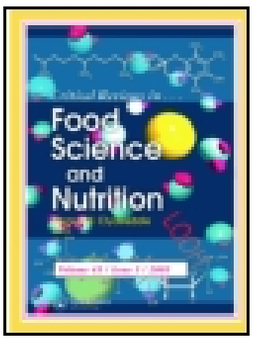

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REVIEW

Rare mono- and disaccharides as healthy alternative for traditional sugars and sweeteners?

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ABSTRACT

Obesity and type 2 diabetes are major health problems affecting hundreds of millions of people. Caloric overfeeding with calorie-dense food ingredients like sugars may contribute to these chronic diseases. Sugar research has also identified mechanisms via which conventional sugars like sucrose and fructose can adversely influence metabolic health. To replace these sugars, numerous sugar replacers including artificial sweeteners and sugar alcohols have been developed. Rare sugars became new candidates to replace conventional sugars and their health effects are already reported in individual studies, but overviews and critical appraisals of their health effects are missing. This is the first paper to provide a detailed review of the metabolic health effects of rare sugars as a group. Especially allulose has a wide range of health effects. Tagatose and isomaltulose have several health effects as well, while other rare sugars mainly provide health benefits in mechanistic studies. Hardly any health claims have been approved for rare sugars due to a lack of evidence from human trials. Human trials with direct measures for disease risk factors are needed to allow a final appraisal of promising rare sugars. Mechanistic cell culture studies and animal models are required to enlarge our knowledge on understudied rare sugars.

KEYWORDS

Rare sugars; low calorie sweeteners; diabetes; metabolic health effects; allulose; sugar substitutes

Introduction

Sugars are widely used in the food industry and are extensively consumed by humans, as they can serve as food preservatives or bulk products and their taste is often considered as pleasant. Sugar stimulates hedonic centers in the brain as well as the release of opioid and dopamine (Avena, Rada, and Hoebel 2008). In the past when high-caloric foods were scarce, the hedonic effects of sugars were beneficial for survival. However, sugars and other high-caloric food ingredients are highly available now and consumption of added sugars has increased globally over the past decades (Siervo et al. 2014; Tilman and Clark 2014). Although sugar consumption in the United States and other rich countries has decreased slightly in the last decade, sugar consumption remains high here (Knutson, Westhoff, and Sherwell 2010; Welsh et al. 2011; Siervo et al. 2014). In the current obesogenic environment with a high availability of sugars, the preference for sweet sugar-rich foods has become a negative trait. In the 21st century, many people suffer from diet-related non-communicable diseases such as diabetes type 2. In their most recent report on diabetes, the World Health Organization (WHO) reported that 422 million people were suffering from diabetes in 2014 (World Health Organization 2016). This number is expected to rise even more in the future, especially in low- and middle-income countries (Guariguata et al. 2014). As a consequence of public health issues related to a high sugar consumption, the WHO strongly recommended to limit intake of free sugars to less than 10% of the total energy intake (World Health Organization 2015). The WHO notes that further benefits can be expected with a sugar intake of less than 5% of the total calories. These recommendations are mainly based on low to moderate evidence that sugar can increase the risk for obesity and tooth decay, rather than on the incidence of type 2 diabetes.

From a legislative point of view, the definition of 'free sugar' (as used for the WHO recommendations) includes both all mono- and disaccharides added to foods or drinks, and sugars which are naturally present in products for which the structure has been broken down, such as fruit juices, syrups pastes and purées (Swan et al. 2018). Sugars naturally present in intact fruits and vegetables or lactose naturally present in dairy products, are not included in this definition (Swan et al. 2018). Furthermore only mono-and disaccharides are considered sugars, which distinguishes them from oligo- and polysaccharides with a degree of polymerization higher than two (Cummings and Stephen 2007). Nevertheless, multiple studies demonstrate that the digestibility and health properties of sugars strongly depend on monosaccharide structure, and the type of glycosidic bond between the monosaccharide units (Brown et al. 2008;

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Schaafsma 2008; Hodoniczky, Morris, and Rae 2012; Maeda et al. 2013). Unusual and potentially more beneficial monosaccharide structures and glycosidic bonds are found among rare sugars, which have been defined by the International Society of Rare Sugars as 'monosaccharides and their derivatives that are present in limited quantities in nature' (Hayashi et al. 2014). Recent technological advances, such as enzymatic engineering using genetically modified microorganisms, now allow to produce a wide diversity of otherwise rare sugars in relatively pure forms and substantial quantities (Beerens, Desmet, and Soetaert 2012). Rare sugars also have a highly similar texture, taste and bulk properties as sucrose, which is often not the case for artificial sweeteners, which are compounds with a sweet taste but are structurally different from conventional mono- and disaccharides (Chattopadhyay, Raychaudhuri, and Chakraborty 2014). In addition, although artificial sweeteners are nowadays often added to foods and beverages as sugar substitutes, their beneficial effect on health is under debate and is even strongly questioned in some publications (Brown, De Banate, and Rother 2010; Swithers 2013). Several individual studies have been performed to assess metabolic effects of one or more rare sugars (Iida et al. 2008; Häberer et al. 2009; Holub et al. 2010), though reviews on this topic are scarce and the few existing reviews either discuss only one rare sugar (Chung, Oh, and Lee 2012), or mention metabolic effects of rare sugars very briefly (Chattopadhyay, Raychaudhuri, and Chakraborty 2014). In the absence of overviews truly focusing on metabolic effects of multiple rare sugars, it remains challenging to assess the suitability of rare sugars as future sugar replacers.

Therefore, we aim in this review to focus on the metabolic health effects of these 'rare sugars' with low prevalence in nature, but with a structure similar to conventional mono- and disaccharides, and assess their potential to act as healthy substitutes for conventionally used sucrose or glucose/fructose-based syrups and sweeteners, at least from a biological point of view. To this end, we will (i) briefly describe the biological mechanisms by which excessive sugar intake may contribute to health issues, (ii) discuss briefly the definition, prevalence and production methods of 'rare' sugars, (iii) give a detailed overview of the biological effects of the most commonly used sugar alternatives (sweeteners) as well as the most prevalent rare sugars and (iv) make a critical appraisal of the potential of rare sugars to substitute conventional sugars and sweeteners, identify the gaps in knowledge, and formulate recommendations for future research in this field.

Chronic diseases associated with elevated sugar intake

Sugars naturally occur in foods like fruits and dairy products, but more than half of the total sugar intake amongst Europeans consists of sugars added to food products (Azaïs-Braesco et al. 2017). In Europe, most of the added sugar intake originates from the consumption of sweet products like confectionary and chocolate, followed by sugar sweetened beverages (Azaïs-Braesco et al. 2017). Cohort studies suggest that sugar and sugar-sweetened beverages are associated with an increased risk for both obesity and type 2 diabetes (Malik et al. 2010; Hu and Malik 2010; De Koning et al. 2011; Greenwood et al. 2014). Although diet is recognized as a major factor to influence diabetes, it is heavily debated whether sugar may directly cause diabetes (Johnson et al. 2009; Kahn and Sievenpiper 2014). A clear example of the diet-diabetes relationship is caloric overfeeding, which has been shown to rapidly induce insulin resistance in skeletal muscle and liver (Schenk, Saberi, and Olefsky 2008). Therefore, the replacement of the high-caloric nutrients, amongst which free sugars but also fats, by low- and zero calorie alternatives is nowadays a commonly used strategy for the production and commercialization of 'light' substitutes of mainly highly processed foods. The disease of diabetes is often preceded by metabolic abnormalities, which are collectively known as the metabolic syndrome. In fact, the metabolic syndrome is basically a cluster of risk factors for diabetes and cardiovascular diseases (Eckel, Grundy, and Zimmet 2005; Alberti, Zimmet, and Shaw 2005). A crucial element of the metabolic syndrome is central obesity, though a high waist circumference has to been accompanied by at least two of the following factors before the someone is considered to have the metabolic syndrome: elevated triglyceride levels, reduced HDL-cholesterol, elevated plasma glucose levels and hypertension (Alberti, Zimmet, and Shaw 2005). The occurrence of the metabolic syndrome is promoted by an accumulation of abdominal fat, which is accompanied by inflammatory reactions that may interfere with insulin signaling (Després and Lemieux 2006; Shoelson, Herrero, and Naaz 2007). As insulin regulates blood sugar levels, problems with insulin sensitivity can lead to elevated glucose levels. Permanently elevated glucose levels as in diabetes are considered harmful, as they contribute to neuropathy and damage to arteries (Porte and Schwartz 1996; Yagihashi, Mizukami, and Sugimoto 2011). The artery damage in diabetes may eventually result in heart disease, kidney failure or blindness (Porte and Schwartz 1996). Sugars containing glucose raise blood glucose levels, which induces insulin secretion by the pancreas. Insulin promotes additional storage of nutrients by promoting cellular uptake and by inhibiting use of macronutrients as fuel (Schenk, Saberi, and Olefsky 2008). Nevertheless, insulin secretion is required for glycemic control, as it stimulates uptake of sugar from the blood and inhibits continuous gluconeogenesis in the liver (Baron et al. 1988; Puigserver et al. 2003). Therefore, metabolic problems may arise upon impaired insulin activity. When insulin sensitivity declines, the body needs more insulin for its glycemic control. As a mechanism to ensure the increased insulin needs, pancreatic beta cells undergo hypertrophy and hyperplasia, processes that are stimulated under conditions of elevated glucose levels (Cerf 2013). This compensatory hyperinsulinemia is often not maintained in diabetes, due to apoptosis of beta cells and concomitant loss of beta cell mass (Cerf 2013). Eventually, this results in a reduced production of insulin that can no longer meet the insulin needs that are required to counteract hyperglycemia.

Metabolic effects of conventional sugars

Glucose, fructose, sucrose and maltose

The most commonly consumed and added sugar is sucrose, which is composed of glucose and fructose, connected with an α1-2 bond. These two monosaccharides differ with regard to their metabolism, resulting in differences in their influence on the insulin response and their lipogenic potential (Basciano, Federico, and Adeli 2005). After consumption of sucrose, the molecule is almost completely broken down by digestive enzymes and the monosaccharides are absorbed at the brush border of the intestinal cells. Glucose can be transported actively via sodium-dependent transporters like SGLT1, while intestinal uptake of fructose occurs in a facilitative way by GLUT5 transporters (Thorens 1996; Wood and Trayhurn 2003). Both sugars are then transported out of the intestinal epithelial cells via GLUT2 (Thorens 1996). The complete digestion and absorption of sucrose makes it a highly caloric sugar. Following intestinal uptake of the monosaccharides, glucose enters the bloodstream whereas fructose is partly converted to glucose by the liver and only partly enters the bloodstream in the form of glucose (Kolderup and Svihus 2015). The rest of the fructose entering the liver is oxidized, converted in lactic acid or used as a substrate for *de novo* lipogenesis (Kolderup and Svihus 2015). As a consequence, glucose increases blood glucose levels much more than fructose does and therefore requires a stronger insulin response. In healthy humans, glucose consumption induced a more than five times higher glucose and insulin response over time compared to consumption of only fructose (Lee and Wolever 1998). However, experiments with mice showed that a high fructose intake can also contribute to the development of insulin resistance (Hwang et al. 1987; Huang et al. 1997). Stanhope et al. performed an intervention with overweight and obese humans, in which either glucose or fructose-sweetened beverages provided 25% of the required energy for 10 weeks. Only the fructose-sweetened beverages induced significant visceral fat gain, with a three times larger increase in visceral fat in the fructose group compared to the glucose group (Stanhope et al. 2009). Furthermore, only fructose reduced insulin sensitivity, based on increased insulin and glucose responses during an oral glucose tolerance test in the fructose group after the intervention compared to baseline (Stanhope et al. 2009). Although the weight gain was similar in both groups, hepatic *de novo* lipogenesis was specifically increased upon fructose consumption (Stanhope et al. 2009). Unlike glucose, high amounts of fructose can be converted to fat without the negative feedback of the enzyme phosphofructokinase, potentially resulting in a larger fat accumulation and elevation of triglyceride levels in the blood (Kolderup and Svihus 2015). Furthermore, fructose has stimulatory effects on lipogenic enzymes, while inhibiting fat oxidation specifically in the liver (Prager and Ontko 1976; Jensen et al. 2018). Related to its lipogenic potential and hepatic metabolism, fructose is known to promote fat accumulation in the liver at a high intake, yet it is not known whether it can cause nonalcoholic liver disease in humans (Vos and Lavine 2013). In addition, fructose promotes the formation of uric acid, which inhibits insulin-induced endothelial nitric oxide synthase phosphorylation (Choi et al. 2014). This results in a reduced production of the important vasodilator and signaling molecule nitric oxide (NO) and may hereby even cause endothelial dysfunction (Choi et al. 2014). Lanaspa et al. showed that uric acid was also able to promote fat accumulation dose-dependently in HepG2 cells, even in the absence of additional calories (Lanaspa et al. 2012). Therefore, high-fructose alternatives are not necessarily the best alternatives for metabolic health. Although fructose can induce unfavorable metabolic changes, it remains questionable whether a normal fructose intake in humans will adversely influence metabolic health. MacDonald recently reviewed the literature about the relationship between fructose and diabetes. According to this review, it is clear that abnormally high amounts of fructose can have detrimental effects in animals, but it questions the value of these results for the human situation (MacDonald 2016). Regarding human studies, high fructose interventions increased serum triglyceride levels and reduced fasting insulin sensitivity when daily intakes exceeded 150 g (MacDonald 2016). However, these interventions contained both excessive fructose and excessive energy. The conclusion of the review was that fructose can have adverse health effects as a part of a diet with excessive calories, but that there is no evidence for detrimental health effects of fructose in an isocaloric situation (MacDonald 2016). Similarly, Rizkalla argues that unrealistically high amounts of fructose have been used to evaluate health effects of fructose. According to his review, fructose has no deleterious effect on lipid and glucose control under 50 g/day and no influence on body weight below 100 g/day (Rizkalla 2010). Other sugars abundant in the human diet have a different monosaccharide composition than sucrose. Maltose is an easily digestible disaccharide consisting of two α1-4 linked glucose molecules and is formed during the digestion of starch. In starch digestion, the brush border enzymes maltase-glycoamylase and sucrase-isomaltase work complementary by respectively degrading linear and branched linkages (Nichols et al. 2003). As an easily digestible sugar composed of only glucose, the metabolic effects of maltose are considered to be similar to those of pure glucose. Wahlqvist et al. reported that maltose and even glucose polymer mixtures with an average chain-length of 5 glucose units (caloreen®) have similar effects on blood glucose levels than the monosaccharide glucose in healthy human subjects (Wahlqvist et al. 1978). Likewise, peak glucose concentrations in diabetics and insulin responses did not differ between glucose and glucose polymer administration (Wahlqvist et al. 1978). However, certain differences in absorption may occur between maltose and glucose as reported by Jones et al. These researchers performed carbohydrate infusions in the human jejunum and found that glucose absorption from maltose is significantly faster than glucose absorption from glucose itself (Jones et al. 1983). The explanation for this observation would be that higher local concentrations of glucose at the transport sites are reached after oligosaccharide hydrolysis with brush border

enzymes compared to diffusion of free glucose (Jones et al. 1983). This appears to be true only for disaccharides and medium-chain oligosaccharides with an α1-4 bond as hydrolysis of the α1-6 bond is rate limiting for absorption of glucose and absorption is slower for molecules with more than 10 glucose units as well (Jones et al. 1983). In an experiment with male Wistar rats, the effects of diet containing 70% maltose was compared with isocaloric diets containing 70% sucrose or starch. After 4 and 6 weeks of intervention, maltose and sucrose both significantly increased the 15 min insulin response to a glucose challenge and the triglyceride levels compared to starch, without differences between the two sugars (Laube et al. 1978). Overall, maltose can be considered an easily digestible and highly glycemic sugar.

