PRODUCTION OF SUGAR ALCOHOLS WITH BIOTECHNOLOGICAL METHODS[1*]

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ABSTRACT

Sugar alcohols, which are increasingly used in industries worldwide, are sugar substitutes that are formed by the reduction of sugars. With its low calorie advantage, they have sweetness, such as non-carcinogenic, low glycemic index and non–insulin resistance, it strengthens the nutritional properties in food products and improves product properties in terms of technological properties. It also has positive contributions to health against the increase of diseases such as obesity and diabetes. Although these compounds are generally produced by catalytic hydrogenation of sugars in the industry, they are receiving increasing attention as they can be obtained on a microbial basis. Several interesting metabolic engineering studies were carried out in recent years to improve the ability of bacteria and yeast to overproduce xylitol, mannitol, and sorbitol. The aim of this review is to provide information about sugar alcohols and production using biotechnology.

Keywords: *Sugar alcohols, Xylitol, Mannitol, Sorbitol, Biotechnology*

INTRODUCTION

A class of polyols, sugar alcohols resemble sugars and strengthen the nutritional profile of food products due to their low calorie content, being non-carcinogenic and having low glycemic index **[1, 2].** Polyols, the sugar alcohols of polyhydric alcohols or polyalcohols **[3]**, are defined as saccharide derivatives with chemical exchange of an aldehyde or ketone group with a hydroxyl group and are classified according to the saccharide units found in the molecule **[4]**. Though sugar alcohols are found naturally in fruit and vegetables, most contain low amounts. Production of these compounds at industrial scale uses catalytic hydrogenation, though currently microbial-based processes have gained attention **[5].** Sugar alcohols have areas of use including medication

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applications to personal care products and as chemical intermediate agents, in addition to the food sector. They are encountered for food production from the confectionary industry to chocolate, from chewing gum, frozen dessert products, flour-based products, and diet products to drinks **[6-8**]. Most sugar alcohols in traditional industrial production are obtained from hydrogenation of sugars under high pressure and temperature conditions with nickel catalysts. Metabolic engineering has gained importance to increase the microbial production of the common sugar alcohols of xylitol, mannitol and sorbitol **[2].** After sugar alcohols are digested by the human body, they convert to fructose and do not immediately elevate blood sugar levels. In other words, sugar alcohols are absorbed slowly. Due to digestive and metabolic features, some sugar alcohols have calorie values varying from 0-3.2 kcal/g, and generally have low levels of glycemic index value. Sugar alcohols have lower degree of sweetness than saccharose, with the highest sweetness determined for xylitol and the lowest sweetness for lactitol **[9].** Table 1 gives some properties of sugar alcohols.

Table 1. Some properties of sugar alcohols **[10-14]**

Scientific name	Degree of Sweetness[a]	Glycemic index[b]	Areas of use in the food industry	Functional use
Lactitol	0.3-0.4	6	Chocolate, hard candies, caramel, fondant, chewing gum, confectionary, frozen desserts, ice creams, flour products, water products, biscuits	Sweetener, volumizer, texture agent
Xylitol	1.0	13	Sugar-free sweeteners, chewing gum, confectionary, chocolate, desserts, reduced-sugar jams and marmalade production, ice cream, yogurt, sweetener and humidifier in some flour products, sweetener in drinks	Sweetener, Humidifier
Sorbitol	0.5-0.7	9	Confectionary, Baked goods, low calorie foods, sugar-free sweetened chewing gum, diet drinks, ice cream, biscuits, peanut butter, jams	Sweetener, humidifier, texture, volumizer, stabilizer
Mannitol	0.5-0.7	0	Hard candies, cake products, dried fruit, chewing gum, chocolate, baked goods, ice creams	Sweetener, volumizer, anti-coagulant
Maltitol	0.9	35	Sugar-free rock candy, sugar, chewing gum, chocolate, ice cream	Sweetener, volumizer, humidifier, stabilizer
Isomalt	0.45-0.65	9	In sugar-free sugar production, hard candy, chocolate, coated foods, nutritional supplement, pastilles	Sweetener, volumizer, anti-thickening agent
Eritritol	0.8	0	Some types of cheese, milk powder, milk desserts, ice cream, breakfast cereals, processed meat products, products like egg desserts and sauces, confectionary, biscuits, sugar-free chewing gum, some drinks	Flavor enhancer, humidifier, sweetener, carrier, thickener, stabilizer

