patients with diabetes and people suffering from insulin resistance or metabolic syndrome (Lina, Jonker, and Kozianowski 2002; van Can et al. 2009). Therefore, isomaltulose is a sweetener with a low glycemic index and increasingly used for the production of food and beverages instead of sucrose (Maresch et al. 2017).

Application

Isomaltulose is successfully added to sports drinks (up to 7%), energy and nutrition bars (15%), breakfast cereals (30%), chocolate (25%), or energy tablets (97%) (Table 4). It has a slightly lower melting point (123–124 °C) than sucrose (160–185 °C) (Sawale et al. 2017). Due to the stable glycosidic bond between glucose and fructose, isomaltulose is more resistant to hydrolysis than sucrose in acidic fruit or sports drinks (pH value of ∼3) (Brouns et al. 2006 (US20060096587A1)). Moreover, isomaltulose is a desired ingredient in food and drinks for athletes (Berg et al. 2010 (US2010004194A1)). In a study by Achten et al. (2007), it was found that the oxidation rate of isomaltulose was only 59% of that of sucrose. The intake of isomaltulose during physical activity higher glycogen and fat utilization compared to sucrose (Achten et al. 2007). Isomaltulose in dairy products such as yogurts extends their shelf life and ensures a constant level of sweetness. It turned out to be more resistant to degradation by *Lactobacillus acidophilus* and *Lactobacillus bifidus* in comparison with sucrose (Dörr et al. 2005 (WO2004008870A1); Sawale et al. 2017). Moreover, substituting sucrose with isomaltulose in children's teas allows for the creation of a palatable and tooth-friendly product (M. Elger and Elger 2008 (DE102008050591A1)), especially since the tolerance of isomaltulose (no gastrointestinal intolerance in doses up to 50 g/day) is higher than that of polyols and other slowly absorbed carbohydrates (Lina, Jonker, and Kozianowski 2002).

D-Tagatose

Physical and chemical properties. Regulatory status

D-Tagatose, known by its brand name Natrulose, is a rare monosaccharide - a stereoisomer of D-fructose (with a melting point of 134° C) occurring naturally in fruits (apples, oranges, and pineapple) which is 92% as sweet as sucrose. D-Tagatose was original produced as a sugar substitute for calorie and weight control (Levin 2002), having only 1.5 kcal/g compared with sucrose or maltodextrin (4 kcal/g) and a very low glycemic index (GI) of 3 (values for a portion containing 50 g of total carbohydrates) (glycaemicindex.com) (Table 1). It is naturally found in heated cow's milk (Troyano, Martinez-Castro, and Olano 1992) and is commercially produced by chemical or enzymatic isomerization of D-galactose, using lactose as a starting material (Ibrahim 2018; Lu, Levin, and Donner 2008) (Figure 5). Thus, the potential danger of allergenicity exists. Nevertheless, D-tagatose is harmless for milk-allergic individuals (Taylor, Lambrecht, and Hefle 2005). FDA (U.S. Food and Drug Administration) established D-tagatose as GRAS in 2001 (Levin 2002), a product used in foods with no reported incident of allergic or any other toxic event. The WHO Joint Expert Commission for Food Additives (JEFCA) in 2004 did not specify an ADI (acceptable daily intake) for D-tagatose, which means that high consumption of D-tagatose does not have any expected long term toxic effects. ADI is an amount of food supplement that can be ingested

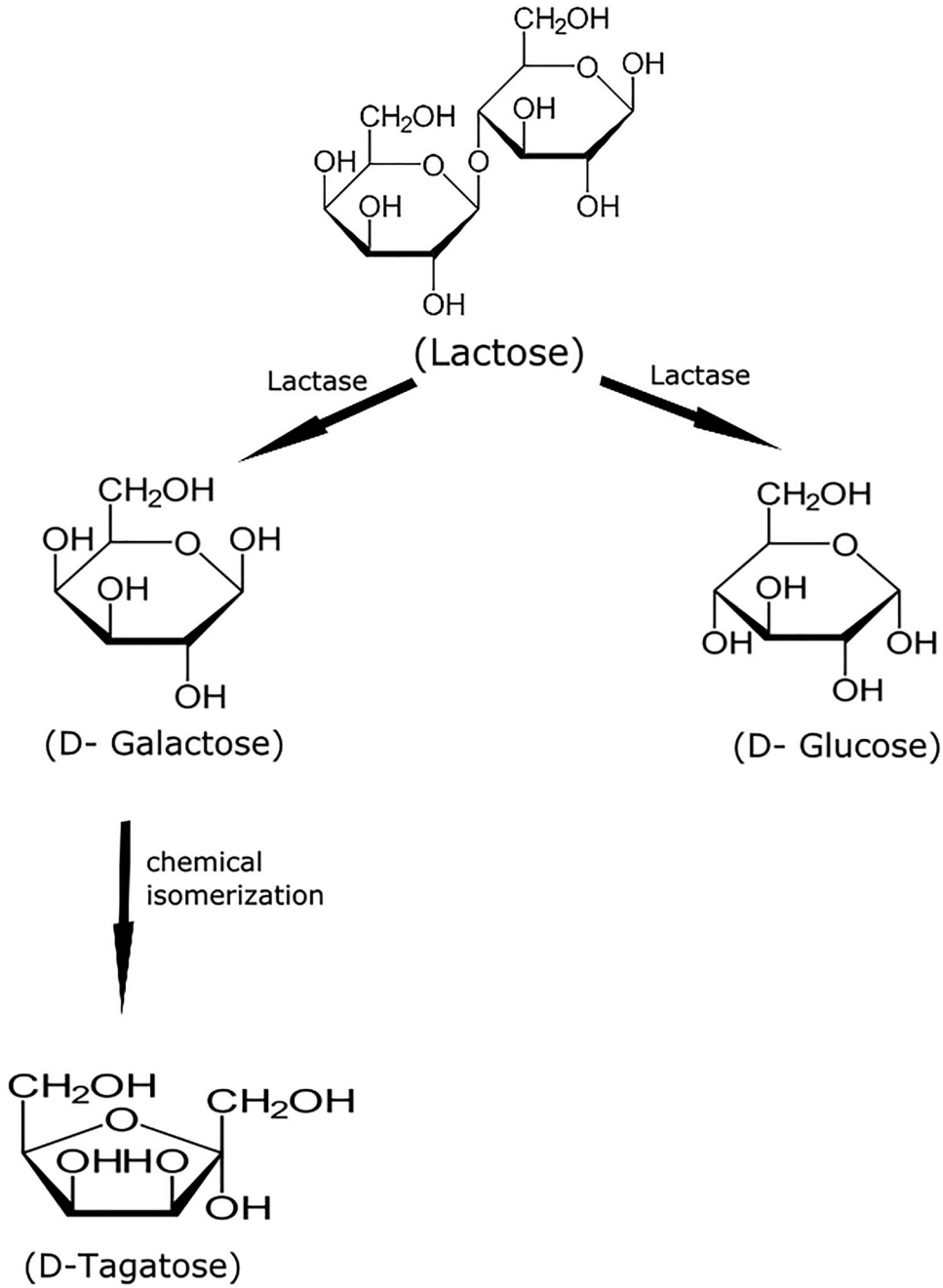

Figure 5. The substrate for the production of D-tagatose is lactose, which is hydrolyzed to D-galactose and D-glucose. The conversion of D-galactose into D-tagatose occurs by chemical isomerization in the presence of calcium chloride. Based on: Ibrahim 2018.

daily throughout life without any adverse health effects. In the European Union, ADI is established by the Scientific Committee on Food (SCF) to protect the health of consumers. Following this, the European Union allowed D-tagatose as a novel food ingredient, with no restrictions on the amount in which it can be used (Lu, Levin, and Donner 2008).

Influence on metabolic parameters

Preliminary animal and preclinical studies of D-tagatose showed its ability to reduce blood glucose and lipoprotein content. Compared to sucrose, D-tagatose reduces levels of total cholesterol, very low-density lipoprotein cholesterol (VLDL-C), LDL-C in mice (Police et al. 2009) and humans (Ensor et al. 2015), and increases HDL-C (Donner, Magder, and Zarbalian 2010). The suggested mechanism of action may include decreased pyruvate formation from glycolysis or reducing acetyl-CoA within the Krebs cycle, which is a precursor for cholesterol and fatty acid biosynthesis (Muddada 2012). Muddada (2012) also suggested that D-tagatose blocks the absorption of fructose through the gut and can effectively reduce diet-induced dyslipidemia. The described beneficial effects of D-tagatose on lipids may indicate its importance in supporting the treatment of obesity with appropriate dietary management.

Different clinical trials (Table 2) conducted in both healthy subjects and diabetic patients confirm the ability of

D-tagatose to decrease postprandial blood glucose rise and reduce glycosylated hemoglobin (HbA1c) (Buemann et al. 1999b; Ensor et al. 2014 (only dose 7,5 g TID), 2015; Kwak et al. 2013; Williams, Spitnale, and Lodder 2013). A phase 2 study conducted by Ensor et al. (2014) determines that the lowest dose of D-tagatose capable of lowering HbA1c is 5.0 g taken three times a day. Nevertheless, only 25% of patients taking 7.5 g of D-tagatose immediately before a meal shows significantly decreased HbA1c levels (Table 3). Further investigations revealed that the regular consumption of D-tagatose by type 2 diabetic patients results in a decrease in HbA1c in both short-term and long-term trials (Donner, Magder, and Zarbalian 2010; Lu, Levin, and Donner 2008).

Carriers transporting fructose in the small intestine do not show an affinity for D-tagatose therefore, only 20% of consumed D-tagatose is absorbed in the small intestine and then metabolized in the liver by the same route as fructose but at a slower rate (Muddada 2012). The rest of the undigested D-tagatose, like other low-digestible carbohydrates (dietary fiber), is fermented in the large intestine by indigenous microflora, resulting in the production of short-chain fatty acids (SCFA), specifically butyrate (reported to combat colon cancer) (Wu et al. 2018). Next, SCFAs are absorbed into the bloodstream from the digestive tract as a source of energy. Furthermore, D-tagatose limits the digestion and absorption of sucrose and maltose by inhibiting the activity of sucrases and maltases in the small intestine (Lu, Levin, and Donner 2008). Therefore, it causes a slight or no increase in postprandial blood glucose. Studies in healthy volunteers and patients with type 2 diabetes have shown that oral administration of D-tagatose alone causes minor glycemic and insulin responses. Donner, Wilber, and Ostrowski (1999) showed that oral intake of 75 g D-tagatose did not increase blood glucose and insulin levels in both healthy patients and type 2 diabetes. D-Tagatose (75 g) administered to eight healthy patients and eight with type 2 diabetes 30 minutes before oral glucose load (75 g) significantly reduced the increase in blood glucose and insulin levels without signs of hypoglycemia (Donner, Wilber, and Ostrowski 1999). The inhibition of postprandial glucose increase by D-tagatose was observed in healthy volunteers when given 4 h and 15 min before a meal (Buemann et al. 2000). Moreover, D-tagatose promotes systematic weight loss, and thus effectively counteracts obesity (Donner, Magder, and Zarbalian 2010), a significant and growing health problem among patients with diabetes. Donner, Magder, and Zarbalian (2010) conducted a pilot study to evaluate the metabolic effects of 15 g D-tagatose taken three times a day to eight people with T2DM for one year. Body weight declined from 108.4 ± 9.0 to 103.3 ± 7.3 kg ($p = 0.001$), HbA1c fell nonsignificantly from 10.6% ± 1.9% to 9.6% ± 2.3% ($p = 0.08$), HDL cholesterol progressively rose from a baseline level of 30.5 ± 15.8 to 41.7 ± 12.1 mg/dL ($p < 0.001$). Nevertheless, a larger placebo-controlled trial is needed to determine whether the use of D-tagatose in patients with T2DM improves glycemic control and, if so, the extent to which improved glycemic control correlates with weight loss.

The mechanism of postprandial sugar lowering is likely to involve a reduction in carbohydrate absorption in the intestine by inhibiting disaccharidase activity, but also by impaired glucose transport or inhibition of hepatic glycogenolysis (Lu, Levin, and Donner 2008). However, after oral administration of D-tagatose, fasting glucose and insulin levels remain unchanged (Ensor et al. 2014). Muddada (2012) explains that D-tagatose competitively inhibits glycogen phosphorylase and promotes the metabolism of glucose-6-phosphate so that glucose is stored as glycogen. On the other hand, D-tagatose 1-phosphate (intermediate of D-tagatose metabolism) promotes glucokinase activity by increasing glucose phosphorylation to glucose-1-phosphate, which activates glycogen synthase. Simultaneously D-tagatose 1-phosphate inhibits glycogen phosphorylase activity, preventing glycogen degradation (Guerrero-Wyss, Agüero, and Dávila 2018; Lu, Levin, and Donner 2008). D-Tagatose, when administered together with glucose, reduces its glycemic index by about 20% (Madenokoji et al. 2003; Muddada 2012). All this indicates that the very low glycemic effect of D-tagatose and a slight blunting effect in glucose levels may be the basis for its use in foods intended for consumption in a low-glycemic diet.

D-Tagatose, like fructose, stimulates GLP-1 without affecting GIP (Wu et al. 2012, 2018), which significantly reduces blood glucose. GLUT5 (Glucose Transporter 5, fructose transporter) can probably mediate early gastrointestinal responses to D-tagatose, including rapidly slowing gastric emptying (Wu et al. 2012).

In humans, intake of 10 g of D-tagatose three times a day for two weeks led to changes in microbial population species and density (Bertelsen, Jensen, and Buemann 1999). The data indicate that D-tagatose has a positive influence on the intestinal flora, on the one hand promoting the development of *Lactobacillus* species and lactic acid bacteria, and on the other hand, limiting the multiplication of pathogenic microorganisms. Bertelsen, Jensen, and Buemann (1999, Bertelsen, Andersen, and Tvede 2001) showed that none of the 11 strains of pathogenic enteric bacteria could degrade D-tagatose. Furthermore, it shows antioxidant and cytoprotective properties, which may be relevant to cancer prevention. D-Tagatose is a candidate for use in the treatment of anemia and hemophilia, as it increases the production of fibrinogen and erythrocytes in blood (Levin 2000 (EP1173186A4)). D-Tagatose also improves fertility and has a positive effect on fetal development (Levin 2001 (US2001020008A1)).

