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XYLITOL : PRODUCTION AND APPLICATIONS

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Abstract

Microbial production of Xylitol has received increasing attention in recent years, it is excepted to be cheaper. Microorganism such as Yeasts (*Candida gulliermondii* and *Candidida tropicalis*), Fungi (*Penicillium, Aspergillus, Rhizopus, Glicolodium, Byssochlamyz, Myrothecium* and *Neurospora*), Bacteria (*Mycobacterium smegnatis*) were examied for Xylitol productio. A number of agroresidues, sugarcane baggase, corncobs, as well as Wheat, rice straw, casew apple baggase, Vine waste and eucalyptus globules explored as feed stock for Xylitol production. Xylitol production is sensitive to environmental conditions such as nutrition, temperature, pH, inoculum, cell density, substrate, aeration, nitrogen and carbon sources were also investigated for Xylitol production. This review emphasizes the need and dema nd of Xylitol production from waste by microorganisms.

Keywords: D- Xylose, Xylitol, Hemicellulose, Pentose sugar

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1. INTRODUCTION

Xylitol ($C_5H_{12}O_5$) is a pentose sugar alcohol used as sweetener. Emil Fisher and Stahel first synthesized xylitol in 1891 (Fischer and Stahel, 1891). Its chemical structure is shown in Fig. 1. Xylitol is an acyclic five-carbon sugar alcohol. Xylitol molar mass is 152.15 g/mol. Xylitol has a sweetening power similar to sucrose, nearly twice that of sorbitol and approximately three times that of mannitol. The calorific content (17 kJ/kg) is nearly equal to that of sucrose and thus has the potential to replace sucrose in low-calorie products. The physical and chemical properties of xylitol are listed in Table 1. The special properties of xylitol find use in food and pharmaceutical industry.

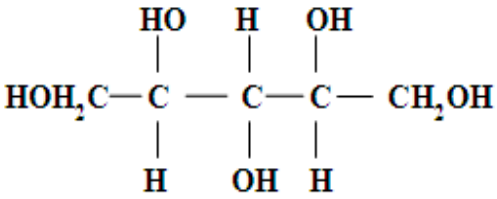

Figure 1. Xylitol chemical structure (Beutler, 1984)

Xylitol occurs in humans and animals as an intermediary product of carbohydrate metabolism. Xylitol occurs in nature in fruits and vegetables, among which the yellow plum and greengages have the highest xylitol content, nearly 1 % of dry weight (Aminoff *et al.*, 1978). Human adults have been shown to produce about 5 to 15 g xylitol per day (Pepper and Olinger, 1988)

Table 1. . Physical properties of xylitol (Jaffe, 1978; Bar, 1991)

Property	**Xylitol**
Formula	$C_5H_{12}O_5$
Molecular Weight	152.15
Appearance	White, crystalline powder
Odor	None
Solubility at 20 °C	169 g/100 g H_2O

pH in water (1 g/10 mL)	5 – 7
Melting Point (°C)	93 – 94.5
Boiling Point (at 760 mmHg)	216 °C
Density (bulk density) (15 °C)	1.50 g l^{-1}
Caloric value 4.06 cal/g	(16.88 J/g)
Relative sweetness	Equal to sucrose; greater than sorbitol and mannitol

Table 2. Xylitol presence in fruits and vegetables (Jaffe, 1978)

Product	**Xylitol (mg/100 g dry substance)**
Brewer's Yeast	4.5
Carrot Juice	12
Chestnut	14
Banana	21
Carrot	86.5
Onion	89
Pumpkin	96.5
Spinach	107
White Mushroom	128
Eggplant	180
Raspberry	268
Cauliflower	300
Strawberry	362

It is present in some fruits and vegetables (E. modi, 1978 and Wang et al., 1981) though the xylitol (Table 2) present in fruits and vegetables is very low (Parajo et al., 1998).

2. XYLITOL APPLICATIONS

2.1. Food and confectionery

Xylitol does not undergo Maillard reaction, and so it does not darken or reduce the nutritional value of the proteins. Hence in the food industry, xylitol is used in the ingredients and formulations of food to improve storage properties, color and taste of food products. Hyvonen and Slotte (1983) reported beneficial effects of xylitol in yogurts either as a sole sweetener or combined with other sweeteners. Xylitol is used for preparation of jams, jellies, marmalades, desserts and relishes (E modi, 1978). Xylitol is used in confectionary products for infants and adults. It is used solely or in combination with other sugar substitutes in the manufacture of sugarless chocolates, chewing gums, hard caramels, licorice sweets, wafer fillings, chocolate, pastilles, and other confectioneries for diabetics (Bar, 1991).

2.2. Antiviral drugs

According to the World Health Organization, more than 350 million people are chronically infected with hepatitis B virus (HBV). A safe and effective vaccination is available in the developed countries, but there is still a need for medication for the millions of chronically ill individuals. Especially in eastern Asia and sub-Saharan Africa chronic liver disease and liver cancer caused by hepatitis B are major health problems. Human immunodeficiency virus (HIV) has infected more than 60 million people since the start of the epidemic, and almost 20 million people have died of AIDS. Despite all the effort, no effective vaccine against HIV has been developed to date. Evidently there is a great need for effective antiviral drugs against HBV and HIV.

. Consequently, in the beginning of the 1990's L-nucleoside analogues became a new class of antiviral drugs (Wang *et al.*, 1998).

Nowadays a large number of L-nucleoside analogues have been synthesized and their antiviral activities have been evaluated. It seems that in general L-nucleoside analogues are less toxic, have greater metabolic stability and similar or even greater antiviral activity than their D-counterparts (Gumina *et al.*, 2001).

2.3. Other medicinal uses

Several types of viruses are found to have strong association with cancer. These viruses can cause chronic infections in humans. It is assumed that the inhibition of virus replication could

thus help in prevention of these types of cancers. It is shown that L-nucleoside analogues that inhibit the replication of HBV can help prevent hepatocellular carcinoma (liver cancer associated with hepatitis B). In addition to L-nucleosides, L-glucose and D-allose (Lim and Oh, 2011) have been shown to have more potential in cancer treatment. They can be used in conjunction with radiation (D-allose) or with other cancer treatments (L-glucose) to improve the results of the therapy. In addition, D-arabinose and D-lyxose can be used as a starting material for the synthesis of antitumor compounds (Moran *et al.*, 1993; Savage *et al.*, 2006).

