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Xylitol: Production and its applications – A Review

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ABSTRACT

Xylitol is important chemical due to its various applications. The use of xylitol as a sweetener for diabetic patients has made it a high valuable special chemical. As xylitol is present in low concentrations in fruits and vegetables, therefore its extraction is unaffordable from these sources. Thus, xylitol can be produced chemically by reduction of xylose in presence of suitable reducing agents and microbial route method. Although several species of yeast, fungi and bacteria synthesize xylitol by the species of the genus *Candida, Saccharomyces, Pichia, Debaryomyces, Trichosporon, Enterobacter, Corynebacterium, Mycobacterium* etc. The chemical synthesis of xylitol from xylose is the dominant production method of xylitol production. The industrial process to produce xylitol involves the chemical hydrolysis of D-xylose followed by the hydrogenation of the resultant hemicellulose hydrolysate by catalysts including palladium and nickel. For the chemical synthesis of xylitol, high temperatures and high pressure are required. These processes are very expensive which makes the production costs of synthesizing xylitol because of the highly energy intensive, high temperature, pressure and metal catalyst used for a sustained period of time. Therefore, in this review article we study the microbial route of xylitol production from agricultural residues.

Key words*: Xylitol, Xylose Reductase, Agricultural residues, Sweetener*

Introduction

Sweetener is a substance with the ability to impart a sweet taste to foods and beverages (Sharma *et al*., 2016). Sugar alcohols are a class of polyols having applications in improvement of food nutritional characteristics. They present health advantages such as: lower caloric content, cancer fighting effects and lowering of the glycemic index (Lucia *et al*., 2006). Xylitol ($C_5 H_{12}O_5$) is a five-carbon sugar alcohol. Its chemical structure is shown in Fig. 1. It occurs widely in nature but it is also a normal intermediate in humans (Ahmad *et al*., 2012). One gram of xylitol contains 2.43 kilocalories (kcal), as compared to one gram of sugar, which has 3.87 kcal. Because of these characteristics and benefits, its dietary and chemical properties have been extensively studied (Parajo *et al*., 1998). It is used in the pharmaceutical, cosmetic, dental, and food industry (Mohamad *et al*., 2015). It issued as an alternative non caloric sweetener. Xylitol is dissolved in water, and it is sweet as sucrose, having only approximately two-third of its calories, and is also approximately twice a sweet as sorbitol and nearly three times sweet as mannitol (Winkelhausen *et al*., 1998). In industry, xylitol is mostly produced through a chemical method, which is based on catalytic xylose dehydrogenation (Granstrom *et al*., 2007).

A German and French chemist concurrently discovered xylitol in 1891(Rehman *et al*., 2016). After several years, xylitol crystals were purified successfully, and it was widely used as sugar substitute during World War II (Rehman *et al*., 2013). Xylitol is a non-fermentable sugar alcohol. Because xylitol absorption in the body does not require insulin, it is safe to use as a food sweetener for people having diabetes. Xylitol produces a cool sensation, heat resistant, and slow absorption by the intestine.

Chemical hydrolysis and biological hydrolysis are two types of standard hydrolysis methods for xylitol. Chemical hydrolysis uses acid or base as a catalyst at high temperatures and pressure (Saini *et al*. 2015). Because of this quick process, it must be closely detected to avoid the coproduction of numerous degradative compounds.

Xylitol is found mostly in chewing gum and mints. Xylitol inhibits the growth of the bacteria which cause cavities in tooth. In nature, D-xylitol is found in various fruits, berries, corn husks, oats, vegetables, cauliflowers, and also in mushrooms. Xylitol can be extracted from birch, raspberries, plums and in corn fibres. The content of D-xylitol in fruits and vegetables is usually low, and thus it is unaffordable to extract large amounts of D-xylitol from such sources. In industrial scale production, hemicellulose is utilized as the material to separate pure D-xylose, which is subsequently reduced to D-xylitol. (Xi Chen *et al*., 2010). Xylitol is industrially produced by the chemical reduction of D-xylose derived from photosynthetic biomass hydrolysates. Photosynthetic biomass is the most renewable resources in the world which consist cellulose, hemicellulose, lignin and a low quantity of pectin, protein, extractives, and ash (Perez *et al*., 2002).

Xylitol is an intermediary metabolite of xylose utilization by microbial strains (Yokoyama, 1995). Xylose reductase (XR; EC 1.1.1.21) and xylitol dehydrogenase (XDH; EC 1.1.1.9) are the crucial enzymes in xylose fermentation and xylitol bioproduction by organisms. These two enzymes require pyridine nucleotide coenzymes with specificity towards its different forms (nicotinamide adenine dinucleotide; NADH or NADPH) in different yeasts. Under aerobic conditions, the NADH is formed during xylose metabolism that reoxidized in the electron transport system, and as a result, xylitol is not produced. (Parajo *et al*., 1998).