Toxicity

D-Tagatose does not cause toxic side effects, but it can provoke mild digestive problems, such as nausea, flatulence, and diarrhea, due to osmotic influences resulting from its incomplete absorption (approximately 20%) (Buemann et al. 1999b, 2000; Buemann, Toubro, and Astrup 1999a; Donner, Magder, and Zarbalian 2010). However, Buemann et al. (2000) demonstrated the hyperuricemic effect of D-tagatose, which may be an essential contraindication for use in people predisposed to hyperuricemia or gout. In the large intestine,

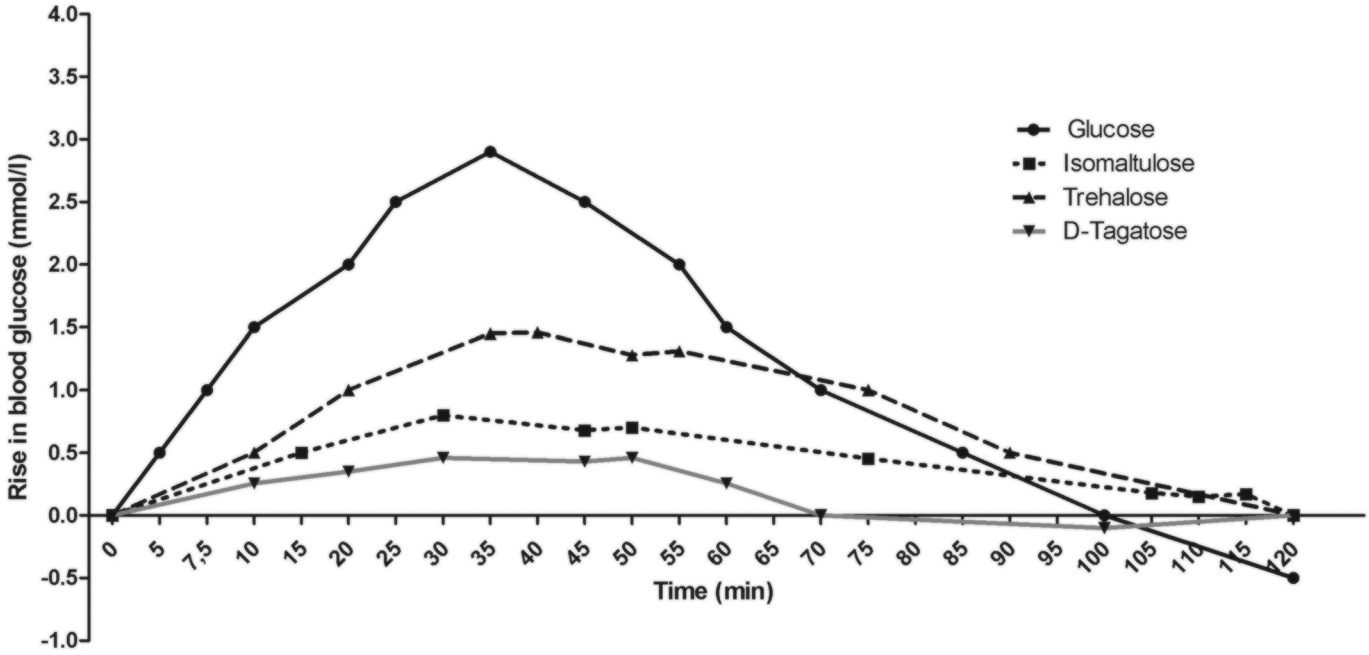

Figure 6. Fast absorbed carbohydrates result in a rapid increase in plasma glucose (e.g., glucose), while slowly digested carbohydrates (e.g., isomaltulose, D-tagatose, trehalose) provide a gradual and enduring release of glucose in the blood. Based on: Kawai, Okuda, and Yamashita 1985; Keyhani-Nejad et al. 2016; van Can et al. 2009; Williams, Spitnale, and Lodder 2013.

previously undegraded D-tagatose retains colonial fluid and increases the water content in the feces, contributing to diarrhea. At the same time, fermentation by the microflora generates gas, which leads to flatulence. A single high dose of 29 g of D-tagatose was well tolerated and the gastric symptoms were consistent with a prediction (e.g., flatulence) (Buemann et al. 1999b) regarding a single dosage of 20 g lactitol (not absorbed disaccharide sugar alcohol) (Lee and Storey 1999). Repeated daily doses of 15 g D-tagatose taken with main meals for 28 days did not change fasting uric acid levels in 12 healthy volunteers (Boesch et al. 2001). Conventional toxicity tests with diets containing 10% to 20% D-tagatose revealed changeable liver enlargement in Sprague-Dawley rats without raising liver enzymes (Bär et al. 1999; Kruger et al. 1999). In the studies conducted by Donner, Magder, and Zarbalian (2010) during a 12-month D-tagatose therapy period, no changes in biochemical parameters or toxic effects on kidney or liver function were found.

Application

D-Tagatose does not have a broad industrial application yet. However, it may be used like other sugars (sucrose, glucose, fructose) as a sweet-tasting, nutritive substance (Table 1). It is known as a low-calorie sweetener in many foods, drinks, and dietary supplements, as well as in toothpaste (noncariogenic) and mouthwash (Oh 2007). However, the future of D-tagatose seems promising because of its properties of high sweetness, low calorific value, low glycemic index, and desirable physicochemical properties for food formulation (as a bulking agent, texturizer, humectant, stabilizer). D-Tagatose also exhibits prebiotic properties, mainly due to its ability to ferment in the large intestine, leading to elevated concentrations of butyrate, which is essential to nourish the intestinal epithelial cells and has proven to protect against colorectal cancer (Andersen and Vigh 2000 (EP1056358A1); Bertelsen, Jensen, and Buemann 1999; Venema, Vermunt, and Brink 2005; Wu et al. 2018). Among all the lactose-derived substances, D-tagatose has the highest potential to be used in large amounts. It has an exquisite taste reminiscent of sucrose, has no cooling effect, a strong aroma reflection, and no aftertaste, unlike stevia, which has a characteristic bitter residual taste (Osman et al. 2013). The chemical properties of this compound, combined with its excellent biological tolerance, explain the extensive interest of scientific and commercial groups. As a reducing sugar, D-tagatose is highly Maillard reactive, which causes nonenzymatic browning of bakery products during heat treatment (Cho et al. 2010). As a result, D-tagatose creates specific aromas of toffee and malt used in confectionery as a flavoring agent. Furthermore, due to its good solubility (58% *w*/*w* at 21 °C) in yogurts (Torrico et al. 2019) and soft drinks, D-tagatose enhances the taste effect in combination with high-intensity sweetener blends of aspartame and acesulfame potassium, saccharine, and sucralose. At doses of 0.2% to 1%, it improves the aftertaste, reduces the taste potentially resulting from the added sweeteners, and reduces the persistent sweetness (Andersen and Vigh 1999 (WO1999034689A1)). While consumers do not need to worry about calories when using non-nutritive sweeteners, they are known to have a different taste than their full-calorie counterparts. The so-called 'dietetic taste' is commonly described as a slow but long-lasting sweet taste accompanied by a bitter or metallic undesirable aftertaste and a watery taste in the mouth. In practice, the combination of D-tagatose with aspartame or blends of aspartame and acesulfame potassium ensures constant changes in taste attributes, since D-tagatose effectively

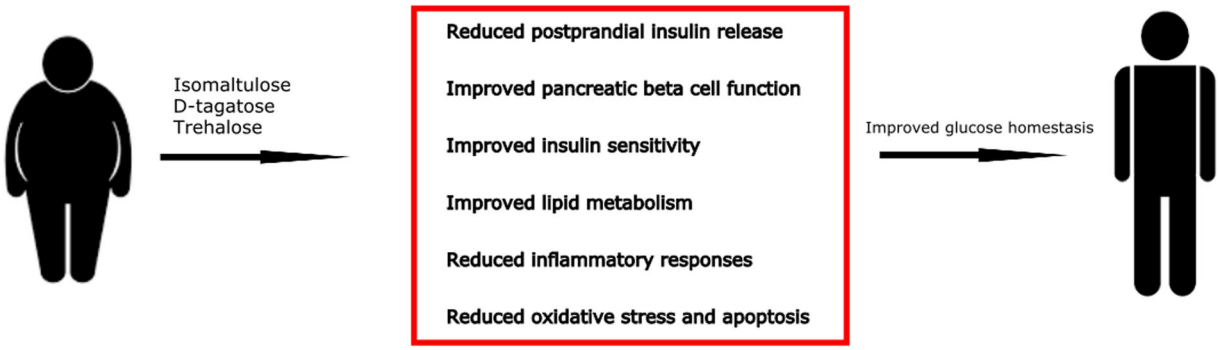

Figure 7. Isomaltulose, D-tagatose, and trehalose improve glucose homeostasis in obese individuals with insulin resistance and reduce obesity and the risk of developing diabetes. Based on: Arai et al. 2007; Beattie et al. 1997; Chen et al. 2016; Donner, Magder, and Zarbalian 2010; Ensor et al. 2015; Henry et al. 2017; Kwak et al. 2013; Lightowler et al. 2019; Liu et al. 2016; Lu, Levin, and Donner 2008; Oizumi et al. 2007; Police et al. 2009; Taya, Hirose, and Hamada 2009.

masks the bitter taste of potassium acesulfame as aspartame degrades. That extends the shelf life of soft drinks (Andersen and Vigh 2002 (US6432464B1)). Moreover, D-tagatose is a better ingredient in mixtures with a high sweetener content because it delivers only a few calories and, in contrast to lactose or maltodextrin, which are often used as carriers of intense sweeteners, it is tooth-friendly (Vastenavond et al. 2012). Hitherto, D-tagatose cannot successfully rival the market for low-calorie foods due to its high production costs of USD 4–6 per pound, and a high market cost of over USD 10 per pound (Richards and Dexter 2012). Arla Food Ingredients amba from Denmark in 1996 licensed all patents for D-tagatose usage in food and beverages. Furthermore, despite its GRAS status, the 61st JECFA (Food and Agriculture Organization of the United Nations (FAO), Joint FAO/WHO Expert Committee on Food Additives (2004) has introduced a list of products using D-tagatose and its permissible limits (1% in carbonated beverages, 2% in bakery products, 15% in hard candies, 15% in breakfast cereals, 25% in chocolate (useful for the formulation of chocolate-type coating of diet and healthy bars), and 60% in chewing gum (tooth-friendly, has a smaller cooling effect than monosaccharide polyols such as xylitol, sorbitol, and mannitol, but higher sweetness than disaccharide polyols such as isomalt, lactitol, and maltitol)) (Table 1). D-Tagatose can be added to dairy products thanks to its prebiotic properties. The daily intake should be then several grams (3–5 g per serving), as the addition of 0.2–1% improves the taste profile of dietary fruit yogurt (Torrico et al. 2019). Paterson and Kellam (2009) estimated that the production of D-tagatose in 2009 was 900 tons, with a market value of USD 1.3 million, and its further increase in production to 20,000–30,000 tons per year after 2015, with a market value of USD 37.5 million.

Trehalose (mycose)

Physical and chemical properties. Regulatory status

Trehalose, known under brand name as Ascend, is a naturally-occurring, nonreducing sugar formed by two D-glucose molecules linked by a-1,1-glycosidic bindings (Feofilova et al. 2014; Richards et al. 2002; Thammahong et al. 2017). The low energy of the glycoside oxygen binding to its two hexose rings ensures high trehalose stability and a lack of reactivity (Schiraldi, Di Lernia and De Rosa 2002). While humans are incapable of synthesizing trehalose, several species of prokaryotes, fungi, invertebrates, insects, yeast, and plants can (Feofilova et al. 2014). The production of trehalose using enzymatic processes began in 1995 (Kobayashi et al. 1997; Kubota et al. 2004), and since then it serves as a food stabilizer (Yoshizane et al. 2017). In comparison with sucrose, trehalose has a lower sweetening value (45 vs. 100 for sucrose) (Table 1) and is decomposed by the enzyme trehalase into two glucose molecules, which provides a high amount of energy (Feofilova et al. 2014; Moriano and Alamprese 2017). Richards et al. (2002) suggest that trehalase works in a manner dependent on insulin levels. Hence, trehalase activity directly affects the blood glucose level after its ingestion (Mizote et al. 2016). In 1995, trehalose, produced by Hayashibara Company, Ltd of Okayama, was approved in Japan as a food additive and since then has been used in hundreds of Japanese food, cosmetics, and body care products in Japan, Europe, and the USA. In 1998 in Korea and Taiwan trehalose obtained the status of food ingredient without any use restrictions. JEFCA in 2000 did not specify ADI (acceptable daily intake) for trehalose. Since 2001, trehalose has been used as a novel food in the EU and has GRAS status in the United States.

Influence on metabolic parameters

Arai et al. (2010), using a mouse model of metabolic syndrome, showed that trehalose intake in mice fed with a high-fat diet (HFD) suppressed mesenteric adipocyte hypertrophy and decreased impaired glucose tolerance in an oral glucose tolerance test (OGTT). In mice fed with HFD, they also found that trehalose intake mitigated insulin resistance, reduced mRNA expression of plasminogen activator inhibitor-1 (PAI-1) (Arai et al. 2010), and increased serum high molecular weight (HMW) adiponectin (Arai et al. 2013). HMW adiponectin may decrease insulin resistance by up-regulating the expression of IRS-1 and IRS-2 mRNA in the muscle (Arai et al. 2013). These effects were also apparent in an obese mouse model when 0.3 or 2.5% (weight/volume) trehalose was consumed through its supplement to drinking water (Arai et al. 2013). A daily intake of 2,5% of trehalose

corresponds to 1.6 g/kg body weight/day in a mouse and 10 g/day in a person weighing 60 kg (Yoshizane et al. 2020). This effect is exerted either directly on glucose signaling pathways or indirectly via alleviating pathophysiologic pathways, such as oxidative stress, inflammation, or improvement in lipid metabolism (Arai et al. 2010).

Trehalose potentially prevents the development of the metabolic syndrome and improves glucose tolerance in humans. Maki et al. (2009) showed that the consumption of trehalose by obese men effectively reduces postmeal insulin bursts. According to a placebo-controlled, double-blind trial in 34 subjects with a body mass index (BMI) $\geq$23 conducted by Mizote et al. (2016), a daily intake of 10 g trehalose for 12 weeks enhances glucose metabolism in healthy humans assessed by oral glucose tolerance tests (OGTT). Additionally, trehalose does not cause a rapid increase in postprandial glucose (Yoshizane et al. 2017). Given that postprandial hyperglycemia contributes to the progression of cardiovascular complications of diabetes mellitus (Lebovitz 2001) and coronary artery disease associated with diabetes (Haffner et al. 1998). Hanefeld's (1996) has proven for the first time the importance of postprandial hyperglycemia assessed based on the determination of glycemia in the two-hour post load glycemia (2 h-PG) obtained during the oral glucose tolerance test (OGTT) of atherosclerosis development. The DECODE study (1999) showed that glycemia above 7.8 mmol/l in the 2-h PG increased the risk of coronary artery disease by 58% while fasting hyperglycemia above 6.1 mmol/l - by 38%.

Trehalose induces lower insulin secretion than glucose in oral saccharide tolerance test in female students (age 21.8 ± 5.4) (Oku and Nakamura 2000) and makes the active GIP less secretive (Yoshizane et al. 2017). The mean individual blood GIP iAUC (incremental Area Under the Curve) ratio of trehalose loading to glucose loading was only 14% (Yoshizane et al. 2017). The relationship between GIP and obesity has been explained as the physiological role of GIP in the intake of nutrients into adipose tissue, thus linking overnutrition to obesity (Getty-Kaushik et al. 2006). Furthermore, GIP receptor-deficient mice fed a high-fat diet were protected from obesity (Nasteska et al. 2014). GIP stimulates islet growth (Herbach et al. 2011) and proliferation of β-cells (Renner et al. 2010), and reduces β-cell apoptosis (Kim et al. 2005, Widenmaier et al. 2010). In adipose tissues, GIP promotes fat deposition (Getty-Kaushik et al. 2006; Seino, Fukushima, and Yabe 2010). Also, insulin promotes the storage of lipids in adipocytes, and its excessive secretion can cause hypertrophy of these cells (Kokta et al. 2008). Thus, it seems that trehalose reduces insulin-dependent adipocyte accumulation after a carbohydrate-rich meal (Arai et al. 2010; Yoshizane et al. 2017) and has a beneficial effect on islet function (Beattie et al. 1997; Chen et al. 2016), limiting or inhibiting apoptotic processes, and improving the efficiency of pancreatic beta cells in patients with diabetes (Beattie et al. 1997). In contrast, GLP-1 protects pancreatic β-cells and suppresses appetite. Yoshizane et al. (2017) showed that the active GLP-1 levels following trehalose loading were higher than those following glucose loading from 45 to 180 min after ingestion.

