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MINI-REVIEW

Health benefits of xylitol

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Abstract

Many diseases, including caries, chronic inflammatory diseases, diabetes, and obesity, are associated with uncontrolled sugar consumption. Artificial sweeteners are commonly used in food and pharmaceutical industries as sugar substitutes for the prevention of several dental and body diseases; they also have a favorable impact on body weight as they may help to restrict simple sugar consumption. Xylitol is a sugar alcohol that is commonly used as a sweetener. It can be found naturally or artificially prepared mainly from plant materials chemically or by fermentation of hemicelluloses from agricultural biomass by yeast or bacteria strains. This polyol has a significant antiplaque effect on teeth surface and can reduce the gingival inflammation; it is being used as a preventive agent for dental caries due to decreasing the growth levels of pathogenic *Streptococcus mutans* and *Streptococcus sangui* at the very early stages. Xylitol can bind with calcium ion leading to consequent remineralization of teeth enamel; it is also able to prevent osteoporosis. This polyol can treat respiratory tract and middle ear diseases due to its antibacterial and anti-inflammatory potential and prevent some diseases which cannot be cured through antibiotics or surgery. Xylitol can reduce constipation, diabetes, obesity, and other body syndromes or illnesses; it has also revealed its stimulating effect on digestion and immune system. However, it can produce some side effects such as irritable bowel syndrome, diarrhea, nephrolithiasis, etc., when consumed in excessive amounts. Different vehicles are used for delivering the xylitol into the human body, but chewing gums occupy a leading position. The present review is devoted to comprehensive analyses of the positive and negative effects of this polyol on human health.

Key Points

- *The health benefits of xylitol are not limited to oral hygiene.*
- *Xylitol efficiently stimulates the immune system, digestion, lipid and bone metabolism.*
- *Xylitol helps in glycemic and obesity control; reduces ear and respiratory infections.*
- *Xylitol treats diseases that cannot be cured through antibiotics or by surgery.*

Keywords Xylitol · Artificial sweetener · Oral microbiota · Caries · Metabolic disease · Health care · Preventive effect

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Introduction

The global increase in sugar consumption causes health problems, including exacerbation of caries, gingivitis, metabolic syndrome, obesity, and diabetes mellitus (Burt 2006; Wolnerhanssen and Meyer-Gerspach 2019; Wolnerhanssen et al. 2019). This has driven consumers to demand healthier sweeteners such as sugar alcohols. These polyols are present in many natural products, such as fruits and vegetables, and are also added to foods and pharmaceuticals as artificial sweeteners. Commonly used polyols are xylitol, sorbitol, erythritol, maltitol, lactitol, mannitol, and isomalt (Rice et al. 2019). They are widely used in the manufacturing of food and pharmaceuticals because of their favorable physicochemical properties (Ortiz et al. 2013). Xylitol is a 5-carbon sugar alcohol, white crystalline carbohydrate, and commonly used as an artificial sweetener (Fig. 1). It was identified in the late nineteenth century, naturally present in numerous edible plants (including fruits and berries) and mushrooms. It is also artificially manufactured in the industry from xylan-rich plant material, such as beechwood and birch wood (El-Marakby et al. 2017).

According to the World Health Organization, dental caries is a widely spread disease linked to the prevalence of pathogenic microorganisms (mainly *Streptococcus mutan*s and *Streptococcus sobrinus*) in the oral cavity and with the quantity of fermentable carbohydrates ingested (Petersen 2004). Strategies to maximize caries prevention, of course, foresee the use of sugar substitutes (Mäkinen 2011). Xylitol has a great potential to inhibit or reduce the growth of oral pathogenic bacteria. Its antibacterial potential has made it famous in diverse preventive dental medicines or products. Clinical studies revealed that xylitol, as physiologic sugar alcohol of natural origin, can be used as an effective caries-limiting sweetener (Honkala et al. 2014; Mäkinen 2011; Silva et al. 2009).

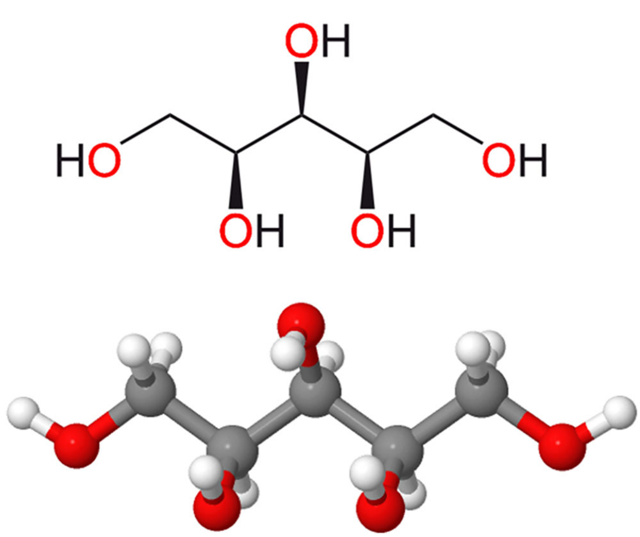

Fig. 1 The structure of xylitol ((2R,3R,4S)-pentane-1,2,3,4,5-pentol)

Throughout World War II, the Scandinavian countries faced a severe sugar shortage. Then, they used xylitol as a substitute for sugar. After that, dental professionals started using xylitol to prevent dental caries and to improve oral health.

