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Published in:
Critical Reviews in Food Science and Nutrition

DOI:
[10.1080/10408398.2018.1516621](https://doi.org/10.1080/10408398.2018.1516621)

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Document Version
Publisher's PDF, also known as Version of record

Publication date:
2020

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Citation for published version (APA):

Gangoiti, J., Corwin, S. F., Lamothe, L. M., Vafiadi, C., Hamaker, B. R., & Dijkhuizen, L. (2020). Synthesis of novel α -glucans with potential health benefits through controlled glucose release in the human gastrointestinal tract. *Critical Reviews in Food Science and Nutrition*, 60(1), 123-146. <https://doi.org/10.1080/10408398.2018.1516621>

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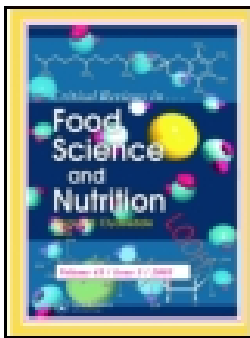
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To cite this article: Joana Gangoiti, Sarah F. Corwin, Lisa M. Lamothe, Christina Vafiadi, Bruce R. Hamaker & Lubbert Dijkhuizen (2018): Synthesis of novel α -glucans with potential health benefits through controlled glucose release in the human gastrointestinal tract, Critical Reviews in Food Science and Nutrition, DOI: [10.1080/10408398.2018.1516621](https://doi.org/10.1080/10408398.2018.1516621)

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Published online: 11 Dec 2018.



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Synthesis of novel α -glucans with potential health benefits through controlled glucose release in the human gastrointestinal tract

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ABSTRACT

The glycemic carbohydrates we consume are currently viewed in an unfavorable light in both the consumer and medical research worlds. In significant part, these carbohydrates, mainly starch and sucrose, are looked upon negatively due to their rapid and abrupt glucose delivery to the body which causes a high glycemic response. However, dietary carbohydrates which are digested and release glucose in a slow manner are recognized as providing health benefits. Slow digestion of glycemic carbohydrates can be caused by several factors, including food matrix effect which impedes α -amylase access to substrate, or partial inhibition by plant secondary metabolites such as phenolic compounds. Differences in digestion rate of these carbohydrates may also be due to their specific structures (e.g. variations in degree of branching and/or glycosidic linkages present). In recent years, much has been learned about the synthesis and digestion kinetics of novel α -glucans (i.e. small oligosaccharides or larger polysaccharides based on glucose units linked in different positions by α -bonds). It is the synthesis and digestion of such structures that is the subject of this review.

KEYWORDS

Dietary carbohydrates; starch; sucrose; slowly digestible; α -glucans; transglycosylases

Hyperglycemia and health

There is abundant evidence that postprandial hyperglycemia is an indicator for risk of coronary heart disease (CHD), stroke, and overall mortality (Almdal et al. 2004; Hanefeld et al. 1996); rapid rise in blood glucose levels increases low-level inflammatory effects, oxidative stress, and harmful effects on beta cells which decreases insulin sensitivity (Figure 1) (Ceriello et al. 2004; Wallander et al. 2005). Hyperglycemia lasting more than 2 hours postprandial has been shown to be a better predictor of CHD, stroke, and overall mortality than hemoglobin A1c levels (Jackson, Yudkin, and Forrest 1992; Meigs et al. 2002). Many have hypothesized that postprandial hyperglycemia contributes to diabetes complications through damaging the vasculature tissue, such as retinopathy and nephropathy, which is likely why the cardiovascular disease incidence is so highly correlated to poorly controlled diabetes (Ceriello et al. 2004; Meigs et al. 2002). Even in non-diabetics, a meal high in rapidly digestible starches allows for some postprandial and post-challenge hyperglycemia that may contribute to cardiovascular damage (Hanefeld and Schaper 2007). Poor insulin secretion and decreased insulin sensitivity are key characterizations of type 2 diabetes, as well as progressive beta cell dysfunction (Wallander et al. 2005).

In addition to vascular damage caused by acute postprandial hyperglycemia, there may be an increase in oxidative stress when excessive blood glucose fluctuations occur pre- and postprandially, with quick absorption of glucose from meals (Monnier et al. 2006). Furthermore, activation of protein kinase C, MAP-kinase, and NF- κ B are promoted with intracellular hyperglycemia, increasing reactive oxygen species (Brownlee 2001; Monnier et al. 2006). It has been reported that “overproduction of superoxide by the mitochondrial electron-transport chain” is the common factor linking the increased cell abnormalities in diabetes (Brownlee 2001; Campos 2012; Du et al. 2000; Nishikawa et al. 2000).

Value of slowly digestible carbohydrates to health

Inhibition of the enzymes that digest starch, such that glucose release into the bloodstream is slowed, is one treatment method for type 2 diabetes. Currently, acarbose is used as a competitive inhibitor affecting the activities of enzymes in the human digestive tract, i.e. pancreatic α -amylase and various α -glucosidases (Hanefeld and Schaper 2007; Martin and Montgomery 1996). While enzyme inhibition is one method clinically used to slow

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Effects of Chronic Hyperglycemia

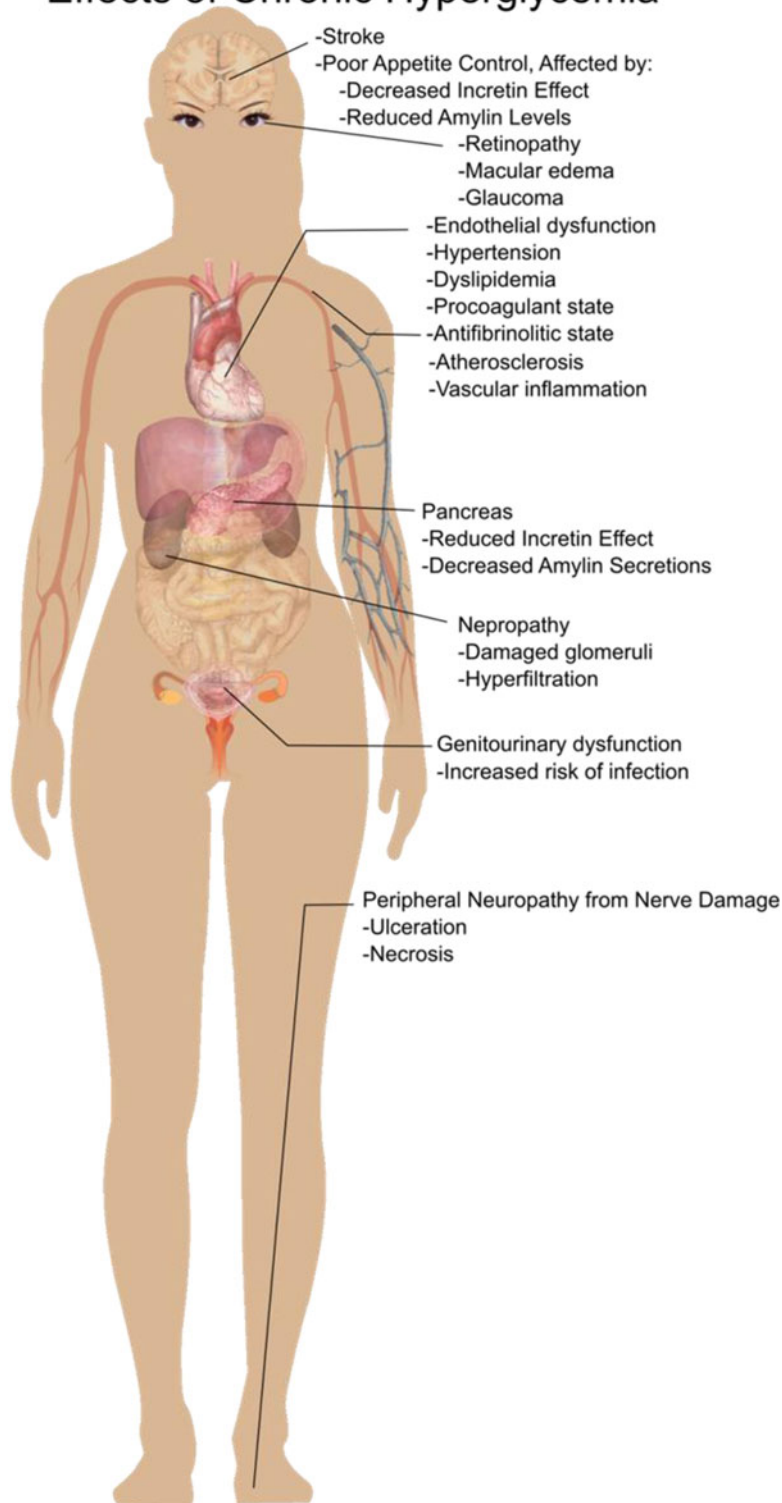


Figure 1. Effects of chronic hyperglycemia.

the glucose release of carbohydrate digestion, as mentioned, this review will examine the potential to modulate glycemic response through the use of α -glucans with structures and glycosidic linkages that do not allow for immediate hydrolysis.

In addition to the effect of modulating glycemic response, slowly digestible carbohydrates which are digested into the ileal (distal) region of the small intestine may stimulate

endocrine L-cells to reduce appetite and slow gastric emptying. This has recently been demonstrated in rats using fabricated slowly digestible carbohydrate microspheres that were shown to digest into the ileum. Long-term feeding (11 weeks) of the microspheres to diet-induced obese rats produced lower daily food intake and reduced gene expression of the hypothalamic appetite-stimulating neuropeptides (Hasek et al. 2017).

Glycemic carbohydrates and their structure

Oligo- and polysaccharides are built of multiple sugar molecules, or monosaccharides, joined by glycosidic linkages occurring between the hydroxyl group of one monosaccharide with an anomeric carbon of another. The human digestive tract, as well as mammals in general, contains carbohydrate-digesting enzymes consisting of α -amylases secreted in salivary and pancreatic fluids that digest starch and starch products to linear di-, tri- and tetra-oligosaccharides (maltose, maltotriose, maltotetraose) and branched α -limit dextrins, mixtures of D-glucopyranose units linked by (α 1 \rightarrow 4) or (α 1 \rightarrow 6) glycosidic bonds. Then the small intestine mucosal α -glucosidases [maltase-glucoamylase (MGAM) and sucrose-isomaltase (SI)] that hydrolyze these and other digestible glycans to monosaccharides prior to their absorption (Zhang and Hamaker 2009). The human body absorbs and metabolizes glucose, fructose, and galactose. The common glycosidic bonds that are digestible by humans include (α 1 \rightarrow 4) and (α 1 \rightarrow 6) glucose-glucose that make up (iso)maltose, (iso)maltooligosaccharides, and starch; sucrose, (α 1 \rightarrow 2) glucose-fructose; and lactose, (β 1 \rightarrow 4) galactose-glucose. Uncommon linkages that can be hydrolyzed by the α -glucosidases include (α 1 \rightarrow 1), (α 1 \rightarrow 2), and (α 1 \rightarrow 3) glucose-glucose; and (α 1 \rightarrow 3), (α 1 \rightarrow 4), (α 1 \rightarrow 5), and (α 1 \rightarrow 6) glucose-fructose (Lee et al. 2016). When multiple monosaccharides are linked together, they form polysaccharides, which are used for energy storage and structure. For example, glycogen is a storage polysaccharide within the human body, consisting of (α 1 \rightarrow 4)-linked glucose molecules that are relatively highly branched through (α 1 \rightarrow 6) linkages. Starch, which is the glucose storage form in plants and the most common dietary polysaccharide, consists of two types of polymers: Amylose and amylopectin. Amylose, is principally a linear (α 1 \rightarrow 4)-linked glucan, whereas in amylopectin the (α 1 \rightarrow 4) linear chains are connected via (α 1 \rightarrow 6) branching points. β -Glucans (polymers of glucose with β -glycosidic linkages), such as cellulose [(β 1 \rightarrow 4)-linked] and β -glucan [in cereals, (β 1 \rightarrow 4)- and (β 1 \rightarrow 3)-linked], is another commonly consumed polysaccharide; humans lack cellulase enzymes to digest these β -bonds.

