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PREVENTIVE EFFECT OF XYLITOL ON DENTAL CARIES IN CHILDREN: A SYSTEMATIC REVIEW

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1. ABSTRACT

Introduction: Dental caries is a common chronic disease affecting children. It is caused mainly by acidogenic bacteria influenced by numerous risk factors such as cariogenic diets and host characteristics, but also incorrect oral hygiene, socioeconomic conditions and other environmental factors dictate the prognose of this worldwide disease. Children are especially vulnerable due to their dental structure, diet and motor skills. Prevention includes good oral hygiene and a healthy diet. Xylitol, a natural sugar alcohol derived from plants, is a suitable option for caries prevention in children. It has a lower glycemic index and does not cause dental caries. It has antibacterial effects, stimulates saliva flow, and helps neutralize acids.

Material and methods: An electronic search was performed in the PubMed, Scopus, and Web Of Science databases on anticaries effect of xylitol up to December 2022.

Results: A total of 968 articles were initially obtained, with 745 articles remaining after removing duplicates. Among these, 5 articles met the inclusion criteria and were included in this systematic review. Additionally, 3 additional studies were found through manual search. The main variables analyzed before and after the intervention of xylitol were the count of oral bacteria with a mean concentration of SM per millilitre of saliva of $69x_{10}^{5}$ CFU/mL and 5,67 log_{10}CFU/g for dental plaque ; interdental pH mean value of 7,2 for LX and 7,4 for HX without rinse and with rinsing LX of 6,35 for LX and 6,85 for HX ; the incidence of dental caries with a mean value of 24,17 caries onsets for stick gums, 15,52 caries onsets for pellets and for the topical oral syrup X2 a mean value of 24,2% whereas X3 was 40,6% of tooth with decay; and finally the visible dental plaque amount with an average of 25% of children having between 0 and 3 carious lesions.

Conclusion: Despite the limitations, xylitol seems to have an anticaries effect on children but more studies should be carried out to prove its real effectiveness.

Key words: Xylitol, Dental caries, Prevention, Diet, Child, Dental plaque, Biofilms, Saliva, Bacteria, Dental bacteria, Anti-infective agents, Antimicrobial, Antibacterial, Bacteriostatic, Bactericidal.

2. KEY WORDS

I. Xylitol
II. Dental caries
III. Prevention
IV. Diet
V. Child
VI. Dental plaque
VII. Biofilms
VIII. Saliva
IX. Bacteria
X. Dental bacteria
XI. Anti-infective agents
XII. Antimicrobial
XIII. Antibacterial
XIV. Bacteriostatic
XV. Bactericidal

3. ABBREVIATIONS

SM = *Streptococcus Mutans*

CFU = Colony Forming Units

LX = low-dosed xylitol

HX = high-dosed xylitol

CRR = Crude Caries Rates

X2 = administered topically 2 times daily

X3 = administered topically 3 times daily

4. INTRODUCTION

4.1 Dental caries

Dental caries is the most noncommunicable chronic disease in the world. In industrialised countries, between one and two out of three children have dental caries and almost every adult does (1). Dental decay is commonly called dental ‘caries’, from the Latin word meaning rottenness (2). Dental caries can be defined as the disease that affects the hard tissues of the teeth, leading to cavitation if not treated properly and during early stages of its development. It affects the surface and the hard tissues of the teeth. Nowadays, it is a multifactorial disease. It cannot be associated with only one factor. For a caries lesion to develop, different elements such as: host factors, bacteria, the availability of fermentable sugars and other environmental conditions are needed (3). It also depends on the shape of the tooth, the oral hygiene habits, the composition of the saliva, etc. (4).

If dental caries is not treated on time, it can lead to serious health issues. It will mainly affect mastication and will cause oral pain. Moreover, the patient will notice a deterioration of his smile, his phonation, his social relationships, and his quality of life in general (5). Dental caries has serious consequences, especially on children. Dental decay on children will deteriorate their quality of life as children but will also have consequences on their adult life. Having dental caries on primary teeth leads to a higher risk to develop dental decay in permanent dentition, but also to a premature loss of primary dentition and thus orthodontic problems (6).

4.2 Etiology and pathogenesis of dental caries

The physiological process of the appearance of a caries starts with a shift of the bacterial environment, generally due to the frequent ingestion of dietary fermentable carbohydrates. This frequent ingestion of carbohydrates leads to an increased production of acids, thus the increase of acidogenic and aciduric bacteria concentration in the oral environment (7). These acids have the potential to dissolve tooth enamel which leads to dental caries. The acidity of the oral environment promotes the demineralization process, which weakens and makes the dental structure more prone to dental decay by allowing minerals like calcium and phosphate to be removed from it (8). Moreover, the disruption or the increase of potentially cariogenic microorganisms of the oral microbiota induces dental caries. Potentially cariogenic microorganisms already exist in the dental plaque, but because of the pH balance, they are unable to prevail and they only make up a small portion of the entire biofilm. However, if the demineralization-remineralization process is unbalanced, cariogenic microorganisms start predominating. A low pH promotes the demineralisation of tooth enamel and therefore dental decay. The frequent ingestion of fermentable carbohydrates induces a decrease of the oral pH, an acidification of the dental plaque and thus the demineralization of the tooth surface (4).

4.3 Risk factors for dental caries in children

4.3.1 Host

The diet of children, their motor abilities, and the structure of their teeth make them susceptible to dental cavities.

4.3.1.1 Dental structures of paediatric patients

First and foremost, regarding the dental structures of children's teeth, it is widely known that the enamel is the hardest tissue in the human body and is highly mineralized. Its first component is hydroxyapatite (97%). Enamel is produced by ameloblasts. These ameloblasts create numerous proteins and attract calcium and phosphate ions which crystallise them, limiting ameloblast’s ability to produce enamel to just once. So, when enamel is broken, any new enamel can be synthesized as it happens with dentin, which cells, odontoblasts, can form new reparative dentin (9). In comparison with permanent teeth, the enamel of primary teeth is formed in a much shorter amount of time (24 months). The production of a very thin enamel (half the thickness of that of the permanent teeth) and a less structured microstructure are the results of the shorter period for this enamel development. As a result, acids can demineralize the enamel of primary teeth faster than that of permanent teeth (10). Moreover, the anatomy of primary teeth makes them more prone to dental decay. For example, the occlusal surfaces of primary molar have deeper grooves than permanent one (11).

4.3.1.2 Motor skills of children

Regarding motor skills, the dexterity of a child according to his age and capacities is also a crucial element to prevent dental decay. Children start to develop their fine motor skills, such as gasping a pencil (pincer or two-finger grasp), around 8-12 months but it will not be until they are 5 years old when children will begin to be more comfortable with toothbrushing. Moreover, primary school is a significant indicator for many children and caregivers. It is usually the moment when parents start to let their children assume a larger and more independent role in their daily personal care such as oral hygiene (13-15).

The American Academy of Paediatric Dentistry (AAPD) recommends that caregivers should supervise children’s toothbrushing. The older the child is, the more effective his toothbrushing will be. An issue is that there is no precise age in the guidelines for which children can transition from an assisted toothbrushing to an independent one. It depends more on the motor skills of the child more than on its chronological age alone (13) .

Oral hygiene is a crucial factor in preventing the appearance of dental cavities. In fact, immediately after teeth brushing, the dental biofilm starts to form and within 24 hours, it has formed individual microcolonies. Brushing teeth is a valuable social habit that makes teeth look better, avoids halitosis, and prevents periodontal diseases. If performed, toothbrushing enables to remove plaque sufficiently to reduce dental decay inset.

It is recommended that children should brush daily twice a day (preferably after breakfast in the morning and at night before going to bed), for at least 2 minutes.

On the other hand, toothbrushing can be an important indicator of a neurodevelopmental maturation disorder if the child is unable of doing some specific movements (lateral movements, up-down movements, circular movements…) that he should be able to do at his age. As stated by Chua et al., children of 7 years old showed greater capacity to follow oral hygiene instructions compared to 5-year-old children. Those older children understand and remember better the importance of toothbrushing and the steps and also showed more patience than those younger (12) According to Mafla et al., above 8 years old is the age of ideal manual dexterity necessary for toothbrushing. It is attributable to more developed motor skills and a better comprehension of the child (13). As we saw in different studies (13–15), parents value more the cognitive and motor abilities of the children than their chronological age alone. It means that some children are on age to have developed certain abilities (toothpaste top screwing, small movements, grasping movements…) that are necessary to brush their teeth without supervision, but are not able to do it in reality. That is why parents assess the independence for the daily self-care of their children more on their real abilities than according to their chronological age. Gerber and al. explained that those children that were not brushing adequately, even if they were above 7/8 years old, were still brushing with assistance (16).

Regarding dental brushing techniques for children, the 3 most popular techniques are modified Bass technique, horizontal scrub technique and the Fones technique. A study lead by Patil et al. (17) and another by Mathur et al. (4) demonstrated that the modified Bass technique was the most efficient one, followed by horizontal scrub technique and the least efficient was the Fones technique. The modified Bass technique consists of holding the toothbrush at a 45° angle to the gumline, doing circular movements with gentle pressure. Then, after the circular movements, children should move the toothbrush in a back-and-forth or vibrating motion and repeat during 2 to 3 minutes. The ideal is to also brush their tongue (17).

4.3.2 Cariogenic microorganisms

4.3.2.1 Streptococci and Lactobacillus

Millions of bacteria are present in our mouth. Some of them are harmful. Traditionally, the main bacteria known for being responsible of dental decay are Mutans Streptococci (SM) and Lactobacilli. However, Bifidoba, S. Sobinus and Scardovia wiggsiae are linked to early childhood caries and also play an essential role in the development of caries. Dentin caries lesions appear to contain DNA from other bacteria like Schlegelella or Pseudoramibacter, but evaluation of their cariogenic potential has been hindered by the absence of experimental studies on these organisms (18).

If we focus on children, one of their particularities is that they acquire those bacteria through close contact with their mothers. This is the vertical transmission: from the mother to the infant. Horizontal transmission also allows the transmission of *S. mutans* (from children to children). The earlier the child will be in contact with *S. mutans*, the more susceptible he will be to develop dental caries. *S. sobrinus* is also known for its cariogenic effect but if it is associated with *S. mutans*, the cariogenicity is especially increased (19,20). Apart from vertical and horizontal transmissions, according to DNA-based research, each person has a unique oral microbiota that may be shaped by factors such as diet, level of exposure to the environment, oral health status and host-related factors. These factors may also influence the shaping and diversity of the oral microbiota (20).

Lactobacilli are late colonisers, or “secondary colonisers”. These are microorganisms that do not initially colonise the freshly cleaned tooth surfaces. It may be possible to use salivary lactobacilli levels as a useful indicator for a cariogenic diet because they also seem to reflect the acidogenic conditions linked to consumption of carbohydrates (21).

4.3.3 Factors that modify caries risk

The main factors that modify caries risk in children are the motor skills, as we have seen before but also the socioeconomic conditions in which the children live in. It is a point that is not always taken in consideration when thinking about the influence of the diet and caries in children is the socioeconomic level of the later. According to some studies, poor eating habits, such as consuming more free or added sugar or other carbohydrates that are easily fermentable, are linked to socioeconomic status. This indicates that children with lower socioeconomic status have higher rates of dental caries (22).

4.4 Caries prevention factors and strategies for paediatric patients

As previously stated, in dental caries, the acid produced by acidogenic bacteria in the oral environment breaks down the enamel, causing cavities, so an antibacterial effect of a product would therefore serve as a preventive factor for the disease. Improving host resistance to dental decay can be achieved by reducing the levels of harmful bacteria in the oral environment, decreasing the solubility of enamel to acid, enhancing the capacity of demineralized enamel for remineralization, and creating a barrier between dental plaque and enamel by covering the enamel surfaces. These are all ways to prevent dental decay (2).