In previous decades, researchers mainly were focused on the influences of xylitol and other artificial sweeteners on oral health care while the antihyperglycaemic effects have only been studied recently (Wolnerhanssen et al. 2019). Xylitol has many beneficial characteristics for humans (Fig. 2) (Chukwuma and Islam 2017); for example, it is involved in the release of a minimal amount of insulin. It is considered a good sugar substitute for the people who have diabetes and are on a very low carbohydrate diet to overcome the high glycemic index in their bloodstream. Xylitol does not require insulin hormone to enter in the cells; that is why it is considered as a good energy source for people with diabetes. It is found in many food items, particularly labeled as a "low-carb" diet. It is considered a non-toxic compound in mammals with the exception of dogs.

Nowadays, xylitol has been studied worldwide and accepted as an artificial sweetener globally (Peterson 2013). Xylitol and other polyols are approved for use in a wide range of foods, and many of them have common designations, for instance: xylitol (E 967), isomalt (E 953); lactitol (E 966); maltitol (E 965); mannitol (E 421); sorbitol (E 420) (Tennant 2014).

What is xylitol?

The word "Xylitol" derived from the Greek word "Xylo" means wood, and "itol" is the suffix denotes the sugar alcohols. Xylitol is an alcoholic compound that is naturally present in plants and is produced by some bacteria and fungi (Ortiz et al. 2013). It is generally classified as sugar alcohol or polyalcohol. Its chemical formula is consisting of 5 carbon skeleton $CH_2OH(CHOH)_3CH_2OH$ (Fig. 1) (Granstrom et al. 2007). Physically, it is comprised of white solid, crystalline, or granular structure that is soluble in water.

Xylitol occurs in a very low quantity in fruits, vegetables, and plant raw materials, as well as its precursor xylose (Olennikov et al. 2009; Shanaida et al. 2017; Ur-Rehman et al. 2015). It is mainly obtained commercially from birch wood or other plants that are used as raw material to manufacture food additives and medicinal products (Riley et al. 2015). Recovery of waste constituents from plants manufacturing have both economic and social importance (Fierascu et al. 2020).

Xylitol can be produced chemically or by biotechnological processes (Fig. 2) (Rice et al. 2019). Chemical production uses extensive machinery and expensive chemicals, thus increasing the basic cost. The biotechnological method utilizes

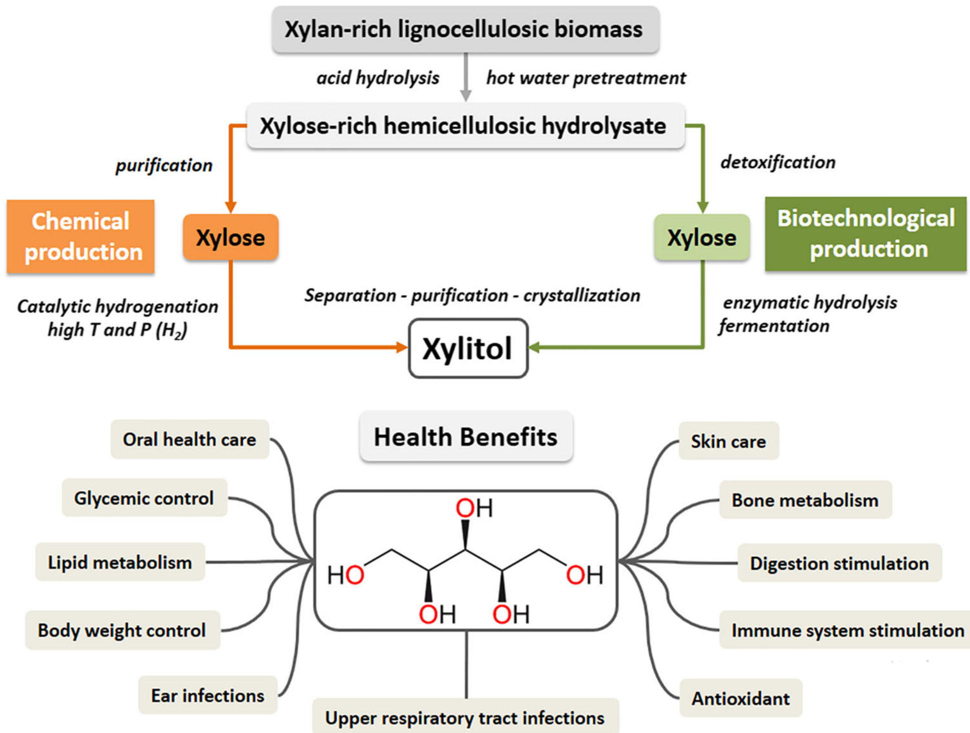

Fig. 2 Xylitol production and health benefits

agricultural wastes, which offer the possibilities of economic production of xylitol. The precursor xylose is produced from agricultural biomass by enzymatic hydrolysis and can be converted to xylitol primarily by yeast or bacteria strains (Carneiro et al. 2019; Felipe Hernandez-Perez et al. 2019; Jain and Mulay 2014; Stoklosa et al. 2019; Ur-Rehman et al. 2015). Hemicellulosic hydrolysates are the primary raw materials for the production of xylitol (Felipe Hernandez-Perez et al. 2019; Sene et al. 2011; Yuan et al. 2020). Recombinant *Escherichia coli* has been revealed the better producer of xylitol (Abd Rahman et al. 2020; Yuan et al. 2020).

Biotechnologically engineered *Zymomonas mobilis* ATCC ZW658 strain showed the ability to co-utilize glucose and xylose, exhibiting a 1.65-fold increase in the xylose utilization rate compared with the parent one (Sarkar et al. 2020). There has been constructed a strain of recombinant yeast *Saccharomyces cerevisiae* efficiently producing xylitol using wheat stalk hydrolysate as a source of xylose (Reshamwala and Lali 2020). Biosynthesis of value-added functional sugars, including xylitol using biotechnologically engineered yeast *Yarrowia lipolytica* as sustainable carbon sources, are also among promising trends in the latest investigations (Bilal et al. 2020; Xu et al. 2019).