2.4 . Nutriceuticals

Due to the growing concern of obesity in the developed countries, the need for lowcalorie sweeteners is evident. Even for non-obese people, energy restriction has been shown to increase healthy years, retard the development of many diseases and possibly also increase lifespan. Dietary energy restriction also maintains low plasma glucose and insulin levels and inhibits autoimmune diseases (Levin *et al.*, 1995).

. However, because most rare sugars are digested incompletely, they may have a laxative effect when used in large amounts (Kroger *et al.*, 2006).

3. PRODUCTION METHODS

Currently xylitol is produced chemically, but several biotechnological methods xylitol production method and the current status of biotechnological methods are also reviewed for its production has also been developed. Different raw materials and their treatment for xylitol production will be introduced, as well as the chemical.

3.1. Waste (Substrate) utilization for xylitol production

Lignocelluloses are organic plant materials, which are abundant and renewable. Their major components – cellulose, hemicellulose and lignin – vary in composition and in proportion. Hemicellulose is a plant cell wall polysaccharide that is a mixture of hexosans and pentosans. It can comprise up to 40 % of the total dry material of certain plants. Hemicelluloses are easily hydrolyzed and the resulting hydrolysate will consist of a mixture of sugars such as glucose, xylose and L-arabinose. The pentose fraction, which is composed of xylose and L-arabinose, is much more abundant in hardwoods than in softwoods. High amounts of pentosans are also

present in agricultural residues, such as in sugarcane bagasse, corn cobs, corn fiber as well as in wheat and rice straw (Sreenivas Rao *et al.,* 2007;Winkelhausen and Kuzmanova, 1998; Parajó *et al.,* 1998a).

The use of sugarcane bagasse has been studied as its hydrolysate contains xylose as the main component (Sreenivas Rao *et al.,* 2007). Although hydrolysis can be performed enzymatically, most fermentation studies have focused on hydrolysates derived by acid hydrolysis. Because of its heterogeneous structure and relatively low degree of polymerization, hemicellulose is much easier to hydrolyze than the crystalline cellulosic components of biomass (Sreenivas Rao *et al.,* 2007).

Process for bioproduction of xylitol from lignocellulosic material and the process of converting xylose to xylitol have a significant economic role regarding biomass employment (Prakash *et al*., 2011). Thus, the development and optimization of methods both for obtaining xylose from lignocellulosic wastes and for then converting this sugar into products with higher added value, such as xylitol, is of great interest. Fig. 2 shows a simplified flowchart of the steps performed to produce xylitol using lignocellulosic materials. The employment of waste generated by agribusiness has been widely investigated for potential use of its raw materials in xylitol production. It is known that these materials, after undergoing a pretreatment, can release fermentable sugars such as d-xylose, themain carbon source for xylitol production. Many of the pretreatments or hydrolysis steps that release xylose from the hemicellulosic structure employ acids at dilute concentrations, such as phosphoric acid (Martinez *et al*., 2012) and sulphuric acid (Garcia *et al*., 2011)..

Albuquerque *et al*., (2015) observed the production of xylitol, from cashew apple bagasse hydrolysate (CABH) by a new strain of *Kluyveromyces marxianus*. Initially, the use of activated charcoal in the detoxification of hydrolysates from CABH was evaluated. Then, the influence of the supplementation of CABH with various nitrogen sources was studied. The activated charcoal reduced the concentration of acid and phenolic compounds. *K. marxianus* CCA510 was able to produce xylitol using CABH, with the highest yield of 0.36 g g^{-1} and maximum concentration of 12.73 g l^{-1}

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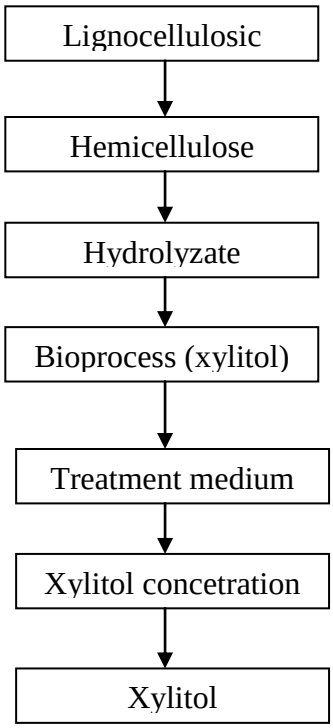

Refrence : Wei *et al*. (2010)

Figure: 2 Process for bioproduction of xylitol from lignocellulosic material

The data on xylitol production from hemicellulosic hydrolysates with yeasts are summarized in Table 3. *C. guilliermondii* FTI 20037 grown on rice straw hydrolysate exhibited the highest production rate of 0.56g/Th, whereas *D. hansenii* NRRL Y-7426 grown on chips of *Eucalyptus globlus* had in fact the highest yield, 0.73 g/g. The presence of inhibitory substances in hydrolysates very often imposes the necessity of purification of the hydrolysates prior to their utilization and/or adaptation of the microorganisms to the sugar which will be used.

Table 3. Xylitol production by different yeast strains and operational conditions using lignocellulosic waste as feedstock

Microorganism	Waste	Culture conditions			Maximum xylitol production (g l^{-1})	Fermentation mode	Yield (g g−1)	Productivity (g $l^{-1}h^{-1}$)	Reference
		pH	Temperature (◦C)	Time (h)					
Candida athensensis SB18	Vegetable waste	7.0	30.0	102	100.1	Batch mode (bioreactor)	0.81	0.98	(Zhang *et al.*, 2012)
Candida guilliermondii FTI20037	Sugar cane bagasse	5.5	30.0	120	50.5	5 Batch mode (Erlenmeyer flasks)	0.81	0.60	(Arruda *et al.*, 2011)
Candida magnoliae	Bamboo culm	--	30.0	30	10.5	Batch mode (bioreactor)	0.59	0.42	(Miura *et al.*,2013)
Candida tropicalis CCTCC M2012462	Corncob	6	35.0	14	38.8	Fed-batch mode (bioreactor)	0.70	0.46	(Ping *et al.*, 2013)
Candida tropicalis NBRC 0618	Olive pruning waste	5.0	30.0	25	53	Batch mode (bioreactor)	0.49	----	(Garcia *et al.*, 2011)
Debaryomyces hansenii	Sugar cane bagasse	6.0	40.0	156	71.2	Batch mode (immobilized cells)	0.82	0.46	(Prakash *et al.*, 2011)
Hansenula polymorpha ATCC 34438	Sunflower stalks	5.5	30.0	169	0.31	Batch mode (bioreactor)	0.00	----	(Martinez *et al.*,2012)
Pichia stipitis NRRL Y-30785	Corn stover	5.6	30.0	72	12.5	Batch mode (Erlenmeyer flasks)	0.61	0.18	(Rodrigues *et al.*, 2011)