4.4.1 Oral hygiene

A preventive effect for dental caries can be achieved through various means, such as good oral hygiene. Brushing and flossing must be done regularly to remove dental plaque (oral biofilm) and prevent the accumulation of bacteria.
Moreover, other factors are important regarding children's oral hygiene. It is important for them to star early, before their first tooth erupts. The sooner the parents introduce toothbrushing, the better. Parents should use wipes or a wet clean cloth to clean their babies gum. About the frequency of toothbrushing, children should brush their teeth at least twice a day: once in the morning and

once before bedtime. As we have seen before, the technique used is also important (17). It is also important to use the adequate tools (toothbrushes adapted to their children's age and motor skills), such as soft-bristled toothbrushes and an adapted toothpaste composition and amount. For children from 0 to 6 years old, the fluorine concentration should be 1000 ppm, and above 6 years old 1450 – 2500 ppm. For the amount of toothpaste, for children from 0 to 3 years old it should be the size of a rice grain, and for children from 3 to 6 years old pea size amount. However, we know that only removing the dental plaque through dental brushing is not enough to completely avoid dental caries. We need some chemical components, like fluoride (23).

4.4.2 Fluoride therapies

Fluoride is the gold standard to prevent dental caries in children (24). It is a mineral that can strengthen tooth enamel and help to prevent the formation of caries lesions. Fluoride can be found in toothpastes, mouthwashes, and fluoridated drinking water. However, it has some limitations, especially for children that are more vulnerable and reactive to substances than adults. Indeed, an over exposition to fluor can lead to dental fluorosis (25) or even skeletal fluorosis (26). That is why it is useful to think about new safer ways to prevent dental caries for children.

4.4.3 Pits and Fissure sealants

We can also use dental sealants (27). Pits and fissure sealants are dental materials that protect the tooth surface. It is a widely used treatment for children prone to dental caries. It is painless and safe for the children. The aim is to make the surface less retentive by sealing the pits and the fissures of the occlusal surfaces of the tooth. According to Ahovuo-Saloranta et al. (28), it prevents the development of dental caries thanks to a physical barrier that inhibits microorganisms and the accumulation of food particles. They can be made of different materials. The main ones are resin and glass ionomer based sealants. The latter releases fluoride that protects the enamel surface (28).

4.4.4 Healthy diet

Diet is the most significant factor in the development of dental caries in children. The sensation of sweetness is an important consideration for children. Simple sugars have different levels of sweetness. The sensation of sweetness is acquired from sugars binding to specific receptors located on the tongue surface. That is on that surface that we can find the taste buds and gustatory cells that send signals to our brain. The differential affinity of sugars to those receptors influences the perception of sweetness (29). Therefore, we can say that there is an objective but also a subjective component in the way that children consume sugary foods and beverages. When asked to name their favourite and least favourite foods, children frequently rank sweet foods as their favourites and vegetables as their least favourites (22). Children are known to have preferences for sweet taste and to eat aliments that are different from the adults. Children's diet differs from an adult's diet by the type of food they eat. We are concerned about the high consumption of foods and drinks with added sugars among children of all ages. That has been happening for a few decades now (30). Added sugars are used by food manufacturers for their properties as preservatives, texturizers. Sugar-sweetened beverages are overconsumed by children nowadays in Europe. They exceed the usual recommendations. What we call "sugar-sweetened beverages" are those drinks that contain added caloric sweeteners such as sucrose, fruit-juice concentrates, etc. This is concerning since young children have an inbuilt predisposition for sweet flavours that may be modified and reinforced by pre- and post- natal experiences, yet free sugars are not nutritionally necessary. Those sugars increase the risk of dental caries but also the risk to suffer obesity and all the health issues related to obesity in children (cardiovascular risk, endocrine pathologies (type II diabetes mellitus), joint problems, respiratory problems, etc.) (31).

Developing dental decay is closely linked to the ingestion of fermentable carbohydrates. Carbohydrates are divided into three major groups depending on their structures:

- Simple sugars: monosaccharides and disaccharides (glucose or sucrose)
- Complex carbohydrates: glycogen (starch and cellulose). They are multiple conjugated glucose molecules.
- Glycoconjugates: modified forms of glucose covalently attached to either proteins (glycoproteins) or lipids (glycolipids). They participate in processes like immunity and are parts of the cell membrane (29).

Those carbohydrates are responsible for making the oral environment acidic. Also known as "free sugars", fermentable carbohydrates include:

- All monosaccharides and disaccharides added to any foods or drinks by us (cook, customer, fabricator…)
- Sugars naturally present in syrups, honey, unsweetened fruit juices and fruit juice concentrate (9).

Carbohydrates that create dental decay are the simple sugars. They are the ones responsible for decreasing the pH of the oral environment and initiating dental caries. The most relevant one is sucrose. Sucrose is the main determinant to cause dental caries due to its metabolism by bacteria to different types of acids (4). Cariogenic bacteria metabolise monosaccharides to produce acids which are harmful for the tooth enamel**.** When it comes to dental caries, many different factors should be taken into consideration. Some studies have shown that the frequency of ingestion of fermentable carbohydrate and its consistency appear to be the main factors responsible for the development of dental caries. Others believe that amount, the time of the day or number of times a week, etc (32). However, it is still unclear which factor is most important. The debate to know which characteristic between the amount, timing, frequency of consumption or even the consistency of sugar is the most pertinent (30). Indeed, even non-sugary food can produce caries if it is sticky and is hard to remove from the tooth surface, for example. The retention time of fermentable carbohydrates in the oral cavity is considered the primary factor in the initiation and advancement of dental caries. During the retention period, bacteria convert the carbohydrates into simple sugars (monosaccharides and disaccharides), which can initiate or contribute to the progression of dental caries (4).

4.5 Xylitol

As previously stated, we have seen, diet plays a central role in the process of dental decay. Sugars naturally present in whole foods are an essential component of a healthy and well-balanced diet (33). Xylitol has many properties corresponding to the previous expectations.

4.5.1 Role of xylitol in caries prevention

The word “Xylitol” derived from the Greek word “Xylo” that means wood, and “itol” which is the suffix for the sugar alcohols (34). It was discovered in the late nineteenth century. Seemingly, during World War II, the Scandinavian countries had to face a crucial lack of sugar. That is why they used xylitol as a substitute for sugar (34). It is naturally present in numerous edible plants, fruits, berries and even in mushrooms. (35) Xylitol is not an artificial sweetener but a natural sugar alcohol that is found in small amounts in fruits and vegetables. Sugar alcohols, also known as polyols, are a type of carbohydrate and have a chemical structure similar to sugar. They are used as sweeteners. They provide less calories than regular sugar, thus their conversion to sugar is slower and less insulin is required for its metabolization. Food manufacturers use sugar alcohols to sweeten their products while reducing calories. They stimulate the tongue’s sweet taste buds, adding flavour without extra sugar or calories (36,37).

To clarify the difference between “sugar” and “sugars”: the term “sugars” in the plural refers to the chemical signification. They are simple sugars (mono- and di- saccharides) in a chemically way; While “sugar” singular is what we call “sugar” in the daily life, the “table sugar”. Sugars, like xylitol, are naturally present in foods. They are not necessarily bad for our health. They are a necessary element of a healthy and well-balanced diet (33). They are different from “artificial sweetener". Artificial sweeteners are manufactured replacements for sugar because they have far higher sweetening capacity per unit of weight than sugar. In real life, artificial sweeteners are usually mixed with sugar substitutes to make the sweetness of the products more pleasant and to hide their little bitter aftertaste (33). Unlike artificial sweeteners, which are chemically manufactured, xylitol is produced from corn cobs, birch trees, or other natural sources. Additionally, it is produced synthetically in the industry using xylan-rich plant materials like beechwood and birch wood (38). Although it is not a sugar, it has a similar taste and can be used as a sugar substitute in a variety of food and beverage products. It is chemically a type of sugar alcohol, which is a type of carbohydrate. It can be used as a sweetener. Xylitol is often used as a sugar substitute because it has fewer calories and a lower glycaemic index than regular sugar and does not cause dental caries as monosaccharides and disaccharides do. Moreover, it is absorbed by the body more slowly, making it a popular alternative for people with diabetes mellitus or those looking to limit their sugar intake. It is relevant to improve dental health, especially of children with a high risk for caries development. Common xylitol vehicles are (39) :

- Chewing gums
- Toothpastes
- Mouthwashes
- Sugar-free peanut butter and other nut butters
- Sugar-free syrups and sauces
- Sugar-free jelly and jams

It can also be purchased as a standalone product and used as a sugar substitute in cooking and baking. In scholar-children, the most popular form of consumption of xylitol is chewing-gum. Xylitol alimentary products can also be ingested through xylitol gummy bear or even snacks. It is reported that eating foods that contain xylitol can reduce the concentration of S. mutans in the oral cavity (34)

Moreover, sugar substitutes, such as xylitol, have been shown to have an antibacterial effect for dental caries because xylitol cannot be fully fermented by oral bacteria which produce the acid that causes the demineralisation of enamel and thus dental cavities (40).

In addition, according to Gasmi Benahmed et al. (34), xylitol has a notable antiplaque effect and can also reduce gingival inflammation. It binds to calcium ions to promote the remineralization of the enamel. Xylitol plays a role in the calcium and phosphate uptake (41).

Furthermore, the main form of consumption of xylitol are chewing-gums. The chewing process stimulates the saliva flow (34), which together with the property of xylitol to stimulate production and secretion of saliva, helps to neutralise acid produced by some bacteria (8). Another advantage desirated from saliva flow is food particles clearances and buffer capacity due to Ca and P ions. All of these lead to cries prevention. Xylitol has shown to increase saliva flow, which helps to neutralize acids and wash away food particles, reducing the risk of tooth decay. The more the saliva flow increases, the more the pH and the buffer capacity will also increase (42).

Xylitol has some side effects, like every substance does. The over-consumption of xylitol leads to problems of:

- Digestion: Consuming large amounts of xylitol can cause digestive symptoms like bloating, gas and diarrhoea.
- Allergic Reactions: hives, itching, or difficulty breathing.
- Blood Sugar Fluctuations (34).

Finally, the high economic cost of xylitol compared to usual refined sugars reinforces the differences between children from different social backgrounds. Since access to alternatives to refined sugars are even more difficult for them, and they will keep being exposed even more to developing dental caries (43).

4.3.2.2 Antimicrobial and antibacterial effects

An antimicrobial effect refers to the ability of a substance, such as xylitol, to inhibit the growth or even kill microorganisms, like bacteria. It helps to prevent or treat a disease, reduce the spread of this disease or even improve hygiene and health. They are specific and usually target a specific microorganism. Its effectiveness can depend on different factors: the type of microorganisms it attacks, its concentration, its duration of exposure or even its specificity to recognise the microorganism (susceptibility to the substance) (21). “Antibacterial” refers specifically to the ability of a substance to kill or inhibit the growth of a bacteria. It means that antibacterial agents are antimicrobial but not all antimicrobial agents are antibacterial (44).

5. JUSTIFICATION AND HYPOTHESIS

JUSTIFICATION

Dental caries is the most prevalent non-communicable disease worldwide. More than two thirds of children suffer from dental caries and almost every adult does too (1). Its prevention is a key element in the management of its onset. It is a burden for our health. Dental decay leads to pain, problems of mastication, phonation and even aesthetics. It is also a problem in our society since its treatments represent a big cost. We also know that it is a preventable disease. Diet and oral hygiene are the most important elements in its prevention. Children have preferences for sweetness and controlling their diet is crucial to prevent caries. The traditional strategies to prevent it are adequate oral hygiene, regular revisions at the dentist, fluoridation, sealants and to limit the consumption of refined sugars. Alternatives to refined sugars are sugar substitutes as xylitol.

The use of xylitol could be a simple way to prevent dental caries among children. It is a natural sugar that we can find in fruits and vegetables. Reviewing what xylitol is and the ways to use it in order to protect children’s dentition will benefit children’s oral and general health in the short term.

Other systematic revisions do not focus on a specific aspect of the preventive effect of xylitol on dental caries. No review focuses on its microbial effect and on its ability to reduce the concentration of bacteria promoting the development of dental caries (45–50). Understanding the antibacterial mechanism of xylitol will give both dentists and patients another tool for caries prevention strategies and help in the improvement of oral health.

HYPOTHESIS

The working hypothesis of our study considers that xylitol will have a protective anticaries effect in the oral environment of children.

6. OBJECTIVES

Main objective

1. To identify caries prevention factors of xylitol in pediatric patients.

Secondary objectives

1. To determine caries prevention practices related to xylitol.
2. To know the limitations of the preventive effect of xylitol.