Xylitol vehicles

Xylitol is considered as a safe and efficient tooth decay preventive substance when used regularly, although its uses have been restricted due to the absence of formulations. Xylitol can, among others, be taken from candies, chewing gums, sweets, and syrups (Jones 2000). Substantial research proposes that 5–6 g and a minimum of three exposures per day from candies or chewing gums are required for a better clinical effect (Milgrom et al. 2009a). Most xylitol clinical trials include almost entirely lozenges or chewing gums and tooth decay assessed in school-going children's teeth (Lynch and Milgrom 2003). To get the effective results of xylitol, almost two vehicles are adequate and safe for toddlers. Many studies have been conducted to evaluate the effective results of xylitol by using topical xylitol syrups during primary teeth eruption in toddlers (Milgrom et al. 2009b).

The common modality for the delivery of xylitol is chewing gum (Soderling 2009b). It enhances the process of cleaning away acid and acts as remineralized for tooth by uptaking calcium phosphate. The prescribed time for chewing the gum is 20 min after eating. The study also showed that the regular consumption of xylitol gummy bear canapés or snacks helps reduce germs responsible for producing dental caries in school-going children. It is adequately reported that eating gummy bear snacks consisting of xylitol is responsible for reducing mutans streptococci growth levels (Ganter et al. 2020; Nayak et al. 2014).

Mouth rinses comprised of xylitol can reduce the development of biofilms. They also reduce the growth levels of *S. sanguis* and *S. mutans* at the very early stages. Among both, the *S. mutans*' colonies are highly sensitive to xylitol mouth rinses. In the USA, xylitol is used in small nonclinical quantities as an artificial sweetener in a gimmick or in several food items and in children's supplements, including vitamins (El-Marakby et al. 2017). Meanwhile, there has also been a debate in previous literature about whether xylitol-containing toothpaste at lower doses is most effective.

However, the synergistic effect of fluoride and xylitol cannot be ruled out. Researches have been conducted on new xylitol vehicles, for example, xylitol-releasing dummy or pediatric xylitol syrups. (Milgrom et al. 2009a). Fluoride toothpaste with 10% xylitol reduced caries by 13% when compared to a fluoride-only toothpaste analyzed in 4216 children (Duane 2015). Chewing sugar-free gums reduced caries increment more effectively in comparison to non-chewing controls using alternatives such as rinses, tablets, and candies (Newton et al. 2019). Hence, this substance can be used as an active element in gums, toothpaste, and antimicrobial mouthwashes, especially in patients with candidiasis (Talattof et al. 2018).

Artificially sweetened soft drinks have appeared as an alternative sweetness without changes in caloric intake because most of the sugars are obtained from such drinks; also, sweeteners are often used to replace sugars in various yogurts, puddings, and ice cream (Sylvetsky et al. 2011). Inclusion of a xylitol drinking water additive for seven months reduced the tooth plaque in dogs on 5.1% and the calculus accumulation on 14.9% (Lowe and Anthony 2020). Natural sweeteners have a positive influence on body weight as they may help to restrict simple sugar consumption (Mooradian et al. 2017). It should be noted that xylitol present in beverages causes side effects (such as diarrhea) at lower levels than when present in solid food (Mäkinen 2016).

Antiplaque, antigingivitic, and remineralizing properties of xylitol

Biofilm formation is a natural process in the oral cavity but needs to be under the control of regular brushing to prevent the development of periodontal diseases and caries (Verkaik et al. 2011). Dental plaque is a biofilm produced by bacterias, salivary proteins, and food substances (Badet et al. 2008).

Lactobacillus, *S. mutans*, and *S. sobrinus*, and *Actinomyces viscosus* are four major components of the oral cavity microflora producing acid through the fermentation of sugars from consumed food (Thabuis et al. 2013). This acid can induce a partial dissolution of minerals in tooth enamel, followed by the formation of a dental cavity infected by oral bacteria. As bacteria of the oral cavity do not ferment polyols, their use does not increase the acid content there.

Xylitol has significant antiplaque effect on teeth; thus, it is being used as a preventive agent for dental caries. Xylitol cannot be fermented by the microorganisms of dental plaque (Takahashi et al. 2003). Studies showed evidence that oral flora cannot metabolize xylitol. The use of xylitol daily has shown a severe reduction of colonies of *S. mutans* in dental plaque. Xylitol decreases the growth of bacteria. *S. mutans* carry the xylitol sugar inside the cell during an energy-consuming cycle, and this phenomenon is responsible for inhibition of growth and, ultimately, inhibition of plaque (Alves et al. 2013). Xylitol is further converted into the xylitol-5-phosphate by phosphoenolpyruvate. This phenomenon results in the production of intracellular vacuoles and degradation of the cell membrane. Therefore, *S. mutans* bacteria are responsible for their own death. *S. mutans* then also dephosphorylates the xylitol-5-phosphate, and this dephosphorylated sugar molecule is ejected from the cell. This ejection occurs with an energy expenditure without energy contribution from the metabolism of xylitol.

Consequently, xylitol reduces or inhibits the growth of mutans streptococci through starving the bacteria (El-Marakby et al. 2017). The antimicrobial effects of xylitol, xylitol-probiotic, and fluoride toothpaste on *S. mutans* plaque were observed in 13–15-year-old children (Arat Maden et al. 2017). Thus, regular use of toothpaste containing a combination of fluorides and other appropriate components can prevent some oral diseases. There has been a study about the individuals having xylitol regularly. Their plaque sample examination showed that there is a substantial reduction in plaque adhesiveness, and there is a significant reduction of extracellular polysaccharides produced by *S. mutans* to develop biofilms (Burt 2006). The anti-caries potential of xylitol is mainly related to its effect on dental plaque and cariogenic bacteria (El-Marakby et al. 2017).