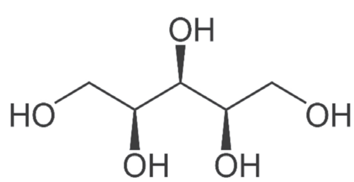

Fig. 1. Xylitol Structure

Agricultural residues

Agricultural residues are any material that remains in the field after harvest such as mixture of stems, leaves, and pods, commonly called straws (Sun *et al*. 2010). The processing of crops seeds generates large amounts of waste such as cobs and husks. Agricultural waste is an abundant source of organic compounds such as cellulose, hemicellulose, lignin, minerals, lipids, proteins and pectin (Saini *et al*. 2015). It has been known that a number of hydrolysates from agricultural residues contain a high level of pentoses that could be used for bioconversion into xylitol from pentoses. For examples, Apple pomace, Banana leaves, Cocoa pod husks, Olive pomace, Rice straw, Wheat bran. Sugarcane bagasse is a lignocellulosic material having high content of hemicellulose. The extraction process from such sources is not cost effective.

Pathway of Xylitol Biosynthesis

To produce xylitol from xylose is proceed by the presence of the enzyme xylose reductase within cell. Xylose reductase catalyses the reduction of xylose by NADPH to the polyalcohol xylitol and NADP+. Xylitol reductases can use NADH as a cofactor. The xylose reductase from cells has been purified by dye ligand affinity chromatography and ion exchange chromatography. The xylose reductase prefers NADPH compared to NADH as a cofactor based on binding specificity and it has been shown that NADP+ is a strong competitive inhibitor of the reaction. The xylose reductase contains a catalytic tetrad consisting of tyrosine, lysine, aspartic acid and histidine residues essential for its activity. The lysine residue has been shown to be located near the coenzyme binding site. The xylose reductase was highly hydrophobic relative to amino acid composition including many leucine residues.

Further metabolism of xylulose is a common phenomenon for both eukaryotes and prokaryotes. Xylulose participates in the pentose phosphate pathway and glycolysis for energy generation. Thus, the microbes with active xylose reductase pathway are possible biocatalysts for xylitol production at alarge scale.

Xylitol Production by Microorganisms

Xylitol production from microorganisms have been considered a sustainable process for numerous industrial applications because, the process can be