7. MATERIAL AND METHOD

This systematic review was carried out following the statement of the PRISMA Guide (Preferred Reporting Items for Systematic reviews and Meta Analyzes).

7.1 Identification of the PIO question

The Medline-PubMed (United States National Library of Medicine) database, Web of Science, and Scopus were used to perform a search of indexed articles on the antibacterial effect of xylitol to prevent dental caries in children, published until December 2022 according to the following question: In children susceptible to develop dental caries, does xylitol have an anticaries effect to prevent the disease?

This study question was established according to the PIO structured question. The format of the question was established as follows:

- P (population): Children susceptible to develop dental caries
- I (Intervention): Xylitol
- O (Outcome):
    - O1: Antimicrobial effect on the bacteria responsible for the development on dental caries.
    - O2: Alkalization of dental biofilm.
    - O3: Stimulation of saliva flow.
    - O4: Calcium and phosphate uptake.

7.2 Eligibility criteria

The inclusion criteria were:

- <u>Type of study</u>: Randomized controlled clinical trials, prospective and retrospective cohort studies, in vivo studies, in vitro studies, case series; studies on human subjects (children); Publications in English or French; Published until December 2022.

● Type of patient: Children susceptible to have dental caries

● Type of intervention: Direct exposure of pediatric patients or bacteria cell cultures to xylitol (toothpaste, mouthwash, chewing gum…),

●Type of results variables: Studies that provided data related to the antimicrobial effect of xylitol (antibacterial effect, bactericidal effect, bacteriostatic effect...). And as secondary variables: Studies including data about alkalization of dental biofilm; Studies providing data about the stimulation of saliva flow; Studies providing data about remineralization (Calcium and phosphate uptake).

The exclusion criteria were: systematic reviews, meta-analysis, reviews about a case, letters or comments to the editor, expert reports and animal experimental studies, studies including adult patients and children above 16 years old.

Year of publication: No restrictions were imposed based on the year of publication.

7.3 Information sources and data search strategy

An automated search was carried out in the three aforementioned databases (PubMed, Scopus and Web of Science) with the following keywords: “child”, “dental plaque”, “biofilms”, “saliva”, “bacteria”, “scholar children”, “dental bacteria”, “xylitol”, “xylitol toothpaste”, “xylitol mouthrinse”, “xylitol mouthwash”, “xylitol chewing gum”, “Anti-Infective agents”, “antimicrobial”, “antibacterial”, “bacteriostatic” and “bactericidal”.

Keywords were combined with the boolean operators AND, OR and NOT, as well as the controlled terms (“MeSH” for Pubmed) to obtain the best and broadest search results.

The Pubmed search was as follows:

((((((((children[MeSH Terms]) OR (dental plaque[MeSH Terms])) OR (biofilms[MeSH Terms])) OR (bacteria[MeSH Terms])) OR (saliva[MeSH Terms])) OR (dental bacteria)) OR (scholar children)) AND (((((xylitol[MeSH Terms]) OR (xylitol toothpaste)) OR (xylitol mouthwash)) OR (xylitol chewing gum)) OR (xylitol mouthrinse))) AND ((((agents, anti-infective [MeSH Terms]) OR (antimicrobial)) OR (bacteriostatic)) OR (bactericidal))

The SCOPUS search was as follows:

(ALL ("child" OR "dental plaque" OR "biofilms" OR "saliva" OR "bacteria" OR scholar AND children OR dental AND bacteria)) AND (ALL ("xylitol" OR xylitol AND toothpaste OR xylitol AND mouthrinse OR xylitol AND mouthwash OR xylitol AND chewing AND gum)) AND (ALL ("anti-infective agents" OR antimicrobial OR antibacterial OR bacteriostatic OR bactericidal))

The Web Of Science search was as follows:

((TS=(child OR dental plaque OR biofilms OR saliva OR bacteria OR scholar children OR dental bacteria)) AND TS=(xylitol OR xylitol toothpaste OR xylitol mouthrinse OR xylitol mouthwash OR xylitol chewing gum)) AND TS=(Anti Infective Agents OR antimicrobial OR antibacterial OR bacteriostatic OR bactericidal)

Table 1: Summary of the searches of each of the consulted databases

Database	Research	Number of articles	Date
PubMed	((((((((children[MeSH Terms]) OR (dental plaque[MeSH Terms])) OR (biofilms[MeSH Terms])) OR (bacteria[MeSH Terms])) OR (saliva[MeSH Terms])) OR (dental bacteria)) OR (scholar children)) AND (((((xylitol[MeSH Terms]) OR (xylitol toothpaste)) OR (xylitol mouthwash)) OR (xylitol chewing gum)) OR (xylitol mouthrinse))) AND ((((agents, anti-infective[MeSH Terms]) OR (antimicrobial)) OR (bacteriostatic)) OR (bactericidal))	177	02.12.22
Scopus	(ALL (“child" OR "dental plaque" OR "biofilms" OR "saliva" OR "bacteria" OR scholar AND children OR dental AND bacteria)) AND (ALL ("xylitol" OR xylitol AND toothpaste OR xylitol AND mouthrinse OR xylitol AND mouthwash OR xylitol AND chewing AND gum)) AND (ALL ("anti-infective agents" OR antimicrobial OR antibacterial OR bacteriostatic OR bactericidal)) AND (EXCLUDE (DOCTYPE , "re"))	455	29.12.22
Web of Science	((TS=(child OR dental plaque OR biofilms OR saliva OR bacteria OR scholar children OR dental bacteria)) AND TS=(xylitol OR xylitol toothpaste OR xylitol mouthrinse OR xylitol mouthwash OR xylitol chewing gum)) AND TS=(Anti Infective Agents OR antimicrobial OR antibacterial OR bacteriostatic OR bactericidal)	336	10.01.23

In order to identify any eligible studies that the initial search might have missed, we completed the search with a review of the references provided in the bibliography of each of the studies.

Finally, a cross search for potentially interesting articles for analysis was carried out. Duplicate studies were removed from the review.

7.4 Study selection process

A selection process was carried out in three stages. Study selection was carried out by one reviewer (MD).

The titles were initially filtered to eliminate publications that were not relevant. In the second stage, abstracts and summary were read and a selection was done according to the type of study, type of intervention, age of patients and results variables. In the third stage, it was filtered in accordance with the complete text reading, and the information was taken out using a previously created data collecting form to certify the studies' eligibility.

7.5 Data extraction

The following information was extracted from the studies and arranged in tables according to the type of use of xylitol (oral topical syrup, mouthwash, chewing gum): authors with the year of publication, type of study (Randomized controlled clinical trials, prospective and retrospective cohort studies, in vivo studies, in vitro studies, case series), number of patients and samples, age of patients (children under 16 years old), time of exposure to xylitol, concentration of xylitol used, association of the xylitol to other products (fluoride, chlorhexidine, salbutamol), antibacterial effect, alkalization of dental plaque, stimulation of saliva.

Main variable :

- Antibacterial effect of xylitol: Xylitol has shown to reduce the growth and acid production of cariogenic bacteria, such as Streptococcus mutans, which is a major contributor to tooth decay.

Secondary variables:

- Alkalization of dental biofilm: Xylitol has shown to increase the pH in the mouth, making the environment less acidic and less conducive to bacterial growth.

- Stimulation of saliva flow: Xylitol has shown to increase saliva flow, which helps to neutralize acids and wash away food particles, reducing the risk of tooth decay.
- Calcium and phosphate uptake: Xylitol has shown to increase the uptake of calcium and phosphate in the teeth, which can help to remineralize enamel and reduce the risk of tooth decay.
- Limitation of the effects of xylitol: Xylitol by itself has limited effects on dental caries prevention.

7.6 Quality assessment

The risk of bias assessment was assessed by one reviewer (MD) in order to analyze the methodological quality of the included articles.

For the evaluation of the quality of the randomized controlled clinical studies, the Cochrane guide 5.1.0 was used.
Publications were considered:

- "High risk of bias" when one or more criteria were not met and therefore the study is considered to have a possible bias that weakens the reliability of the results.
- "Low risk of bias" when they met all the criteria.
- “Unclear bias” either due to lack of information or uncertainty about the potential for bias.

To measure the quality of pseudo experimental studies, the Newcastle-Ottawa scale was used (51); we considered “high risk of bias” for a star score ≤6 and “low risk of bias” for a star score >6.

7.7 Data synthesis

In order to summarize and compare the outcome variables between the different studies, the means of the values of the main variables were grouped according to the study group.

8. RESULTS

8.1 Selection of studies. Flow chart

A total of 968 articles were obtained from the initial search process: Medline - PubMed (n=177), Web of Science (n=336) and SCOPUS (n=455). There were 223 duplicates, so without those duplicates we obtained 745 articles. Among those 745 publications, 697 were identified as potentially eligible articles through title screening, 171 through the reading of the abstract and 29 through the full-reading. Full-text articles were subsequently retrieved and thoroughly evaluated. As a result, 5 articles met the inclusion criteria and were included in the present systematic review. The information related to the excluded articles and the reason for their exclusion is presented in Table 2. In addition, 3 additional studies were obtained through manual search (list of references and primary sources). As a result, 8 articles met the inclusion criteria and were finally included in this systematic review (Figure 1).

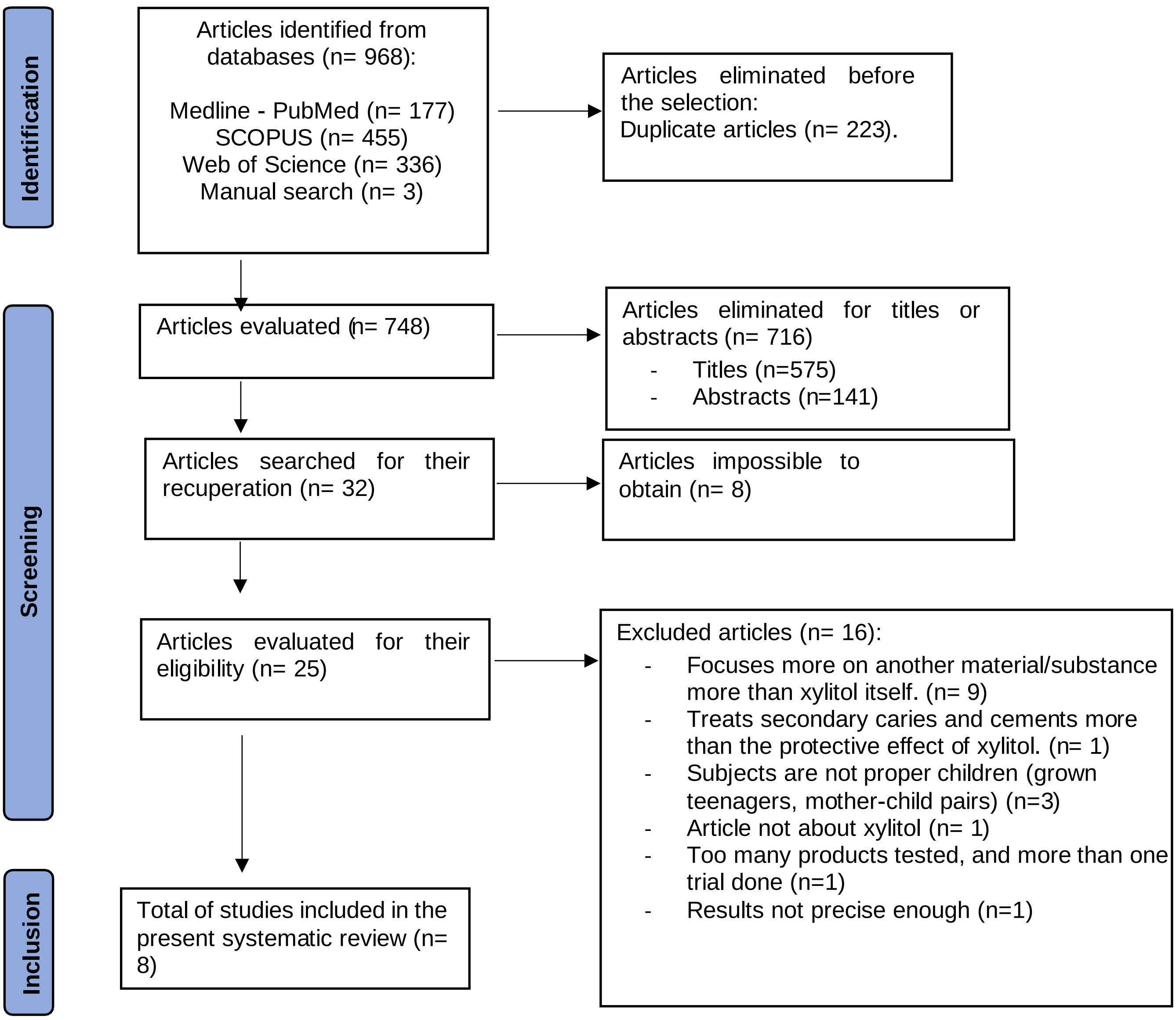

Figure 1: Flowchart and title selection process during systematic review

Table 2: Articles excluded from this systematic review (and their reason for exclusion)