Lactose and galactose

Lactose is a sugar found in dairy products, that consists of glucose and galactose connected through a β1-4 bond, which delays the breakdown of lactose and the release of the monosaccharides. Following digestion and intestinal uptake, galactose is metabolized via the Leloir pathway in an UDP-dependent manner (Szablewski 2011). Like fructose, galactose is transported to the liver where it can be converted to glucose (Szablewski 2011). Information on the relationship between galactose and insulin resistance is limited and the effects may be more beneficial compared to glucose or fructose. A 9-week rat intervention study investigated glucose clearance with a hyperinsulinemic-euglycemic clamp in rats receiving 15% of either galactose, glucose or fructose in their diet. In this clamp method, insulin is infused via a catheter followed by a continuous infusion of insulin and a variable infusion of glucose. Hence, plasma glucose levels are kept at a constant level and the amount of glucose that needs to be infused depends on the insulin-induced glucose uptake. In this study, galactose administration significantly increased the glucose infusion rate by 53% and significantly decreased endogenous glucose production by 57% compared to glucose and fructose (Stahel et al. 2017). Instead, galactose promoted liver glycogen storage. These observations collectively suggest an improvement of glucose handling. In a small intervention study with obese women, galactose feeding at 325 g/day in a drink resulted in 11% lower glucose and 55% lower insulin levels compared to an isocaloric glucose drink, whereas fat oxidation increased (Mohammad et al. 2011). Furthermore, Kase et al. demonstrated that human skeletal muscle cells had a 66% higher glucose uptake and double as high glucose oxidation after they were grown in medium with 5.5 mM of galactose instead of glucose (Kase et al. 2013). This study suggested an improved handling of glucose and increased oxidative capacity in skeletal muscle cells grown with galactose compared to those grown with glucose (Kase et al. 2013). Nevertheless, extremely high intakes of galactose may be dangerous. Mangeot et al. fed rats with a diet in which galactose provided 50% of the energy for 38 days and found that this diet resulted in growth retardation and cataracts (Mangeot et al. 1987). Humans suffering from galactosemia can develop renal tube dysfunction, cataracts and sepsis upon galactose consumption. In this disease, there is a deficiency of the enzymes in the Leloir pathway (Bosch 2011). In the rat study, these enzymes were increased in activity and likely overloaded. Galactose is also used in mice models to simulate aging of the brain (Parameshwaran et al. 2010). Finally, galactose can contribute to the formation of reactive oxygen species (ROS) and advanced glycation end products (AGEs) (Song et al. 1999). The latter are described to contribute to ROS production and depletion of NO, which may lead to hypertension and endothelial dysfunction (Singh et al. 2001). In addition, AGEs promote unfavorable cross-linking of sub-endothelial structural proteins and alter thrombogenesis (Singh et al. 2001). However, the possibility to contribute to formation of AGEs and ROS is not specific for galactose. In fact, especially fructose is described as a sugar with a strong effect on endogenous AGE production (Aragno and Mastrocola 2017). In conclusion, metabolism and health outcomes differ between conventional sugars, although they may all have adverse health effects when consumed in large amounts. It should be noted that part of the negative health effects in studies were found at physiological sugar concentrations, while other effects were found at concentrations that exceed the normal intake in humans, which does not mean that these effects cannot occur in vivo when the exposure duration exceeds the duration used in the intervention studies.

Rare sugars: definitions, occurrence, physiological function and production methods

As excessive consumption of conventional sugars can have an impact on our health, there is a need for alternatives to lower our sugar intake. Relatively new candidates to substitute conventional sugars, can be found among the rare sugars. As briefly mentioned, these rare sugars have been defined by the International Society of Rare Sugars as 'monosaccharides and their derivatives that are present in limited quantities in nature' (Hayashi et al. 2014). In this review, we focus on the metabolic effects of specifically mono- and disaccharide types of rare sugars, and not on oligo- or polysaccharides, which have already been reviewed extensively in the context of their prebiotic potential (Rastall and Gibson 2002; Swennen, Courtin, and Delcour 2006; Seifert and Watzl 2007), and are strictly spoken not considered as 'sugar'. So far, it is hard to estimate how many structurally different mono- and disaccharides exist in nature, and only a few of them have been investigated in detail so far. In 2004, Granström et al. listed 42 known monosaccharides that are either naturally found or producible. The list includes 24 hexoses, 12 pentoses and 6 tetroses of which 50% is in the D-configuration and 50% is in the L-configuration (Granström et al. 2004). The actual number of monosaccharides will be even higher, since some natural deoxy-sugars like L-rhamnose were not included in this list. Among all these monosaccharides, only seven monosaccharides are considered as non-rare, namely D-glucose, D-fructose, D-galactose, D-mannose, D-ribose, D-xylose

and L-arabinose (Beerens, Desmet, and Soetaert 2012). Theoretically, numerous disaccharides can be constructed from these monosaccharides, which may not only be different in type of monosaccharides used, but also in type and position of the glycosidic bond. The best characterized disaccharides are generally glucose-glucose sugars like maltose and glucose-fructose sugars like sucrose. Examples of known rare glucose-glucose and glucose-fructose sugars include the rare sucrose isomers turanose (Glc-α1,3-Fruc), leucrose (Glc-α1,5-Fruc) & isomaltulose (Glc-α1,6-Fruc), the rare α-glucobioses kojibiose (Glc-α1,2-Glc), nigerose (Glc-α1,3-Glc) & isomaltose (Glc-α1,6-Glc) and rare β-glucobioses like sophorose (Glc-β1,2-Glc), laminaribiose (Glc-β1,3-Glc) and gentiobiose (Glc-β1,6-Glc) (Hodoniczky, Morris, and Rae 2012).

Although quantities of the naturally occurring rare monosaccharides and disaccharides are small in nature, they are found in a variety of foods. Honey is an example of a food containing a large variety of sugars including rare disaccharides like kojibiose, nigerose and turanose (Doner 1977). The rare disaccharide trehalose can be found in multiple dietary sources including honey, cherries, mushrooms and in larger amounts in baker's yeast (Richards et al. 2002) . The rare monosaccharide allulose is naturally found in wheat, but is more likely to be consumed via fructose-containing foods that undergo heating processes. Examples of products in which several milligram of allulose per 100 g is formed during processing, are fruit juices, dried fruits, ketchup and Worcester sauce (Chung, Oh, and Lee 2012). The limited presence of rare sugars in nature hampers their use in the food industry since isolation of rare sugars, if possible at all, gives a very low yield and involves the use of many chemicals (Beerens, Desmet, and Soetaert 2012; Beerens et al. 2017). However, nowadays, rare sugars can also be produced by means of genetically engineered enzymes using widely available sugars such as galactose and glucose as start substrate (Granströ m et al. 2004; Beerens, Desmet, and Soetaert 2012; Beerens et al. 2017). Certain wildtype enzymes can already synthesize rare disaccharides with a low yield, which is for example the case with kojibiose production using kojibiose phosphorylase (Chaen et al. 2001) or glucansucrase (Monsan and Ouarné 2009). Mutant variants can produce larger amounts of rare disaccharides, which is for example the case with new sucrose phosphorylase variants that enhance nigerose (Kraus et al. 2016; Franceus et al. 2019) and kojibiose production (Verhaeghe et al. 2016; Beerens et al. 2017). Immobilization of rare sugar producing enzymes has been shown to be a successful method for the production of rare monosaccharides with a relatively high yield (Zhang et al. 2017). These innovations have made it possible to obtain higher quantities needed for studying the health effects of for instance tagatose, allulose and isomaltulose, as well as the estimation of their caloric content in animals and humans (1.5–3 kcal/g for tagatose and practically 0 kcal/g for allulose) compared to conventional sugars (4 kcal/g) (Matsuo et al. 2002; Espinosa and Fogelfeld 2010; Turck et al. 2016).

The minimal presence of rare sugars in nature raises the question whether they have a natural function and if so, what function this would be. The human body uses glucose as its primary energy source and has the ability to convert other nutrients into glucose, which makes sense considering the efficiency of this energy source. However, in times of an obesity epidemic, replacement of efficient energy sources like glucose and sucrose by less efficient energy sources like rare sugars, may be preferred. For now, it remains speculation whether rare sugars might have a physiological role in humans. However, it has been reported that rare sugars play a role in the physiology of insects and plants. This may not but the case for all naturally occurring rare sugars, but trehalose is an example for which this is the case. In insects, trehalose and not glucose is the primary sugar circulating in the blood stream (Thompson 2003). In higher plants, trehalose concentrations are often undetectable (Wingler 2002). Although trehalose synthesis occurs, trehalase activity keeps trehalose levels low and experiments have shown that trehalase inhibition results in trehalose accumulation in higher plants (Wingler 2002). Synthesis and degradation of trehalose may occur for regulatory purposes. Trehalose precursor trehalose-6-phosphate is involved in the regulation of sugar influx and metabolism, and enhances photosynthesis capacity in plants (Wingler 2002; Grennan 2007). Therefore, natural presence of rare sugars is at least not in all cases a coincidence, although we cannot generalize this statement for all rare sugars.

In the following paragraphs, we will discuss the metabolic effects of a selection of rare sugars, including five monosaccharides (allulose, tagatose, sorbose, allose and L-arabinose) and three disaccharides (isomaltulose, trehalose and kojibiose), that have been relatively well-studied, including potential mode-of-action and an overall view of their potential to substitute conventional sugars.

Chemical structure of rare sugars

Rare sugars differ in chemical structure compared to the conventional sugars, although these differences are subtle for both monosaccharides and disaccharides. Figure 1 shows the structures of rare sugars discussed in this review as well as the conventional sugars they are related to (Figure 1A–C).

Figure 1A shows that the only difference between glucose (1) and allose (3) is the position of a hydrogen atom and hydroxyl group at the third carbon atom. Likewise, tagatose and allulose have a different arrangement of a hydrogen atom and hydroxyl group, compared to fructose. Allulose (6) differs from fructose at the third carbon atom, while tagatose (7) differs from fructose (5) at the fourth carbon atom. Sorbose (8) differs from fructose at both the third and the fourth carbon atom. Sorbose has the same arrangement as allulose at the third carbon atom and the same arrangement as tagatose at the fourth carbon atom. Galactose (2) differs from glucose by the arrangement of the hydrogen atom and hydroxyl group at the fourth carbon atom. L-arabinose (4) has a structure that is most similar to galactose, although it is a pentose meaning that it has one carbon

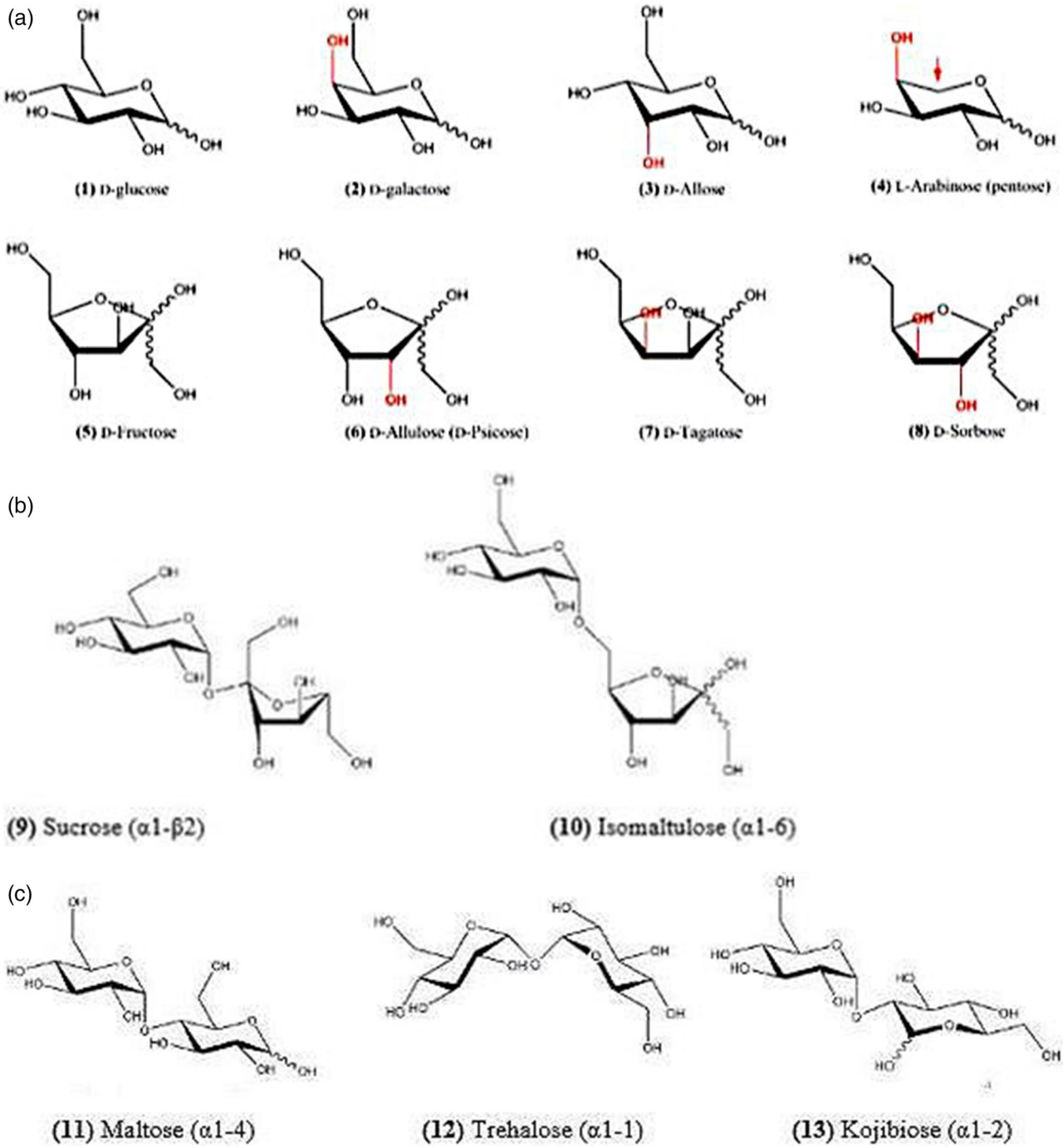

Figure 1. Differences in chemical structure between common and rare sugars. A, B and C show the chemical structures of various conventional and rare monosaccharides (A), glucose-fructose disaccharides (B) and glucose-glucose disaccharides (C). Monosaccharides 2 and 3 have a similar structure as glucose (1), while sugars 6–8 are structurally close to fructose (5). OH groups in red indicate differences with glucose/fructose. *Sugar structures were created using Chemdraw.

atom less compared to galactose. Sucrose (9) and isomatulose (10) are both disaccharides of glucose and fructose, although the configuration differs and isomaltulose contains an α1-6 bond while the monosaccharides in sucrose are connected with an α1-2 bond (see Figure 1B). Trehalose (12) and kojibiose (13) are disaccharides containing two glucose molecules, like maltose (11). Kojibiose with the α1-2 bond and trehalose with an α1-1 bond differ in configuration from maltose with the α1-4 bond, as shown in Figure 1C.

