

## Anti-Cariogenic Effect of Five-Carbon Sugar: Xylitol

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### Abstract

Dental caries, the most chronic disease affecting mankind, has been in the limelight with regard to its prevention and treatment. Professional clinical management of caries has been very successful in cases of different severities of disease manifestations. However, tertiary management of this disease has been gaining attention, with numerous methods and agents emerging on a daily basis. Non-nutritive sweeteners have gained popularity as they are sweeter and are required in substantially lesser quantities. Xylitol, a nutritive sweetener, is five-carbon sugar polyol, has been found to be promising in reducing dental caries disease and also reversing the process of early caries. This paper throws light on the role and effects of various forms of xylitol on dental caries and oral hygiene status of an individual.

**Keywords:** Xylitol, Dental caries, Oral flora, Five-carbon sugar

### Introduction

Xylitol, a naturally occurring five-carbon sugar polyol, is a white crystalline carbohydrate known since a century ago. It has been widely studied during the last 40 years for its effect on dental caries. It is found naturally in fruit, vegetables, and berries and is artificially manufactured from xylan-rich plant materials such as birch and beech wood [1]. Since a study conducted in Turku, Finland, evaluating the effectiveness of xylitol on dental plaque reduction in 1970, xylitol has been widely researched and globally accepted as a natural sweetener approved by the US Food and Drug Administration (FDA), the American Academy of Pediatric Dentistry and the European Food Safety Agency (EFSA) [2].

It has been observed that when all associated factors of dental caries, such as age, sex, race, number of teeth, and oral hygiene, were controlled, taste was found to be the only variable that was related to overall caries experience [3]. In the recent past, sugar consumption has increased, especially in children and adolescents, to 120 pounds per person each year or 20 teaspoons of table sugar per day [4]. This excessive consumption of sugar has led to negative health concerns like diabetes mellitus and dental caries and has increased awareness among the public and medical and dental professionals regarding the benefits of replacing sugar with nonsugar sweeteners. Hence, artificial sweeteners or noncaloric sweeteners are effective in weight management and obesity associated health disorders. However, an artificial sweetener is 300-400 times sweeter than table sugar, and a small amount of it can provide the same level of sweetness.

Sweeteners can be divided into nutritive and non-nutritive sweeteners. The nutritive sweeteners contain carbohydrates and provide energy (with the exception of sugar alcohols that provide energy even if it is not contain carbohydrates). The non-nutritive sweeteners offer little or no energy when they are consumed. The US Department of Agriculture pattern for 2,000 kcal recommends no more than 32 g (8 tsp added sugars per day) or 6% of 2,000 kcal. The FDA regulates health claims on food labels, and the claim that sweeteners do not promote dental caries has been successfully approved for sugar alcohols, isomaltulose, erythritol, D-tagatose, and sucralose [5].

Currently, more than 35 countries have approved the use of xylitol in foods, pharmaceuticals, and oral health products, principally in chewing gums, toothpastes, syrups, and confectioneries.

Habitual xylitol consumption may be defined as daily consumption of 5-7 g of xylitol at least three times a day [6]. The recommended dose for dental caries prevention is

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6-10 g/d. For those with temporomandibular joint dysfunction and who have difficulty in chewing, xylitol candy should be used instead of chewing gum. At high dosages, xylitol can cause diarrhea in children at 45 g/d and 100 g/d in adults. The amount tolerated varies with individual susceptibility and body weight. Most adults can tolerate 40 g/d.

### Mechanism of Action

Xylitol reduces the levels of mutans streptococci (MS) in plaque and saliva by disrupting their energy production processes, leading to futile energy cycle and cell death [7]. It reduces the adhesion of these microorganisms to the teeth surface and also reduces their acid production potential [8,9].

Xylitol promotes mineralization by increasing the salivary flow when used as chewing gum or large xylitol pastille. The uniqueness of xylitol is that it is practically nonfermentable by oral bacteria. Also, there is a decrease in levels of MS, as well as the amount of plaque, when there is habitual consumption of xylitol [10].

Streptococcus mutans transports the sugar into the cell in an energy-consuming cycle that is responsible for growth inhibition. Xylitol is then converted to xylitol-5-phosphate via phosphoenolpyruvate: fructose phosphotransferase system by S. mutans resulting in development of intracellular vacuoles and cell membrane degradation [11]. Unwittingly contributing to its own death, S. mutans then dephosphorylates xylitol-5-phosphate. The dephosphorylated molecule is then expelled from the cell. This expulsion occurs at an energy cost with no energy gained from xylitol metabolism. Thus, xylitol inhibits S. mutans growth essentially by starving the bacteria. Xylitol can inhibit the growth of harmful oral bacteria such as S. mutans, but its benefits do not stop in the oral cavity [12]. Xylitol has been shown to impact growth of nasopharyngeal bacteria such as S. pneumonia and S. mitis, and hence has a role to play in nasopharyngeal pneumonia.