Accumulation of visceral fat, which is closely related to adipocyte hypertrophy, is one of the main criteria for diagnosing metabolic syndrome. Hypertrophy contributes to hypoxia of adipocytes, leads to cell stress, initiates the cells death, and activates transcription factor NFκB, which increases expression of genes encoding pro-inflammatory cytokines, adipokines, and a chemoattractant (e.g., MCP-1; monocyte chemotactic protein-1) which result in interference with insulin signaling (Sokolowska and Blachnio-Zabielska 2019). In experimental studies, trehalose intake significantly reduces the concentration of inflammatory cytokines, such as TNF-α (tumor necrosis factor-alpha) and LPS-induced IL-1β in mouse peritoneal macrophages (Taya, Hirose, and Hamada 2009), MCP-1, and PAI-1 (plasminogen activator inhibitor-1), whereas a significant increase in the MCP-1 mRNA expression was observed in the high-fat diet raised animals with given drinking water containing 2.5% glucose, maltose, or distilled water ad libitum (Arai et al. 2010; Taya, Hirose, and Hamada 2009). Also, Mizote et al. (2016) showed that trehalose improves insulin resistance by adiponectin release and PAI-1 down-regulation in people at risk of metabolic syndrome. Echigo et al. (2012) described the anti-inflammatory effect of trehalose in subarachnoid hemorrhage models. Thus, trehalose intake partially improves insulin sensitivity by minimizing the inflammatory response (Taya, Hirose, and Hamada 2009). Particularly, trehalose activates canonical hepatic fasting-like responses, including hepatocyte autophagic flux, transcription factor EB (TFEB) and peroxisome proliferative activated receptor, gamma, coactivator 1 alpha (PPARGC1A), and hepatic fibroblast growth factor 21 (FGF21) release (DeBosch et al. 2016; Mayer et al. 2016; Zhang et al. 2018; Zhang and DeBosch 2019). Higgins et al. (2018) revealed that trehalose triggers ALOXE3 (epidermis-type lipoxygenase 3) activation which, in turn, induces insulin sensitivity via PPAR-γ (peroxisome proliferator-activated receptor-gamma)-dependent mechanisms in mice. These responses improve mitochondrial function and total energy expenditure, reduce diet-induced hepatic steatosis, and enhance insulin sensitivity (Higgins et al. 2018; Zhang et al. 2018).

Trehalose has received attention as a promising autophagy-inducing therapeutic agent in humans and rodent models against several disorders in which autophagy plays an important role, such as neurodegenerative diseases, cancer, aging, cardiometabolic disorders, and other infectious diseases (DeBosch et al. 2016; Hosseinpour-Moghaddam, Caraglia and Sahebkar 2018; Lim et al. 2014; Mardones, Rubinsztein, and Hetz 2016; Rusmini et al. 2019; Sarkar et al. 2007). Initially, the protective effect of trehalose was attributed to its chemical properties of a chaperone (Diamant et al. 2001). However, Sarkar et al. (2007) identified trehalose as an autophagic enhancer. Autophagy is a highly conservative intracellular digestion process, regulated by the mammalian target of rapamycin (mTOR) (Jung et al. 2010; Saxton and Sabatini 2017). Interestingly, trehalose induces autophagy independent of mTOR (Sarkar et al. 2007). In mammalian cell cultures, trehalose-induced autophagy enhanced the clearance of autophagy substrates

like mutant huntingtin and the A30P and A53T mutants of alpha-synuclein, associated with Huntington and Parkinson's diseases, respectively (Sarkar et al. 2007). DeBosch et al. (2016) analyzed the effect of trehalose on lipid accumulation in the liver. They discovered that trehalose effectively inhibits NAFLD development in the mouse model. Moreover, trehalose blocked glucose absorption into the cells by inhibiting glucose transporters in the plasma membrane (GLUT1, GLUT2, GLUT3, GLUT4, and GLUT8). Consequently, induces a hunger reaction, that activates autophagy, stimulates the activation of adenosine monophosphate kinase (AMPK) and phosphorylation of ULK1 (Unc-51 Like Autophagy Activating Kinase 1). Although the protective effects of trehalose have been confirmed in vitro or in vivo, there is still little information available on the physiological function of trehalose in humans.

Toxicity

A limited number of reports of trehalose intolerance have appeared in the literature and seem to be less common (<1%) than lactose intolerance (Richards et al. 2002). Toxicity of trehalose was investigated during acute and subchronic toxicity studies in mice, rats, and dogs. The results of the study indicate that trehalose is well tolerated, even when consumed in high doses (10% daily dietary intake), with no signs of maternal toxicity, embryotoxicity, or teratogenicity (Richards and Dexter 2012). Trehalose causes self-limiting loose stools, the same as that characteristic of lactose intolerance or excessive consumption of sugar alcohols. A very few people have a trehalase deficiency. Western populations have adequate trehalase activity and can consume at least 50 g of trehalose without digestive disorders (Bergoz, Bolte, and Meyer Zum Bueschenfelde 1973). However, a deficiency of trehalase in Greenland was reported in at least 8% of the 94 adults screened, which is significantly higher than elsewhere (Gudmand-Høyer et al. 1988). Oku and Okazaki (1998) have shown that a 33 g amount of trehalose for one eating occasion is well tolerated by a person weighing 50 kg. While trehalose could provide significant benefits as an antiviral treatment, studies showed that trehalose consumption elevates the expansion and virulence of *Clostridioides difficile* that metabolize trehalose through trehalose-6-phosphate hydrolase (Collins et al. 2018). Furthermore, it should be noted that despite intensive research on the administration of trehalose in adults, there is still insufficient data on its safety in children, adults with health problems, and the elderly.

Application

Trehalose, due to several properties such as high thermostability, hydrolytic resistance, or low hygroscopicity, is an attractive ingredient for improving the stability and humidity of food products and extending their shelf life (Richards et al. 2002). It stabilizes cell membranes and prevents protein denaturation by increasing plasma membrane tolerance to dehydration, shrinkage, and temperature shock (Chen and Haddad 2004). Additionally, trehalose has an osmoprotective effect, especially against ethanol (Schiraldi, Di Lernia and De Rosa 2002). Thanks to its high stability and resistance to heat and hydrolysis, it is an excellent choice for parenteral preparations as it can be autoclaved or irradiated (Caballero et al. 2005). It can also replace sucrose in products where a reduction in sweetness levels is desired. In baked products, trehalose seems to be more effective than other sugars in inhibiting starch retrograde during storage, thus providing better stability (Richards et al. 2002). Moreover, due to its identical calorific value to sucrose (4 kcal/g) (Table 1), it is a source of carbohydrates intended for use before and during physical training (Cooper et al. 2001 (GB2356788)) (Table 4). Especially when consumed before prolonged aerobic effort, trehalose maintains blood glucose levels as effectively as glucose, while producing lower plasma insulin response (Jentjens and Jeukendrup 2003). As an ingredient in hydrating drinks for athletes, it increases the use of lipids, which leads to saving energy for later training intervals. Thus, it can be successfully used as a functional sports drink (Wadazumi et al. 2019). Nowadays, trehalose is manufactured enzymatically from starch by Hayashibara Biochemical Laboratories and is distributed in Japan for about USD 3.00 per kilo (Richards and Dexter 2012). The current production is estimated at 25.0000-30.000 tons per year (Richards et al. 2002).

Comparison of sweeteners

Artificial sweeteners- health aspect

Sugars and sweeteners are essential in the human diet as ingredients improving the carbohydrate and nutritional profile of many manufactured products. The sweet taste is associated by people with a safe, energizing food product and often decides on acceptance or rejection of a grocery product (Breslin 2013). Yet the choice of their appropriate amounts has an impact on health. The American Diabetes Association (2002) does not recommend reducing carbohydrate intake below 40% of the total daily calorie intake in people with type 2 diabetes mellitus. Appropriately selected sugars and sweeteners offer a wide range of potential health effects, including reduced dental caries, calorie value limitation, and therefore reduced risk of obesity and improved survival. However, the use of artificial (non-nutritive) sweeteners remains controversial. They have been shown to cause adverse effects in mice, rats, dogs, and humans. Some studies have associated artificial sweeteners with higher rates of headaches (aspartame, acesulfame-K, neotame) (Blumenthal and Vance 1997), gastrointestinal disorders like nausea, vomiting, diarrhea (aspartame, saccharin, sucralose) (Whitehouse, Boullata, and McCauley 2008), the severity of the symptoms of phenylketonuria by ingestion of aspartame (L-aspartyl-L-phenylalanine methyl ester) containing phenylalanine (Güttler and Lou 1985) as well as potentially life-threatening cancer such as thyroid tumors in rats (acesulfame-K) (Findikli and Turkoglu 2014), leukemias in rats (aspartame) (Soffritti et al. 2006), bladder cancer in rodents (cyclamate) (Price et al. 1970), cancer in offspring of breast-

fed animals (saccharin) (Arnold et al. 1980). These studies have been partially challenged, and some have shown that sweeteners are safe (Baird et al. 2000; Gallus et al. 2007; Mayhew, Comer, and Stargel 2003). Nevertheless, long-term testing appears necessary to alleviate concerns arising from limited human studies.

Swithers and Davidson (2008) have indicated that high-intensity sweeteners are not suitable substitutes for sugar and can promote weight gain through increased intake of calorie-free and sugar-free products, but such relationship is questioned (Rolls 1991). Thanks to the successful marketing efforts of the diet drinks industry and to changing dietary preferences, artificial sweeteners are considered a healthy alternative to table sugar (de la Peña 2010; Vartanian, Schwartz, and Brownell 2007). But do artificial sweeteners support weight loss? Some epidemiological data suggest the opposite. National Health and Nutrition Examination Survey (NHANES) Study and San Antonio Heart Study showed higher weight gain and BMI in people consuming sweeteners (Brown, de Banate and Rother 2010; Colditz et al. 1990; Fowler et al. 2008; Stellman and Garfinkel 1986). Also, the European E3N study (Fagherazzi et al. 2013), Health Professionals Follow-up Study (HPFS) (de Koning et al. 2011), the European Prospective Investigation into Cancer and Nutrition (EPIC) Study (Romaguera et al. 2013) linked the consumption of artificial sweeteners to an increased risk of developing type 2 diabetes. In contrast, a pilot study by Porikos, Booth, and Van Itallie (1977) showed that secretly converting a sugar-containing diet to aspartame on a metabolic ward resulted in an immediate 25% reduction in energy intake. Mattes (1990) indicated that planned intake of aspartame was associated with an increase in overall energy intake, suggesting an offset to the expected caloric reduction. However, there are little data that conclusively link artificial sweeteners to weight gain or loss in humans (Anderson et al. 2012).

Functional magnetic resonance imaging in five healthy, normal-weight men showed that glucose ingestion caused a prolonged and significant decrease in signal in the superior hypothalamus ($P < 0.05$). Water, aspartame, and maltodextrin had no such effect (Smeet et al. 2005). The sweet taste receptor is a heterodimer of two T1R2 and T1R3 receptors coupled through G protein, α-gustducin, and transducin, to activate phospholipase C $\beta 2$ and increase intracellular calcium concentration (Mace et al. 2007). These receptors can respond to almost any sweet molecule, including natural sugars, artificial sweeteners, and sweet-tasting proteins (Cui et al. 2006). In vitro studies have shown that the G-protein gustducin and other elements of the taste signals (T1r1, T1r2, T1r3, TRPM5, PLC$\beta 2$) are expressed on enteroendocrine L cells and are responsible for the secretion of cholecystokinin (CCK), peptide tyrosine (PYY), neurotensin, GLP-1, GLP-2, and GIP (Jang et al. 2007; Margolskee et al. 2007; Temizkan et al. 2015). Presumably, the gut senses glucose and sweet compounds such as artificial sweeteners, leading to the release of glucagon-like peptide-1 (GLP-1) from enteroendocrine cells (Temizkan et al. 2015). Margolskee et al. (2007), in animal studies, showed that activation of sweet taste receptors by artificial sweeteners increases sodium-dependent glucose cotransporter 1 (SGLT-1) expression and enhances intestinal glucose absorption through upregulation of GLUT2.

Haase, Cerf-Ducastel, and Murphy (2009) showed that sucrose caused significantly greater global activation of higher gustatory areas, such as the insula, orbitofrontal cortex, and amygdala, especially in the hungry state, than other tastes, both sweet (artificial sweetener saccharin) and bitter (caffeine). Researchers indicate that artificial sweeteners have no nutritional value and, therefore, the brain may respond less to them. Frank et al. (2008) showed that sucrose, but not sucralose, engages dopaminergic midbrain areas concerning the behavioral response to pleasure. Thus, the brain response distinguishes a caloric from a non-caloric sweetener, although the conscious mind cannot. Brown, de Banate, and Rother (2010), in a systematic review of the effects of sweeteners on adolescent metabolic outcomes, note that artificial sweeteners may reduce total caloric intake when consumed between meals. Lenoir et al. (2007) compared the saccharin sweet taste addiction (an intense sweetener without calories) dissolved in drinking water with intravenous cocaine addiction in rats. Surprisingly, 94% of 132 Wistar rats preferred the sweet taste of saccharine, which indicates the generation of a strong reward signal in the brain (signaling dopamine in the ventral striatum), with the possibility of bypassing self-control mechanisms and thus leading to addiction.

Impact of GI and GL values on clinically relevant outcomes

Functional alternative sweeteners are used in a variety of foods and beverages but are not preferred by consumers due to their low sweetness and poor aftertaste. Therefore, research is ongoing to develop functional alternative sweeteners that can provide both the sweetness of traditional sugar and the right taste, aroma, and aftertaste. Certain sugars such as D-tagatose are a substrate for butyrate production and potentially mitigate the risk of colorectal cancer (Bertelsen, Andersen, and Tvede 2001; Feofilova et al. 2014; Levin 2002; Paterson and Kellam 2009; Wu et al. 2018). Especially important are their effects on the glycemic response and the possibility of participating in low glycemic index (GI, which classifies carbohydrate foods according to the degree of postprandial glycemia) or glycemic load (GL) (Augustin et al. 2015). The type of carbohydrates consumed and their source of origin are determinants influencing the absorption rate and glycemic response of the body. It has been shown that the consumption of low GI (<70) and GL (<10 for a single product and <120 per day) food results in the reduction in postprandial elevated blood glucose levels and the gradual normalization of glycemia, which is associated with reduced postprandial hyperinsulinemia (Augustin et al. 2015; Berra and Rizzo 2009; Monro and Shaw 2008). Salmerón et al. (1997b) found a positive association between GI and the development of type 2 diabetes in women after adjusting for age, body mass index (BMI), smoking, physical activity, family history of diabetes, alcohol and cereal fiber consumption, and total energy intake. In the EURODIAB

Complications Study, patients from northern, eastern, and western Europe who followed a low-GI diet had higher HDL-C levels and lower HbA1c values. The observed relationships between GI and HDL-C concentrations were independent of dietary fiber intake (Buyken et al. 2001). In the Framingham Offspring Cohort Study, both dietary GI and GL were positively associated with insulin resistance (McKeown et al. 2004). There was no such association in the Zutphen Elderly (van Dam et al. 2000), IRAS (Liese et al. 2005), Health ABC (Sahyoun et al. 2005), and Inter99 studies (Lau et al. 2005). Some epidemiological evidence also showed no significant association between LDL-C, total cholesterol (TC), triglyceride (TG), and low-GL diet (Buyken et al. 2001; Frost et al. 1999; van Dam et al. 2000). Moreover, Liu et al. (2000) found a positive association between a high-GI diet and the development of coronary heart disease, whereas van Dam et al. (2000) found no association. According to prospective cohort studies of GI and GL and chronic disease risk, the lowering of postprandial glycemia and insulinemia levels through an appropriate choice of sugars, including lower energy intake and exercise, can improve glycemic control, leading to a reduction in the incidence or development of metabolic diseases, comprising metabolic syndrome, diabetes, cardiovascular disease, arthritis, hypertension, stroke, elderly related macular degeneration, and some cancers (Barclay et al. 2008).

