

Antibacterial and anticariogenic properties of xylitol: a literature review

Guilherme Goulart Cabral de Oliveira,¹ Débora Marinho Teixeira Freires,¹ Simone Gomes de Oliveira,¹ Ana Luiza de Mattos Guaraldi,² Sérgio de Carvalho Weyne,³ Raphael Hirata Júnior²

¹School of Dentistry, Rio de Janeiro State University (UERJ), Rio de Janeiro, RJ, Brazil

²Department of Microbiology and Immunology, Faculty of Medical Sciences, Rio de Janeiro State University (UERJ), Rio de Janeiro, RJ, Brazil

³Department of Microbiology and Immunology, Estácio de Sá University, Rio de Janeiro, RJ, Brazil

• **Conflicts of interest:** none declared.

ABSTRACT

Objective: the purpose of this study was to review some properties of xylitol as an antimicrobial agent and the role of this sugar alcohol in the prevention and control of dental caries activity. **Material and Methods:** the study was based on PubMed scientific papers, in addition of evaluating older researches, to obtain a more complete view of this polyol, encompassing its biochemical, antibacterial, antibiofilm and toxic properties, as well as its different forms of use. **Results:** the study carried out highlighted the positive characteristics of xylitol in relation to its use in humans and its possible therapeutic use as a substance for the prevention and control of caries disease. **Conclusion:** It was concluded that, though the scientific documentation that reinforce its efficiency in caries prevention, some authors still do not consider the clinical evidence as satisfactory about the effects of xylitol, and recommend better controlled clinical investigations, especially in relation to the prolonged use of this polyol, in order to provide more conclusive data.

Keywords: Xylitol; Biofilm; Antimicrobial properties; *Streptococcus mutans*; Polyol.

Introduction

Xylitol is a sugar-alcohol (polyol) that has been used in food and pharmaceutical industries as well as in dentistry as a substitute for cane sugar or glucose since the 1970s. Studies correlate the activity of this substance with the mechanism of action of important enzymes for the viability, proliferation and biofilm formation by *Streptococcus mutans* and other microbial species. Xylitol is not adequately metabolized by dental biofilm (bacterial plaque) and favors the mineralization process of dental enamel surfaces.¹ Caries is a multifactorial and polymicrobial disease that remains a public health problem worldwide.²⁻⁴ The imbalance (dysbiosis) between host, microorganisms and environmental condition (feeding) leads to an increase in lactic acid production by the bacterial biofilm accumulated on the dental surfaces when fermentable sugars, especially sucrose, are frequently ingested, altering the demineralization-remineralization (DES-RE) process, which tends to demineralization.²⁻⁴ This literature review aims to address the biological and toxic properties of xylitol and underscore its effects on various microorganisms, including mutans group streptococci (MGS) as well as its role on the transmission and interference on the processes involved in dental caries.

Material and Methods

A search on PubMed electronic database was performed between July 2016 and December 2017 using the key words “xylitol” and “biofilm”. The titles and abstracts of the papers were evaluated in order to select those that matched study’s purposes. After this first screening, the references of each

paper were examined and those that matched study’s purposes were also included. Combining both approaches, 50 papers were retrieved for this the literature review.

Results

Chemical and Biological Properties and Toxicity of Xylitol

Xylitol is chemically defined as a sugar-alcohol with five carbon atoms (polyol) that occurs naturally in some fruits and other vegetables. As it can be artificially produced from the xylan contained in the wood, it is also known as “wood sugar”.⁵ Xylitol is an intermediate of human metabolism, and some grams can be produced daily by the liver, which is also able to metabolize xylitol from an exogenous source, yielding glucose, pyruvate, lactate and glycogen synthesis.⁶ Xylitol can also be produced from fermentation processes by lactic acid bacteria (LAB), like *Leuconostoc mesenteroides*, from soybean fermentation.⁷

Among the sugar alcohols, xylitol and erythritol are those that have the highest sweetening power, exhibiting a sweetening pattern similar to that of sucrose. In addition to these properties, it is sugar substitute that can be used by diabetics, patients with hyposalivation (xerostomia) and poly-traumatized patients (having been indicated as a parenteral nutrition agent), in addition to promoting beta oxidation (lipid metabolism) of endogenous fatty acids.⁸ The systemic administration of xylitol also assists in the prevention of insulin shock and in treatment of extensive burns (especially in diabetic patients). It is also used as an emulsifying agent in the pharmaceutical industry.⁹ In a study in rats, xylitol

reduced fat deposition in certain organs as well as plasma insulin and fat levels and plasma fat rate comparing animals fed xylitol and controls fed a hypercaloric diet. It was also observed a decrease in obesity in the rats that received xylitol.¹⁰