### Oral Health Benefits of Xylitol

Xylitol decreases the incidence of dental caries by increasing salivary flow and pH [13] and reducing the number of cariogenic (MS) and periodontopathic (*Helicobacter pylori*) bacteria, plaque levels, xerostomia, gingival inflammation, and erosion of teeth [14].

Xylitol is well tolerated by the human body as a sweetener, but its absorption rate in the small intestine is very slow. Excess xylitol is known to induce osmotic diarrhea, indicating there is an upper limit to its dosage that can be tolerated [12]. Optimal inhibition of S. mutans growth by xylitol occurs with its total daily consumption of 5-6 g at a frequency of three or more times per day; a dose that remains well below the tolerance threshold. The plaque samples of habitual xylitol users showed a significant reduction in plaque adhesiveness and insoluble extracellular polysaccharides produced by S. mutans when compared with those who did not consume xylitol, et al. [12].

### Xylitol Chewing Gum

The predominant modality for xylitol delivery has been chewing gum [15]. Chewing gum accelerates the processes of rinsing away acid and uptake of beneficial calcium phosphate molecules to remineralize tooth enamel. The recommended

length of time for chewing after eating is approximately 20 minutes [12].

Daily consumption of 5-6 g at a frequency of three or more times per day for certain weeks may lead to both long-term and short-term reduction in salivary and plaque S. mutans levels [16,17]. A decrease in caries incidence has been reported among children exposed to the daily use of xylitol for 12-40 months [18]. The long-term benefits have been observed up to 5 years after cessation of xylitol use [19]. A prospective controlled, double-blind clinical trial confirmed that MS levels in plaque decreased as exposure to xylitol increased. However, a plateau effect was observed between 6.88 g/d and 10.32 g/d. The caries preventive effect was observed to be long term in relation to the teeth erupting during the period of xylitol use [20].

A study among Montreal children showed that children who chewed xylitol gum had significantly lower caries progression after 24 months than those who did not use gum. These children exhibited a significantly higher number of reversals of carious lesions than the control group, suggesting that remineralization has occurred [21]. In a long-term study it was confirmed that by using xylitol chewing gum, caries risk can be reduced by 59%, and the optimum time for introducing the chewing gum for caries prevention is at least 1 year prior to the eruption of permanent teeth [22].

The effectiveness of various dosages of xylitol in the chewing gum was studied on S. mutans growth in adults. In a study by Milgrom, et al. [23] in 2006, a daily xylitol dose of 3.44 g/d, 6.88 g/d, and 10.32 g/d was given to the first, second, and third group, respectively. No xylitol gum was given to control group subjects. Saliva samples were obtained at the beginning of the study as well as after 5 weeks and 6 months of chewing gum with the indicated dosage of xylitol. S. mutans colonization in plaque and saliva was observed to decrease with increasing xylitol dosage. The S. mutans levels for subjects receiving 6.88 g and 10.32 g of xylitol per day were reduced over time compared with control subjects. There was no significant difference between subjects receiving 3.44 g/d and the control group; this indicated that xylitol levels of 3.44 g/d were insufficient to alter S. mutans levels in plaque and saliva. However, a plateau effect was evident between 6.88 g and 10.32 g when comparing the 5-week plaque and saliva samples and also in samples of 6 months of using chewing gum. This plateau effect showed no significant difference in the S. mutans plaque and saliva levels between the 6.88 g/d and 10.32 g/d samples in any time period; however, both groups showed a reduction in S. mutans levels in plaque and saliva compared with the control and 3.44 g/d samples in any time period. Chewing xylitol gum did not change colonization of the aerobic or facultative microbiota; this suggests that xylitol specifically impacts S. mutans without significantly altering the overall microbiota. The lack of difference of effect between 6.88 g and 10.32 g suggests that dosages >10.32 g would not have any additional inhibitory effect on S. mutans.

### Xylitol Gummy Bear Snacks

Milgrom, et al. [23] studied the effect of habitual consumption of xylitol gummy bear snacks (11.7 g/d) in reducing cariogenic microorganisms in school-going children. There was a significant reduction in S. mutans and S. sobrinus. A plateau effect was observed at higher xylitol doses (>11.7 g/d). Ly, et al. [24] reported that consumption of gummy bear snack containing xylitol (11.7

or 15.6 g/day divided in three exposures) causes reductions in *S. mutans*/*sobrinus* levels.