Metabolic effects of rare sugars

Metabolic health effects of rare sugars are discussed. Tables 1–3 summarize the health effects of rare sugars based on respectively human trials, animal experiments and in vitro experiments. Figure 2 provides a visual representation of metabolic effects provided by rare sugars (as well as some conventional sugars and sweeteners) and their modes of action (Figure 2).

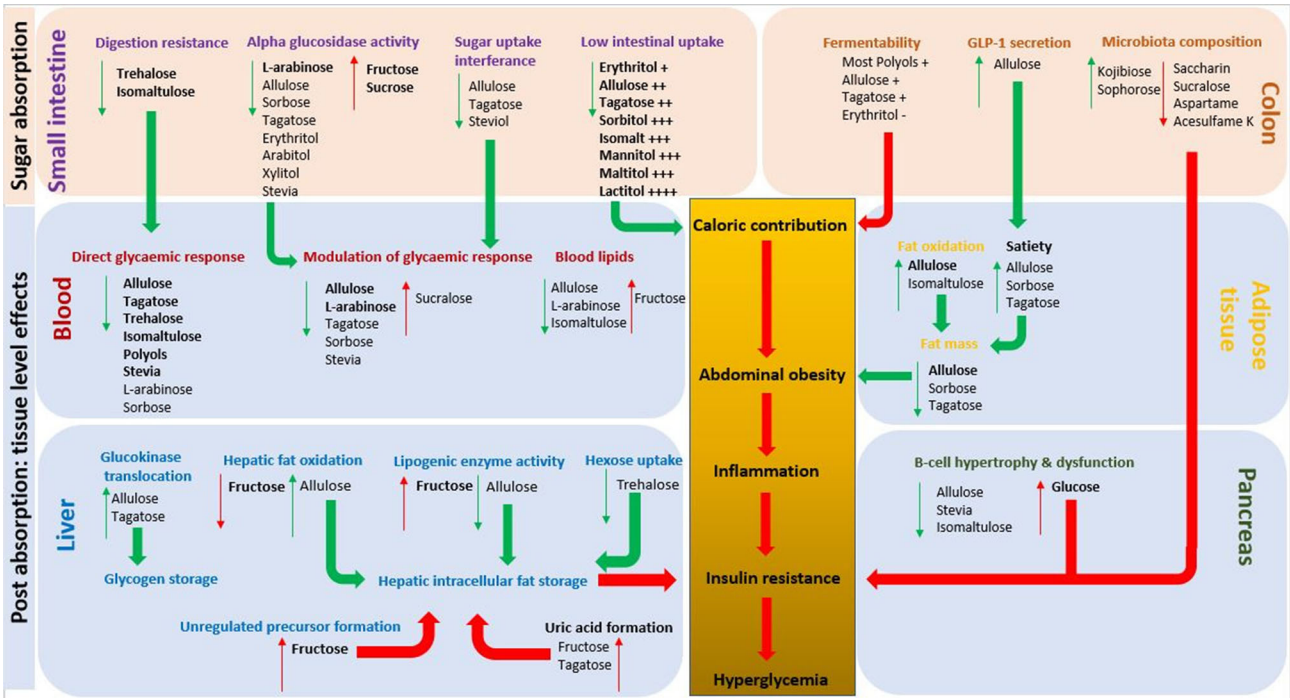

Figure 2. Overview scheme of metabolic actions of sugars in the human body. Effects of sugars and sweeteners on the health parameters are indicated with thin red (negative influence on health) and green arrows (beneficial effect), focusing on the effects of rare sugars. Arrow pointing upwards indicate that the indicated factor is increased, whereas arrow pointing down indicate a decrease. Thick arrows indicate which factors are stimulated by the effects of a sugar or sweetener. Bold names of sugars or sweeteners indicate that the compound had a convincing effect often based on several human trials, whereas non-bold names indicate potential effects based on mechanistic studies or findings in one or a few human trials.

Mixtures of rare sugars in syrups

Evidence of improved metabolic effects of rare sugars, is partly based on human and animal studies performed with syrups of mixed rare sugars. These rare sugar syrups have been developed by alkaline isomerization of high fructose corn syrup and are often compared with the conventional high fructose corn syrup. Hayashi et al. performed a human randomized controlled trial to compare the health effects of daily consumption of 30 g syrup with rare sugars and an isocaloric drink consisting of high-fructose corn syrup (HFCS). The two syrups consisted primarily of glucose and fructose with small amounts of oligosaccharides, though part of the glucose and fructose were converted into rare sugars in the rare sugar syrup under alkaline conditions. The rare sugar syrup contained 7.5% mannose and sorbose, 6% allulose and about 1% of both allose and isomaltulose. Within a 12-week intervention period, the researchers reported a significant time-x-treatment effect of the rare sugar syrup on body weight, fat percentage and waist circumference (Hayashi et al. 2014). Whereas participants in the HFCS group did not lose any weight, an average of 1.85 kg was lost in the rare sugar syrup group in addition to a 2 cm extra loss of waist circumference. The researchers did not detect any adverse effects of the rare sugar syrup on blood biochemistry or hepatic function. Although interesting, these results by Hayashi et al. were observed in a study with 17 participants per group and were only significant based on treatment effects in analyses of change, which has been criticized as a misleading way to analyze data from randomized controlled trials (Bland and Altman 2015). Shintani et al. performed an 8-week intervention study with rare sugar syrup containing 5% allulose, 5% sorbose, 2% tagatose and 1% allose, compared to HFCS and water in Wistar rats and then studied the response on a challenge with 2 g glucose per kilogram body weight. The two syrups were diluted until they contained 7% of fructose and were added to the drinking water. The total sugar concentration after dilution was 25% for the rare sugar syrup and 15% for HFCS. The rare sugar syrup significantly reduced the glycemic response after the challenge. The 3-h area under the curve for glucose and insulin were about 30% and 60% lower in the rare sugar syrup group compared to the HCFS group (Shintani et al. 2017). After 10 weeks, the fat mass of rats in the rare sugar syrup group was about 45% lower compared to the HFCS and about 30% lower than in the group that just received water. In addition, hepatic glycogen was more than 3 times higher in the rare sugar syrup group and export of hepatic glucokinase from the nucleus was significantly higher as well (Shintani et al. 2017). These studies indicate that rare sugars could provide health benefits compared to the conventional sugars in a mixed form, although a structure-function relationship could not be established because of the diverse composition of the syrups. In the next paragraphs, we will discuss the health impact of individual rare sugars.

Rare monosaccharides

In this review, we will discuss the 'rare' monosaccharides L-arabinose, D-sorbose, D-allulose, D-tagatose and D-allose. The rare sugar L-arabinose is not necessarily rare in nature, but has interesting properties and usually occurs as a component of large undigestible molecules like hemicellulose instead of appearing in the form of a separate sugar, and is thus rarely present in its free form.

Table 1. Effects of rare sugars in human trials.

Effect	Sugar	Population	Comparison
Improved glycemic control in a challenge	*L-arabinose* (Krog-Mikkelsen et al. 2011)	Healthy humans	4% to 75 g sucrose solution
	Allulose (Iida et al. 2008; Noronha, Braunstein, Glenn, et al. 2018; Braunstein et al. 2018)	Healthy and diabetic subjects	2.5–7.5 g combined with 75 g maltodextrin or 0–10 g combined with 75 g glucose (inconsistent results)
	Tagatose (Donner, Wilber, and Ostrowski 1999)	Healthy and diabetic subjects	75 g versus 75 g glucose before challenge
	Isomaltulose (Arai et al. 2007; Holub et al. 2010; Maeda et al. 2013; Suklaew et al. 2015; Van Can et al. 2012)	Healthy men, healthy subjects, obese men, overweight subjects	500 ml isomaltulose- versus dextrin formula; 50 g/day versus sucrose; 40 g versus sucrose; 75 g in 400 ml versus sucrose
	Trehalose (Van Can et al. 2012)	Overweight subjects	75 g in 400 ml versus sucrose
Body weight reduction	*L-arabinose* (Yang et al. 2013)	Humans with the metabolic syndrome	
	Tagatose (Donner, Magder, and Zarbalian 2010)	Diabetic subjects	3 × 15 g/day
	Rare sugar syrup (Hayashi et al. 2014)	Healthy subjects	30 g/day versus high fructose corn syrup
Increase in fat oxidation (short term)	*Allulose* (Kimura et al. 2017)	Healthy subjects	5 g versus 10 mg aspartame
	Isomaltulose (Arai et al. 2007)	Healthy men	500 ml isomaltulose- versus dextrin formula
Loss of subcutaneous and abdominal fat	*Allulose* (Han et al. 2018)	Korean subjects	2x daily 7 g or 4 g combined with 0,012 g sucralose versus sucralose
Long-term reduction fasting triglyceride levels	*L-arabinose* (Yang et al. 2013)	Humans with the metabolic syndrome	
	Isomaltulose (Brunner et al. 2012)	Diabetic subjects	50 g/day versus sucrose
Increase in uric acid levels	*Tagatose* (Saunders et al. 1999; Buemann et al. 2000)	Healthy and diabetic subjects; Healthy male subjects	75 g versus 75 g glucose before challenge; 30 g versus 30 g fructose
Increase short chain fatty acids	*Tagatose* (Normén et al 2001); Venema, Vermunt, and Brink 2005)	Ileostomy subjects; healthy subjects	15 g/day; 7,5 or 12 g
Increased excretion of glucose and sucrose	*Tagatose* (Normén et al 2001);	Ileostomy subjects	15 g/day

L-arabinose: a sucrase inhibitor with additional health effects

L-arabinose was found to be a potent sucrase inhibitor at 9.1 mM in brush border vesicles of rat intestine, in which it inhibited sucrase activity by more than 80% (Oku et al. 2014). In a study with porcine intestinal mucosa, both L-arabinose and xylose at 10 mM inhibited sucrase activity slightly over 50%, without significant effects on other glucosidases (Seri et al. 1996). The inhibitory effect of L-arabinose on sucrase activity has been found in differentiated Caco-2 cells as well at concentrations ranging from 0.84 till 2.8 mM (Krog-Mikkelsen et al. 2011). The ability of L-arabinose to inhibit sucrase activity may influence glycemic responses in vivo. In rats, the glycemic response was measured 15 min after sucrose loading and addition of 100 mg/kg of L-arabinose suppressed the rise in glucose levels by 50% and insulin levels by more than 60% (Seri et al. 1996). This effect of L-arabinose on the rise in glucose levels was 2.4 times more potent that the effect of xylose in the same study. In a challenge test with healthy humans, addition of 4% L-arabinose to beverages containing 75 g of sucrose resulted in an 11% reduction of the glucose peak and a 33% reduction of the insulin peak measured after 3 h (Krog-Mikkelsen et al. 2011). These effects of L-arabinose related to α-glucosidase activity are clearly different from the effects of sucrose, which stimulates sucrase and maltase activity compared to isocaloric amounts of glucose (Rosensweig and Herman 1968; Goda, Bustamante and Koldovský 1985). The presence of fructose is believed to be responsible for this effect (Rosensweig and Herman 1968). The health benefits of L-arabinose are not limited to effects on the glycemic response. Oral exposure of 400 mg/kg per day of L-arabinose to rats with the metabolic syndrome reduced body weight by 8%, fasting glucose and insulin levels by almost 25%, triglyceride levels by 36%, total cholesterol by 17% and liver triglycerides by more than 50% (Hao et al. 2015). Furthermore, L-arabinose prevented a rise in TNF-α and leptin in rats with diet-induced metabolic syndrome (Hao et al. 2015). In a study by Osaki et al., rats received several amounts of sucrose (up to 30% of the diet) combined with L-arabinose (up to 1% of the diet) for 10 days. L-arabinose at 1% in addition to 30% sucrose, reduced plasma and liver triglycerides both by about one third compared to 30% sucrose alone (Osaki et al. 2001). At these sugar levels, L-arabinose inhibited the hepatic activity of the lipogenic enzymes acetyl-CoA carboxylase, fatty acid synthase and ATP citrate-lyase (Osaki et al. 2001). In humans with metabolic syndrome, 6 months of exposure to L-arabinose decreased waist circumference, fasting glucose, serum uric acid, triglyceride levels and body weight (Yang et al. 2013). Lastly, L-arabinose is considered non-caloric as it is not involved in metabolic processes (Hao et al. 2015). However, arabinosyl residues from arabinoxylan are fermentable by certain species from the microbiota including *Bifidobacterium longum* strains, and may therefore provide some energy via the production of short-chain fatty acids (Crittenden et al. 2002). Many

Table 2. Effects of rare sugars in animal experiments.

Effects	Sugars	Species
Reduced food intake	*Sorbose* (Furuse et al. 1990; Kita et al. 1992) *Allulose* (Iwasaki et al. 2018)	Laying hens; Gold-thioglucose exposed rats Rats and mice
Increase in Glp-1	*Allulose* (Iwasaki et al. 2018)	Rats and mice
Weight loss	*Sorbose* (Kita et al. 1992) *Allulose* (Hossain et al. 2011; Itoh et al. 2015) *Tagatose* (Kruger et al. 1999)	Gold-thioglucose exposed rats OTEFL rats; leptin deficient mice Rats
Reduction body weight gain	*Sorbose* (Furuse et al. 1990) *Allulose* (Matsuo et al. 2002; Matsuo et al. 2003; Itoh et al. 2015) *Kojibiose* (Laparra et al. 2015)	Laying hens Male Wistar rats; Wistar rats; leptin deficient mice Female Wistar rats
Reduction fat mass/adipocyte size	*Allulose* (Hossain et al. 2011; Itoh et al. 2015; Chen, Huang, and Jiang 2017) *Isomaltulose* (Sato et al. 2007) *Trehalose* (Arai et al. 2010) *Rare sugar sirup* (Shintani et al. 2017)	OTEFL rats; leptin deficient mice; Wistar rats Zucker fatty rats Mice Wistar rats
Reduction glucose levels (long-term)	*Sorbose* (Furuse et al. 1993) *L-arabinose* (Hao et al. 2015) *Allulose* (Hossain et al. 2011) *Isomaltulose* (Sato et al. 2007)	Diabetic mice Rats with metabolic syndrome OTEFL rats Zucker fatty rats
Reduction triglyceride levels (long-term)	*Sorbose (*Furuse et al. 1990) *L-arabinose* (Osaki et al. 2001; Hao et al. 2015) *Allulose* (Hossain et al. 2011; Chen, Huang, and Jiang 2017) *Isomaltulose* (Arai et al. 2004)	Laying hens Rats; Rats with metabolic syndrome OTEFL rats; Wistar rats Sprague-Dawley rats
Reduction insulin levels (Long-term)	*Sorbose* (Yamada et al. 2014) *L-arabinose* (Hao et al. 2015) *Isomaltulose* (Arai et al. 2004) *Trehalose* (Arai et al. 2010)	Sprague-Dawley rats Rats with metabolic syndrome Sprague-Dawley rats Mice
Reduction glycemic response	*Sorbose* (Oku et al. 2014) *L-arabinose* (Seri et al. 1996) *Tagatose* (Zehner et al. 1994) *Isomaltulose* (Häberer et al. 2009) *Rare sugar sirup* (Shintani et al. 2017)	Rats Mice and rats Rats Rats Wistar rats
Reduction liver fat/improvement of steatosis	*L-arabinose* (Osaki et al. 2001 ; Hao et al. 2015) *Allulose* (Baek, Park, and Lee 2010; Itoh et al. 2015; Han et al. 2016; Iwasaki et al. 2018) *Trehalose* (DeBosch et al. 2016)	Rats; Rats with metabolic syndrome Genetically diabetic mice; leptin deficient mice; mice; Rats and mice Mice
Increase short chain fatty acids	*Allulose* (Matsuo et al. 2003)	Wistar rats

other bacteria are not able to ferment arabinoxylan, and arabinosyl residues may therefore provide specific growth benefits for beneficial *Bifidobacteria* (Crittenden et al. 2002).