[a]Saccharose=1**[15, 16]**; [b]Glucose **[15, 17]** =100

Xylitol

Xylitol was the first sugar alcohol obtained from seaweed and yeasts. Found at very low levels in fruit and vegetables, xylitol was first obtained from mushrooms (*Psalliota campestris)***[18, 19]**. In 1891, it was extracted and produced as a syrup by Bertran Fischer Stabel and in later years pure xylitol was obtained. Stable and unstable forms of xylitol have been developed. Studies used *Penicillium chrysogenum* yeasts to reduce xylose to xylitol [**20**]. In industry xylose, a pentose not found in free form in plants, is converted to xylitol by hydrogenation. Xylitol comprising D-xylose units is combined with cellulose in xylan form [**21**]. Though xylose is present in nature, commercial production is difficult due to difficulties with separation from other carbohydrates like xylose. For this reason, obtaining xylose from plants and then performing the hydrogenation process represents the basis of xylitol production. Plant materials used with this aim include hardwoods like beech, oats and cottonseed husks, corn cobs, sugar beet pulp, straw and nutshells. These materials contain 20-30% dry weight of xylan and xylose material [**21**]. As a result of hydrolysis with acid from xylan, D-xylose and catalysts are hydrogenated to produce xylitol. Many microorganisms do not have the ability to use xylitol. Even the bread yeast of *Saccoramyces cerevisiae* cannot ferment xylitol. When xylitol is added to dough, just as fermentation does not occur, in situations involving other sugars the fermentation rate reduces [**22**]. A study by Gehrin et al. (1974) proved that xylitol does not undergo fermentation by oral microflora **[23]**. For this reason, it is very important in terms of oral health [**24**].

Area of Use in Food Production

As xylitol does not have sufficient viscous structure for food production, it is generally not used alone as a sweetener. Xylitol may be used instead of glucose with gum Arabic in chewing gum. Xylitol can also assist in controlling kneading processes [**25**]. Xylitol, the 5-carbon sugar alcohol, is obtained by reduction of xylose. In recent times, microbial production of xylitol has attracted attention **[1]**. Xylitol production has annual 340 million dollar market share **[26].** When examined from a microbial aspect, yeasts, especially *Candida* species, appear to be the best xylitol producer. Xylitol production by yeast is obtained by reduction of xylose to xylitol with the xylose reductase (XR) enzyme or by oxidation of xylitol to xylulose with NAD^+ and xylitol dehydrogenase (XDH). After converting to glyceraldehyde 3 phosphate and pyruvate in order via the pentose phosphate route, xylose 5 phosphate converts by reduction to ethanol or enters the tricarboxylic cycle. As NAD is produced again in anaerobic conditions, the xylitol produced in the first step is continuously consumed and mainly ethanol production is observed. Under fully aerobic conditions, NADH accumulation and as a result inhibition