## Xylitol Syrups

Xylitol syrup is indicated in young children with early childhood caries, as they are more likely to develop dental caries in permanent teeth than those without early childhood caries. This method of administration of xylitol is most acceptable and safe for toddlers and young children. Twice-daily administration of xylitol oral syrup at a total daily dose of 8 g was observed to be effective in preventing caries [25]. The studies confirm that the anticaries effect is attributed to xylitol itself and not to chewing and digestion activities of products consumed.

The syrup needs to be applied twice daily for effectiveness, thereby increasing the compliance as well as therapeutic effect. As xylitol syrup is not currently available in the retail market, commercially available products such as pudding jam and maple syrup may be used alternatively. The therapeutic dose of 4 g per serving can sometimes result in loose stools and diarrhea [6]. Hence, a gradual increase in dose can acclimatize the patient to xylitol, thereby reducing potential gastrointestinal problems.

## Xylitol Mouth Rinse

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 has been studied in comparison with xylitol and chlorhexidine alone [26]. The xylitol/chlorhexidine combination inhibited streptococci more when compared with xylitol or chlorhexidine being used alone. This newly discovered synergistic action could be used for high-risk caries patients or for reducing MS transmission from mother to child. 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, while *S. mutans* colonies were more sensitive to the xylitol/chlorhexidine solution.

## Xylitol Dentifrice

Toothpaste with xylitol led to a decrease in *S. mutans* colonies in saliva, the amount of secreted saliva, and the increase of pH value. It has a positive effect on the quality of the oral environment and it would be useful introducing it into prophylactic programmes [27]. Low xylitol concentration in fluoride toothpastes has been shown to improve the cariostatic effects on tooth enamel [28]. Synergistic use of xylitol with small doses of fluoride ions helps in caries control and avoiding contact of fluoride with tooth enamel during stages of mineralization [29].

Chewing gum has been the most widely used xylitol medium. Holgerson confirmed that continuous and long-term exposure of the teeth to xylitol is required irrespective of whether the medium used is chewing gum, toothpaste, mouth rinse, sucking tablets, or candy tablets. A clinician can choose from the various options available in a given situation. For example, an individual with temporomandibular joint disorder would not be able to chew xylitol gum.

## Xylitol on Dental Caries

Five FDA-approved non-nutritive sweeteners with intense sweetening power are acesulfame-K, aspartame, neotame,

saccharin, and sucralose [5]. These have estimated intakes below the acceptable daily intake (level that a person can safely consume every day over a lifetime without risk). By increasing palatability of nutrient-dense foods/beverages, sweeteners can promote diet healthfulness. Scientific evidence supports neither that intake of nutritive sweeteners by themselves increases the risk of obesity nor that nutritive or non-nutritive sweeteners cause behavioral disorders. However, nutritive sweeteners increase risk of dental caries.

MS are the target organisms of xylitol, though several other bacterial species are also inhibited. Only certain strains of MS are inhibited by xylitol, and the degree of inhibition differs among the different strains [30]. It has been observed that 80% of the total MS count was resistant to xylitol among the habitual xylitol consumers. However, the MS not inhibited by xylitol were found to be less virulent [31].

High concentrations of xylitol have been found to inhibit *Lactococcus lactis* over time, but not *S. salivarius* and *Lactobacillus casei*. Xylitol prevents the adherence of pneumococcal and *Haemophilus influenzae* to nasopharyngeal cells due to fructose phosphotransferase system-mediated uptake and phosphorylation of xylitol in the cell.

Xylitol reduces the levels of MS in plaque by various mechanisms. Firstly, plaque microorganisms cannot ferment xylitol and it replaces a fermentable cariogenic sweetener, usually sugar, the ability of certain organisms to ferment xylitol is negated by inaction of other plaque organisms, which prevents the plaque pH from falling [32]. Secondly, xylitol is incorporated into the cells of MS as xylitol-5-phosphate through the phosphoenolpyruvate phosphotransferase system. This results in inhibition of both growth and acid production [31]. Thirdly, when exposed to xylitol, MS develop resistance to xylitol. These resistant strains are less virulent in an oral environment [33]. Fourthly, xylitol increases the concentrations of ammonia and amino acids in plaque, thereby neutralizing plaque acids [34].

Milestone studies like the Turku sugar study and trials of partial substitution suggest that xylitol decreases the formation of plaque compared with sugars and other polyols. However, there is no evidence that xylitol is superior to any other sweetener in increasing the salivary flow rate during and immediately after chewing over varying lengths of time [35].

Remineralization of initial caries lesions has been documented by various clinical and laboratory-based studies. However, remineralization has been observed in all such experiments where nonsugar sweeteners were used. The remineralization occurs due to increased flow of saliva rich in calcium and phosphate and a shorter time interval of low plaque pH. The anticaries action of xylitol is mainly attributed to its effect on plaque and cariogenic microorganisms [36]. Remineralization in vivo is generally considered to be a slow process, and it is perhaps surprising that significant remineralization occurs within 3 weeks.