Authors and date	Publication	Motive
Shinde et al. 2020 (52)	Journal of clinical and experimental dentistry	Focuses more on Stevia than xylitol.
Staszczyk et al. 2020 (53)	International journal of environmental research and public health	Treats secondary caries and cements more than the preventive effect of xylitol on primary carious lesions.
Martins et al. 2020 (54)	Biofouling	Subjects are not proper children.
Decker et al. 2008 (55)	Quintessence International	Focuses on the combination of xylitol and chlorhexidine more than xylitol itself.
Söderling et al. 2015 (56)	Clinical oral investigations	Focuses only on the microbiological part of our subject (Stre*ptococcus Mutans*).
Juric et al. 2003 (57)	Central European journal of public health	Focuses on fluoride.
Moraes et al. 2011 (58)	Pediatric Dentistry by the American Academy of Pediatric Dentistry	Focuses only on the association of chlorhexidine and xylitol, not only xylitol.
Tulsani et al. 2014 (59)	Indian journal of dental research: official publication of Indian Society for Dental Research	Focuses only on the association of propolis and xylitol, not only xylitol
Maden et al. 2018 (60)	Nigerian journal of clinical practice	Focuses on probiotics more than xylitol.
Arends et al. 1990 (61)	Caries research	Focuses on fluoride more than xylitol.
Zhan et all. 2012 (62)	Journal of Dental Research	Subjects are not proper children.
Almaz et al. 2017 (63)	Clinical oral investigations	Article not about xylitol.
Roberts et al. 2012 (64)	Journal of the American Dental Association	Subjects are not proper children.
Lif Holgerson et al. 2006 (65)	Caries research	Too many products tested, and more than one trial done.
Petersson et al., 1991 (66)	Caries research	Focuses on fluoride more than xylitol
Mäkinen et al., 1989 (67)	Caries research	Results are not precise enough.

8.2 Analysis of the characteristics of the reviewed studies

Among the 8 included articles, 5 of them are about chewing-gums ((68–72)), 2 are about mouthwashes (73,74) and 1 is about topical oral syrup (75). They all evaluate the protective effect of xylitol by focusing on the concentration of the main bacteria of the oral cavity (*Streptococcus Mutans*, *Lactobacilli*…) with the intervention of xylitol.

8 are clinical trials (68–71,73–75) and one is cohort study where the patient was the unit of randomisation (72).

There were in total 1105 patients: 94 used mouthwashes, 94 used topical oral syrup and 877 used chewing-gum.

The follow-ups of certain studies were the same and some others were different. 2 studies about mouthwash had a 2 week follow-up (73,74), 2 studies about chewing-gum had a 4 week follow-up (69,70), and the others were really different, going from 21 days up to 3 years (68,71,72,75).

They did not all evaluate the same variable. The most analysed variable was the count of the main oral bacteria such as *Streptococcus mutans* either in saliva (68–71,74) or dental plaque (73). Other variables were analysed including the incidence of dental caries (72,75), visible dental plaque amount (69) or the pH of interdental plaque (70).

Table 3: General characteristics of the included studies

Title	Author and Year	Number of paediatric participants	Type of study	Type of interventi on	Patient follow-up time	Analysed
Antimicrobial efficacy of Xylitol, Probiotic and Chlorhexidine mouth rinses among children and elderly population at high risk for dental caries (73)	(Krupa et al., 2022	30	Randomized clinical trial	Mouthwas h	2 weeks	Count of Streptococcus mutans levels in dental plaque
Comparative evaluation of efficacy of "Green Tea" and "Green Tea with Xylitol" mouthwashes on the salivary streptococcus mutans and lactobacillus colony count in children (74)	Hajiahmadi et al., 2019	64	Randomized Clinical Trial	Mouthwas h	2 weeks	Count of Streptococcus mutans and Lactobacillus colonies in saliva
Effect of chewing xylitol containing and herbal chewing gums on salivary Mutans Streptococcus count among school children (68)	Chavan et al., 2015	72	Randomized, clinical, follow-up study	Chewing gum	21 days	Count of Streptococcus mutans colonies in saliva
Dental plaque formation and salivary mutans streptococci in schoolchildren after use	Lif Holgerson et al., 2007	128	Double-blind randomized controlled trial	Chewing gum	4 weeks	Count of Streptococcus mutans levels in saliva Visible dental plaque amount

of xylitol-containing chewing gum (69)						
Effect of xylitol-containing chewing gums on interdental plaque-pH in habitual xylitol consumers (70)	Lif Holgerson et al., 2005	11	Single-blind crossover (clinical trial)	Chewing gum	4 weeks	pH of interdental plaque Count of Streptococcus mutans levels in saliva
A Comparative Evaluation of Xylitol Chewing Gum and a Combination of IgY + Xylitol Chewable Tablet on Salivary Streptococcus mutans Count in Children (71)	Jain et al. 2022	120	Double-blind Randomized Controlled Trial	Chewing gum	3 months	Count of Streptococcus mutans levels in saliva
Xylitol Pediatric Topical Oral Syrup to Prevent Dental Caries A Double-blind Randomized Clinical Trial of Efficacy (75)	Milgrom et al., 2009	94	Double-blind randomized controlled trial	Topical oral syrup	12 months	Incidence of dental caries
Polyol chewing gums and caries rates in primary dentition: A 24-month cohort study (72)	Mäkinen et al., 1996	510	Double-blind cohort study	Chewing gum	24 months	Incidence of dental caries

8.3 Assessment of methodological quality and risk of bias

Table 4: Measurement of the risk of bias of the randomized studies according to the Cochrane guidelines.

	Generate randomized sequence (selection bias)	Allocation concealment (selection bias)	Blinding outcome assessment (detection bias)		Follow-up and exclusions (attrition bias)	Selective description (reporting bias)	Other biases
Krupal et al. 2022 (73)	−	−	+		+	+	+
Hajiahmadi et al., 2019 (74)	+	+	+		?	+	+
Chavan et al., 2015 (68)	+	+	−		−	+	+
Lif Holgerson et al., 2007 (69)	+	+	+		?	+	+
Lif Holgerson et al., 2005 (70)	+	+	+		+	+	?
Jain et al. 2022 (71)	+	+	+		−	+	+
Milgrom et al., 2009 (75)	+	+	+		−	−	?

Table 5: Measurement of the risk of bias of non-randomized observational studies with the Newcastle-Ottawa scale - observational cohort studies, no control group.

	Definition of the cases	Representativeness	Selection of controls	Definition of controls	Comparability (most important factor)	Comparability (any other variable)	Exposure check	Same method for both groups	Dropout rate	Total
Mäkinen et al.,1996 (72)	☆	☆	☆	☆	☆	-	☆	☆	-	7

For randomized studies, a high risk of bias was considered in 3 studies and an unclear risk of bias in 4 (table 4). For non-randomized observational studies, the risk of bias was considered high in 1 study (table 5).

8.4 Results synthesis

8.4.1 Caries prevention factors of xylitol in pediatric patients

Regarding the caries prevention factors of xylitol in pediatric patients, 5 articles measured the count of *Streptococcus mutans* in saliva (68–71,74). The mean concentration of Streptococcus mutans per millilitre of saliva was $69x_{10}^{5}$ CFU/mL with a range of 75.56 CFU/mL (74) to 138_{x10}^{5} CFU/mL (71).

One article referred to the *Streptococcus mutans* levels in dental plaque (73). The SM count is 5,67 log_{10}CFU/g.

One article (70) mentioned the pH of interdental plaque as an indicator of caries incidence. They measured the pH after 10 minutes of chewing either a low-dosed xylitol chewing-gum or a high-dosed xylitol chewing-gum. They measured it at 0, 5, 10, 15, 20, 25 and 30 minutes after chewing. They also measured the pH with and without rinsing with 10% sucrose solution for one minute. The mean value for the interdental pH 0 minute after 10 minutes of chewing without rinsing after was 7,2 for the low-dosed xylitol (LX) and 7,4 for the high-dosed xylitol (HX); with rinsing for the LX it was 6,35 and 6,85 for the HX.

2 articles (72,75) evaluated the preventive effect of xylitol through the incidence of dental caries. One study (72) measured the number of caries onsets per 1000 surfaces. They used xylitol pellets and xylitol stick gums. The mean value was 24,17 caries onsets for the xylitol stick gums and 15,52 caries onsets for the xylitol pellets. The other study examining dental caries (75) measured the percentage with decayed teeth. It evaluates a xylitol topical oral syrup either twice or 3 times a day. The mean value for the syrup given twice a day was 24,2% whereas the syrup given 3 times a day was 40,6% of tooth with decay.

One article (69) assessed the visible dental plaque amount. The mean value after 4 weeks of use of xylitol-containing chewing-gum according the different affected surface of the tooth was 44,5% for score 0, 40,6% for score 1, 25,1% for score 2, 2,5% for score 3. The score corresponds to the Greene–

Vermillion simplified oral hygiene index (OHI-S). The values are based on clinical assessment on 6 predetermined sites (the buccal sites of teeth 16, 11, 26, 36, 31 and 46).

8.4.2 Caries prevention practices related to xylitol.

Caries prevention practices related to xylitol were discussed through its different forms and different actions. Its different ways to be consumed are chewing gum (68–72) and mouth rinses (73,74) but it also exists in other forms such as topical oral syrup (75). Its mechanisms of action were considered in all of the articles (68–75): counts of the main bacteria responsible for dental caries in children (68,69,71,73,74), pH of interdental plaque (70), amount of dental plaque (69) and incidence of dental caries in children (72,75).

Table 6: Descriptive results of the caries prevention practices related to xylitol collected by the studies.

Articles and anticaries factor studied	Number of paediatric participants	Before intervention value				After intervention value				Follow-up (in days)
Streptococcus Mutans count in saliva										
Chavan et al., 2015 (68)	72	18,9x10^5 CFU/mL				12,6x10^5 CFU/mL				21 days
Lif Holgerson et al., 2007 (69)	128	2,1x10^4 CFU/mL				8,4x10^3 CFU/mL				28 days
Jain et al. 2022 (71)	120	181x10^5 CFU/mL				138x10^5 CFU/mL				90 days
Hajiahmadi et al., 2019 (74)	64	204,87 CFU/mL				75,56 CFU/mL				14 days
Lif Holgerson et al., 2005 (70)	11	LX		HX		LX		HX		28 days
		-		-		4,2x10^6 CFU/mL		1,6x10^3 CFU/mL		
Total (Weighted average)		5 002 801,22 CFU/mL				3 211 679,26 CFU/mL				
Streptococcus Mutans count in dental plaque										
Krupal et al. 2022 (73)	36	6,60log$_{10}$CFU/g				5,67 log$_{10}$CFU/g				14 days
Total (Weighted average)		6,60log$_{10}$CFU/g				5,67 log$_{10}$CFU/g				
Interdental plaque pH										
Lif Holgerson et al., 2005 (70)	11	No 10% sucrose rinse		10% sucrose rinse		No 10% sucrose rinse		10% sucrose rinse		28 days
		LX 6,55	HX 6,65	LX 6,65	HX 6,7	LX 7,2	HX 7,4	LX 6,35	HX 6,85	
Total (Weighted average)		6,6375				6,95				
Incidence of dental caries										
Mäkinen et al.,1996 (72)	510	Sticks		Pellets		Sticks		Pellets		730 days
		65,8 cavity-free surfaces per subject		65,9 cavity-free surfaces per subjects		24,17 CCR		15,52 CRR		
Milgrom et al., 2009 (75)	99	X2		X3		X2		X3		
						24,2% of decayed teeth		40,6% of decayed teeth		365 days
Total (Weighted average)		65,8 cavity-free surfaces per subject		65,9 cavity-free surfaces per subject		24,2% of decayed teeth		40,6% of decayed teeth		
Visible dental plaque amount										
		Baseline				28 days				
Lif Holgerson et al., 2007 (69)	128	0 24,6%	1 47,8%	2 25,1%	3 2,5%	0 44,5%	1 40,6%	2 14,0%	3 0,9%	28 days
Total (Weighted average)		0 24,6%	1 47,8%	2 25,1%	3 2,5%	0 44,5%	1 40,6%	2 14,0%	3 0,9%	

8.4.3 Limitations of the preventive effect of xylitol

The limitations of xylitol were addressed in different articles (70–72). One article showed its temporal limitation (70). Indeed, this study showed that xylitol had a short effect and needed to be in a high quantity to exert its preventive effect on dental caries in children. According to the authors, there is an evident dose-response relationship, and a high amount of xylitol is needed to affect the interdental plaque-pH in habitual xylitol consumers.