The enzymes responsible for mammalian α -glucan digestion

To digest the dietary available carbohydrates to the monosaccharides glucose, fructose, and galactose, the mammalian body employs the salivary and pancreatic α -amylases (EC 3.2.1.1.) and the small intestine mucosal two-enzyme complexes of maltase-glucoamylase (MGAM) (EC 3.2.1.20 and 3.2.1.3) and sucrose-isomaltase (SI) (EC 3.2.1.48 and 3.2.10). The α -amylases are classified in glycoside hydrolase (GH) family GH13, and the four catalytic subunits of MGAM and SI in GH31 (Nichols et al. 2003). The four enzyme subunits of these α -glucosidases have different roles in the conversion of glycemic carbohydrates to glucose (and of sucrose to glucose and fructose). α -Glucans with structures and linkages that are less easily hydrolyzed by these enzymes potentially are of interest as slowly digestible carbohydrates. Following

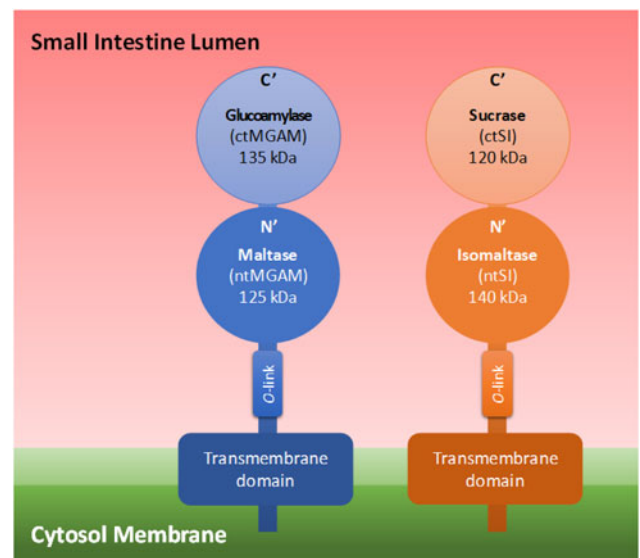


Figure 2. α -Glucosidase arrangement on the cytosol membrane.

digestion of starch by salivary and pancreatic α -amylase to linear maltooligosaccharides and branched α -limit dextrins, in the small intestine the α -linked glucans and sucrose are hydrolyzed by the mucosal α -glucosidases, MGAM and SI, into free glucose (Zhang and Hamaker 2009). Each α -glucosidase has a unique role, and understanding their roles can aid in designing carbohydrates with low digestibility carbohydrates. The α -glucosidase dimers are composed of N- and C-terminal subunits; for MGAM the N- and C-terminal subunits are maltase and glucoamylase, and for SI these are isomaltase and sucrase, respectively (Quezada-Calvillo et al. 2008). In the literature, they are also termed N- and C-terminal MGAM and SI. The N-terminal domains of both α -glucosidase complexes are connected to the enterocyte membrane, with the C-terminal subunits linked and facing the internal cavity of the intestine. The domains are anchored by an O-glycosylated stalk that branches out of the N-terminal domain (Lee et al. 2014; Sim et al. 2010) (Figure 2).

Glucoamylase digests (α 1 \rightarrow 4) glucosidic bonds and acts faster on longer chain α -glucans than maltase does, and even can digest native dispersed starch (Lin et al. 2012). The ability of the mammalian α -glucosidases to hydrolyze different α -linked glucose-glucose disaccharides has been studied using recombinantly expressed and purified enzymes. Glucoamylase was shown to act (enzyme efficiency of glucose generation) on maltose (α 1 \rightarrow 4) (K_{cat}/K_m 51.0 $\text{mM}^{-1}\text{s}^{-1}$), kojibiose (α 1 \rightarrow 2) (K_{cat}/K_m 0.9 $\text{mM}^{-1}\text{s}^{-1}$), and nigerose (α 1 \rightarrow 3) (K_{cat}/K_m 2.7 $\text{mM}^{-1}\text{s}^{-1}$); with higher maltase activity than the maltase subunit itself (K_{cat}/K_m 51.0 vs. 12.7 $\text{mM}^{-1}\text{s}^{-1}$) (Lee et al. 2016). Glucoamylase is reported to be inhibited by maltotriose and maltotetraose at high concentrations (Quezada-Calvillo et al. 2008).

In addition for digesting maltose, kojibiose, and nigerose, maltase has minor activity towards isomaltose (α 1 \rightarrow 6) (K_{cat}/K_m 0.1 $\text{mM}^{-1}\text{s}^{-1}$). Maltase does not digest larger maltooligosaccharides efficiently; under *in vitro* experimental conditions, full hydrolysis by maltase took place in 60 min for maltotriose, maltotetraose, and maltopentaose, while

Table 1. Kinetic Parameters of Each Recombinant Mucosal α -Glucosidase on Differently α -Linked Disaccharides with Two Glucoses. Adapted from Lee et al. (2016).

	ctMGAM (Glucoamylase)	ntMGAM (Maltase)	ctSI (Sucrase)	ntSI (Isomaltase)
Trehalose	Not detected	Not detected	Not detected	Not detected
Kojibiose	12.7 ± 2.5 ^c	11.6 ± 1.2 ^c	17.3 ± 2.2 ^c	53.7 ± 13.7 ^c
	11.5 ± 0.6 ^b	17.6 ± 0.5 ^b	0.5 ± 0.0 ^b	3.2 ± 0.3 ^b
	0.9 ± 0.2 ^a	1.5 ± 0.4 ^a	0.3 ± 0.0 ^a	0.1 ± 0.0 ^a
Nigerose	35.2 ± 3.6 ^c	27.1 ± 2.6 ^c	63.6 ± 13.0 ^c	44.4 ± 6.4 ^c
	96.0 ± 3.3 ^b	120.9 ± 3.7 ^b	11.0 ± 1.0 ^b	24.8 ± 1.3 ^b
	2.7 ± 0.9 ^a	4.4 ± 1.4 ^a	0.2 ± 0.1 ^a	0.6 ± 0.2 ^a
Maltose	2.6 ± 0.6 ^c	8.7 ± 1.3 ^c	4.2 ± 1.4 ^c	11.1 ± 1.5 ^c
	133.9 ± 4.3 ^b	110.2 ± 3.8 ^b	11.4 ± 0.8 ^b	18.3 ± 0.6 ^b
	51.0 ± 7.0 ^a	12.7 ± 3.0 ^a	2.7 ± 0.5	1.7 ± 0.4 ^a
Isomaltose	Not detected	128.0 ± 8.4 ^c	Not detected	15.2 ± 2.0 ^c
		8.9 ± 0.3 ^b		18.1 ± 0.7 ^b
		0.1 ± 0.0 ^a		1.2 ± 0.3 ^a

^a K_{cat}/K_m (mM⁻¹ s⁻¹).^b K_{cat} (s⁻¹).^c K_m (mM).

maltose was hydrolyzed in 20 min (Lee et al. 2014). Compared to glucoamylase, or the SI subunits, maltase has a higher hydrolyzing activity on kojibiose and nigerose (Table 1).

Per their common names, sucrase hydrolyzes sucrose ($\alpha 1 \rightarrow 2$, glucose-fructose) and isomaltase hydrolyzes isomaltose ($\alpha 1 \rightarrow 6$, glucose-glucose). However, the SI complex is notably responsible for the majority of mucosal maltase activity, because the human intestine may contain 40-50 times more SI than MGAM (Lee et al. 2013; Quezada-Calvillo et al. 2007). Recombinant mammalian α -glucosidase, sucrase and isomaltase had K_{cat}/K_m values for the hydrolysis of maltose of 2.7 and 1.7, respectively; both enzymes showed some, though lesser, hydrolysis activity for kojibiose and nigerose compared to the MGAM subunits (Lee et al. 2013) (Table 1). Some sucrose hydrolyzing activity was also found for glucoamylase, and interestingly isomaltulose ($\alpha 1 \rightarrow 6$, glucose-fructose) was hydrolyzed mostly by isomaltase. Both SI subunits digested longer linear maltooligosaccharides (e.g. G5 compared to G2) quite slowly compared to the MGAM subunits (Lee et al. 2013). Lee et al. (Lee et al. 2014) proposed that selective inhibition to target MGAM subunits would slow down the release of glucose to the rates of the SI subunits, as MGAM digests more efficiently maltooligosaccharides than SI.

Heymann et al. (Heymann, Breitmeier, and Gunther 1995), upon measuring SI kinetics, proposed that the sucrase subunit has maximal activity against maltose ($\alpha 1 \rightarrow 4$)-G2, and the isomaltase subunit has high activity against ($\alpha 1 \rightarrow 6$) branched oligosaccharides composed of up to 4 glucopyranose residues (Heymann, Breitmeier, and Gunther 1995). Lee et al. (Lee et al. 2014) showed though that sucrase and isomaltase have similar hydrolyzing capabilities for maltose.

It is known that ($\alpha 1 \rightarrow 6$)-linked branched structures, such as the α -limit dextrins, the digested products of salivary and pancreatic α -amylases, are hydrolyzed at a much slower rate than ($\alpha 1 \rightarrow 4$)-linked linear glucans (Zhang and Hamaker 2009). Studies on α -amylase showed that optimal enzyme activity occurs when five or more ($\alpha 1 \rightarrow 4$)-linked glucose molecules are in the substrate. ($\alpha 1 \rightarrow 6$)-branched linkages of

amlyopectin molecules hinder α -amylase activity (Quezada-Calvillo et al. 2008).

The precise roles of the individual α -glucosidases are now well documented, and a synergistic picture of their concerted action seems to appear. Larger starch digestion products are effectively digested by the outer located glucoamylase enzyme and the small linear and branched maltooligosaccharide products are further digested to glucose by the inner located maltase and isomaltase (Figure 2). Glucoamylase and maltase can digest unusual $\alpha 1 \rightarrow 2$ - and $\alpha 1 \rightarrow 3$ -linked glucans, though maltase has higher capacity.

Inhibition of the α -glucosidases

While carbohydrate molecular structure influences digestion rate by α -glucosidases, phytochemical inhibitory molecules that are present at the time of digestion may also influence the rate of glucose release by these enzymes. Plant phenols (e.g. chlorogenic acid, caffeic acid and gallic acid) are a family of metabolites reported to have inhibitory effects on SI and MGAM. Chlorogenic acid has been shown to have α -glucosidase inhibitory effects when consumed with maltose or sucrose; one study by Ishikawa et al. (Ishikawa et al. 2007) showed that, when consumed before a meal, leaves of *Nerium indicum* (oleander) lowered postprandial glucose levels by inhibiting α -glucosidases (Ishikawa et al. 2007). Coffee contains chlorogenic acid, and green tea contains caffeic acid and catechins which are known α -glucosidase inhibitors (Adisakwattana et al. 2009; Nguyen et al. 2012). In a study by Simsek et al. (Simsek et al. 2015), chlorogenic acid, epigallocatechin gallate, (+)-catechin, caffeic acid, and gallic acid were examined for their effect on the kinetics of maltose digestion and mechanism of inhibition against each α -glucosidase subunit. It was found that the inhibition constants (K_i) for epigallocatechin gallate against glucoamylase ($1.7 \pm 0.7 \mu\text{M}$) and chlorogenic acid against sucrase ($1.8 \pm 0.3 \mu\text{M}$) were the lowest compared to any other phenolics acting on any other subunits (Simsek et al. 2015). Therefore, there is benefit in focusing further research on the effect of epigallocatechin gallate and chlorogenic acid on slowing the α -glucosidase C-terminal subunit digestion.

Acarbose is produced by some Gram-positive bacteria and is a potent selective inhibitor of the C-terminal α -glucosidase subunits (Lee et al. 2012). 1-Deoxynojirimycin which is found in the mulberry plant bark and root was shown to be a potent competitive MGAM inhibitor (Breitmeier, Günther, and Heymann 1997), but against which subunit has yet to be determined (Breitmeier, Günther, and Heymann 1997; Hanefeld and Schaper 2007; Liu et al. 2015; Martin and Montgomery 1996). The glucoamylase C-terminal MGAM subunit acts very rapidly on smaller starch units and its inhibition could potentially be used to slow the rate of hydrolysis on longer chain maltooligosaccharides.

