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REVIEW ARTICLE

Production of natural and rare pentoses using microorganisms and their enzymes

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Biochemical methods, usually microbial or enzymatic, are suitable for the production of unnatural or rare monosaccharides. D-Arabitol was produced from D-glucose by fermentation with *Candida famata* R28. D-xylulose can also be produced from D-arabitol using *Acetobacter aceti* IFO 3281 and D-lyxose was produced enzymatically from D-xylulose using L-ribose isomerase (L-RI). Ribitol was oxidized to L-ribulose by microbial bioconversion with *Acetobacter aceti* IFO 3281; L-ribulose was epimerized to L-xylulose by the enzyme D-tagatose 3-epimerase and L-lyxose was produced by isomerization of L-RI. L-ribose and L-arabinose were prepared biochemically from ribitol by oxidation using *Acetobacter aceti* IFO 3281 and isomerization using L-RI and L-arabinose isomerase (L-AI), respectively. Other pentoses can be produced as well by cell or enzyme bioconversions.

Importance of rare carbohydrates

Biotransformation of carbohydrates is a classical example of the application of the regiospecificity of enzymes. Next to significance to the production of monosaccharides from the corresponding biopolymers, the microbial transformations of monosaccharides have become an important bioprocess. In the past few years, the medicinal application of L-carbohydrates and their derived nucleosides have greatly increased. L-sorbose has been used for many decades as the starting material for the industrial production of L-ascorbic acid, and only recently it has been used as a precursor for the facile synthesis of the potent glycosidase inhibitor 1-deoxygalactonojirimycin (Huwig et al. 1998). Several modified nucleosides derived from L-sugars have shown to be potent antiviral agents and also usable in antigens therapy. Derivatives of rare sugar have also been used as anti-hepatitis B virus and human immunodeficiency virus (HIV) agents (Beach et al. 1992; Tianwei et al. 1996). As antitumor agents, such as bleomycin (Oshitari et al. 1997), are active against several murine tumors and making them useful for cancer treatment (Morita et al. 1996; Takagi et al. 1996). Recently, researchers have found many important applications of L-arabinose in medicine as well as in biological sciences. In a recent investigation, Seri et al. (1996) reported that L-arabinose selectively inhibits intestinal sucrase activity in an uncompetitive manner and suppresses the glycemic response after sucrose ingestion by such inhibition. Furthermore, Sanai et al. (1997) reported that L-arabinose is useful in preventing postprandial hyperglycemia in diabetic patients. The 2-deoxy-2-fluoro-5-methyl-β-L-arabinofuranosyl uracil (L-FMAU), a potent anti-HBV (Hepatitis B Virus) (Tianwei et al. 1996) and anti-EBV (Epstein-Barr virus) agent (Ma et al. 1997) can also be prepared from L-arabinose (Du et al. 1999). Fischer (1890) and Sowden and Fischer (1947) have reported that L-mannose, an expensive sugar that has not yet been detected in nature, can be prepared by the condensation of L-arabinose with cyanohydrin and nitromethane, respectively. Platelet-activating factors, like 2,3-O-isopropylidene-sn-glycerol, can also be produce from L-arabinose by a very simple method (Kanda and Wells, 1980). Saha and Bothast (1996) reported that L-arabitol could also be obtained from L-arabinose by *Candida entomaea* and *Pichia guilliermondii*. Moreover, rare sugars are usually sweet like the natural sugars, but unlike them, rare sugars are either not metabolized by the body or metabolized to a lesser extent than natural sugars. Due to these features, rare sugars are desirable as low-calorie sweeteners and are well tolerated by diabetics. It was also found that L-monosaccharides have antineoplastic characteristics (Bicher, 1997) and are useful in combination with all major forms of cancer therapy including surgery, biological, chemical and radiation therapies and hyperthermia. In addition to increasing the mortality rate of neoplastic cells, they can reduce the metastatic potential of the tumor, and slow down the growth of malignant cells. Other advantage of rare sugars is the absence of an objectionable aftertaste, commonly experienced with artificial sweeteners such as

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saccharin or cyclamates (Horwath and Colonna, 1984). Some important applications of various rare carbohydrates are shown in Table 1. However, in spite of the demand for these rare sugars, their commercial availability, application or usefulness is negligible as they are expensive to prepare and unavailable in nature.