Moreover, 2 articles demonstrated another limitation of xylitol which is its necessity to be combined with other substances to be powerful enough to show its carioprotective effect (71,72).

Table 7: Limitations of the preventive effect of xylitol collected by the studies.

Article	**Type of limitation**		**Number of paediatric participants**
	Product needed to enhance xylitol activity	**Time**	
Lif Holgerson et al., 2005 (70)	-	Decrease of interdental pH only with short, limited time (4 weeks)	11
Jain et al. 2022 (71)	IgY	-	120
Mäkinen et al.,1996 (72)	Sorbitol	-	510

9. DISCUSSION

This systematic review provides information based on scientific evidence on the results of the preventive effect of xylitol on dental caries in children. The aim of this review was to identify caries prevention factors of xylitol in pediatric patients; and secondarily to determine caries prevention practices related to xylitol, as well as to know the limitations of the preventive effect of xylitol.

9.1 Caries prevention factors of xylitol in pediatric patients

The protective effect of xylitol on dental caries has been tested and debated for many years (76–78).

The results of this systematic review, based on 8 scientific investigations (68–75), show that xylitol does have a protective effect against dental caries in children.

These results agree with other systematic reviews (77,78) also evaluating the effect of xylitol on oral health. Wand et al. (77) reported that xylitol presented anti-caries effects on primary and permanent dentition in children using wipes, tablets, snacks or even gummy bears. They also evaluated the ability of xylitol to reduce the concentration of *Streptococcus Mutans* and *Lactobacilli* too. In another systematic review and meta-analysis, Janakiram et al. (78) also evaluated the preventive effect of xylitol on dental caries through DMFS/dmfs index (Decayed, Missing, and Filled Surfaces index) and SM counts. They found that xylitol could be favourable in comparison to other caries preventive strategies (chlorhexidine or even fluor). In their systematic review, xylitol was found to be effective as a self-applied caries preventive agent.

The results obtained in our articles (66,68–75) confirm that xylitol has significant anti-caries effect on children thanks to its capacity to reduce the concentration in both saliva and dental plaque of the most cariogenic bacteria: *Streptococcus Mutans*. Concerning SM counts in saliva, the studies (68–71,74) show a significant decrease of the concentration of SM in saliva before and after xylitol intervention. The mean value is 5 002 801,22 CFU/mL before xylitol intervention and 3 211 679,26 CFU/mL after intervention. Regarding SM counts in dental plaque, only one article evaluates the ability of xylitol to decrease SM counts (73). According to the study made by Krupa et al., the difference in SM counts in dental plaque of children before (6,60log10CFU/g) and after (5,67 log10CFU/g) the use of xylitol mouth rinse is significant. However, there is an important point that we need to emphasize regarding the articles of our systematic review evaluating SM counts in saliva. These results can be explained by the fact that xylitol reduces the levels of SM by disrupting the bacteria's energy production process which leads to cell death. It also reduces the adhesion of microorganisms to the surface of teeth and diminishes their acid production potential (79). One of our selected study (69) has very different results from the others of the systematic review evaluating the same characteristic. Truly, the order of magnitude of the CFUs is quite different from the other studies. The difference coming from that study cannot be explained. We suspect that there is some missing information or some mistakes in the methodology or conditions of the experiment. According to Holgerson et al. (69), the order of magnitude was only in the thousands whereas the order of magnitude of other studies dealing with the number of SM CFUs in saliva was in the order of several million. Nevertheless, all our studies examining SM counts agree that xylitol has an effect on its reduction in children.

Another significant variable related to the protective effect of xylitol is the incidence of dental caries. According to Makinen et al. (72) and Milgrom et al. (75), xylitol is capable of reducing the incidence of dental caries in children. In the study lead by Makinen et al. (72), the CCR (crude caries rate) after the use of xylitol sticks is 24,17 CCR and 15,52 CRR for xylitol pellets. They only mentioned the average number of cavity-free surfaces per subject. They did not indicate the values in the same units or measured elements for the baseline and the end point (24 months), which makes it difficult to evaluate the anticaries effect of xylitol in this study. The other study evaluating the incidence of dental caries in children (75) also did not measure the percentage of dental surfaces with carious lesions before xylitol intervention but they compared it with a control group. However, they found a significant effect of topical oral syrup to prevent caries: 24,2% of decayed teeth for xylitol oral syrup administered topically 2 times/day; 40,6% of decayed teeth for xylitol oral syrup administered topically 3 times/day. Other studies analyse the relationship between the incidence of dental caries and the intervention of xylitol. Alanen et al. (80) and Zhan et al. (81) conclude that either candies, chewing gums or even wipes applied by mothers on their babies are able to significantly decrease the onset of dental caries in children and babies. Indeed, significantly fewer children in the xylitol-wipe group developed new caries lesions at 1 year compared with those in the placebo-wipe group (81). All studies of our systematic review agree that xylitol is capable in a certain measure to reduce the incidence of dental caries in children. The authors explained that this reduction can be explained by the fact that xylitol being of polyol, has the ability to stabilize calcium phosphate solutions and stimulate salivation (82,83). Moreover, the mechanism of action of xylitol in reducing caries rate is also based on simultaneously operating in salivary and microbiologic effects. As stated previously, it has been shown to interfere with the metabolism of SM and other streptococci implicated in the development of dental caries.

Visible dental plaque amount is well-known to be related to dental caries inset (69,84–86). In our systematic review, only the study made by Holgerson et al. (69) evaluated this element. They demonstrate that the amount of visible dental plaque was significantly reduced in both groups after the use of xylitol-containing chewing gum for 4 weeks. According to Holgerson et al. (69), it can be explained by the fact that chewing-gums stimulate salivary flow, which helps with food debris clearance, buffering, antibacterial properties, etc. Moreover, they explain that xylitol is hypo-acidogenic. It has the ability to produce lower levels of acid in response to carbohydrates or sugar consumption. Additionally, another reason why xylitol is able to decrease dental plaque is that xylitol-influenced plaque contains less polysaccharide compared to other polyols (69). They conclude that the plaque scores was no different between children with and without caries experience. It means that according to their study, xylitol is able to reduce the amount of dental plaque whether children had dental caries or not.

The last factor that we studied in this systematic review related to the anticaries effect of xylitol was the interdental plaque pH. Only one study investigated this topic (70). Lif Holgerson et al. measured the pH of interdental plaque through the consumption of either a low-dosed xylitol chewing-gum (2,0 g) or a high-dosed xylitol chewing-gum (6,0 g) in children. The results of their study exhibit that a single high dose of xylitol has a short and limited beneficial effect on interdental plaque-pH ; whereas a low single dose was not different from the control group. Their study displays the capability of xylitol to influence and benefit interdental plaque-pH but also that it is dose dependent. It is mentioned that the required doses may vary according to the subjects. For instance, in he case of mother-child transmission, the required doses to exert an anticaries effect would be different. More research is required to provide a deeper understanding of this concern through clinical studies. Another study about the interdental plaque acidogenicity was realized by Cagetti et al. (87). Even if they do not study children, their results concord to the study of Lif Holgerson et al. (70). The increased acidity of the dental plaque pH, when a proximal carious lesion is present in primary maxillary molars, shows an extra risk for the adjacent surface. It means that the incidence of dental caries is related to the interdental-pH. Another point of the article of Lif Holgerson et al. is the presence of a sucrose mouthrinse after the consumption of the chewing-gum. They concluded that the anticaries effect tend to disappear immediately after the mouthrinse, which is in agreement with other studies carried out on the same subject (88,89). They did not explain this precise mechanism. However, they did mention the different mechanisms that explain the anticaries effect of xylitol through its ability to modify the interdental plaque pH. According to Lif Holgerson et al., it is mainly due to the xylitol vehicle (chewing-gum). As stated before, chewing allows the stimulation of salivary flows, which plays a key role in protecting our teeth from dental caries (buffering capacity, cleaning food, antibacterial, etc.).

All those factors (*Streptococcus Mutans* count in saliva and dental plaque, incidence of dental caries, visible dental plaque amount and interdental plaque-pH) are related to the preventive effect of xylitol on dental caries in children. They are all connected one to each other through different complex mechanisms that are investigated in other studies (86,87,90–93).

9.2 Caries prevention practices related to xylitol

In this systematic review, we focused on 3 forms of xylitol: chewing-gums (68–72), mouthwashes (73,74) and topical oral syrup (75). The most used ones are chewing-gums mostly mainly for their easy way to be used, which is an important factor for children but also its ease of access. However, many different other ways to consume xylitol exist, such as: toothpaste (94–99), topical wipes (100), gummies/candies (97,99,101) or even lollipop (102,103). The fact that xylitol can be utilized through a lot of different forms make it even more interesting. Indeed, it means that it is suitable for many people and age groups (73), such as children. The fact that children do not realize that they are taking care of their oral health is an important factor because a certain number of children struggle to achieve a good oral hygiene (12,14).

If we focus on chewing gums, lollipops, gummies and candies, we can say that those ways of consuming xylitol allow children to take care of their oral health in a really easy way and even pleasant one (63,103). They do not realize that they are consuming a product that will have beneficial effects on their oral health and will help them not to have caries. The ease of consuming xylitol may be one explanation why the dropping rate were low in the studies selected for this systematic review.

Toothpastes and mouthwashes are also a really suitable way to use xylitol for children. Different studies demonstrate its efficacy, especially when combined with other substances such as fluoride (95,98,104–111), chlorhexidine (108,112–117) or even Stevia (52). These substances are traditional gold standards in the field of oral hygiene. Xylitol being a new product, it is a good idea to combine it with other products already known to be effective in order to enhance both the preventive effect of those substances and the xylitol one too.

9.3 Limitations of the preventive effect of xylitol

As stated before, xylitol is usually used combined with other more traditional substances such chlorhexidine or fluoride already known to be effective in the prevention of dental caries (95,98,104–111,118,119). This combination is indeed to enhance the properties of both substances but also and mainly because xylitol is not powerful enough alone by itself (97). Different studies conclude that xylitol was not potent enough alone to produce a significant protective effect on dental caries in children or that the effects were quite limited (reduction of SM counts, effect on interdental-plaque pH, etc.) (69,70,120).

Moreover, xylitol has side effects. The most frequent side effect of xylitol is digestive. Consuming large amounts of xylitol can cause bloating, gas and diarrhea. The authors of one of our study even did a pilot study to evaluate the compliance and analyse the possible side effects of consuming relatively high xylitol dose (6.18 g/day) (69). If a child consumes more than 10g of xylitol, it can cause allergic reaction reactions (itching or difficulty to breath) or even blood sugar fluctuations, especially for diabetic people. The threshold dose at which blood fluctuations may occur in a child may vary depending on factors such as age, weight and individual tolerance. There is no established precise dose for blood fluctuations in children, as it depends on individual sensitivity.(34). Those side effects can also be a limitation in its use, especially for children that are usually more susceptible than adults to high doses (121).