α -Glucans: Current and future ingredients for the food industry

Health concerns are important drivers of consumer preferences and demands on food product development are based on taste, nutritional value, and healthfulness. As mentioned, digestible carbohydrates such as starch and its derivatives (maltodextrins and maltooligosaccharides) are the predominant α -glucans in our diets, and have recently come under scrutiny for their postulated negative impact on health, particularly when consumed in excess. α -Glucan ingredients that have slowly digestible or non-digestible profiles constitute a healthful alternative to highly processed starches and its derivatives. There is a wide range of synthetic or naturally-occurring α -glucan ingredients that differ in digestibility profiles and technological properties. The α -glucans include a large group of linear, branched or cyclic oligo- and polysaccharides that are composed of glucose moieties joined via (α 1 \rightarrow 2), (α 1 \rightarrow 3), (α 1 \rightarrow 4), and (α 1 \rightarrow 6) glycosidic linkages. In this section, we describe the most prominent α -glucan ingredients with current or potential uses in the food industry.

Commercially available α -glucan ingredients

Starch

Starch is the most abundant α -glucan as it is the main storage carbohydrate in cereals, pulses and tubers. Normal starches are composed of around 20% of amylose and 80% of amylopectin, but this ratio differs depending on the starch source (van der Maarel and Leemhuis 2013; van der Maarel et al. 2002). Also, the branching pattern and the average length of the (α 1 \rightarrow 4) chains varies with the origin of the starch. Based on the rate of digestion, starch is classified into rapidly digestible starch (RDS), slowly digestible starch (SDS) and resistant starch which largely defines its nutritional quality (Englyst, Kingman, and Cummings 1992). In its native form, starch is characterized by a granular structure that renders it slowly digestible or resistant (Oates 1997; Valk et al. 2015). It has been shown, for example, that native cereal starches are slowly digestible due to their layered structure constituted by crystalline and amorphous regions (Zhang, Ao, and Hamaker 2006). As mentioned, the health benefits of SDS mainly pertain to a slower rate of glucose release that results in a reduced postprandial glycemia (Lehman and Robin 2007). However, as starch is cooked and gelatinized it loses its granular structure which results in a significant increase in its digestibility (Bornet et al. 1989). When discussing gelatinized starches that have lost their crystalline structure, their molecular features then become the main determinant factors for digestibility. In particular, the fine structure of amylopectin (e.g. average length of (α 1 \rightarrow 4) chains and branching pattern) and the ratio of amylose to amylopectin are the main determinants of gelatinized starch physical state and digestibility. Amylopectin molecules with either higher amounts of long or short chains were found to have a similar high content of SDS due to two different mechanisms. Whereas the presence

of long chains leads to the formation of physical structures that decrease enzyme accessibility, a highly branched structure limits itself the accessibility of digestive enzymes (Zhang, Ao, and Hamaker 2008). Starches that are high in amylose content have a resistant starch character both in their native state and after gelatinization and retrogradation, the latter caused by amylose formation of long-chain double-helical crystallites that are resistant to digestion (Jiang et al. 2010). Consumption of resistant starch has been shown to positively influence bowel health, blood lipids profile, and to reduce the glycemic and insulinemic responses (Nugent 2005).

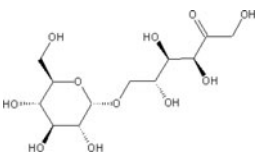
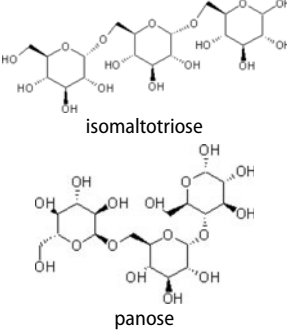
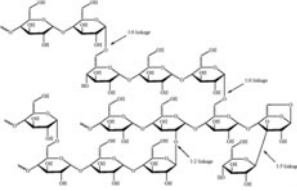
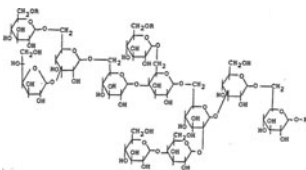
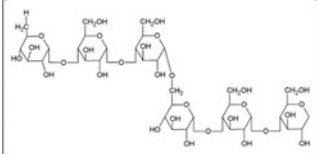
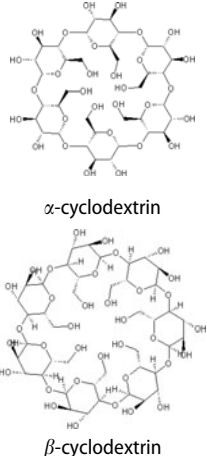
Isomaltulose

Isomaltulose is a disaccharide composed of glucose and fructose linked by an (α 1 \rightarrow 6)-glycosidic linkage (Table 2). It has about 42% of the sweetness of sucrose, and has been identified to occur naturally at low levels in honey and sugar cane extract (Siddiqui and Furgala 1967; Takazoe 1985). It is commercially produced by the enzymatic rearrangement of sucrose (glucose- (α 1 \rightarrow 2)- β -fructose) using a sucrose mutase (EC.5.4.99.11) found in bacteria e.g. *Protaminobacter rubrum* (Pelzer et al. 2012). It is commonly used as a non-cariogenic sucrose replacer. *In vitro* studies of the digestibility properties of isomaltulose with mammalian intestinal α -glucosidases (including human) indicate that the rate of hydrolysis of this sugar is significantly slower than that of sucrose and maltose (Tsuji et al. 1986). Animal studies have shown that isomaltulose is completely digested and absorbed in the small intestine, but the postprandial glycemic and insulinemic responses rise at a slow rate, with maximum concentrations of glucose and insulin being lower than for sucrose (Kawai, Okuda, and Yamashita 1985; van Can et al. 2012). This slowly digestible property makes isomaltulose a suitable ingredient for products targeted to consumers with diabetic and pre-diabetic dispositions. Furthermore, due to its complete digestion, clinical studies have shown that both healthy and diabetic subjects can tolerate doses of up to 50 g without presenting intestinal discomfort. Isomaltulose is a white crystalline substance, characterized by a similar sweetness profile as sucrose which leaves no aftertaste. It has a melting point of 123 to 124 °C, lower to that of sucrose, and is stable under acidic conditions (Irwin and Sträter 1991).

Isomaltooligosaccharides (IMOs)

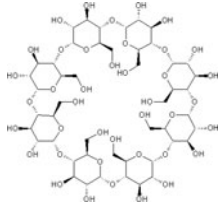
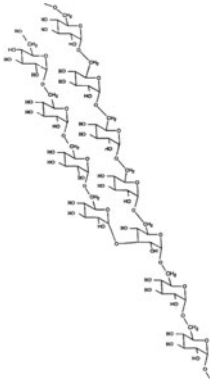
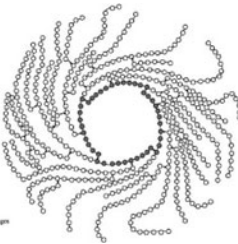

IMOs are found naturally in various fermented foods such as miso, sake, or soy sauce but also in honey (Playne and Crittenden 2004). Commercial IMOs are produced enzymatically and are the market leader in the dietary carbohydrate sector of functional foods (Mountzouris, Gilmour, and Rastall 2002). They are generally obtained industrially from starch hydrolysates (maltose and maltodextrins) through the action of α -transglucosidases (EC 2.4.1.24) (Roper and Koch 1988; Yasuda, Takaku, and Matsumoto 1986), or from sucrose using dextran sucrases (Paul et al. 1992; Remaud-Simeon et al. 1994). IMOs, also called glucosyl saccharides,

Table 2. α -Glucan ingredients: Chemical structures, properties and applications in food industry.

α -Glucan ingredient	Structure	Properties	Food application(s)
Isomaltulose (Irwin and Sträter 1991) (α -D-glucopyranosyl-1 \rightarrow 6- α -D-fructofuranose)		White crystalline substance Sweet	Sweetener
Isomalto-oligosaccharides (Goffin et al. 2011) (glucoligosaccharides linked with (α 1 \rightarrow 4) and/or (α 1 \rightarrow 6) glycosidic bonds)		White powder or syrup, water soluble, sweet	Low caloric sweetener, prebiotic ^b
Resistant dextrins (Ohkuma and Wakabayashi 2000) (highly-branched glucan with (α 1 \rightarrow 2), (α 1 \rightarrow 3), (α 1 \rightarrow 4), and (α 1 \rightarrow 6) in α - and β -configuration)		White and odorless water-soluble powder	Low calorie, bulking agent
(Simpson 2011)			
Polydextrose (Mitchell, Auerbach, and Moppet 2001) (highly-branched glucan with (α 1 \rightarrow 2), (α 1 \rightarrow 3), (α 1 \rightarrow 4), and (α 1 \rightarrow 6) in α - and β -configuration. Contains citric acid and sorbitol)		White, water-soluble powder	Low calorie, bulking agent
(Putala 2013)			
Pullulan (Khan, Park, and Kwon 2007, Park and Khan 2009) (linear glucan consisting of maltotriosyl units linked with (α 1 \rightarrow 6) glycosidic linkages)		Water-soluble, white, odorless & tasteless	Filler, glazing agent film-forming Agent, thickener, binder
(Ferreira et al. 2015)			
Cyclodextrins (Astray et al. 2009) (cyclic oligomers of 6 (α), 7 (β) or 8 glucose units (γ) linked via (α 1 \rightarrow 4) glycosidic linkage)		Solubility in water: $\gamma > \alpha > \beta$ -CDs, formation of inclusion complexes	Encapsulation of flavours, protection against oxidative degradation, heat and light induced changes, cholesterol sequestrant and preservatives.
α -cyclodextrin			
β -cyclodextrin			

(continued)

Table 2. Continued.

α -Glucan ingredient	Structure	Properties	Food application(s)
Dextran (Jeanes et al. 1954; Maina et al. 2011; Park and Khan 2009) (glucan polysaccharides with 50 – 97% (α 1 \rightarrow 6) glycosidic linkages)	 <p>γ-cyclodextrin</p>	High solubility, promotes low solution viscosities ^c Molecular weight range: 1 > Mw >10kDa	Sourdough baking improver, natural thickeners in dairy products
Alternan-oligosaccharides (Evoxx Technologies GmbH 2017) (oligosaccharides consisting of alternating (α 1 \rightarrow 6) and (α 1 \rightarrow 3) of various length)	 <p>(Leathers, Hayman, and Côté 1997)</p>	Water soluble, low viscosity and sweet syrups	Low glycemic ingredient
Cyclic cluster dextrin (FDA 2010; Takata et al. 1996; Takii et al. 1999) (highly-branched cyclic dextrin consisting of (α 1 \rightarrow 4) and (α 1 \rightarrow 6)-linked glucose units)	 <p>(Kadota et al. 2015)</p>	Highly water soluble, tasteless. Formation of inclusion complexes Mw 160 kDa with narrow size distribution	Slowly digestible carbohydrate that accelerates gastric emptying, spray-drying aid
Alternan (Grysmann, Carlson, and Wolever 2008; Khan, Park, and Kwon 2007; Park and Khan 2009) (α -glucan consisting of alternating (α 1 \rightarrow 6) and (α 1 \rightarrow 3) glycosidic linkages)	 <p>(Leathers, Hayman, and Côté 1997)</p>	High solubility and low viscosity, hygroscopic, white, tasteless powder	Low caloric bulking agent, binder

^aCommercial IMO syrup is generally accepted as a mixture of glucosyl saccharides with both (α 1 \rightarrow 6)-linkages and (α 1 \rightarrow 4) linkages and (α 1 \rightarrow 3), nigerooligosaccharides or (α 1 \rightarrow 2), kojooligosaccharides.

^bThe prebiotic properties are under question due to recent studies showing IMOs being digested in the upper intestinal track (Lin, Lee, and Chang 2016).

^cDepending on molecular weight and polydispersibility.

not only containing ($\alpha 1 \rightarrow 6$) linkages, but also ($\alpha 1 \rightarrow 4$) linkages, and nigerooligosaccharides comprised of ($\alpha 1 \rightarrow 3$) and/or kojiligosaccharides comprised of ($\alpha 1 \rightarrow 2$) linkages, can be found in commercially available products (Chaen et al. 2001; Kobayashi et al. 2003; Konishi and Shindo 1997; Yamamoto et al. 2004; Yun, Lee, and Song 1994) (Table 2).