of the XDH enzyme dependent on NAD produces xylitol at high rates **[1].** For microbial-based natural xylitol production from yeasts, *Candida sp.* has gained importance in recent times **[27, 28]**. A study by Kwon SG et al. **[29]** produced 260 g/L zylose with an osmophilic strain of *Candida tropicalis* isolated from honey and produced 234 g/l xylitol in 48 hours as a result of fermentation within a glucose feed batch **[29].** Ko et al. **[*30*]** studied xylitol production with the disrupted mutant XYL2 xylitol dehydrogenase gene (XDH) of *Candida tropicalis* and obtained xylitol with oxygen transfer and the effect of glycerol. It was determined that 0.98 mol xylitol (mol xylose^{-1}) was obtained in aerobic conditions with 20 g glycerol from mutant D-xylose [**30**]. A study by Jin et al. [**31**] completed xylitol production in aerobic and limited oxygen culture environments by alternative metabolic routes with a *Pichia stipitis* (FLP-YS30 XYl3) mutant strain and determined the highest production was in anaerobic conditions [**31**]. As *Saccharomyces cerevisiae* does not contain natural xylose special carriers **[32],** xylose production is not effective. A study completed production with xylose recombinant species of *S. cerevisiae* **[33].** Apart from yeasts, it was determined that xylitol can be produced from bacteria. Xylitol may be produced from *Corynebacterium* and *Enterobacter* species containing enzymes reducing xylose to xylitol. However, bacteria are not good xylitol producers due to low amounts of xylitol production [**34**]. Due to this situation, studies were completed for bacteria to acquire the features that yeast has for xylitol production. A study by Cirino et al. [**35**] about this completed xylitol production from *E. coli* which does not have the ability to produce xylitol but has the ability to assimilate both hexose and pentose sugar. Positive results were obtained from studies about *E. coli* strains that may act as biocatalyst for conversion of biological mass to valuable products like glucose and xylose **[2, 36]**. It was determined that the key enzyme for the central metabolism of *E. coli* for xylitol production was an NADPH source. All xylitol dehydrogenases contained in *Candida boidinii* (CbXR enzyme), *Candida tenuis* (CtXR enzyme), *P. stipitis* derived xylose reductases (PsXR enzyme), *S. cerivisiae* (ScXR enzyme), *Glucono bacteroxydans* (GoXDH enzyme) and *P. stipitis* (PsXDH enzyme) microorganisms are functional to a variety of degrees in *E. coli.* Among these enzymes, the highest xylitol concentrations were produced with shake flask cultures with over expression of CbXR dependent on NADPH **[35**]. A similar study was performed by Yukimato et al**. [37]**. High xylitol production was performed with *E. coli* expression of the xylitol producer of D-xylose permease (xylE) with the addition of an XR chromosome linked to NAPH from *Kluyveromyces lactis* (XYL1)**[37]**. A study by Nyyssola et al. (2005) produced xylitol from xylose with XR expression from *P. sitipitis* (XYL1) with recombinant *Lactococcus lactis* [**38**]. A study by Povelainen and Miasnikov [**39**] reported completion of xylitol production

from glucose with *Basillus subtilis*. Xylitol was produced with nearly 23% yield with expression of the *B. subtilis* strain producing the XPDH enzymes for d-ribulose and d-xylulose contained in *Lactobacillus rhamnosus* and *Clostridium difficile* [**39**].

Some molds

Penicilium aspergillus and *Neurospora rhizopus* molds produce xylitol. However, xylitol production from molds is low, and xylitol production from molds is limited due to their metabolism of xylitol [**34**].

Mannitol

Mannitol, with a pleasant taste, is a carbohydrate alcohol like xylitol and sorbitol. It is the most abundant polyol found in nature, found in microorganisms such as bacteria, yeast, as well as in various plants such as pumpkin, celery, olive, onion and mistletoe. It is frequently used in pharmaceuticals and some nutritional tablets as it maintains its stable structure in humid environments and does not experience color loss at high temperatures. Just as it is dentally friendly, it is only absorbed in the small intestine and the section that cannot be absorbed by colonic bacteria is metabolized like indigestible carbohydrates **[40-42]**. Mannitol, which stands out with its antioxidant effect, is assumed to be an unmetabolized sweetener. For this reason, mannitol may be used in foods with health-promoting effects (functional foods). Studies determined that mannitol, which may be directly produced by LAB, can be applied in food production of fermented food products. While large amounts of mannitol production occur from fructose by heterofermentative LAB, only small amounts of mannitol production occur with homofermentative LAB **[43]**.