Overall, promising effects of L-arabinose have been found in both rats and humans, although only a few in vivo studies have been performed so far. The ability of L-arabinose to inhibit sucrase activity is well documented and stronger compared to other monosaccharides at the same concentration. Via inhibition of sucrase, L-arabinose has been found to lower post-prandial glycemic responses. In humans this effect has been observed for L-arabinose concentrations of 4%, as briefly discussed (Krog-Mikkelsen et al. 2011).

(D-)Sorbose: a rare sugar with interesting effects in animal experiments

Sorbose has beneficial metabolic effects in animal studies. In a 6-week intervention study with diabetic mice, substitution of sucrose for sorbose (both 200 mg/kg of diet) resulted in a decrease of blood glucose concentrations and prevented urinal glucose excretion (Furuse et al. 1993), suggesting an anti-diabetic effect. The same amounts of sorbose and sucrose were compared in a 2-week study with control rats and rats that were treated with gold thioglucose as obesity-inducer. In the thioglucose-treated rats, the *ad libitum* food intake was 43% lower in the sorbose group and these rats lost 10 g of body weight, whereas rats in the sucrose group gained 9 g of body weight (Kita et al. 1992). In the control rats, more weight loss and less food intake was observed in the sorbose group compared to the sucrose group, though the effects on weight and food intake were less pronounced than in thioglucose-treated rats. In a study by Yamada et al., Sprague-Dawley rats receiving 3% sorbose for 28 days as part of their diet, had almost 40% lower insulin levels and 22% lower uric acid levels compared to a control diet without sorbose (Yamada et al. 2014). This control diet contained more dextrinized corn starch to compensate for the absence of sorbose. Body weight and glucose levels were non-significantly lower in the 3% sorbose group. In a challenge test with rats, addition of 33 mg/ml of sorbose to a

Table 3. Effects of rare sugars in in vitro experiments.

Effect	Sugar	Method	Dose
Inhibition sucrase activity	*Sorbose* (Oku et al. 2014)	Rat and human intestinal homogenate	9.1 mM
	L-arabinose (Oku et al. 2014; Seri et al. 1996; Krog-Mikkelsen et al. 2011)	Rat and human intestinal homogenate; porcine intestinal mucosa; differentiated Caco-2 cells	9.1 mM; 10 mM; 0.84–2.8 mM
	Tagatose (Oku et al. 2014)	Rat and human intestinal homogenate	9.1 mM
Slower digestion compared to maltose/sucrose	*Kojibiose* (Chaen et al. 2001; Hodoniczky, Morris, and Rae 2012; Lee et al. 2016	Digestion with rat intestinal acetone powder; Crude rat intestinal alpha-glucosidases	Digestion at concentrations ranging from 10 to 40 mM
	Isomaltulose (Hodoniczky, Morris, and Rae 2012; Lee et al. 2016)		Digestion at concentrations ranging from 10 to 40 mM
	Trehalose (Lee et al. 2016)	Crude rat intestinal alpha-glucosidases	
Inhibition ROS	*Allose* (Murata et al. 2003; Ishihara et al. 2011)	Neutrophils; Neuro2A cells	15 min exposure at a concentration range till 50 mM; 10 mM allose with 10 and 25 mM glucose
	Trehalose (Mizunoe et al. 2018)	Intracellular ROS assay In Hepa 1-6 cells	24 h exposure to 50 mM trehalose, followed by 2 mM paraquat as oxidative stress inducer
Anti-inflammatory effect	*Allulose* (Murao et al. 2007)	HUVEC cells	5 day exposure at a concentration range till 22,4 mM
Increased survival upon stress	*Trehalose* (Benaroudj, Lee, and Goldberg 2001; Tang et al. 2017)	Yeast cells; cell counting with primary mice chondrocytes	500 mM trehalose for 30 min; 24 h exposure to trehalose 25–100 mM and 25 μM TBHP as inducer for oxidative stress
Reduction liver fat	*Trehalose* (DeBosch et al. 2016)	Primary hepatocytes, using the infinity triglyceride assay in the homogenate	48 h exposure to 100 mM trehalose, combined with either 5 mM fructose or 500 μM FFA
Beneficial change of microbiota	*Kojibiose* (Sanz, Gibson, and Rastall 2005)	In vitro fermentation model	In vitro fermentation with 7 g carb, 0,7 ml basal medium and 1% fecal bacteria
GLUT1 inhibition	*Allose* (Noguchi et al. 2016)	Neuroblastoma, liver cancer & breast cancer cells	7 days exposure at 12,5-50 mM
Anti-cancer effect	*Allose* (Hoshikawa et al. 2011; Noguchi et al. 2016)	Head and neck cancer cells; neuroblastoma, liver cancer & breast cancer cells	6 h exposure with 10–25 mM allose prior to radiation treatment; 7 days exposure at 12.5–50 mM

300 mg/ml sucrose solution resulted in a 50% suppression of the 30 min rise in glucose and insulin levels compared to sucrose without sorbose (Oku et al. 2014). In the same study by Oku et al. sorbose at 9.1 mM added ex vivo to a reaction mixture strongly inhibited sucrase activity (more than 60%) and weakly inhibited maltase activity (20%) in rat and human intestinal homogenate. In laying hens, a 4-week sorbose intervention dose-dependently decreased serum triglyceride, cholesterol and LDL levels (Furuse et al. 1990). In addition, the body weight and feed intake of the hens were reduced with increasing amounts of sorbose.

Overall, several promising effects of sorbose have been reported. However, our knowledge on the health effects of sorbose is mainly based on a small number of small-scale animal experiments. Effects of sorbose were already observed at 3% of the dietary intake (Yamada et al. 2014).

(D-)Allulose (D-psicose): the most promising sucrose substitute?

Allulose is one of the most intensively studied rare monosaccharides with a potential as a healthier substitute for sucrose. This sugar recently received a GRAS status in the USA and applications for approval of allulose as food ingredient in the European Union are under investigation. Already in 2002, Matsuo et al. identified the low caloric content of fructose C-3 epimer allulose. In their study, male Wistar rats received a 20 day intervention consisting of a normal diet supplemented with 0.5–2 g of sucrose, fructose or allulose. The rats gained weight in the additional sucrose and fructose condition, but not in the allulose condition (Matsuo et al. 2002). The net energy gain calculated from the weight gain compared to a water control was 2.29 kcal/g for sucrose, 1.76 kcal/g for fructose and only 0.007 kcal/g for allulose. In 2003, Matsuo et al. investigated the metabolism and excretion of allulose in Wistar rats. They found that allulose is partly absorbed and is traceable in the urine and feces 24 h after intake, though colonic fermentation occurs as well. The amount of allulose that is absorbed and excreted via the urine is estimated to be 70% (Hossain et al. 2015). Diets containing 0, 10, 20 and 30% of allulose resulted in a concentration dependent decrease in body weight gain and an increase in acetic acid, propionic acid and butyric acid levels (Matsuo et al. 2003). The diet with 30% allulose increased propionic acid 2-fold, acetic acid more than 4-fold and butyric acid more than 6-fold compared to the 0% allulose diet (Matsuo et al. 2003). In another study with Wistar rats, Tsukamoto et al. demonstrated that oral allulose can reach the bloodstream, starts to appear in the urine after 30 min and accumulates in the liver (Tsukamoto et al. 2014). Iida et al. presented further evidence for a very low caloric value of allulose despite the

ability of the body to absorb it. These researchers measured carbohydrate energy expenditure by indirect calorimetry, urinary allulose excretion, breath hydrogen gas and fermentability in human participants. In this study carbohydrate energy expenditure did not increase upon exposure to allulose at 0.35 g/kg body weight and the fermentability of allulose was only a fraction of the fermentability of fructose-oligosaccharides (Iida et al. 2010). Based on a plot of the breath hydrogen concentration, the caloric content of allulose was estimated to be less than 0.5 kcal/g (Iida et al. 2010). Metabolic effects of allulose have been studied as well. In a 13-week intervention study, Hossain et al. found that addition of 5% allulose instead of 5% glucose to the drinking water of OLETF rats resulted in lower glucose (38%) and triglyceride (33%) levels, as well as a significantly reduced body weight (17%) and abdominal fat mass (34%) (Hossain et al. 2011). In addition, the rats receiving 5% allulose had a 43% smaller increment in glucose and insulin levels 60 min after a glucose challenge compared to the rats receiving 5% glucose. In the liver, allulose reduced fat accumulation and stimulated glycogen synthesis via translocation of glucokinase. Lastly, allulose prevented pathological changes to the pancreatic islets, thereby preserving β-cell function (Hossain et al. 2011). Itoh et al. found that a 15 week supplementation with 5% allulose in leptin deficient mice significantly decreased body and liver weight by approximately 20% and 15% respectively (Itoh et al. 2015). Fat mass was lost whereas muscle mass was preserved and hepatic histology revealed amelioration of hepatic steatosis as a result of the allulose supplementation (Itoh et al. 2015). Chen et al. tested the effects of 4 weeks exposure to 5% allulose in Wistar rats and compared it with 5% glucose, fructose and cellulose. They found that blood lipid profile and antioxidant levels improved in the allulose condition (Chen, Huang, and Jiang 2017). At the level of gene expression, allulose inhibited genes for lipogenesis and increased the expression of genes involved in fat oxidation (Chen, Huang, and Jiang 2017). Baek et al. found that allulose ameliorates liver triglyceride and cholesterol levels, but not plasma triglycerides and cholesterol levels in diabetic mice. In this study, genetically diabetic mice received 200 mg of allulose, fructose or glucose per kg body weight for 28 days. Allulose supplementation to diabetic mice prevented almost the entire diabetes-induced increase (about 95% prevention) in liver triglyceride and cholesterol levels, while the increase was clearly present in rats receiving glucose or fructose (Baek, Park, and Lee 2010). Han et al. investigated the effects of 16 weeks supplementation with 5% allulose versus glucose, fructose and erythritol in mice on a high fat diet. In this study, allulose gave a one third reduction of the increase in hepatic fatty acids induced by the fat diet, while the other sugars had no effect (Han et al. 2016). Furthermore, only allulose prevented a high fat diet (HFD) induced increase in leptin and resistin. In the adipose tissue, allulose prevented a HFD-induced reduction of β-oxidation and blunted the increase of fatty acid synthase by about 50% (Han et al. 2016). Apart from its intrinsic health effects, some studies suggest that allulose could reduce the increase of plasma glucose levels following consumption of digestible sugars with glucose. Iida et al. found a concentration-dependent ameliorating effect of allulose on blood sugar control in healthy humans after consumption of 75 g maltodextrin (Iida et al. 2008). In the two hours following the maltodextrin challenge, addition of 7.5 g of allulose resulted in a 31–32% reduction of the area under the curve for both glucose and insulin. Similarly, Noronha et al. found that 10 g of allulose but not fructose significantly reduced the area under the curve for plasma glucose levels following an oral glucose test in their randomized controlled crossover trial with 24 participants (Noronha, Braunstein, Blanco Meija, et al. 2018). However, this effect of allulose on the postprandial glucose response is not consistently found in all studies. A highly similar study (regarding study setup, exposures and population size) by Braunsteig et al. did not observe significant effects of 5 or 10 g fructose or allulose on the blood glucose response following an oral glucose test (Braunstein et al. 2018). Furthermore, a potential acute effect of allulose on postprandial glucose responses does not provide information on how this sugar impacts long-term glycemic control. A meta-analysis on sustained effects of allulose on glycemic control in controlled feeding studies, concluded that evidence for a long-term effect of allulose is low (Noronha, Braunstein, Blanco Meija, et al. 2018). In this meta-analysis, allulose only provided a borderline significant effect on fasting glucose levels, without impacting HbA1c levels or the fasting insulin response (Noronha, Braunstein, Blanco Meija, et al. 2018). A recent RCT in Korean participants found that a 12-week allulose intervention significantly reduced abdominal and subcutaneous fat compared to the artificial sweetener sucralose control group without differences in nutrient intake between the groups (Han et al. 2018). On average, participants receiving 8 g of allulose per day lost an additional 10 cm of abdominal fat compared to the control group, while participants receiving 14 g of allulose per day lost an extra 20 cm of abdominal fat and 18 cm of subcutaneous fat compared to the control group. These findings suggest that allulose may have beneficial metabolic effects beyond a reduction in energy intake. In healthy humans, a single dose of 5 g allulose increased 4-h fat oxidation by 9% compared to 10 mg of aspartame, suggesting that fat oxidation contributes to the weight-reducing effects of allulose (Kimura et al. 2017). In addition to the metabolic health effects that have been investigated in human trials and animal experiments, absorption of allulose has been studied in cell models. Hishiike et al. investigated the effects of allulose in a Caco-2 cell model. Using specific transporter inhibitors, they found that this rare sugar is transported via GLUT5 into the enterocyte and that allulose is further transported via GLUT2 (Hishiike et al. 2013). The transport of allulose via GLUT5 is suppressed in the presence of glucose or fructose (Hishiike et al. 2013). Since allulose shares transporters with glucose/fructose and its uptake is suppressed by glucose/fructose, it may compete with glucose and fructose for its uptake. This hypothesis is in line with the review of Hossain et al. and the findings of Moon et al., who found that allulose inhibited uptake of 2-deoxyglucose and fructose