IMOs are considered as non-digestible carbohydrates with prebiotic properties with benefit to the human microbiome (Goffin et al. 2011; Rycroft et al. 2001). Commercial IMO ingredients are used as a source of a soluble dietary fiber, a prebiotic and/or a low-calorie sweetener. For instance, Gu et al. (Gu et al. 2003) observed an increase of reproduction of *Bifidobacterium* and *Lactobacillus* and an inhibition of growth of *Clostridium perfringens* after ingestion of IMOs in mice and humans. However, other studies have shown that IMOs are hydrolyzed at least partially by mammalian digestive enzymes before they reach the colon (Hodoniczky, Morris, and Rae 2012; Kohmoto et al. 1992; Tsunehiro et al. 1999). More specifically, *in vitro* studies using mammalian brush border intestinal enzymes showed that glucose disaccharides containing ($\alpha 1 \rightarrow 6$), ($\alpha 1 \rightarrow 4$), ($\alpha 1 \rightarrow 2$) and ($\alpha 1 \rightarrow 3$) are digested by the different small intestine mucosal α -glucosidases (Lin, Lee, and Chang 2016). A recent survey of commercially available IMO-based ingredients challenges current labeling as “dietary fibers”, “low glycemic” and “zero calorie”. The authors performed a two-subject blood glucose response acute study in which a commercial IMO ingredient proved as glycemic as glucose (Madsen et al. 2017).

Resistant maltodextrins (RMDs)

RMDs are formed when liquefied starch is heated under acidic conditions in order to rearrange the glycosidic linkages. The treatment causes an increase in the proportion of ($\alpha 1 \rightarrow 6$) linkages and introduces ($\alpha 1 \rightarrow 2$) and/or ($\alpha 1 \rightarrow 3$)-linkages as well as linkages of β -anomeric configuration (Dermaux and Wills 2007) (Table 2). It is the combination of these linkages that render them poorly digestible. During heat treatment, starch undergoes pyroconversion, which involves hydrolysis, transglucosidation, and, in some cases, repolymerization of the branched oligosaccharides generated in the previous reactions. The rearrangement of glycosidic linkages that occurs during pyroconversion is what renders these dextrins resistant to digestion. They are popular ingredients in the food industry because they are soluble, have low viscosity, and have little to no impact on taste and color. Depending on their level of purification, resistant dextrins can contain up to 92% non-digestible carbohydrate content. In addition, they exhibit a high degree of thermal and pH stability (Ohkuma and Wakabayashi 2000). This ingredient is predominantly used to increase the dietary fiber content of food products without conferring negatively-perceived sensory attributes. RMDs are also suitable replacers of fully-caloric carbohydrates such as sucrose (4 kcal/g) since the caloric value for resistant dextrins is estimated to range between 1 and 2.5 kcal/g (Panasevich et al. 2015). Due to this property, this ingredient can also be used

to replace fully-digestible maltodextrins in the formulation of food products of medium to low glycemic index.

Polydextrose

Polydextrose is a synthetic, soluble, and non-viscous glucan polymer that is manufactured by melt condensation of glucose and sorbitol in acidic and vacuum conditions. This manufacturing process results in a highly-branched, low molecular weight polymer ($M_w = 2000$ Da; Degree of Polymerization [DP] = 12) constituted by glucose units linked by ($\alpha 1 \rightarrow 2$), ($\alpha 1 \rightarrow 3$), ($\alpha 1 \rightarrow 4$), or ($\alpha 1 \rightarrow 6$) glycosidic bonds, present in both α - and β -anomeric configuration (Rennhard 1973) (Table 2). Polydextrose is poorly digested in the small intestine and, thus, has reduced caloric availability. Its other applications in food include glazing agent, humectant, stabilizer and thickener (Srisuvor et al. 2013; Voragen 1998). Its complex structure also results in its poor degradation by microbes making it non-cariogenic and only a small fraction is metabolized by cecal/colonic microbiota.

Cyclodextrins (CDs)

CDs are cyclic oligosaccharides of glucose molecules linked by ($\alpha 1 \rightarrow 4$)-glycosidic linkages. They are classified depending on the number of glucose units, namely, α -, β - and γ -CDs for 6, 7, and 8 glucose units, respectively (Table 2). CDs are formed enzymatically from hydrolyzed starch by cyclodextrin glycosyltransferases (CGTases; E.C.2.4.1.19), enzymes that catalyze the cleavage of ($\alpha 1 \rightarrow 4$) linkages in starch and the subsequent transfer of the newly produced reducing end to a non-reducing end of the same molecule (Thiemann et al. 2004). Purified α -, β - and γ -CDs have been approved for their use as food additives (EFSA 2007; JECFA 1993, 1995, 1999, 2002, 2006). Different applications of CDs include flavor encapsulation, taste modification by elimination of bitter or off-flavors as well as odors, food preservation, and as cholesterol sequestrants (Astray et al. 2009) in a variety of food products as indicated by the Codex Alimentarius, General Standard for Food Additives (CODEX Alimentarius Commission for International Food Standards 2017). More specifically, the use of β -CD is limited to a few food categories (i.e., chewing gum, pre-cooked pastas and noodles, starch-based snacks, water-based, and flavored drinks) (Thiemann et al. 2004). α - and β -CDs are not hydrolyzed by gastrointestinal enzymes, but fermented by the colon microbiota. According to the EFSA Health Claim (EFSA Panel on Dietetic Products, Nutrition and Allergies 2012), α -CDs have been shown to effect a significant reduction in postprandial glycemic response at a dose of at least 5 g per 50 g of starch. The reduction in glycemic response is due to the tight helix of the α -CD, the inhibitory effect of α -CD on pancreatic amylase, and that α -CD may delay gastric emptying (Buckley et al. 2006; Gentilcore et al. 2011; Koukiekolo et al. 2001; Larson, Day, and McPherson 2010). In contrast, γ -CD is readily digested in the gastrointestinal tract yielding mainly maltose, maltotriose and glucose. Therefore, the metabolism of γ -CD closely resembles that of

starch and maltodextrins. Although they are rapidly metabolized and absorbed in the small intestine, γ -CDs have also been reported to impact glycemic response with a similar inhibitory effect on pancreatic α -amylase as α -CD (Koukiekolo et al. 2001; Wolf, Chow, and Lai 2006).

Novel α -glucan ingredients

Neo-amyloseTM

Neo-amyloseTM is an α -glucan obtained through the polymerization of sucrose by the action of amylosucrase (E. C. 2.4.1.4) derived from *Neisseria polysaccharea* (Büttcher et al. 1997). It is a water insoluble, unbranched polymer composed of (α 1 \rightarrow 4) glucosidic linkages with a chain length ranging from 35 up to 100 glucose units (Peters, Rose, and Moser 2010). It is an ingredient classified as a type 3 resistant starch (retrograded starch formed by cooking followed by cooling) that is around 90% non-digestible which makes it a suitable ingredient for use as a dietary fiber (Bengs and Brunner 2000).

Cyclic cluster dextrin (CCD)

CCD is made from amylopectin through the cyclization reaction of glycogen branching enzyme (E.C. 2.4.1.18) from the hyperthermophilic bacterium *Aquifex aeolicus* (Takata et al. 2003). It has relatively long chains which adopt a helical conformation enabling the formation of inclusion complexes with guest molecules such as organic acids (Table 2). CCD is typically used in baked products, beverages, powder soups made from fruit and vegetables. It has also been used as a spray-drying aid. CCDs have received an FDA GRAS status (FDA 2010; Takata et al. 1996) and animal studies have shown that they may accelerate gastric emptying and that they are slowly digestible (Takii et al. 1999).

Dextran

Luis Pasteur discovered dextran in wine and van Tieghem (Van Tieghem 1878) designated the dextran-producing bacterium as *Leuconostoc mesenteroides*. Dextrans are microbial α -glucans with 50–97% (α 1 \rightarrow 6) linkages (Table 2). They are produced from sucrose via large scale fermentation or enzymatic synthesis involving extracellular dextransucrase (E.C. 2.4.1.5) enzymes (Jeanes et al. 1954). Alternatively, these dextrans can be produced from starch by dextrin dextrinases (E.C. 2.4.1.2) (Yamamoto, Yoshikawa, and Okada 1993). Dextrans are approved as GRAS ingredients for their use in food products and feed. Also, the European Commission approves the use of dextran in baked goods at levels up to 5%; dextrans of high molecular weight are used in sourdough baking to produce good quality bread (SCO 2000; Maina et al. 2011). Furthermore, dextran was described as a thickening agent, an alternative cryostabilizer, fat replacer, or low-calorie bulking agent of interest for the food processing industry (Park and Khan 2009). Dextran is only partially hydrolyzed to monosaccharides by small

intestine α -glucosidases. The remaining dextran that escapes small intestine digestion is fermented in the colon resulting in short chain fatty acid production. Due to its low digestibility by intestinal enzymes, this polysaccharide represents a source of dietary fiber (Dahlqvist 1963; Dahlqvist 1961; Jeanes 1975).

Alternan and alternan-oligosaccharides

Alternan is a α -glucan consisting of alternating (α 1 \rightarrow 6) and (α 1 \rightarrow 3) linkages with a low degree of branching (Table 2). It is produced from sucrose by an enzyme of the glucansucrase family, known as alternansucrase (EC 2.4.1.140), that is found mainly in *Leuconostoc mesenteroides* (Côté and Robyt 1982; Leemhuis, Pijning, et al. 2013; Park and Khan 2009). (Côté and Robyt 1982; Leemhuis, Pijning, et al. 2013; Park and Khan 2009). Alternan is resistant to most known microbial and mammalian enzymes and can only be hydrolyzed by isomaltodextranases, and alternanases. Due to its resistance to digestion it can be used for production of ingredients for functional foods such as prebiotics (Leathers, Hayman, and Côté 1997; Park and Khan 2009). It has also been reported that alternan oligosaccharides derived from alternanase activity are used as low-glycemic sweeteners. Some studies state that these oligosaccharides are potential prebiotics (Leathers, Hayman, and Côté 1997), however *in vivo* trials in humans showed that they are slowly but fully digestible by human digestive enzymes in the gastrointestinal track (2008, Grysman, Carlson, and Wolever 2008; Vanschoonbeek et al. 2009). A recent study on α -glucan oligomers containing (α 1 \rightarrow 6) and (α 1 \rightarrow 3) linkages with DP ranging from 3-12, showed similar glucose and insulin response curves as the dextrose control in humans. In the same study, (α 1 \rightarrow 2) branching points were introduced into these oligomers, resulting in increased resistance to digestion *in vivo* in mice. However, this observation hasn't been confirmed in humans (Hasselwander et al. 2017).

Highly branched α -glucans

It has been shown that the shorter side chains make highly-branched starch less prone to α -amylase degradation resulting in a slower glucose release rate (Le et al. 2009; van der Maarel and Leemhuis 2013). Different enzymatic modification strategies have been successfully used to increase the degree of (α 1 \rightarrow 6) branching points in starch (e.g. treatment with branching enzymes). In experiments by Ao et al. (Ao, Quezada-Calvillo, et al. 2007; Ao, Simsek, et al. 2007), normal corn starch was modified through treatment with β -amylase, or β -amylase- and transglucosidase (BAMTG), or maltogenic α -amylase and transglucosidase (MAMTG). *In vitro* methods were used to analyze digestion rates of the derived starches by pancreatic α -amylase, pancreatin, and amyloglucosidase. Starch treated with MAMTG showed an *in vitro* digestion rate, measured by reducing sugars produced, after 10 (69%) and 180 min (55%) of digestion, compared to control untreated gelatinized corn starch (100%). Analysis of the slowest digesting starch from this experiment

showed considerably greater proportions of low molecular weight starch molecules with reduced amylopectin B₁ and B₂ branch chains (short and medium linear chain lengths in amylopectin), and lower ratios of (α 1 \rightarrow 4) to (α 1 \rightarrow 6)-linkages (13% (α 1 \rightarrow 6) in BAMTG-modified starch and 23% in MAMTG-modified starch). Thus, increased (α 1 \rightarrow 6)-linkages in shorter molecular size starch molecules had a slow and extended digestion (Le et al. 2009; van der Maarel and Leemhuis 2013). In a study by Lee et al in 2013, rats gavaged with a highly branched maltodextrin, made with maltogenic α -amylase together with β -amylase, had higher and extended blood glucose levels 1 hour postprandial than did those gavaged with unmodified starch or starch modified with just branching enzyme alone (Lee et al. 2013).