Area of Use in Food Production

Different from sorbitol, mannitol is used as powder with the aim of preventing adhesion of chewing gum to the production machinery in chewing gum production as it is not hygroscopic [**16**]. Mannitol has volumizing properties and may be used as sweetener [**44**]. It has a high share of the global market for Mannitol [**45**]. Mannitol and sorbitol formation occurs with catalytic reduction of a glucose and fructose mixture and these are separated by selective crystallization to gain mannitol. As chemical production of mannitol has low products and costs, interest in production from glucose or fructose with selective fermentation has increased [**45**]. Mannitol production by LAB and other microorganisms which can be used in food offers several significant advantages. The first of these advantages is that microorganisms and products which can be used in food can be directly applied to food products without any limitation. Another advantage is that some lactic acid bacteria are proposed to be beneficial to the gastrointestinal system [**43**]. Mannitol production by these bacteria has positive health effects. A study by Kiviharjuet al. [**46**] used lactic acid bacteria, yeast and molds for natural mannitol production and obtained high

degree titers of mannitol with manipulation. Lactic acid bacteria are important in industrial terms for food and medication production. Mannitol production may be completed by heterofermentative lactic acid bacteria and homofermentative lactic acid bacteria. Heterofermentative lactic acid bacteria, mannitol from fructose, it is produced by catalyzed mannitol dehydrogenase (MDH) and by NADH [**43**]. The *Lactobacillus intermedius* strain NRR-B-3693 has commercial potential for mannitol production from fructose syrup [**47**]. Glucose is used as NADH source for mannitol production by heterofermentative LAB [**48**]. In homofermentative situations, after conversion of fructose-6-phosphate (F6P) to mannitol-1-phosphate dehydrogenase (Mtl1PDH) and mannitol-1-phosphate (Mtl1P) linked to NADH, it occurs by phosphorylation of Mtl1P **[49, 50]**. As a result of fermentation, by-products like lactic acid and acetic acid are obtained **[51, 52].** A study by Von Weyman et al. [**48**] used *Leuconostoc mesenteroides* and obtained 93-97% rates of mannitol from fructose [**53**]. However, as the process is linked to sugar consumption, mannitol may be produced with 61-62% yield per sugar consumed as a result of additional nutritional requirements [**54**]. In the study by Reshamwalaet al.[**54**] originally mannitol synthesis was completed by mannitol-1 phosphate expression from *Eimeria tenella* (M1 Pase)from an *E. coli* strain to transform D-glucose into D-mannitol. Kaup et al. [**55**] used *E. coli* to convert fructose to mannitol. Biotransformation developed in the whole cell by founding an oxidation/reduction cycle within recombinant *E. coli* to convert D-fructose into D-mannitol. Additionally, another study defined the structure of recombinant *E. coli* for conversion of glucose to mannitol without adding extracellular enzymes and completed mannitol production with 87% yield with carbon flow from fructose 6-phosphate for mannitol biosynthesis [**56**].

Sorbitol

Found abundantly in nature, sorbitol **[13, 57]** is found in many fruits with and without seeds like apple, prune, cherry and grapes **[6].** Sorbitol is used as sweetener in diabetic products as it does not cause an increase in blood glucose [**13**]. Globally, the market is constantly increasing, with 25% of sorbitol production being used for vitamin C synthesis **[5, 6, 58].** Sorbitol has hygroscopic structure. It may absorb and release moisture very slowly under varying humidity conditions. Safety was supported by many scientific studies, so JECFA defined the acceptable daily intake (ADI) amount for sorbitol as 'undetermined' and for this reason there is no limit to its use **[59]**. The sorbitol base can be used by *Lactobacillus* species, just as it can be used as a carbon source by intestinal *Bifidobacteria* in humans so it is qualified as a prebiotic **[60, 61].**

Area of Use in Food Production

Sorbitol is used in the dessert, beverage industry with its non-calorie sweetening feature, and because it gives a sweet cold and

