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Xylitol in Systemic and Oral Health

RE Carlson[1]*, V Koneru[2] and JA Von Fraunhofer[3]

[1]Executive Director, Research and Analytical Sciences, D. Gary Young Research Institute, Lehi, UT, USA

[2]Senior Director, Product Development, D. Gary Young Research Institute, Lehi, UT, USA

[3]Professor Emeritus, University of Maryland, Baltimore, USA

***Corresponding Author**: RE Carlson, Executive Director, Research and Analytical Sciences, D. Gary Young Research Institute, Lehi, UT, USA.

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Abstract

This communication reviews the characteristics of the naturally-occurring sugar alcohol/polyol, xylitol and its use as a substitute sweetener to sucrose or table sugar. The role of xylitol in gastric health, notably its role as a functional sweetener with prebiotic effects, and its importance as a valuable adjunct to maintaining oral health are reviewed. In particular, the ability of xylitol to address dental caries and periodontal disease is discussed in detail. The antibacterial properties of xylitol with regard to treating the streptococcal bacteria involved in dental caries and periodontal disease by means of chewing gum, mouth rinses and dentifrices as well as nasopharyngeal issues such as rhinosinusitis are discussed.

Keywords: *Sugar Alcohol; Oral Health; Obesity*

Introduction

Obesity is a growing and serious problem world-wide with many causes but, notably, due to the consumption of high fat, sugar-rich foods. In fact, not only is excessive sugar intake deleterious to dentition and promotes the formation of adipose tissue, but there have also been some controversial suggestions that excessive sugar may play an important role in certain degenerative diseases [1]. A common approach to dealing with this issue is to substitute low/zero calorie sugar substitutes for sucrose (table sugar), of which a great many are now widely available.

A sugar substitute or artificial sweetener may be defined as a food additive that replicates the taste of sugar in food but usually makes a lower caloric contribution to the diet. However, it has been reported that animal studies have shown that some artificial sweeteners can cause weight gain, brain tumors, bladder cancer and many other health hazards including carcinogenicity in humans [1]. Overall, the extensive literature on artificial indicates that many sweeteners are "safe under all conditions" or GRAS (generally recognized as safe) whereas others might be deemed "unsafe at any dose". In short, the literature on the safety of artificial sweeteners, as well as numerous online articles and blogs, are divided on this issue and, consequently, discussions of sweetener safety should be on a case-by-case basis. The subject of this review, xylitol, is a sugar alcohol or polyol that has been approved as a food additive by the FDA since 1963 and is commonly used as a diabetic sweetener.

General characteristics

The xylitol molecule has a 5-carbon backbone with a hydroxyl (-OH) group attached to each carbon atom, figure 1.

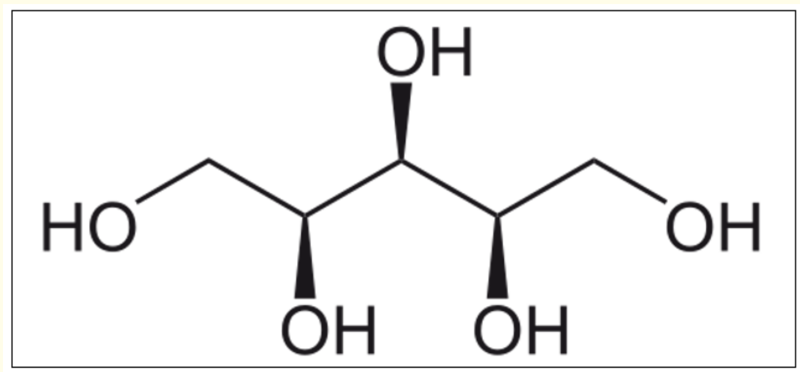

Figure 1: *Molecular structure of xylitol.*

Xylitol occurs naturally in small amounts in cauliflower, mushrooms, oats, plums, pumpkin and strawberries as well as being produced in trace amounts by humans and other mammals during metabolization of carbohydrates [2,3]. Although xylitol can be produced by chemical processes, chemical production is costly and requires a number of purification steps. In contrast, biotechnological production utilizes agricultural and forestry waste, and has a lower energy requirement. In essence, xylan[1] is extracted from waste biomass[2], hydrolyzed (chemically and enzymatically) into xylose, a monosaccharide sugar, which is then catalytically hydrogenated into xylitol. Various fermentation inhibitors also occur as by-products during the hydrolytic reactions, and these have to be removed in the overall production process to maintain both efficiency and productivity [2,3]. Interestingly, xylitol production by fermentation from waste biomass apparently is one of the most valuable renewable chemicals for commerce and is forecast to be a $1.4 billion industry by 2025 [4].