Production of keto-pentoses using whole cell and cell –free oxidoreductases

Polyol dehydrogenases of widely varying substrate and electron or hydrogen carrying specificity have been studied in microorganisms. Studying the production of rare ketoses, *Acetobacter* sp. was found to be a potent oxidizer of polyols (Moses and Ferrier, 1962) with particular steric configurations to keto-pentoses. *Acetobacter suboxydans*, in particular, can perform quantitatively very specific oxidations of this type and has been used for the preparative scale to obtain previously unknown or rare substances, *i.e.* the oxidation of D-gluco-D-ido-heptitol to D-ido-heptulose, D-arabitol to D-xylulose, ribitol to L-ribulose and erythritol to L-erythrulose.

L-xylulose production

L-xylulose is a ketopentose, which is not abundant in nature, but it can be easily produced from xylitol by dehydrogenation. The bacteria *Klebsiella pneumoniae*, *Alcaligenes* sp. 701B (Khan et al. 1991) and *Erwina uredovora* Dm 122 (Doten and Mortlock, 1985) were reported to produce L-xylulose from xylitol. It seems that the corresponding dehydrogenase is mostly responsible for the whole-cell transformation of xylitol to L-xylulose.

D-xylulose production

D-xylulose can be produced by whole cell or enzyme biocatalysis (Mitsuhashi and Lampem, 1953; Misawa et al. 1967; Doten and Mortlock, 1985; Pronk et al. 1988). Microbial and enzymatic production of D-xylulose from D-arabitol has been reported previously (Moses and Ferrier, 1962; Compello and Veiga, 1973; Schwartz et al. 1994). D-xylulose can also be produced from D-xylose (Chiang et al. 1981; Olsson et al. 1994). *Acetobacter* sp. IFO 3281 was extremely active in the transformation of D-arabitol to D-xylulose at a relatively high substrate concentration (~50%) and showed no product consumption or by-product formation. Nearly stoichiometric conversion of D-arabitol to D-xylulose was achieved with *A. aceti* IFO 3281 (Ahmed et al. 1999a; Ahmed and Bhowmik, 2000).

L-ribulose production

The production of L-ribulose from ribitol has been studied using various acetic acid bacteria and the highest activity was found in *G. frateurii* IFO 3254, followed by *A. aceti* IFO 3281 (Ahmed et al. 1999b). These strains showed very broad substrate specificity and possessed a constitutive enzyme system capable of oxidizing ribitol to L-ribulose. There are other reports of the production of L-ribulose from ribitol (Moses and Ferrier, 1962; Compello and Veiga, 1973). Osao et al. (2001) identified an NAD-dependent ribitol dehydrogenase (EC 1.1.1.56) from *Gluconobacter suboxydans*, responsible for the oxidation of ribitol to L-ribulose. The oxidation of ribitol to L-ribulose, in all these cases, was followed by a long lag period to attain complete oxidation, resulting in the formation of by-products. In contrast, *A. aceti* IFO 3281 transformed ribitol to L-ribulose at high substrate concentration (~20%) without any by-product formation and did not show any tendency of product consumption (Ahmed et al. 1999b; Ahmed and Bhowmik, 2000). In the case of repeated use of cells for L-ribulose production from ribitol, decreasing quantities of L-ribulose were observed, as also reported by Moses and Ferrier (1962). They also suggested that the delay between the first and second stage of oxidation might be due to the formation of an adaptive enzyme system required to continue the metabolism of L-ribulose produced in the first stage of ribitol oxidation.

Production of pentitols using whole cell and cell –free oxidoreductases

Pentitol catabolism is an interesting phenomenon in microbial metabolism, which can serve as an excellent model system for studying the acquisition of new metabolic capabilities by microbes.