pleasant taste effect **[62, 63]**. Sorbitol is used in the dessert, beverage industry with its non-calorie sweetening feature, and because it gives a cold and pleasant taste effect. It is also used as an important precursor in the production of vitamin C, sorbose and surfactants. **[6, 64, 65].** While in the industry sorbitol can be obtained from glucose and sucrose via catalytic hydrogenation, some yeast and bacterial strains, particularly *Zymomonas mobilis* and *Candida boidini*, appear to be potential producers of sorbitol **[16].** It has been biotechnologically derived from glucose and fructose by *Z. mobilis* bacteria **[6, 66].** In the fermentative food class, dehydrogenases from the LAB of *Lactobacillus plantarum* and *Lactobacillus casei* have the ability to be used as different electron receivers for NAD^+ regeneration, making this a valuable field for polyol production via metabolic engineering **[43].** Ladero et al. **[65]** by reversing the catabolic route **[40]** of sorbitol from production from F6P of a strain of by expression from a mutant strain of *Lb. plantarum* (sorbitol-6-phosphate dehydrogenase (Stl6PDH) gene), sorbitol production was synthesized **[66].** A similar study by Yebra et al. **[67]r¦r¿** constructed the gene coding stlgph containing remnant chromosomal lactase with a recombinant strain of *Lb. casei* producing sorbitol. They produced 0.024 moles of sorbitol from 1 mole of glucose from the parent strain lactose **[67].**

CONCLUSION

Demands for sugar alcohols are increasing every day. Biotechnologically, microbial production of xylitol, mannitol and sorbitol has gained importance in recent years. In vitro production of synthetic sugar alcohols are costly. Due to the costly reproduction of enzyme preparations and cofactors in enzyme-based production of sugar alcohols, biotechnological approaches for production of these compounds have gained importance. For this reason, production of these compounds using all cells in raw sugar stocks has become attractive. At the same time, microorganisms which do not produce sugar alcohol offer production possibilities with biotechnological methods. Yeasts like *Candida, Pichia,* and *Saccharomyces cerevisiae*, lactic acid bacteria and *E. coli* have gained an important place in sugar alcohol production.

REFERENCES

[1] Granström, T. B., Izumori, K. & Leisola, M. (2007a). A rare sugar xylitol. Part I: the biochemistry and biosynthesis of xylitol. *Applied microbiology and biotechnology*, 74(2), 277-281.

[2] Schiweck, H. (2003). Bä r A, Vogel R, Schwarz E, Kunz M: Sugar alcohols: Ullmann's Encyclopedia of Industrial Chemistry Wiley–VCH.

[3] Bhise, S. & Kaur, A. (2013). Polyols to improve quality and shelf life of baked products: A review. *International Journal of*

Advanced Scientific and Technical Research, 1(3), 262-272.

[4] Zumbe, A., Lee, A. & Storey, D. (2001). Polyols in confectionery: the route to sugar-free, reduced sugar and reduced calorie confectionery. *British Journal of Nutrition*, 85(S1), S31-S45.

[5] Akinterinwa, O., Khankal, R. & Cirino, P. C. (2008). Metabolic engineering for bioproduction of sugar alcohols. *Current opinion in biotechnology*, 19(5), 461-467.

[6] Silveira, M. & Jonas, R. (2002). The biotechnological production of sorbitol. *Applied microbiology and biotechnology*, 59(4-5), 400-408.

[7] Blankers, I. (1995). Properties and applications of lactitol. *Food technology (Chicago)*, 49(1), 66-68.

[8] Sych, J., Lacroix, C. & Carrier, M. (1991). Determination of optimal level of lactitol for surimi. *Journal of food science*, 56(2), 285-290.

[9] Ünal, D. (2011). Farklı oranlarda laktitol ve sakkaroz ilavesiyle hazırlanan Tekirdağ peynir helvalarının bazı özelliklerinin belirlenmesi. Namık Kemal Üniversitesi.

[10] Gültekin, F., Öner, M. E., Savaş, H. B. & Doğan, B. (2017). Tatlandırıcılar, Glikoz İntoleransı ve Mikrobiyota. *Journal of Biotechnology And Strategic Health Research*, 1, 34-38.

[11] Newman, A. W., Vitez, I. M., Mueller, R. L., Kiesnowski, C. C., Findlay, W. P., Rodriguez, C. & McGeorge, G. (1999). *Sorbitol Analytical profiles of drug substances and excipients* (Vol. 26, pp. 459-502): Elsevier.

[12] Krüger, C. (1994). *Sugar Industrial chocolate manufacture and use* (pp. 25-42): Springer.

[13] Güldane, M. (2014). Şeker alkolleri ve yeni nesil antioksidan etkili tatlandırıcıların bisküvi kalite özelliklerine etkileri. Pamukkale Üniversitesi Fen Bilimleri Enstitüsü.