Although xylitol is used commercially as a sugar substitute in a wide variety of manufactured foodstuffs and domestic products, it is not a common household or table-top packeted sweetener [5]. The commercial applications of xylitol include pharmaceuticals, dietary supplements, confectionary, toothpaste and chewing gum. Xylitol has a similar if not slightly greater sweetness than sucrose but it is sweeter than other sugar alcohols such as sorbitol and mannitol [2,3]. Its food energy contribution is 2.4 kcal/g and like many other sugar alcohols, xylitol is heat stable and can be used in baking because, unlike sucrose and other sugars, it does not caramelize on heating.

Gastric system effects

Xylitol is considered to be a functional sweetener as it has prebiotic[3] effects which can reduce blood glucose, triglyceride and cholesterol levels [2]. This prebiotic activity is because xylitol is absorbed within the gut more slowly than sucrose. In particular, because xylitol is a non-digestible carbohydrate, it passes through the gut and small intestine into the colon where it is fermented by colonic microbiota.

[1]Xylan is a type of hemicellulose polysaccharide found in plant cell walls and is the third most abundant biopolymer.

[2]The waste biomass typically includes hardwoods, softwoods and agricultural waste from processing maize (corncobs in the US), wheat or rice.

[3]A prebiotic is a a nondigestible food ingredient that promotes the growth of beneficial microorganisms in the intestines.

The non-digestible but fermentable nature of xylitol also contributes to a constipation-relieving effect and improves bone mineral density. As a non-digestible carbohydrate, xylitol enters the colon where it is fermented by members of the colonic microbiota; species of the genus *Anaerostipes* have been reported to ferment xylitol and produce butyrate [6]. Butyrate formed by such fermentation in colon is important for energy metabolism, helps normal development of colonic epithelial cells and plays an important role in protecting colonic disease [7]. It has also been suggested that xylitol can assist in increasing the numbers of bifidobacteria within the large intestine [8].

Other studies suggest that the main metabolic route for xylitol occurs in cytoplasm[4] via an enzymatic reaction that transforms xylitol to the monosaccharide D-xylulose, which then undergoes further processing within the body [9]. It has also been reported that the key enzymes involved in xylitol digestion by different bacteria can support the growth of a micro-ecology and enhanced the concentration of propionate [10]. The latter lowers the colonic pH which in turn can restrict proliferation of pathogenic bacteria like *Escherichia* and *Staphylococcus* [9]. In other words, xylitol can dynamically balance proportions of the gut microbiome to promote the proliferation of beneficial bacteria and the production of short-chain fatty acids (SCFAs) such as propionic acid [9].

Overall, it appears that about 50% of ingested xylitol is absorbed via the intestines while of the remaining unabsorbed 50% of xylitol in the gut, about 50-70% is fermented by gut bacteria into short-chain organic acids and gases, the latter often causing flatulence. Residual unabsorbed and unfermented xylitol is excreted unchanged, mostly in feces with less than 2% of ingested xylitol being excreted via urine [11].

Xylitol ingestion also increases motilin[5] secretion, possibly accounting for the sweetener's ability to relieve constipation and its potential for causing diarrhea when consumed in excess [3,6,12,13]. The lower absorption of xylitol compared to that of sucrose would account for its suitability as a sweetener for diabetics. It is also suggested that the non-digestible but fermentable (i.e., prebiotic) nature of xylitol also contributes to a constipation relieving effect and also to improved bone mineral density. Xylitol also modulates the immune system [6,10,12,14], which, together with its antimicrobial activity, contribute to a reduced risk of respiratory tract infections, sinusitis and otitis media, the latter effects being discussed below.

In this context, it should be mentioned that xylitol is toxic to dogs, and ingestion of 100 mg/kg of body weight (bw) causes dogs to experience a dose-dependent insulin release which can lead to life-threatening hypoglycemia. Higher dosages (500 mg/kg bw) can result in liver failure and other serious health issues [15]. On the other hand, xylitol is safe for cats and they can tolerate ingesting xylitol doses of 1000 mg/kg bw [16]. It follows that feeding animals, especially dogs, with treats that contain non-caloric sweeteners might be injurious to their health even if this potentially helps limit weight gain while providing some degree of gustatory satisfaction.