D-arabitol production

Extensive studies have been carried out on the production of polyols, such as glycerol, erythritol, xylitol, D-arabitol and D-mannitol, during the fermentation of soy sauce by halotolerent yeasts (Onishi and Suzuki, 1966; Onishi and Suzuki, 1968; Onishi and Suzuki, 1969; Onishi and Suzuki, 1970; Jennings, 1984). It was revealed that *Candida* sp. was one of the most potent microorganisms for D-arabitol production (Kiehn et al. 1979; Bernard et al. 1982; Gold et al. 1983; Wong and Brauer, 1988). *C. famata* R28 produced D-arabitol from D-glucose without producing any by-product (Ahmed et al. 1999a). In one report it was proposed that *Candida* spp. produced D-arabitol from D-ribulose with NAD-dependent D-arabitol dehydrogenase in which D-ribulose was derived by dephosphorylating D-ribulose-5-PO_4 in the pentose pathway (Wong et al. 1995). *Candida pelliculosa* produced D-arabitol from D-glucose but concomitantly produced D-ribose as a by-product (De-Wulf et al. 1996). Certain osmophilic yeast (such as *Pichia misa*) grown in the presence of high glucose concentration (~30%) produced, in addition to ethanol and CO_2, a variety of polyhydric alcohols: glycerol, erythritol, D-arabitol and mannitol (Spencer and Sallans, 1956; Blakely and Spencer, 1962; Onishi and Suzuki, 1966). It was also reported that D-arabitol is the intermediate in the interconversion of aldose and ketose in *Candida albicans*, *C. utilis* and

Penicillium chrysogenum (Chiang and Knight, 1960; Onishi and Suzuki, 1966).

Xylitol production

Xylitol is a naturally occurring sugar with a wide spectrum of interesting applications. Xylitol can be extracted from bagasse, an abundantly available waste material, but can also be found in small quantities in various plants, fruits and vegetables, such as raspberries, strawberries, yellow plums, cauliflower and spinach. Xylitol, with a sweetening power matching that of sucrose (table sugar), is applicable as a sugar substitute in the food processing industry. Xylitol produces a perceived sensation of coolness in the mouth as it comes in contact with the saliva because of its negative heat of solution. This property makes it quite desirable in certain food products, especially chewing gum. Another significant property of xylitol is the prevention of dental cavities, as established by the Dental Caries Prevention Studies thus making it the best nutritive sugar substitute at this respect. Xylitol metabolizes easily and independently from insulin in humans and produces the same amount of energy (4 Kcal/gm) which highlights its application in all diabetic foods. It is particularly attractive as a non-sugar sweetener for chewing vitamins and gums, tablets, cough syrups, mouth washes, tooth pastes etc. Apart from the above, the adhesive properties of xylitol have been reported adequate to replace phenolic resin for plywood bonding. It can be used as an additive in foods, beverages and pharmaceuticals (Biswas and Vashishtha, 1998). Currently, the major use of xylitol has been in the manufacture of chewing gums. The synthesis of xylitol from natural products is based on the chemistry of pentosans occurring in many plants. Xylan, a constituent of pentosan, is a polysaccharide that can be hydrolyzed into D-xylose, which is also known as wood sugar. Xylitol can be synthesized by hydrogenation of xylose. Xylitol can also be produced by microbial transformation reactions, such as from D-xylose by yeast or from D-glucose by yeast and bacteria (Izumori and Tuzaki, 1988). Xylitol has also been produced from D-xylulose using *Mycobacterium smegmatis* and from D-xylose using the commercial immobilized D-xylose isomerase of *Bacillus coagulans* or immobilized cells of *M. smegmatis* (Izumori and Tuzaki, 1988). Sud-Chemie AG, Munich, Germany in their patents granted in 1976 (US Patent Number 3980719) had described a process for preparing xylitol by acid hydrolysis of xylan. Another US Patent (Number 4008285), applied from Finland and granted in 1977, describes a method of producing xylitol on a commercial scale by acid hydrolysis of pentosan-containing raw materials such as wood, corncobs, straw, bran, and cotton-seed hulls.

Ribitol production

Ribitol is a naturally occurring polyol, which is commercially available and very cheap. In a previous report, it was found that D-ribose could be reduced to give an optically inactive ribitol. Onishi and Suzuki (1966) reported that ribitol can be produced as end product from D-ribose dissimilation by the salt-tolerant yeast *Candida polymorpha*.

Production of aldo-pentoses using whole cell and cell -free oxidoreductases

D-lyxose production

D-lyxose is unavailable and thus rare in nature, and can be obtained by chemical synthesis (Fletcher et al. 1950; Fletcher, 1962; Bilk and Caplovic, 1973; Giudici and Griffin, 1974). The microbial production of D-lyxose from D-xylulose was reported using L-ribose isomerase of *Acinetobacter* sp. DL 28 (Ahmed et al. 1999a; Ahmed and Izumori, 2001). The success of this D-lyxose synthesis was due to three factors: (a) all reactions were selective only for product formation; (b) the production of D-lyxose from D-glucose was a continuous process, which means that product separation or purification at each step was not needed; and (c) most importantly, the final product (D-lyxose) was very easily separated from the reaction mixture with no effect on the desired product and without producing by-products. From this result, it was estimated that about 35% D-lyxose could be produced from D-glucose.