[14] Munro, I., Shubik, P. & Hall, R. (1998). Principles for the safety evaluation of flavouring substances. *Food and Chemical Toxicology*, 36(6), 529-540.

[15] Livesey, G. (2003). Health potential of polyols as sugar replacers, with emphasis on low glycaemic properties. *Nutrition Research Reviews*, 16(2), 163-191.

[16] Grembecka, M. (2015). Sugar alcohols-their role in the modern world of sweeteners: a review. *European Food Research and Technology*, 241(1), 1-14.

[17] Commission, E. (2008). Regulation (EC) No 1333/2008 of the European Parliament and of the Council of 16 December 2008 on food additives. *Official Journal of the European Communities*, 50, 18.

[18] Kratzl, K. & Silbernagel, H. (1963). ‹ ber das Vorkommen von Xylit im Speisepilz Champignon (*Psalliota campestris*). NW,

50(5), 154-154.

[19] Makınen, K. K. & Söderllng, E. (1980). A quantitative study of mannitol, sorbitol, xylitol, and xylose in wild berries and commercial fruits. *Journal of food science*, 45(2), 367-371.

[20] Chiang, C. & Knight, S. (1959). D-Xylose metabolism by cell-free extracts of *Penicillium chrysogenum*. *Biochimica et Biophysica Acta*, 35, 454-463.

[21] Spalt, H. & Niketas, P. (1973). Production of crystalline xylose: Google Patents.

[22] Varo, P. (1979). The baking behavior of different sugars and sugar alcohols as determined by high pressure liquid chromatography.

[23] Gehring, F., Mäkinen, K., Larmas, M. & Scheinin, A. (1974). Turku sugar studies IV. An intermediate report on the differentiation of polysaccharide-forming streptococci (*S. mutans*). *Acta Odontologica Scandinavica*, 32(6), 435-444.

[24] Pepper, T. & Olinger, P. (1988). Xylitol in sugar-free confections. *Food technology (Chicago)*, 42(10), 98-106.

[25] Voirol, F. (1978). The value of xylitol as an ingredient in confectionery. *Xylitol*, 11-20.

[26] Kadam, K. L., Chin, C. Y. & Brown, L. W. (2008). Flexible biorefinery for producing fermentation sugars, lignin and pulp from corn stover. *Journal of industrial microbiology & biotechnology*, 35(5), 331.

[27] Ko, C.-H., Chiu, P.-C., Yang, C.-L. & Chang, K.-H. (2008). Xylitol conversion by fermentation using five yeast strains and polyelectrolyte-assisted ultrafiltration. *Biotechnology letters*, 30(1), 81-86.

[28] Granström, T. B., Izumori, K. & Leisola, M. (2007b). A rare sugar xylitol. Part II: biotechnological production and future applications of xylitol. *Applied microbiology and biotechnology*, 74(2), 273.

[29] Kwon, S.-G., Park, S.-W. & Oh, D.-K. (2006). Increase of xylitol productivity by cell-recycle fermentation of *Candida tropicalis* using submerged membrane bioreactor. *Journal of Bioscience and Bioengineering*, 101(1), 13-18.

[30] Ko, B. S., Rhee, C. H. & Kim, J. H. (2006). Enhancement of xylitol productivity and yield using a xylitol dehydrogenase gene-disrupted mutant of *Candida tropicalis* under fully aerobic conditions. *Biotechnology letters*, 28(15), 1159-1162.

[31] Jin, Y.-S., Cruz, J. & Jeffries, T. W. (2005). Xylitol production by a *Pichia stipitis* D-xylulokinase mutant. *Applied microbiology and biotechnology*, 68(1), 42-45.

[32] Jeffries, T. W. (2006). Engineering yeasts for xylose metabolism. *Current opinion in biotechnology*, 17(3), 320-326.

[33] Jeppsson, M., Bengtsson, O., Franke, K., Lee, H., Hahn-Hägerdal, B. & Gorwa-Grauslund, M. F. (2006). The expression of

a Pichia stipitis xylose reductase mutant with higher KM for NADPH increases ethanol production from xylose in recombinant *Saccharomyces cerevisiae. Biotechnology and bioengineering*, 93(4), 665-673.

