fermentation

MDPI

Review

Food Industrial Production of Monosaccharides Using Microbial, Enzymatic, and Chemical Methods

Tomoya Shintani

United Graduate School of Agriculture, Ehime University, Matsuyama 790-8577, Japan; 6742004b@stu.kagawa-u.ac.jp; Tel.: +81-6-6621-5122

Received: 8 May 2019; Accepted: 6 June 2019; Published: 11 June 2019

Abstract: Most monosaccharides in nature are hexoses, which have six carbon atoms; the most well-known hexose is D-glucose. Various hexoses with distinct characteristics can be produced from inexpensive polysaccharides for applications in the food industry. Therefore, identification of the health-related functions of hexose will facilitate the consumption of hexoses in food products to improve quality of life. The hexoses available in foods include *N*-acetyl glucosamine, D-glucosamine, D-fructose, D-mannose, D-galactose, other D-hexoses, and L-hexoses. Here, an updated overview of food industrial production methods for natural hexoses by microbial, enzymatic, and chemical methods is provided.

Keywords: food ingredients; food enzymes; fermentation process; downstream processing; *N*-Acetyl glucosamine; D-glucosamine; D-fructose; D-galactose; L-sugars; monosaccharides

1. Introduction

In nature, carbohydrates exist mainly as polysaccharides, including chitin, chitosan, cellulose, and starch (Figure 1). Most monosaccharides making up these polysaccharides are hexoses, which have six carbon atoms. D-Glucose is a representative hexose. Hexoses are produced at an industrial scale for food production using polysaccharides that are abundant in nature and available at low cost. Thus, identification of hexoses with functional value may facilitate the improvement of the human diet and lead to greater quality of life. In this review, various hexoses are described (e.g., *N*-acetyl-D-glucosamine (GlcNAc), D-glucosamine, D-fructose (Fru), D-mannose, D-galactose, other D-hexoses, and L-hexoses) and the health benefits and industrial production methods of natural hexoses for use in dietary supplements, processed foods, and beverages, are discussed.

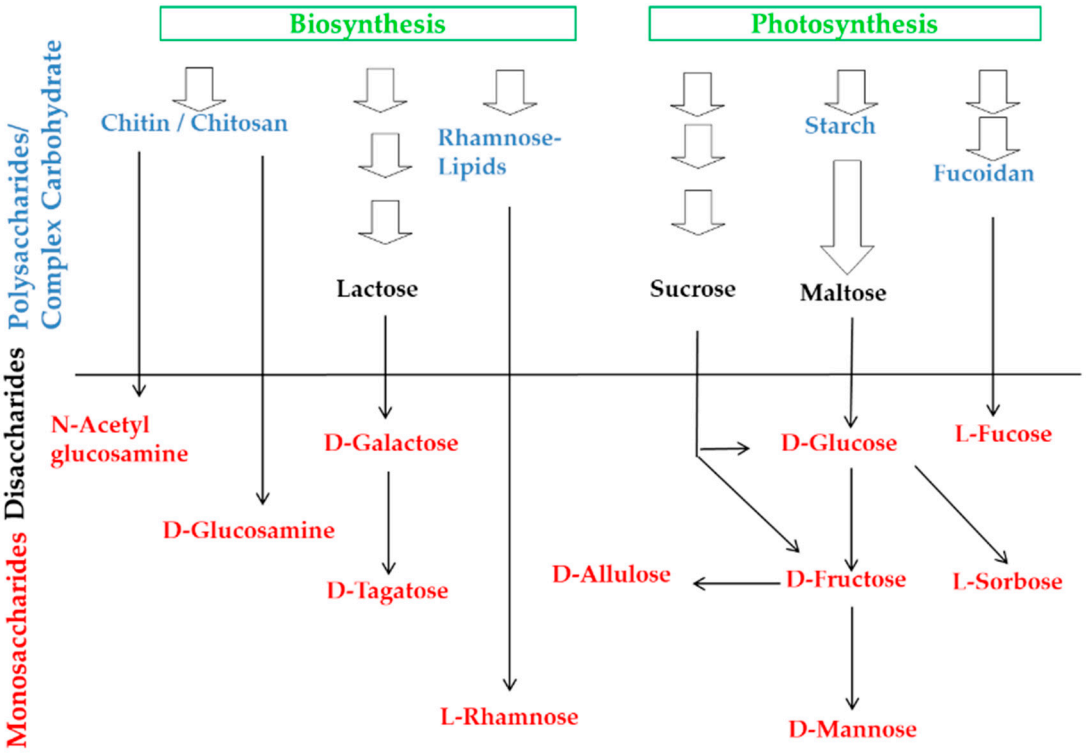

Figure 1. Hexoses derived from natural resources in the food industry.

2. *N*-Acetyl-D-Glucosamine

GlcNAc is a monosaccharide in which the 2-hydroxyl group of glucose is substituted with an acetylamino group (Figure 2). GlcNAc is a chitin-based monomer that is found in animal casings, such as those of insects and crustaceans. In the human body, this amino sugar is a component of the extracellular matrix and the sugar chain of glycoprotein [1]. In foods, GlcNAc is also found in milk [2].

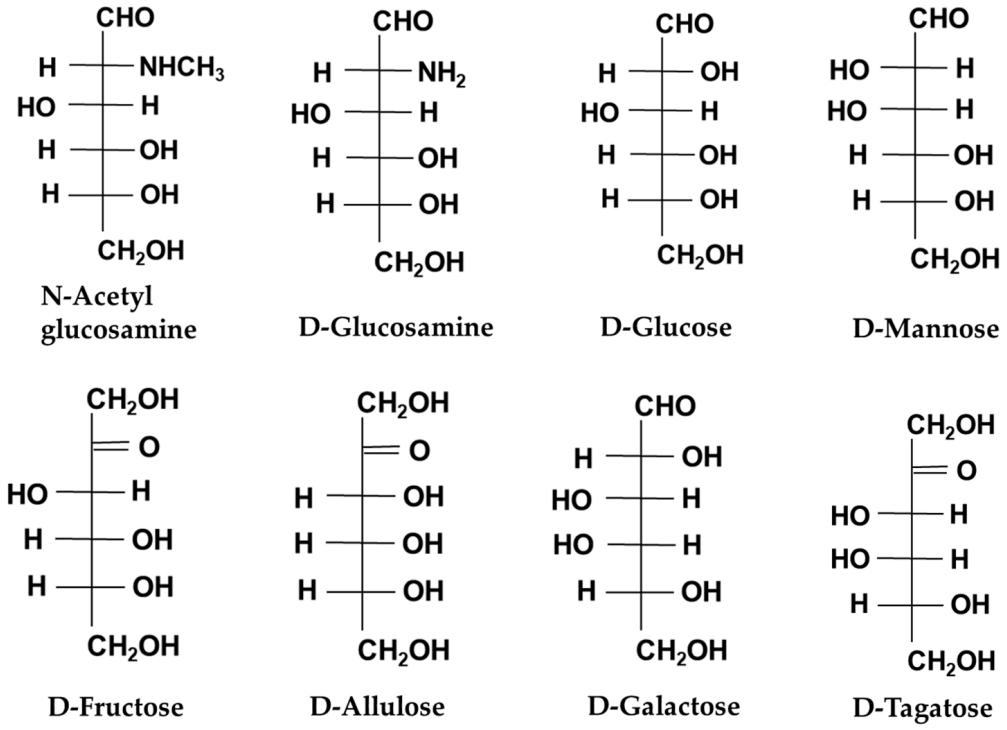

Figure 2. D-Hexoses in the food industry.