Comparison of the effects of isomaltulose, D-tagatose, and trehalose on glycemia

The glycemic response to glucose, isomaltulose, D-tagatose, and trehalose (Figure 6) illustrates new possibilities to create sweeteners with a predictable blood glucose control. Other examples, including the insulin response, are summarized in Table 1. It seems that isomaltulose, D-tagatose, and trehalose are agents that aid in managing the blood glucose profile. Trehalose has a glycemic response comparable to maltose (Table 1) in terms of GL (100 g of glucose). Its peak values are less acute (approximately 38% vs. glucose) (Yoshizane et al. 2017), and elevated glycemia remains at levels that are likely to prevent hypoglycemia in sensitive individuals. Isomaltulose gives a similar but lower profile, i.e., lower GL, which is due to weaker hydrolysis and absorption of its α-1,6 glycosidic bond between glucose and fructose. The response after ingestion of D-tagatose (in the form of insulin secretion and an increase in blood glucose levels) is only 3% of the same amount of glucose (Kwak et al. 2013). D-Tagatose also reduces intestinal glucose absorption (Donner, Wilber, and Ostrowski 1999) and promotes glycogen synthesis (Muddada 2012). By inhibiting the breakdown of sucrose into glucose and fructose, it slows down the absorption of glucose and prevents fluctuations in blood glucose levels (Donner, Wilber, and Ostrowski 1999). It is worth noting that leap changes in blood glucose levels in the postprandial period are likely to affect the blood vessels in the heart, brain, kidneys, eyes, and feet (Ceriello 2004; Hippisley-Cox and Coupland 2016; Prasad et al. 2014; Yoshizane et al. 2017). Studies have shown that the consumption of D-tagatose does not promote hyperglycemia and adipose cell proliferation, which facilitates weight control and the fight against diabetes. This fact makes D-tagatose a perfect substitute for sucrose for both patients with diabetes and people with insulin resistance and obesity (Donner, Wilber, and Ostrowski 1999). All this indicates that low-glycemic sweeteners, including isomaltulose, D-tagatose, and trehalose, are useful in controlling weight, treating diabetes, and reducing obesity risks (Figure 7).

Isomaltulose minimize large fluctuations in blood glucose levels in obese adults with normal (van Can et al. 2009) or impaired glucose tolerance (König et al. 2012; van Can et al. 2009), as well as in individuals with type 1 (Bracken et al. 2012) and noninsulin-dependent type 2 diabetes (Ang and Linn 2014; Keyhani-Nejad et al. 2016). Henry et al. (2017) pointed out that isomaltulose added to the diet reduces glycemic response and promotes fat oxidation when compared to a higher glycemic diet with sucrose. Moreover, the effect lasts a whole day, implying that small nutritional modifications, such as the substitution of high glycemic index carbohydrates for lower glycemic alternatives, can contribute to weight and glycemic management. Furthermore, regular meals with isomaltulose resulted in lower blood glucose and insulin levels and increased fat oxidation by up to 18% (König et al. 2012) (Table 3, Figure 7).

Several studies have shown a potential of D-tagatose in blood glucose controlling levels by limiting postprandial increases in glucose and reducing HbA1c in both healthy and diabetic individuals (Buemann et al. 1999b; Buemann et al. 2000; Buemann, Toubro, and Astrup 1999a; Donner, Magder, and Zarbalian 2010; Ensor et al. 2014, 2015). According to preliminary studies (Donner, Magder, and Zarbalian 2010; Donner, Wilber and Ostrowski 1999), D-tagatose can be a useful supplement to the therapy of oral antidiabetic drugs. Clinical trials in phases 1 and 2 revealed, that D-tagatose can be helpful in control of HbA1c, postprandial hyperglycemia, and hyperinsulinemia, as well as an increase in high-density lipoprotein cholesterol (Donner, Magder, and Zarbalian 2010, Ensor et al. 2015), simultaneously leading to weight loss at a medically desired rate, which indirectly reduces cardiovascular risk. However, Ensor et al. (2015) revealed that D-tagatose was unable to lower triglycerides or raise HDL. Other benefits identified increased butyrate production, as well as its antioxidant and prebiotic properties (Bertelsen, Jensen, and Buemann 1999; Venema, Vermunt, and Brink 2005).

The use of trehalose also enhances glucose metabolism by influencing oxidative stress, apoptosis, and inflammation, increasing pancreatic beta cells function, lowering postprandial insulin secretion, and normalization of lipid profile (Arai et al. 2010; Maki et al. 2009; Mizote et al. 2016). Such molecular mechanisms indicate the use of trehalose as a nonpharmacological option in the control of glycemia in diabetic patients. (Mizote et al. 2016) (Figure 7).

Market share of sweeteners

According to Transparency Market Research (transparencymarketresearch.com), the global sweetener market is expected to reach USD 82.6 billion by 2024. It is currently dominated

by sucrose, whose share in 2018 was 77.2%. However, due to the reported health benefits of low-calorie sweeteners, global consumption of low-glycemic index foods and beverages peaked at over USD 9 billion in 2016. The development of alternatively-sweetened foods for diabetic patients, combined with the growing demand for dietary drinks, is expected to drive further growth in their market share. Most of these products contain calorie-free artificial sweeteners such as aspartame and sucralose or low-calorie sugar alcohols such as sorbitol and xylitol. These products are helpful in weight control and are used by diabetic patients, as they do not increase blood sugar levels. Nevertheless, alternatives to sucrose—isomaltulose, trehalose, and D-tagatose—have an organoleptic quality and, above all, valuable nutritional and functional properties for use in the food industry.

The inclusion of low-glycemic nutrition as one of the elements of a "healthy diet" in diabetes therapy is becoming increasingly important. Strategies for a new approach to functional foods combine reduced GI or GL, saturated fat reduction, and reduced energy value. Desirable properties are found in alternative sugars and sweeteners. The European Food Safety Authority (EFSA) noted the pro-healthy impact of a reduction in the glycemic response for the whole population, taking into account food ingredients such as isomaltulose and D-tagatose (Panel members. Regulation (EC) No 1924/2006). This is in line with the WHO/FAO recommendations (1998) to food producers, which state that existing and new technologies should be used to provide low-glycemic index foods, which will help to achieve the dietary targets for the amount and nutritional properties of carbohydrates in food.

Conclusion

Meals with low GI reduce postprandial blood glucose levels, reduce insulin secretion, and reduce serum triglycerides (Frost et al. 1996, Wolever et al. 1992). Moreover, the inclusion of slowly digested starch in the diet delays the occurrence of insulin resistance in rodents and humans (Byrnes, Miller, and Denyer 1995; Miao et al. 2015). Some epidemiological studies suggest that a low GI diet is associated with a reduced risk of developing non-insulin diabetes in men (Salmerón et al. 1997a) and women (Meyer et al. 2000; Salmerón et al. 1997b). Isomaltulose, D-tagatose, and trehalose are a unique choices over high glycemic carbohydrates, with all the nutritional and physiological benefits of low GI foods, which are generally only partially digested, providing long term energy sources and no adverse effects on human health. Moreover, undigested D-tagatose increases the amount of short-chain fatty acids through intestinal fermentation. This affects the systemic metabolism of nitrogen and lipids, as well as the potential protective effect against colorectal cancer (Wu et al. 2018). Nevertheless, there are negative effects on human health, ranging from diarrhea, flavulation and elevated uric acid (Buemann et al. 1999b; 2000). Therefore, the use of isomaltulose, D-tagatose, and trehalose may support health and limit common metabolic diseases such as insulin resistance, type 2 diabetes, and obesity, having no negative impact on product quality and human health.

Despite numerous data showing the benefits of isomaltulose, D-tagatose, and trehalose as a replacement for certain sweeteners, their widespread use in different industries and countries may ultimately depend on production costs, the interest of potential customers, and the difficulties of commercialization due to intellectual property. The economic barrier has been significantly reduced in the production of trehalose and isomaltulose. D-Tagatose still seems to be an expensive sugar. The reluctance of the producer/consumer may be the next challenge in the broadermarketing of products. The sugars and sweeteners that isomaltulose, D-tagatose, and trehalose can replace (including sucrose, mannitol, lactose, erythritol, stevia) have long been used in the food and pharmaceutical industries. Thus there must be a cost-effective encouragement for a change in existing production. Besides, the application of isomaltulose, D-tagatose, and trehalose in various fields of interest or countries may be limited, as shown by the number of patent applications (Table 4). So far, the use of isomaltulose, D-tagatose, and trehalose is much more widespread in Asian countries. However, with the development of new manufacturing methods to improve efficiency and thus affordability, isomaltulose, D-tagatose, and trehalose are expected to represent a significant share of the global sweetener market in an increasing number of products and applications.

Author contributions

Writing–original draft preparation, E.S.; writing–review and editing, E.S., A.S., D.S., J.K-B. and H.C.

Availability of data and material

The data used to support the findings of this study are available from the corresponding author upon request.

Conflicts of interest

The authors declare no conflict of interest.

Abbreviations

ADI	acceptable daily intake
Akt	protein B kinase
ALOXE3	Epidermis-type Lipoxygenase 3
AMPK	adenosine monophosphate kinase
BMI	body mass index (kg/m2)
CCK	cholecystokinin
DiRECT	Diabetes Remission Clinical Trial
EFSA	European Food Safety Authority
EGP	endogenous glucose production
EI	energy intake
EU	European Union
FAO	Food and Agriculture Organization of the United Nations
FDA	U.S. Food and Drug Administration
FFA	free fatty acids
FFM	free fat mass
FGF21	fibroblast growth factor 21
FM	fat mass
FMD	flow-mediated dilation

FO	fat oxidation
GADA	glutamate decarboxylase antibodies
GI	glycemic index
GIP	glucose dependent insulinotropic polypeptide, gastric inhibitory protein
GL	glycemic load
GLP-1	glucagon-like peptide 1
GLUT5	Glucose Transporter 5
GRAS	generally recognized as safe
HbA1c	glycosylated hemoglobin
HDL-C	high-density lipoprotein cholesterol
HFD	high-fat diet
HMW	high molecular weight
HOMA2	homeostatic model 2
iAUCIR	incremental area under the curveinsulin resistance
IRS-1	insulin-1 receptor substrate
ISO	isomaltulose
JEFCA	WHO Joint Expert Commission for Food Additives
LDL-C	low-density lipoprotein cholesterol
MAGE	mean amplitude of glycemic excursion
MCP-1	monocyte chemotactic protein-1
mTOR	mammalian target of rapamycin
NAFLD	non-alcoholic liver diseases
NEFA	nonesterified fatty acids
ns	non-significant
OGTT	oral glucose tolerance test
PAI-1	plasminogen activator inhibitore1
PI3K	phosphatidylinositol 3-kinase
PPAR-γ	peroxisome proliferator-activated receptor-gamma
PPARGC1A	peroxisome proliferative activated receptor, gamma, coactivator 1 alpha
PYY	peptide tyrosine
REE	resting energy expenditure
RGR	relative glycemic response
RIR	relative insulin response
RQ	respiratory quotient
SGLT-1	sodium-dependent glucose cotransporter 1
SCF	Scientific Committee on Food
SCFA	short-chain fatty acids
Socs2	suppressor of cytokine signaling 2
SUC	sucrose
TAG	d-tagatose
TC	total cholesterol
TG	triglyceride
2 h-PG	two-hour post load glycemia
T2DM	type 2 diabetes mellitus
TFEB	transcription factor EB
TNF-α	tumor necrosis factor-alpha
ULK1	Unc-51 Like Autophagy Activating Kinase 1
VLDL-C	very low-density lipoprotein cholesterol
WC	waist circumference
WHO	World Health Organization

Funding

This work was supported by the National Science Centre, Poland Grant DEC-2018/02/X/NZ5/02339, Operational Programme Smart Growth 2014–2020, Programme "INKUBATOR INNOWACYJNOŚCI 2.0", and by funds from Medical University of Bialystok Grant SUB/3/NN/20/001/3327.

ORCID

Emilia Sokołowska http://orcid.org/0000-0002-8695-5304
Anna Sadowska http://orcid.org/0000-0002-5478-8732
Diana Sawicka http://orcid.org/0000-0002-6804-3459
Halina Car http://orcid.org/0000-0002-4926-3405

References

Achten, J., R. L. Jentjens, F. Brouns, and A. E. Jeukendrup. 2007. Exogenous oxidation of isomaltulose is lower than that of sucrose during exercise in men. *The Journal of Nutrition* 137 (5):1143–8. doi: 10.1093/jn/137.5.1143.

Ahlqvist, E., P. Storm, A. Käräjämäki, M. Martinell, M. Dorkhan, A. Carlsson, P. Vikman, R. B. Prasad, D. M. Aly, P. Almgren, et al. 2018. Novel subgroups of adult-onset diabetes and their association with outcomes: A data-driven cluster analysis of six variables. *The Lancet. Diabetes & Endocrinology* 6 (5):361–9. doi: 10.1016/S2213-8587(18)30051-2.

American Diabetes Association. 2002. Evidence-based nutrition principles and recommendations for the treatment and prevention of diabetes and related complications. *Diabetes Care* 25 (1):202–12. doi: 10.2337/diacare.25.1.202.

Andersen, H., and M. L. Vigh. 1999. Use of d-tagatose as synergiser and flavour enhancer. WO1999034689A1. Accessed April 10, 2020. https://worldwide.espacenet.com.

Andersen, H., and M. L. Vigh. 2000. Use of d-tagatose as a prebiotic food component. EP1056358A1. Accessed April 10, 2020. https://worldwide.espacenet.com.

Andersen, H., and M. L. Vigh. 2002. Synergistic combination of sweeteners including D-tagatose. US6432464B1. Accessed April 10, 2020. https://worldwide.espacenet.com.

Anderson, G. H., J. Foreyt, M. Sigman-Grant, and D. B. Allison. 2012. The use of low-calorie sweeteners by adults: Impact on weight management. *The Journal of Nutrition* 142 (6):1163S–9S. doi: 10.3945/jn.111.149617.

Ang, M., and T. Linn. 2014. Comparison of the effects of slowly and rapidly absorbed carbohydrates on postprandial glucose metabolism in type 2 diabetes mellitus patients: A randomized trial. *The American Journal of Clinical Nutrition* 100 (4):1059–68. doi: 10.3945/ajcn.113.076638.

Arai, C., M. Miyake, Y. Matsumoto, A. Mizote, C. Yoshizane, Y. Hanaya, K. Koide, M. Yamada, T. Hanaya, S. Arai, et al. 2013. Trehalose prevents adipocyte hypertrophy and mitigates insulin resistance in mice with established obesity. *Journal of Nutritional Science and Vitaminology* 59 (5):393–401. doi: 10.3177/jnsv.59.393.

Arai, C., N. Arai, A. Mizote, K. Kohno, K. Iwaki, T. Hanaya, K. Koide, M. Yamada, T. Hanaya, S. Arai, et al. 2010. Trehalose prevents adipocyte hypertrophy and mitigates insulin resistance. *Nutrition Research* 30 (12):840–8. doi: 10.1016/j.nutres.2010.10.009.

Arai, H., A. Mizuno, M. Sakuma, M. Fukaya, K. Matsuo, K. Muto, H. Sasaki, M. Matsuura, H. Okumura, H. Yamamoto, et al. 2007. Effects of a palatinose-based liquid diet (Inslow) on glycemic control and the second-meal effect in healthy men. *Metabolism* 56 (1):115–21. doi: 10.1016/j.metabol.2006.09.005.