It has been experimentally demonstrated that xylitol has toxicity to cells derived from various types of cancer, especially A549 lung epithelial cells (type II pneumocytes). The LD50 (toxic dose to 50% of the treated cells) was significantly lower for cancer cells than for the gingival fibroblasts (primary cell line), suggesting the use of xylitol as an adjunct to anticancer therapy.¹¹ A study using canine cells of several organs with different toxic components, showed that xylitol did not induce an increase of reactive oxygen species or nitrogen, indicating that the cell death pattern observed did not derived from mechanisms related xylitol use.¹²

Xylitol toxicity for humans is minimal. The use of xylitol in amounts ranging from 40 to 100 grams/day over 18 days induced, in a few cases, osmotic diarrhea that ceased within 24 hours after symptom onset. There was no systemic toxicity pattern, like increase in hepatic enzymes or any other indicator of toxicity. A decrease in blood cholesterol was observed when the individuals that received xylitol were compared with those who received sucrose (control).¹³ Similar toxicity patterns were observed in a study conducted in Finland where no toxic effects of xylitol use were observed in humans.¹⁴ The human liver can metabolize the polyol by converting it into glucose, glycogen and lactic acid.¹⁵ In food industry, xylitol is present in the composition of tablets and chewing gums. In the dental industry, xylitol is found in mouthrinsing solutions and dentifrices at various concentrations.

However, xylitol is toxic to animals like dogs, cats, rabbits and rats. In dogs, xylitol can induce lethal hepatic failure in a dose-dependent manner. At lower doses, the animals may progress to hypoglycemia. In these situations, the treatment is held according to the symptoms, with the administration of serum glucose to maintain glycemia.^{16,17}

The absence of toxicity in humans has guided the use of xylitol as a sweetener (sugar cane substitute) in several products. Its non-cariogenic effects also justify its use in products like chewing gums and tablets.

Anti-infectious and Antimicrobial Activities of Xylitol

In a review article on alternative therapeutic processes,¹⁸ the only investigations with controlled double-blind trials were those performed using xylitol and that apparently had a preventive effect on otitis media cases. In a clinical study, Uhari *et al.*¹⁹ observed that xylitol administered in five daily doses (total 8.4 g/day) reduced the occurrence of acute otitis media in 41% of the subjects. Additionally, in the group of patients that received xylitol, antimicrobial agents had to be

prescribed as a treatment to only few children. Uhari *et al.*²⁰ observed a 40%, 30% and 20% reduction in acute otitis media cases in patients that used xylitol-containing chewing gum, xylitol syrup and xylitol-containing tablets, respectively. However, in another study,²¹ there was no reduction in acute otitis media evolution in patients who started using xylitol as an auxiliary treatment method in any of the proposed formulations.

An *in vitro* study with biofilm and planktonic bacterial cells showed that xylitol was effective against *Staphylococcus epidermidis* and *S. aureus* biofilms. However, at 5% or 10% concentrations, xylitol had no effect on *Pseudomonas aeruginosa* biofilms or planktonic cells. The authors concluded that xylitol may have interesting effects in cases of sinusitis and that clinical studies must be performed to establish adequate doses for the treatment of sinusitis with xylitol-containing solutions. In fact, xylitol has shown good antimicrobial activity and can be safely used in clinical trials. New proposals of combining xylitol and antimicrobial agents might lead to promising treatment modalities to sinusitis.²²

Xylitol has antimicrobial properties against different microorganisms. Uhari *et al.*²³ observed the inhibitory effects of xylitol on *S. pneumoniae* in culture media. In addition, the exposure of *S. pneumoniae* and *Haemophilus influenzae* to xylitol modified the adherence profile of these microorganisms to human pharyngeal epithelial cells. Kurola *et al.*²⁴ reported that xylitol present in the culture medium inhibited the expression of the *S. pneumoniae* capsular polysaccharide (Cps), affecting the bacterial capsule structure, which is one of the main virulence mechanisms of pneumococci, possibly interfering microorganism's escape to phagocytosis and complement system activation. Pneumococci resistance to penicillin has contributed to reinforce research on the use of xylitol as a form of preventing bacterial infections.²⁵

Bacterial adherence to human buccal mucosa cells after exposure of both cell models to 5% xylitol reduced significantly the adherence of species involved in otitis media onset, including *S. pneumoniae*, *H. influenzae* and *Moraxella catarrhalis*. The main anti-adherent effects were observed when bacterial cells and buccal mucosa cells were treated with xylitol. When the treatment was targeted only to *H. influenzae* and *M. catarrhalis*, no change in the adherence pattern to buccal epithelial cells was observed when compared with control. These findings show that both treatments (target to host cells and target to microorganisms) are important to reduce the bacterial adhesion profile on cell models.²⁵

Oral Bacterial Biofilms

Biofilms are communities of microorganisms with a complex three-dimensional structure, embedded in an extracellular matrix and arranged, preferably on a solid surface. The biofilm protects the microorganisms from dehydration,

host's immune system and antimicrobial agents. The study of biofilms is relatively recent, dating to around 35 years, and is a multidisciplinary science, involving several areas of scientific knowledge.²⁶ Dental biofilm (also known as bacterial dental plaque) is the term used to describe the accumulation of adhered and structured microorganisms on mineralized dental surfaces: enamel, dentin and cementum. Biofilms can also be formed on the surfaces of partial and complete dentures, dental implants, orthodontic appliances, and tubes used for orotracheal or nasotracheal intubation. In all cases, as the biofilm becomes mature over time, the diversity of bacterial/fungal species increases as a result of microbial coaggregation, the capacity of microorganisms to bind to other bacterial species through molecule/receptor interactions.