in Caco-2 and AtT20ins (mouse pituitary gland neoplasm) cells (Moon et al. 2012; Hossain et al. 2015). A competition between the uptake of sugars may contribute to the reduced glucose and lipid levels that were found following allulose interventions. In fact, Moon et al. performed an animal experiment to test the hypothesis of competition for intestinal transporters. A 15-week intervention with 58% fructose and 58% fructose + 5% allulose was performed. The researchers found that body weight gain, fat storage, leptin and MCP-1 were significantly lower in the group with added allulose (Moon et al. 2012). These findings do not exclude other mechanisms that may contribute to the health benefits of allulose, but inhibition of glucose and fructose uptake is likely to play a role. As mentioned earlier, the translocation of hepatic glucokinase may be another mechanism that contributes to the beneficial metabolic effects of allulose. Furthermore, allulose was found to stimulate GLP-1 release in mice in a dose-dependent manner (Iwasaki et al. 2018). At the highest allulose concentration of 3 g per kg body weight, active GLP-1 increased 4-fold compared to the saline control or the same amount of glucose. Considering the use of GLP-1 agonists as diabetes medicines and their role in satiety regulation, this can be seen as an interesting finding. Iwasaki et al. administered allulose to mice and found evidence that the enhanced GLP-1 release contributes to the metabolic health effects of allulose. In their study, allulose at 1 g/kg significantly lowered food intake at all timepoints within 6 h and ameliorated glucose intolerance in a glucose challenge, while these effects were blunted or prevented in GLP-1 receptor knock-out mice and mice receiving GLP-1 antagonists (Iwasaki et al. 2018). In addition, addition of 1 g/kg of allulose for 10 days reduced visceral fat mass by approximately 10% and liver fat content by about 30% in mice on a high fat diet (Iwasaki et al. 2018). On top of all these beneficial effects of allulose, this sugar may also have anti-inflammatory or anti-oxidant properties. In a review about allulose by Chung et al., inhibition of lipid peroxidation and inflammatory gene expression as well as enhancement of ROS scavenging and intracellular glutathione levels were mentioned as potential effects of allulose (Chung, Oh, and Lee 2012). However, all these effects were found in in vitro studies. An interesting study on the anti-inflammatory effects of allulose was published by Murao et al. They found that allulose inhibited glucose-induced MCP1 expression in endothelial HUVEC cells. After 5 days of exposure, allulose reduced MCP1 expression in a concentration dependent manner, reaching a 30% inhibition at 22.4 mM (Murao et al. 2007). P-38 expression as mediator of glucose-induced MCP1 expression was inhibited significantly by 5.6 mM allulose after it was induced with 22.4 mM of glucose (Murao et al. 2007). So far, toxicological studies in animals have not found any toxic effects of allulose that would counteract its benefits. Toxicological studies with allulose have been performed with acute doses of up to 4 g/kg in dogs and long-term (ranging from 90 days to 18 months) in male rats at 3% of the dietary intake. These studies all concluded that allulose had no or no severe toxic effects, although diarrhea was observed in dogs receiving 4 g/kg of allulose (Nishii et al. 2016; Yagi and Matsuo 2009; Matsuo, Ishii, and Shirai 2012).

To conclude, considering the variety of beneficial effects of allulose in both in vitro and in vivo studies without known disadvantages from metabolic and toxicological studies, allulose may currently be the most promising rare sugar. Concentrations of 5% of the diet have provided beneficial effects in animal studies and beneficial health effects in humans have already been reported at daily intakes ranging from 5 to 8 g (Chen, Huang, and Jiang 2017; Hossain et al. 2011; Kimura et al. 2017; Iida et al. 2008). Benefits of allulose were found compared to conventional sugars, sugar alcohols and artificial sweeteners.

(D-)Tagatose: a fructose epimer with health benefits

Tagatose is a C-4 epimer of fructose, which is generally produced from whey. Since end 2005, tagatose is approved by the European Union as novel food ingredient without restrictions for its use (Lu, Levin, and Donner 2008). Tagatose is absorbed for up to 20% in rats and the absorbed tagatose is metabolized in the liver (Levin 2002). In a book chapter by Vastenavond et al., the absorption rate of tagatose was estimated to be around 20% in humans as well Vastenavond et al. 2012). The absorbed tagatose is almost completely metabolized via the glycolytic pathway and the unabsorbed tagatose was completely fermented in the colon Vastenavond et al. 2012). However, other sources report higher absorption rates of tagatose in humans. Normén et al. found that tagatose is absorbed for 81% in humans following a dose of 15 g and that tagatose slightly, but significantly increases excretion of sucrose and glucose (Normén et al. 2001). In Sprague-Drawley rats, tagatose also inhibited fructose absorption in a concentration dependent way. In these rats, tagatose at 6 g/kg inhibited absorption of 2 g/kg of fructose by 30% within 60 min (Williams, Spitnale, and Lodder 2013). Most studies on tagatose absorption focused on the proportion of tagatose that is absorbed, rather than the mechanism behind its uptake, which is only partly understood. Like fructose, tagatose is not a substrate for SGLT1 (Guerrero-Wyss, Durán Agüero, and Angarita Dávila 2018), although its affinity for GLUT5 is clearly lower compared to fructose (Tatibouët et al. 2000). Nevertheless, tagatose still has a higher affinity for GLUT5 compared to allulose (Tatibouët et al. 2000), which has been reported to be absorbed via this receptor in Caco-2 cells (Hishiike et al. 2013). Like allulose, tagatose undergoes fermentation by the microbiota and its consumption results in short-chain fatty acid production (Levin 2002). In healthy human subjects, a 2-week intervention consisting of daily consumption of 12.5 g of tagatose resulted in a significant and gender-specific increase in lactobacilli in men (Venema, Vermunt, and Brink 2005). Test tube experiments in which tagatose was incubated with fecal samples from the human trail, showed that the butyrate production was about 3 times higher in samples from the high tagatose condition (12.5 g/day) compared to samples from subjects who received fructose-oligosaccharides and about 4 times higher compared to samples from participants who received sucrose instead (Venema,

Vermunt, and Brink 2005). As a result of its metabolic faith, tagatose is considered a sugar with a considerably lower caloric value than sucrose (Gougeon et al. 2004). In their chapter on tagatose as alternative sweetener, Vastenavond et al. reported that the caloric content of tagatose is 1.1–1.4 kcal/g based on calculations with a factorial method, which is in accordance with experiments in rats and pigs (Vastenavond et al. 2012). A similar value of 1.5 kcal/g has been reported for tagatose in several articles (Espinosa and Fogelfeld 2010; Wiebe et al. 2011). However, EFSA estimated the caloric content of tagatose to be higher. In their report from 2016, EFSA concluded that 1 g of tagatose for human consumption delivers 3 kcal (Turck et al. 2016). EFSA estimated uptake of tagatose in humans to be around 80%, which would correspond with an energy content of at least 2.8 kcal/g. The rounded estimation of 3 kcal/g takes intestinal fermentation of unabsorbed tagatose into account as well. In a small human intervention study with diabetic subjects, 1 year tagatose supplementation (3×15 g per day) resulted in a significant weight loss of 5.1 kg and increased HDL levels by 37% compared to baseline (Donner, Magder, and Zarbalian 2010). The reduction in body weight may be related to a satiety effect of tagatose that has been found in rats and humans (Donner, Magder, and Zarbalian 2010). Buemann et al. for example reported an increased perception of fulness in humans 2.5 h after consumption of 30 g of tagatose compared to the same amount of sucrose (Buemann, Toubro, and Astrup 1998). However, Kruger et al. found that a 90 day tagatose intervention in rats reduced body weight gain in a concentration-dependent manner without significant effects on food intake, suggesting that the weight-reducing effect of tagatose is not entirely satiety-mediated (Kruger et al. 1999). In this study, rats received 0, 5, 10, 15 or 20% tagatose supplemented in their diet. Tagatose supplementation resulted in a significantly lower body weight at a minimum of 10% tagatose in female rats or at least 15% tagatose in male rats (Kruger et al. 1999). Regarding the metabolic effects of tagatose, rat experiments described in a patent by Zehner et al. found that a single tagatose dose of 1 g/kg body weight did not increase blood glucose levels compared to a water control, while the same dose of glucose caused a strong peak in the blood glucose levels (Zehner et al. 1994). The insulin response in this study was even reduced in the tagatose group compared to the water control, suggesting potential antihyperglycemic effects (Zehner et al. 1994). In a human challenge trial with subjects with and without type 2 diabetes who received 75 g of tagatose, tagatose in the absence of a glucose challenge did not influence fasting glucose and insulin levels, but attenuated the rise in serum glucose after an oral glucose challenge (Donner, Wilber, and Ostrowski 1999). The attenuation in non-diabetic subjects was non-significant, while it was significant at all timepoints in diabetic subjects with an almost 50% smaller increase of the glucose level after 2 h. In their previously mentioned meta-analysis, Noronha et al. concluded that there is moderate evidence for an effect of tagatose on fasting glucose, fasting insulin and HbA1c levels, indicating that an effect of tagatose is more likely than an effect of allulose (Noronha, Braunstein, Blanco Meija, et al. 2018). The ability of tagatose to attenuate glucose level increases, may be related to competitive inhibition of intestinal glucose transport and inhibition of sucrase and maltase activity, which are described as gastro-intestinal health effects of tagatose in the review by Espinosa and Fogelfeld (Espinosa and Fogelfeld 2010). In addition to these gastro-intestinal effects, hepatic accumulation of tagatose-1-phosphate results in enhanced glucokinase activity and inhibition of glycogen phosphorylase which collectively contribute to an increased conversion of glucose to glycogen (Espinosa and Fogelfeld 2010). A potential concern with tagatose is its potential to stimulate uric acid formation. Buemann et al. found that human consumption of 30 g of tagatose results in significantly higher uric acid levels compared to the consumption of water or even the same amount of fructose (Buemann et al. 2000). The tagatose exposure increased serum uric acid levels by 32% before lunch and 17% after lunch compared to the water control. By contrast, Saunders et al. did not find an increase in fasting uric acid levels after an 8-week human intervention with a daily tagatose intake of 75 g (Saunders et al. 1999). However, uric acid levels increased transiently in healthy and diabetic subjects after a single bolus of 75 g of tagatose in the study of Saunders et al. One hour after the challenge with 75 g tagatose, uric acid levels had increased 13-50% from baseline depending on the subgroup, while no increase was observed with 75 g of sucrose (Saunders et al. 1999). Another potential concern with tagatose could be gastro-intestinal side-effects, which were rare up to 30 g of tagatose (Donner, Wilber, and Ostrowski 1999). However, subjects receiving 75 g of tagatose commonly experienced diarrhea (81%), nausea (44%) or bloating (31%) (Donner, Wilber, and Ostrowski 1999).

Overall, tagatose is an interesting rare sugar for which some health benefits have been found in human studies. However, its higher caloric content (which is still considerably lower than the caloric content of conventional sugars), potential to raise uric acid levels and its gastrointestinal complaints at high concentrations are drawbacks of tagatose compared to allulose. Health effects of tagatose were mainly found at higher concentrations compared to those of the previously discussed monosaccharides.

(D-)Allose: a rare sugar with potential medical applications

Allose is a glucose epimer that is described as a non-caloric sucrose alternative and bulking agent, which was found to have protective effects on oxidative stress (Chattopadhyay, Raychaudhuri, and Chakraborty 2014). This rare sugar was found to have a higher scavenging activity for ROS compared to glucose and fructose, although the scavenging ability of allose was slightly less than that of allulose and only about 5% of strong antioxidants like superoxide dismutase (Murata et al. 2003). However, allose had more potent inhibitory effects on ROS production in rat neutrophils, reducing ROS production by 50% at concentrations at which allulose, fructose and glucose did not have any effect. The

effects of allose on ROS production in rat neutrophils were concentration-dependent and ROS production was inhibited by 75% at 20 mM of allose (Murata et al. 2003). In Neuro2A neuroblastoma cells, allose attenuated glucose-induced ROS production generated via the uncoupler rotenone. In the presence of rotenone, 10 mM allose reduced the ROS increase induced by 10 mM glucose by more than 50% (Ishihara et al. 2011). These researchers suggested that the antioxidant effect of allose is at least partly due to competition with glucose on the cellular level. In Dahl rats, a 4-week intervention with 2 g/kg of allose per day suppressed both superoxide production and blood pressure in rats with salt-induced hypertension, but not in spontaneous hypertensive rats (Kimura et al. 2005). In the rats receiving a diet with 4% salt, systolic blood pressure rose 39 mm Hg and aortic superoxide production increased about 60%, while addition of 2 g/kg of allose prevented the entire increase in superoxide production and two third of the rise in systolic blood pressure (Kimura et al. 2005). Furthermore, allose had beneficial immunosuppressive effects in male Lewis rats undergoing a liver transplantation. When allose was provided for 1 month prior to the surgery at 0.4 g/kg, the number of neutrophils in the venous blood of the rats was reduced by almost 20% compared to the potent immunosuppressor FK506 at 0.05 mg/kg (Hossain et al. 2000). This effect of allose was suggested to ameliorate ischemic reperfusion (Hossain et al. 2000). Little is known about the metabolic effects of allose. However, it has been found that allose cannot be metabolized by isolated fat cells, even though allose can be transported into these cells (Loten, Regen, and Park 1976). Interestingly, allose can influence GLUT transporters, as it down-regulates GLUT1 expression and lowers glucose uptake in cancer cells to such an extent that the growth of cancer cells was inhibited (Noguchi et al. 2016). The inhibitory effects of allose on sugar transport was not limited to effects in cells of cancer origin, as it has been reported in hamster fibroblasts as well (Germinario et al. 1990). The effects of allose on cancer cells may even be useful in the context of cancer prevention or treatment and seem to go beyond interference with glucose uptake. Noguchi et al. investigated the epigenetic effects of allose at concentrations ranging from 12.5 till 50 mM in neuroblastoma, liver cancer and breast cancer cells. The researchers found that allose had concentration-dependent inhibitory effects on GLUT1 expression, while increasing the expression of the tumor suppressor gene TXNIP 5–10-fold in all of the cell lines (Noguchi et al. 2016). Furthermore, Hoshikawa et al. found that a 6-h pretreatment with allose resulted in a strong and concentration-dependent enhancement of the ability of radiation to kill human head and neck cancer cells (Hoshikawa et al. 2011). The combination of allose and radiation had almost 5 times as potent effects on apoptosis as radiation alone in this study. Similarly, allose and radiation combined had a strong stimulating effect on ROS production in cancer cells that exceeded the effect of the individual treatments (Hoshikawa et al. 2011). A recent review by Chen et al. discussed the anti-cancer, antioxidant and anti-inflammatory effects of allose, while confirming that the metabolic effects of this sugar remain largely unknown (Chen et al. 2018). Furthermore, this review stresses the need for research on metabolism, toxicity and safety of allose, for which human studies are completely missing.

To conclude, research on allose has focused on its medical applications, which include anti-cancer effects. As a result, the metabolic health effects of allose remain largely unknown which makes it hard to speculate on its extra metabolic value as a sweetener.