L-lyxose production

L-lyxose, a rare sugar in nature, is structurally related, according to its stereoconfiguration, to the 6-deoxyhexose L-rhamnose or to the hexose L-mannose. L-lyxose is very expensive due to its scarcity in nature and it can be obtained only by chemical synthesis (Whistler and BeMiller, 1962; Kazuhara et al. 1971; Bilk and Caplovic, 1973; Petrusova et al. 1991). In a previous study, Bhuiyan et al. (1998) reported an enzyme biotrasformation of L-lyxose from ribitol, where the complete biotransformation of ribitol to L-ribulose was achieved using *A. aceti* IFO 3281 at high substrate concentrations ranging from 5-20% and then L-ribulose was used as a starting substrate. L-lyxose was prodeced from L-ribulose at a ratio of 6: 3: 1 (L-lyxose: L-xylulose: L-ribulose). It was concluded from this result that about 5 g of L-lyxose crystal could be recovered from 10 g of ribitol.

L-ribose production

L-ribose is not abundant in nature and therefore is an expensive and rare aldo-pentose that can only be obtained by a series of chemical reactions (Austin and Humoller, 1934a; Humoller, 1962; Bilk and Caplovic, 1973; Yamaguchi and Mukaiyama, 1981; Matteson and Peterson, 1987; Jung and Xu, 1997). Shimonishi and Izumori (1996) isolated, purified and characterized a constitutive L-ribose isomerase (L-RI) from *Acinetobacter* sp. strain DL-28. The purified enzyme can catalyze the isomerization of D-mannose, D-lyxose and L-ribose, with the highest activity observed on L-ribose. L-ribose can also be produced from ribitol by whole cell oxidation with *Acetobacter aceti* IFO

3281 and isomerization using L-RI (Ahmed et al. 1999b; Ahmed and Izumori, 2001).

D-ribose production

Several methods have been reported for the preparation of D-ribose (Yamaguchi and Mukaiyama, 1981) and many of them are patented. The production of D-ribose by fermentation has received much attention lately, possibly because of its use for the production of antiviral and anticancer drugs (De-Wulf and Vandamme, 1997). It has been reported that D-ribose can be obtained from D-glucose by fermentation using *Bacillus subtilis* strain ATCC 21951 (De-Wulf et al. 1997) or *Candida pelliculosa* (De-Wulf et al. 1996). Berstein (1953) reported the synthesis of D-ribose from D-glucose in the early fifties. Zhao (1999) stated that a mutant strain of *Bacillus subtilis* BS-9 can produce D-ribose from D-glucose. The BS-9 strain was found to grow well using glucose as carbon source and corn steep liqueur and $(NH_4)_2SO_4$ as nitrogen source and the content of D-ribose was more than 67.6 g·L. Zubay (1998) developed a lead-catalyzed system for the synthesis of D-ribose. He established conditions that selectively precipitated ribose from a mixture of four pentoses in the presence of lead nitrate. Since L- and D-ribose form distinct aggregates, it is possible to isolate D-ribose.

L-arabinose production

The pentose L-arabinose is structurally related to the poorly sweet-testing hexose, D-galactose. L-arabinose is a natural sugar and a constituent of a variety of plant carbohydrates which is commonly found in hemicelluloses such as L-arabinnans, L-arabino-D-xylans and L-arabino-D-galactans. This L-aldopentose, can only be obtained by a series of chemical reactions (Hudson, 1951; White, 1962). During the study on carbohydrate metabolism by *Mycobacterium smegmatis* strain SMDU, it was found that this strain can transform about 90% of L-ribulose into L-arabinose by means of its L-arabinose isomerase (L-AI) (Ahmed et al. 1999b; Ahmed and Izumori, 2001).