Arnold, D. L., C. A. Moodie, H. C. Grice, S. M. Charbonneau, B. Stavric, B. T. Collins, P. F. Mcguire, Z. Z. Zawidzka, and I. C. Munro. 1980. Long-term toxicity of orthotoluenesulfonamide and sodium saccharin in the rat. *Toxicology and Applied Pharmacology* 52 (1):113–52. doi: 10.1016/0041-008X(80)90253-7.

Atkinson, F. S., K. Foster-Powell, and J. C. Brand-Miller. 2008. International tables of glycemic index and glycemic load values: 2008. *Diabetes Care* 31 (12):2281–3. doi: 10.2337/dc08-1239.

Augustin, L. S., C. W. Kendall, D. J. Jenkins, W. C. Willett, A. Astrup, A. W. Barclay, I. Björck, J. C. Brand-Miller, F. Brighenti, A. E. Buyken, et al. 2015. Glycemic index, glycemic load and glycemic response: An international scientific consensus summit from the International Carbohydrate Quality Consortium (ICQC). *Nutrition, Metabolism, and Cardiovascular Diseases : NMCD* 25 (9):795–815. doi: 10.1016/j.numecd.2015.05.005.

Baird, I. M., N. W. Shephard, R. J. Merritt, and G. Hildick-Smith. 2000. Repeated dose study of sucralose tolerance in human subjects. *Food and Chemical Toxicology* 38 (2):123–9. doi: 10.1016/S0278-6915(00)00035-1.

Bär, A., B. A. Lina, D. M. de Groot, B. de Bie, and M. J. Appel. 1999. Effect of D-tagatose on liver weight and glycogen content of rats .

Regulatory Toxicology and Pharmacology : RTP 29 (2 Pt 2):S11–S28. doi: 10.1006/rtph.1998.1266.

Barclay, A. W., P. Petocz, J. McMillan-Price, V. M. Flood, T. Prvan, P. Mitchell, and J. C. Brand-Miller. 2008. Glycemic index, glycemic load, and chronic disease risk-a meta-analysis of observational studies . *The American Journal of Clinical Nutrition* 87 (3):627–37. doi: 10.1093/ajcn/87.3.627.

Beattie, G. M., J. H. Crowe, A. D. Lopez, V. Cirulli, C. Ricordi, and A. Hayek. 1997. Trehalose: A cryoprotectant that enhances recovery and preserves function of human pancreatic islets after long-term storage. *Diabetes* 46 (3):519–23. doi: 10.2337/diab.46.3.519.

Benton, D., and S. Nabb. 2003. Carbohydrate, memory, and mood. *Nutrition Reviews* 61(5): 61–67.S61–S67. doi: 10.1301/nr.2003.may.

Berg, A., D. König, J. Kowalczyk, G. Kozianowski, and S. Theis. 2010. Use of isomaltulose in food products having a regenerative effect. US20100004194A1. Accessed September 10, 2020. https://worldwide.espacenet.com.

Bergoz, R., J. P. Bolte, and K.-H. Meyer Zum Bueschenfelde. 1973. Trehalose tolerance test. Its value as a test for malabsorption. *Scandinavian Journal of Gastroenterology* 8 (7):657–63. doi: 10.1080/00365521.1973.12096765.

Berra, B., and A. M. Rizzo. 2009. Glycemic index, glycemic load, wellness and beauty: The state of the art. *Clinics in Dermatology* 27 (2): 230–5. doi: 10.1016/j.clindermatol.2008.04.006.

Bertelsen, H., B. B. Jensen, and B. Buemann. 1999. D-tagatose-a novel low-calorie bulk sweetener with prebiotic properties . *World Review of Nutrition and Dietetics* 85:98–109. doi: 10.1159/000059685.

Bertelsen, H., H. Andersen, and M. Tvede. 2001. Fermentation of D-tagatose by human intestinal bacteria and dairy lactic acid bacteria. *Microbial Ecology in Health and Disease* 13 (2):87–95. doi: 10.1080/08910600119905.

Blumenthal, H. J., and D. A. Vance. 1997. Chewing gum headaches. *Headache* 37 (10):665–6. doi: 10.1046/j.1526-4610.1997.3710665.x.

Boesch, C., M. Ith, B. Jung, K. Bruegger, S. Erban, I. Diamantis, R. Kreis, and A. Bär. 2001. Effect of oral D-tagatose on liver volume and hepatic glycogen accumulation in healthy male volunteers. *Regulatory Toxicology and Pharmacology : RTP* 33 (2):257–67. doi: 10.1006/rtph.2001.1470.

Bracken, R. M., R. Page, B. Gray, L. P. Kilduff, D. J. West, J. W. Stephens, and S. C. Bain. 2012. Isomaltulose improves glycemia and maintains run performance in type 1 diabetes. *Medicine & Science in Sports & Exercise* 44 (5):800–8. doi: 10.1249/MSS.0b013e31823f6557.

Brand-Miller, J., S. Dickinson, A. Barclay, and D. Celermajer. 2007. The glycemic index and cardiovascular disease risk. *Current Atherosclerosis Reports* 9 (6):479–85. doi: 10.1007/s11883-007-0064-x.

Breslin, P. A. 2013. An evolutionary perspective on food and human taste. *Current Biology : CB* 23 (9):R409–18. doi: 10.1016/j.cub.2013.04.010.

Brouns, F. J., J. G. Simon, D. Bonnet, and J. Vanhemelrijck. 2006. Comestibles containing isomaltulose and trehalose for sustained carbohydrate energy release and reduced glycemic/insulinemic responses, and for preserving osmolality. US20060096587A1. Accessed September 10, 2020. https://worldwide.espacenet.com.

Brown, R. J., M. A. de Banate, and K. I. Rother. 2010. Artificial sweeteners: A systematic review of metabolic effects in youth. *International Journal of Pediatric Obesity : IJPO : An Official Journal of the International Association for the Study of Obesity* 5 (4):305–12. doi: 10.3109/17477160903497027.

Brown, R. J., M. A. de Banate, and K. I. Rother. 2010. Artificial sweeteners: A systematic review of metabolic effects in youth. *International Journal of Pediatric Obesity : IJPO : An Official Journal of the International Association for the Study of Obesity* 5 (4):305–12. doi: 10.3109/17477160903497027.

Brunner, S., I. Holub, S. Theis, A. Gostner, R. Melcher, P. Wolf, U. Amann-Gassner, W. Scheppach, and H. Hauner. 2012. Metabolic effects of replacing sucrose by isomaltulose in subjects with type 2 diabetes: A randomized double-blind trial. *Diabetes Care* 35 (6): 1249–51. doi: 10.2337/dc11-1485.

Buemann, B., S. Toubro, A. Raben, and A. Astrup. 1999b. Human tolerance to a single, high dose of D-tagatose. *Regulatory Toxicology and Pharmacology : RTP* 29 (2 Pt 2):S66–S70. doi: 10.1006/rtph.1998.1252.

Buemann, B., S. Toubro, and A. Astrup. 1999a. Human gastrointestinal tolerance to D-tagatose. *Regulatory Toxicology and Pharmacology : RTP* 29 (2 Pt 2):S71–S7. doi: 10.1006/rtph.1998.1265.

Buemann, B., S. Toubro, J. J. Holst, J. F. Rehfeld, B. M. Bibby, and A. Astrup. 2000. D-tagatose, a stereoisomer of D-fructose, increases blood uric acid concentration. *Metabolism: Clinical and Experimental* 49 (8):969–76. doi: 10.1053/meta.2000.7724.

Buyken, A. E., M. Toeller, G. Heitkamp, B. Karamanos, R. Rottiers, M. Muggeo, and J. H. Fuller. 2001. Glycemic index in the diet of European outpatients with type 1 diabetes: Relations to glycated hemoglobin and serum lipids. *The American Journal of Clinical Nutrition* 73 (3):574–81. doi: 10.1093/ajcn/73.3.574.

Byrnes, S. E., J. C. Miller, and G. S. Denyer. 1995. Amylopectin starch promotes the development of insulin resistance in rats. *Journal of Nutrition* 125 (6):1430–7. doi: 10.1093/jn/125.6.1430.

Caballero, I., A. Castillo, V. Naydenov, and B. Tilquin. 2005. Radiosensitivity study of glucose and trehalose to gamma irradiation. *American Pharmaceutical Review* 8 (4):50–4.

Cade, W. T. 2008. Diabetes-related microvascular and macrovascular diseases in the physical therapy setting. *Physical Therapy* 88 (11): 1322–35. doi: 10.2522/ptj.20080008.

Ceriello, A. 2004. Impaired glucose tolerance and cardiovascular disease: The possible role of post-prandial hyperglycemia. *American Heart Journal* 147 (5):803–7. doi: 10.1016/j.ahj.2003.11.020.

Chaudhury, A., C. Duvoor, V. S. Reddy Dendi, S. Kraleti, A. Chada, R. Ravilla, A. Marco, N. S. Shekhawat, M. T. Montales, K. Kuriakose, et al. 2017. Clinical review of antidiabetic drugs: Implications for type 2 diabetes mellitus management. *Frontiers in Endocrinology* 8 (8):6. doi: 10.3389/fendo.2017.00006.

Chen, C.-H., T. Yao, Q. Zhang, Y.-M. He, L.-H. Xu, M. Zheng, G.-R. Zhou, Y. Zhang, H.-J. Yang, and P. Zhou. 2016. Influence of trehalose on human islet amyloid polypeptide fibrillation and aggregation. *RSC Advances* 6 (18):15240–6. doi: 10.1039/C5RA27689F.

Chen, Q., and G. G. Haddad. 2004. Role of trehalose phosphate synthase and trehalose during hypoxia: From flies to mammals. *The Journal of Experimental Biology* 207 (Pt 18):3125–9. doi: 10.1242/jeb.01133.

Cheng, A.Y.Y., and I.G. Fantus. Oral antihyperglycemic therapy for type 2 diabetes mellitus. 2005. *Canadian Medical Association Journal* 172 (2): 213–26. doi: 10.1503/cmaj.1031414.

Cho, I. H., S. Lee, J. Hae-Roung, R. Hoe-Jin, and K. Young-Suk. 2010. Comparison of volatile Maillard reaction products from tagatose and other reducing sugars with amino acids. *Food Science and Biotechnology* 19 (2):431–8. doi: 10.1007/s10068-010-0061-7.

Colditz, G. A., W. C. Willett, M. J. Stampfer, S. J. London, M. R. Segal, and F. E. Speizer. 1990. Patterns of weight change and their relation to diet in a cohort of healthy women. *The American Journal of Clinical Nutrition* 51 (6):1100–5. doi: 10.1093/ajcn/51.6.1100.

Collins, J., C. Robinson, H. Danhof, C. W. Knetsch, H. C. van Leeuwen, T. D. Lawley, J. M. Auchtung, and R. A. Britton. 2018. Dietary trehalose enhances virulence of epidemic Clostridium difficile. *Nature* 553 (7688):291–4. doi: 10.1038/nature25178.

Cooper, J. M., M. A. Acaster, C. H. M. Gleeson, and R. L. Botham. 2001. Trehalose for use in exercise. GB2356788A. Accessed April 10, 2020. https://worldwide.espacenet.com.

Cui, M., P. Jiang, E. Maillet, M. Max, R. F. Margolskee, and R. Osman. 2006. The heterodimeric sweet taste receptor has multiple potential ligand binding sites. *Current Pharmaceutical Design* 12 (35): 4591–600. doi: 10.2174/138161206779010350.

Dahlqvist, A., S. Auricchio, G. Semenza, and A. Prader. 1963. Human intestinal disaccharidases and hereditary disaccharide intolerance. The hydrolysis of sucrose, isomaltose, palatinose (isomaltulose), and a 1,6-alpha-oligosaccharide (isomalto-oligosaccharide) preparation. *The Journal of Clinical Investigation* 42 (4):556–62. doi: 10.1172/JCI104744.

Dávila, L. A., V. Bermúdez, D. Aparicio, V. Céspedes, C. Escobar, S. Durán-Agüero, S. Cisternas, J. de Assis Costa, D. Rojas-Gómez, N. Reyna, et al. 2019. Effect of oral nutritional supplements with sucromalt and isomaltulose versus standard formula on glycaemic index, entero-insular axis peptides and subjective appetite in patients with

type 2 diabetes: A randomised cross-over study. *Nutrients* 11 (7): 1477. doi: 10.3390/nu11071477.

de Groot, E., L. Schweitzer, and S. Theis. 2020. Efficacy of isomaltulose compared to sucrose in modulating endothelial function in overweight adults. *Nutrients* 12 (1):141. doi: 10.3390/nu12010141.

de Koning, L., V. S. Malik, E. B. Rimm, W. C. Willett, and F. B. Hu. 2011. Sugar-sweetened and artificially sweetened beverage consumption and risk of type 2 diabetes in men. *The American Journal of Clinical Nutrition* 93 (6):1321–7. doi: 10.3945/ajcn.110.007922.

de la Peña, C. 2010. Artificial sweetener as a historical window to culturally situated health. *Annals of the New York Academy of Sciences* 1190:159–65. doi: 10.1111/j.1749-6632.2009.05253.x.

DeBosch, B. J., M. R. Heitmeier, A. L. Mayer, C. B. Higgins, J. R. Crowley, T. E. Kraft, M. Chi, E. P. Newberry, Z. Chen, B. N. Finck, et al. 2016. Trehalose inhibits solute carrier 2A (SLC2A) proteins to induce autophagy and prevent hepatic steatosis. *Science Signaling* 9 (416):ra21 doi: 10.1126/scisignal.aac5472.

Decode Study Group. European Diabetes Epidemiology Group. 1999. Glucose tolerance and mortality: Comparison of WHO and American Diabetes Association criteria. *Lancet* 354 (9179):617–21.

Diamant, S., N. Eliahu, D. Rosenthal, and P. Goloubinoff. 2001. Chemical chaperones regulate molecular chaperones in vitro and in cells under combined salt and heat stresses. *Journal of Biological Chemistry* 276 (43):39586–91. doi: 10.1074/jbc.M103081200.

Donner, T. W., J. F. Wilber, and D. Ostrowski. 1999. D-tagatose, a novel hexose: Acute effects on carbohydrate tolerance in subjects with and without type 2 diabetes. *Diabetes, Obesity and Metabolism* 1 (5):285–91. doi: 10.1046/j.1463-1326.1999.00039.x.

Donner, T. W., L. S. Magder, and K. Zarbalian. 2010. Dietary supplementation with d-tagatose in subjects with type 2 diabetes leads to weight loss and raises high-density lipoprotein cholesterol. *Nutrition Research* 30 (12):801–6. doi: 10.1016/j.nutres.2010.09.007.

Dörr, T., L. Guderjahn, T. Keme, A. Sentko, and J. Kowalczyk. 2005. Isomaltulose-containing instant beverage powder. WO2004008870A1. Accessed September 10, 2020. https://worldwide.espacenet.com.

Echigo, R., N. Shimohata, K. Karatsu, F. Yano, Y. Kayasuga-Kariya, A. Fujisawa, T. Ohto, Y. Kita, M. Nakamura, S. Suzuki, et al. 2012. Trehalose treatment suppresses inflammation, oxidative stress, and vasospasm induced by experimental subarachnoid hemorrhage. *Journal of Translational Medicine* 10:80. doi: 10.1186/1479-5876-10-80.