Pullulan

Pullulan is a linear polysaccharide consisting of maltotriose units interconnected by single (α 1 \rightarrow 6) glycosidic linkages (Table 2). This alternating pattern is responsible for the slow digestibility of pullulan in humans (Wolf et al. 2003). It is a white soluble polymer without taste and odor (Khan, Park, and Kwon 2007). It is produced from starch by the fungus *Aureobasidium pullulans* (Bender, Lehmann, and Wallenfels 1959). As a food additive, it is known by the E number E1204.

Enzymatic tools for the synthesis of novel α -glucans from sucrose and starch

In view of the above there remains a need for novel α -glucans from sucrose and starch that are less or only slowly digestible in the human body. Microbial α -transglycosylase enzymes acting on starch and sucrose substrates are known to convert the high glycemic index sucrose and starch carbohydrates into α -glucans of interest for the food industry. Some relevant commercial examples are the dextran and CDs, described above. In general, these α -transglycosylase enzymes are stable, they act on renewable cheap substrates, and display high regio- and stereo-selectivity. Other strategies for the production of α -glucans do not have these advantages. For example, chemical approaches require many tedious protection and deprotection steps of the hydroxyl groups in order to achieve regio- and stereo-selectivity, toxic catalysts and solvents. Other enzymatic strategies are based on the use of “Leloir” glycosyl transferases, which require expensive nucleotide-activated sugars (e.g. uridine diphosphate glucose) and will not be the focus of this review. According to the amino acid sequence-based CAZy classification system (<http://www.cazy.org/>), most of these sucrose- and starch-acting α -transglycosylases (EC 2.4.) are members of families GH13, GH31, GH57, GH70 and GH77, also covering hydrolases (i.e. amylase, α -glucosidases, E.C. 3.2.) and isomerases (i.e. isomaltulose synthase, trehalose synthase, E. C. 5.4.). Despite the fact that they differ in reaction and product specificity, members of these families employ a similar double displacement α -retaining mechanism which involves the cleavage of the α -glycosidic bond of the glucose

donor substrate and the formation of a covalent enzyme-glycosyl intermediate. In a second step, the enzyme-glycosyl intermediate reacts with an acceptor substrate, which can be a water molecule or an acceptor carbohydrate, yielding substrate hydrolysis or a new transglycosylation α -glucan product, respectively (Figure 3). In α -glycosidases or hydrolases (EC 3.2.), water usually acts as acceptor, whereas in α -transglycosylases the binding of an acceptor carbohydrate is favored; consequently, these latter enzymes naturally display very efficient transglycosylation activities (Light et al. 2017). Although α -glycosidases/hydrolases catalyze the hydrolysis of α -glucans *in vivo*, many of these enzymes display a certain degree of transglycosylation activity that can be used for synthesis of glycosidic bonds *in vitro*. For example, the transglycosylation activity of α -glucosidases (EC 3.2.1.20), neopullulanases (EC3.2.1.135) and maltogenic amylases (EC 3.2.1.133) has been used for the production of isomaltooligosaccharides and branched oligosaccharides (Goffin et al. 2011; Lee et al. 1995; Niu et al. 2017; Yoo et al. 1995). Many sucrose- and starch-acting enzymes have been characterized as natural α -transglycosylases with different specificities (<http://www.cazy.org/>). Interestingly, protein structure studies have provided important insights in the molecular basis for product specificity of several α -transglycosylases. This also has resulted in valuable clues for subsequent steps aiming to develop tailor-made enzyme variants capable of synthesizing any desirable α -glucan structures. Most of these sucrose- and starch-acting enzymes belong to the GH13, GH70 and GH77 families that constitute the GH-H clan. Members of the GH-H clan are evolutionarily related, displaying similar protein structures and activity mechanisms. GH13, GH70 and GH77 enzymes share a catalytic (β/α)₈ barrel domain and have four conserved amino acid sequence motifs containing the three catalytic Asp, Glu and Asp residues and some of the substrate binding residues (Leemhuis, Pijning, et al. 2013; Meng, Gangoiti, Pijning, and Dijkhuizen 2015) (Figure 4). GH31 enzymes differ in their catalytic residues, but they adopt a similar (β/α)₈ fold and were found to display a remote evolutionary relatedness with GH-H clan members (Janecek, Svensson, and MacGregor 2007). GH57 family enzymes, however, have a catalytic (β/α)₇ barrel domain and possess their own five conserved motifs and catalytic machinery (Suzuki and Suzuki 2016). The main types of natural α -transglycosylases used for the production of slowly digestible or less digestible α -glucans will be illustrated in the following sections. Particular attention will be given to the variety of existing sucrose- and starch-acting GH70 enzymes, reviewing the surge of new enzymes that have been characterized in recent years. Due to their broad product specificity, GH70 enzymes represent attractive enzymatic tools for the synthesis of tailor-made α -glucans with a defined glycemic response.

Cyclodextrin glucanotransferases

Cyclodextrin glucanotransferases (CGTase; EC 2.4.1.19) mainly convert starch into cyclic (α 1 \rightarrow 4)-linked oligosaccharides, named cyclodextrins (CDs). Depending on their

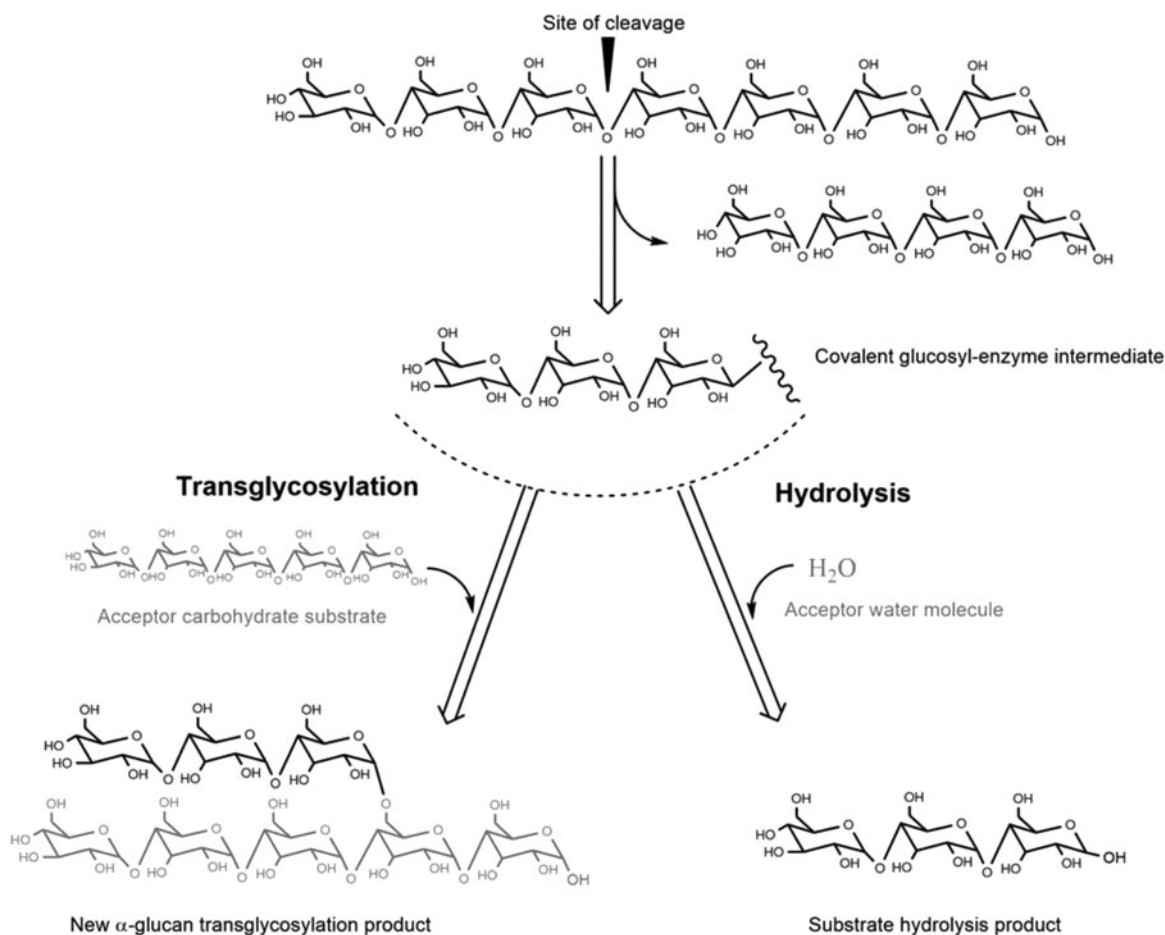


Figure 3. Examples of transglycosylation and hydrolysis reactions.

main CD product, as discussed above, these enzymes are classified as α -, β -, and γ -CGTases, with 6, 7 and 8 glucose units, respectively. Apart from their main cyclization activity, CGTases also catalyze hydrolysis and intermolecular transglycosylation reactions using linear ($\alpha 1 \rightarrow 4$) glucans (disproportionation reaction) or their own CD products (coupling reaction) as substrates, yielding linear products (van der Veen et al. 2000). CGTases are found in Bacteria and Archaea, and based on their sequences they are placed in the GH13 family, which is the largest family of glycoside hydrolases acting on starch and related α -glucans. Several three-dimensional structures of CGTases from bacteria of different genera (e.g. *Bacillus*, *Thermoanaerobacterium* and *Geobacillus*) are currently available without or complexed with several substrates (Han et al. 2014; Leemhuis, Kelly, and Dijkhuizen 2010). CGTase enzymes consist of 5 domains: A, B, C, D and E. Domains A, B and C are present in most GH13 family members (Figure 4). Domain A comprises the catalytic (β/α)₈ barrel, and together with domain B forms the substrate binding groove. Domains C and E participate in starch binding, whereas the role of domain D has remained unclear. The reaction mechanisms and substrate-binding subsites of CGTases have been analyzed in detail allowing identification of amino acid residues determining CD size specificity (Uitdehaag et al. 1999; Uitdehaag et al. 2000; van der Veen et al. 2000). Most CGTases synthesize a mixture of CD of different sizes, and thus, a selective

purification step is required to obtain a single type of CD only (Leemhuis, Kelly, and Dijkhuizen 2010). Using protein engineering approaches many CGTase variants with an improved α -, β -, and γ -CD selectivity have been obtained (Han et al. 2014; Leemhuis, Kelly, and Dijkhuizen 2010).

4- α -Glucanotransferases

4- α -Glucanotransferases (4- α -GTase; EC 2.4.1.25) also designated as amyloamylases, or D-enzymes, display disproportionating activity (see below) on starch-like substrates containing consecutive ($\alpha 1 \rightarrow 4$) glycosidic linkages (e.g. amylose, amylopectin, maltodextrins and glycogen). These enzymes are distributed in plants and microorganisms, where they participate in starch biosynthesis and glycogen metabolism, respectively (Boos and Shuman 1998; Colleoni et al. 1999; Wattedled et al. 2003). Enzymes with 4- α -GTase activity are distributed in the GH13, GH57 and GH77 families, only the GH77 family contains exclusively 4- α -GTases. Three-dimensional structures in free form or in complex with substrates are available for several GH77 family enzymes, including industrially important thermostable and thermoactive enzymes from *Thermus thermophilus* HB8 (PDB codes 1FP8 and 1FP9) (Kaper et al. 2007), *Thermus aquaticus* ATCC 33923 (PDB code 1CWY (Przylas et al. 2000)); and *Aquifex aeolicus* VF5 (PDB code 1TZ7;