Chitin from shells of crabs and shrimps is mildly hydrolyzed into chitin oligosaccharides [3]. Chitin oligosaccharides are degraded by chitinase [4]. However, it is difficult to obtain GlcNAc inexpensively using this method, and the amino group of the molecule is largely enhanced under acid conditions, needing precise control of the reaction. A method in which chitinase and a reverse osmosis membrane were combined was developed for efficient production of GlcNAc [5]. Recently, Zhang et al. presented an efficient and integrated affinity adsorption-enzymatic reaction to produce GlcNAc from crude chitin powder [6]. The product GlcNAc was easily separated from hydrolysates after destaining, concentrating, crystallizing, and drying processes with a high purity of 98%. Additionally, a high yield of 29.6 g/L GlcNAc from 30 g/L chitin as the substrate was reported.

GlcNAc has low solubility in water and is a neutral molecule that is different from glucosamine (2-amino-2-deoxy-D-glucose (GlcN)), which contains a free amino group. Thus, it is necessary to refine the reaction solution by cooling crystallization after desalting the GlcNAc-containing solution after the reaction [4]. The production of GlcNAc is more complex and demanding than that of GlcN; accordingly, the cost of GlcNAc production is higher than that of GlcN production, despite the fact that the raw material is the same as chitin (Table 1).

Table 1. Characteristics of hexose production and its use.

Sugar	Production Method	Use or Origin Microbe	Raw Material	Use	Health Benefits	References
N-Acetyl-D-glucosamine	Enzymatic/Acidic hydrolysis	*Streptomyces* species	Chitin	Dietary supplement	Skin health	[3–5]
D-Glucosamine	Hydrolysis by HCl	-	Chitin/Chitosan	Dietary supplement	Joint health/Anti-aging	[7–9]
D-Fructose	Immobilized enzyme from hydrolysis	*Streptomyces* species	Glucose from starch	Bulk sweetener	Low glycemic response	[10–14]
D-Mannose	Immobilized enzyme/Hydrolysis by HCl	*Agrobacterium radiobacter*	Fructose/Mannan	Dietary supplement	Prevention of urinary-tract infection	[15–18]
D-Allulose	Immobilized enzyme/Alkaline reaction by NaOH	*Arthrobacter* species	Fructose	Food ingredient	Anti-metabolic syndrome	[19–21]
D-Galactose	Enzymatic hydrolysis	*Kluyveromyces* species	Lactose	Food ingredient	Immunostimulation	[22,23]
D-Tagatose	Immobilized enzyme/Alkaline reaction by CaOH	*Thermotoga* species	Galactose	Food ingredient	Anti-metabolic syndrome/Tooth friendly	[24–26]
L-Sorbose	Fermentation	*Gluconobacter* or *Acetobacter* species	Sorbitol from glucose	Sweetener	Low calorie	[27,28]
L-Fucose	Hydrolysis by HCl	-	Fucoidan	Food ingredient	Immunostimulation	[29–31]
L-Rhamnose	Fermentation extraction	*Acinetobacter* species	A *Rhamnus* or *Toxicodendron vernix* plant	Cosmetic/Food ingredient	Skin health	[32,33]

3. D-Glucosamine

GlcN is the main unit of chitosan and chitin, which are produced in nature by arthropods, fungi, and cephalopods. GlcN is different from GlcNAc with regard to the presence or absence of the free amino group. GlcN is industrially manufactured for dietary supplements by the hydrolysis of crustacean exoskeletons, which are mainly composed of chitin. GlcN has been reported to prevent and treat osteoarthritis in humans [7,34] and has been found to alleviate symptoms of skin aging in a clinical study [35].

To produce GlcN, shells of crustaceans, such as crabs and shrimps, are generally used as the starting material. Chitin extracts are purified to remove protein in a dilute sodium hydroxide solution, followed by dicalcium treatment in dilute hydrochloric acid (Figure 3). Next, the purified chitin (α-chitin) is hydrolyzed at a high temperature in concentrated hydrochloric acid to produce GlcN [8]. To obtain highly purified GlcN for use in the food industry, the GlcN is dissolved in water, impurities are filtered out, and low-temperature concentration is performed [9]. GlcN is a polar molecule; thus, cation/anion ion exchange is usually employed. Refinement is performed using a trap during ion exchange, and the trap is released by HCl to yield pure GlcN as GlcN-Cl salt. The crystallization is conducted using salt, resulting in lower solubility, which is called "salting-out". Bao et al. reported three enzymes, isolated from *Thermococcus kodakaraensis*, that catalyze the sequential conversion of α-chitin into GlcN and developed a multi-enzyme assembly cascade system immobilized on a biofilm, which enabled a one-pot reaction [36]. This system also exhibited a superior reaction temperature, good pH stability, and high survival rate for enzyme activity.

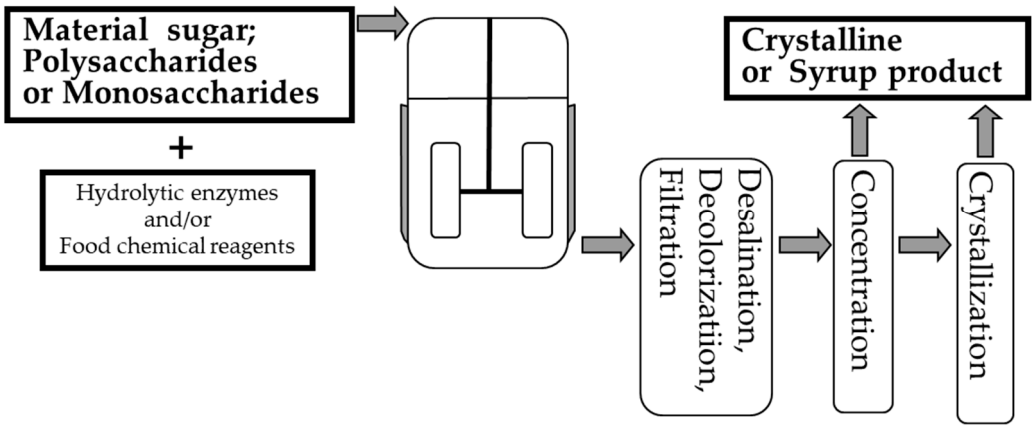

Figure 3. Schematic diagram of hexose production using hydrolytic enzymes or food chemical reagents.