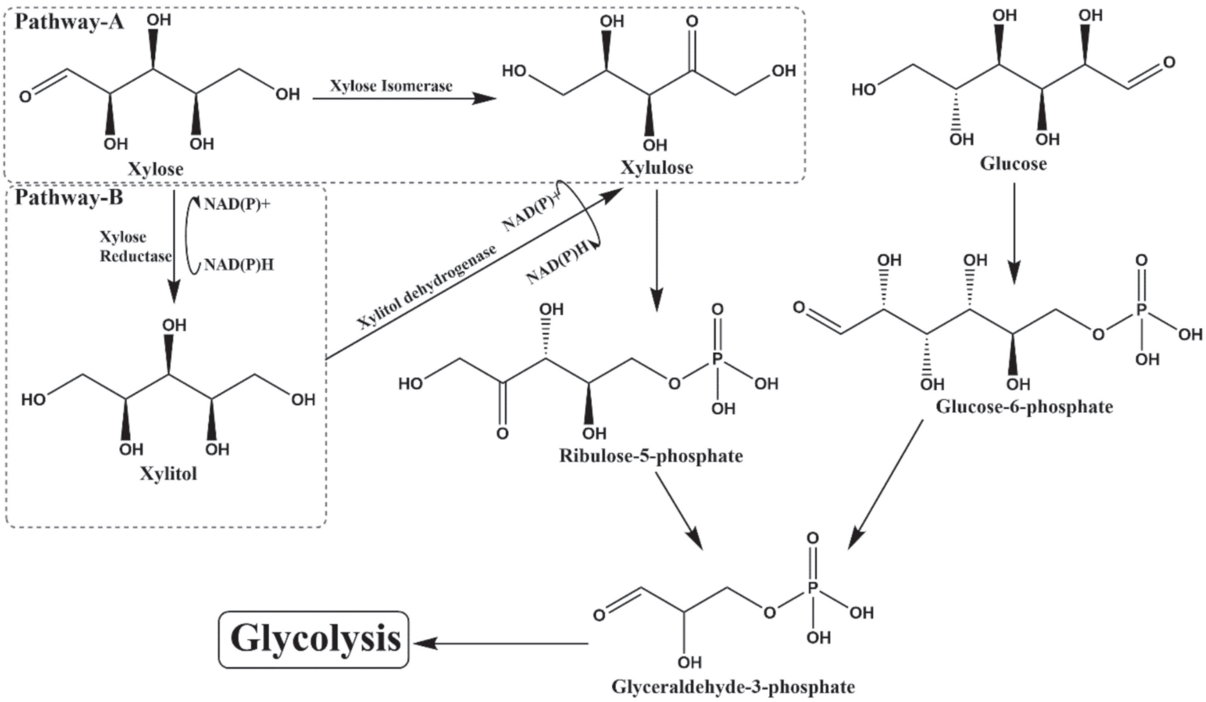

Fig. 2. Xylose metabolism: (A) Xylitol non-producers (B) Xylitol producer. Pathway A: Among prokaryotes, intracellular xylose is directly transformed to xylulose by xylose isomerase while in pathway B: In eukaryotes, the conversion of xylose to xylulose is a two-step process NAD(P)H/NADH-dependent xylose reductase reduces intracellular xylose to xylitol, which further oxidizes to xylulose by NAD+-dependent xylitol dehydrogenase (Park*et al*. 2014)

conducted under mild controlled conditions. The basis for biotechnological production of xylitol from lignocellulosic materials resides on xyloses hydrogenation to form hemicelluloses, using several microorganisms such as yeast, bacteria, and fungi, of which, yeasts are best to produce xylitol (Linares *et al*., 2018). Xylose hydrolysed to xylitol by the enzyme xylose reductase in the presence of NADPH or NADH co-enzymes (Parajo *et al*., 1998). During the enzymatic hydrolysis rate of lignocellulosic biomass dependents on catalytic properties of enzymes, their loading concentrations, the hydrolysis period, reaction parameters employed biomass type, pretreatment method employed and compounds produced during pretreatment process (Zhu *et al*., 2008). The most feasible way to remove impurities and produce xylitol while there is the use of microorganisms that tolerate inhibitor compounds. These microorganisms can produce xylitol in adequate quantities in the presence of that inhibitory compounds (Orozco *et al*., 2018). Several scientific research reviewed the molecular strategies, challenges, progress and perspectives to improve biotechnological production of xylitol using lignocellulosic residues (Dasgupta *et al*., 2017). All of these investigations provide a clear idea of the advantages and disadvantages of xylitol production using biotechnological routes (Table 1).

Potential applications of xylitol

The shelf life, colour, and taste of food products are enhanced by using xylitol. The sugar-free chocolate, chewing gum, hard candies, wafer fillings, chocolate, pastilles, and other sweets for diabetics are produced by using xylitol along with other sugars (Bar, 1991). Xylitol shows non-toxicity to the body via all routes of administration.

In the food industry

Xylitol is used as a sweetener in jams, jellies, deserts, confectionery, chewing gum, and baked goods. The most important use has been as a substitute for sugar in confectionery products and baked goods (Ur-Rehman *et al*., 2015). In confectionery products such as candy or chewing gum, the use of xylitol is important because it provides a quick source of sweetness, flavour, and a refreshing effect. In baked products, xylitol reduces the

Table 1. Advantages and disadvantages of xylitol production through biotechnological pathways

Advantages	Disadvantages
Use of renewable raw materials	Difficult recovery
Use of multiple microorganism	Multiple steps of purification
Eco-friendly processes	Relatively long production times
Moderate production conditions	High production cost
Less generation of toxic effluents	Difficult to scale at industrial level
Lower price of xylitol	
Non-caloric sweetener	

caramelization of sugars, which produce a darkening of the product due to the Millard reactions that occur between sugars and proteins. These reactions do not occur by the addition of xylitol, since it does not contain aldehyde or ketone groups. Investigations on the potential application of xylitol include baked goods such as bread and biscuits. It has been shown that biscuits prepared by replacing sucrose with xylitol up to 50% are sensory acceptable, microbiologically safe and has a longer shelf life (Mushtaq *et al.* 2010; Winkelhausen *et al.*, 1998). Xylitol is regarded to be an advantage alternate sweetener for diabetic patients, since of controlling glucose stage of blood glucose, decreasing lipid stage, controlling weight.