Bacterial adhesion, in either an abiotic or a biotic surface, is the first stage in the complex process of biofilm formation. The primary adhesion between bacteria and abiotic surfaces is mediated by nonspecific physicochemical interactions, whereas the adhesion to biotic surfaces is accompanied by molecular interactions mediated by specific receptor-ligand bonds.^{2,26}

Under normal conditions, the tooth is covered by biopellicle formed by the adsorption of proteins and glycoproteins from saliva and gingival fluid known as acquired enamel pellicle, while different, can be considered as the primary stage of biofilm formation.²

In the initial phase of biofilm formation, during the first hours, cocci and Gram-positive rods colonize the tooth surfaces. The increase in sucrose availability favors colonization by *S. mutans* and *S. sobrinus* because MGS have enzymes that cleave sucrose into glucose and fructose, and polymerize levans and dextrans. These are important molecules for biofilm structuration by those microorganisms, promoting adhesion of bacteria to themselves and to the dental enamel. It takes at least 24 hours undisturbed for the biofilm to become clinically evident. After this period, the streptococcal community is reduced and the number Gram-positive filaments increase. Thereafter, the proportion of Gram-negative bacteria rises, characterizing the intermediate community. The progressive accumulation of bacteria and dental plaque thickening create conditions for the development of anaerobic microorganisms, contributing to increase the diversity of microorganisms present in the biofilm.²

Regarding cariogenic biofilms, the capacity of *S. mutans* to predominate in polysaccharide-rich biofilms contributes, not only to its survival and persistence in the oral cavity, but also to its pathogenicity. In addition to MGS, other microorganisms such as *S. sanguinis*, *S. oralis* and *S. gordonii*, can also be found in the dental biofilm.²⁷ Cariogenic associations were observed when multispecies biofilms were formed with *Bifidobacterium sp.* and *S. mutans* or *S. sobrinus*, showing

that such combinations of microorganisms had a much stronger enamel demineralizing capacity than monospecies biofilms.²⁸

As biofilm maturation occurs, through the fermentative process of biofilm microorganisms, a favorable environment is created to anaerobiosis. At the same time, the metabolism of biofilm microorganisms also generates nutritional factors that favor colonization by strict anaerobic Gram-negative bacteria and spirochetes.² The level of microbial diversity characterizes the biofilm climax community, harboring diverse microorganisms, including those considered periodontal pathogens.

***Streptococcus mutans* and Adhesion Specificity**

S. mutans is a Gram-positive coccus normally present in the human oral cavity. Although the presence of these bacteria in the oral microbiota is small, their expressiveness may change with a sucrose-rich diet. Biofilm formation and growth by *S. mutans* are regulated by its bacterial population-density-dependent system or *quorum sensing* (QS) and are composed mainly by competence-stimulating peptide (CSP) and by the *comE* and *comD* gene products involved in signal transduction, CSP transfer and gene expression. In addition to inducing biofilm formation and development, the CSP-mediated QS system in *S. mutans* affects its acidic and acidogenic nature and bacteriocin production, which are properties that provide a significantly stronger expression to biofilm microorganisms compared with planktonic microorganisms.²⁹

S. mutans has at least seven enzymes capable of hydrolyzing sucrose, converting it into low molecular weight polymers, free fructose and glucose. One of the enzymes also cleaves the sucrose-6-phosphate generated by sucrose carriers, which are molecules with substrate phosphorylation capacity. The glycosyltransferases (GTFs) exoenzymes produced by *S. mutans* are able to cleave sucrose, producing extracellular glucan (glucose homopolymers) and free fructose. The extracellular glucans are fundamental constituents for biofilm matrix structuration, associated with the virulence of *S. mutans* in experimental animals. GTF adhesive polymer is relatively water-insoluble and rich in α -1,3-bonds with α -1,6 ramifications. The polysaccharide polymeric structure is responsible for the stability of the multispecies biofilm formed in the oral cavity. Although there are numerous oral microbial species, most of them are unable to produce insoluble glucans. Although the dextranases present in the biofilms attack the α 1,6 bonds, dental biofilm microorganisms, nor even *S. mutans*, are capable of hydrolyzing α 1,3 bonds. This fact reinforces the role of *S. mutans* as a microorganism involved in the formation and structuring of dental biofilms. Apart from the glucan matrix, other factors found in biofilms include pH, free carbohydrates, c-di-