Concluding Remarks

The configurations of various diastereoisomeric sugars are related to a natural alditol, such as, D-arabinose, D-arabitol, and D-lyxose and this relationship offers a simple route for the synthesis of unnatural aldoses from natural ones. Most abundant six carbon sugars in nature are D-glucose, D-fructose, D-galactose and D-mannose. Several studies have been carried out with microorganisms and their enzymes to produce various rare L- and D- sugars from inexpensive carbohydrates. Many aldose-ketose isomerization of free sugars have also been reported. Of the total of eight aldopentoses and four pentitols, three pentoses (D-xylose, L-arabinose and D-ribose) and two pentitols (ribitol and D-arabitol) are common in nature. The remaining pentoses are unknown or rare and are not abundant in nature, being xenobiotic compounds. These rare carbohydrates are difficult to produce and can only be produced by chemical reactions. However, the chemical route is time-consuming, requires many steps and costly chemicals and produce unnecessary by-products being not feasible for mass production of these rare sugars. Therefore, the developments of simple methods are extremely important for increasing the production of these sugars. Moreover, to produce enough amounts of these rare aldopentoses, natural substrates have to be used which are abundant in nature and cheap.

D-glucose is the most abundant aldose occurring in nature. In many parts of the world D-glucose is an abundant carbon source, produced enzymatically from starch, sucrose or even cellulose, which can be metabolized by aerobic and anaerobic organisms. The use of microbial cellulase to generate D-glucose from cellulosic wastes is of considerable commercial interest and, as a consequence, much research is being done on the enzymes required (Eriksson and Wood, 1985; Wood, 1991; Wood, 1994). If it is possible to produce these aldopentoses economically from D-glucose through whole microbial cell or enzyme biocatalysts, it will also be possible to use them as valuable starting materials for the manufacture of various live saving drugs and other important high-value products.

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Table 1. Some important applications of rare monosaccharides

Rare Monosaccharides	Application (s)	Reference (s)
Hexoses		
D-tagatose	Low caloric carbohydrate sweeteners and bulking agents	Muniruzzaman et al. 1996; Livesey and Brown, 1996
D-sorbose	Building blocks for the synthesis of interesting natural and biological active products	Huwig et al. 1996; Huwig et al. 1998
	Insect control agent and as a starting materials for producing industrially significant compounds, such as L-*threo*-2, 5-hexodiulose	Huwig et al. 1998
D-gulose	Drug-formulation agents and food additives	James et al. 1993
L-fructose	Inhibitors of various glycosidase Mixture of L- and D-fructose kill ants and house flies	Levin et al. 1995 Gilbert and Zehner, 1990
L-tagatose	Starting materials for the synthesis of 1-deoxygalactonojirimycin	Huwig et al. 1998
L-glucose	Cytostatic and cytotoxic properties with regards to neoplastic cells that can be used for cancer therapy	Bicher, 1997
L-talose	Its nucleoside derivatives, L-talofuranosyladenine, can be used as slow-reacting substrate for calf intestinal adenosine deaminase and an inhibitor for the growth of leukemia L1210 cells *in vitro*	Lerner and Mennitt, 1994
D-/L- talitol	Potential glycosidase inhibitor	Buchanan et al. 1990
D-allose	Use for the treatment of chronic myeloid leukemia	Arnold and Silady, 1997
	Reduce thrombus formation during post-operative period in combination with other anti-clotting drugs	Austin and Humoller, 1934a
Pentoses		
D-lyxose	Starting materials for the production of antitumoral and immunosti mulatory galactosylcer-amide agents, against several murine tumors; useful for cancer therapy	Morita et al. 1996; Takagi et al. 1996
L-ribose	Starting materials for the production of two rare aldohexoses, L-allose and L-altrose	Austin and Humoller, 1934b
	Use as a potent anti-Hepatitis B virus (HBV) and anti-Epstein Barr virus (EBV) agents	Tianwei et al. 1996
L-xylulose	Potential inhibitors of various glycosidase	Levin et al. 1995
D-arabinose	Starting material for the synthesis of antitumor agents	Yoshikawa et al. 1993
	Starting material for the synthesis of dehydroamino acid derivatives, act as azinomycin antitumor antibiotics	Moran et al. 1993
	Production of D-erythroascorbic acid and oxalic acid	Loewus et al. 1995
	Synthesis of maytansinoid model compounds with significant anti-cancer activity	Goodwin et al. 1998
L-xylose	Starting material for the synthesis of 9-(2-deoxy-2-fluro-β-L-ara binofuranosyl) purine nucleosides with anti-hepatitis B virus activity	Ma et al. 1997
	Starting materials for the synthesis of L-ribofuranose derivatives	Chelain et al. 1995