As a consequence of the regular use of xylitol, numerous effects appear. The first effect is very selective in *S. mutans,* which become xylitol-resistant. A second effect is an increase in the concentration of ammonia and many basic amino acids when the dental plaque is exposed to xylitol. Consequently, plaque acids become neutralized. So that is how xylitol showed its antiplaque properties (Maguire and Rugg-Gunn 2003).

Candidiasis is the most common fungal infection among the human population caused mostly by *Candida albicans* (Talattof et al. 2018). As sugar intake promotes the *C. albicans* growth, xylitol can decrease the risk of candidiasis in the oral mucosa; the minimum inhibition concentration of xylitol for *C. albicans* was found to be 20×10^4 μg/mL (Talattof et al. 2018).

Xylitol is also responsible for increasing mineralization on dental tissues. Several clinical and laboratory studies reported the remineralization of dental caries by consuming xylitol gums regularly. It increases the salivary flow in case of consuming as chewing gum or large xylitol tablets. Chewing gums with xylitol demonstrated good antibiofilm and remineralized potential on damaged by caries teeth areas (Gargouri et al. 2018). Xylitol- and sorbitol-containing chewing gums are also responsible for reducing gingival inflammation (Shyama et al. 2006). Such gums enhance the potential of remineralization. Gums containing xylitol showed some superior effects regarding remineralization and reduction of plaque formation (Steinberg et al. 1992). Although remineralization has been noticed on all such experiments carried with non-sugar sweeteners substances, the remineralization process occurs due to enhanced saliva flow that is rich in phosphate and calcium.

The efficiency of xylitol chewing gums enriched with propolis was established *in vitro* by the remineralizing effect of softly demineralized dentin (Gargouri et al. 2020).

Effect of xylitol on oral, nasopharyngeal, and gut microbiota

Biofilm control is crucial for preventing of such oral infections as caries and periodontal diseases. Xylitol can provoke decreasing oral biofilm formation by the inhibition of bacterial β-glucosidase in human saliva, which is essential for biofilm formation in the oral cavity (Teixeira Essenfelder et al. 2019). *S. mutans* can incorporate xylitol, which then can inhibit the process of glycolysis of these microorganisms by the use of a fructose phosphotransferase system. Inside the bacteria cell, the molecule of this sugar is phosphorylated, resulting in the production of xylitol-5-phosphate, which cannot be metabolized (Teixeira Essenfelder et al. 2019).

A 30-day supplementation with xylitol and maltitol chewing gums led to a significant decrease in the presence of oral pathogenic microorganisms *S. mutans*, *S. sobrinus*, and *Actinomyces viscosus*; that effect was directly linked to an increase in plaque pH by these polyols which cannot be fermented by oral bacteria and can similarly improve general oral health (Thabuis et al. 2013). The chewing gum with xylitol decreased the *S. mutans*, and *S. sobrinus* counts significantly comparatively to the sorbitol gum group (Bahador et al. 2012).

The everyday use of xylitol and isothiazolinone demonstrated the pronounced antimicrobial effect against *Pseudomonas aeruginosa* ATCC 9027 and *Staphylococcus aureus* ATCC 6538 biofilms in a dose-dependent manner and may be applied to reduce the undesirable biofilms in vitro (Zhou et al. 2019). High levels of antimicrobial activity against among others *S. aureus* and *C. albicans* were demonstrated by the essential oils of plants containing such predominant components as thymol, carvacrol, and other aromatic terpenoids (Kozlowska et al. 2015; Marchese et al. 2016). It would be interesting to investigate the combined cumulative effect of xylitol and essential oil components, such as menthol, in chewing gum (Santos et al. 2014). It was revealed the positive effect of chewing gums containing probiotics (*Lactobacillus reuteri*) and xylitol on *S. mutans* counts and gingival scores (Kaur et al. 2018).

Factors such as oral hygiene and fermentable carbohydrate exposure frequency should also be controlled during the studies of the anti-cariogenic effect of xylitol (Janket et al. 2019). However, the contrast between xylitol and other sweeteners, such as sorbitol or sucralose, was not significantly different (Janket et al. 2019). Xylitol can inhibit the glucosyltransferase, which blocks the utilization of glucose by *S. mutans* and adhesion this pathogenic microorganism to the tooth surface (Janket et al. 2019). The effects of xylitol, sucrose, and their combination have been studied *in vitro* on *S. mutans* and *S. sobrinus* (Salli et al. 2016). While the addition of 1% sucrose significantly increased the degree of bacterial strains, the study performed with increasing the concentration (2–5%) of xylitol showed a decrease in bacterial counts also in the presence of sucrose.

Xylitol-containing chewing gum inhibited the increase in total salivary bacteria in the case of short-term research of 70 healthy adult men (Takeuchi et al. 2018).

Xylitol reduces the *S. mutans* counts and *lactobacilli* in saliva. There are very few other species that are beneficial in the oral microbiome (Badet et al. 2008). According to a study, by consuming xylitol, the lactobacilli were unidentified in oral microbiome while the *S. mutans* were observed in a minimal amount in the oral cavity. Therefore, this proved that xylitol has excellent effects on oral microbiome communities as it has anti-caries and antiplaque potential. It inhibits the growth of all those bacterial colonies which have a role in chronic periodontitis (Rafeek et al. 2019).

The recent research outcomes of a randomized clinical trial among children concerning the comparison of effectiveness for mouthwashes comprising green tea with xylitol vs. green tea alone (two times daily during 14 days). The salivary *S. mutans* and *Lactobacillus* colony count revealed a more significant reduction with the administration of green tea with xylitol mouthwash (Hajiahmadi et al. 2019).