Table 4. Xylitol production by yeasts from hemicellulose hydrolysates

Yeast	Substrate	Hydrolysis	Hydrolysate	Released compounds a (g l-1)		Refrences
				D-Xylose	D-Glucose	
C. guilliermondii FTI 20037	sugar cane bagasse	35 mM H_2S0_4, 19O"C, 5 min. steam Explosion, solid/liquid ratio l/6	$Ca(OH)_2$, pH 6.5	61	15	Roberto *et al*., 1991
C. mogii ATCC 18364	Wheat straw	15 % H_2S0_4,121^oC, 30 min		28	3	Rizzi *et al*., 1992
Candida sp. 11-2	sugar cane bagasse	2-3 % H_2S0_4, 100^oC	$CaCO_3$, pH 4.5-6	58	n.r .	Dominguez *et al*., 1996
Debaryomyces hansertii NRRL Y-1426	Eucaliptus, globulus	3.5% H_2S0_4,	Vacuum concentration, $CaCO_3$, pH 6.5, charcoal treatment	73	2	Parajo *et al*., 1996

Thus, in the process of xylitol production by *C. guilliermondii* FTI 20037 from sugar cane bagasse hemicellulosic hydrolysate, the hydrolysate was treated in seven different ways (Roberto *et al*., 1991). The best results were obtained following over titration of the hydrolysate with $Ca(OH)_2$

and subsequent use of H_2SO_4 (Table 4). A single hydrolysis stage in *Eucaliptus globulus* led to the formation of about 17 g l^{-1} o-xylose with a low concentration of inhibitors (Parajo *et al*., 1996). However, the relatively low substrate concentration limited both the productivity and yield of the subsequent fermentation step. Therefore, the D-xylose content was raised by vacuum evaporation. In the comparatively high range of xylose concentrations studied (57-78 g l^{-1}), a single charcoal treatment was unable to reduce the amount of inhibitors to a satisfactory level and convert the hydrolysate to a suitable fermentation medium. Because of this, the combined strategy involving both charcoal adsorption of concentrated hydrolysates and a high initial cell concentration of up to 80 g l^{-1} was applied. When the yeasts C. *guilliermondii* FTI 20037 (Roberto *et al*., 1991) and C. *mogii* ATCC 18364 (Rizzi *et al*., 1992) were grown on hemicellulose hydrolysates for xylitol production, a sequential pattern of sugar consumption was observed

When D-glucose, D-mannose or n-galactose was present in the medium with D-xylose, C. ***guilliermondii*** NRC 5578 exhibited a sequential pattern of utilization with the hexoses being consumed before D-xylose (Lee *et al*., 1996). The utilization of various single sugars, other than Dxylose, was studied in batch cultures of *C. guilliermondii* NRC 5578. Meyrial *et al.* (1991) found that D-glucose, Dmannose and D-galactose were rapidly fermented with specific uptake rates being 2.2, 1.8 and 1.5 times higher than for D-Xylose, although the hexoses were utilized by the strain only for growth and ethanol production; their corresponding polyols were not detected. On studying the same yeast, Lee *et al.* (1996) found that D-glucose was the most rapidly utilized, followed by D-mannose, Dxylose, D-galactose and D-fructose.

3.2. Chemical production

On an industrial scale, xylitol is currently produced by chemical reduction of xylose derived mainly from beech and other hardwoods. The process starts with the production of xylose from the hemicellulosic fraction of biomass by acid catalyzed hydrolysis (Winkelhausen and Kuzmanova 1998; Parajó *et al*., 1998 a; Sreenivas Rao *et al.*, 2007). In order to prevent the contamination of the catalyst, pure xylose is needed. Thus the hydrolysate is subjected to a complicated purification process to remove contaminating substances. Ion exclusion chromatography is used for this purpose and finally xylose is crystallized. The mother liquor can be recycled into the process, and thus about 95 % of the xylose can be crystallized (Aminoff *et al.*, 1978). After the purification, xylose is hydrogenated to xylitol. This is carried out in the presence of a Raney nickel catalyst, at about 125 °C and at hydrogen pressure of 3 bar (Albert *et al.*, 1980). The chemical process for xylitol production is rather expensive because of the need for very pure xylose as a starting material and the high temperature and pressure required for the hydrogenation step (Sreenivas Rao *et al.*, 2007).

The currently used large-scale production is divided into several steps: Step 1. Acid hydrolysis of the xylan-rich natural material; Step 2. Hydrolysate purification up to the point where a solution of pure xylose isobtained; Step 3. Catalytic hydrogenation of pure xylose to xyli-tol with a catalyst (a Ni-Al_2 alloy); Step 4. Purification of the xylitol solution obtained; Step 5. Xylitol crystallization (Jaffe *et al*., 1974). The high temperatures and pressures employed required spe-cialized and expensive equipment to achieve conditions necessaryfor the process (Kelloway & Daoutidis, 2014; Nigam & Singh, 1995; Franceschin *et al*., 2011), not to mention the numerous purification steps required, render the process of obtaining xylitol expensive(Kelloway & Daoutidis, 2014; Nigam & Singh, 1995); therefore, new means of production that can be as effective as many of the traditional methods have been sought (Ping *et al*., 2013).

3.3. Microbial production

Microorganisms more readily assimilate and ferment glucose than xylose. However, although in small numbers, there are bacterias, yeasts and fungi capable of assimilating and fermenting xylose to xylitol, ethanol and other compounds (Yoshitake *et al*., 1971).

Perhaps the most significant characteristic of xylitol, however, is the fact that it is not utilized by the acid producing, cariogenic bacteria of the human oral cavity and therefore inhibits demineralization of tooth enamel (Bar, 1988). A number of long-term field trials in different countries and hence in different nutritional, social and economic environments demonstrated that the consumption of even relatively small amounts of xylitol can significantly reduce the formation of new dental caries (Bar, 1988; Isokanges *et al*., 1988; Makinen, 1992; Kandelman & Gagnon, 1987). In the light of the scientific evidence currently available, it may be regarded as the best of all alternative sweeteners with respect to caries prevention (Makinen, 1992; Bassler, 1978).