Additionally, another limitation of xylitol that was not mentioned in the studies of our systematic review is that xylitol is expensive compared to the gold standards. Since it is a relatively new product, its recent notoriety makes it difficult to access (43).

Also, it is interesting to invest the capacities of xylitol to replace refined sugars. It is relevant to look for alternatives to these products, especially when these alternatives have a beneficial effect on our health. We have seen previously that children are a particularly sugar-consuming population (22,31,37). Therefore, it is relevant that more and more studies are made on xylitol in order to democratize it and that this product enters the eating habits of a greater number of people. The more studies will be done on this, the more this product will be known and used. So, even if xylitol is perhaps not the most powerful product in terms of anticaries effect, it remains as a promising substance for the future.

9.4 Study limitations

Regarding the limitations of this systematic review, one of the most important limitation was the small sample sizes of participants. Half of the studies included in the systematic review agreed that the number of participant was too small to be really significant (71–74). The study of Chavan et al. (68) only has 72 participants, Hajiahmadi et al. (74) 64 participants, Krupa et al. (73) have 30 participants, and the smallest sample size was the study of Lif Holgerson et al. (70) with only 11 participants. Another systematic review made by Marghalani et al. (122) agrees that the sample size of the studies made about xylitol are too small to really be considered as significant. This lack of participants may be explained by the fact that our systematic review only focuses on children making it even more difficult because we are limited in the population we select. Moreover, since they are children, additional steps such as parental consent or going through institutions (school, nursery…) to recruit participants complicate the work.

Even when classified according to the type of factor assessed (*Streptococcus Mutans* count in saliva and dental plaque, incidence of dental caries, visible dental plaque amount and interdental plaque-pH), it was sometimes difficult to make averages because the units or measurement tools used were not the same from one study to another. For example, Mäkinen et al. (70) and Milgrom et al. (73) both evaluate the incidence of dental caries but they do not use the same unit: Mäkinen et al. (70) measure the CCR, and Milgrom et al. (73) measure in percentage the surfaces with dental decay.

Another limitation could be the short follow-up of some of our studies. Some authors themselves enunciate it their studies (70,72,74,75), going from 2 weeks to a year.

Some authors of articles selected for this systematic review said in their conclusion or closing remarks that they were nevertheless rather sceptical in relation to the real effect of xylitol on its ability to protect children from dental caries (70). Other systematic reviews made about the same subject raised the same limitations, such as the ones writing by Riley et al. (123) or Marghalani et al. (122). Indeed, as stated before, xylitol usually needs to be combined with another substance to be used and to be potent enough to produce its protective effect on children.

Additionally, as mentioned in the systematic reviews made by Riley et al. (123) and Marghalani et al. (122), since it is a rather new and recent product in the field of dentistry, it is also hard to step back on the results found because the number of studies is not yet high, even less on children. Most of them support the idea that more studies should be done. Moreover, another limitation which is directly linked to the previous ones, is that some studies focusing on the same topic have very different results. This element works in favour of the authors who are sceptical about the real effectiveness of xylitol. Having very different results when the same thing is measured is rather confusing for researchers. It raises the question if the results are really trustable or not.

10. CONCLUSIONS

Principal conclusions

1- Caries prevention factors of xylitol in pediatric patients are a reduction of *Streptococcus Mutans* counts both in saliva and dental plaque, reduction of visible dental plaque amount, decrease of interdental plaque-pH and a reduction in the incidence of dental caries.

Secondary conclusions

2- Caries prevention practices related to xylitol are the use of:
   a. Chewing-gum for 10 minutes
   b. Mouthwash, topical oral syrup, toothpaste, wipes, lollipops, candies and gummies.

3- The limitations of the preventive effect of xylitol are:
   a. It needs to be combined with other substances such as fluoride.
   b. It has systemic side effects if more than 10 gr daily are ingested.
   c. Its little power and its relative novelty in dentistry.

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12. ANNEXES

Table 1: Summary of the searches of each of the consulted databases

Database	Research	Number of articles	Date
PubMed	((((((((children[MeSH Terms]) OR (dental plaque[MeSH Terms])) OR (biofilms[MeSH Terms])) OR (bacteria[MeSH Terms])) OR (saliva[MeSH Terms])) OR (dental bacteria)) OR (scholar children)) AND (((((xylitol[MeSH Terms]) OR (xylitol toothpaste)) OR (xylitol mouthwash)) OR (xylitol chewing gum)) OR (xylitol mouthrinse))) AND ((((agents, anti-infective[MeSH Terms]) OR (antimicrobial)) OR (bacteriostatic)) OR (bactericidal))	177	02.12.22
Scopus	(ALL (“child" OR "dental plaque" OR "biofilms" OR "saliva" OR "bacteria" OR scholar AND children OR dental AND bacteria)) AND (ALL ("xylitol" OR xylitol AND toothpaste OR xylitol AND mouthrinse OR xylitol AND mouthwash OR xylitol AND chewing AND gum)) AND (ALL ("anti-infective agents" OR antimicrobial OR antibacterial OR bacteriostatic OR bactericidal)) AND (EXCLUDE (DOCTYPE , "re"))	455	29.12.22
Web of Science	((TS=(child OR dental plaque OR biofilms OR saliva OR bacteria OR scholar children OR dental bacteria)) AND TS=(xylitol OR xylitol toothpaste OR xylitol mouthrinse OR xylitol mouthwash OR xylitol chewing gum)) AND TS=(Anti Infective Agents OR antimicrobial OR antibacterial OR bacteriostatic OR bactericidal)	336	10.01.23

Table 2: Articles excluded from this systematic review (and their reason for exclusion)

Authors and date	Publication	Motive
Shinde et al. 2020 (52)	Journal of clinical and experimental dentistry	Focuses more on Stevia than xylitol.
Staszczyk et al. 2020 (53)	International journal of environmental research and public health	Treats secondary caries and cements more than the preventive effect of xylitol on primary carious lesions.
Martins et al. 2020 (54)	Biofouling	Subjects are not proper children.
Decker et al. 2008 (55)	Quintessence International	Focuses on the combination of xylitol and chlorhexidine more than xylitol itself.
Söderling et al. 2015 (56)	Clinical oral investigations	Focuses only on the microbiological part of our subject (Stre*ptococcus Mutans*).
Juric et al. 2003 (57)	Central European journal of public health	Focuses on fluoride.
Moraes et al. 2011 (58)	Pediatric Dentistry by the American Academy of Pediatric Dentistry	Focuses only on the association of chlorhexidine and xylitol, not only xylitol.
Tulsani et al. 2014 (59)	Indian journal of dental research: official publication of Indian Society for Dental Research	Focuses only on the association of propolis and xylitol, not only xylitol
Maden et al. 2018 (60)	Nigerian journal of clinical practice	Focuses on probiotics more than xylitol.
Arends et al. 1990 (61)	Caries research	Focuses on fluoride more than xylitol.
Zhan et all. 2012 (62)	Journal of Dental Research	Subjects are not proper children.
Almaz et al. 2017 (63)	Clinical oral investigations	Article not about xylitol.
Roberts et al. 2012 (64)	Journal of the American Dental Association	Subjects are not proper children.
Lif Holgerson et al. 2006 (65)	Caries research	Too many products tested, and more than one trial done.
Petersson et al., 1991 (66)	Caries research	Focuses on fluoride more than xylitol
Mäkinen et al., 1989 (67)	Caries research	Results are not precise enough.

Table 3: General characteristics of the included studies

Title	Author and Year	Number of paediatric participants	Type of study	Type of intervention	Patient follow-up time	Analysed
Antimicrobial efficacy of Xylitol, Probiotic and Chlorhexidine mouth rinses among children and elderly population at high risk for dental caries (73)	(Krupa et al., 2022	30	Randomized clinical trial	Mouthwash	2 weeks	Count of Streptococcus mutans levels in dental plaque
Comparative evaluation of efficacy of "Green Tea" and "Green Tea with Xylitol" mouthwashes on the salivary streptococcus mutans and lactobacillus colony count in children (74)	Hajiahmadi et al., 2019	64	Randomized Clinical Trial	Mouthwash	2 weeks	Count of Streptococcus mutans and Lactobacillus colonies in saliva
Effect of chewing xylitol containing and herbal chewing gums on salivary Mutans Streptococcus count among school children (68)	Chavan et al., 2015	72	Randomized, clinical, follow-up study	Chewing gum	21 days	Count of Streptococcus mutans colonies in saliva
Dental plaque formation and salivary mutans streptococci in schoolchildren after use	Lif Holgerson et al., 2007	128	Double-blind randomized controlled trial	Chewing gum	4 weeks	Count of Streptococcus mutans levels in saliva Visible dental plaque amount

of xylitol-containing chewing gum (69)						
Effect of xylitol-containing chewing gums on interdental plaque-pH in habitual xylitol consumers (70)	Lif Holgerson et al., 2005	11	Single-blind crossover (clinical trial)	Chewing gum	4 weeks	pH of interdental plaque Count of Streptococcus mutans levels in saliva
A Comparative Evaluation of Xylitol Chewing Gum and a Combination of IgY + Xylitol Chewable Tablet on Salivary Streptococcus mutans Count in Children (71)	Jain et al. 2022	120	Double-blind Randomized Controlled Trial	Chewing gum	3 months	Count of Streptococcus mutans levels in saliva
Xylitol Pediatric Topical Oral Syrup to Prevent Dental Caries A Double-blind Randomized Clinical Trial of Efficacy (75)	Milgrom et al., 2009	94	Double-blind randomized controlled trial	Topical oral syrup	12 months	Incidence of dental caries
Polyol chewing gums and caries rates in primary dentition: A 24-month cohort study (72)	Mäkinen et al., 1996	510	Double-blind cohort study	Chewing gum	24 months	Incidence of dental caries

Table 4: Measurement of the risk of bias of the randomized studies according to the Cochrane guidelines.

	Generate randomized sequence (selection bias)	Allocation concealment (selection bias)	Binding outcome assessment (detection bias)	Follow-up and exclusions (attrition bias)	Selective description (reporting bias)	Other biases
Krupal et al. 2022 (73)	−	−	+	+	+	+
Hajiahmadi et al., 2019 (74)	+	+	+	?	+	+
Chavan et al., 2015 (68)	+	+	−	−	+	+
Lif Holgerson et al., 2007 (69)	+	+	+	?	+	+
Lif Holgerson et al., 2005 (70)	+	+	+	+	+	?
Jain et al. 2022 (71)	+	+	+	−	+	+
Milgrom et al., 2009 (75)	+	+	+	−	−	?

Table 5: Measurement of the risk of bias of non-randomized observational studies with the Newcastle-Ottawa scale - observational cohort studies, no control group.

	Definition of the cases	Representativeness	Selection of controls	Definition of controls	Comparability (most important factor)	Comparability (any other variable)	Exposure check	Same method for both groups	Dropout rate	Total
Mäkinen et al.,1996 (72)	☆	☆	☆	☆	☆	-	☆	☆	-	7

Table 6: Descriptive results of the caries prevention practices related to xylitol collected by the studies.