Consequences of structural differences between rare and conventional monosaccharides. The structural similarities between rare monosaccharides and the common monosaccharides to which they are related, may explain some of the effects that have been observed for these rare sugars. For example, the intestinal competition between tagatose and fructose for their uptake is likely due to their similarity in structure. Also, the ability of allose to interfere with the glucose uptake in cancer cells could be due to their similarity in structure. Interestingly, 2-deoxyglucose which also has a highly similar structure as glucose, targets tumor metabolism as well (Stein et al. 2010; Ben Sahra, Tanti, and Bost 2010). However, metabolic differences between common and rare monosaccharides are much more diverse than interference with the actions of the conventional monosaccharides. Epimers of highly caloric monosaccharides can even be non-caloric as described earlier. The effects of tagatose and allulose on glucokinase and weight maintenance, the inhibitory effects of sorbose and L-arabinose on sucrase activity and the antioxidant properties of allose, are all examples of clearly distinct effects of rare monosaccharides. Considering the subtle chemical differences between sugar epimers, the metabolic differences between different epimers can be considered striking. The metabolic differences between monosaccharides are visible on the level of gene expression as well. Nagata et al. investigated the effects of several rare sugars on the lipid metabolism in Sprague-Drawley rats and found differences between rare sugars after 4 weeks of exposure with diets containing 3% of a certain rare sugar (Nagata et al. 2018). Allulose and sorbose significantly decreased hepatic lipogenic enzyme activity by about 20–25%, while the activity of these enzymes was approximately 20% increased by tagatose. Similarly, the gene expression of fatty acid synthase and the cholesterol-related genes SREBP-2 and HMG CoA reductase was down regulated by sorbose and allulose, although these effects were not statistically significant and mostly around a 1.5–2 fold reduction. In addition, sorbose significantly increased fecal fatty acid excretion by more than 50% and significantly decreased adiponectin levels by 37% compared to the control with 3% additional corn starch instead of rare sugars (Nagata et al. 2018). This illustrates that the monomer structure as such can already have distinct metabolic properties. As mentioned previously, concentrations similar to 3% of sorbose or allulose were also effective to provide health effects on the physiological level. Unfortunately, the health effects of rare monosaccharides remain unpredictable as their structure-

effect relationships are not known, which can be considered one of the knowledge gaps. Systematic comparisons between similar monosaccharides are needed to determine the consequences of subtle chemical differences between sugars. Only with these direct comparisons, we can determine whether rare monosaccharides should all be considered as individual sugars or whether they may be grouped based on their structure and related health effects.

Rare disaccharides

Rare disaccharides, as described in this review, have a rare presence in nature in their disaccharide form, but do not necessarily contain rare monosaccharides, and may therefore also consist of conventional sugars like glucose and fructose linked by an unusual glycosidic bond for the combination of monosaccharides. On top of the differences that are caused by the monosaccharide composition, these sugars differ with regard to their digestion rate. In this paragraph, the metabolic effects of isomaltulose, kojibiose and trehalose will be discussed as these rare disaccharides are relatively well investigated.

Isomaltulose (palatinose): the slowly digestible sucrose isomer

Isomaltulose is one of the most extensively investigated rare disaccharide and like sucrose consists of glucose and fructose. However, in isomaltulose, monosaccharides are linked with an α1-6 bond instead of an α1-2 bond. Isomaltulose is one of the few rare sugars that has already been approved by the European Union for use in food and beverages. In vitro, isomaltulose is one of the slowest digestible sugars, with a digestion rate of 39% relative to sucrose based on experiments with crude rat intestinal α-glucosidases (Lee et al. 2016). However, the rate of isomaltulose digestion depends strongly on the type of enzyme to which it is exposed (Lee et al. 2016). Lee et al. found that isomaltase digests 91.6% of isomaltulose and only 0.9% of sucrose within 72 h, thereby pointing to the selectivity of the α-glucosidases (Lee et al. 2016). Holub et al. studied the effects of consumption of 50 g of isomaltulose compared to 50 g of sucrose in healthy volunteers. They found that isomaltulose is almost completely absorbed and digested, but had less effects on postprandial glucose and insulin levels compared to sucrose (Holub et al. 2010). Thirty minutes after the challenge, the increase in blood glucose levels was 2-fold lower and the rise in insulin levels almost 3-fold lower for isomaltulose compared to sucrose. The blood glucose delivery was extended in the isomaltulose condition, suggesting a slower release of the monosaccharides. Interestingly, 4-week supplementation with isomaltulose resulted in a slightly, but significantly lower fasting glucose and reduced insulin resistance compared to baseline in hyperlipidemic individuals (Holub et al. 2010). Likewise, Maeda et al. found that plasma glucose and insulin levels in healthy obese subjects were significantly lower after a single dose of 50 g isomaltulose compared to the same amount of sucrose (Maeda et al. 2013). The differences between the sugars regarding glucose and insulin responses after 30 min, were almost identical to the results found by Holub et al. Suklaew et al. investigated the effect of a high fat meal with a 40 g sucrose or isomaltulose beverage on glucose and triglyceride levels over time in obese men. The researchers used a cross-over design and found that glucose and triglyceride levels were significantly lower in the isomaltulose group over a period of 480 min. The incremental area under the curve was 50% for both glucose and triglyceride levels in the isomaltulose group compared to the sucrose group (Suklaew et al. 2015). Interestingly, Arai et al. found that also Sprague-Dawley rats receiving an isomaltulose-based formula containing 0.9 g/kg of carbohydrates had a 2-fold smaller rise in blood glucose after 30 min compared to the rats receiving a similar glucose-based formula (Arai et al. 2004). Häberer et al. found that the early blood glucose and insulin responses are still significantly smaller with isomaltulose when rats were first adopted for 14 days to a diet containing sucrose or isomaltulose (Häberer et al. 2009). An 8-week intervention study in Zucker fatty rats suggests that isomaltulose can provide longer term benefits besides the effects on glycemic control. In this study, the sugars sucrose and isomaltulose (353 g/kg diet) were combined with linoleic acid and oleic acid in a factorial design. After 8 weeks, the mesenteric visceral fat mass and the expression of PEPCK, SREBP 1c and SREBP 2 were significantly lower in the isomaltulose groups compared to the sucrose groups, suggesting a relative reduction in lipogenesis and gluconeogenesis (Sato et al. 2007). Furthermore, the pancreatic islet size was more than 50% smaller in the isomaltulose groups compared to the sucrose groups, suggesting prevention of pancreatic islet hypertrophy (Sato et al. 2007). Another 2-month intervention study with rats found benefits of daily consumption of 16.4 g isomaltulose-based formula that was made from a standard formula by replacing 55.7% of dextrin by isomaltulose (Arai et al. 2004). Rats fed with the isomaltulose-based formula had a 43% smaller triglyceride content in the liver, an almost 40% lower abdominal fat mass, one third lower fasting insulin levels and 59% lower fasting triglyceride levels compared to rats on the dextrin-based standard formula (Arai et al. 2004). When this isomaltulose-based formula was later used for a challenge test in healthy humans receiving standardized meals, fat oxidation was significantly higher for 3 h and glucose and insulin levels were significantly lower in participants receiving isomaltulose formula instead of the dextrin formula (Arai et al. 2007). The longer term effects of isomaltulose in humans were investigated by Brunner et al. in 110 diabetic subjects, who received 50 g of isomaltulose or 50 g of sucrose for 12 weeks. Although this amount of isomaltulose provided benefits on acute glycemic control in other studies, Brunner et al. found that 50 g of isomaltulose did not have significant effects on HbA1c levels as marker for middle-long term glycemic control (Brunner et al. 2012). However, there was a significant difference for triglyceride levels which decreased 10% in the isomaltulose group and increased 18% in the sucrose group compared to baseline (Brunner et al. 2012). To elucidate the mechanisms that

underlie the health effects of isomaltulose and the isomaltulose-based formula 'Inslow', Matsuo et al. studied the effects of the Inslow formula on expression of genes that play a role in the glucose and lipid metabolism. Although the most important difference between inslow and the standard formula is the replacement of dextrin by isomaltulose and branched dextrin, inslow also contains more oleic acid and less linoleic acid. They found that the hepatic PPAR-α expression was almost 2-fold higher and adipocyte PPAR-γ expression 3-fold higher in rats that received the isomaltulose formula compared to the dextrin-based standard formula (Matsuo et al. 2007). These changes in gene expression resulted in a higher expression of β-oxidation genes in the liver and a more than 2-fold higher expression of UCP-2 in the liver and adipocytes (Matsuo et al. 2007). On top of the effects on gene expression, rats receiving the isomaltulose-based formula gained 58% less weight, had 35% lower plasma insulin levels and 53% lower triglyceride levels compared to the rats receiving the standard formula. Lastly, the pancreatic islet area was more than 50% smaller in the rats that received isomaltulose for 8 weeks, like in the study with the Zucker fatty rats. Henry et al. performed a human intervention study with Chinese men to investigate differences in substrate usage between a high GI diet containing sucrose and a low GI diet containing isomaltulose. Using 10 h indirect calorimetry, the researchers found that a breakfast, lunch and snack with isomaltulose instead of sucrose all resulted in a significantly higher fat oxidation (Henry et al. 2017).

Overall, isomaltulose may be a rare sugar with clinically relevant benefits regarding glycemic control in humans when used as replacement for sucrose at amounts of 40 or 50 g (Holub et al. 2010; Maeda et al. 2013; Suklaew et al. 2015). Furthermore, animal studies suggest that replacing sucrose by isomaltulose results in beneficial effects on weight maintenance and lipid metabolism. Nevertheless, isomaltulose is still a digestible sugar with less pronounced metabolic effects than certain rare monosaccharides.

Kojibiose: an interesting sugar for future research

Kojibiose consists of two glucose molecules connected with an α1-2 bond. Kojibiose is more resistant to enzymatic digestion compared to other glucose disaccharides like maltose (Chaen et al. 2001; Hodoniczky, Morris, and Rae 2012). Whereas maltose was digested for 87% using rat intestinal acetone powder, kojibiose was digested 57% and the longer molecules kojitriose and kojitretraose with an α1-2 bond were completely resistant to digestion (Chaen et al. 2001). Hodoniczky et al. investigated the digestion rate of many sugars with rat intestinal acetone powder and found that kojibiose is digested more than twice as slow compared to maltose (Hodoniczky, Morris, and Rae 2012). Lee et al. used crude rat intestinal α-glucosidase to investigate the digestion rate of many sugars at 10 mg/ml and found that kojibiose is digested at a rate that is only 36% of the digestion rate of maltose (Lee et al. 2016). The digestion resistance of sugars like kojibiose may result in a lower bioavailability of the monosaccharaides and a potential to be used as a prebiotic in the colon. Sanz et al. studied the ability of various disaccharides to be fermented by colon microbiota, and found that kojibiose was more fermentable than any of the other sugars included in their study (Sanz, Gibson, and Rastall 2005), which was due to the presence of the α1-2 linkage. In addition to its fermentability and resistance to digestion, kojibiose has an inhibitory effect on the activity of several α-glucosidases. Ugalde et al. found that kojibiose at 1 mM inhibited the activity of a mannosyl-oligosaccharide glucosidase from rat origin by 91%, while none of the other tested sugars inhibited the activity of the enzyme by more than 10% (Ugalde, Staneloni, and Leloir 1980). However, the inhibitory effect of kojibiose was enzyme-dependent and other glucosidases were inhibited to a lesser extent. As an inhibitor of α-glucosidases, kojibiose may further decrease the bioavailability of glycemic monosaccharides. However, it is not yet known to which degree kojibiose can inhibit sucrase and the enzymes for starch digestion in humans. Therefore, it is hard to tell whether kojibiose could reduce glycemic response after consumption of the most common carbohydrates in our diet. In general, α-glucosidase inhibitors are used as treatments to decrease postprandial hyperglycemia in diabetes (Kumar et al. 2011). A meta-analysis of forty-one randomized controlled trials confirmed the effectiveness of α-glucosidases to decrease HbA1c, blood glucose and blood insulin levels in diabetic subjects (Van De Laar et al. 2005). The detailed metabolic and caloric effects of kojibiose remain to be determined. Nevertheless, a prebiotic effect may influence other processes in the body, such as low-grade inflammation. Laparra et al. performed a 20-day intervention with female Wistar rats to study potential anti-inflammatory effects of kojibiose. The researchers found that arachidonic acid at 0.3 mg/day increased intrahepatic macrophages by 31.5%, while this increase was not observed in rats receiving arachidonic acid with 22 mg/day of kojibiose (Laparra et al. 2015). Furthermore, rats receiving only arachidonic acid had on average 472 mmol/l higher triglyceride levels than control rats that did not receive arachidonic acid, while more than 60% of the increase in triglyceride levels was prevented in rats receiving kojibiose in addition to arachidonic acid (Laparra et al. 2015). In addition, rats receiving both arachidonic acid and kojibiose had a 20% lower body weight than rats receiving arachidonic acid as the only intervention.

To summarize, kojibiose has some interesting metabolic properties, but more research is needed to allow a detailed evaluation of its suitability to replace conventional sugars. The effects of kojibiose in humans remain to be determined. The in vitro digestion rate of kojibiose is higher compared to isomaltulose, although this has not been confirmed in vivo either.

Trehalose: a rare sugar with many potential applications

Trehalose consists of two glucose molecules connected with an α1-1 bond and has been approved by the European Union as a novel food. Trehalose circulates in the blood of insects, like glucose in humans (Thompson 2003). Intestinal absorption of trehalose in mice was studied by Dahlqvist and Thomson. In

this study, absorption of trehalose or maltose during the first two hours of administration did not differ significantly from the absorption of glucose (Dahlqvist and Thomson 1963). However, during the later phase of absorption, trehalose was absorbed much slower than glucose and maltose, likely due to a rate limiting lack of trehalase in the lower small intestine. As a result, a considerable part of the trehalose reached the colon (Dahlqvist and Thomson 1963). The digestion rate of trehalose by rat intestinal α-glucosidases in the study by Lee et al. was only 13% compared to maltose, indicating that trehalose is the slowest digestible glucose-glucose disaccharide (Lee et al. 2016). The aforementioned kojibiose was digested at a rate of 36% of maltose in this study (Lee et al. 2016). Regarding metabolic effects, trehalose was found to have beneficial metabolic effects in mice and other organisms. Mice receiving a high fat diet for 8 weeks in combination with 2.5% trehalose in the drinking water had significantly less fat hypertrophy than mice on a high fat diet in combination with 2.5% glucose, maltose or fructose (Arai et al. 2010). Specifically, mesenteric adipocyte size in high fat fed mice was 30% smaller for mice receiving drinking water with 2.5% trehalose compared to the mice receiving 2.5% glucose or maltose in their drinking water. In the same study by Arai et al., mice on a high fat diet receiving trehalose had significantly lower fasting insulin levels after 7 weeks than the mice receiving glucose and maltose (Arai et al. 2010). Finally, HOMA IR as measure for insulin resistance was twice as low in the trehalose group compared to the maltose group. Van Can et al. investigated the glycemic effects of loads of different sugars (75 g in 400 ml) with a challenge test in overweight human subjects. In their study, trehalose attenuated the rise in glucose levels with 33% and insulin levels with 14% compared to glucose, while isomaltulose attenuated the rise in levels with 43% and insulin 34% compared to sucrose (Van Can et al. 2012). Related to the lower insulin response, Honda et al. found that trehalose reduced insulin/IGF1 signaling in Caenorhabditis elegans (Honda, Tanaka, and Honda 2010). Trehalose at 5 mM increased lifespan in these organisms by 30% or more depending on their age, while the effects were abolished in mutants with a naturally high rate of trehalose biosynthesis (Honda, Tanaka, and Honda 2010). Interventional inactivation of the genes for trehalose biosynthesis decreased lifespan in these mutants (Honda, Tanaka, and Honda 2010). DeBosch et al. found that trehalose can improve liver health and prevent hepatic steatosis in liver cells as well as in vivo in mice. Mice that obtained 60% of their calories from fructose experienced a strong increase in hepatic fat accumulation after 10 days, while the increase in hepatic fat was two third smaller in mice that first received 3% of trehalose in the drinking water for 2 days (DeBosch et al. 2016). In the same study, the researchers found that 5 mM of fructose increased hepatic fat almost 3-fold in primary hepatocytes in vitro, while no increase was observed with 5 mM fructose combined with 100 mM trehalose. Similarly, 100 mM trehalose reduced the increase in hepatic fat upon 48 h exposure to 500 µM free fatty acids by one third (DeBosch et al. 2016). In addition, a role for trehalose in the free radical defense has been postulated. Mizunoe et al. reported that trehalose reduces oxidative stress via Nrf-2 antioxidant expression. In their study with Hepa 1-6 cells, 24 h pre-exposure with 50 mM trehalose prevented the increase in intracellular ROS induced by 15 h exposure to 2 mM paraquat (Mizunoe et al. 2018). Tang et al. found that survival of primary mice chondrocytes after 24 h exposure to oxidative stress inducer tert-butyl hydroperoxide, was enhanced in a concentration dependent manner by trehalose concentrations ranging from 0 till 100 mM (Tang et al. 2017). Furthermore, yeast cells accumulate trehalose upon a mild heat shock and pretreatment with 500 mM trehalose enhances survival of these cells during free radical exposure (Benaroudj, Lee, and Goldberg 2001). Ninety minute survival with 500 mM trehalose was higher than without sugar or with sucrose, and similar to the effect of the known antioxidant mannitol (Benaroudj, Lee, and Goldberg 2001). Moreover, trehalose has been reported to enhance maintenance of cell viability of mammalian cells under several stress conditions including desiccation (Luyckx and Baudouin 2011).