A few bacteria such as *Corvnebacteriurn* sp. (Yoshitake, 1971*)* and *Enterobacter liquefaciens* (Yoshitake,1973; Yoshitake,1976) have been reported to produce xylitol. For the first two bacteria, D-xylose was mainly used as a substrate while for the last one, the substrate was D-xylulose or D-xylose isomerized by commercially immobilized D-xylose isomerase. However, due to the relatively small quantities of xylitol formed, xylitol-producing bacteria do not presently attract researchers' interest. Regarding the fungi, there is only one significant report regarding *Petromyces albertensis (*Dahiya, 1991*).*

3.2.1. Microorganisms

Various types of microorganisms, including bacteria and filamentous fungi, can be used in the process. Rangaswamyand Agblevor (2002), for example, selected 17 bacterial cultures ofthe genera Serratia, Cellulomonas and Corynebacterium for potential xylitol production (with trials carried for 48 h at 30 ^{o}C and130 rpm in Erlenmeyer flasks), and found out that Corynebacterium sp. B-4247 was the strain with the highest production rates (10.05 gl^{-1}). Cirino *et al*. (2006) described the production of xylitol using Escherichia coli W3110, a genetically modified strain, andachieved a production of up to 38 g $l^{-1}$of xylitol (30°C, 250 rpmfor 80 h). Other genetically modified bacteria are also promisingfor xylitol production, such as *Bacillus subtilis* (Povelaainen & Miasnikov, 2010) and *Corynebacterium glutamicum* (Sasaki *et al*., 2010). Studies with filamentous fungi for xylitol production are scarce, but some researchers have reported positive results with Hypocrea jecorina (Berghall *et al*., 2007) and (Dashtban *et al*., 2013).. Misra *et al*. (2012) also investigated xylitol production by 18 strains of

yeasts and, coincidentally, the Candida yeasts showed better pro-duction performance. A strain of *C. tropicalis* achieved productionof 12.11 g $l^{-1}$of xylitol using 50 g l^{-1} initial xylose concentration at 30°C, pH 5 and 200 rpm for 72 h. It can be readily observed that the results are very discrepant and are related to the different microbial species andgrowth conditions involved (carbon and nitrogen sources, pH, aeration, and so forth). Controlling these conditions is therefore offundamental importance for optimizing the xylitol production process. Zikou *et al.* (2013) employed a *Thamnidium elegans* strain that produced a maximum xylitol quantity of 31 g l^{-1} during growth onblends on xylose and glucose. Zhang *et al.* (2012) studied xylitol production using the yeast *Candida athensensis* SB18 in agitated flasks and bioreactor performedin both batch and fed-batch systems. The concentration, productivity and yield of xylitol obtained in this study were 100 g l^{-1} ,0.81 g $g^{-1}$and 0.98 g l^{-1} h^{-1}, respectively, using hydrolysed hor-ticultural waste containing 200 g l^{-1} xylose. Villarreal *et al.* (2006) evaluated the xylitol production from eucalyptus hemicellulosic hydrolyzate by *Candida guilliermondii* and,under the best employed operating conditions, 32.7 g l^{-1} of xylitol were produced after 48 h fermentation, which correspond to 0.68 g l^{-1} h^{-1}volumetric productivity.

. In general, yeasts are considered to be the best microbial xylitol producers, and among them, the most efficient producers belong to the genus *Candida* (Sreenivas Rao *et al.*, 2007;Granström *et al.*, 2007a). However, the use of these yeasts in the food industry is problematic because of the pathogenic nature of many *Candida* species (Fridkin and Jarvis, 1996). Recombinant strains have been constructed for the production of xylitol in a safer host strain than *Candida* by introducing the *XYL1*-gene, which encodes xylose reductase activity, into *Saccharomyces cerevisiae*. However, the highest productivities achieved with natural *Candida* strains have usually not been met (Govinden *et al.*, 2001; Meinander and Hahn-Hägerdal, 1997; Lee *et al*., 2000; Parajó *et al*., 1998b). A few bacteria have been reported to produce xylitol from xylose. Both natural (Rangaswamy and Agblevor, 2002) and recombinant production strains have been investigated. However, the reported productivities and final xylitol concentrations have been significantly lower than with yeasts (Yoshitake *et al.* 1973; Parajó *et al.*, 1998a).

3.2.1.1. Yeasts

In an effort to produce xylitol by microbiological method, yeasts have been screened for xylitol production. Forty-four yeast strains in five genera of Candida, Hansenula, Kluveromyces, Pichia and Pachysolen were screened for their ability to convert D-xylose to xylitol by Barbosa *et al*. (1988). *Candida guilliermondii* and *Candida tropicalis* were found to be good xylitol producers. Candida yeasts fermented about 40% D-xylose in 24-48 h (Onishi and Suzuki *et al*., 1966). Vandeska *et al*. (1995) selected D. hansenii, which gave a high yield (0.47-0.48 g/g) than other yeasts.*Candidamogii* gave the highest yield (0.7g/g) comparison with eleven other yeasts studied by Sirisansaneeyakul *et al*. (1995).

Yuuichi *et al*., (1996) studied D-Glucose fed-batch cultivation wa for effective production of xylitol from o-xylose by *Candida tropicalis.*

In an experiment by Dominguez *et al*. (1996) comparing six yeast strains, D. hansenii gave a yield of 0.71 g/g. A production rate of 2.67 g l-1.h xylitol with D-xylose as substrate was obtained using *C. tropicalis* by Horitsu *et al*. (1992). Other Candida species screened were Candida pelliculosa (Kitpreechsvanisch *et al*., 1984 and Nishio *et al*., 1989), C. boidinii (Vongsuvanlert *et al*., 1989), *C. guilliermondi* (Barbosa *et al*., 1988; Lee, 1988 and Meyerial *et al*., 1991), *C. shehatae* (du Preez *et al*., 1986) and *C. tropicalis* (Barbosa *et al*., 1988).

3.2.1.2. Fungi

Production of xylitol has been studied to a lesser extent in fungi and bacteria. Dahiya (1991) studied the xylitol production in Petromyces albertensis and reported a yield of 0.4 g of xylitol/g of xylose after 10 days of fermentation. Ueng and Gong (1982) detected low amounts of xylitol in the fermentation of Mucor sp. on sugarcane bagasse hemicellulose hydrolyzate. *Penicillium, Aspergillus, Rhizopus, Glicoladium, Byssochlamyz, Myrothecium, and Neurospora* sp. have been shown to produce small quantities of xylitol in xylose-containing media .

3.2.1.3. Bacteria

Screening for xylose utilizing bacteria by Yoshitake J. *et al.* (1973) showed that an Enterobacter strain grew on D-xylose and accumulated xylitol extracellularly. Xylitol production by the Enterobacter strain No. 553 using D-xylose was through NADPH-dependent D-xylose reductase.