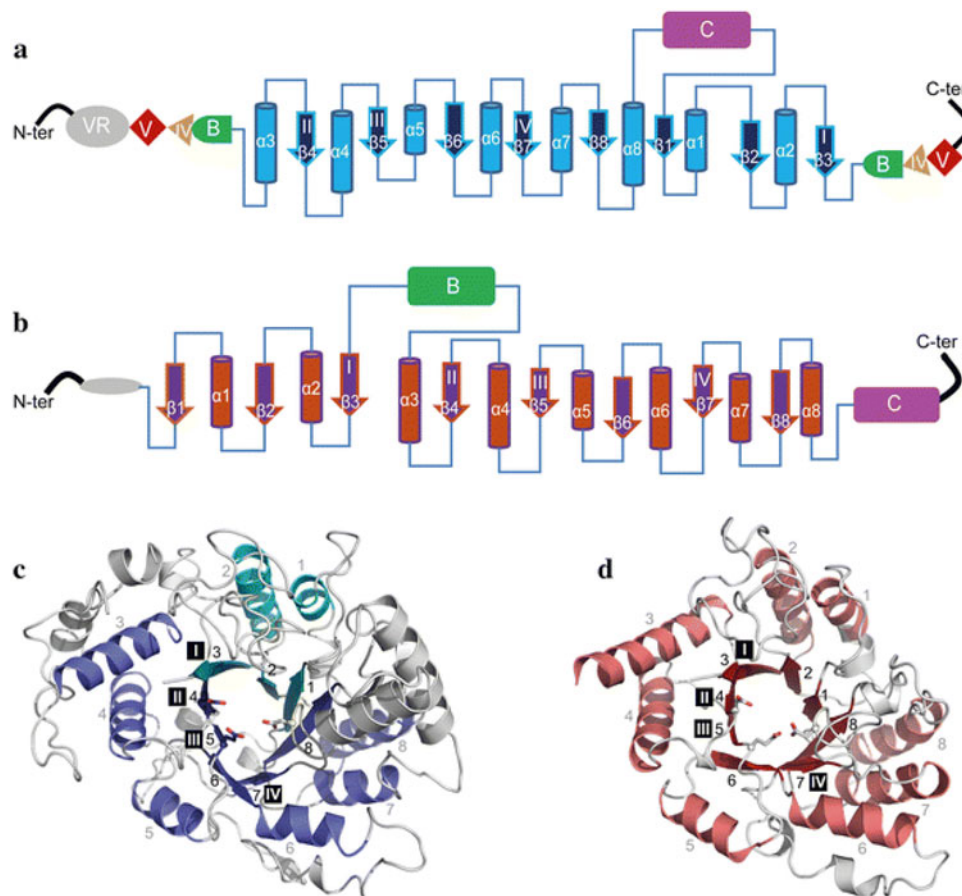


Figure 4. Topology diagram models of family GH70 Glucansucrases (GS) with a circularly permuted $(\beta/\alpha)8$ barrel (a) and the family GH13 α -amylase $(\beta/\alpha)8$ barrel (b). Cylinders represent α -helices and arrows represent β -strands. The equivalent α -helices and β -strands in GH70 GSs and GH13 α -amylases are numbered the same. The different domains in GH70 and GH13 enzymes are indicated. Domain C of GH70 GSs is inserted between α -helix 8 and β -strand 1 while that of GH13 family α -amylase locates C-terminally of the $(\beta/\alpha)8$ barrel. Domain B of GH13 α -amylases is inserted between β -strand 3 and α -helix 3 while that of GH70 GS is formed by two discontinuous polypeptide segments from both the N- and C-termini. The same is true for domains IV and V of GH70 GS. A variable region (VR) is present in the N-terminus of GH70 GSs. The four conserved sequence motifs (I–IV) which are located in β -strands 3, 4, 5, and 7, respectively, and are shared between family GH70 GS and GH13 enzymes, are indicated within the β -strand. The structure of the catalytic domain in the GH70 GS representative GTF180- Δ N (c, PDB: 3KLK) of *L. reuteri* 180 and in the GH13 representative α -amylase of *Bacillus licheniformis* (d, PDB: 1BPL). The $(\beta/\alpha)8$ barrel is colored for a better representation. α -Helices and β -strands are numbered, and the conserved sequence motifs (I–IV) are indicated at the corresponding β -strand. The circularly permuted $(\beta/\alpha)8$ barrel of GH70 GS is formed by two separate polypeptide segments (N-terminal parts colored in deep blue and C-terminal parts colored in cyan), which is caused by the insertion of domain C.

Uitdehaag et al., unpublished work). The main structural feature that distinguishes GH77 enzymes from the evolutionary related GH13 proteins is the lack of domain C. Crystal structures of 4- α -GTases belonging to the GH13 and GH57 protein families have also been solved from thermophilic organisms [e.g. the archaeon *Thermococcus litoralis* GH57 4- α -GTase (PDB codes 1K1W, 1K1X and 1K1Y (Imamura et al. 2003); and the bacterium *Thermotoga maritima* MSB8 GH13 4- α -GTase (PDB codes 1LWH, 1LWJ, 1GJU and 1GJW) (Roujeinikova et al. 2001; Roujeinikova et al. 2002). 4- α -GTases preferably catalyze the cleavage of an $(\alpha 1 \rightarrow 4)$ -glucan from the non-reducing end of a donor substrate and its transfer to the non-reducing end of an acceptor $(\alpha 1 \rightarrow 4)$ - α -glucan via the formation of a new $(\alpha 1 \rightarrow 4)$ glycosidic linkage. Amylomaltase activity on starch results in the formation of a starch derivative free of amylose (consumed as donor substrate) and consisting of an amylopectin product with a mixture of both shortened and elongated side-chains (Van der Maarel et al. 2005). This product (e.g. Etenia) can be used as a replacement of gelatin, which is an animal-derived

product widely used as a hydrocolloid in food. The presence of these relatively long chains, and its relatively high molecular weight, provide this polymer with thermoreversible gelling properties (Hansen et al. 2008). 4- α -GTase treated corn starch is rather resistant to digestion (Jiang et al. 2014). Some 4- α -GTases also catalyze intramolecular transglycosylation reactions resulting in the formation of large cyclic $(\alpha 1 \rightarrow 4)$ -glucans, designated as cycloamyloses (Terada et al. 1999). Structurally, cycloamyloses resemble cyclodextrins, however, they have a higher degree of polymerization (from 16 to several hundreds of glucose units). In view of their large ring size, cycloamyloses are not expected to display the slowly digestible properties described for α - and β -cyclodextrins, however, they may have many other applications in the pharmaceutical and biotech industry due to their capacity to encapsulate hydrophobic guest molecules within their hydrophobic cavity (Roth et al. 2017). Interestingly, the 4- α -GTase disproportionation activity, in combination with maltogenic amylase and pullulanase, has been used for the synthesis of starch-derived IMO and a

resistant starch-like product, respectively (Lee et al. 2002; Norman et al. 2007).

Branching Enzymes

Branching enzymes (BE, EC 2.4.1.18) act on (α 1 \rightarrow 4) glucans, cleaving an internal (α 1 \rightarrow 4) linkage and transferring the cleaved-off part to the same or another (α 1 \rightarrow 4) glucan chain via an (α 1 \rightarrow 6) branch point (Roussel et al. 2013; Shinohara et al. 2001). BE are widespread in nature and can be found in bacterial, archaeal, and eukaryotic species, where they catalyze the formation of (α 1 \rightarrow 6)-branching points during glycogen or starch biosynthesis (Suzuki and Suzuki 2016). BE are therefore critical determinants of the structure and properties of these intracellular storage polysaccharides. BE have gained substantial interest for the production of different starch-derived products such as highly-branched α -glucans (Kittisuban et al. 2014; Lee et al. 2013), synthetic glycogen (Kajiura et al. 2006), and CCD (Takata et al. 2003). In particular, thermostable glycogen BE enzymes from *Aquifex aeolicus* and *Rhodothermus obamensis* are the most commercially exploited (Van der Maarel and Leemhuis 2013). BE are placed in the GH13 and GH57 family proteins, which differ in their overall 3-dimensional structures, catalytic residues and geometry around the active site (Suzuki and Suzuki 2016). Numerous BE have been characterized showing differences in their substrate specificity and generating products with varied frequency and branch chain length. Whereas, some BE preferentially convert amylose (Binderup, Mikkelsen, and Preiss 2000; Hayashi et al. 2015; Palomo et al. 2011; Roussel et al. 2013), others display higher activity on amylopectin substrates (Jo et al. 2015; Palomo et al. 2009). Also, the minimal length of the donor glucan, the length of the transferred glucan, and the distance between two successive branch points differ from one BE to another (Hayashi et al. 2015; Jo et al. 2015; Palomo et al. 2009; Roussel et al. 2013; Sawada et al. 2014; Takata et al. 2003). Several experimental approaches including site-directed mutagenesis (Hayashi et al. 2017; Liu et al. 2017), domain-swapping and truncation experiments (Jo et al. 2015; Palomo et al. 2009; Welkie, Lee, and Sherman 2015) and X-ray crystallography studies (Abad et al. 2002; Feng et al. 2015; Hayashi et al. 2015; Na et al. 2017; Pal et al. 2010; Palomo et al. 2011) have been used to understand the mechanism of branching activity. Very recently the *Cyanothece* sp. ATCC 51142 BE1 structure with an oligosaccharide bound in the active site cleft has been solved providing a better understanding of the reaction catalyzed by these enzymes (Hayashi et al. 2017). However, the relationship between the reaction specificity (e.g. preferred chain lengths transferred) and the BE protein structure remains unclear, and it is possible that variation exists in the mode of oligosaccharide binding depending on the BE species (Hayashi et al. 2017). This information may allow a better control of the degree of branching and the average length of branches of the reaction product by the engineering of BE with altered specificity.

Amylosucrases

Amylosucrases (AS, EC 2.4.1.4) catalyze the synthesis of linear (α 1 \rightarrow 4) glucans from sucrose, and have been characterized from various bacterial sources (see below). Although most sucrose-active α -transglycosylases belong to the GH70 family (Monsan, Remaud, and Andre 2010), in view of its amino acid sequence AS have been classified in the GH13 family, mostly containing starch-acting enzymes. AS activity with sucrose results in synthesis of an amylose-like polymer with a molecular weight that is significantly lower (DP up to 8) (Potocki-Veronese et al. 2005) than the α -glucan polysaccharides synthesized by sucrose-utilizing GH70 members (Moulis, Andre, and Remaud-Simeon 2016). This (α 1 \rightarrow 4) glucan is insoluble and shows a high degree of B-type crystallinity, which makes this product resistant to hydrolysis by digestive enzymes (Norman et al. 2007). In addition to the amylose-like polymer, sucrose isomers are usually also formed by AS, which reduce the α -glucan yield. It has been proposed that AS *in vivo* are involved in energy storage through glycogen elongation (Albenne et al. 2004). In *in vitro* studies, when glycogen and other polymers containing (α 1 \rightarrow 4) or (α 1 \rightarrow 4) and (α 1 \rightarrow 6) linkages are used as acceptor substrates, AS elongate some of their external chains yielding polymers with higher slowly digestible and resistant starch content (Kim et al. 2014; Rolland-Sabaté et al. 2004; Shin et al. 2010). With the aim of designing α -glucans with defined structures using only sucrose as raw material, the *Neisseria polysaccharea* AS has been combined with other α -transglycosylases, including the BE from *Rhodothermus obamensis* and the CGTase from *Bacillus macerans*, resulting in the production of glycogen and cyclodextrins, respectively (Grimaud et al. 2013; Koh et al. 2016). AS have been identified in various bacterial species (e.g. *Deinococcus*, *Arthrobacter*, *Alteromonas*, *Methylobacillus*, *Synechococcus*); the AS from *N. polysaccharea* has been studied in most detail (Moulis, Andre, and Remaud-Simeon 2016). Crystal structures of AS in free form, and in complex with different substrates, have been solved (Guérin et al. 2012; Jensen et al. 2004; Mirza et al. 2001; Skov et al. 2013). In addition to the 3 domains A, B and C common to all GH13 family members (Figure 4), AS have 2 extra domains named N and B' that are unique to these enzymes. These 3D structures have allowed the identification of key residues involved in the polymerization process, and have guided the construction of AS mutants which produce in a controlled way either short maltooligosaccharides or insoluble amylose from sucrose (Albenne et al. 2004; Cambon et al. 2014; Schneider et al. 2009).