Elger, M., and T. Elger. 2008. Beverage, useful to promote dental health of children, comprises sugar-free teas, e.g., rooibos tea, and sugar substitute, e.g., xylitol, which inhibits growth of cariogenic microorganisms. DE102008050591A1. Accessed September 12, 2020. https://worldwide.espacenet.com.

Ensor, M., A. B. Banfield, R. R. Smith, J. Williams, and R. A. Lodder. 2015. Safety and efficacy of D-tagatose in glycemic control in subjects with type 2 diabetes. *Journal of Endocrinology, Diabetes and Obesity* 3 (1):1065.

Ensor, M., J. Williams, R. Smith, A. Banfield, and R. A. Lodder. 2014. Effects of three low-doses of D-tagatose on glycemic control over six months in subjects with mild type 2 diabetes mellitus under control with diet and exercise. *Journal of Endocrinology, Diabetes & Obesity* 2 (4):1057.

Fagherazzi, G., A. Vilier, D. Saes Sartorelli, M. Lajous, B. Balkau, and F. Clavel-Chapelon. 2013. Consumption of artificially and sugar-sweetened beverages and incident type 2 diabetes in the Etude Epidemiologique aupres des femmes de la Mutuelle Generale de l'Education Nationale-European Prospective Investigation into Cancer and Nutrition cohort. *The American Journal of Clinical Nutrition* 97 (3):517–23. doi: 10.3945/ajcn.112.050997.

Feofilova, E., A. Usov, I. Mysyakina, and G. Kochkina. 2014. Trehalose: Chemical structure, biological functions, and practical application. *Microbiology* 83 (3):184e94–194. doi: 10.1134/S0026261714020064.

Findikli, Z., and S. Turkoglu. 2014. Determination of the effects of some artificial sweeteners on human peripheral lymphocytes using the comet assay. *Journal of Toxicology and Environmental Health Sciences* 6 (8):147–53.

Fowler, S. P., K. Williams, R. G. Resendez, K. J. Hunt, H. P. Hazuda, and M. P. Stern. 2008. Fueling the obesity epidemic? Artificially sweetened beverage use and long-term weight gain. *Obesity* 16 (8): 1894–900. doi: 10.1038/oby.2008.284.

Frank, G. K., Oberndorfer, T. A. A. N. Simmons, M. P. Paulus, J. L. Fudge, T. T. Yang, W., and H. Kaye. 2008. Sucrose activates human taste pathways differently from artificial sweetener. *Neuroimage* 39 (4):1559–69. doi: 10.1016/j.neuroimage.2007.10.061.

Frost, G., A. A. Leeds, C. J. Doré, S. Madeiros, S. Brading, and A. Dornhorst. 1999. Glycaemic index as a determinant of serum HDL-cholesterol concentration. *The Lancet* 353 (9158):1045–8. 27 doi: 10.1016/S0140-6736(98)07164-5.

Frost, G., B. Keogh, D. Smith, K. Akinsanya, and A. Leeds. 1996. The effect of low-glycemic carbohydrate on insulin and glucose response in vivo and in vitro in patients with coronary artery disease. *Metabolism* 45 (6):669–72. doi: 10.1016/S0026-0495(96)90129-8.

Gallus, S., L. Scotti, E. Negri, R. Talamini, S. Franceschi, M. Montella, A. Giacosa, L. Dal Maso, and C. L. Vecchia. 2007. Artificial sweeteners and cancer risk in a network of case-control studies. *Ann Oncol* 18 (1):40–4. doi: 10.1093/annonc/mdl346.

Getty-Kaushik, L., D. H. Song, M. Boylan, B. E. Corkey, and M. M. Wolfe. 2006. Glucose-dependent insulinotropic polypeptide modulates adipocyte lipolysis and reesterification. *Obesity (Silver Spring, Md.)* 14 (7):1124–31. doi: 10.1038/oby.2006.129.

glycaemicindex. Accessed June 17, 2020. http://glycaemicindex.com

Gudmand-Høyer, E., H. J. Fenger, H. Skovbjerg, P. Kern-Hansen, and P. R. Madsen. 1988. Trehalase deficiency in Greenland. *Scandinavian Journal of Gastroenterology* 23 (7):775–8. doi: 10.3109/00365528809090759.

Guerrero-Wyss, M., S. D. Agüero, and L. A. Dávila. 2018. D-Tagatose is a promising sweetener to control glycaemia: A new functional food. *BioMed Research International* 2018:8718053–7. doi: 10.1155/2018/8718053.

Güttler, F., and H. Lou. 1985. Aspartame may imperil dietary control of phenylketonuria. *Lancet (London, England)* 1 (8427):525–6. doi: 10.1016/S0140-6736(85)92130-0.

Haase, L., B. Cerf-Ducastel, and C. Murphy. 2009. Cortical activation in response to pure taste stimuli during the physiological states of hunger and satiety. *Neuroimage* 44 (3):1008–21. doi: 10.1016/j.neuroimage.2008.09.044.

Haffner, S. M., S. Lehto, T. Ronnemaa, K. Pyörälä, and M. Laakso. 1998. Mortality from coronary heart disease in subjects with type 2 diabetes and in nondiabetic subjects with and without prior myocardial infarction. *New England Journal of Medicine* 339 (4):229–34. doi: 10.1056/NEJM199807233390404.

Hanefeld, M., S. Fischer, U. Julius, J. Schulze, U. Schwanebeck, H. Schmechel, H. J. Ziegelasch, and J. Lindner. 1996. Risk factors for myocardial infarction and death in newly detected NIDDM: The Diabetes Intervention Study, 11-year follow-up. *Diabetologia* 39 (12): 1577–83. doi: 10.1007/s001250050617.

Henry, C. J., B. Kaur, R. Y. C. Quek, and S. G. Camps. 2017. A low glycaemic index diet incorporating isomaltulose is associated with lower glycaemic response and variability, and promotes fat oxidation in Asians. *Nutrients* 9 (5):473. doi: 10.3390/nu9050473.

Hensrud, D. D. 2001. Dietary treatment and long-term weight loss and maintenance in type 2 diabetes. *Obesity Research* 9 (S11):348S–53. doi: 10.1038/oby.2001.141.

Herbach, N., M. Bergmayr, B. Göke, E. Wolf, and R. Wanke. 2011. Postnatal development of numbers and mean sizes of pancreatic islets and beta-cells in healthy mice and GIPR(dn) transgenic diabetic mice. *PLoS One* 6 (7):e22814. doi: 10.1371/journal.pone.0022814.

Higgins, C. B., Y. Zhang, A. L. Mayer, H. Fujiwara, A. I. Stothard, M. J. Graham, B. M. Swarts, and B. J. DeBosch. 2018. Hepatocyte ALOXE3 is induced during adaptive fasting and enhances insulin sensitivity by activating hepatic PPARg. *JCI Insight* 3 (16):e120794. doi: 10.1172/jci.insight.120794.

Hippisley-Cox, J., and C. Coupland. 2016. Diabetes treatments and risk of amputation, blindness, severe kidney failure, hyperglycaemia, and hypoglycaemia: Open cohort study in primary care. *BMJ (Clinical Research ed.)* 352:i1450. doi: 10.1136/bmj.i1450.

Hira, T., M. Muramatsu, M. Okuno, and H. Hara. 2011. GLP-1 secretion in response to oral and luminal palatinose (isomaltulose) in

rats. *Journal of Nutritional Science and Vitaminology (Tokyo))* 57 (1):30–5. doi: 10.3177/jnsv.57.30.

Holub, I., A. Gostner, S. Theis, L. Nosek, T. Kudlich, R. Melcher, and W. Scheppach. 2010. Novel findings on the metabolic effects of the low glycaemic carbohydrate isomaltulose (palatinose). *The British Journal of Nutrition* 103 (12):1730–7. doi: 10.1017/S0007114509993874.

Hosseinpour-Moghaddam, K., Caraglia, M., and A. Sahebkar. 2018. Autophagy induction by trehalose: Molecular mechanisms and therapeutic impacts. *Journal of Cellular Physiology* 233 (9):6524–43. doi: 10.1002/jcp.26583.

Ibrahim, O. 2018. A new low calorie sweetener D-tagatose from lactose in cheese whey as a nutraceutical value-added product. *Journal of Food Health and Technology Innovations* 1:11–28.

International Diabetes Federation. 2017. *IDF Diabetes Atlas*. 8th ed. Brussels, Belgium: International Diabetes Federation. Accessed September 15, 2020. http://www.diabetesatlas.org.

International Diabetes Federation. 2019. *IDF Diabetes Atlas*. 9th ed. Brussels, Belgium: International Diabetes Federation. Accessed September 15, 2020. http://www.diabetesatlas.org.

Jang, H. J., Z. Kokrashvili, M. J. Theodorakis, O. D. Carlson, B. J. Kim, J. Zhou, H. H. Kim, X. Xu, S. L. Chan, M. Juhaszova, et al. 2007. Gut-expressed gustducin and taste receptors regulate secretion of glucagon-like peptide-1. *Proceedings of the National Academy of Sciences of the United States of America* 104 (38):15069–74. doi.org/10.1073/pnas.0706890104. doi: 10.1073/pnas.0706890104.

Jentjens, R. L. P. G., and A. E. Jeukendrup. 2003. Effects of pre-exercise ingestion of trehalose, galactose and glucose on subsequent metabolism and cycling performance. *European Journal of Applied Physiology* 88 (4):459–65. doi: 10.1007/s00421-002-0729-7.

Joint FAO/WHO Expert Committee on Food Additives, World Health Organization and Food and Agriculture Organization of the United Nation. 2004. Evaluation of certain food additives and contaminants: sixty-first report of the Joint FAO/WHO Expert Committee on Food Additives (WHO technical report series No 922). Italy: World Health Organization. Accessed May 28, 2020. https://apps.who.int/iris/handle/10665/42849.

Jonker, D., B. A. R. Lina, and G. Kozianowski. 2002. 13-Week oral toxicity study with isomaltulose (Palatinose) in rats. *Food and Chemical Toxicology : An International Journal Published for the British Industrial Biological Research Association* 40 (10):1383–9. doi: 10.1016/S0278-6915(02)00106-0.

Jung, C. H., S. H. Ro, J. Cao, N. M. Otto, and D. H. Kim. 2010. mTOR regulation of autophagy. *FEBS Letters* 584 (7):1287–95. doi: 10.1016/j.febslet.2010.01.017.

Kawaguchi, T., D. Nakano, T. Oriishi, and T. Torimura. 2018. Effects of isomaltulose on insulin resistance and metabolites in patients with non-alcoholic fatty liver disease: A metabolomic analysis . *Molecular Medicine Reports* 18 (2):2033–42. doi: 10.3892/mmr.2018.9223.

Kawai, K., Y. Okuda, and K. Yamashita. 1985. Changes in blood glucose and insulin after an oral palatinose administration in normal subjects. *Endocrinologia Japonica* 32 (6):933–6. doi: 10.1507/endocrj1954.32.933.

Keyhani-Nejad, F., M. Irmler, F. Isken, E. K. Wirth, J. Beckers, A. L. Birkenfeld, and A. F. Pfeiffer. 2015. Nutritional strategy to prevent fatty liver and insulin resistance independent of obesity by reducing glucose-dependent insulinotropic polypeptide responses in mice. *Diabetologia* 58 (2):374–83. doi: 10.1007/s00125-014-3423-5.

Keyhani-Nejad, F., M. Kemper, R. Schueler, O. Pivovarova, N. Rudovich, and A. F. H. Pfeiffer. 2016. Effects of palatinose and sucrose intake on glucose metabolism and incretin secretion in subjects with type 2 diabetes. *Diabetes Care* 39 (3):e38–e39. doi: 10.2337/dc15-1891.

Kim, S. J., K. Winter, C. Nian, M. Tsuneoka, Y. Koda, and C. H. McIntosh. 2005. Glucose-dependent insulinotropic polypeptide (GIP) stimulation of pancreatic beta-cell survival is dependent upon phosphatidylinositol 3-kinase (PI3K)/protein kinase B (PKB) signaling, inactivation of the forkhead transcription factor Foxo1, and down-regulation of bax expression. *The Journal of Biological Chemistry* 280 (23):22297–307. doi: 10.1074/jbc.M500540200.

Kobayashi, K., T. Komeda, Y. Miura, M. Kettoku, and M. Kato. 1997. Production of trehalose from starch by novel trehalose-producing enzymes from Sulfolobus solfataricus KM1. *Journal of Fermentation and Bioengineering* 83 (3):296–8. doi: 10.1016/S0922-338X(97)80996-8.

Kokta, T. A., A. L. Strat, M. R. Papasani, J. I. Szasz, M. V. Dodson, and R. A. Hill. 2008. Regulation of lipid accumulation in 3T3-L1 cells: Insulin-independent and combined effects of fatty acids and insulin. *Animal* 2 (1):92–9. doi: 10.1017/S1751731107000936.

König, D., S. Theis, G. Kozianowski, and A. Berg. 2012. Postprandial substrate use in overweight subjects with the metabolic syndrome after isomaltulose (Palatinose™) ingestion. *Nutrition* 28 (6):651–6. doi: 10.1016/j.nut.2011.09.019.

Kruger, C. L., M. H. Whittaker, V. H. Frankos, and G. W. Trimmer. 1999. 90-Day oral toxicity study of D-tagatose in rats. *Regulatory Toxicology and Pharmacology : RTP* 29 (2 Pt 2):S1–S10. doi: 10.1006/rtph.1998.1262.

Kubota, M., I. Sawatani, K. Oku, K. Takeuchi, and S. Murai. 2004. The developoment of α,α-trehalose production and its applications. *Journal of Applied Glycoscience* 51 (1):63–70. doi: 10.5458/jag.51.63.

Kwak, J. H., M. S. Kim, J. H. Lee, Y. J. Yang, K. H. Lee, O. Y. Kim, and J. H. Lee. 2013. Beneficial effect of tagatose consumption on postprandial hyperglycemia in Koreans: A double-blind crossover designed study. *Food & Function* 4 (8):1223–8. doi: 10.1039/c3fo00006k.

Lau, C., K. Faerch, C. Glümer, I. Tetens, O. Pedersen, B. Carstensen, T. Jørgensen, and K. Borch-Johnsen. 2005. Inter99 study. Dietary glycemic index, glycemic load, fiber, simple sugars, and insulin resistance: The Inter99 study. *Diabetes Care* 28 (6):1397–403. doi: 10.2337/diacare.28.6.1397.

Lean, M. E. J., W. S. Leslie, A. C. Barnes, N. Brosnahan, G. Thom, L. McCombie, C. Peters, S. Zhyzhneuskaya, A. Al-Mrabeh, K. G. Hollingsworth, et al. 2019. Durability of a primary care-led weight-management intervention for remission of type 2 diabetes: 2-year results of the DiRECT open-label, cluster-randomised trial. *The Lancet Diabetes & Endocrinology* 7 (5):344–55. doi: 10.1016/S2213-8587(19)30068-3.

Lebovitz, H. 2001. Effect of the postprandial state on nontraditional risk factors. *The American Journal of Cardiology* 88 (6):20–25H. doi: 10.1016/S0002-9149(01)01833-1.

Lee, A., and D. M. Storey. 1999. Comparative gastrointestinal tolerance of sucrose, lactitol, or d-tagatose in chocolate. *Regulatory Toxicology and Pharmacology : RTP* 29 (2 Pt 2):S78–S82. doi: 10.1006/rtph.1998.1255.

Legry, V., S. Francque, J. T. Haas, A. Verrijken, S. Caron, O. Chávez-Talavera, E. Vallez, L. Vonghia, E. Dirinck, A. Verhaegen, et al. 2017. Bile acid alterations are associated with insulin resistance, but not with NASH, in obese subjects. *The Journal of Clinical Endocrinology and Metabolism* 102 (10):3783–94. doi: 10.1210/jc.2017-01397.