Xylitol has also affect on the growth of nasopharyngeal microbiota. This could be important when noticing the respiratory pathologies caused by nasopharyngeal bacteria, such as *S. pneumoniae.* These bacteria respond to xylitol in the same way as *S. mutans* respond to xylitol in the oral cavity. To evaluate this statement, a study has been conducted in which they grew some nasopharyngeal bacteria in media that was consisted of xylitol sugar. The results of this study showed that xylitol could significantly reduce the growth levels of *S. pneumoniae* and *S. mitis* during the growth phase (Sakallioglu et al. 2014). This effect enhanced with an increase in the concentration of xylitol in growth media. There also was observed the slight inhibition of growth of β-hemolytic streptococci only by 5% xylitol concentration. However, no inhibition in the case of *Haemophilus influenzae* and *Moraxella catarrhalis* has been demonstrated (Kontiokari et al. 1995). Xylitol (5% and 10%) significantly decreased the biomass of such pathogenic bacteria like *Staphylococcus* *aureus* and *S. epidermidis*, and *Pseudomonas aeruginosa* involved in the formation of biofilms in case of chronic rhinosinusitis (Jain et al. 2016).

In an experimental model of rhinitis medicamentosa in rats, the application of xylitol solution during 15 days demonstrated the effectiveness for nasal mucosas, evaluated histopathologically, as of a reference drug mometasone (Cam et al. 2019).

Gut microbiota is responsible for forming many bioactive compounds from dietary substances which can maintain the whole-body metabolism (Ruiz-Ojeda et al. 2019, 2020). For example, better glucose metabolism can be induced by the help of dietary fibers that are linked with the greater quantity of *Prevotella* (Kovatcheva-Datchary et al. 2015). Same as some food additives and derivatives can produce some effects on the metabolism of the host after association with microbiota present in the gut. The study has been conducted with xylitol on mice model to check xylitol's effect on gut microbiota. They supply the xylitol 40 mg/kg bodyweight of mice in the diet. Xylitol induced substantial changes in the gut microbiota of mice (Tamura et al. 2013). They observed the changes in genera *Barnesiella*, which was significantly reduced in gut microbiota while the *Feacalibaculum* was significantly increased. *Barnesiella* and *Feacalibaculum* both have been spotted in the mice gut microbiota as well as human gut microbiota. The study concluded that the xylitol could induce changes in gut microbiota or bacterial colonies present in the gut, but it does not affect lipid metabolism (Uebanso et al. 2017).

Xylitol in the prevention of dental caries

Dental caries is one of the most common infections that affect the oral cavity associated with high costs for families. Research shows that it is still a significant health concern in most developing countries, affecting 60–90% of school-going children and many adults (Riggs et al. 2019). The broadening of the available spectrum of prophylactic substances (specifically xylitol) in an accessible form is hugely relevant at present. It was suggested that the positive effect of polyols in caries prevention might depend on the number of OH-groups in their molecule: erythritol ≥ xylitol > sorbitol (Mäkinen 2010). According to some authors, the prevalence of permanent tooth decay in children aged 6-16 exceeds 70 percent with an intensity of 2,86 index SIC – 5,20 ± 0,26. The highest increase in permanent tooth decay is observed in the age groups of 6–7 years (by 2.91-fold) and 11–12 years (by 1.37-fold) (Chukhray 2018). Dental caries is a multifactorial disease, which depends on the use of fermentable carbohydrates by acidogenic and aciduric microorganisms forming the dental biofilms. It has been established that natural protective mechanisms of the oral cavity of children with high-intensity decay are lowered. In particular, the level of IgA secretion is approximately 2.4 g/L, lysozyme (29.44 L/g), *Lactobacillus* concentration (41.02 percent), all who are below normal levels (Cherepyk 2017). The consumption of sucrose in large quantities at the age of 3 years can enhance the risk of increased colonies of mutans streptococci and increase the risk for dental caries. Several studies conclude that refined sugar like sucrose is a significant cause of developing caries in children and even in adults. *S. mutans* is the main producer of acids during the metabolism of sugars, mainly sucrose. The spreading of these acids at the interface between dental biofilms and enamel promotes a fast decrease of pH and a resultant stimulus to the demineralization process. Acids further diffuse into the enamel and dentin layer and dissolve the minerals there.

S. mutans forms biofilms known as dental plaque on the tooth surfaces, and it can also be responsible for the infective endocarditis (Lemos et al. 2019). *S. mutans* was firstly isolated from carious lesions by J. Clarke in 1924. However, it was considered an important etiologic agent in caries by the middle of the 1960s only (Lemos et al. 2019). Xylitol sugar has the potential to reduce the growth of *S. mutans* and, consequently, the production of dental caries.

Xylitol disturbs the bacterial metabolism and especially their energy production. It triggers the process of energy consumption cycle, and bacterial cell death occurs due to this phenomenon. Xylitol can reduce plaque formation. It decreases the demineralization of enamel and dentin (Ly et al. 2006). It also has an inhibitory effect on bacterial adherence and the production of biofilms in the oral cavity (Ammons et al. 2011). Very first dental caries prevention by xylitol was studied and researched in Finland in the 1970s, by using different animal models. The first xylitol related study in humans is referred to as "Turku Sugar Studies," and it was demonstrated a reduction of dental plaque through xylitol consumption. In Finland, for the first time, xylitol was introduced into chewing gum to cure dental caries by improving the health of the oral cavity.

The use of xylitol as a caries-preventing agent has been endorsed by many public regulatory affairs (Kitchens 2005; Mäkinen 2011). Xylitol-containing food and oral hygiene adjuvants have been shown to reduce the growth of dental plaque by decreasing the growth of caries-associated bacteria (Mäkinen 2011). Application of xylitol wipes might be a useful complement in reducing the cariogenic bacteria, especially *S. mutans*, and thus could be considered as an adjunct oral hygiene tool for caries prevention in children (Kayalvizhi et al. 2018).