4. D-Fructose

Fru is an isomer of D-glucose (Figure 2). Fru is the most popular hexose in the food industry (except D-glucose) and is present in most fruits, including grapes, bananas, strawberries, oranges, and apples [10]. This monosaccharide is a component of sucrose and is highly sweet (140% the sweetness of sucrose), leading to its frequent use in the food industry, particularly for beverage production. Thus, Fru consumption is common in the beverage industry, in which more sweetness is often needed [10]. In the field, Fru is used as a mixture of glucose and Fru, e.g., high Fru corn syrup, which is easy and inexpensive to manufacture from glucose. Notably, Fru may have health benefits compared with some other sugars because of its low glycemic response [37]. On the other hand, excessive consumption of Fru could lead to metabolic syndrome, which has become a problem [38,39].

The corn industry produces abundant amounts of D-glucose, which is a simple product of starch hydrolysis. In the 1960s and 1970s, Takasaki and other researchers found an enzyme that catalyzed the conversion of glucose to Fru [40–42], whereas Kainuma developed an alkaline isomerization to produce Fru from D-glucose [43,44]. Owing to some difficulties with this latter chemical method, the enzymatic method is more commonly used in the corn industry [11]. Immobilized enzymes for

glucose isomerase (Fru-producing enzyme) have also been developed [12,13]. Industrial production of Fru is one of the first examples of the industrial utilization of immobilized enzymes.

D-Glucose solutions containing 50–60% glucose can be incubated at 50–70 °C for reaction through an immobilized *Streptomyces* species enzyme, which is obtained after immobilizing the enzyme and/or microorganism using a carrier binding and covalent bonding method with polymers. The mixture of D-glucose and Fru can be separated chromatographically after desalination. High-purity Fru syrup undergoes crystallization at 10–50 °C after concentration (Figure 4). Thus, Fru crystals are continuously produced [14] and refined. The raw material, i.e., D-glucose solution, is easily obtained from the corn industry, thereby reducing the cost of Fru. Recently, as research and development in the starch industry has progressed, starches have been produced at lower costs than other carbohydrates. Accordingly, the starch industry tends to use starch or starch degradation products as research and development materials. For example, 1,5-anhydro-D-fructose, which is a product of the starch degradation reaction, has been developed and produced industrially [45].

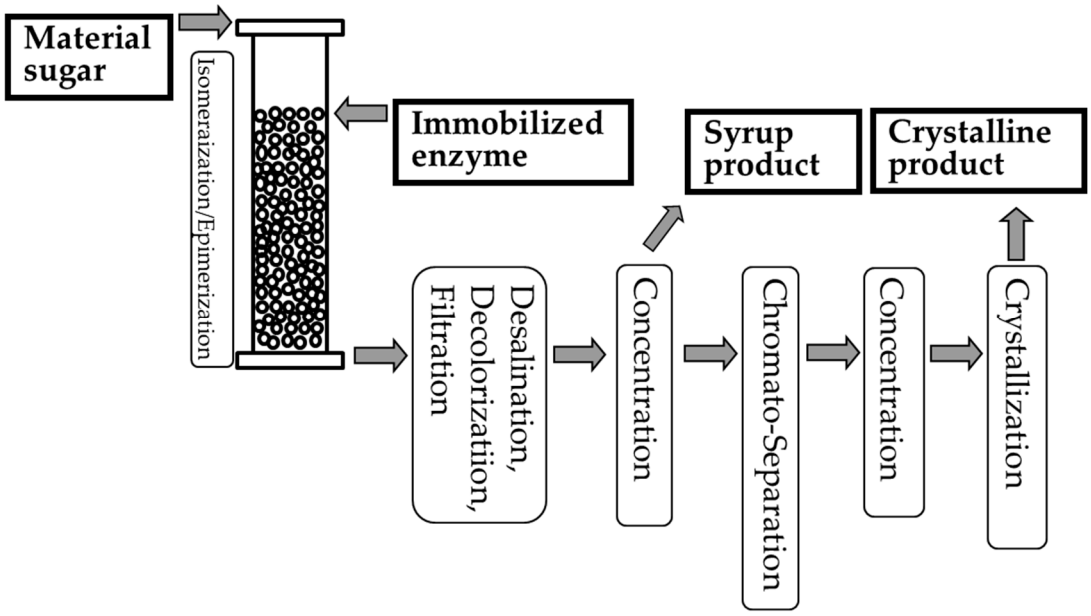

Figure 4. Schematic diagram of hexose production using immobilized enzymes.

5. D-Mannose and other Fru-Related Hexoses

D-Mannose is a C-2 epimer of glucose and an isomer of Fru (Figure 2). D-Mannose is abundantly present in nature as part of the polysaccharide mannan and a sugar chain of glycoprotein [46]. This sugar is also used as a dietary supplement to prevent urinary tract infections [46]. D-Mannose is also reduced to mannitol, similar to the reduction of D-glucose to sorbitol [47].

Fru can be isomerized to D-mannose using immobilized *Agrobacterium radiobacter*, which produces a thermostable mannose isomerase [15]. The microbe cells are immobilized by adsorption on chitosan or by glutaraldehyde crosslinking in the presence of albumin. Optimum conditions for mannose isomerase activity are 60 °C and pH 7.5. Continuous reaction at 55 °C was achieved with immobilized cells packed in a column to produce D-mannose [16]. Additionally, cellobiose 2-epimerase from *Caldicellulosiruptor saccharolyticus* was cloned, expressed in *Escherichia coli*, and applied for mannose production [17]. A recent review described the details of D-mannose production [18].

D-Allulose is a C-3 epimer of Fru and suppresses metabolic syndrome [48]. This sugar has been discussed in so many reports by Izumori [49–51]. D-Allulose-containing sugar syrup is produced from high Fru corn syrup at an industrial scale by an alkaline isomerization method [19,20]. Moreover, in a study using the immobilized enzyme column reaction method, the total D-allulose production yield was 215 kg/L immobilized enzyme, which is the highest reported enzyme yield to date [21].

D-Allose is an isomer of D-allulose, is also a C-3 epimer of D-glucose, and has inhibitory effects on cancer for experimental animals [52]. This production method from D-allulose using L-Rhamnose isomerase enzymes and/or the immobilized enzyme was previously reported by Izumori et al. [53,54].