AMP and microRNA signaling molecules. The regulating capacity of the biofilm integrative matrix network remains poorly defined. In addition, *S. mutans* has high-capacity transport systems for a variety of carbohydrates, which are mainly mediated by the sugar transport system: the phosphotransferase system (PTS). PTS can rapidly internalize mono- and disaccharides, including glucose, mannose and fructose, which can be metabolized to acids. When sugar is present in excess, the cells produce mainly lactic acid through the lactate dehydrogenase enzyme. In conditions of low carbohydrate content, the pyruvate formate lyase enzyme converts pyruvate into acetate and formate, when another phosphorylation stage occurs at the substrate level generating additional ATP. Biofilm bacteria rapidly transport and efficiently metabolize different sugars to produce acids through the action of catabolic enzymes and carriers. These properties (with acid tolerance) allow *S. mutans* to interact with and settle in an acidified habitat that becomes a hallmark of cariogenic biofilms.²

Regarding dental caries etiology, Simón-Soro and Mira³ stated that MGS do not exhibit the expected numerical importance in the context of biofilms as etiological agents of dental caries. The same research group later stated that it cannot be underestimated the role of MGS in the activation of the dysbiotic state, promoting adherence and acidification during the initial ecological changes in dental caries process.⁴ These aspects were reinforced by Hajishengallis *et al.*,³⁰ who considered *S. mutans* as important agents in the consolidation of the biofilm structure (through the polysaccharide matrix assembly), essential for the dysbiotic process to occur. Therefore, the present literature review aimed at the effects of xylitol on several microorganisms, including *S. mutans*, which are the most studied bacteria in dental caries microbiology. However, it must be underscored that dental caries relies on a microbial consortium (to which *S. mutans* belongs) associated with lactic acid production.

An example of QS system found in oral biofilms is the one mediated by autoinducer 2 (AI-2), which induces the increase of dextran-dependent aggregation (DDA) in some bacteria. It has been stated that *S. mutans*, *S. sobrinus*, *Haemophilus influenzae* and *Aggregatibacter actinomycetemcomitans* are able to interpret AI-2-mediated QS system.³¹ Thus, segmentation strategies of *S. mutans* QS system to mitigate biofilm formation and/or virulence are being used to develop therapeutic or preventive measures against dental caries. Ribose²⁹ has the capacity to intervene in AI-2-mediated QS, having a similar structure to AI-2, competing with this molecule for the binding site on the intracellular structure responsible for its transport.³¹ Thus, it is likely that other sugar alcohols have an action on the QS system, which could be important to inhibit the system and interfere with biofilm formation by such microorganisms.

Antibiofilm Properties of Xylitol

Studies have shown conflicting outcomes on xylitol antiplaque/antibiofilm properties. An *in vitro* study³² using *S. mutans* ATCC 25175 showed that biofilms treated with a suspension of a children's dentifrice containing sodium fluoride (500 ppm) and xylitol (2.5%) was more effective in inhibiting biofilm formation on new surfaces. Only 10% xylitol alone was not as effective as the sodium fluoride and xylitol combination. However, both xylitol and sodium fluoride were more effective in reducing the formation of *de novo* biofilm (i.e., bacteria from the biofilm when treated with the suspension formed less biofilm when induced in a sucrose-containing culture medium) compared with the dentifrice base (without sodium fluoride and xylitol) and saline solution ($p < 0.05$).³²

An investigation that proposed the *in vitro* formation of biofilms from microorganisms of the oral cavity showed that xylitol was very effective in inhibiting biofilm formation. The conclusion was that xylitol would be able to inhibit not only acid formation by the biofilm, but also the conversion of the planktonic forms into sessile forms (bacterial biofilms).³³

An *in vivo* study using a dentifrice containing 49% xylitol demonstrated that the use of the dentifrice once a day (4-min toothbrushing after lunch) drastically reduced plaque formation and was able to inhibit biofilm accumulation after 30 days.³⁴

Alamoud *et al.*³⁵ compared caries incidence among mothers and children who received chewing gums or tablets containing xylitol and mothers and children who received fluoride varnish. The authors found that the pairs that received xylitol had a significantly lower incidence of caries and a significant reduction in dental plaque index.

Mechanism of Action and Different Presentations of Xylitol

The caries preventive effect of chewing gums containing polyols is based on salivary flow stimulation, and xylitol is the most widely used polyol. An increased salivary flow aids controlling the DES-RE process that occurs in the oral cavity. Because it has antimicrobial properties and is poorly fermentable by oral and respiratory tract bacteria, xylitol could reduce *S. mutans* counts and biofilm formation.³⁶

Among oral bacteria, *S. mutans* seem to be the most sensitive to xylitol. Some strains are inhibited (*S. mutans* sensitive), whereas others are not (*S. mutans* resistant), and the level of inhibition varies among the strains. A significant growth inhibition can be obtained with xylitol at concentrations as low as 0.01% (0.66 mM). These results may be useful in predicting the effects of xylitol when diluted from slow-releasing vehicles. *S. mutans* incorporate xylitol as a common sugar but, in this case, as xylitol-5-phosphate through the

main sugar transport pathway, the phosphoenolpyruvate (PEP):carbohydrate phosphotransferase system (PTS). Xylitol-5-phosphate inhibits glycolytic enzymes, resulting in the inhibition of growth, metabolism and acid production of planktonic and biofilm bacteria. Xylitol interferes with PEP-PTS activity, which is related to the level of bacterial growth inhibition.^{37,38}