This showed that enzymatic conversion was not confined to fungi and yeasts. A productivity of 0.35 g L^{-1} h^{-1} was reported with this strain. Corynebacterium species produced xylitol extracellularly only when grown in media having both D-xylose and gluconate (Yoshitake J. *et al*., 1971 and Yoshitake J. *et al*., 1973). The author suggested that the NADPH source required for the reduction derived from the oxidation of 6-phosphogluconate by the enzyme phosphogluconate dehydrogenase. An 80% xylitol yield with D-xylose as substrate was reported by Izumori and Tuzaki (1988), using immobilized D-xylose isomerase enzyme and immobilized Mycobacterium smegmatis. These workers found that the *M. smegmatis* needed D-xylulose to be present in the media for xylitol production to occur. The authors also concluded that complete transformation of D-xylose to xylitol was not possible, due to the inhibition of D-xylose isomerase by xylitol.

4. GROWTH CONDITIONS

The microbial conversion of xylose into xylitol is governed by several factors: strain, inoculum age, cell line history, culture conditions, fermentation type, medium composition (synthetic substrates or composite or lignocellulosic hydrolyzates), presence of inhibiting compounds and the influence of other sugars (Watson *et al*., 1984; Parekh *et al*., 1987; Bjorling and Lindman, 1989; Girio *et al*., 1990).

4.1. Inoculum

On studying the effect of initial cell concentration of *Candida* sp. B-22 on xylitol production from n-xylose, Cao *et al.* (1994) found that the rate of xylitol production was linear and the fermentation time was dramatically reduced over an initial concentration range of 3.8 to 26 g l^{-1}. With an initial yeast cell concentration of 26g l-1, 21 g l^{-1} xylitol was produced from 26 g l^{-1} o-xylose. A high initial concentration was also beneficial for xylitol production by C. *boidinii* NRRL Y- 17213. With an initial D-xylose concentration of 5g l^{-1}, the xylitol yield and specific productivity doubled when the inoculum level increased from 1.3 to 5.1 g l^{-1} (vandeska *et al*., 1995).

The effect of inoculum size on the microbial production of xylitol from hemicellulose hydrolysates was also investigated (Roberto et al.,1996; Parajo et al., 1996). In addition to

inoculum size, the culture age, which is related to the metabolic activity of cells, was also studied. Varying the inoculum age of *C. guilliermondii* FTI 20037 from 15 to 70 h demonstrated that 15-h-old cells gave poor results, whereas 24-h-old and older cells had similar effects and influenced only the productivity of xylitol but not its final concentration and yield (Silva *et al*., 1997; Pfeifer *et al*., 1996). Cultivation of the inoculum using different carbon sources (o-xylose, mixture of n-xylose and glucose in a 4: 1 ratio and glucose) had only a minor influence othe bioconversion of D-xylose (Pfeifer *et al*., 1996).

4.2. Cell density

The effect of cell density on xylitol production has been studied in most xylitol producing yeasts. High cell density has been shown to increase the xylitol yield and specific productivity of xylitol in *C. boidinii* (Saha and Bothast, 1997 and Winkelhausen *et al*., 1998). Increase in the initial cell concentration from 0.3 g l-1 to 3 g l^{-1} increased xylitol productivity from 0.68 g l^{-1}.h to 2.25 g l^{-1}.h in *Debaryomyces hansenii* (Dominguez *et al*., 1997). Cao *et al*. (1994) reported an increase in xylitol production when the initial cell mass was increased from 3.8 to 14 g l^{-1} in *Candida species*. Vandeska *et al*. (1995) reported a similar trend in both productivity and xylitol yield. In an initial D-xylose concentration of 50 g l^{-1} the xylitol yield and specific production rate doubled when the cell density was increased from 1.3 g l^{-1} to 5.1 g l^{-1}. At higher cell density *D. hansenii* NRRL Y-7426 grown on wood hydrolyzate was shown to produce more xylitol (Winkelhausen *et al*., 1998). In contrast, 0.67 - 2.41 g l^{-1} cell density increase in *C. guilliermondii* FTI 20037 growing on rice straw hydrolyzate did not increase xylitol production (Roberto *et al*., 1996).

4.3. Effect of pH

4.4. The optimum initial pH for xylitol production depends on the microorganism used. The initial optimum pH for xylitol production for some of the yeasts reported is listed in Table 5.

Table 5. Initial optimum pH for xylitol production for some of the yeasts

Yeast	Initial pH	Reference
C. tropicalis	4	Yahashi *et al*. (1996 a)
C. shehatae	4.5	Kastner *et al*. (1996 a)
C. parapsilosis	4 –5.5	Nolleau *et al*. (1995)
Candida sp.	4-6	Cao *et al*. (1994)

Debaryomyces hansenii	5.5	Dominguez *et al*. (1996)
C guilliermondii	6.0	Nolleau *et al*. (1995)
C. boidinii	7.0	Vandeska *et al*. (1995); Vongsuvanlert and Tani (1989)
P. tannophilus	8.0	Debus *et al*. (1983)

Maria *et al*., (1997) studied on effect of pH on *Candida guilliermondii* FTI 20037 was grown in sugar cane bagasse hydrolysate supplemented with (NH_4 SO_4, 2.0 g l^{-1}, $CaCl_2$, 0.1 g l^{-1} and rice bran 20.0 g l^{-1}, through 45-h batch tests (agitation of 200 min.' and temperature of 3O'C) with initial pH varying from 2.5 to 7.5. Under pH < 4.5 the consumption of glucose, xylose and arabinose as well as the production of xylitol and cells were inhibited. Nevertheless, at pH values >- 5.5 the yeast produced xylitol with a yield of 0.75 g g^{-1} and productivity of 0.57 g l^{-1} h^{-1}. Moreover, the yeast was also capable of metabolizing the acetic acid, which is always present in media made from hydrolysates of plant material. The inhibition of xylose/xylitol bioconversion could be related to the effects of low pH and undissociated acetic acid concentration over 5.0 g l^{-1}.

If uncontrolled, pH drops during the fermentation, and therefore under such conditions the initial pH values have to be higher than under controlled conditions. The optimum initial pH value for best xylitol yield in C. *boidinii* was 7 (Vandeska *et al*.,1995; Vongsuvanlert & Tani, 1989), whereas under controlled conditions a pH of 5.5 was better (Vandeska *et al*., 1995). Batch culture of C. *parapsilosis* ATCC 28474 (Furlan et al., 1994) was performed at pH 6, while for continuous culture, a pH of 4.5 was used (Cao *et al*., 1994).