6. D-Galactose and D-Tagatose

Lactose is a disaccharide derived from the condensation of D-galactose and D-glucose, which forms a β-1→4 glycosidic linkage. Lactose makes up around 2–8% of milk [55]. Several million tons of lactose are produced annually as a by-product of the dairy industry [56]. Milk is consumed by people worldwide; however, lactose in milk may cause health problems in individuals with lactose intolerance [57,58]. Thus, methods for lactose degradation in milk have been extensively studied [59,60].

D-Galactose is a C-4 epimer of glucose (Figure 2). D-Galactose can be produced industrially by lactase (β-galactosidase) derived from food microorganisms [61]. However, due to its low sweetness and limited research regarding its safety and functions [62], utilization of pure galactose in the food industry is not yet widespread [63]. Notably, marine algal biomass, including *Gelidium amansii*, have been reported to produce galactose [22]. Optimal conditions for the production of galactose have been identified as a reaction temperature of 108 °C, reaction time of 45 min, and catalyst concentration of 3%. From these studies, more economical and efficient systems for the production of galactose and chemicals from marine biomass have been developed [22]. Neutral β-galactosidase from *Kluyveromyces* sp. was immobilized on porous glass modified by glutaraldehyde binding, with retention of high activity [23]. Thus, D-galactose has attracted attention as a raw material for tagatose production [24], as described below.

D-Tagatose is a C-3 epimer of D-galactose (Figure 2). D-Tagatose is contained in many dairy products [64]. With regard to health benefits, this sugar has low caloric value [65], has inhibitory effects against metabolic syndrome, and is beneficial to teeth by suppressing the growth of *S. mutans* [66]. Recent reviews on the efficacy of tagatose have described this sugar in detail [25]. Tagatose is manufactured by chemical methods or enzymatic methods. In alkaline solution, D-galactose is isomerized to tagatose via enolization reaction through enediol. Moreover, this chemical catalyst (a solid Lewis acid which is presented by Sn-BEA zeolite) was recently reported to enable selective transformation of D-galactose, giving rise to D-tagatose in 24% yield at 29% conversion of the substrate [26]. Using the chemical method, raw material sugar and food chemical additives are mixed in the reaction tank and agitated at a high temperature for conversion reaction. The mixture is separated chromatographically after desalting. The D-tagatose syrup after concentration is crystallized (Figure 4). Compared with the chemical method, enzymes from some microbes (ex. *Thermotoga* species), including L-arabinose isomerase, also catalyze the conversion of D-galactose to D-tagatose [25]. Thus, D-tagatose production has been achieved by chemical and enzymatic methods.

7. L-Hexoses

Among L-hexoses, L-sorbose, L-fucose, and L-rhamnose are commonly used in the food industry (Figure 5). The former is made from starch [67], whereas the latter two products are respectively obtained from natural polysaccharides [68] and complex carbohydrates [32,69].

L-Sorbose is a ketose monosaccharide containing a ketone group [70]. This compound has a sweetness that is equivalent to that of sucrose [27]. In the food industry, L-sorbose has been used as a low-calorie sweetener and a source material for the preparation of other products. The commercial production of vitamin C often begins with L-sorbose [28]. L-Sorbose is the configuration of the naturally occurring sugar and is obtained by fermenting D-glucose or sorbitol with *Gluconobacter* species or *Acetobacter* species [28]. In the general fermentation method, raw sugar, microbes, and food chemical reagents are mixed in a fermentation tank and agitated at optimal temperature with bubbling. The mixture is separated into microbes and solution by centrifugation or using a membrane filter. The syrup produced after desalting, separation, and concentration is then crystallized (Figure 6).

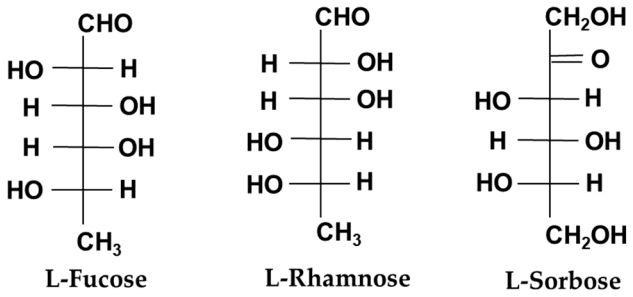

Figure 5. L-hexoses in the food industry.

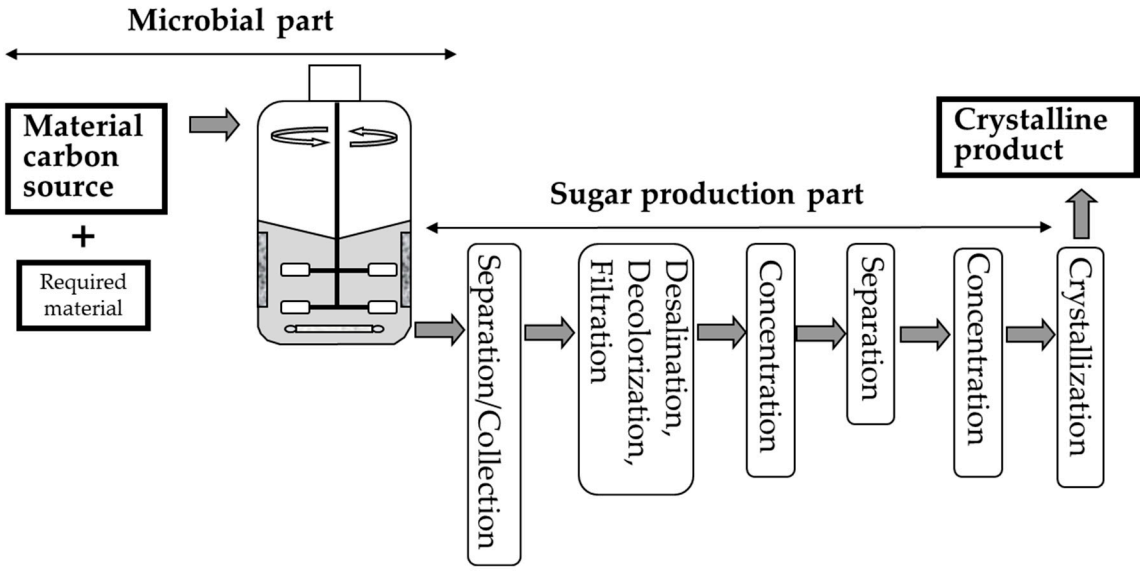

Figure 6. Schematic diagram of hexose production using fermentation.