The use of xylitol to reduce caries risk is an interesting research area because it is a natural sugar with properties that can reduce the formation of *S. mutans* biofilm as well as *S. mutans* salivary counts. In young children, xylitol can be administered in the form of a syrup or topically, while older children can use xylitol chewing gums or tablets.³⁹

The frequent use of xylitol would produce inhibitory effects on *S. mutans* metabolism. The suggested daily use would be around of 5-7 g xylitol/day, with a frequency of at least three times a day. Approaches such as the use of xylitol to reduce the early transmission of *S. mutans* from mother to child would result in a primary prevention of dental caries in young children. In conditions of continuous use of xylitol, the percentage of resistant strains represented more than 80% of the total counts, but with a lower virulence than strains not exposed to xylitol. However, the outcomes on the continued use of xylitol are not conclusive.³⁷

The use of xylitol in patients undergoing radiotherapy has also been proposed. The decrease of blood perfusion in the irradiated tissues causes a progressive reduction of tissue oxygenation, host's immune response mechanisms, and quantity and quality of saliva, which loses its antimicrobial action, buffering capacity and remineralization potential.⁴⁰

Discussion

The American Dental Association (ADA) published the results of an expected meta-analysis review on non-fluoride agents for caries prevention. None of the agents gave rise to unequivocal evidence, including polyols. Nevertheless, the sugarless chewing gums and xylitol-containing tablets have been suggested as an additional indication of preventive method according to dentist's judgment and the patient's needs and preferences.⁴¹

Deshpande and Jadad,⁴² in a meta-analysis, evaluated the effect of 14 polyol-containing chewing gums that had been evaluated in randomized trials or observational studies. The authors found a broad preventive fraction for chewing gums containing the combinations xylitol-sorbitol or sorbitol-mannitol. Another systematic review evaluated the effects of candies and tablets containing xylitol. After excluding studies that did not allow an adequate interpretation, only 3 studies were included in the meta-analysis, and the results indicated a caries-preventive effect of evaluated products.⁴³ According to Huebner *et al.*,⁴⁴ literature reviews on the use of xylitol are important because the dissemination

of research-based information on xylitol to dentists in clinical practice is quite limited. As a result, published evidence on mother-to-child transmission of *S. mutans* or xylitol efficacy is practically unknown, which limits the interest on the action of this polyol as well as the emergence of new research. In addition, the transmissibility does not determine the progression of the dysbiotic process that ultimately causes dental caries. It is possible that the use of polyols, including xylitol, can aid factors related to eubiosis, reducing biofilm thickness and modifying the expression of polymeric matrix components in biofilms. Considering that evidence suggests that: 1) *S. mutans* is a target organism of xylitol in vivo as a structural agent of biofilms; 2) *S. mutans* counts are reduced and remain low during a long-term use of xylitol and even for a period after its consumption; 3) the use of xylitol reduces biofilm accumulation; 4) maternal consumption of xylitol decreases *S. mutans* mother-to-child transmission; 5) consumption of xylitol and other polyols reduces caries incidence in children.³⁷

Olak *et al.*⁴⁵ and Nakai *et al.*⁴⁶ carried out studies with mothers in Estonia and Japan in which xylitol was used as chewing gum and tablets during or after gestation. The authors observed inhibition or reduction of colonization by *S. mutans* in some children and delayed colonization in others, in which case the children in the xylitol group acquired the microorganism 8.8 months later than the children in the control group. In a randomized clinical study with 60 adults aged 20 to 25 years, two groups consumed chewing gum three times a day over a three-week period, after which their salivary levels of *S. mutans* was evaluated. Group A used a chewing gum containing casein phosphopeptide-amorphous calcium phosphate (CPP-ACP) and group B used a xylitol-containing gum. Although the salivary levels of *S. mutans* dropped in both groups, a greater decrease was observed in the CPP-ACP group.⁴⁷ Studies like this prove that there are other substances capable of reducing *S. mutans* counts in the oral cavity, but studies on xylitol are more substantiated by research evidence, especially those addressing to early mother-to-child transmission and colonization by these microorganisms. According to Söderling,³⁴ the preventive action of xylitol goes far beyond replacing the consumption of fermentable sugars, as other sucrose substitutes. Xylitol stands out as a preventive agent because, in addition to be practically not fermented by oral microorganisms, it inhibits the growth, metabolism and synthesis of insoluble polysaccharides, through which a stable bacterial colonization is achieved on the dental surfaces and allows biofilm structuration. The avoidance of mother-to-child transmission observed in some new mothers can be explained, at least in part, by xylitol's inhibition of the growth and synthesis of insoluble polysaccharides by *S. mutans*. Among the polyols studied, xylitol may be of interest

in inhibiting the expression of *S. mutans* extracellular matrix, which is essential in biofilm structure. In the context of these studies, it is important to emphasize that, although mother-to-child transmission is important, the colonization of the child's oral cavity by *S. mutans* does not necessarily imply caries development. However, such results indicate that xylitol seems to interfere with the adherence of *S. mutans* in vivo (related to transmissibility) and to polysaccharide formation/structuring of biofilms.