4.5. Effect of temperature

Xylitol is produced by most yeast at temperature range of 24 - 45°C, and the optimum temperature range is 28 - 30°C. Xylitol production was uninterrupted in temperature range of 35 - 40°C for Candida sp. (Cao *et al*., 1994) and at a temperature range of 28 - 37°C for *D. hansenii* (Dominguez *et al*., 1997). Barbosa *et al*. (1988) reported maximum xylitol concentration and product yield for *C. guilliermondii* at 30 - 35°C range, though maximum growth occurred at 35°C. In *P. tannophilus* a 7°C increase in temperature from the initial 30°C led to a reduction in xylitol production (Barbosa et al., 1990).

The most suitable temperature for xylitol production in yeasts was shown to be 30°C. Small temperature variations above this temperature, do not significantly affect xylitol production in C. *tropicalis* DSM 7524. The xylitol yield was, for the most part, temperature-independent when the yeast was cultured in a temperature range between 30°C and 37°C but above 37°C the xylitol yield decreased sharply (de Silva & Afschar, 1994). Xylitol formation in *C. guilliermondii* FTI 20037 was the same at 30 and 35"C, but decreased when the temperature increased to 40°C (Barbosa *et al*., 1988). The conversion of D-xylose to xylitol by *Candida* sp. B-22 was relatively constant over the temperature range of 35-40°C. At temperatures of 45°C and higher, the conversion was sharply reduced (Cao *et al*., 1994). This was probably due to loss of the activities of both NADPH and NADH-dependent xylose reductase, as the temperature increased. When investigating the effect of temperature on ethanol and xylitol production, du Preez *et al.* (1986) found that at higher temperatures, production of xylitol is favored over that of ethanol. Xylitol production of *C.shehatae CSIR-Y492* increased & fold as the temperature increased from 22 to 36°C. *P. stipitis CSIR-Y633* produced xylitol at 36°C but no detectable amounts at lower temperatures.

Most studies employing yeasts in biotechnological processes have been carried out by adjusting the temperature in the rangeof 30–37^{o} C, which proves to be optimal for these microorganisms in xylitol production (Ping *et al*., 2013; Misra *et al*., 2013). Rodrussamee *et al*. (2011) studied the potential of *K. marxianus* DMKU3-1042 for xylitol and ethanol production from sugars present in hemicelluloses hydrolysates at high temperatures (30^{o}C, 40^{o}C and 45^{o}C). Cellgrowth and sugar consumption were observed at all temperatures studied, confirming that the strain can grow at high temperatures.. Srivani and Setty (Srivani & Setty; 2012) attempted to find the optimal environ-mental conditions for xylitol production by Candida parapsilosis NCIM-3323, studying variations in temperature (25–35^{o}C) and initial pH (3–6). Over the range of initial pH studied. Ramesh *et al*. (2013) investigated xylitol production from corncob hemicellulosic hydrolysate by *Debaryomyces hansenii var. hansenii* (MTTC 3034) using a statistical optimization of response surface approach. Inthis study, the optimum temperature and pH for production of the polyol were 31.8^{o}C and 7.25 g l^{-1} , respectively.With *C. tropicalis*, several studies have considered temperaturesof 30–35^{o}C for xylitol production. Ping *et al*. (2013), for example, utilized *C. tropicalis* CCTCC M2012462 for xylitol production from hydrolysed corncob at 35^{o}C, reaching

38.8 g l^{-1} after 84 h of bio-processing. Misra *et al*. (2013) also used a corncob hydrolysate to obtain 11.89 g l^{-1} xylitol at 30°C using a strain of *C. tropicalis*. El-Baz *et al*. (2011) studied the production of xylitol in synthetic media at 30◦C for *C. tropicalis*, obtaining a maximum concentration of 36.25 g l^{-1}.

4.6. Nitrogen sources

Various nitrogen sources are being investigated in biotechnological studies to optimize the growth of microorganisms and the production of metabolites of interest. Among the most studiedorganic sources are peptone, yeast extract and casamino acid (Wang *et al*., 1971). There have been many studies investigating the influence of urea utilization as a nitrogen source for xylitol production.Rodrigues *et al*. (2011) investigated the effects of employing ureaand ammonium sulphate as nitrogen sources on xylitol production by Pichia stipitis YS-30. The medium, containing corn stover hydrolysate, was supplemented with either 5.0 g l^{-1} urea or 5.0 g l^{-1} ammonium sulphate. It was observed that when ureawas used instead of $(NH_4)_2SO_4$, xylose consumption and ethanolproduction rates increased by 25% and 34%, respectively. Ko *et al*. (2008) studied xylitol production employing waste wood fermentation. The use of urea as a nitrogen source in the fermentation medium was tested, replacing the yeast extract with 10 g l^{-1} urea or 10 g l^{-1} soybean meal. The yield obtained using urea was 1.3-fold higher than that obtained with yeast extract. Zhang *et al*. (2012) evaluated ethanol and xylitol athensensis SB18 from vegetable waste, supplementing the production medium with 2.0 g l^{-1} urea.

The results indicated that, among the nitrogen sources investigated, urea is themost promising for the studied strain.In contrast, Hongzhi *et al*. (2011) conducted an experimental statistical design to optimize a culture medium for xylitol productionfrom corn bagasse hydrolysate. The nitrogen sources used in theexperiments were ammonium nitrate, peptone, urea, ammoniumsulphate and yeast extract. Among these sources, only $(NH_4)_2SO_4$ and yeast extract had a significant influence, with optimal concen-trations of these components of 5.0 g l^{-1} and 4.6 g l^{-1} respectively.