The stimulated saliva remineralizes enamel crystals damaged by initial caries attack more effectively than unstimulated saliva because it has a higher concentration of ions that make up the lattice structure of hydroxyapatite ( $\text{Ca}^{2+}$ ,  $\text{PO}_4^{3-}$ ,  $\text{OH}^-$ ). Remineralization of the enamel lesions was observed to be twice more with gum than without the gum [37].

An anticaries effect of xylitol and sorbitol usage has been demonstrated and compared among primary and permanent teeth. The xylitol group had 27% fewer caries than the sorbitol group. This experiment also concluded that xylitol positively impacts permanent teeth.

Recently, Murthykumar [38] reported in 2013 that xylitol in milk demonstrated a beneficial anticaries effect and is well accepted by both children and adults.

## Xylitol and mother-child Transmission of Salivary *S. Mutans*

An intriguing link between mothers who chew xylitol and a decrease in their children's caries development has been observed [11]. Until the age of around 3 years, children's immune systems are underdeveloped, and hence newborns are extremely susceptible to bacterial colonization. These age group children frequently receive affectionate kisses from their parents/caretakers and also share utensils with them while eating. Due to these practices, parents transmit *S. mutans* from their mouths to their children's mouths.

Regular use of xylitol is reported to reduce vertical transmission of dental caries from mother to child [39]. The compliance of the patient is an important contributing factor that influences the efficacy of xylitol.

Pregnancy can be an appropriate time for reducing mother-child transmission of MS. Studies have reported that children using xylitol exhibited significantly more nondetectable, MS-negative levels on the tooth ridges or tongue and the gingival ridge at 9, 12 and 24 months. The xylitol group children were also significantly less likely to be MS positive than the control group children at and after 9 months of age. The children whose mothers did not chew xylitol gum acquired MS 8.8 months earlier than did those whose mothers did chew the gum [40].

Xylitol chewing gum consumption among pregnant women with high salivary MS counts was compared with fluoride and chlorhexidine varnish treatments in a randomized controlled field study. The mothers were consuming 6-7 g of xylitol per day, whereas fluoride and chlorhexidine varnishes were applied biannually until the child was aged 2 years. The percentage colonization of MS was 10% in the xylitol group, 29% in the chlorhexidine group, and 49% in the fluoride varnish group at the children's age of 2 years. At the age of 5 years, the caries occurrence was observed to be 71% lower in the xylitol group as compared with the fluoride varnish group. After 10 years, the need for restoration was least in the xylitol group [41].

## Xylitol and Oral Hygiene

Xylitol consumption reduced MS counts in plaque but had no effect on the microbial composition of plaque or saliva in general. In a study, xylitol was compared with manuka honey and chlorhexidine mouthwash for its antiplaque efficacy. This study was performed among dental students aged between 21 and 25 years, and their plaque score was reduced to zero by performing the oral prophylaxis prior to the onset of the study. However, it was observed that chlorhexidine and manuka honey had significantly better antiplaque action than did xylitol [42]. It has been confirmed by previous studies that chlorhexidine is more effective as an antiplaque agent when the oral hygiene

status of the patient is reasonably good. At the same time, xylitol is recommended, especially in those children or individuals who lack manual dexterity and when their brushing cannot be supervised [43].

When used in mentally handicapped children, regular use of xylitol candies thrice daily effectively reduces plaque and gingival index scores, thereby supporting its role in oral hygiene routines in such children [44].

Limited studies are available in literature on the synergistic effects of xylitol and other oral health-promoting products like fluorides, chlorhexidine, and probiotics. Xylitol when combined with probiotics has been proved to beneficially influence the gut microflora [45]. Probiotics like *L. reuteri* and *L. rhamnosus* GG are very effective in decreasing the counts of these oral pathogens and benefit from the presence of xylitol in them [46].

## Conclusion

In spite of the abundant literature on xylitol, still more research is needed on the mechanisms of action of xylitol, the clinical significance of xylitol resistance, and the effect of xylitol on the plaque-saliva distribution of MS. Properly designed randomized controlled clinical trials are needed to demonstrate the feasibility of xylitol prevention in different populations with different dietary and oral hygiene habits. Further, suitable delivery vehicles for xylitol and the extent to which xylitol can be "diluted" with other polyols without losing the caries-preventive effects have to be ascertained methodically. A minimum daily dose and frequency necessary for xylitol effects on MS, plaque, and caries occurrence should be calibrated. While these issues of xylitol still need to be expanded, the benefits it offers are literally worth salivating over.

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