L-Fucose is the main unit of fucoidan and is an abundant component of the plant cell wall [29,30]. Human milk oligosaccharides also contain this sugar [30]. There are only a few industrial production processes for L-fucose, and chromatographic separation of this valuable component from hemicellulose hydrolysates could be a feasible alternative. However, chromatographic separation of L-fucose with sufficient purity from various other monosaccharides is difficult at the industrial level [31]. Additionally, the price of this sugar in the food market is still high because fucoidan is relatively difficult to obtain from natural resources, such as seaweeds.

L-Rhamnose is a naturally occurring deoxy sugar that occurs as 6-deoxy-L-mannose [33]. As a method for obtaining L-rhamnose for cosmetic ingredients or food additives, glycoside contained in the pericarp, bark, or flowers of *Rutin* or *Citrus* is isolated, and the fermented product is then concentrated, separated, hydrolyzed, and separated again to obtain L-rhamnose. Recent studies have described a process for readily and efficiently preparing L-rhamnose using a marine alga. Briefly, rhamnan sulfate is extracted from a marine alga belonging to the family *Monostromaceae*, and the obtained extract is hydrolyzed by adding acids, followed by heating or treating with a cation exchange resin and subsequent heating to give a solution containing free L-rhamnose. Because this solution contains large amounts of salts, the removal of these salts is essential for the preparation of L-rhamnose [32]. Thus, an effective process may be obtained by combining this new approach with a conventional method using an ion exchange resin to establish an efficient desalting process. Alternatively, to increase the purity of L-rhamnose, baker's yeast, which selectively ferments various sugars, may be added to the solution containing L-rhamnose [32].

8. Other Monosaccharides

Among other monosaccharides and related polyols, D-xylose, L-arabinose, D-ribose, xylitol, and erythritol are sometimes used in foods (Figure 7). D-Xylose, L-arabinose, D-ribose, and xylitol are pentoses, which have five carbon atoms, whereas erythritol is a tetrose, which has four carbon atoms.

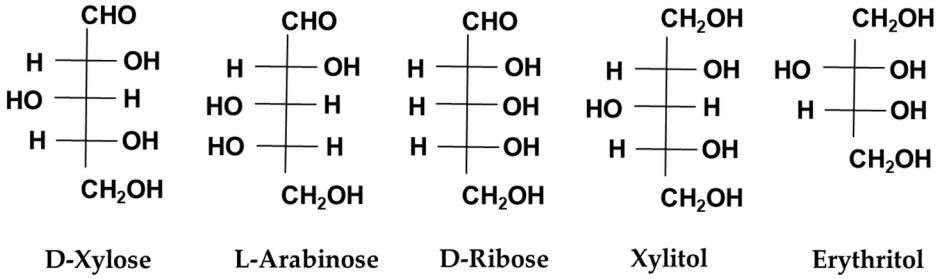

Figure 7. Pentoses and sugar alcohols in the food industry.

D-Xylose and L-arabinose are produced industrially from plant biomass. D-Xylose is often used as a food browner [71]. The sugar causes Mallard reactions with amino acids during food processing. L-Arabinose is sometimes used as a dietary supplement that can suppress blood glucose levels after meals [72]. D-Ribose is a component of ribonucleic acid in living organisms. In the food industry, D-ribose is sometimes used as a dietary supplement [73] or a component of energy drinks. D-Ribose can be produced by fermentation of D-glucose [74]. In contrast, xylitol and erythritol are sugar alcohols rather than pure sugar. These two products are bulk, low-calorie sweeteners. Xylitol is often used as a component of chewing gum or dental-related products [75,76], whereas the latter is often used as a component of beverages or general processed foods [77,78]. Although D-xylose is chemically reduced to xylitol [79], erythritol is converted from D-glucose by fermentation under a reduction state in yeast [80]. Both are commercially available, produced in large quantities, and not expensive. Additionally, in some countries, gluconic acid as sodium gluconate is used as a food additive to adjust pH or increase shelf-life. Gluconic acid can be produced chemically by oxidation of D-glucose. Gluconic acid is a mild organic acid derived from glucose by a simple oxidation reaction catalyzed by the enzymes D-glucose oxidase from fungi and D-glucose dehydrogenase from bacteria, such as *Gluconobacter* [81].

9. Discussion and Summary

Hexoses are carbohydrates that have six carbon atoms. In the food industry, these sugars are industrially produced by microbial, enzymatic, and chemical methods rather than organic synthesis methods owing to difficulties in the latter approach for industrial-scale production and similarities in the molecular structures of carbohydrates and material resources. Three methods have been used to convert 1-3-position of the molecular structure's carbons. To date, fermentation, chemical, and enzymatic methods have been used to produce monosaccharides. These above-mentioned methods for producing hexoses are inexpensive and produce high yields, making these compounds useful for applications in the food industry. Thus, the research and development of these three manufacturing methods will continue. However, new microorganisms and catalysts are also emerging, and new approaches are expected. On the other hand, if we identify the new uses of monosaccharides, research on the production of such monosaccharides may progress rapidly. Moreover, these compounds may have various beneficial effects on health [18,37,78,82,83]. Accordingly, the addition of hexoses to foods during food production may improve the health and quality of life of consumers.

Funding: This study was partially supported by the Sasakawa Scientific Research Grant from The Japan Science Society [2018-6021].

Acknowledgments: I thank Masashi Sato (Kagawa University, Kagawa, Japan), Ken Izumori (Kagawa University, Kagawa, Japan), Hisashi Ashida (Kindai University, Wakayama, Japan), Kenji Yamamoto (Kyoto University, Kyoto,

Japan), Kazuhide Totani (Ichinoseki National College of Technology, Iwate, Japan), Yoshiharu Matahira (Yaizu Suisankagaku Industry Co., Ltd., Shizuoka, Japan), Yukifumi Nishimoto (Nagase & Co., Ltd., Osaka, Japan), Iwao Kojima (Ezaki Glico Co., Ltd., Osaka, Japan) and the late Kazuhiro Okuma (Matsutani Chemical Industry Co., Ltd., Hyogo, Japan) for valuable advice.

Conflicts of Interest: The author declares no conflicts of interest. Tomoya Shintani is an employee of Matsutani Chemical Industry Co., Ltd. (Hyogo, Japan), whose company is manufacturing and selling sugar and carbohydrate products. However, the company provided no financial support for this study.