The most efficient vehicle or mode of delivery of xylitol is, however, considered the chewing gum. The caries preventive effect of 1 year using of xylitol-containing chewing gum in an adult population showed that it had a reduction of caries disease at teeth level of 23% (Cocco et al. 2017). After using a chewing gum containing a high dose of xylitol during the half-year period, it was proved to be efficacious in caries prevention in high-risk children (Campus et al. 2013).

Other professional agents that can prevent dental caries are consisted of some toothpaste and mouthwash that contain xylitol components and fluoride as well. Toothpaste containing xylitol and fluoride may be more effective than toothpaste with fluoride only (Duane 2015). As dental caries are mostly experienced in young school-going children, so to treat dental caries in children xylitol-containing candies, gummy bears, gums, and lozenges are better and fascinating options.

Xylitol is better-tolerated polyol comparatively to d-glucitol or d-mannitol, and its highest safe doses typically range 20–70 g per day; the quantity of xylitol recommended for caries inhibition is about 10 g/day for adults; children should intake smaller quantities (Mäkinen 2016). Researchers revealed the need for well-designed clinical studies with adequate control groups after studying the prevention of caries after consuming xylitol-containing candies and lozenges (Antonio et al. 2011). A systematic review (Marghalani et al. 2017) examined the effectiveness of xylitol in reducing dental caries in children compared to placebo, no treatment, or other preventive strategies revealed a small effect size in randomized trials and a very low level of evidence that makes its preventive effect uncertain. Anyway, from all the studies and researches until now, it is concluded that the xylitol products are very beneficial and helpful to treat dental caries, to reduce the growth of mutans streptococci, to eliminate the plaque, and ultimately to improve the health of oral cavity (Janakiram et al. 2017).

Xylitol and insulin

Research showed that the administration of xylitol could induce a rapid release of insulin in plasma. The study has been done in dogs (0.4 g/kg xylitol, intravenously). The prompt rise in plasma insulin was observed as a result, though the procedure or mechanism behind the stimulation of the release of insulin is still ambiguous. Xylitol enters the pentose phosphate pathway through D-xylulose-5-phosphate. Therefore, it shares the mutual metabolic pathway with glucose. The researchers further also checked the effects of insulin by changing the doses of xylitol and its administration by the oral route.

The results showed that oral administration of xylitol incites a more substantial effect on the secretion of insulin than the intravenous route (Kuzuya et al. 1969). In another research (Kuzuya et al. 1971) performed on humans and some mammals, both xylitol and glucose were administered intravenously in equal quantity. The significant differences in insulin responses among different species have been observed. In man, glucose produced a definite increase in plasma insulin as compared to xylitol. While in cows and goats, glucose and xylitol both increased the plasma insulin markedly to an approximate extent. In horses, the insulin release was instead a bit poor and sluggish after administration of glucose and xylitol. Rabbits also showed the same extent of insulin release in response to glucose and xylitol. In rats, glucose showed higher insulin releases in plasma as compared to xylitol (Kishore et al. 2012). However, in dogs, the results were a bit different from all other mammals: xylitol showed a definite higher insulin peak as compared to glucose. The reason behind this species variation could not be explained (Kuzuya et al. 1971).

The utilization of carbohydrates has been studied and compared the results with glucose utilization during the endogenous insulin secretion inhibition. The experiment has been carried out in 28 healthy volunteers, and they were divided into further five groups (sorbitol, fructose, glucose, xylitol, and saline). The results concluded that sorbitol, fructose, and xylitol are oxidized more as compare to glucose during the suppression of insulin secretion without any substantial increase in glycemic index (de Kalbermatten et al. 1980). Therefore, low glycemic and insulinemic influences of xylitol are beneficial (Janket et al. 2019).

Xylitol and inflammation

Xylitol has an inhibitory effect on inflammatory reactions. The important and vital process that is involved in inflammation is angiogenesis, which occurs during tumor formation and metastasis. Many research studies have been carried out on natural compounds that are responsible for reducing or inhibiting inflammatory responses. Xylitol is one of the natural compounds that can inhibit inflammatory responses. Xylitol can inhibit the expression of inflammatory cytokines that are triggered by lipopolysaccharides (LPS). It has been discovered that inflammation and angiogenesis share a mutual or common signaling pathway. Xylitol is responsible for inhibiting the invasion, migration, and tube formation of human umbilical vein endothelial cells (HUVECs). *In vivo* studies on rats showed that xylitol also inhibited angiogenesis in a mouse Matrigel plug assay. By treating the rats with xylitol, there was a decreased mRNA expression of vascular endothelial growth factor (VEGF), matrix-metalloproteinase-2 (MMP-2), and basic fibroblast growth factor (BFGF). This anti-inflammatory and anti-angiogenic potential of xylitol can be exerted via inhibition of the NF-κB pathway and Akt activation pathway. These results showed that xylitol has a beneficial role against inflammation and angiogenesis (Yi and Kim 2013).