[34] Uysal, R. S., Sabancı, S., Sapçı, B. & Akpınar, Ö. (2015). Lignoselulozik Materyallerden Ksilitol Üretimi ve Kullanım Alanları. *Academic Food Journal/Akademik GIDA*, 13(2).

[35] Cirino, P. C., Chin, J. W. & Ingram, L. O. (2006). Engineering Escherichia coli for xylitol production from glucose-xylose mixtures. *Biotechnology and bioengineering*, 95(6), 1167-1176.

[36] Khankal, R., Chin, J. W. & Cirino, P. C. (2008). Role of xylose transporters in xylitol production from engineered *Escherichia coli. Journal of biotechnology*, 134(3-4), 246-252.

[37] Hibi, M., Yukitomo, H., Ito, M. & Mori, H. (2007). Improvement of NADPH-dependent bioconversion by transcriptome-based molecular breeding. *Applied and environmental microbiology*, 73(23), 7657-7663.

[38] Nyyssölä, A., Pihlajaniemi, A., Palva, A., Von Weymarn, N. & Leisola, M. (2005). Production of xylitol from D-xylose by recombinant *Lactococcus lactis*. *Journal of biotechnology*, 118(1), 55-66.

[39] Povelainen, M. & Miasnikov, A. N. (2007). Production of xylitol by metabolically engineered strains of *Bacillus subtilis*. *Journal of biotechnology*, 128(1), 24-31.

[40] Jacobsen, J. H. & Frigaard, N.-U. (2014). Engineering of photosynthetic mannitol biosynthesis from CO_2 in a cyanobacterium. *Metabolic engineering*, 21, 60-70.

[41] Gombás, Á., Szabó-Révész, P., Regdon, G. & Erős, I. (2003). Study of thermal behaviour of sugar alcohols. *Journal of thermal analysis and calorimetry*, 73(2), 615-621.

[42] Sweeteners, A. (2012). O, Brien Nabors, L., Ed: CRC Press: Boca Raton, FL, USA.

[43] Wisselink, H., Weusthuis, R., Eggink, G., Hugenholtz, J. & Grobben, G. (2002). Mannitol production by lactic acid bacteria: a review. *International Dairy Journal*, 12(2-3), 151-161.

[44] Wang, J., Kim, Y. M., Rhee, H. S., Lee, M. W. & Park, J. M. (2013). Bioethanol production from mannitol by a newly isolated bacterium, *Enterobacter sp*. JMP3. *Bioresource technology*, 135, 199-206.

[45] Saha, B. C., & Racine, F. M. (2011). Biotechnological production of mannitol and its applications. *Applied microbiology and biotechnology*, 89(4), 879-891.

[46] Kiviharju, K. & Nyyssola, A. (2008). Contributions of biotechnology to the production of mannitol. *Recent patents on biotechnology*, 2(2), 73-78.

[47] Racine, F. M. & Saha, B. C. (2007).

Production of mannitol by *Lactobacillus intermedius* NRRL B-3693 in fed-batch and continuous cell-recycle fermentations. *Process Biochemistry*, 42(12), 1609-1613.

[48] von Weymarn, N., Hujanen, M. & Leisola, M. (2002). Production of D-mannitol by heterofermentative lactic acid bacteria. *Process Biochemistry*, 37(11), 1207-1213.

[49] Wisselink, H. W., Moers, A. P., Mars, A. E., Hoefnagel, M. H., De Vos, W. M., & Hugenholtz, J. (2005). Overproduction of heterologous mannitol 1-phosphatase: a key factor for engineering mannitol production by *Lactococcus lactis*. *Applied and environmental microbiology*, 71(3), 1507-1514.

[50] Ferain, T., Schanck, A., & Delcour, J. (1996). 13C nuclear magnetic resonance analysis of glucose and citrate end products in an ldhL-ldhD double-knockout strain of *Lactobacillus plantarum*. *Journal of bacteriology*, 178(24), 7311-7315.