References

1. Prydz, K.; Dalen, K.T. Synthesis and sorting of proteoglycans. *J. Cell Sci.* **2000**, *113*, 193–205. [PubMed]
2. Hoff, J.E. Determination of the N-acetylglucosamine-1-phosphate content of cow milk from the difference between the values obtained for total and free N-acetylglucosamine. *J. Dairy Sci.* **1963**, *46*, 573–574. [CrossRef]
3. Gooday, G.W. The Ecology of Chitin Degradation. In *Advances in Microbial Ecology*; Springer: Boston, MA, USA, 1990; ISBN 0147-4863.
4. Sakai, K.; Uchiyama, T.; Matahira, Y.; Nanjo, F. Immobilization of chitinolytic enzymes and continuous production of N-acetylglucosamine with the immobilized enzymes. *J. Ferment. Bioeng.* **1991**, *72*, 168–172. [CrossRef]
5. Techikawara, K.; Kobayashi, H.; Fukuoka, A. Conversion of N-acetylglucosamine to protected amino acid over Ru/C catalyst. *ACS Sustain. Chem. Eng.* **2018**, *6*, 12411–12418. [CrossRef]
6. Zhang, A.; Gao, C.; Wang, J.; Chen, K.; Ouyang, P. An efficient enzymatic production of N-acetyl-D-glucosamine from crude chitin powders. *Green Chem.* **2016**, *18*, 2147–2154. [CrossRef]
7. Reginster, J.Y.; Deroisy, R.; Rovati, L.C.; Lee, R.L.; Lejeune, E.; Bruyere, O.; Giacovelli, G.; Henrotin, Y.; Dacre, J.E.; Gossett, C. Long-term effects of glucosamine sulphate on osteoarthritis progression: A randomised, placebo-controlled clinical trial. *Lancet* **2001**, *357*, 251–256. [CrossRef]
8. Rege, P.R.; Block, L.H. Chitosan processing: Influence of process parameters during acidic and alkaline hydrolysis and effect of the processing sequence on the resultant chitosan's properties. *Carb. Res.* **1999**, 235–245. [CrossRef]
9. KOYO Glucosamine. Available online: http://www.koyochemical.jp/english/glucosamine (accessed on 15 April 2019).
10. Park, Y.K.; Yetley, E.A. Intakes and food sources of fructose in the United States. *Am. J. Clin. Nutr.* **1993**, *58*, 737S–747S. [CrossRef]
11. Shintani, T.; Iida, T. Kishoutou no kaihatsu to riyou. *Food Ind. Tomorrow* **2015**, *4*, 34–41.
12. Tosa, T.; Shibatani, T. Industrial application of immobilized biocatalysts in Japan. *Ann. N. Y. Acad. Sci.* **1995**, *750*, 364–375. [CrossRef]
13. Vasic-Racki, D. History of industrial biotransformations—Dreams and realities. In *Industrial Biotransformations*, 2nd ed.; Wiley: Weinheim, Germany, 2006; pp. 1–36.
14. Hanover, L.M.; White, J.S. Manufacturing, composition, and applications of fructose. *Am. J. Clin. Nutr.* **1993**, *58*, 724–732. [CrossRef] [PubMed]
15. Takasaki, Y.; Ohya, T. Mannose Isomerase and Process for Mannose Production Using It. U.S. Patent 5,124,262A, 23 June 1992.
16. Hirose, J.; Kinoshita, Y.; Fukuyama, S.; Hayashi, S.; Yokoi, H.; Takasaki, Y. Continuous isomerization of D-fructose to D-mannose by immobilized Agrobacterium radiobacter cells. *Biotechnol. Lett.* **2003**, *25*, 349–352. [CrossRef] [PubMed]
17. Park, C.S.; Kim, J.E.; Choi, J.G.; Oh, D.K. Characterization of a recombinant cellobiose 2-epimerase from *Caldicellulosiruptor saccharolyticus* and its application in the production of mannose from glucose. *Appl. Microbiol. Biotechnol.* **2011**, *92*, 1187–1196. [CrossRef] [PubMed]
18. Hu, X.; Shi, Y.; Zhang, P.; Miao, M.; Zhang, T.; Jiang, B. D-Mannose: Properties, production, and applications: An overview. *Compr. Rev. Food Sci. Food Saf.* **2016**, *15*, 773–785. [CrossRef]
19. Takamine, S.; Nakamura, M.; Iida, T.; Okuma, K.; Ken, I. Manufacturing method of rare sugar syrup through alkali isomerization and its inhibitory effect of α-glucosidase. *Bull. Appl. Glycosci.* **2015**, *5*, 44–49. [CrossRef]
20. Shintani, T.; Yamada, T.; Hayashi, N.; Iida, T.; Nagata, Y.; Ozaki, N.; Toyoda, Y. Rare sugar syrup containing D-allulose but not high-fructose corn syrup maintains glucose tolerance and insulin sensitivity partly via