Articles and anticaries factor studied	Number of paediatric participants	Before intervention value				After intervention value				Follow-up (in days)
Streptococcus Mutans count in saliva										
Chavan et al., 2015 (68)	72	18,9x10^{5} CFU/mL				12,6x10^{5} CFU/mL				21 days
Lif Holgerson et al., 2007 (69)	128	2,1x10^{4} CFU/mL				8,4x10^{3} CFU/mL				28 days
Jain et al. 2022 (71)	120	181x10^{5} CFU/mL				138x10^{5} CFU/mL				90 days
Hajiahmadi et al., 2019 (74)	64	204,87 CFU/mL				75,56 CFU/mL				14 days
Lif Holgerson et al., 2005 (70)	11	LX		HX		LX		HX		28 days
		-		-		4,2x10^{6} CFU/mL		1,6x10^{3} CFU/mL		
Total (Weighted average)		5 002 801,22 CFU/mL				3 211 679,26 CFU/mL				
Streptococcus Mutans count in dental plaque										
Krupal et al. 2022 (73)	36	6,60log$_{10}$CFU/g				5,67 log$_{10}$CFU/g				14 days
Total (Weighted average)		6,60log$_{10}$CFU/g				5,67 log$_{10}$CFU/g				
Interdental plaque pH										
Lif Holgerson et al., 2005 (70)	11	No 10% sucrose rinse		10% sucrose rinse		No 10% sucrose rinse		10% sucrose rinse		28 days
		LX 6,55	HX 6,65	LX 6,65	HX 6,7	LX 7,2	HX 7,4	LX 6,35	HX 6,85	
Total (Weighted average)		6,6375				6,95				
Incidence of dental caries										
Mäkinen et al.,1996 (72)	510	Sticks		Pellets		Sticks		Pellets		730 days
		65,8 cavity-free surfaces per subject		65,9 cavity-free surfaces per subjects		24,17 CCR		15,52 CRR		
Milgrom et al., 2009 (75)	99	X2		X3		X2		X3		
						24,2% of decayed teeth		40,6% of decayed teeth		365 days
Total (Weighted average)		65,8 cavity-free surfaces per subject		65,9 cavity-free surfaces per subject		24,2% of decayed teeth		40,6% of decayed teeth		
Visible dental plaque amount										
		Baseline				28 days				
Lif Holgerson et al., 2007 (69)	128	0 24,6%	1 47,8%	2 25,1%	3 2,5%	0 44,5%	1 40,6%	2 14,0%	3 0,9%	28 days
Total (Weighted average)		0 24,6%	1 47,8%	2 25,1%	3 2,5%	0 44,5%	1 40,6%	2 14,0%	3 0,9%	

Table 7: Descriptive results of the limitations of the preventive effect of xylitol collected by the studies.

Article	Type of limitation		Number of paediatric participants
	Product	**Time**	
Lif Holgerson et al., 2005 (70)	-	Decrease of interdental pH only with short, limited time (4 weeks)	11
Jain et al. 2022 (71)	IgY	-	120
Mäkinen et al.,1996 (72)	Sorbitol	-	510

Section and Topic	Item #	Checklist item	Location where item is reported
TITLE			
Title	1	Identify the report as a systematic review.	Frontpage
ABSTRACT			
Abstract	2	See the PRISMA 2020 for Abstracts checklist.	1
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of existing knowledge.	17
Objectives	4	Provide an explicit statement of the objective(s) or question(s) the review addresses.	19
METHODS			
Eligibility criteria	5	Specify the inclusion and exclusion criteria for the review and how studies were grouped for the syntheses.	20-21
Information sources	6	Specify all databases, registers, websites, organisations, reference lists and other sources searched or consulted to identify studies. Specify the date when each source was last searched or consulted.	21
Search strategy	7	Present the full search strategies for all databases, registers and websites, including any filters and limits used.	21
Selection process	8	Specify the methods used to decide whether a study met the inclusion criteria of the review, including how many reviewers screened each record and each report retrieved, whether they worked independently, and if applicable, details of automation tools used in the process.	24
Data collection process	9	Specify the methods used to collect data from reports, including how many reviewers collected data from each report, whether they worked independently, any processes for obtaining or confirming data from study investigators, and if applicable, details of automation tools used in the process.	24
Data items	10a	List and define all outcomes for which data were sought. Specify whether all results that were compatible with each outcome domain in each study were sought (e.g. for all measures, time points, analyses), and if not, the methods used to decide which results to collect.	20
	10b	List and define all other variables for which data were sought (e.g. participant and intervention characteristics, funding sources). Describe any assumptions made about any missing or unclear information.	20
Study risk of bias assessment	11	Specify the methods used to assess risk of bias in the included studies, including details of the tool(s) used, how many reviewers assessed each study and whether they worked independently, and if applicable, details of automation tools used in the process.	25
Effect measures	12	Specify for each outcome the effect measure(s) (e.g. risk ratio, mean difference) used in the synthesis or presentation of results.	20
Synthesis methods	13a	Describe the processes used to decide which studies were eligible for each synthesis (e.g. tabulating the study intervention characteristics and comparing against the planned groups for each synthesis (item #5)).	26
	13b	Describe any methods required to prepare the data for presentation or synthesis, such as handling of missing summary statistics, or data conversions.	26

Section and Topic	Item #	Checklist item	Location where item is reported
	13c	Describe any methods used to tabulate or visually display results of individual studies and syntheses.	29
	13d	Describe any methods used to synthesize results and provide a rationale for the choice(s). If meta-analysis was performed, describe the model(s), method(s) to identify the presence and extent of statistical heterogeneity, and software package(s) used.	26
	13e	Describe any methods used to explore possible causes of heterogeneity among study results (e.g. subgroup analysis, meta-regression).	31-32
	13f	Describe any sensitivity analyses conducted to assess robustness of the synthesized results.	33
Reporting bias assessment	14	Describe any methods used to assess risk of bias due to missing results in a synthesis (arising from reporting biases).	26
Certainty assessment	15	Describe any methods used to assess certainty (or confidence) in the body of evidence for an outcome.	26
RESULTS			
Study selection	16a	Describe the results of the search and selection process, from the number of records identified in the search to the number of studies included in the review, ideally using a flow diagram.	27
	16b	Cite studies that might appear to meet the inclusion criteria, but which were excluded, and explain why they were excluded.	29
Study characteristics	17	Cite each included study and present its characteristics.	30-32
Risk of bias in studies	18	Present assessments of risk of bias for each included study.	33-34
Results of individual studies	19	For all outcomes, present, for each study: (a) summary statistics for each group (where appropriate) and (b) an effect estimate and its precision (e.g. confidence/credible interval), ideally using structured tables or plots.	36-37
Results of syntheses	20a	For each synthesis, briefly summarise the characteristics and risk of bias among contributing studies.	33-34
	20b	Present results of all statistical syntheses conducted. If meta-analysis was done, present for each the summary estimate and its precision (e.g. confidence/credible interval) and measures of statistical heterogeneity. If comparing groups, describe the direction of the effect.	35-38
	20c	Present results of all investigations of possible causes of heterogeneity among study results.	35-38
	20d	Present results of all sensitivity analyses conducted to assess the robustness of the synthesized results.	33-34
Reporting biases	21	Present assessments of risk of bias due to missing results (arising from reporting biases) for each synthesis assessed.	33-34
Certainty of evidence	22	Present assessments of certainty (or confidence) in the body of evidence for each outcome assessed.	33-34
DISCUSSION			

Section and Topic	Item #	Checklist item	Location where item is reported
Discussion	23a	Provide a general interpretation of the results in the context of other evidence.	39-44
	23b	Discuss any limitations of the evidence included in the review.	45-46
	23c	Discuss any limitations of the review processes used.	45-46
	23d	Discuss implications of the results for practice, policy, and future research.	45-46
OTHER INFORMATION			
Registration and protocol	24a	Provide registration information for the review, including register name and registration number, or state that the review was not registered.	
	24b	Indicate where the review protocol can be accessed, or state that a protocol was not prepared.	
	24c	Describe and explain any amendments to information provided at registration or in the protocol.	
Support	25	Describe sources of financial or non-financial support for the review, and the role of the funders or sponsors in the review.	
Competing interests	26	Declare any competing interests of review authors.	
Availability of data, code and other materials	27	Report which of the following are publicly available and where they can be found: template data collection forms; data extracted from included studies; data used for all analyses; analytic code; any other materials used in the review.	

PRISMA GUIDE 2022

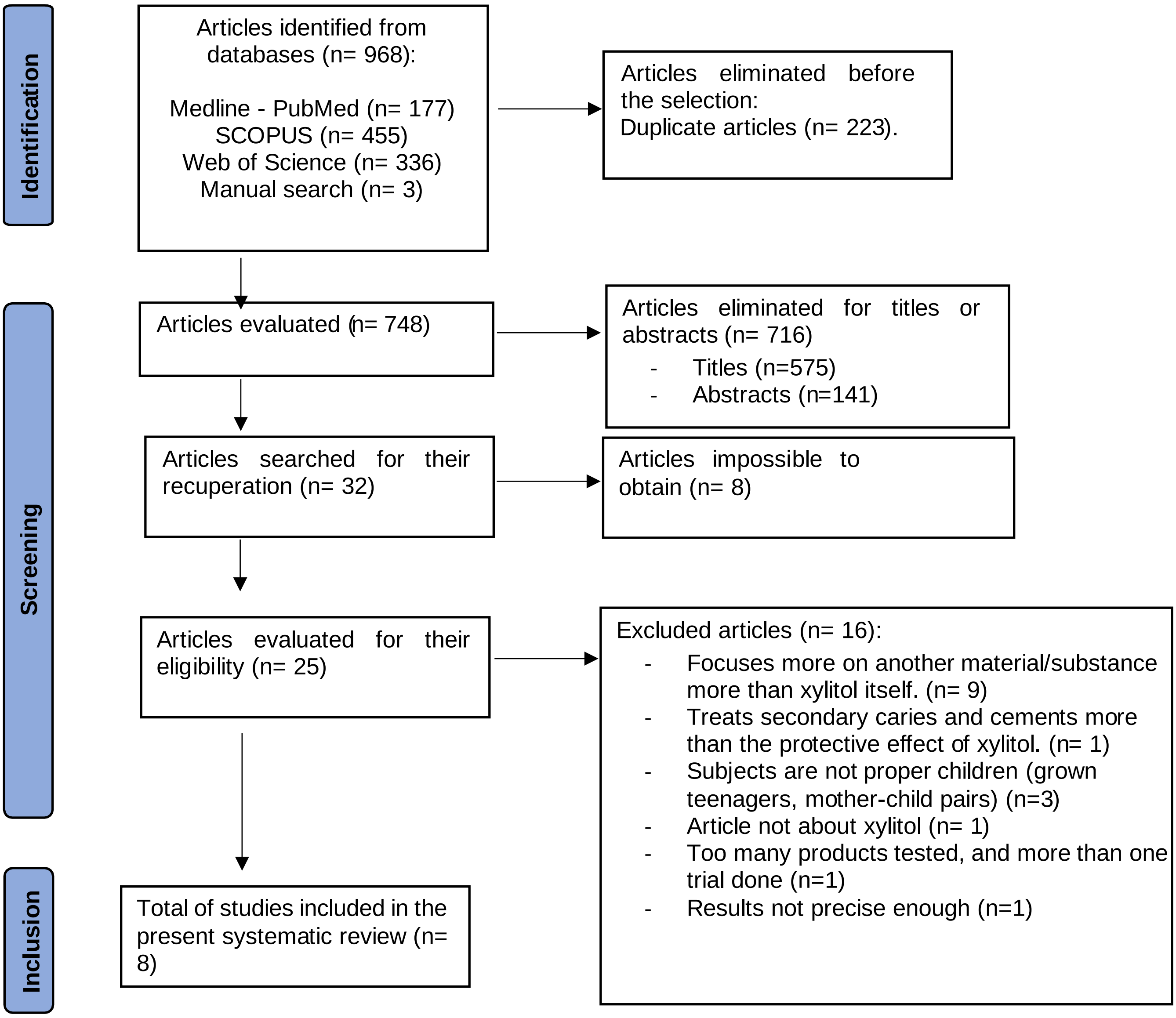

Figure 1: Flowchart and title selection process during systematic review

PREVENTIVE EFFECT OF XYLITOL ON DENTAL CARIES IN CHILDREN. SYSTEMATIC REVIEW.

Running title: Preventive effect of xylitol on dental caries in children.

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Abstract

Backgrounds: Dental caries is a common chronic disease affecting children. It is influenced by factors like host characteristics, bacteria, diet, and oral hygiene. Risk factors include cariogenic bacteria and socioeconomic conditions. Prevention includes good oral hygiene and a healthy diet. Xylitol, a natural sugar alcohol derived from plants, is a suitable option for caries prevention in children. It has a lower glycemic index and doesn't cause dental caries. It has antibacterial effects, stimulates saliva flow, and helps neutralize acids.

Aims: To identify caries prevention factors of xylitol in pediatric patients; as well as to determine caries prevention practices related to xylitol and to know the limitations of the preventive effect of xylitol.

Material and methods: An electronic search was performed in the PubMed, Scopus, and Web Of Science databases on anticaries effect of xylitol up to December 2022.