In a recent systematic review, Janaldrum *et al.*⁴⁸ defended the use of xylitol over other preventive strategies. They considered that the use of xylitol in products suitable for self-application could be considered an effective strategy. However, they underscored that the studies included in their meta-analysis did not allow evaluating potential bias. In particular, they recommend that future clinical research are randomized and controlled trials, with the inclusion of a larger number of individuals, with more robust control groups, due to high dropout rates observed in clinical studies that need a follow up period of at least 3 years.

In a recent systematic review on the preventive action of xylitol, the authors concluded that the major finding was that after two and a half to three years of use of a dentifrice containing 10% xylitol, there was a 13% reduction in dental caries compared with the use of a fluoride dentifrice without xylitol (positive control). According to the conclusions of that review article, however, the effect should be interpreted with caution because a high risk to tendency was observed in the studies and because both studies were conducted by the same authors.⁴⁹ However, the fluoride + xylitol combination seems be interesting for establishing eubiosis and reducing the incidence of dental caries.

According to Milgrom *et al.*,⁵⁰ it would be interesting to

test the use of a slow-releasing vehicle for xylitol in such a way that frequent applications would not be necessary, which is impractical for everyday use. For these authors, however, there is still a need for high-quality studies that have some kind of correlation among them in order to produce more uniform and reliable outcomes.

The use of xylitol as an auxiliary method for dental caries prevention can be considered expensive, but its use may be advantageous if an actual prevention is achieved.³⁷ Within this perspective, the use of this polyol can become an important auxiliary strategy to traditional methods of controlling and preventing caries onset. However, most studies evaluating xylitol either used chewing gums containing the substance or were in vitro experiments. However, little research has been done on the continuous clinical use of xylitol and its administration in small doses over a long period of time. In addition, as in all narrative reviews, there is a risk of biases regarding the found issues, considering that an exhaustive literature search was not carried out because it was not intended to perform a systematic review.

Conclusion

This literature review allows concluding that there are some advantages on the use of xylitol regarding the prevention of dental caries and its action against several microorganisms. However, further research on the use of xylitol and its efficacy as an auxiliary strategy to reduce the cariogenic potential of oral microbiota is necessary, especially a broader investigation regarding its clinical use, which could allow eubiotic conditions related to dental caries. Although other polyols also have anticariogenic and preventive effects and could also be used, xylitol still is the most widely studied polyol for this purpose.

References

- Söderling E. Controversies around Xylitol. *Eur J Dent.* 2009;3(2):81-2.
- Bowen WH, Burne RA, Wu H, Koo H. Oral Biofilms: Pathogens, Matrix, and Polymicrobial Interactions in Microenvironments. *Trends Microbiol.* 2017;S0966-842X(17)30213-5.
- Simón-Soro A, Mira A. Solving the etiology of dental caries. *Trends Microbiol.* 2015;23(2):76-82.
- Mira A, Simon-Soro A, Curtis MA. Role of microbial communities in the pathogenesis of periodontal diseases and caries. *J Clin Periodontol.* 2017;44(18):23-38.
- Hyvonen L, Koivistoinen P, Voirol F. Food technological evaluation of xylitol. *Adv Food Res.* 1982;28:373-403.
- Ylikahri R. Metabolic and nutritional aspects of xylitol. *Adv Food Res.* 1979;25:159-80.
- Ortiz ME, Bleckwedel J, Raya RR, Mozzi F. Biotechnological and in situ food production of polyols by lactic acid bacteria. *Appl Microbiol Biotechnol.* 2013;97(11):4713-26.
- Georgieff M, Moldawer LL, Bistrian BR, Blackburn GL. Xylitol, an energy source for intravenous nutrition after trauma. *J Parenter Enteral Nutr.* 1985;9(2):199-209.
- Roshan NM, Sakeenabi B. Practical problems in use of sugar substitutes in preventive dentistry. *J Int Soc Prev Community Dent.* 2011;1(1):1-8.
- Amo K, Arai H, Uebanso T, Fukaya M, Koganei M, Sasaki H, et al. Effects of xylitol on metabolic parameters and visceral fat accumulation. *J Clin Biochem Nutr.* 2011;49(1):1-7.
- Park E, Park MH, Na HS, Chung J. Xylitol induces cell death in lung cancer A549 cells by autophagy. *Biotechnol Lett.* 2015;37(5):983-90.
- Choi K, Ortega MT, Jeffery B, Riviere JE, Monteiro-Riviere NA. Oxidative stress response in canine in vitro liver, kidney and intestinal models with seven potential dietary ingredients. *Toxicol Lett.* 2016;241:49-59.
- Förster H, Quadbeck R, Gottstein U. Metabolic tolerance to high doses of oral xylitol in human volunteers not previously adapted to xylitol. *Int J Vitam Nutr Res Suppl.* 1982;22:67-88.
- Mäkinen KK, Ylikahri R, Mäkinen PL, Söderling E, Hämäläinen M. Turku sugar studies XXIII. Comparison of metabolic tolerance in human volunteers to high oral doses of xylitol and sucrose after long-term regular consumption of xylitol. *Int J Vitam Nutr Res Suppl.* 1982;22:29-49.
- Renko M, Valkonen P, Tapiainen T, Kontiokari T, Mattila P, Knuuttila M, et al. Xylitol-supplemented nutrition enhances bacterial killing and prolongs survival of rats in experimental pneumococcal sepsis. *BMC Microbiol.* 2008;8:45.
- DuHadway MR, Sharp CR, Meyers KE, Koenigshof AM. Retrospective evaluation of xylitol ingestion in dogs: 192 cases (2007-2012). *J Vet Emerg Crit Care (San Antonio).* 2015;25(5):646-54.
- Schmid RD, Hovda LR. Acute Hepatic Failure in a Dog after Xylitol Ingestion. *J Med Toxicol.* 2016;12(2):201-5.
- Levi JR, Brody RM, McKee-Cole K, Pribitkin E, O'Reilly R. Complementary