hepatic glucokinase translocation in Wistar rats. *J. Agric. Food Chem.* **2017**, *65*, 2888–2894. [CrossRef] [PubMed]
21. Yoshihara, A.; Kozakai, T.; Shintani, T.; Matsutani, R.; Ohtani, K.; Iida, T.; Akimitsu, K.; Izumori, K.; Gullapalli, P.K. Purification and characterization of D-allulose 3-epimerase derived from *Arthrobacter globiformis* M30, a GRAS microorganism. *J. Biosci. Bioeng.* **2017**, *123*, 170–176. [CrossRef] [PubMed]
22. Jeong, G.T.; Park, D.H. Production of sugars and levulinic acid from marine biomass *Gelidium amansii*. *Appl. Biochem. Biotechnol.* **2010**, *161*, 41–52. [CrossRef] [PubMed]
23. Szczodrak, J. Hydrolysis of lactose in whey permeate by immobilized β-galactosidase from Kluyveromyces fragilis. *J. Mol. Catal. B Enzym.* **2000**, *10*, 631–637. [CrossRef]
24. Izumori, K. Izumoring: A strategy for bioproduction of all hexoses. *J. Biotechnol.* **2006**, *124*, 717–722. [CrossRef] [PubMed]
25. Jayamuthunagai, J.; Gautam, P.; Srisowmeya, G.; Chakravarthy, M. Biocatalytic production of D-tagatose: A potential rare sugar with versatile applications. *Crit. Rev. Food Sci. Nutr.* **2017**, *57*, 3430–3437. [CrossRef] [PubMed]
26. Drabo, P.; Delidovich, I. Catalytic isomerization of galactose into tagatose in the presence of bases and Lewis acids. *Catal. Commun.* **2018**, *107*, 24–28. [CrossRef]
27. Grenby, T.H. *Advances in Sweeteners*; Blackie Academic & Professional Publisher: Detroit, MI, USA, 2012.
28. Uchihori, Y.; Sekitani, Y.; Yoshida, I. Process for producing L-sorbose by subculture of seed. U.S. Patent 4,945,048, 31 July 1990.
29. Vanhooren, P.T.; Vandamme, E.J. L-Fucose: Occurrence, physiological role, chemical, enzymatic and microbial synthesis. *J. Chem. Technol. Biotechnol.* **1999**, *74*, 479–497. [CrossRef]
30. Boehm, G.; Stahl, B. Oligosaccharides from milk. *J. Nutr.* **2007**, *137*, 847S–849S. [CrossRef] [PubMed]
31. Saari, P.; Häkkä, K.; Heikkilä, H.; Jumppanen, J.; Hurme, M. A novel chromatographic production scale separation process for L-fucose. *J. Liq. Chromatogr. Relat. Technol.* **2009**, *32*, 2050–2064. [CrossRef]
32. Trummler, K.; Effenberger, F.; Syldatk, C. An integrated microbial/enzymatic process for production of rhamnolipids and L-(+)-rhamnose from rapeseed oil with *Pseudomonas* sp. DSM 2874. *Eur. J. Lipid Sci. Technol.* **2003**, *105*, 563–571. [CrossRef]
33. Zorbach, W.; Tio, C. A new synthesis of D-rhamnose (6-deoxy-D-mannose). *J. Org. Chem.* **1961**, *26*, 3543–3545. [CrossRef]
34. Kanzaki, N.; Ono, Y.; Shibata, H.; Moritani, T. Glucosamine-containing supplement improves locomotor functions in subjects with knee pain a randomized, double-blind, placebo-controlled study. *Clin. Interv. Aging* **2015**, *10*, 1743. [CrossRef]
35. Gueniche, A.; Castiel-Higounenc, I. Efficacy of glucosamine sulphate in skin ageing: Results from an ex vivo anti-ageing model and a clinical trial. *Skin Pharmacol. Physiol.* **2017**, *30*, 36–41. [CrossRef]
36. Bao, J.; Liu, N.; Zhu, L.; Xu, Q.; Huang, H.; Jiang, L. Programming a biofilm-mediated multienzyme-assembly-cascade system for the biocatalytic production of glucosamine from chitin. *J. Agric. Food Chem.* **2018**, *66*, 8061–8068. [CrossRef]
37. Jenkins, D.J.; Wolever, T.M.; Taylor, R.H.; Barker, H.; Fielden, H.; Baldwin, J.M.; Bowling, A.C.; Newman, H.C.; Jenkins, A.L.; Goff, D. V Glycemic index of foods: A physiological basis for carbohydrate exchange. *Am. J. Clin. Nutr.* **1981**, *34*, 362–366. [CrossRef] [PubMed]
38. Tappy, L.; Lê, K.A. Metabolic effects of fructose and the worldwide increase in obesity. *Physiol. Rev.* **2010**, *90*, 23–46. [CrossRef] [PubMed]
39. Stanhope, K.L.; Schwarz, J.M.; Keim, N.L.; Griffen, S.C.; Bremer, A.A.; Graham, J.L.; Hatcher, B.; Cox, C.L.; Dyachenko, A.; Zhang, W. Consuming fructose-sweetened, not glucose-sweetened, beverages increases visceral adiposity and lipids and decreases insulin sensitivity in overweight/obese humans. *J. Clin. Investig.* **2009**, *119*, 1322–1334. [CrossRef] [PubMed]
40. Takasaki, Y. Studies on sugar-isomerizing enzyme: Production and utilization of glucose isomerase from *Streptomyces* sp. *Agric. Biol. Chem.* **1966**, *30*, 1247–1253. [CrossRef]
41. Yamanaka, K. Sugar isomerases: Part I. Production of D-glucose isomerase from heterolactic acid bacteria Part II. Purification and properties of D-glucose isomerase from *Lactobacillus brevis*. *Agric. Biol. Chem.* **1963**, *27*, 265–278.
42. Ryu, D.Y.; Chung, S.H.; Katoh, K. Performance of the continuous glucose isomerase reactor system for the production of fructose syrup. *Biotechnol. Bioeng.* **1977**, *19*, 154–184. [CrossRef]