Dextran dextrinases

Some strains of *Gluconobacter oxydans* are known to produce an intracellular enzyme named dextran dextrinase (DDase, EC 2.4.1.2) catalyzing the synthesis of dextran using maltodextrins as substrate. DDase is able to transfer the non-reducing terminal glucosyl residues of maltodextrins to an acceptor substrate forming consecutive (α 1 \rightarrow 6) linkages (Naessens et al. 2005; Sadahiro et al. 2015). As a result of

this activity a dextran polymer is produced, which contains some ($\alpha 1 \rightarrow 4$) branches and ($\alpha 1 \rightarrow 4$) linkages in ($\alpha 1 \rightarrow 6$) glucosyl linear chains (Yamamoto, Yoshikawa, and Okada 1993). DDase also disproportionates ($\alpha 1 \rightarrow 6$) glucans indicating that it is also active on its own products. The gene encoding the DDase from *G. oxydans* ATCC 11894 has been recently identified revealing that the protein encoded belongs to the GH15 family. With the exception of the DDase from *G. oxydans* ATCC 11894, all characterized GH15 family members employ an inverting mechanism yielding β -anomeric products (Pedro M. Coutinho, "Glycoside Hydrolase Family 15" in CAZylopedia, available at URL <http://www.cazylopedia.org/>, accessed 19 May 2017). In view of its α -retaining mechanism, the DDase enzyme is an atypical member of the GH15 family.

Generation of structurally diverse α -glucans by novel GH70 α -transglycosylases

The GH70 family was established for glucansucrases (GS), exclusively found in lactic acid bacteria (LAB), which convert sucrose into high molecular mass α -glucan polymers (Leemhuis, Pijning, et al. 2013; Monchois, Willemot, and Monsan 1999). GS catalyze polymer synthesis by the successive transfer of single glucosyl units from sucrose to the non-reducing end of a growing glucan chain. Alternatively, in the presence of a low-molecular mass acceptor substrate such as maltose, GS switch from polysaccharide to low molecular mass oligosaccharide synthesis, using sucrose as donor substrate. The various characterized GS synthesize a large diversity of α -glucan products from sucrose, and with all possible linkages ($\alpha 1 \rightarrow 2$), ($\alpha 1 \rightarrow 3$), ($\alpha 1 \rightarrow 4$), and ($\alpha 1 \rightarrow 6$).

Also, these α -glucans may be linear or branched and may differ in their type and degree of branching, size, and conformation, resulting in oligo- and poly-saccharides with different physicochemical properties (e.g. viscosity, adhesiveness, solubility, etc.). The α -glucans synthesized by GS are classified into four categories based on their dominant glycosidic linkage type: dextran with a majority of ($\alpha 1 \rightarrow 6$) linkages, mutan with a majority of ($\alpha 1 \rightarrow 3$) linkages, reuteran with a majority of ($\alpha 1 \rightarrow 4$), and alternan with alternating ($\alpha 1 \rightarrow 3$) and ($\alpha 1 \rightarrow 6$) linkages (Table 3). Three-dimensional structures are available for 5 GS proteins with different product specificity (Brison et al. 2012; Ito et al. 2011; Pijning et al. 2012; Vujicic-Zagar et al. 2010). These crystal structures show that in GS the catalytic (β/α)₈-barrel domain is circularly permuted compared to GH13 and GH77 enzymes, confirming earlier predictions (MacGregor, Jespersen, and Svensson 1996). Interestingly, GS display a unique U-fold organized in five structural domains (A, B, C, IV and V) (Figures 4 and 5). The domains A, B and C form the catalytic core, and are also found in GH13 enzymes, whereas the remote domains IV and V are only present in GH70 enzymes. Thus far, 60 GS enzymes have been characterized (www.cazy.org, 21st September 2017), most of them producing dextran polymers. The industrially most relevant GS is the *Leuconostoc mesenteroides* NRR B-512F DSR-S dextranucrase converting sucrose into a polymer with 95% ($\alpha 1 \rightarrow 6$) linkages in the main chains and 5% ($\alpha 1 \rightarrow 3$) branch linkages (Monchois et al. 1997; Passerini et al. 2015). In addition, GH70 enzymes displaying dextran branching specificity have been identified providing novel tools for the production of dextrans with a controlled degree of ($\alpha 1 \rightarrow 2$) and ($\alpha 1 \rightarrow 3$) branching points (Brison et al. 2010, 2012; Vuillemin et al. 2016). First, *L. mesenteroides* NRRL B-1299

Table 3. Examples of products synthesized by sucrose- and starch-active GH70 enzymes.

Enzyme	Substrate	Linkage composition of the product (%)			
		($\alpha 1 \rightarrow 2$)	($\alpha 1 \rightarrow 3$)	($\alpha 1 \rightarrow 4$)	($\alpha 1 \rightarrow 6$)
Dextran					
<i>Leuconostoc mesenteroides</i> NRRL B-512F DSR (Monchois et al. 1997)	Sucrose		5		95
<i>Leuconostoc citreum</i> B-1299 DSRE ^a (Fabre et al. 2005)	Sucrose	5	10	3	81
<i>Leuconostoc citreum</i> B-1299 BSR-A (Passerini et al. 2015)	Sucrose and linear dextran	37			63
<i>Leuconostoc citreum</i> BSR-B (Vuillemin et al. 2016)	Sucrose and linear dextran		50		50
<i>Weissella cibaria</i> DSRWC (Kang, Oh, and Kim 2009)	Sucrose				100
<i>Lactobacillus reuteri</i> 180 Gtf180 (van Leeuwen et al. 2008)	Sucrose		31		69
<i>Streptococcus mutans</i> GS5 GTFD (Hanada and Kuramitsu 1989)	Sucrose		30		70
Mutan					
<i>Streptococcus mutans</i> GS5 GTFB (Shiroza, Ueda, and Kuramitsu 1987)	Sucrose		88		12
<i>Lactobacillus reuteri</i> ML1 (Kralj et al. 2004)	Sucrose		65		35
<i>Leuconostoc mesenteroides</i> NRRL B-1118 DSRI (Côté and Skory 2012)	Sucrose		50		50
Alternan					
<i>Leuconostoc mesenteroides</i> NRRL B-1355 ASR (Côté and Robyt 1982)	Sucrose		43		57
Reuteran					
<i>Lactobacillus reuteri</i> 121 GtfA (Kralj et al. 2002)	Sucrose			58	42
<i>Lactobacillus reuteri</i> ATCC 55730 GtfO (Kralj et al. 2005)	Sucrose			79	21
<i>Azotobacter chroococcum</i> NCIMB 8003 GtfD (Gangoiti, Pijning, and Dijkhuizen 2016)	Amylose			68	32
<i>Lactobacillus reuteri</i> NCC 2613 GtfB (Gangoiti, van Leeuwen, Meng, et al. 2017)	Amylose			75	25
Isomalto/Malto-Polysaccharide					
<i>Lactobacillus reuteri</i> 121 GtfB (Leemhuis et al. 2014)	Amylose			9	91
Isomalto/Malto-Oligosaccharide					
<i>Exiguobacterium sibiricum</i> GtfC (Gangoiti et al. 2015)	Amylose			40	60
Branched ($\alpha 1 \rightarrow 3$), ($\alpha 1 \rightarrow 4$)-α-glucan					
<i>Lactobacillus fermentum</i> NCC 2970 GtfB (Gangoiti, van Leeuwen, Meng, et al. 2017)	Amylose		40	60	

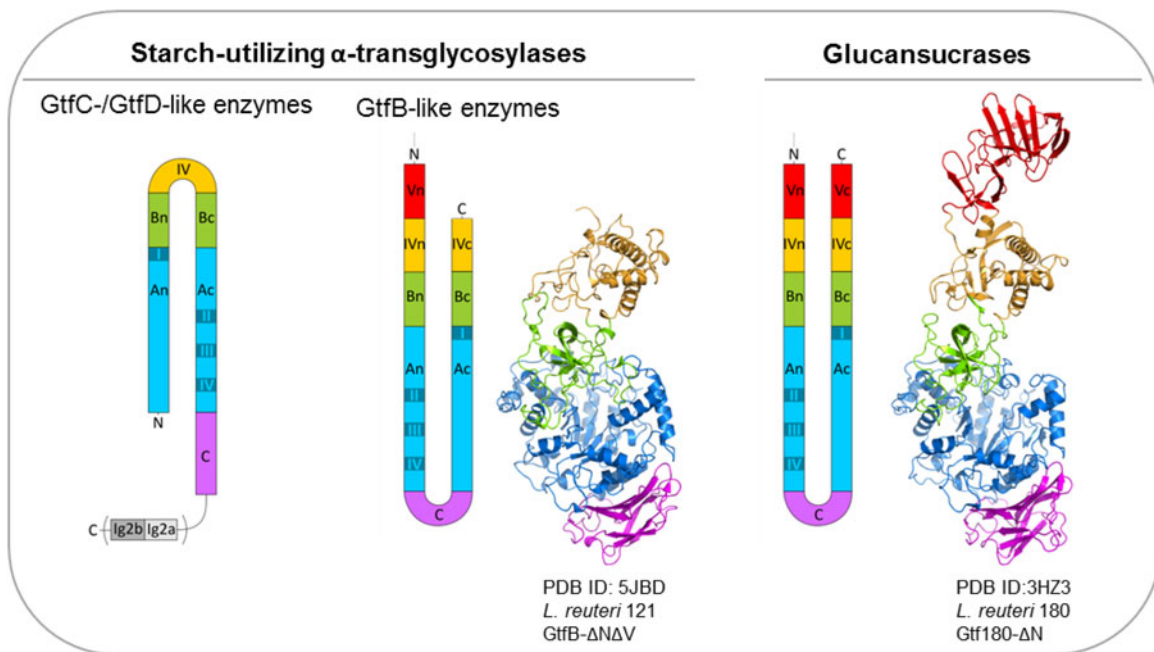


Figure 5. Domain arrangement of sucrose- and starch-converting GH70 enzymes.

Crystal structures of the *L. reuteri* 121 GtfB 4,6- α -GTase (middle), and the *L. reuteri* 180 Gtf180 GS (right). Domains A, B, C, IV and V are highlighted in blue, green, magenta, yellow and red, respectively. Ig2-like domains are colored in grey. As apparent from the order of the conserved regions (indicated by grey rectangles), the catalytic barrel of the GH70 glucansucrases and GH70 GtfB-like enzymes is circularly permuted (order = II-III-IV-I).

was found to encode two GH70 enzymes (named DSRE and BRS-A) specialized in (α 1 \rightarrow 2) transglycosylation from sucrose to a dextran acceptor substrate (Brison et al. 2012; Passerini et al. 2015). The gluco-oligosaccharides containing (α 1 \rightarrow 2) linkages synthesized by *L. mesenteroides* NRRL B-1299 DSRE were found to be highly resistant to the action of digestive enzymes in both humans and animals (Valette et al. 1993). Recently, genome analysis of *Leuconostoc citreum* NRRL B-742 allowed the identification of the first (α 1 \rightarrow 3) branching sucrose (named BRS-B) responsible for the high content of (α 1 \rightarrow 3) branching linkages present in the dextran produced by this strain (Vuillemin et al. 2016).