Personal Care

Besides other mechanisms, low transepithelial permeability is also responsible for antimicrobial potential of xylitol against skin pathogens. Its efficiency was further increased in combination with chlorhexidine (Paula *et al*., 2010). Xylitol was also evaluated for its hydration and antimicrobial potential against skin associated bacteria, including *Staphylococcus aureus, Staphylococcus epidermidi*s and *Cutibacterium acnes*. It was reported that xylitol had both growth-inhibiting and growth-promoting effects on pathogenic microbes in a concentration-dependent manner. *S. epidermidis* growth was promoted at 1% xylitol, but 5% xylitol inhibited the growth of *S. aureus*, *C. acnes* and *S. epidermidis* aswell. The results suggested the possible use of xylitol in the formulation of personal care products (Anglenius *et al*., 2020).

Diabetes

Energy balance and controlled energy intake are matter of concern for obese individuals, diabetics and people with other metabolic syndromes. This tolerance is attributed to the lower effect of xylitol on a person's blood sugar, compared to that of regular sugars as it has an extremely low glycemic index of 7 (glucose has a GI of 100). Hence, lowcalorie substances such as saccharin, aspartame, neotame, sucralose or acesulfame potassium are preferred to sugar in order to avoid hyperglycemia. Prolonged consumption of synthetic sweeteners also exhibited detrimental or life-threatening side effects such as gastric, pancreatic, endometrial cancers, lymphomas, migraines, fibromyalgia, reduced antioxidation potential of the liver and genetic diseases (Neacsu *et al*., 2014). Metabolically, xylitol plays a dual role: as a sweetening agent and as an energy provider with better anti-catabolicaction (insulin resistance, e.g., postoperative and posttraumatic states); thus, it is also referred to as anutritive sweetener (Ruiz-Ojeda *et al*., 2019). Early metabolic fate of exogenous and endogenous xylitol is different (Touster *et al.*, 1969). In contrastto other cells, hepatic cells are highly permeable and metabolically active for xylitol. Exogenous xylitol reaches to intestine and uptake by intestinal mucosa by passive or facilitated diffusion. The absorption of xylitol is still much slower than glucose (Lang *et al*., 1971; Makinen *et al*., 1976).

Pharmaceutical Industry

The biological potential of xylitol has been a topic of research interest recently. Xylitol consumption reduces plaque levels, xerostomia, gingival inflammation and nasopharyngeal pneumonia, and hence,is a valuable product for pharmaceutical industry. It reduces the microbial load by multiple mechanisms including anti-adhesive, oxidative stress, low permeability and futile metabolism (Gargouri *et al*., 2018; Goli *et al*., 2012; Janakiram *et al.,* 2017 and Marttinen *et al*., 2012).

Oral Hygiene and Dental Caries

Otopathogens produce acid from the sugar fermentation, which demineralizes teeth. Xylitolimproves salivary flow, raises saliva pH and suppress the growth of otopathogens such as *Streptococcus* mutants and *Helicobacter pylori* (Gargouri *et al*. 2018). The effect of xylitol concentration on subgingival plaque and cariogenic and periodontal bacteria was evaluated.

Osteoporosis

Osteoporosis, a type of systemic skeletal diseases, occurs due to an increase in bone resorption,which is manifested by low bone mass, microarchitectural deterioration of bone tissue and fragile bone. Treatment with estrogens, bisphosphonates and calcitonin may be used to reduce or preventosteoporotic bone loss. Dietary supplementation of xylitol increased calcium and phosphorus levels in bones, promoted the restoration of bone calcium.

Ear infection

Xylitol chewing gum appears to decrease rates of acute otitis (inflammation of the ear) media in children going to daycare by 25%. Xylitol nasal sprays have also been shown to decrease incidence of acute otitis media as well as being a very effective way of both assisting and stimulating the body's own natural nasopharyngeal washing, and reducing both bacterial colonization and allergenic pollution (Steinberg *et al*., 1992).

Conclusion

A number of investigations have examined the ability of microbial species to utilize hydrolysates of agricultural residues and grasses to support xylitol synthesis. In general, it can be concluded that hydrolysates of agricultural residues supported higher levels of xylitol production. The microbial and enzymatic processes have emerged as an efficient and cost-effective approaches for xylitol production. Still, their commercial utilization is hindered due to the simultaneous degradation by microbes and substrate specificity for enzymes. Therefore, the biological approach is promising for the large-scale production of useful products such as xylitol. Screening of microbial community, strain improvement and process development involving alternate low-cost substrates such as lignocellulose are essential areas with immense future possibilities.

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Author Contributions

All authors listed have significantly contributed to the development and the writing of this article.

Conflicts of Interest

The authors declare no conflict of interest.

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