Porphyromonas gingivalis is the most identified bacteria responsible for causing dental pathologies. The LPS secreted by *P. gingivalis* is the main factor in the development of periodontitis. Inflammatory cytokines, induced by LPS, play a significant role in the destruction of gingival tissues. Xylitol can inhibit the production of inflammatory cytokines and reduce the secretion of LPS by *P. gingivalis*. The pretreatment with xylitol can suppress the expression of cytokines that cause inflammation (Han et al. 2005). Xylitol also inhibits the TNF-α and IL-1β gene expression and, ultimately, protein synthesis. Studies showed that LPS-induced activation of the NF-κB pathway could also be inhibited by xylitol that is involved in inflammatory responses. Xylitol also displayed an inhibitory effect on the growth of *P. gingivalis.*

All these findings collectively indicate that xylitol can have an excellent clinical effect not only for dental pathologies but also to inhibit LPS-trigger inflammatory cytokine expression (Han et al. 2005). Preparations containing xylitol are known to be used effectively in the comprehensive treatment of endogenous intoxication in suppurative diseases in maxillofacial surgery (Medvid 2011).

Xylitol in the prevention of obesity and metabolic syndrome

Obesity has become a significant health concern in the whole world by being the principal risk factor for several diseases, such as cardiovascular diseases, metabolic syndrome, stroke, atherosclerosis, and even cancer. Obesity is caused by several environmental factors involving diet and nutrient composition. A diet containing high-fat components is responsible for causing metabolic syndromes, among others, obesity, dyslipidemia, and hyperglycemia. Xylitol is used in medications as low-calorie sugar. While taking xylitol, a small increase in blood glucose level can be observed, a rapid release of insulin occurs, and glucose level can overcome in diabetic and healthy individuals due to the release of insulin. Therefore, it is recommended that diabetic patients can uptake xylitol as a sugar substitute and as an energy source in place of other carbohydrates dietary products. In the liver, xylitol is first phosphorylated and then converted into xylulose-5-phosphate through a metabolic pentose phosphate pathway. This xylitol metabolite, xylulose-5-phosphate, is responsible for activating nuclear transport activities and DNA-binding activities of carbohydrates response element of a binding protein (ChREBP) via the activation of another enzyme known as protein phosphatase 2A(PP2A). ChREBP is a commonly known transcription factor that triggers or stimulates the genes associated with a lipogenic enzyme such as acetyl coenzyme A carboxylase (ACC) and fatty acid synthase (FAS).

Consequently, this increased lipogenesis in the liver results in obesity or stenosis. Therefore, in that case, excessive consumption of xylitol combined with a high-fat diet can activate lipogenesis genes, and it induces obesity in people and ultimately leading to metabolic syndrome. However, still, the long-term effects of xylitol on carbohydrate and lipid metabolism cannot be fully understood—more studies and research are required to reveal its mechanism. Because xylitol has been used in appropriate doses for some beneficial effects such as it is useful to reduce the postprandial hyperglycemia and, ultimately, diabetes, obesity, and metabolic syndrome (Amo et al. 2011; Pearlman et al. 2017). It was observed that gastric emptying was significantly slower with xylitol intake; thus, it can prevent the hunger sensation and food intake (Janket et al. 2019). The impact of xylitol sugar is very low on the blood glycemic index as compared to other sugars, so it indicates that xylitol can be a beneficial substitute for natural sugars that, among others, can develop cardiac diseases and diabetes (Soderling 2009a).

Xylitol and prevention from other diseases

Except for the diseases already discussed, such as oral cavity diseases, obesity, and metabolic syndrome, some researches showed that xylitol could prevent some other diseases, too, for example, some respiratory diseases, among others pneumonia and middle ear infection (Lee and Park 2014).

The bacterium responsible for pneumonia is *S. pneumonia*. This bacterium is becoming resistant to beta-lactam antibiotics and penicillin day by day. Pneumonia affects mostly young children. The currently developed antibiotics and vaccines do not have the potential to overcome this disease because its pathogen has developed resistance against them. Alternative preventive treatment or cure is necessary to overcome this disease. Studies showed that the five-carbon sugar alcohol xylitol could cure this disease. The derivative of xylitol, known as xylitol phosphate that is produced by *S. pneumonia*, has the potential to inhibit the growth of them. Consequently, the growth of these resistant bacteria can be stopped by using xylitol (Palchaudhuri et al. 2015).

The most common middle ear infection in the USA among young children is known as acute otitis media. In this infection, bacteria create a sticky fluid in the middle ear right behind the eardrum. Severe pain can be experienced in that situation. Fever and ear secretion can also occur in this disease among children, although no severe complications are noted in acute otitis media (Uhari et al. 2000). The treatment of this disease is a bit costly, and the pathogen can develop antibiotic resistance. Surgery is also an inappropriate and costly option to manage middle ear infection in children. Therefore, xylitol is considered an appropriate option.

Xylitol can be found naturally in many fruits, among other strawberries, raspberries, plums, and rowan berries. Artificially, it is present in among others gums, gummy bears, candies, and pills. So, children can easily and happily consume xylitol to treat their oral cavity infections and middle ear infections.

The xylitol syrup is also available as a medicine for young children. Xylitol can be administered in gums, syrups, and lozenges, and these products can eliminate acute otitis media among young children with no severe respiratory infections and side effects (Azarpazhooh et al. 2016). Another study reported that young individuals have a very low incidence of acute otitis media if they are consuming xylitol oral solution in a dose of 2–5 g daily. Despite all these studies, xylitol is not being used at the global level consistently (Vernacchio et al. 2014).

Xylitol has been reported to improve barrier function and inhibit the growth of potential skin pathogenic microorganisms. As a non-digestible organic compound, xylitol enters the colon where it is fermented by the colonic microbiota such as *Anaerostipes* species to produce butyrate (Salli et al. 2019). Sugar alcohols have some prebiotic properties (Mäkinen 2016). Xylitol can improve bone mineral density and modulate the immune system, which, together with its antimicrobial effect, contributes to a reduced respiratory tract infection risk. Safety and efficacy of aerosolized xylitol (15%, 5 ml) used twice a day for 2 weeks in patients hospitalized with pulmonary cystic fibrosis, has been proven (Singh et al. 2020). As a low caloric sweetener, xylitol may contribute to weight management due to its ability to increase satiety (Salli et al. 2019).