- and alternative medicine for pediatric otitis media. *Int J Pediatr Otorhinolaryngol*. 2013;77(6):926-31.
19. Uhari M, Kontiokari T, Koskela M, Niemelä M. Xylitol chewing gum in prevention of acute otitis media: double blind randomised trial. *BMJ*. 1996;313(7066):1180-4.
 20. Uhari M, Kontiokari T, Niemelä M. A novel use of xylitol sugar in preventing acute otitis media. *Pediatrics*. 1998;102(4 Pt 1):879-84.
 21. Tapiainen T, Luotonen L, Kontiokari T, Renko M, Uhari M. Xylitol administered only during respiratory infections failed to prevent acute otitis media. *Pediatrics*. 2002;109(2):E19.
 22. Jain R, Lee T, Hardcastle T, Biswas K, Radcliff F, Douglas R. The in vitro effect of xylitol on chronic rhinosinusitis biofilms. *Rhinology*. 2016;54(4):323-8.
 23. Uhari M, Tapiainen T, Kontiokari T. Xylitol in preventing acute otitis media. *Vaccine*. 2000;8(19):144-7.
 24. Kurola P, Tapiainen T, Kaijalainen T, Uhari M, Saukkoriipi A. Xylitol and capsular gene expression in *Streptococcus pneumoniae*. *J Med Microbiol*. 2009;58(11):1470-3.
 25. Kontiokari T, Uhari M, Koskela M. Antiadhesive effects of xylitol on otopathogenic bacteria. *J Antimicrob Chemother*. 1998;41(5):563-5.
 26. Trentin DS, Giordani RB, Macedo AJ. Biofilmes bacterianos patogênicos: aspectos gerais, importância clínica e estratégias de combate. *Revista Liberato*. 2013;14:113-238.
 27. Evans A, Leishman SJ, Walsh LJ, Seow WK. Inhibitory effects of children's toothpastes on *Streptococcus mutans*, *Streptococcus sanguinis* and *Lactobacillus acidophilus*. *Eur Arch Paediatr Dent*. 2015;16(2):219-26.
 28. Valdez RM, Dos Santos VR, Caiaffa KS, Danelon M, Arthur RA, Negrini TC, et al. Comparative in vitro investigation of the cariogenic potential of bifidobacteria. *Arch Oral Biol*. 2016;71:97-103.
 29. Senadheera D, Cvitkovitch DG. Quorum sensing and biofilm formation by *Streptococcus mutans*. *Adv Exp Med Biol*. 2008;631:178-88.
 30. Hajishengallis E, Parsaei Y, Klein MI, Koo H. Advances in the microbial etiology and pathogenesis of early childhood caries. *Mol Oral Microbiol*. 2017;32(1):24-34.
 31. Lee HJ, Kim SC, Kim J, Do A, Han SY, Lee BD, et al. Synergistic inhibition of Streptococcal biofilm by ribose and xylitol. *Arch Oral Biol*. 2015;60(2):304-12.
 32. Coutinho Filho WP, Guaraldi ALM, Hirata Júnior R, Passos M, Weyne SC. Efeito de componentes de dentifrícos infantis sobre *Streptococcus mutans* cultivados em biofilmes. *Rev Bras Odontol*. 2008;65(1):80-4.
 33. Badet C, Furiga A, Thébaud N. Effect of xylitol on an in vitro model of oral biofilm. *Oral Health Prev Dent*. 2008;6(4):337-41.
 34. Hopper BL, Garcia-Godoy F. Plaque reduction in school children using a disposable brush pre-pasted with xylitol toothpaste. *J Tenn Dent Assoc*. 2014;94(2):29-30.
 35. Alamoudi NM, Hanno AG, Masoud MI, Sabbagh HJ, Almushayt AS, Masoud IM. Effects of xylitol on salivary mutans streptococcus, plaque level, and caries activity in a group of Saudi mother-child pairs. An 18-month clinical trial. *Saudi Med J*. 2012;33(2):186-92.
 36. Van Loveren C. Sugar Alcohols: What Is the Evidence for Caries-Preventive and Caries-Therapeutic Effects? *Caries Res*. 2004;38(3):286-93.
 37. Söderling EM. Xylitol, Mutans Streptococci, and Dental Plaque. *Adv Dent Res*. 2009;21(1):74-8.
 38. Söderling EM, Ekman TC, Taipale TJ. Growth Inhibition of *Streptococcus mutans* with Low Xylitol Concentrations. *Curr Microbiol*. 2008;56(4):382-5.