In recent years, novel GH70 enzymes inactive on sucrose, but displaying clear disproportionating activity on starch/maltodextrin substrates, have been identified (Table 3) (Gangoiti et al. 2015; Gangoiti, Pijning, and Dijkhuizen 2016; Gangoiti, Lamothe, et al. 2017; Gangoiti, van Leeuwen, Gerwig, et al. 2017; Gangoiti, van Leeuwen, Meng, et al. 2017; Kralj et al. 2011; Leemhuis, Dijkman, et al. 2013). Regarding their substrate specificity, these starch-converting GH70 enzymes resemble GH13 family enzymes also acting on starch-like substrates, however, they share higher amino acid sequence similarity with GS from the GH70 family. Based on their sequences, these enzymes were classified into 3 new GH70 subfamilies designated as GtfB, GtfC and GtfD, which differ in their microbial origin, product specificity and domain organization (Gangoiti et al. 2015; Gangoiti, Pijning, and Dijkhuizen 2016; Gangoiti, van Leeuwen, Gerwig, et al. 2017; Kralj et al. 2011). Whereas GtfB enzymes are mainly found in *Lactobacillus* strains and display a GS-like fold with a circularly permuted catalytic (β/α)₈-barrel, GtfC and GtfD enzymes are present in non-LAB and possess a non-permuted domain organization

resembling that of GH13-like enzymes (Figure 5) (Gangoiti et al. 2015; Gangoiti, Pijning, and Dijkhuizen 2016; Gangoiti, Lamothe, et al. 2017). In view of their intermediate position between GH13 α -amylases and GH70 GS, the emergence of GtfB, GtfC and GtfD type of enzymes have provided clues about the evolutionary history of GH70 family proteins. It has been proposed that evolution from an ancestor α -amylase to present-day GS occurred via these GtfB-, GtfC-, and GtfD-like intermediates (Gangoiti et al. 2015; Gangoiti, Pijning, and Dijkhuizen 2016; Gangoiti, van Leeuwen, Gerwig, et al. 2017; Kralj et al. 2011). In addition to their scientific relevance, GtfB, GtfC and GtfD type of enzymes represent very interesting and powerful enzymatic tools for the conversion of the starch present in food matrices into soluble novel dietary fibers and/or slowly-digestible carbohydrates, and thus, they have gained substantial interest for the development of healthier starchy food products (Gangoiti, van Leeuwen, Meng, et al. 2017). However, only few starch-converting GH70 enzymes have been characterized so far. Whereas GS display a broad linkage specificity, most of the starch-converting GH70 enzymes characterized act as 4,6- α -glucanotransferases (GTases), cleaving (α 1 \rightarrow 4) linkages and synthesizing new (α 1 \rightarrow 6) linkages (Table 3). Depending on the enzyme, different products are synthesized as a result of this 4,6- α -GTase activity on starch/maltodextrin substrates. For example, the *Lactobacillus reuteri* 121 GtfB and *Exiguobacterium sibiricum* 255-15 GtfC disproportionation activity on starch-like substrates results in the synthesis of linear IsoMalto-/Malto-Polysaccharides (IMMP) and IsoMalto-/Malto-Oligosaccharides (IMMO) (Figure 6), respectively (Gangoiti et al. 2015; Leemhuis et al. 2014). Both IMMP and IMMO are 'hybrid molecules' and consist of linear (α 1 \rightarrow 6) glucan chains attached to the non-reducing

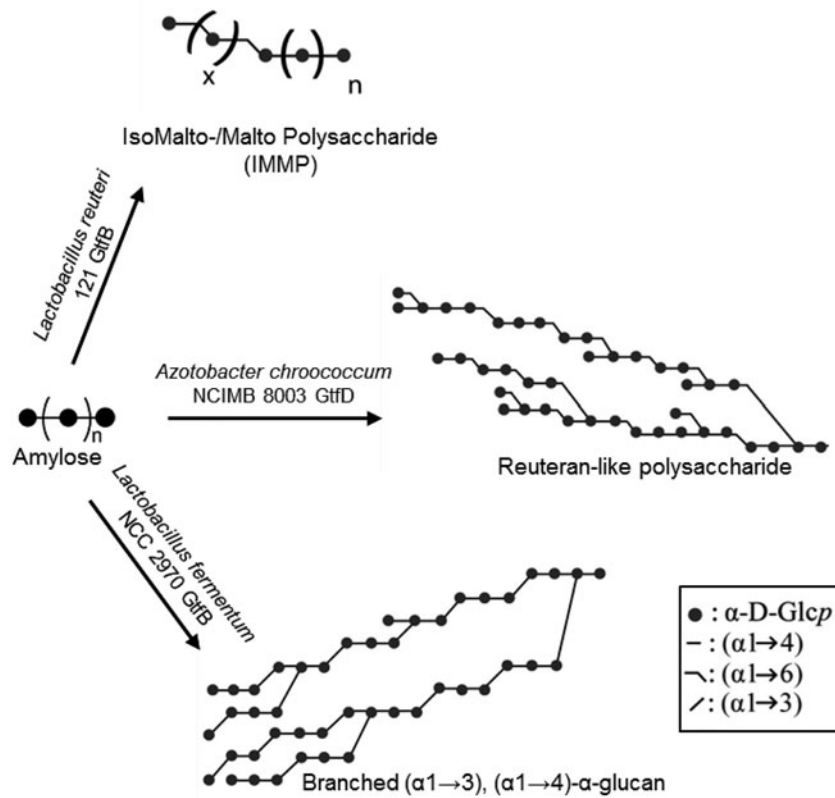


Figure 6. Composite models of representative novel α -glucans synthesized by starch-converting GH70 enzymes.

ends of starch or malto-oligosaccharide fragments, but they significantly differ in their molecular mass. Unlike the *L. reuteri* 121 GtfB and *E. sibiricum* GtfC enzymes, the *Azotobacter chroococcum* and *Paenibacillus beijingensis* GtfD 4,6- α -GTases are unable of forming consecutive (α 1 \rightarrow 6) linkages. Using these GtfD enzymes, branched polymers containing mostly (α 1 \rightarrow 4) linkages and single (α 1 \rightarrow 6) bridges in linear and branched orientations are obtained from amylose (Figure 6) (Gangoiti, Pijning, and Dijkhuizen 2016; Gangoiti, Lamothe, et al. 2017; Meng, Gangoiti, Pijning, and Dijkhuizen 2016). These polymers resemble the reuteran polysaccharide synthesized by the *L. reuteri* 121 GtfA GS from sucrose (Dobruchowska et al. 2013; Meng, Dobruchowska, et al. 2016; Meng, Pijning, et al. 2016; van Leeuwen et al. 2008), described as a health-promoting food ingredient (Ekhart et al. 2006; Plijter et al. 2009). *In vitro* digestibility assays, using either pancreatic α -amylase and amyloglucosidase or rat intestinal maltase-glucoamylase and sucrase-isomaltase, simulating the digestive power of the gastrointestinal tract revealed that the IMMP and reuteran type of polymers have a high dietary fiber content (Gangoiti, Lamothe, et al. 2017; Leemhuis et al. 2014). The limited diversity in linkage specificity found within these starch-converting GH70 subfamilies of enzymes recently was expanded with the discovery of the *Lactobacillus fermentum* NCC 2970 GtfB displaying 4,3- α -GTase activity (Gangoiti, van Leeuwen, Gerwig, et al. 2017). This *L. fermentum* NCC 2970 GtfB converts amylose into a branched α -glucan composed of linear (α 1 \rightarrow 4) segments interconnected by single (α 1 \rightarrow 3)

and (α 1 \rightarrow 3,4) linkages (Figure 6). The characterization of this *L. fermentum* NCC 2970 GtfB 4,3- α -GTase represents an important breakthrough because its 4,3- α -glucan product is unique and different from other naturally occurring, synthetic and enzymatically produced α -glucans.

Compared to the limited linkage specificity displayed by other sucrose- and starch-converting α -transglycosylases, glucans with different types of glycosidic linkages can be obtained [(α 1 \rightarrow 2), (α 1 \rightarrow 3), (α 1 \rightarrow 4) and (α 1 \rightarrow 6)] by using GS. Over the years, many studies have tried to elucidate what determines the glycosidic linkage specificity in GS enzymes, resulting in synthesis of such a large variety of α -glucans. Variations in product specificity were proposed to be determined by the way in which the acceptor α -glucan is guided into the catalytic center (Leemhuis, Pijning, et al. 2013; Vujicic-Zagar et al. 2010). The crystal structure of GTF180- Δ N in complex with maltose revealed the residues interacting with this acceptor substrate in subsites +1 and +2 (Vujicic-Zagar et al. 2010). Mutagenesis of these key residues have demonstrated that it is the interplay of different amino acid residues defining the acceptor binding subsites what determines the glycosidic linkage specificity in GS (Meng, Pijning, et al. 2015; Meng, Dobruchowska, et al. 2016; Meng et al. 2017). These studies also have shown that predicting the effects of mutations is still complicated. Nevertheless, mutant variants have been obtained producing α -glucans differing in their linkage type, degree of branching, and/or molecular weight. These studies have been recently reviewed by Meng, Gangoiti, Pijning, and

Dijkhuizen (2016). Overall, these efforts have significantly enlarged the panel of α -glucans that can be enzymatically produced. Despite the lack of data related to their physico-chemical properties, this structural variability is expected to result in differences in a wide range of specific properties, such as solubility, viscosity and resistance to enzymatic hydrolysis by digestive enzymes. Another important advance in GH70 research was the elucidation of the *L. reuteri* 121 GtfB 4,6- α -GTase 3D structure (Figure 5). However, binding of oligosaccharides at the acceptor binding subsites has not been observed yet in any of the *L. reuteri* 121 GtfB crystal structures obtained (Bai et al. 2017). It also remains to be studied whether the repertoire of α -glucans synthesized by the starch-converting GtfB, GtfC and GtfD GH70 enzymes could be further expanded by protein engineering approaches. Very recently, the structure of the DSR-M dextranase from *Leuconostoc citreum* NRRL B-1299, producing a single low molar mass dextran has been reported providing important clues about the structural features determining glucan size (Claverie et al. 2017).

Attempts to diversify the structure and product size distribution of the α -glucans synthesized by GS using reaction engineering approaches already have been reported. Specifically, the effects of sucrose and enzyme concentrations, temperature and pH have been evaluated. Studies by Robyt and co-workers have shown that the molecular size of dextran is inversely proportional to the concentration of dextranase, and directly proportional to the concentration of sucrose and the temperature (Falconer, Mukerjea, and Robyt 2011; Robyt, Yoon, and Mukerjea 2008). Thus, it was proposed that the best method to obtain α -glucans with a defined molecular mass was the selection of specific enzyme/sucrose concentrations and temperature values. In case of the *L. mesenteroides* B-512FMCM dextranase, changes in sucrose concentration and temperature were found to affect the product size distribution, whereas the pH of the reaction did not have a significant effect (Kim et al. 2003). In a more recent study, synthesis of reuteran by *L. reuteri* 121 GtfA GS at different sucrose concentrations revealed that the ratio of polysaccharide versus oligosaccharide can be modulated by sucrose concentrations (Meng, Dobruchowska, et al. 2015). With increasing sucrose concentrations, the production of polysaccharides decreased, while the amount of oligosaccharides increased. However, the linkage distribution and molecular mass of the polysaccharides synthesized at different sucrose concentration was not changed. Another strategy to direct the synthesis toward the production of oligosaccharides at the expense of polymer formation is by adding “good” acceptor substrates (e.g. maltose or isomaltose) to the reaction (Côté and Sheng 2006; López-Munguía et al. 1993; Meng, Gangoiti, Pijning, and Dijkhuizen 2016; Su and Robyt 1993). In the presence of low-molecular mass acceptor sugars, GS transfers the glucosyl moieties from sucrose to the acceptor molecule, forming a series of oligosaccharides. The final product distribution can be varied by changing the reaction ratios of sucrose, acceptor substrate and enzyme. A similar approach was used for the synthesis of dextrans with a controlled degree of

($\alpha 1 \rightarrow 2$) and ($\alpha 1 \rightarrow 3$) linkages using branching sucrases (Brison et al. 2010; Vuillemin et al. 2016). As dextran is the natural acceptor of branching sucrases, the amount of ($\alpha 1 \rightarrow 2$) and ($\alpha 1 \rightarrow 3$) side chains was found to be directly dependent on the initial [Sucrose]/[Dextran] molar ratio. Using a suitable [Sucrose]/[Dextran] ratio, dextran polymers grafted with up to 30% of ($\alpha 1 \rightarrow 2$) linkages and 50% of ($\alpha 1 \rightarrow 3$) linkages, were obtained using the GBD-CD2 and BRS-B enzymes, respectively (Brison et al. 2010; Brison et al. 2012; Vuillemin et al. 2016).

Conclusions

The discovery of novel α -transglycosylases with diverse product specificities has provided important tools for the conversion of starch or sucrose into commercially-valuable slowly digestible or resistant α -glucans. These new carbohydrate ingredients hold a promise of providing digestion controlled materials that can modulate glycemic response or being new dietary fiber sources. At present, α -glucans with different structures (linkage type, branching degree) can be produced by using selected α -transglycosylases. These structural differences result in different digestion rates. A further understanding of the relationship between the structure of these α -glucans and their digestibility is key for the development of α -glucans with a tailored glycemic response. In parallel, a deeper comprehension of α -transglycosylases specificities at the molecular level is still needed to guide the rational design of enzyme variants capable of synthesizing any type of desirable α -glucan regardless of size, linkage type and degree of branching of the product. These joint efforts are expected to allow the synthesis of health-promoting α -glucans of interest for the food-industry.

Declaration of Conflicting Interests

The author(s) declared the following potential conflicts of interest with respect to the research, authorship, and/or publication of this article: LML and CV are employed by the Nestlé Research Center. BRH and LD have received grant/research support from Nestlé Research Center, at least partly used to employ JG and SFG. Authors have jointly filed multiple patent applications around this topic of research and potential products.

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