Safety and eventual adverse effects of xylitol in adults

Despite xylitol sugar possess many positive effects, its consumption is usually associated with irritable bowel syndrome (IBS) in adults. Abnormal flatulence also has been observed by consuming xylitol (Mäkinen 2016). Therefore, xylitol consumption can also affect human health negatively. It is thought to be a burden in economic terms of health care costs. Although it has been found that sugar alcohols can be useful in the treatment of severe or chronic constipation. For instance, D-glucitol has been utilized in many commercial preparations (Mäkinen 2016). No previous study has primarily focused on osmotic diarrhea linked with the overuse of sugar alcohol substances. Fewer studies are present in which difficulties related to sugar alcohols have been discussed. It is necessary to focus that osmotic diarrhea, which can be observed by consuming slowly absorbed polyols and carbohydrates, is not considered as a disease but somewhat an unpretentious physiochemical response of the gastrointestinal tract in the presence of polyols in the gut (Mäkinen 2016). When an individual consumes carbohydrate or polyol solutions, in response, water draw from the body into the lumen of the gut, this phenomenon causes osmotic diarrhea (Grillaud et al. 2005). Osmotic diarrhea can also be seen in some diseases like pancreatic diseases (Oku and Nakamura 2007). It is also necessary to focus that severe osmotic effects can also be seen when people eat a large number of grains, cereals, vegetables, and certain fruits. In healthy people, consuming the extra-large amount of substances, for example, vitamin C, salts containing magnesium, and some antibiotics can cause acute cases of osmotic diarrhea and bowel diseases (Mäkinen 2016).

Xylitol can be tolerated well, even in large quantities. Though susceptible persons may require adapting to digest higher intake of xylitol, by adapting to tolerate the higher amounts, xylitol can increase the activity levels of enzyme polyol dehydrogenase. This enzyme is beneficial to tolerate and absorb the xylitol in the body. Xylitol sugar is slowly absorbed and metabolized by the body. It can induce minimal alterations in insulin release.

Xylitol in the body can bind with calcium ion and some other cations. This phenomenon contributes to the remineralization of the enamel of teeth. The complexes of xylitol-calcium facilitate the absorption of calcium throughout the gut wall. This indicates that xylitol can be beneficial in preventing osteoporosis (Vasilescu et al. 2011).

However, several studies reported increased the risk factors for urolithiasis in the case of long-term xylitol intake, which could be attributable to osmotic diarrhea that may cause metabolic acidosis (Janket et al. 2019).

Safety and eventual adverse effects of xylitol in children

Xylitol is a useful option to prevent dental caries and acute otitis media (AOM) in children. A study (Vernacchio et al. 2007) has described its efficiency when xylitol is given to the children five times a day to prevent AOM. Despite this advantage, xylitol is not considered as the best option worldwide to cure acute otitis media in young children because there are two significant reasons. One of them is the impractical schedule of dosing five times, which is difficult to follow. The other actual reason is that xylitol can produce some gastrointestinal side effects while treating acute otitis media in young children and especially in infants (Mäkinen 2016). The study (Vernacchio et al. 2007) was done to check the xylitol side effects in children. The researchers did the dosing of xylitol five times a day in children 6–36 months of age. The subjects tolerate the xylitol solution very well. Only three subjects out of 30 developed the gastrointestinal side effects. The subjects who developed side effects were usually infants. The side effects observed among children were comprised of the development of excessive gas, loose stool, and diarrhea. The rates of diarrhea were more significant as compared to other side effects in children reported by parents (Vernacchio et al. 2007). Therefore, this study concluded that infants have more chances to develop gastrointestinal side effects while consuming xylitol solution daily. However, still, further research is required to approve these observations.

Overuse of xylitol is responsible for the accumulation of xylitol in the gut lumen that will lead to retention of water and consequently cause diarrhea in young children. Also, other studies showed that an excessive quantity of xylitol would lead to the development of gas and bloating (Storey et al. 2007). Xylitol solution, which cannot be absorbed, is eliminated after metabolizing into carbon dioxide. In 1985 European Union's Scientific Committee on Food published a report in which it has been stated that taking or consuming 50 g of xylitol solution can cause diarrhea. The union also confirmed that if the sweeteners containing xylitol consumed too much, it could induce some laxative side effects in children.

Conclusions

Xylitol is belonging to a carbohydrate class of biomolecules, known as a sugar alcohol, and used as a sweetener. It can be found naturally in a very low quantity. Commercially, xylitol is produced through the recovery of waste constituents from plants manufacturing chemically or by biotechnological processes.

Chewing gums occupy a leading position among the different vehicles used for delivering the xylitol into the human body. This biomolecule has excellent potential to prevent dental caries, to support the remineralization of teeth enamel, and acts as antiplaque and anti-gingivitis to improve the health of the oral cavity among young children. Xylitol also has good prospects in the area of inhibiting the growth of antibiotic-resistant bacteria. This sugar alcohol has excellent anti-inflammatory potential and can cure chronic inflammatory diseases efficiently; it can play a positive role in the treatment, among others, middle ear infections and respiratory diseases such as pneumonia. Xylitol is also responsible for releases insulin in blood plasma in mammals; it can also reduce obesity and some other metabolic syndromes. When taken in excessive amounts, xylitol can produce some side effects, such as diarrhea and loose stools. However, several studies have demonstrated its many beneficial effects on human health. Xylitol can prevent and treat various diseases, which not can be treated with antibiotics or surgery. Still, advanced research is needed to explore more the beneficial effects of xylitol.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no competing interests.

Ethical approval This article does not contain any studies with human participants or animals performed by any of the authors.

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