43. Kainuma, K.; Tadokoro, K.; Suzuki, S. Isomerization of dextrose into fructose. II. Isomerization with various types of alkaline reagents. *Nippon Nogei Kagaku Kaishi* **1966**, *40*, 35. [CrossRef]
44. Kooyman, C.; Vellenga, K.; De Wilt, H.G.J. The isomerization of D-glucose into D-fructose in aqueous alkaline solutions. *Carbohydr. Res.* **1977**, *54*, 33–44. [CrossRef]
45. Yoshinaga, K.; Ishiba, H.; Yoshimoto, Y.; Katano, T. Functional research and production technology development of 1,5-anhydro-D-fructose. *Bull. Appl. Glycosci.* **2011**, *75*, 70–75. [CrossRef]
46. Kranjčec, B.; Papeš, D.; Altarac, S. D-Mannose powder for prophylaxis of recurrent urinary tract infections in women: A randomized clinical trial. *World J. Urol.* **2014**, *32*, 79–84. [CrossRef]
47. Makkee, M.; Kieboom, A.P.G.; Van Bekkum, H. Production methods of D-mannitol. *Starch* **1985**, *37*, 136–141. [CrossRef]
48. Hossain, A.; Yamaguchi, F.; Matsuo, T.; Tsukamoto, I.; Toyoda, Y.; Ogawa, M.; Nagata, Y.; Tokuda, M. Rare sugar D-allulose: Potential role and therapeutic monitoring in maintaining obesity and type 2 diabetes mellitus. *Pharmacol. Ther.* **2015**, *155*, 49–59. [CrossRef]
49. Takeshita, K.; Suga, A.; Takada, G.; Izumori, K. Mass production of D-psicose from D-fructose by a continuous bioreactor system using immobilized D-tagatose 3-epimerase. *J. Biosci. Bioeng.* **2000**, *90*, 453–455. [CrossRef]
50. Granström, T.B.; Takata, G.; Tokuda, M.; Izumori, K. Izumoring: A novel and complete strategy for bioproduction of rare sugars. *J. Biosci. Bioeng.* **2004**, *97*, 89–94. [CrossRef]
51. Izumori, K. Bioproduction strategies for rare hexose sugars. *Naturwissenschaften* **2002**, *89*, 120–124. [CrossRef]
52. Murata, A.; Sekiya, K.; Watanabe, Y.; Yamaguchi, F.; Hatano, N.; Izumori, K.; Tokuda, M. A novel inhibitory effect of D-allose on production of reactive oxygen species from neutrophils. *J. Biosci. Bioeng.* **2003**, *96*, 89–91. [CrossRef]
53. Bhuiyan, S.H.; Itami, Y.; Rokui, Y.; Katayama, T.; Izumori, K. D-Allose Production from D-Psicose Using Immobilized L-Rhamnose Isomerase. *J. Ferment. Bioeng.* **1998**, *89*, 539–541. [CrossRef]
54. Gullapalli, P.K.; Shintani, T.; Nishimoto, Y.; Harazono, K. Method for Producing D-Allose. JP Patent P6209526, 8 May 2014.
55. Ammam, M.; Fransaer, J. Two-enzyme lactose biosensor based on β-galactosidase and glucose oxidase deposited by AC-electrophoresis: Characteristics and performance for lactose determination in milk. *Sens. Actuators B Chem.* **2010**, *148*, 583–589. [CrossRef]
56. Yang, S.T.; Silva, E.M. Novel products and new technologies for use of a familiar carbohydrate, milk lactose. *J. Dairy Sci.* **1995**, *78*, 2541–2562. [CrossRef]
57. Kretchmer, N. Lactose and lactase. *Sci. Am.* **1972**, *227*, 70–79. [CrossRef]
58. Heyman, M.B. Lactose intolerance in infants, children, and adolescents. *Pediatrics* **2006**, *118*, 1279–1286. [CrossRef] [PubMed]
59. Dekker, J.P.; Koenders, D.; Bruins, J.M. Lactose-free dairy products: Market developments, production, nutrition and health benefits. *Nutriets* **2019**, *11*, 551. [CrossRef] [PubMed]
60. Hodges, K.J.; Cao, S.; Cladis, P.D.; Weaver, M.C. Lactose intolerance and bone health: The challenge of ensuring adequate calcium intake. *Nutriets* **2019**, *11*, 718. [CrossRef] [PubMed]
61. Nakanishi, K.; Matsuno, R.; Torii, K.; Yamamoto, K.; Kamikubo, T. Properties of immobilized β-D-galactosidase from *Bacillus circulans*. *Enzym. Microb. Technol.* **1983**, *5*, 115–120. [CrossRef]
62. Michaëlsson, K.; Wolk, A.; Langenskiöld, S.; Basu, S.; Lemming, E.W.; Melhus, H.; Byberg, L. Milk intake and risk of mortality and fractures in women and men: Cohort studies. *BMJ* **2014**, *349*, g6015. [CrossRef] [PubMed]
63. Lai, K.; Elsas, L.J.; Wierenga, K.J. Galactose toxicity in animals. *IUBMB Life* **2009**, *61*, 1063–1074. [CrossRef] [PubMed]
64. Guerrero-Wyss, M.; Agüero, S.D.; Dávila, L.A. D-Tagatose is a promising sweetener to control glycaemia: A new functional food. *BioMed Res. Int.* **2018**, 8718053. [CrossRef] [PubMed]
65. Levin, G.V. Tagatose, the new GRAS sweetener and health product. *J. Med. Food* **2002**, *5*, 23–36. [CrossRef] [PubMed]
66. Vastenavond, C.M.; Bertelsen, H.; Hansen, S.J.; Laursen, R.S.; Saunders, J.; Eriknauer, K. Tagatose (D-tagatose). In *Alternative Sweeteners*; CRC Press: Boca Raton, FL, USA, 2012; pp. 197–222.
67. Xu, S.; Wang, X.; Du, G.; Zhou, J.; Chen, J. Enhanced production of L-sorbose from D-sorbitol by improving the mRNA abundance of sorbitol dehydrogenase in *Gluconobacter oxydansWSH*-003. *Microb. Cell Fact.* **2014**, *13*, 146. [CrossRef]

68. Schweiger, R.G. Preparation of Alpha-L-Fucosides and L-Fucose from Fucoidan. U.S. Patent 3,240,775A, 15 March 1966.
69. Lang, S.; Wullbrandt, D. Rhamnose lipids—Biosynthesis, microbial production and application potential. *Appl. Microbiol. Biotehcnol.* **1999**, *1*, 22–32. [CrossRef]
70. Verstraeten, L.M.J. Infrared spectra of some 2-ketoses. *Anal. Chem.* **1964**, *36*, 1040–1044. [CrossRef]
71. Namiki, M. Chemistry of Maillard reactions: Recent studies on the browning reaction mechanism and the development of antioxidants and mutagens. *Adv. Food Res.* **1988**, *32*, 115–184. [PubMed]
72. Inoue, S.; Sanai, K.; Seri, K. Effect of L-arabinose on blood glucose level after ingestion of sucrose-containing food in human. *J. Jpn. Soc. Nutr. Food Sci.* **2000**, *53*, 243–247. [CrossRef]
73. Pauly, D.F.; Pepine, C.J. D-Ribose as a supplement for cardiac energy metabolism. *J. Cardiovasc. Pharmacol. Ther.* **2000**, *5*, 249–258. [CrossRef] [PubMed]
74. De Wulf, P.; Vandamme, E.J. Production of D-ribose by fermentation. *Appl. Microbiol. Biotechnol.* **1997**, *48*, 141–148. [CrossRef] [PubMed]
75. Burt, B.A. The use of sorbitol-and xylitol-sweetened chewing gum in caries control. *J. Am. Dent. Assoc.* **2006**, *137*, 190–196. [CrossRef] [PubMed]
76. Peldyak, J.; Makinen, K.K. Xylitol for caries prevention. *J. Dent. Hyg.* **2002**, *76*, 276–285.
77. Lee, T.; Olcese, G.; Bell, Z.; Roy, G.; Mutilangi, W.; Hirs, R.; Given, P. Use of Erythritol and D-tagatose in Zero-or Low-Calorie Beverages. U.S. Patent 2,009,028,0232A1, 13 September 2007.
78. Moon, H.J.; Jeya, M.; Kim, I.W.; Lee, J.K. Biotechnological production of erythritol and its applications. *Appl. Microbiol. Biotechnol.* **2010**, *86*, 1017–1025. [CrossRef]
79. Winkelhausen, E.; Kuzmanova, S. Microbial conversion of D-xylose to xylitol. *J. Ferment. Bioeng.* **1998**, *86*, 1–14. [CrossRef]
80. Spencer, J.F.T.; Sallans, H.R. Production of polyhydric alcohols by osmophilic yeasts. *Can. J. Microbiol.* **1956**, *2*, 72–79. [CrossRef]
81. Ramachandran, S.; Fontanille, P.; Pandey, A.; Larroche, C. Gluconic acid: Properties, applications and microbial production. *Food Technol. Biotechnol.* **2006**, *44*, 185–195.
82. Shintani, T.; Okuma, K.; Sakoguchi, H.; Sato, M. Rare sugars D-psicose and D-allose as calorie restriction mimetic-anti-metabolic syndrome effects and anti-aging effects. *J. Brew. Soc. Jpn.* **2013**, *108*, 565–574. [CrossRef]
83. Shintani, H.; Shintani, T.; Ashida, H.; Sato, M. Calorie restriction mimetics: Upstream-type compounds for modulating glucose metabolism. *Nutrients* **2018**, *10*, 1821. [CrossRef] [PubMed]