 39. Chou R, Cantor A, Zakher B, Mitchell JP, Pappas M. Prevention of Dental Caries in Children Younger Than 5 Years Old. *Evidence Syntheses*. 2014;104.
 40. Rolim AEH, Costa LJ, Ramalho LMP. Repercussões da radioterapia na região orofacial e seu tratamento. *Radiol Bras*. 2011;44:388-95.
 41. Rethman MP, Beltrán-Aguilar ED, Billings RJ, Hujoel PP, Katz BP, Milgrom P, et al. Non-fluoride caries-preventive agents: executive summary of evidence-based clinical recommendations. *J Am Dent Assoc*. 2011;142(9):1065-71.
 42. Deshpande A, Jadad AR. The impact of polyol containing chewing gums on dental caries: a systematic review of original randomized controlled trials and observational studies. *J Am Dent Assoc*. 2008;139(12):1602-14.
 43. Antonio AG, Pierro VS, Maia LC. Caries preventive effects of xylitol – based candies and lozenges: a systematic review. *J Public Health Dent*. 2011;71(2):117-24.
 44. Heubner CE, Milgrom P, Conrad D, Lee RS. Providing dental care to pregnant patients: a survey of Oregon general dentists. *J Am Dent Assoc*. 2009;140(2):211-22.
 45. Olak J, Saag M, Vahlberg T, Söderling E, Karjalainen S. Caries prevention with xylitol lozenges in children related to maternal anxiety. A demonstration project. *Eur Arch Paediatr Dent*. 2012;13(2):64-9.
 46. Nakai Shinga-Ishihara C, Kaji M, Moriya K, Takimurai-Yamanaka K, Takimura M. Xylitol gum and maternal transmission of mutans streptococci. *J Dent Res*. 2010;89(1):56-60.
 47. Emamieh S, Khaterizadeh Y, Goudarzi H, Ghasemi A, Baghban AA, Torabzadeh H. The effect of two types chewing gum containing casein phosphopeptide-amorphous calcium phosphate and xylitol on salivary *Streptococcus mutans*. *J Conserv Dent*. 2015;18(3):192-5.
 48. Janaldrum C, Kumar CVD, Joseph J. Xylitol in Preventing Dental Caries: A Systematic Review and Meta-Analyses. *J Nat Sci Biol Med*. 2017;8(1):16-21.
 49. Riley P, Moore D, Ahmed F, Sharif MO, Worthington HV. Xylitol-containing products for preventing dental caries in children and adults *Cochrane Database Syst Rev*. 2015;26(3):CD010743.
 50. Milgrom P, Soderling EM, Nelson S, Chi DI, Nakai Y. Clinical evidence for polyol efficacy. *Adv Dent Res*. 2012;24(2):112-6.

Mini Curriculum and Author's Contribution

1. Guilherme Goulart Cabral de Oliveira - undergraduate dental student. Contribution: search of papers, interpretation of data, preparation and writing of the manuscript.
2. Débora Marinho Teixeira Freires - undergraduate dental student. Contribution: Search of papers, interpretation of data, preparation and writing of the manuscript.
3. Simone Gomes de Oliveira - DDS and MSc. Contribution: Search of papers, interpretation of data, critical review.
4. Ana Luiza de Mattos Guaraldi - DDS and PhD. Contribution: effective scientific and intellectual collaboration for the study and critical review.
5. Sérgio de Carvalho Weyne - DDS and PhD. Contribution: effective scientific and intellectual collaboration for study and critical review and final approval.
6. Raphael Hirata Junior - DDS and PhD. Contribution: Effective scientific and intellectual collaboration for study and critical review and final approval.

Submitted: 12/23/2017 / Accepted for publication: 03/08/2018

Corresponding Author

Raphael Hirata Júnior

E-mail: rhiratajunior@gmail.com