Lenoir, M., F. Serre, L. Cantin, and S. H. Ahmed. 2007. Intense sweetness surpasses cocaine reward. *PLoS One* 2 (8):e698. doi: 10.1371/journal.pone.0000698.

Levin, G. V. 2000. Use of tagatose to enhance key blood factors. EP1173186A4. Accessed September 15, 2020. https://worldwide.espacenet.com.

Levin, G. V. 2001. Increased fertility and improved fetal development drug. US2001020008A1. Accessed December 17, 2020. https://worldwide.espacenet.com

Levin, G. V. 2002. Tagatose, the new GRAS sweetener and health product. *J Med Food* 5 (1):23–36. doi: 10.1089/109662002753723197.

Liang, H., H. M. Habte-Tsion, X. Ge, M. Ren, J. Xie, L. Miao, Q. Zhou, Y. Lin, and W. Pan. 2017. Dietary arginine affects the insulin signaling pathway, glucose metabolism and lipogenesis in juvenile blunt snout bream Megalobrama amblycephala. *Scientific Reports* 7 (1):7864. doi: 10.1038/s41598-017-06104-3.

Liese, A. D., M. Schulz, F. Fang, T. M. Wolever, R. B. Jr D'Agostino, K. C. Sparks, and E. J. Mayer-Davis. 2005. Dietary glycemic index and glycemic load, carbohydrate and fiber intake, and measures of insulin sensitivity, secretion, and adiposity in the Insulin Resistance Atherosclerosis Study. *Diabetes Care* 28 (12):2832–8. doi: 10.2337/diacare.28.12.2832.

Lightowler, H., L. Schweitzer, S. Theis, and C. J. Henry. 2019. Changes in weight and substrate oxidation in overweight adults following isomaltulose intake during a 12-week weight loss intervention: A randomized, double-blind, controlled trial. *Nutrients* 11 (10):2367. doi: 10.3390/nu11102367.

Lim, Y. M., H. Lim, K. Y. Hur, W. Quan, H. Y. Lee, H. Cheon, D. Ryu, S. H. Koo, H. L. Kim, J. Kim, et al. 2014. Systemic autophagy insufficiency compromises adaptation to metabolic stress and facilitates progression from obesity to diabetes. *Nature Communications* 5:4934. doi: 10.1038/ncomms5934.

Lina, B. A. R., A. E. Smits-van Prooije, and D. H. Waalkens. 1997. Embryotoxicity/teratogenicity study with isomaltulose (Palatinose) in rats. *Food and Chemical Toxicology : An International Journal Published for the British Industrial Biological Research Association* 35 (3–4):309–14. doi: 10.1016/S0278-6915(97)00010-0.

Lina, B. A., D. Jonker, and G. Kozianowski. 2002. Isomaltulose (Palatinose): A review of biological and toxicological studies. *Food and Chemical Toxicology : An International Journal Published for the British Industrial Biological Research Association* 40 (10):1375–81. doi: 10.1016/S0278-6915(02)00105-9.

Liu, E., A. Kume, H. Yan, X. Wang, H. Zheng, T. Konno, H. Ding, H. Shen, H. Sasaki, and Z. S. Ji. 2016. Increased insulinogenic indexes after liquid food (Inslow) intake in subjects with impaired glucose tolerance and type-2 diabetes: A randomised controlled trial. *International Journal of Food Science, Nutrition and Dietetics* 5 (4): 278–86. doi: 10.19070/2326-3350-1600050.

Liu, S., W. C. Willett, M. J. Stampfer, F. B. Hu, M. Franz, L. Sampson, C. H. Hennekens, and J. E. Manson. 2000. A prospective study of dietary glycemic load, carbohydrate intake, and risk of coronary heart disease in US women. *The American Journal of Clinical Nutrition* 71 (6):1455–61. doi: 10.1093/ajcn/71.6.1455.

Lu, Y., G. V. Levin, and T. W. Donner. 2008. Tagatose, a new antidiabetic and obesity control drug. *Diabetes, Obesity and Metabolism* 10 (2):109–34. doi: 10.1111/j.1463-1326.2007.00799.x.

Mace, O. J., J. Affleck, N. Patel, and G. L. Kellett. 2007. Sweet taste receptors in rat small intestine stimulate glucose absorption through apical GLUT2. *The Journal of Physiology* 582 (Pt 1):379–92. doi: 10.1113/jphysiol.2007.130906.

Madenokoji, N. I. H., T. Shimizu, J. Hayakawa, and M. Sakashita. 2003. Blunting effect of D-tagatose on blood glucose when administered orally with glucose in volunteer donors of boundary glycemic level. *Journal of Japan Society for Clinical Nutrition* 25 (1):21–8.

Maki, K. C., M. Kanter, T. M. Rains, S. P. Hess, and J. Geohas. 2009. Acute effects of low insulinemic sweeteners on postprandial insulin and glucose concentrations in obese men. *International Journal of Food Sciences and Nutrition* 60 (sup3):48–55. doi: 10.1080/09637480802646923.

Mardones, P., D. C. Rubinsztein, and C. Hetz. 2016. Mystery solved: Trehalose kickstarts autophagy by blocking glucose transport. *Science Signaling* 9 (416):fs2. doi: 10.1126/scisignal.aaf1937.

Maresch, C. C., S. F. Petry, S. Theis, A. Bosy-Westphal, and T. Linn. 2017. Low glycemic index prototype isomaltulose-update of clinical trials. *Nutrients* 9 (4):381. doi: 10.3390/nu9040381.

Margolskee, R. F., J. Dyer, Z. Kokrashvili, K. S. Salmon, E. Ilegems, K. Daly, E. L. Maillet, Y. Ninomiya, B. Mosinger, and S. P. Shirazi-Beechey. 2007. T1R3 and gustducin in gut sense sugars to regulate expression of Na+-glucose cotransporter 1. *Proceedings of the National Academy of Sciences of the United States of America* 104 (38):15075–80. doi: 10.1073/pnas.0706678104.

Mather, H. M., and H. Keen. 1985. The southall diabetes survey: Prevalence of known diabetes in Asians and Europeans. *Br Med J (Clin Res Ed)* 291 (6502):1081–4. doi: 10.1136/bmj.291.6502.1081.

Mattes, R. 1990. Effects of aspartame and sucrose on hunger and energy intake in humans. *Physiology & Behavior* 47 (6):1037–44. doi: 10.1016/0031-9384(90)90350-D.

Mayer, A. L., C. B. Higgins, M. R. Heitmeier, T. E. Kraft, X. Qian, J. R. Crowley, K. L. Hyrc, W. L. Beatty, K. E. Yarasheski, P. W. Hruz, et al. 2016. SLC2A8 (GLUT8) is a mammalian trehalose transporter required for trehalose-induced autophagy. *Scientific Reports* 6:38586. doi: 10.1038/srep38586.

Mayhew, D. A., C. P. Comer, and W. W. Stargel. 2003. Food consumption and body weight changes with neotame, a new sweetener with intense taste: Differentiating effects of palatability from toxicity in dietary safety studies. *Regulatory Toxicology and Pharmacology : RTP* 38 (2):124–43. doi: 10.1016/S0273-2300(03)00074-6.

McKeown, N. M., J. B. Meigs, S. Liu, E. Saltzman, P. W. Wilson, and P. F. Jacques. 2004. Carbohydrate nutrition, insulin resistance, and the prevalence of the metabolic syndrome in the Framingham Offspring Cohort. *Diabetes Care* 27 (2):538–46. doi: 10.2337/diacare.27.2.538.

Meyer, K. A., L. H. Kushi, D. R. Jacobs, Jr, J. Slavin, T. A. Sellers, and A. R. Folsom. 2000. Carbohydrates, dietary fiber, and incident type 2 diabetes in older women. *The American Journal of Clinical Nutrition* 71 (4):921–30. doi: 10.1093/ajcn/71.4.921.

Miao, M., B. Jiang, S. W. Cui, T. Zhang, and Z. Jin. 2015. Slowly digestible starch-a review. *Critical Reviews in Food Science and Nutrition* 55 (12):1642–57. doi: 10.1080/10408398.2012.704434.

Mizote, A., M. Yamada, C. Yoshizane, N. Arai, K. Maruta, S. Arai, S. Endo, R. Ogawa, H. Mitsuzumi, T. Ariyasu, et al. 2016. Daily intake of trehalose is effective in the prevention of lifestyle-related diseases in individuals with risk factors for metabolic syndrome. *Journal of Nutritional Science and Vitaminology* 62 (6):380–7. doi: 10.3177/jnsv.62.380.

Monro J. A., and M. Shaw. 2008. Glycemic impact, glycemic glucose equivalents, glycemic index and glycemic load: Definitions, distinctions, and implications. *The American Journal of Clinical Nutrition* 87(1): 237–43.237S. doi: 10.1093/ajcn/87.1.[10.1093/ajcn/87.1.237S]

Moriano, M. E., and C. Alamprese. 2017. Honey, trehalose and erythritol as sucrose alternative sweeteners for artisanal ice cream. A pilot study. *LWT* 75:329–34. doi: 10.1016/j.lwt.2016.08.057.

Mortensen, A. 2006. Sweeteners permitted in the European Union: Safety aspects. *Scandinavian Journal of Food and Nutrition* 50 (3): 104–16. doi: 10.1080/17482970600982719.

Mu, W., W. Li, X. Wang, T. Zhang, and B. Jiang. 2014. Current studies on sucrose isomerase and biological isomaltulose production using sucrose isomerase. *Applied Microbiology and Biotechnology* 98 (15): 6569–82. doi: 10.1007/s00253-014-5816-2.

Muddada, S. 2012. Tagatose: The multifunctional food ingredient and potential drug. *Journal of Pharmacy Research* 5 (1):626–31.

Nasteska, D., N. Harada, K. Suzuki, S. Yamane, A. Hamasaki, E. Joo, K. Iwasaki, K. Shibue, T. Harada, and N. Inagaki. 2014. Chronic reduction of GIP secretion alleviates obesity and insulin resistance under high-fat diet conditions. *Diabetes* 63 (7):2332–43. doi: 10.2337/db13-1563.

O'Donovan, D. G., S. Doran, C. Feinle-Bisset, K. L. Jones, J. H. Meyer, J. M. Wishart, H. A. Morris, and M. Horowitz. 2004. Effect of variations in small intestinal glucose delivery on plasma glucose, insulin, and incretin hormones in healthy subjects and type 2 diabetes. *The Journal of Clinical Endocrinology & Metabolism* 89 (7):3431–5. doi: 10.1210/jc.2004-0334.

Oh, D. K. 2007. Tagatose: Properties, applications, and biotechnological processes. *Applied Microbiology and Biotechnology* 76 (1):1–8. 8. doi: 10.1007/s00253-007-0981-1.

Oizumi, T., M. Daimon, Y. Jimbu, W. Kameda, N. Arawaka, H. Yamaguchi, H. Ohnuma, H. Sasaki, and T. Kato. 2007. A palatinose-based balanced formula improves glucose tolerance, serum free fatty acid levels and body fat composition. *The Tohoku Journal of Experimental Medicine* 212 (2):91–9. doi: 10.1620/tjem.212.91.

Oku, T., and M. Okazaki. 1998. Transitory laxative threshold of trehalose and lactulose in healthy women. *Journal of Nutritional Science and Vitaminology* 44 (6):787–98. doi: 10.3177/jnsv.44.787.

Oku, T., and S. Nakamura. 2000. Estimation of intestinal trehalase activity from a laxative threshold of trehalose and lactulose on healthy female subjects. *European Journal of Clinical Nutrition* 54 (10):783–8. doi: 10.1038/sj.ejcn.1601091.

Osman, M., N. S. Samsudin, G. Faruq, and A. Nezhadahmadi. 2013. Factors affecting microcuttings of stevia using a mist-chamber propagation box. *The Scientific World Journal* 2013:1–10. doi: 10.1155/2013/940201.

Page, K. A., and T. Reisman. 2013. Interventions to preserve beta-cell function in the management and prevention of Type 2 Diabetes. *Current Diabetes Reports* 13 (2):252–60. doi: 10.1007/s11892-013-0363-2.

Park, J. G., W. Y. Tak, S. Y. Park, Y. O. Kweon, W. J. Chung, B. K. Jang, S. H. Bae, H. J. Lee, J. Y. Jang, K. T. Suk, et al. 2020. Effects of Branched-Chain Amino Acid (BCAA) supplementation on the progression of advanced liver disease: A Korean nationwide, multicenter, prospective, observational, cohort study. *Nutrients* 12 (5):1429. doi: 10.3390/nu12051429.

Paterson, A. H. J., and S. J. Kellam. 2009. Transformation of lactose for value-added ingrediens. In *Dairy-derived ingredients: Food and nutraceutical uses*. 1st ed., ed. M. Correding, 625–43. Boca Raton, FL: Woodhead Publishing: CRC Press.

Police, S. B., J. C. Harris, R. A. Lodder, and L. A. Cassis. 2009. Effect of diets containing sucrose vs. D-tagatose in hypercholesterolemic mice. *Obesity (Silver Spring, Md.)* 17 (2):269–75. doi: 10.1038/oby.2008.508.

Porikos, K. P., G. Booth, and T. B. Van Itallie. 1977. Effect of covert nutritive dilution on the spontaneous food intake of obese individuals: A pilot study. *The American Journal of Clinical Nutrition* 30 (10):1638–44. doi.org/10.1093/ajcn/30.10.1638. doi: 10.1093/ajcn/30.10.1638.

Postic, C., and J. Girard. 2008. Contribution of de novo fatty acid synthesis to hepatic steatosis and insulin resistance: Lessons from genetically engineered mice. *The Journal of Clinical Investigation* 118 (3):829–38. doi: 10.1172/JCI34275.

Prasad, S., R. K. Sajja, P. Naik, and L. Cucullo. 2014. Diabetes mellitus and Blood-Brain Barrier Dysfunction: An Overview. *Journal of Pharmacovigilance* 2 (2):125. doi: 10.4172/2329-6887.1000125.

Price, J. M., C. G. Biava, B. L. Oser, E. E. Vogin, J. Steinfeld, and H. L. Ley. 1970. Bladder tumors in rats fed cyclohexylamine or high doses of a mixture of cyclamate and saccharin. *Science (New York, N.Y.)* 167 (3921):1131–2. doi: 10.1126/science.167.3921.1131.

Prospective Diabetes Study UK (UKPDS) Group. 1998. Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS33). *Lancet* 352:837–53.

Ramlo-Halsted, B. A., and S. V. Edelman. 2000. The natural history of type 2 diabetes: Practical points to consider in developing prevention and treatment strategies. *Clinical Diabetes* 18:80.

Renner, S., C. Fehlings, N. Herbach, A. Hofmann, D. C. von Waldthausen, B. Kessler, K. Ulrichs, I. Chodnevskaja, V. Moskalenko, W. Amselgruber, et al. 2010. Glucose intolerance and reduced proliferation of pancreatic beta-cells in transgenic pigs with impaired glucose-dependent insulinotropic polypeptide function . *Diabetes* 59 (5):1228–38. doi: 10.2337/db09-0519.

Richards, A. B., and L. B. Dexter. 2012. Trehalose. In *Alternative sweeteners*. 4th ed., ed. L. O'Brien-Nabors, 439–72. Boca Raton, FL: Taylor & Francis Group: CRC Press.

Richards, A., S. Krakowka, L. Dexter, H. Schmid, A. Wolterbeek, D. Waalkens-Berendsen, A. Shigoyuki, and M. Kurimoto. 2002. Trehalose: A review of properties, history of use and human tolerance, and results of multiple safety studies. *Food and Chemical Toxicology : An International Journal Published for the British Industrial Biological Research Association* 40 (7):871–98. doi: 10.1016/S0278-6915(02)00011-X.