Considering the attenuated rise of glucose and insulin levels, trehalose may be an interesting sugar replacer. Its benefits on the glycemic response are smaller than those of isomaltulose, but it has additional interesting properties like liver protective and antioxidant effects. Those additional beneficial effects were found in animals at concentrations around 3% (DeBosch et al. 2016), which is similar to effective concentrations of sorbose and allulose.

Health consequences of structural differences between conventional and rare disaccharides

The enzymes for carbohydrate digestion have a specificity for certain glycosidic bonds and the related structural configurations of disaccharides. The degree of branching determines the digestibility, as unbranched chains formed by beta-glycosidic bonds are the least digestible (Berg, Tymoczko, and Stryer 2002). The α1-6 bond is relatively resistant compared to the alpha-1-4 bond (Lee and Hamaker 2017), whereas the α1-2 and α1-3 bonds have an intermediate digestibility. These differences in glycosidic bonds can explain the lower digestion rate of trehalose (α1-1) and kojibiose (α1-2) compared to maltose (α1-4) as well as the lower digestion rate of isomaltulose (α1-6) compared to sucrose (α1-2). The delayed digestion is likely responsible for the smaller glucose and insulin responses following isomaltulose and trehalose intake compared to conventional sugars. Although differences in digestibility between glycosidic bonds are known, it remains hard to predict digestibility solely based on the presence of a glycosidic bond. When comparing the α1-2 and α1-3 bond, turanose with the α1-3 bond is digested slower than sucrose while nigerose with the α1-3 bond has a higher digestion rate than kojibiose (Lee et al. 2016). These examples show that presence of a certain bond alone cannot entirely explain the digestion rate of a sugar. Furthermore, digestibility may not be the only factor that influences metabolic effects of disaccharides. Differences in monosaccharide composition can be responsible for metabolic effects of disaccharides as well. In addition, metabolic differences could be due to effects that disaccharides exert independent of the released monosaccharides, for example via interaction with receptors. The antioxidant and liver

protective effects of trehalose and the beneficial gene expression effects of isomaltulose may be examples of this receptor-based mode-of-action, since these effects could not be expected from the released monosaccharides. Trehalose protected liver accumulation not only in vivo, but also in HepG2 cells without additional digestion system, suggesting that trehalose provides metabolic effects as a disaccharide. However, mammals have some trehalase activity in the liver, meaning that slight trehalose digestion can occur even when the intestine is bypassed (Baumann, Boizard-Callais, and Labat-Robert 1981).

Comparison between rare sugars and other alternatives for sucrose

Unlike rare sugars, most of the alternatives for conventional sugars do not have the chemical structure of a sugar. Polyols (sugar alcohols) are also of sugar origin, but have an additional OH group and do not have the ring structure that many sugars possess. Like rare sugars, polyols are bulk sweeteners with a sweetness similar to or lower than sucrose, while high-intensity sweeteners like artificial sweeteners and stevia are much sweeter than sucrose and are added to foods in very small amounts. In this paragraph, artificial sweeteners, stevia glycosides and polyols will be discussed further as other options to substitute conventional sugars, and the differences between these sugar replacers and rare sugars will be highlighted in more detail.

Artificial sweeteners such as acesulfame K, sucralose and aspartame

Artificial sweeteners are often non-sugar sweeteners with a few hundred-fold the sweetness of sucrose, like the dipeptide methyl ester aspartame and the potassium salt acesulfame K (both about 200 times as sweet as sucrose) (Chattopadhyay, Raychaudhuri, and Chakraborty 2014). An artificial sweetener may as well be a sucrose derivative like sucralose, but they all share a high sweetening potency and the fact that they are synthetically produced or modified. In the case of sucralose, 3 hydroxyl groups from a sucrose molecule are replaced by chloride atoms, resulting in a strongly enhanced sweetening potency of up to 600 times the sweetness of sucrose (Chattopadhyay, Raychaudhuri, and Chakraborty 2014). Artificial sweeteners can provide sweetness with far less calories than sucrose and some beneficial effects compared to sucrose have been reported for artificial sweeteners. For example, Raben et al. executed a 10 week intervention with sucrose and artificial sweeteners in overweight subjects and found that body weight (+1.6 vs −1.0 kg), fat mass (+1.3 vs −0.3 kg) and systolic blood pressure (+3.8 mm vs −3.1 mm Hg) all increased in the sucrose group and all decreased in the artificial sweetener group (Raben et al. 2002). However, it should be noted that the sucrose supplementation provided on average 3.4 MJ per day compared to 1 MJ for the sweetener supplements containing 54% aspartame, 23 cyclamate, 22% acesulfame K and 1% saccharin. A meta-analysis by Miller and Perez found that low calorie sweeteners (which include artificial sweeteners) were associated with a slightly higher BMI in prospective cohort studies, while they modestly but significantly reduced BMI, fat mass and waist circumference in RCTs (Miller and Perez 2014). Furthermore, a recent meta-analysis reported that non-nutritive sweeteners (which includes both artificial sweeteners and stevia) do not increase blood glucose levels (Nichol, Holle, and An 2018). The potential benefits of artificial sweeteners and other low- and non-caloric sweeteners (LNCS) are highlighted in a recent Ibero-American consensus paper, which states that replacement of caloric sweeteners by LNCS may favor sustainable weight loss (in the context of structured diet plans) and may contribute to better glycemic control in diabetic patients (Serra-Majem et al. 2018). However, other publications report less beneficial effects on artificial sweeteners and body weight or BMI. Karalexi et al. reported in a recent meta-analysis, that non-nutritive sweeteners are associated with higher BMI of children in observation studies (Karalexi et al. 2018). In a Canadian cohort study, maternal artificial sweetener usage was associated with increased infant BMI and a 2-fold higher risk of overweight at the age of one (Azad et al. 2016). Although bias from higher consumption of sweeteners among overweight people is possible in observation studies, the beneficial effects of artificial sweeteners on body weight cannot be seen as spectacular or very consistent. Furthermore, the synthetic nature of artificial sweeteners influences consumers trust and there are also several concerns regarding artificial sweeteners and health. Concerns related to the use of artificial sweeteners include a potential compensatory food intake due to a lack of satiety, adverse effects on insulin sensitivity and adverse effects on the microbiota (Swithers 2013; De Matos Feijó et al. 2013; Suez et al. 2015). Although not all of the concerns are backed up with convincing scientific evidence, the papers on safety of artificial sweeteners do not report consistent results either. Therefore, the health benefits and risks of artificial sweeteners remain heavily debated topics in scientific literature. A recent review by Lohner et al. reported that some studies found increased risks for diabetes, headaches and depression, while other studies did not (Lohner, Toews, and Meerpohl 2017). The researchers concluded that there are still knowledge gaps regarding safety of artificial sweeteners, suggesting that more research is required. Whereas several rare sugars ameliorate glucose and insulin responses upon glucose challenges, the artificial sweetener sucralose was found to increase glucose and insulin levels upon a glucose challenge (Pepino et al. 2013). The incremental increase in insulin levels was 20% larger after consumption of 48 mg sucralose instead of only water before the challenge in a human intervention study by Pepino et al. (Pepino et al. 2013). Furthermore, artificial sweeteners had clear adverse effects on the microbiome in mechanistic studies. Recently, Suez et al. published an article in which they reported adverse effects of especially saccharin on the mouse microbiome (Suez et al. 2015). Briefly, these researchers found that adding saccharin to drinking water, induced glucose intolerance in mice, even more than glucose and sucrose

did. The glucose tolerance was improved with antibiotics while transplantation of the microbiota of mice that received sweeteners, induced glucose intolerance in germ-free mice. Similarly, the researchers found in a very small-scale human intervention study that the consumption of acceptable daily intake amounts of saccharin caused glucose intolerance in some human volunteers, and again the microbiota from these humans induced glucose intolerance in germ-free mice (Suez et al. 2015). The studies on this topic mostly found adverse effects of artificial sweeteners on microbial health, except for a study by Daly et al. in which 0.015% saccharin added to the diet increased the proportion of lactobacilli and the lactic acid concentrations 2-fold in pigs (Daly et al. 2014; Suez et al. 2015; Pepino 2015). Although studies have reported these adverse effects of artificial sweeteners, different artificial sweeteners are described to be very diverse and are all absorbed, metabolized and excreted in a unique way (Magnuson et al. 2016). Therefore, effects of saccharin cannot automatically be generalized for all artificial sweeteners. Whereas adverse microbial influences of the artificial sweetener saccharin have been described, some rare sugars were found to induce changes in microbiota composition that are considered beneficial (Sanz, Gibson, and Rastall 2005). Rare sugars often contain bonds that are partly resistant to enzymatic degradation, which allows them to reach the colon where some of them may serve as a prebiotic (Beerens et al. 2017). Furthermore, rare sugars have never been found to disrupt a healthy microbiota or induce insulin resistance. Sanz et al. scored sugars with a prebiotic index depending on the changes in microbiota composition that they induce, with the most prebiotic molecules being kojibiose and sophorose, while turanose had a low score on the prebiotic index (Sanz, Gibson, and Rastall 2005). Kojibiose and sophorose had prebiotic index scores of 21.62 and 18.63 compared to 3.71 for maltose or 7.64 for fructose-oligosaccharides. Therefore, it is hard to generalize but there are interesting compounds with prebiotic properties in the group of rare sugars. Although the resistance for digestion is generally beneficial for glycemic control, it cannot be excluded that accumulation of the sugars in the colon may contribute to bloating and abdominal pain. These gastrointestinal complaints are for example induced by unabsorbed lactose, fructose and sorbitol in the irritable bowel syndrome (Goldstein, Braverman, and Stankiewicz 2000). Furthermore, large amounts of resistant sugars such as lactulose can have a laxative effect (Bass and Dennis 1981), which is beneficial when used as laxative but not when used as sugar replacer.

Stevia

Steviol glucosides like stevioside and rebaudioside A from the stevia plant (*Stevia rebaudiana*) are other compounds that are used as an alternative sweetener. Stevioside and rebaudioside A are the sweetest glucosides from the stevia plant and can both be extracted from the stevia leaves (Magomet et al. 2011). Mixtures of stevia glucosides in methanol can be dried, cooled and purified to obtain the isolated stevioside and rebaudioside A. These two glucosides are high-potency sweeteners with up to 300 times the sweetness of sucrose (Magomet et al. 2011). Studies on the toxicity of stevia, classified it as safe for use as sweetener (Geuns 2003; Shankar, Ahuja, and Sriram 2013). Studies on the glycemic properties of stevia and stevioside have reported beneficial effects on insulin sensitivity and glycemic control (Mohd-Radzman et al. 2013). When a 290 kcal load containing stevia prior to lunch and dinner was compared with loads containing sucrose or aspartame in a small-scale human intervention study, stevia reduced postprandial glucose levels compared to sucrose and postprandial insulin levels compared to both sucrose and aspartame (Anton et al. 2010). Lailerd et al. investigated the effects of stevioside in insulin-resistant and healthy obese Zucker rats and found that oral stevioside administration increased whole body insulin sensitivity in these rats. Furthermore, low concentrations of stevioside modestly increased the uptake of sugar in the skeletal muscles of these rats when tested in vitro (Lailerd et al. 2004). Stevioside is reported to improve the glucose homeostasis via both an increase of the insulin secretion and an inhibition of glucagon (Jeppesen et al. 2002; Mohd-Radzman et al. 2013). Furthermore, anti-inflammatory effects were found for stevioside, which may improve insulin sensitivity (Mohd-Radzman et al. 2013). Beneficial effects of stevia and its glucosides on the pancreas have been reported as well and may partly explain their effect on glycemic control. Sprague-Dawley rats that received 400 mg/kg stevia extract, had increased pancreatic PPARγ and insulin mRNA levels (Assaei et al. 2016). This intervention also resulted in histopathological improvements in the pancreas of diabetic rats (Assaei et al. 2016). Philippaert et al. reported that stevia glucosidases can potentiate glucose-stimulated insulin secretion via activation of TRPM5, which is present on pancreatic β-cells and taste receptor cells (Philippaert et al. 2017). In their study, stevioside (25 mg/kg in drinking water) prevented high fat induced diabetic hyperglycemia in wild type mice, but not in TRPM5 knock out mice (Philippaert et al. 2017). Although the steviol glucosides have beneficial effects on glycemic control, their structure and properties are a little different than those of sugars. The sweetness intensity of steviol glucosides is much higher than that of sugar, they cannot be used as bulking agents and they can give a bitter off-taste via activation of bitter receptors (Hellfritsch et al. 2012). These differences in functionality between steviol glucosides and sugars may limit the ability to use steviol glucosides as substitutes for sugar.