Dental health

Dental caries is a very prevalent infectious disease predominantly involving dental plaque and cariogenic bacteria such as *Streptococcus mutans* (*S mutans*)[6] and *Streptococcus sangui.* Various biological processes occurring within bacterial plaque contribute to the incidence of dental caries, including glycolysis[7].

[4]Cytoplasm is the material or protoplasm within a living cell but not the nucleus.

[5]Motilin is a hormone that stimulates gastric activity

[6]Streptococcus mutans is often referred to as mutans Streptococcus or MS in the literature.

[7]Glycolysis is the breakdown of glucose by enzymes, releasing energy and pyruvic acid, the latter ultimately decomposing to lactic acid.

The literature has numerous references to the dental health benefits of xylitol, notably comments on its ability to reduce the risk for dental caries and prevention of periodontal disease [3,5,6,12,15,17-24]. It has been suggested, however, that there is no evidence for a caries-therapeutic effect of xylitol and that the caries-preventive effects of polyol-containing chewing gums and candies may be ascribed to stimulation of salivary flow although an antimicrobial effect could not be excluded [16]. In contrast, the preponderance of scientific opinion is that xylitol is an effective agent against dental caries because it has the ability to inhibit the growth and reduce the levels of *Streptococcus mutans* and other cariogenic bacteria in plaque and saliva [3,6,12,18,20,21,23,25-28]. In fact, an extensive review of the literature indicated that the reduction in *S. mutans* count was superior to all other caries preventive strategies and was more effective in reducing DMF scores than fluoride varnish [21]. There also is evidence that xylitol is effective when used by the mother prenatally or after delivery to prevent *S. mutans* transmission and subsequent dental caries in offspring [29] Further, children of mothers who used xylitol lozenges after delivery had less dental caries than a comparison group [29]. A similar study confirmed that the use of xylitol chewing gum by the mother either prevented or postponed *S. mutans* transmission to their offspring [30].

Although the literature clearly indicates that xylitol shows great promise in reducing dental caries disease and also reversing the process of early caries [31-33], the optimum mode of delivery and even the most efficacious dose and frequency of use are unknown [27]. Overall, it appears that a high single dose of xylitol had a short and limited beneficial effect on interdental plaque-pH in habitual xylitol consumers, whereas a low single dose, such as normal (apparently single daily) chewing gum use, has little effect. It was found, for example, that whereas xylitol use among schoolchildren delivered *via* a gummy bear confection reduced *S. mutans* levels, a once *per* day use of xylitol-containing toothpaste did not have this effect [29]. However, daily consumption of 5-6 g via chewing gum at a frequency of three or more times per day for 5 weeks leads to both long-term and short-term reductions in salivary and plaque *S. mutans* levels [34,35]. This was confirmed by other studies which have shown that children who chewed gum distributed three times a day at school had a significantly lower net progression of decay over a 24-month period than did the controls, especially for bucco-lingual surfaces [36]. Interestingly, there was no difference found in caries prevention between chewing gums containing 15% and 65% xylitol [36]. This finding is actually in keeping with the observation that there appears to be a plateau in the dose response of *S. mutans* in plaque and saliva at 5 weeks and 6 months to xylitol at 6.44 g/day and 10.32 g/day [33].

Clearly, the consensus of professional opinion based on the extensive literature is that the regular use of xylitol-containing chewing gum can be a very effective part of normal oral hygiene to prevent dental caries [17,18,21,25,31-34].

Presumably in an approach to take advantage of the anti-caries and antiplaque capabilities of xylitol, a number of studies have been performed to evaluate the effect of the inclusion of this particular sugar alcohol/polyol in fluoride-containing dentifrices [3,6,11,17,31,37-46]. In particular, this approach to enhanced oral hygiene is thought to take advantage of the significant antiplaque effect of xylitol on tooth surfaces and can reduce gingival inflammation [12]. In addition to decreasing the growth levels of pathogenic *Streptococcus mutans* and *Streptococcus sangui* bacteria in plaque and saliva at the very early stages of dental caries, it appears that xylitol can bind with calcium ions, leading to subsequent remineralization of tooth enamel [11,26,32,35,38,42]. The latter finding suggests that xylitol not only reduces dental caries disease but may also reverse the process of early caries [30,31].

It has also been reported that the inclusion of 10% xylitol increased the effect of the fluoridated dentifrice against enamel erosion plus abrasion *in vitro* [45]. Other work likewise has suggested that a fluoride toothpaste with 10% xylitol reduced caries in children by 13% when compared to a fluoride-only toothpaste [40]. Interestingly, there has been a study that the addition of 10% xylitol to a triclosan-containing dentifrice reduces the number of *Streptococcus mutans* in saliva and dental plaque [47]. It should be noted, however, that there are some potential drawbacks to using triclosan-containing dentifrices and mouthwashes, however potentially effective they might be. In particular, the FDA in 2017 and the European Union have banned triclosan in personal care products because of possible allergic reactions and long-term adverse health effects.