[51] Erten, H. (1998). Metabolism of fructose as an electron acceptor by *Leuconostoc mesenteroides*. *Process Biochemistry*, 33(7), 735-739.

[52] Gaspar, P., Neves, A. R., Ramos, A., Gasson, M. J., Shearman, C. A. & Santos, H. (2004). Engineering *Lactococcus lactis* for production of mannitol: high yields from food-grade strains deficient in lactate dehydrogenase and the mannitol transport system. *Applied and environmental microbiology*, 70(3), 1466-1474.

[53] Weymarn, F. N. W. v., Kiviharju, K. J., Jääskeläinen, S. T. & Leisola, M. S. (2003). Scale-up of a New Bacterial Mannitol Production Process. *Biotechnology progress*, 19(3), 815-821.

[54] Reshamwala, S. M., Pagar, S. K., Velhal, V. S., Maranholakar, V. M., Talangkar, V. G. & Lali, A. M. (2014). Construction of an efficient *Escherichia coli* whole-cell biocatalyst for D-mannitol production. *Journal of Bioscience and Bioengineering*, 118(6), 628-631.

[55] Kaup, B., Bringer-Meyer, S. & Sahm, H. (2004). Metabolic engineering of *Escherichia coli*: construction of an efficient biocatalyst for D-mannitol formation in a whole-cell biotransformation. *Applied microbiology and biotechnology*, 64(3), 333-339.

[56] Kaup, B., Bringer-Meyer, S. & Sahm, H. (2005). D-Mannitol formation from D-glucose in a whole-cell biotransformation with recombinant *Escherichia coli*. *Applied microbiology and biotechnology*, 69(4), 397.

[57] Washuttl, J. (1973). A qualitative and quantitative study of sugar alcohols in several foods. *J. food Sci.,* 38, 1262-1263.

[58] O'Donnell, K. & Kearsley, M. (2012). Sweeteners and sugar alternatives in food technology: John Wiley & Sons.

[59] Barbieri, G., Barone, C., Bhagat, A., Caruso, G., Conley, Z. R. & Parisi, S. (2014). Sweet compounds in foods: sugar alcohols

The Influence of Chemistry on New Foods and Traditional Products (pp. 51-59): Springer.

[60] Rhodes, M. & Kator, H. (1999). Sorbitol-fermenting bifidobacteria as indicators of diffuse human faecal pollution in estuarine watersheds. *Journal of applied microbiology*, 87(4), 528-535.

[61] Wildman, R. E. (2016). *Handbook of nutraceuticals and functional foods:* CRC press.

[62] Ortiz, M. E., Bleckwedel, J., Raya, R. R. & Mozzi, F. (2013). Biotechnological and in situ food production of polyols by lactic acid bacteria. *Applied microbiology and biotechnology*, 97(11), 4713-4726.

[63] Jonas, R. & Silveira, M. M. (2004). Sorbitol can be produced not only chemically but also biotechnologically. *Applied biochemistry and biotechnology*, 118(1-3), 321-336.

[64] Association, J. o. t. A. D. (2004). Position of the American Dietetic Association: use of nutritive and nonnutritive sweeteners. *Journal of the American Dietetic Association*, 2(104), 255-275.

[65] Ladero, V., Ramos, A., Wiersma, A., Goffin, P., Schanck, A., Kleerebezem, M. & Hols, P. (2007). High-level production of the low-calorie sugar sorbitol by *Lactobacillus plantarum* through metabolic engineering. *Applied and environmental microbiology*, 73(6), 1864-1872.

[66] Loos, H., Krämer, R., Sahm, H. & Sprenger, G. A. (1994). Sorbitol promotes growth of Zymomonas mobilis in environments with high concentrations of sugar: evidence for a physiological function of glucose-fructose oxidoreductase in osmoprotection. *Journal of bacteriology*, 176(24), 7688-7693.

[67] Yebra, M. a. J. & Pérez-Martínez, G. (2002). Cross-talk between the L-sorbose and D-sorbitol (D-glucitol) metabolic pathways in Lactobacillus caseiaaThe GenBank accession number for the sequence reported in this paper is AF396831. *Microbiology*, 148(8), 2351-2359.