Rolls, B. J. 1991. Effects of intense sweeteners on hunger, food intake, and body weight: A review. *The American Journal of Clinical Nutrition* 53 (4):872–8. doi: 10.1093/ajcn/53.4.872.

Romaguera, D., T. Norat, P. A. Wark, A. C. Vergnaud, M. B. Schulze, G. J. van Woudenbergh, D. Drogan, P. Amiano, E. Molina-Montes, M. J. Sánchez, et al. 2013. Consumption of sweet beverages and type 2 diabetes incidence in European adults: Results from EPIC-InterAct. *Diabetologia* 56 (7):1520–30. doi: 10.1007/s00125-013-2899-8.

Rusmini, P., K. Cortese, V. Crippa, R. Cristofani, M. E. Cicardi, V. Ferrari, G. Vezzoli, B. Tedesco, M. Meroni, E. Messi, et al. 2019. Trehalose induces autophagy via lysosomal-mediated TFEB activation in models of motoneuron degeneration. *Autophagy* 15 (4):631–51. doi: 10.1080/15548627.2018.1535292.

Saeedi, P., I. Petersohn, P. Salpea, B. Malanda, S. Karuranga, N. Unwin, S. Colagiuri, L. Guariguata, A. A. Motala, K. Ogurtsova, et al. 2019. Global and regional diabetes prevalence estimates for 2019 and projections for 2030 and 2045: Results from the international diabetes federation diabetes atlas, 9th edition. *Diabetes Research and Clinical Practice* 157:107843. doi.org/10.1016/j.diabres.2019.107843. doi: 10.1016/j.diabres.2019.107843.

Sahyoun, N. R., A. L. Anderson, A. M. Kanaya, P. Koh-Banerjee, S. B. Kritchevsky, N. de Rekeneire, F. A. Tylavsky, A. V. Schwartz, J. S. Lee, and T. B. Harris. 2005. Dietary glycemic index and load, measures of glucose metabolism, and body fat distribution in older adults. *The American Journal of Clinical Nutrition* 82 (3):547–52. doi: 10.1093/ajcn.82.3.547.

Salmerón, J., A. Ascherio, E. B. Rimm, G. A. Colditz, D. Spiegelman, D. J. Jenkins, M. J. Stampfer, A. L. Wing, and W. C. Willett. 1997a. Dietary fiber, glycemic load, and risk of NIDDM in Men. *Diabetes Care* 20 (4):545–50. doi: 10.2337/diacare.20.4.545.

Salmerón, J., J. E. Manson, M. J. Stampfer, G. A. Colditz, A. L. Wing, and W. C. Willett. 1997b. Dietary fiber, glycemic load, and risk of non-insulin-dependent diabetes mellitus in women. *JAMA* 277 (6):472–47. doi: 10.1001/jama.1997.03540300040031.

Saltiel, A. R. 2001. New perspectives into the molecular pathogenesis and treatment of type 2 diabetes. *Cell* 104 (4):517–29. doi: 10.1016/S0092-8674(01)00239-2.

Sarkar, S., J. E. Davies, Z. Huang, A. Tunnacliffe, and D. C. Rubinsztein. 2007. Trehalose, a novel mTOR-independent autophagy enhancer, accelerates the clearance of mutant huntingtin and alpha-synuclein. *The Journal of Biological Chemistry* 282 (8):5641–52. doi: 10.1074/jbc.M609532200.

Sawale, P. D., A. M. Shendurse, M. S. Mohan, and G. P. Patil. 2017. Isomaltulose (Palatinose) – An emerging carbohydrate. *Food Bioscience* 18:46–52. doi: 10.1016/j.fbio.2017.04.003.

Saxton, R. A., and D. M. Sabatini. 2017. mTOR signaling in growth, metabolism, and disease. *Cell* 168 (6):960–76. doi: 10.1016/j.cell.2017.02.004.

Saydah, S. H., J. Fradkin, and C. C. Cowie. 2004. Poor control of risk factors for vascular disease among adults with previously diagnosed diabetes. *Jama* 291 (3):335–42. doi: 10.1001/jama.291.3.335.

Schiraldi, C., I. Di Lernia, and M. De Rosa. 2002. Trehalose production: Exploiting novel approaches. *Trends in Biotechnology* 20 (10):420–5. doi: 10.1016/S0167-7799(02)02041-3.

Seifarth, C., J. Bergmann, J. J. Holst, R. Ritzel, W. Schmiegel, and M. A. Nauck. 1998. Prolonged and enhanced secretion of glucagon-like peptide 1 (7-36 amide) after oral sucrose due to alpha-glucosidase inhibition (acarbose) in Type 2 diabetic patients. *Diabetic Medicine* 15 (6):485–91. doi: 10.1002/(SICI)1096-9136(199806)15:6<485::AID-DIA610>3.0.CO;2-Y.

Seino, Y., M. Fukushima, and D. Yabe. 2010. GIP and GLP-1, the two incretin hormones: Similarities and differences. *Journal of Diabetes Investigation* 1 (1–2):8–23. doi: 10.1111/j.2040-1124.2010.00022.x.

Smeet, P. A., C. de Graaf, A. Stafleu, M. J. van Osch, and J. van der Grond. 2005. Functional magnetic resonance imaging of human hypothalamic responses to sweet taste and calories. *The American Journal of Clinical Nutrition* 82 (5):1011–6. doi: 10.1093/ajcn/82.5.1011.

Soffritti, M., F. Belpoggi, D. Degli Esposti, L. Lambertini, E. Tibaldi, and A. Rigano. 2006. First experimental demonstration of the multipotential carcinogenic effects of aspartame administered in the feed to Sprague-Dawley rats. *Environmental Health Perspectives* 114 (3):379–85. doi: 10.1289/ehp.8711.

Sokolowska, E., and A. U. Blachnio-Zabielska. 2019. The role of ceramides in insulin resistance. *Frontiers in Endocrinology* 10:577. doi: 10.3389/fendo.2019.00577.

Stellman, S. D., and L. Garfinkel. 1986. Artificial sweetener use and one-year weight change among women. *Preventive Medicine* 15 (2):195–202. doi: 10.1016/0091-7435(86)90089-7.

Suzuki, M., D. Shido, K. Goto, Y. Ohno, K. Miyasaka, and M. Mizu. 2017. Effects of a palatinose-containing diet with exercise on

progression of diabetic nephropathy and metabolic syndrome in obese-diabetic rats. *European Journal of Sports & Exercise Science* 5: 27–36. doi: 10.4172/2278-005X.1000104.

Swithers, S. E., and T. L. Davidson. 2008. A role for sweet taste: Calorie predictive relations in energy regulation by rats. *Behavioral Neuroscience* 122 (1):161–73. doi: 10.1037/0735-7044.122.1.161.

Tan, W. S. K., S. Y. Tan, and C. J. Henry. 2017. Ethnic variability in glycemic response to sucrose and isomaltulose. *Nutrients* 9 (4):347. doi: 10.3390/nu9040347.

Taya, K., K. Hirose, and S. Hamada. 2009. Trehalose inhibits inflammatory cytokine production by protecting IkappaB-alpha reduction in mouse peritoneal macrophages . *Archives of Oral Biology* 54 (8): 749–56. doi: 10.1016/j.archoralbio.2009.05.003.

Taylor, S. L., D. M. Lambrecht, and S. L. Hefle. 2005. Tagatose and milk allergy. *Allergy* 60 (3):412–3. doi: 10.1111/j.1398-9995.2005.00701.x.

Temizkan, S., O. Deyneli, M. Yasar, M. Arpa, M. Gunes, D. Yazici, O. Sirikci, G. Haklar, N. Imeryuz, and D. G. Yavuz. 2015. Sucralose enhances GLP-1 release and lowers blood glucose in the presence of carbohydrate in healthy subjects but not in patients with type 2 diabetes. *European Journal of Clinical Nutrition* 69 (2):162–6. doi: 10.1038/ejcn.2014.208.

Thammahong, A., Puttikamonkul, S. J. R. Perfect, R. G. Brennan, R., and A. Cramer. 2017. Central role of the trehalose biosynthesis pathway in the pathogenesis of human fungal infections: Opportunities and challenges for therapeutic development. *Microbiology and Molecular Biology Reviews* 81 (2):e00053. 16. doi: 10.1128/MMBR.00053-16.

Tonouchi, H., T. Yamaji, M. Uchida, M. Koganei, A. Sasayama, T. Kaneko, Y. Urita, M. Okuno, K. Suzuki, J. Kashimura, et al. 2011. Studies on absorption and metabolism of palatinose (isomaltulose) in rats. *The British Journal of Nutrition* 105 (1):10–4. doi: 10.1017/S0007114510003193.

Torrico, D. D., J. Tam, S. Fuentes, C. Gonzalez Viejo, and F. R. Dunshea. 2019. D-Tagatose as a sucrose substitute and its effect on the physico-chemical properties and acceptability of strawberry-flavored yogurt. *Foods* 8 (78):256. doi: 10.3390/foods8070256.

Transparency Market Research. Accessed April 10, 2020. https://www.transparencymarketresearch.com.

Troyano, E., I. Martinez-Castro, and A. Olano. 1992. Kinetics of galactose and tagatose formation during heat-treatment of milk. *Food Chemistry* 45 (1):41–3. doi: 10.1016/0308-8146(92)90010-Y.

van Can, J. G., T. H. Ijzerman, L. J. van Loon, F. Brouns, and E. E. Blaak. 2009. Reduced glycaemic and insulinaemic responses following isomaltulose ingestion: Implications for postprandial substrate use. *The British Journal of Nutrition* 102 (10):1408–13. doi: 10.1017/S0007114509990687.

van Dam, R. M., A. W. Visscher, E. J. Feskens, P. Verhoef, and D. Kromhout. 2000. Dietary glycemic index in relation to metabolic risk factors and incidence of coronary heart disease: The Zutphen Elderly Study. *European Journal of Clinical Nutrition* 54 (9):726–31. doi: 10.1038/sj.ejcn.1601086.

Vartanian, L. R., M. B. Schwartz, and K. D. Brownell. 2007. Effects of soft drink consumption on nutrition and health: A systematic review and meta-analysis. *American Journal of Public Health* 97 (4):667–75. doi: 10.2105/AJPH.2005.083782.

Vastenavond, C. M., H. Bertelsen, S. J. Hansen, R. S. Laursen, J. Saunders, and K. Eriknauer. 2012. Tagatose (D-tagatose). In *Alternative sweeteners*. 4th ed., ed. L. O'Brien-Nabors, 197–222. Boca Raton, FL: Taylor & Francis Group: CRC Press.

Venema, K., S. H. F. Vermunt, and E. J. Brink. 2005. D-tagatose increases butyrate production by the colonic microbiota in healthy men and women. *Microbial Ecology in Health and Disease* 17 (1): 47–57. doi: 10.1080/08910600510035093.

Wadazumi, T., K. Watanabe, H. Watanabe, H. Yokoyama, N. Hongu, and N. Arai. 2019. Effects of a single ingestion of trehalose during prolonged exercise. *Sports* 7 (5):100. doi: 10.3390/sports7050100.

Whitehouse, C. R., J. Boullata, and L. A. McCauley. 2008. The potential toxicity of artificial sweeteners. *AAOHN Journal : Official Journal of the American Association of Occupational Health Nurses* 56 (6): 251–9. doi: 10.3928/08910162-20080601-02.

WHO/FAO. 1998. Carbohydrates in human nutrition. (FAO Food and Nutrition Paper No 66). Food and Agriculture Organisation, Rome, Italy. Accessed May 28, 2020. http://www.fao.org/3/W8079E/W8079E00.htm.

Widenmaier, S. B., S. J. Kim, G. K. Yang, T. De Los Reyes, C. Nian, A. Asadi, Y. Seino, T. J. Kieffer, Y. N. Kwok, and C. H. McIntosh. 2010. A GIP receptor agonist exhibits beta-cell anti-apoptotic actions in rat models of diabetes resulting in improved beta-cell function and glycemic control. *PLoS One* 5 (3):e9590. doi: 10.1371/journal.pone.0009590.

Williams, J., M. Spitnale, and R. Lodder. 2013. The effect of D-tagatose on fructose absorption in a rat model. *Journal of Developing Drugs* 02 (03):1000111. doi: 10.4172/2329-6631.1000111.

Wing, R. R., R. Koeske, L. H. Epstein, M. P. Nowalk, W. Gooding, and D. Becker. 1987. Long-term effects of modest weight loss in type 2 diabetic patients. *Archives of Internal Medicine* 147 (10):1749–53. doi: 10.1001/archinte.1987.00370100063012.

Wolever, T. M. S., D. J. A. Jenkins, V. Vuksan, A. L. Jenkins, G. C. Buckley, G. S. Wong, and R. G. Josse. 1992. Beneficial effect of a low glycaemic index diet in type 2 diabetes. *Diabetic Medicine* 9 (5): 451–8. doi: 10.1111/j.1464-5491.1992.tb01816.x.

Wu, T., B. R. Zhao, M. J. Bound, H. L. Checklin, M. Bellon, T. J. Little, R. L. Young, K. L. Jones, M. Horowitz, and C. R. Rayner. 2012. Effects of different sweet preloads on incretin hormone secretion, gastric emptying, and postprandial glycemia in healthy humans. *The American Journal of Clinical Nutrition* 95 (1):78–83. doi: 10.3945/ajcn.111.021543.

Wu, X., Y. Wu, L. He, L. Wu, X. Wang, and Z. Liu. 2018. Effects of the intestinal microbial metabolite butyrate on the development of colorectal cancer. *Journal of Cancer* 9 (14):2510–7. doi: 10.7150/jca.25324.

Yoshizane, C., A. Mizote, C. Arai, N. Arai, R. Ogawa, S. Endo, H. Mitsuzumi, and S. Ushio. 2020. Daily consumption of one teaspoon of trehalose can help maintain glucose homeostasis: A double-blind, randomized controlled trial conducted in healthy volunteers. *Nutrition Journal* 19 (1):68. doi: 10.1186/s12937-020-00586-0.

Yoshizane, C., A. Mizote, M. Yamada, N. Arai, S. Arai, K. Maruta, H. Mitsuzumi, T. Ariyasu, S. Ushio, and S. Fukuda. 2017. Glycemic, insulinemic and incretin responses after oral trehalose ingestion in healthy subjects. *Nutrition Journal* 16 (1):9. doi: 10.1186/s12937-017-0233-x.

Zajac, A., S. Poprzęcki, A. Żebrowska, M. Chalimoniuk, and J. Langfort. 2010. Arginine and ornithine supplementation increases growth hormone and insulin-like growth factor-1 serum levels after heavy-resistance exercise in strength-trained athletes. *Journal of Strength and Conditioning Research* 24 (4):1082–90. doi: 10.1519/JSC.0b013e3181d321.

Zhang, Y., and B. J. DeBosch. 2019. Using trehalose to prevent and treat metabolic function: Effectiveness and mechanisms. *Current Opinion in Clinical Nutrition & Metabolic Care* 22 (4):303–10. doi: 10.1097/MCO.0000000000000568.

Zhang, Y., C. B. Higgins, A. L. Mayer, I. U. Mysorekar, B. Razani, M. J. Graham, P. W. Hruz, and B. J. DeBosch. 2018. TFEB-dependent induction of thermogenesis by the hepatocyte SLC2A inhibitor trehalose. *Autophagy* 14 (11):1959–75. doi: 10.1080/15548627.2018.1493044.