With regard to periodontal disease, it is well-accepted that biofilm development on dental surfaces eventually leads to the accumulation of plaque and, subsequently, to dental caries and periodontal problems. Chlorhexidine oral rinse has long been used to address periodontal issues and at least one study has investigated the effect of a combination of xylitol and chlorhexidine on the viability of *S. sanguis* or *S. mutans* during the early stages of biofilm development compared to either ingredient alone [48]. Greater inhibition of streptococci occurred with the xylitol/chlorhexidine combination compared with xylitol or chlorhexidine being used alone and it was suggested that this newly discovered synergistic action could be used for high-risk caries patients or for reducing *S. mutans* transmission from mother to child. Although chlorhexidine alone and xylitol/chlorhexidine solutions are effective against both *S. mutans* and *S. sanguis, S. sanguis* was most sensitive to the antiseptic effects of chlorhexidine alone whereas *S. mutans* colonies were more sensitive to the xylitol/chlorhexidine solution [48].

The effectiveness of the chlorhexidine/xylitol combination against the formation and deleterious effects of oral biofilms was supported by the findings of a contemporary *in vitro* study [49]. The latter evaluated the effects of 1% and 3% xylitol solutions on *S. mutans, S. sobrinus, P. gingivalis, Fusobacterium nucleatum, Actinomyces viscosus* and *Lactobacillus rhamnosus*. The study data clearly demonstrated that xylitol had an inhibitory effect on the formation of experimental biofilms, not only efficiently inhibiting acid production by cariogenic bacteria but also prevented the formation of a multispecies biofilm [49]. In contrast, however, it has been reported that regular mouth rinses (3X/day) with fluoride and xylitol, separately or in combination, did not affect the salivary flow rate or oral micro–biota, dental plaque accumulation, gingivitis development, or the acidogenic potential of plaque [50]. This finding suggests that although xylitol-containing products gave elevated concentrations of xylitol in unstimulated whole saliva and dental plaque for at least 8 min after intake [38] anticaries and antiplaque activity requires longer exposure to xylitol alone, as with chewing gum, lozenges, and dentifrices, unless advantage can be taken of synergistic effects such as that observed with chlorhexidine/xylitol combinations. It should also be mentioned in this regard that if rinsing with a xylitol solution or a xylitol/chlorhexidine combination followed the clinician-recommended chlorhexidine rinsing protocol for periodontal treatment, then this extended localized irrigation might ensure prolonged localized exposure to xylitol.

Although not directly related to dentistry and dental care, obstructions of the nasal cavity such as acute or chronic rhinosinusitis impair nasal respiration, forcing sufferers to become mouth breathers, an action that can cause dental problems. In a study to evaluate the tolerability of a xylitol/water mixture, it was found that xylitol irrigations result in greater improvement of symptoms of chronic rhinosinusitis compared to saline irrigation [51]. This finding supports an earlier study performed on NZ white rabbits which investigated whether altering airway surface liquid ionic concentrations could influence the course of sinusitis [52]. When xylitol was administered simultaneously with bacteria (*P. aeruginosa*), it was found to reduce experimental sinusitis. Although the effect of xylitol in established sinusitis is less clear, it was concluded that xylitol might be an useful component in nasal irrigation fluids for treating humans [50]. Other workers have indicated that the antimicrobial activity of xylitol contributes to a reduced risk of respiratory tract infection, sinusitis and otitis media as well as possibly improving the barrier function and suppressing the growth of potential skin pathogens [6].

Conclusions

The literature reviewed here clearly demonstrates that xylitol, perhaps uniquely for a sugar alcohol, has significant antibacterial properties, notably against streptococcal species but also against other pathogens such as *P. aeruginosa*. The germicidal action of xylitol and its importance in maintaining oral health by means of chewing gum, oral rinses and dentifrices are important adjuncts in the continuing battle against dental caries and periodontal disease. Further, the literature also indicates that xylitol contributes to gastric health through its ability to function as a prebiotic, thereby promoting a healthy gut microbiome. Another interesting facet of the antibacterial properties of xylitol is that nasal sprays based on aqueous solutions of xylitol appear to have a useful role in the treatment of acute and chronic rhinosinusitis.

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