Polyols

Sugar alcohols or 'polyols' form another group of sweeteners. They are saccharide derivates in which a ketone or aldehyde group has been replaced by a hydroxyl group and are often present in nature in small amounts (Wolever et al. 2002). Their sweetness ranges from 30 to 100% the sweetness of sucrose (Grembecka 2015). Polyols can be derived from monosaccharides, disaccharides or even starch hydrolysates and have been reviewed several times (Wolever et al. 2002; Livesey 2003; Grembecka 2015). Their benefits compared to sucrose include their non-cariogenic effects and a

lower caloric content (Wolever et al. 2002). Furthermore, polyols provide much lower glycemic loads than sucrose and are partly metabolized in an insulin-independent fashion (Wolever et al. 2002; Livesey 2003; Grembecka 2015). The polyols mannitol and erythritol even have a glycemic score of 0 (Grembecka 2015). These health benefits are related to their absorption, as absorption of many polyols in the small intestine is 50% or less and is even 0% for lactitol (Wolever et al. 2002). Xylitol for example is absorbed for 50% (Wolever et al. 2002) and the remainder is metabolized in the liver and can be slowly converted to glucose, via conversions to xylulose and xylulose-5-phosphate, which can be further converted to other phosphate containing molecules like ribose-5-phosphate, sedoheptulose-7-phosphate, fructose-6-phosphate and finally glucose-6-phosphate (Jacob, Williamson, and Asakura 1971). However, excessive consumption of polyols can have laxative effects or result in bloating, which are problems related to their low absorption rates (Chattopadhyay, Raychaudhuri, and Chakraborty 2014) (Grembecka 2015). These intestinal discomforts are found for many polyols including isomalt, lactitol, maltitol, mannitol and sorbitol (Grembecka 2015). Erythritol is an exceptional polyol that is largely absorbed and therefore well tolerated (Oku and Okazaki 1996; Grembecka 2015; Boesten et al. 2015). As a result of rapid elimination in the urine, erythritol still provides very little calories and does not give a glycemic response (Grembecka 2015; Boesten et al. 2015). Polyols and rare sugars may be similar considering their presence in nature, moderate sweetness, low glycemic effects and reduced caloric content compared to conventional sugars. However, rare sugars may have some unique properties and are expected to provide less gastro-intestinal discomfort than polyols. Currently, severe intestinal problems as observed with sugar alcohols have not been reported for rare sugars, except for tagatose at doses of 75 g/day as mentioned earlier (Donner, Wilber, and Ostrowski 1999). Although more research is needed to exclude severe gastrointestinal complications with rare sugars, these problems are less likely for rare sugars at physiological concentrations, considering that the absorption of rare sugars is not as low as the absorption of many polyols. Many rare sugars consisting of common monosaccharides are slowly but completely digested and rare monosaccharides are absorbed easily compared to polyols. For example allulose is largely absorbed and excreted in the urine like the best tolerated polyol erythritol (Tsukamoto et al. 2014).

Conclusion about the potential of rare sugars as conventional sugar replacers

Overall, rare sugars are described to provide health benefits compared to sucrose which is the most frequently consumed sugar. With rare sugars entering the market, 'free sugars' may no longer be considered as a group of equally unhealthy compounds. Rare sugars differ from each other as well and should either be viewed as individual sugars with their own health effects or should be categorized in groups containing similar sugars. In addition to their health effects, the structural similarity and related similarity in applications of rare sugars and sucrose, make rare sugars attractive sugar replacers compared to artificial sweeteners and stevia. Sugar alcohols have several similarities with rare sugar, but many of them are known to provide gastrointestinal discomfort. Considering the differences in uptake and metabolism between rare sugars and sugar alcohols, rare sugars are expected to provide less gastrointestinal discomfort at physiological concentrations, although toxicity and tolerance remain poorly studied and are important research domains for many rare sugars. With the current knowledge of rare sugars, we can conclude that they will likely have an added value as sugar replacers. However, rare sugars form quite a heterogenous group of sugars and some sugars are more interesting sugar replacers than others. Even though rare sugars are large in number, most metabolic research on rare sugars has been performed with tagatose, isomaltulose and allulose. The rare monosaccharides tagatose and allulose may be interesting options as substitutes for sucrose, since they provide less calories, can support microbial fermentation, are hardly glycemic and can even attenuate the rise of blood glucose levels after sucrose consumption. Tagatose and allulose are epimers of fructose, and fructose itself has a much smaller effect on blood glucose levels than glucose as well. However, other properties of especially allulose are more beneficial than those of fructose. Whereas fructose may be a lipogenic sugar, allulose has beneficial effects on gene expression related to the fat metabolism. The stimulation of beta-oxidation and inhibition of lipogenesis on the level of gene expression combined with its extremely low caloric content make allulose an interesting sugar for weight maintenance. Allulose is a rare sugar that has even provided health benefits compared to the polyol erythritol and the artificial sweeteners sucralose and aspartame (Han et al. 2016; Kimura et al. 2017; Han et al. 2018). Therefore, rare sugars and particularly allulose may have an added value as new sugar replacers and are able to provide health benefits beyond their reduced energy content. The disaccharide isomaltulose has provided clinically relevant benefits on the glycemic response compared to sucrose. Therefore it may be suitable as a less glycemic sweetener, but it is still a digestible and caloric sugar. All the other rare sugars have not been studied extensively and promising effects were often found in vitro or in animal experiments, without confirmation of the effect in humans. Trehalose and allose have been investigated mostly in a medical context, related to their antioxidant activity and medical applications. They may therefore serve another purpose than other rare sugars, but research on their metabolic effects remains relevant. L-arabinose and allulose may be the most promising candidates for medical applications in the field of metabolic health and diabetes. Whereas allulose has the widest range of known anti-diabetic effects, L-arabinose is the most convincingly proven α-glucosidase inhibitor. From these examples, it becomes clear that rare sugars are a group of heterogenous compounds which may differ in applications. Some may be most suitable as sugar replacers, while others are more suitable as prebiotics or medicinal compounds.

Although the future seems bright for rare sugars, there are still several knowledge gaps that hinder a full assessment of the health potential of rare sugars. The first major knowledge gap is related to the lack of well-performed human trials in which their influence on important risk factors for diseases are determined. As a result of the absence of these studies, it may be too early to recommend rare sugars for human consumption. Secondly, the exact metabolic conversions of rare monosaccharides are not fully understood, even for the relatively well-investigated sugars. Even though health effects are described, it would be interesting to know what happens to these sugars in the body and why. As a result of a lack of studies in which many different rare sugars with a similar structure are compared, also the structure-effect relationships of rare sugars remain unknown, especially for rare monosaccharides. Moreover, mechanisms of intestinal absorption have not been studied extensively for many rare sugars, as the focus has often been on proportion and speed of absorption. Finally and related to partial absorption, microbial effects of rare sugars that reach the colon are incompletely understood and it remains to be determined whether rare sugar fermentation is equally beneficial for the microbiota as the fermentation of structurally complex fibers.

Although research on rare sugars is still in an early stage, various mechanisms have been proposed to explain the health effects that rare sugars can provide beyond a low caloric content and resistance for digestion. These effects include competition with glycemic sugars for their uptake, inhibition of enzymes that are involved in carbohydrate digestion, translocation of glucokinase, epigenetic modulation of lipogenesis and beta-oxidation, as well as stimulation of gut-hormone release (see Figure 2). Especially allulose has various known mechanisms via which it may promote health, which are also visualized in Figure 2. Allulose is one of the most intensively investigated rare sugars as well, hence it cannot be excluded that other rare sugars have similar modes of action. Considering the variety of mechanisms supporting promising metabolic effects of investigated rare sugars, the large pool of rare sugars that remain uncharacterized and the diversity between different rare sugars, research on rare sugars has a lot of potential with many different sugar replacers to investigate.

Future perspectives

Future perspectives for the application of rare sugars in food products with improved health benefits include (i) the development of novel technologies to produce these rare sugars in sufficient amounts, (ii) the exploration of structure-function relationships and mechanistic evidence of their biological impact, and (iii) the performance of well-designed human intervention trials demonstrating the metabolic effects in sufficient amounts. In addition, the functionality of these sugars to create appropriate food products in terms of taste, texture, etc. is an important consideration, but is not the scope of this review. These properties of sugars and sweeteners from natural and synthetic origin are described in other reviews (Priya, Gupta, and Srikanth 2011; Martínez-Cervera, Salvador, and Sanz 2014; Chattopadhyay, Raychaudhuri, and Chakraborty 2014).

Enzymatic engineering

Considering the gaps in knowledge about the potential health benefits of rare sugars and their appropriate ranking in function of health impact, there is a persistent need for improved production methods for rare sugars. Promising new technologies are found within the field of enzymatic engineering through genetically modified microorganisms. Mutated enzymes have already been successful for the production of rare monosaccharides like tagatose and L-ribose as well as rare disaccharides like kojibiose and nigerose (Beerens, Desmet, and Soetaert 2012; Beerens et al. 2017). These new technologies make it easier to obtain sufficient amounts of rare sugars, not only to investigate their potential health effects, but also to replace conventional sugars in food products. In addition, enzymatic engineering opens the door for the creation of a new set of sugar substitutes with improved health effects. Therefore, the investigation of the health effects of these sugars is no longer a theoretical issue, but may actively steer innovations in the food industry.

Mechanistic research with human-relevant models

So far, most of the studies on metabolic effects and digestion of rare sugars have been performed either in animals or in vitro with for example rat intestinal extract. Although these studies have provided interesting insights, sugar metabolism strongly differs between humans and rodents regarding diet, gut physiology, and enzymatic degradation (Perlman 2016).

In vitro research has shown his merit in unraveling mechanisms behind the improved health effect of certain rare sugars. Briefly, they may be summarized as models for digestion, absorption and metabolic health. Digestibility rankings for disaccharides have been established using incubation with rat intestinal extract, but these results have not been validated by human in vivo studies yet (Hodoniczky, Morris, and Rae 2012; Lee et al. 2016). Different glucosidase enzymes have their own substrate specificity, meaning that the ability to digest a certain sugar differs between the glucosidases. Furthermore, experiments with rat intestinal extract only provide information on digestibility and not on metabolization or metabolic health effects. Differences in monosaccharide composition may result in metabolic differences that cannot be explained by differences in digestibility.

Digestion, absorption and metabolic effects are currently investigated using cell culture models for the intestine (predominantly Caco-2 cells) or others such as liver, adipocyte and immune cells, mostly as cell monocultures. Nowadays, with the recent advances in tissue culture engineering, it has become clear that co-culture and intercellular crosstalk can contribute to a more physiologically relevant functionality of the cells (Goers, Freemont, and Polizzi 2014). Co-cultures of different cells have been applied for studying complicated matters like drug effects, intestinal inflammation and the cancer microenvironment (Miki et al. 2012; Goers, Freemont, and Polizzi 2014; Kämpfer et al. 2017), but are currently non-existing in the field of sugar research. We expect that these models may improve the understanding of

the mechanisms of rare sugars with diverse mode-of-actions, such as for allulose. Such models may also help to characterize the metabolism of rare monosaccharides, which is not fully understood. Co-culture models with liver cells would be advised, considering the central role of the liver in both sugar metabolism and metabolic health. Nevertheless, co-culture models remain in vitro simulations and should proceed instead of replace in vivo experiments.

Recent advances in cell culture models also include the incorporation of the food and digestive matrix, which is more physiologically relevant as metabolic diseases are usually induced by lifestyles rather than by a single food component. Intestinal sugar absorption is a well-known factor that is influenced by food matrices (Southgate 1995). In addition to digestive matrices, combinations of different dietary compounds have been used to simulate effects of sugars under different conditions. In the field of metabolic health research, in vitro research has shown that high glucose and saturated fatty acids synergistically increase death of pancreatic β cells (El-Assaad et al. 2003). Effects of sugar may be enhanced or modulated by phytonutrients like polyphenols as well. Cell culture studies demonstrated for example that epigallocatechin improves insulin secretion under high glucose conditions as well as glucose uptake in muscle cells (Hanhineva et al. 2010). Therefore, there are clear advantages of models that are able to simulate the complexity of the human diet, in which food interactions enhance or reduce the effects of sugars.

Finally, not only the digestibility and absorption in the upper gastrointestinal tract should be modeled, but also the effects on the intestinal microbiota should be considered. This is especially relevant considering the slow and incomplete absorption of rare sugars, resulting in availability of the sugars in the colon. In addition, studies showed that rare sugars like kojibiose, tagatose, allulose and sophorose can stimulate the production of short-chain fatty acids, but these studies did not elaborate on the actual health effects that are accompanied by the modulation of the microbiota and production of short-chain fatty acids (Matsuo et al. 2003; Venema, Vermunt, and Brink 2005; Sanz, Gibson, and Rastall 2005). Recently, we have developed models in which intestinal microbial digests are combined with Caco-2 cells in the context of polyphenol bioavailability and bioactivity, as well as for investigation of probiotic butyrate-producing bacteria to improve barrier function in Chrohn's disease patients (Geirnaert et al. 2017; Wu et al. 2018). Similar combined models therefore show potential to investigate and rank the bioavailability and bioactivity of rare sugars.

Well-designed human intervention studies

As health claim acceptance by EFSA is mainly based on well-designed human intervention trials, more randomized clinical trials need to be performed with rare sugars. Although more than twenty human studies have been performed with rare sugars, these studies have mainly focused on a limited set of rare sugars. As a result of the lack of clinical trial data on rare sugars, hardly any rare sugars are included in EFSA claims. EFSA approved a claim for several sugar replacers regarding maintenance of tooth mineralization and reduction of the post-prandial glycemic response (EFSA 2011). This claim was approved for 7 polyols, while tagatose and isomaltulose were the only rare sugars included.

Rare sugars may potentially qualify for EFSA claims related to appetite, weight management and blood glucose concentrations. In order for these kinds of claims to be approved, the effects should be beneficial physiological effects and the outcome measures have to be appropriate for the claimed effect. Effects on risk factors for disease are considered beneficial by EFSA when the improved factor is an independent predictor for disease based on human studies, and there is a biologically plausible role for the factor in the development of a disease (EFSA Panel on Dietetic Products and Nutrition and Allergies (EFSA) 2012). Furthermore, these effects have to be established in the general healthy population. Additional criteria that are assessed for these claims are whether the studied group is representative for the study population, whether the study design is sufficiently strong to support the claim (eg. human intervention studies) and whether the studies are performed with the food constituent for which the effect is claimed. For example, a reduction of abdominal body fat in overweight and obese subjects is considered a beneficial effect by EFSA and can result in a claim when the effect has been found in human intervention studies with a duration of 3 months. An increase of fat oxidation without data on other parameters is not considered sufficient for a claim on body weight maintenance. Long term effects on blood glucose control require improvements of HbA1c levels in human interventions of at least 3 months with diabetic subjects. To measure improvements of insulin sensitivity, hyperinsulinaemic-euglycemic clamps are considered appropriate methods for human intervention studies. Many of the health effects of rare sugars would be considered supportive rather than sufficient for a health claim by EFSA. Except for tagatose, isomaltulose and allulose, rare sugars have mostly been investigated in vitro or in animals models. Studies investigating effects of rare sugar on glycemic control have focused on short-term post-prandial effects rather than long term effects on HbA1c. Furthermore, glucose levels, insulin levels and HOMA IR instead of hyperinsuliaemic-euglycemic clamps have been used as markers for insulin sensitivity in these studies. Finally, studies on rare sugars have sometimes demonstrated effects on fat oxidation without direct evidence for weight loss effects or have found effects on weight loss without a follow-up to see if the weight loss persists months after the intervention. The increased availability of rare sugars and changes to the design of studies on rare sugars may result in more health claims on rare sugars in the future. This may require a switch from factors with an indirect influence on health to well-known risk factors of disease, which should be investigated with the appropriate golden standard methods in the population for which the health effect is most desirable. This is especially relevant for rare sugars with the most potential as sugar replacers. For allulose, a few more well-performed human trials investigating

well-recognized risk factors for disease may help to clarify whether this rare sugar is indeed one of the most promising sugar replacers available.

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