The nature and concentration of the nitrogen source in the medium influences the xylitol production and xylose utilization by the microorganism. Organic nitrogen nutrients like yeast extract have been shown to increase xylitol production compared to nitrogen salts (Saha and Bothast, 1997 and Horitsu *et al*., 1992). Results of analyzing eight ammonium salts and four organic nitrogen sources used for xylitol production with *P. albertensis* showed that ammonium acetate was most effective among the salts and yeast extract as the most suitable for xylitol formation (Saha and Bothast, 1997). Winkelhausen *et al*., (1998) observed increased xylitol production rate in *C. tropicalis* DSM 7524 when the medium contained 20 g l^{-1} yeast extract. the maximum yield of xylitol was obtained when the concentration of yeast extract was 1 g l-1 (Silva *et al*., 1997). Sirsansaneeyakul *et al*. (1995) reported improved cell growth, xylitol yield and productivity in C. mogii when the fermentation medium contained yeast extract and peptone. Vongsuvanlert and Tani (1989) observed highest productivities with *C. boidinii* when yeast extract was the nitrogen source. Palnitkar and Lachke (1992) observed increased xylose utilization when an organic nitrogen source was in the media. Barbosa et al. (1990) also observed higher xylose consumption, but decreased xylitol production, when the medium contained 5 g l^{-1} yeast extract with *C. guilliermondi*. Kern *et al*. (1998) observed higher yields of D-xylose reductase and xylitol dehydrogenase in *C. tenuis* CBS 4435 when yeast extract or peptone was used as nitrogen source instead of ammonium salts. Lu *et al*. (1995) studied the influence of aspargine, glycine, traders protein, yeast extract, urea, casein hydrolyzate, NH_4NO_3, $(NH4)_2SO_4$, NH_4Cl, $NH_4H_2PO_4$ and $NaNO_3$ as nitrogen sources on xylitol production with mutant Candida sp. L-102. Barbosa *et al.* (1988) reported a higher xylitol yield with C. *guilliermondii* when urea was used instead of ammonium sulfate in fermentations.

Vandeska *et al.* (1995) observed increased xylitol yields and improved biomass productions by *C. boidinii* when urea was used instead of ammonium sulfate. Thus most studies for xylitol production show organic nitrogen sources such as yeast extract and peptone as better nitrogen sources instead of ammonium salts.

4.7. Carbon source

It is important to understand the effect of hexose and other pentose sugars on xylose utilization and xylitol production as hydrolyzates contain sugar mixtures of varied compositions. D-xylose

utilization is not inhibited by D-galactose, D-cellobiose and L-arabinose while D-mannose and D-glucose affect xylose utilization (Winkelhausen *et al*., 1998; Lee *et al*., 1996; Lucas *et al*., 1986). Feeding glucose to C. tropicalis growing on xylose in 3-L batch fermentation improved xylitol production (104.5 g l^{-1}) as much as 1.3 times (Saha and Bothast, 1997). Saha and Bothast (1997) also observed that glucose was assimilated first in mixed substrates. *C. boidinii* in batch fermentations on a mixture of glucose and xylose showed a faster growth compared to xylose alone in the medium. However, maximum xylitol production (41 g l^{-1}) was lower than the xylitol produced (59.3 g l^{-1}) with xylose alone.

In the presence of glucose a strong repression of xylose utilization occurred and sequential uptake of sugars was observed in *C. tropicalis* ATCC 96745 (Walther *et al*, 2001). In stirred batch fermentation Silva *et al*. (1996) observed 66% conversion efficiency of xylose to xylitol but this decreased to 45% when glucose was present. *C. guilliermondii* utilized mannose, galactose, L-arabinose and glucose to produce ethanol, arabitol and cell mass but no xylitol was produced (Meyrial *et al*., 1991). *C. guilliermondii* has been shown to consume D-glucose very rapidly but D-mannose, D-xylose, D-galactose and D-fructose were shown to be consumed slowly in that sequence (Lee *et al*. 1996). When more than 10 g l^{-1} glucose was present in the medium the xylitol yield decreased and ethanol production was observed (Oh *et al*., 1998). In *C. tropicalis* ATCC 96745 a 50% reduction in yield was observed when the ethanol concentration in the medium was higher than 30 g l^{-1} (Walther *et al*., 2001).

Yuuichi *et al*., (1996) used o-xylose was used as a single carbon source, the yeast consumed o-xylose for production of xylitol as well as for growth and cell maintenance resulting in decreased xylitol yield. To improve the xylitol yield, it is necessary to increase the cell mass using another carbon source.

The use of lignocellulosic materials for the production of high-added value bioproducts is promising, as they represent anabundant and renewable supply of carbon sources. Lignocellulosic materials such as corncobs, rice straw, sugarcane bagasse, cashewbagasse, sawdust and oat hulls, among others, represent an important and cheap source of microbial substrates. The hemi-cellulosic fraction can be hydrolysed to xylose and then fermented to

xylitol (Miura *et al*., 2013). Kamat *et al*. (2003) isolated a yeast strain, from mangrove forests that was capable of producing xylitol (29.1 g l^{-1}) from detoxified corncob hydrolysate (composition: 65 g l^{-1} xylose, 13 g l^{-1} glucose and 6.3 g l^{-1} arabinose).. Misra *et al*. (2013) also studied the potential of corncob hydrolysate for xylitol production using a strain of *C. tropicalis*. These authors achieved amaximum extraction of 20.92 g l^{-1} xylose using 1% (v/v) sulphuric acid in the corncob hydrolysis. Concentrating the hydrolysate upto 52.71 g l^{-1}, in relation to xylose concentration, 15.19 g l^{-1} of xylitol was obtained at 60 h of culture. Ping *et al*. (2013) used a concentrated non-detoxified corncob hydrolysate for xylitol production by *C. tropicalis* CCTCC M2012462, reaching a maximum of 38.8 g l^{-1} xylitol. Detoxified bamboo culm acid hydrolysate (19 g l^{-1} xylose) was fermented by *C. magnoliae* FERM P-16522 in a study by Miura *et al*. (2013) concluded that this raw material has the potential to be utilized in xylitol production, reaching a maximum concentration of 10.5 g l^{-1} for the polyol.

Martinez *et al*. (2012) investigated the production of xylitoland ethanol by *Hansenula polymorpha* from sunflower stems hydrolysed with phosphoric acid. Srivani and Setty (2012) studied the optimiza-tion of several parameters (pH, temperature and initial xylose concentration) for xylitol production from xylose fermentationby *C. parapsilosis* NCIM-3323. It was concluded that the maximum production of xylitol (28.14 g l^{-1}) was achieved with the following values for pH, temperature and initial xylose con-centration: 3.5, 30^{o}C and 60 g l^{-1}, respectively. Vajzovic *et al*.(2012) used a synthetic medium (containing glucose or xylose, 30 gl^{-1}) to evaluate xylitol production in the presence of certain inhibitors (furfural, 5-hydroxymethylfurfural and acetic acid)and the results obtained by these authors showed that high concentrations of inhibitors (above 3 g l^{-1}) negatively affected xylitol production.

4.8. Effect of the initial substrate concentration

The composition of the media and the nature of the carbon source influence the production of polyols in yeast. Increase in initial xylose concentration usually led to decreased growth rate, unless the aeration rate was increased Nolleau *et al*., 1993). Da Silva and Afschar, (1994) observed inhibition in growth due to the high concentrations of substrate.

Optimum initial xylose concentration is essential for growth and xylitol production. Initial xylose concentrations in the range of 20-50 g l^{-1} produced the highest specific growth in *C. guilliermondii* (Meyrial *et al*., 1991). Srisansaneeyakul *et al*. (1995) observed maximum specific growth in *C. mogii* when the initial xylose concentration was 5-10 g/1. The optimum initial xylose concentration reported for xylitol production was 60 g l^{-1} for P. tannophilus, 200 g l^{-1} (Gong *et al*., 1981) and 100 g l-1 (Da Silva and Afschar, 1994) for *C. tropicalis* and 200 g l^{-1} (Meyrial *et al*., 1991) for *C. guilliermondii*. A five-fold increase in initial xylose concentration resulted in a 5.5 fold increase in the product yield and an increase in specific substrate consumption and product generation (Sirisansaneeyakul *et al*., 1995). In the case of Candida sp. B-22 a 249 g l^{-1} initial xylose concentration produced a maximum production rate (0.269 g/g.h) at 84.5% theoretical yield (Chen and Gong, 1985). *C. tropicalis* HXP2 accumulated maximum xylitol (144 g l^{-1}) at initial xylose of 200 g l^{-1}, while *P. albertensis* and *C. boidinii* accumulated xylitol (39 g l^{-1} and 36.8 g l^{-1}) at 100 g l^{-1} initial D-xylose (Saha and Bothast, 1997). At xylose concentrations greater than 10 g l^{-1} *P. tannophilus* accumulated xylitol, but at lower xylose concentrations (5 - 8 g/1) and fed-batch process feeding, ethanol was produced (Woods and Millis, 1985). Meyrial *et al*. (1991) obtained an increase in xylitol production when the initial xylose concentration was increased from 10 g l^{-1} to 300 g l^{-1}, but the increase in xylose affected the specific growth rate and yield. Horitsu *et al*. (1992) observed increased productivity and yield as the initial xylose concentration increased during a *C. tropicalis* fermentation. However in the case of *P. albertensis*, the initial xylose concentration of 150 g l^{-1} decreased the xylitol production. Saha and Bothast (1997) observed hyperbolic xylitol formation in *C. mogii* in oxygen-limited fermentations when the initial xylose concentrations was 5-53 g l^{-1}. Initial xylose concentration of 3.8 - 26 g l^{-1} showed a linear xylitol production rate in fermentations of *Candida sp. B-22* (Cao *et al*., 1994). In most fermentation improved volumetric and specific xylitol productivity was observed when the initial substrate concentrations were high (Parajo *et al*., 1998b).

4.9. Effect of vitamins

Vitamins in the medium have been shown to increase productivity and enhance growth in yeasts. When the medium for *C. guilliermondii* was supplemented with 0.05 µg biotin, Lee *et al*. (1988) observed a productivity increase from 0.002 g l^{-1}.h to 0.009 g l^{-1}.h, while a 0.25 µg l^{-1} biotin

supplementation increased the productivity to 0.044 g l^{-1}.h. They also observed biotin supplementation increased xylitol production in *Pachysolen tannophilus.*

4.10. Effect of Nutrition

Although various media have been used to culture xylitol-producing yeasts, a few generalizations can be made: (i) For some yeasts, yeast extract is an important nutrient for xylitol production. (ii) For other yeasts, sometimes also including yeasts from the first group, but reported by different researchers, yeast extract has no significant effect on xylitol formation. These yeasts prefer urea or urea and Casamino acids. (iii) For kinetic studies, synthetic media are used which provide all the necessary minerals and vitamins.

The culture media for C. *parapsilosis* ATCC 28474, (Furlan, *et al*., 1994) C. *boidinii* no. 2201, (Vongsuvanlert & Tani, 1989) C. *guilliermondii* NRC 5578 (Meyrial *et. al* 1991) and C. *tropicalis* IF0 0618 (Horitsu, 1992) contain yeast extract in concentrations ranging from 10 to 20 g l^{-1}. Yeast extract at a maximum concentration of 1 g l^{-1} was sufficient for C. *tropicalis* DSM 7524. Concentrations higher than 15 g l^{-1}, blocked the conversion of p-xylose to xylitol (de Silva & Afschar, 1994). Increased concentrations of yeast extract of 5 and l0 g l^{-1} increased the biomass production of C. *guilliermondii* FTI 20037, but sharply decreased its xylitol productivity (Silva *et al*., 1997). Similarly, the addition of yeast extract and peptone to the defined medium for *C. lnogii* ATCC 18364 enhanced cell growth markedly but had no significant effect on the yield and specific productivity of xylitol (Vadeska *et al*., 1995). Xylitol formation in C. *guilliermondii* FTl 20037 (Barbosa *et al*., 1988; Nolleau *et al*., 1993) and C. *parapsilosis* ATCC 28474 (Nolleau *et al*., 1993) was highest with urea as a substrate. In most cases, the medium was supplemented with Ca amino acids. In some yeasts, special supplements improved xylitol production. Thus, on studying the effect of biotin, Lee *et al.* (1988) found that in high-biotin media, in P. *tannophilus* NRRL Y-2460 ethanol production was favored over that of xylitol, while in C. *guilliermondii* FTI 20037 xylitol formation was favored. This was explained by the oxidation of methanol, providing NADH to the medium.

Future prospects

Rare and unnatural sugars have many potential uses in both medicine and food industry. L-Sugars are generally as sweet as the corresponding D-sugars, but are not fully absorbed by the human body. Additionally, several rare D-sugars are not substrates of the digestive enzymes, making them ideal low-calorie sweeteners. Rare sugar sweeteners generally also lack the typical aftertaste of artificial sweeteners. Rare sugars and sugar alcohols often possess nutriceutical properties, for example xylitol inhibits caries and D-tagatose lowers blood sugar levels. Furthermore, rare sugars have many possible uses in medicine. Some rare sugars and their derivatives have antiviral and anticancer properties, some act as cardioprotectants or as anti-inflammatory agents. Rare sugars are generally expensive, since they cannot be isolated from natural sources in significant amounts. As new economic production methods are discovered, the sugars can be studied more extensively, and various new pharmaceutical, nutritional and other applications will most likely be found. Instead of the classical approach to the improvement and optimization of xylitol productivity and yield by changing the fermentation variables, metabolic engineering offers opportunities to change the genetic properties of the microorganisms themselves.

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