Results: The main variables analyzed before and after the intervention of xylitol were the colony forming units (CFU) counts of oral bacteria with a mean concentration of SM per milliliter of saliva of 69x105 CFU/mL and 5,67 log10CFU/g for dental plaque ; interdental pH mean value of 7,2 for LX (low-dosed xylitol) and 7,4 for HX (high-dosed xylitol) without rinse and with rinsing LX of 6,35 for LX and 6,85 for HX ; the incidence of dental caries with a mean value of 24,17 caries onsets for stick gums, 15,52 caries onsets for pellets and for the topical oral syrup X2 a mean value of 24,2% whereas X3 was 40,6% of tooth with decay ; finally for the visible dental plaque amount the mean value was 44,5% for score 0, 40,6% for score 1, 25,1% for score 2, 2,5% for score 3.

Conclusion: Despite the limitations, xylitol seems to have an anticaries effect on children but more studies should be carried out to prove its real effectiveness.

Key words: *Xylitol, Dental caries, Prevention, Diet, Child, Dental plaque, Biofilms, Saliva, Bacteria, Dental bacteria, Anti-infective agents, Antimicrobial, Antibacterial, Bacteriostatic, Bactericidal*

Introduction

Dental caries can be defined as the disease that affects the hard tissues of the teeth, leading to cavitation if not treated properly. It is a multifactorial disease but above all, a preventable one. The etiology and pathogenesis of dental caries are well-known: host factors, bacteria, the availability of fermentable sugars and other environmental conditions are needed (1). The development of dental caries starts with a shift in the oral bacterial environment caused by frequent consumption of fermentable carbohydrates. It is therefore wise to find a product that acts on the factors responsible for the development of dental caries in children, but also capable of replacing sugars. Xylitol is a natural sugar alcohol that is found in small amounts in fruits and vegetables. It is not fully fermented by oral bacteria, which helps prevent the production of acid that causes dental caries. Xylitol is commonly consumed through chewing gums, toothpaste, mouthwashes, etc. Its antimicrobial effects inhibit the growth of microorganisms, specifically bacteria. Reviewing what xylitol is and the ways to use it in order to protect children's dentition will benefit children's oral and general health. No review focuses on its microbial effect and on its ability to reduce the concentration of bacteria promoting the development of dental caries (2–5).

The aim of this review was to systematically review the following question: In children susceptible to develop dental caries, does xylitol have an anticaries effect to prevent the disease? This was done by firstly identifying caries prevention factors of xylitol in pediatric patients, secondly by determining caries prevention practices related to xylitol and lastly by knowing the limitations of the preventive effect of xylitol.

<u>Material and Methods</u>

This systematic review complies with the PRISMA statement (Preferred Reporting Items for Systematic reviews and Meta-Analyses) (7).

- **Focus question**:

The focus question was established according to the PIO structured question:

P (population): Children susceptible to develop dental caries

I (intervention): Xylitol

O (outcomes):

- O1: Antimicrobial effect on the bacteria responsible for the development on dental caries
- O2: Alkalization of dental biofilm.
- O3: Stimulation of saliva flow
- O4: Calcium and phosphate uptake.

- **Eligibility criteria**:

The inclusion criteria were:

Study design: Randomized controlled clinical trials, prospective and retrospective cohort studies, in vivo studies, in vitro studies, case series; studies on human subjects (children); Publications in English or French; Published until December 2022.

Patient: Children susceptible to have dental caries.

Intervention: Direct exposure of pediatric patients or bacteria cell cultures to xylitol.

Outcomes: Studies that provided data related to the antimicrobial effect of xylitol.

As secondary variables: Studies including data about alkalization of dental biofilm; Studies providing data about the stimulation of saliva flow; Studies providing data about remineralization (Calcium and phosphate uptake).

The exclusion criteria were systematic reviews, meta-analysis, reviews about a case, letters or comments to the editor, expert reports and animal experimental studies, studies including adult patients and children above 16 years old. No restrictions were imposed according to the year of publication.

- **Information sources and data search**:

An automatized electronic and manual literature searches were conducted in three major electronic databases (PubMed, Scopus and Web of Science) with the following keywords: “child”, “dental plaque”, “biofilms”, “saliva”, “bacteria”, “scholar children”, “dental bacteria”, “xylitol”, “xylitol toothpaste”, “xylitol mouthrinse”, “xylitol mouthwash”, “xylitol chewing gum”, “Anti-Infective agents”, “antimicrobial”, “antibacterial”, “bacteriostatic” and “bactericidal”. Keywords were combined with the boolean operators AND, OR and NOT, as well as the controlled terms (“MeSH” for

Pubmed) to obtain the best and broadest search results. The following search strategy in Pubmed was carried out: ((((((((children[MeSH Terms]) OR (dental plaque[MeSH Terms])) OR (biofilms[MeSH Terms])) OR (bacteria[MeSH Terms])) OR (saliva[MeSH Terms])) OR (dental bacteria)) OR (scholar children)) AND (((((xylitol[MeSH Terms]) OR (xylitol toothpaste)) OR (xylitol mouthwash)) OR (xylitol chewing gum)) OR (xylitol mouthrinse))) AND ((((agents, anti-infective [MeSH Terms]) OR (antimicrobial)) OR (bacteriostatic)) OR (bactericidal)). In order to identify any eligible studies that the initial search might have missed, we completed the search with a review of the references provided in the bibliography of each of the studies. Finally, a cross search for potentially interesting articles for analysis was carried out. Duplicate studies were removed from the review.

- **Study selection process**:

A selection process was carried out in three stages. Study selection was carried out by one reviewer (MD). The titles were initially filtered to eliminate publications that were not relevant. In the second stage, abstracts and summary were read and a selection was done according to the type of study, type of intervention, age of patients and results variables. In the third stage, it was filtered in accordance with the complete text reading, and the information was taken out using a previously created data collecting form to certify the studies' eligibility. At each stage, disagreements between reviewers were settled through discussion and, if necessary, consultation with a third reviewer was done.

- **Date extraction**:

The following information was extracted from the studies and arranged in tables according to the type of use of xylitol (oral topical syrup, mouthwash, chewing gum): authors with the year of publication, type of study (Randomized controlled clinical trials, prospective and retrospective cohort studies, in vivo studies, in vitro studies, case series), number of patients and samples, age of patients (children under 16 years old), time of exposure to xylitol, concentration of xylitol used, association of the xylitol to other products (fluoride, chlorhexidine, salbutamol), antibacterial effect, alkalization of dental plaque, stimulation of saliva. The main is the antibacterial effect of xylitol which has shown to reduce the growth and acid production of cariogenic bacteria, such as SM, which is a major contributor to tooth decay. The secondary ones are the alkalization of dental biofilm which increases the pH in the mouth, making the environment less acidic and less conducive to bacterial growth, the stimulation of saliva flow which helps to neutralize acids and wash away food particles, reducing the risk of tooth decay, calcium and phosphate uptake which helps to remineralize enamel and reduce the risk of tooth decay and the limitations of the effects of xylitol on dental caries prevention.

- **Quality assessment**:

The risk of bias assessment was assessed by one reviewer (MD) in order to analyze the methodological quality of the included articles. For the evaluation of the quality of the randomized controlled clinical studies, the Cochrane guide 5.1.0 was used. Publications were considered: "High risk of bias" when one or more criteria were not met and therefore the study is considered to have a possible bias that weakens the reliability of the results; "Low risk of bias" when they met all the criteria; “Unclear bias” either due to lack of information or uncertainty about the potential for bias. To measure the quality of pseudo experimental studies, the Newcastle-Ottawa scale was used (6) ; we considered “high risk of bias” for a star score ≤6 and “low risk of bias” for a star score >6.

- **Data synthesis**:

To summarize and compare the outcome variables between the different studies, the means of the values of the main variables were grouped according to the study group.

<u>Results</u>

- **Study selection**:

A total of 968 articles were obtained from the initial search process: Medline - PubMed (n=177), Web of Science (n=336) and SCOPUS (n=455). There were 223 duplicates, so without those duplicates we obtained 745 articles. Among those 745 publications, 697 were identified as potentially eligible articles through title screening, 171 through the reading of the abstract and 29 through the full-reading. Full-text articles were subsequently retrieved and thoroughly evaluated. As a result, 5 articles met the inclusion criteria and were included in the present systematic review. The information related to the excluded articles and the reason for their exclusion is presented in Table 2. In addition, 3 additional studies were obtained through manual search (list of references and primary sources). As a result, 8 articles met the inclusion criteria and were finally included in this systematic review (Figure 1).

- **Study characteristics**:

Among the 8 included articles, 5 of them are about chewing-gums ((7–11)), 2 are about mouthwashes (12,13) and 1 is about topical oral syrup (14). They all evaluate the protective effect of xylitol by focusing on the concentration of the main bacteria of the oral cavity (*Streptococcus Mutans* (SM*)*, *Lactobacilli*…) with the intervention of xylitol. 8 are clinical trials (7–10,12–14) and one is cohort study where the patient was the unit of randomisation (11). There were in total 1105 patients: 94 used mouthwashes, 94 used topical oral syrup and 877 used chewing-gum. The follow-ups of certain studies were the same and some others were different. 2 studies about mouthwash had a 2 week follow-up (12,13), 2 studies about chewing-gum had a 4 week follow-up (8,9), and the others were really different, going from 21 days up to 3 years (7,10,11,14). They did not all evaluate the same variable. The most analysed variable was the count of the main oral bacteria such as SM either in saliva (7–10,13) or dental plaque (12). Other variables were analysed including the incidence of dental caries (11,14), visible dental plaque amount (8) or the pH of interdental plaque (9) (Table 1).

- **Risk of bias**:

For randomized studies, a high risk of bias was considered in 3 studies and an unclear risk of bias in 4 (Figure 2). For non-randomized observational studies, the risk of bias was considered high in 1 study (Figure 3).

- **Synthesis of results**:

<u>Caries prevention factors of xylitol in pediatric patients</u>:

Regarding the caries prevention factors of xylitol in pediatric patients, 5 articles measured the count of SM in saliva (7–10,13). The mean concentration of SM/mL of saliva was $69x_{10}^{5}$ CFU/mL with a range of 75.56 CFU/mL (13) to 138_{x10}^{5} CFU/mL (10). One article referred to the SM levels in dental plaque (12). The SM count is 5,67 log_{10}CFU/g. One article (9) mentioned the pH of interdental plaque as an indicator of caries incidence. They measured the pH after 10 minutes of chewing either a low-dosed xylitol chewing-gum or a high-dosed xylitol chewing-gum. They measured it at 0, 5, 10, 15, 20, 25 and 30 minutes after chewing. They also measured the pH with and without rinsing with 10% sucrose solution for one minute. The mean value for the interdental pH 0 minute after 10 minutes of chewing without rinsing after was 7,2 for the LX and 7,4 for the HX; with rinsing for the LX it was 6,35 and 6,85 for the HX. 2 articles (11,14) evaluated the preventive effect of xylitol through the incidence of dental caries. One study (11) measured the number of caries onsets per 1000 surfaces. They used xylitol pellets and stick gums. The mean value was 24,17 caries onsets for the stick gums and 15,52 caries onsets for the pellets. The other study examining dental caries (14) measured the percentage of decayed teeth by evaluating a xylitol topical oral syrup either twice or 3 times a day. The mean value for twice a day was 24,2% whereas given 3 times a day was 40,6% of tooth with decay. One article (8) assessed the visible dental plaque amount. The mean value after 4 weeks of use of xylitol-containing chewing-gum according the different affected surface of the tooth was 44,5% for score 0, 40,6% for score 1, 25,1% for score 2, 2,5% for score 3. The score corresponds to the Greene–Vermillion simplified oral hygiene index (OHI-S). The values are based on clinical assessment on 6 predetermined sites (the buccal sites of teeth 16, 11, 26, 36, 31 and 46).

Caries prevention practices related to xylitol:

Caries prevention practices related to xylitol were discussed through its different forms and different actions. Its different ways to be consume are chewing gum (7–11) and mouth rinses (12,13) but it also exists as topical oral syrup (14). Its mechanisms of action were considered in all of the articles (7–14): counts of the main bacteria responsible for dental caries in children (7,8,10,12,13), pH and amount of interdental plaque(9)(8,9) and incidence of dental caries in children (11,14).

Limitations of the preventive effect of xylitol:

The limitations of xylitol were addressed in different articles (9–11). One article showed its temporal limitation (9). Indeed, this study showed that xylitol had a short effect and needed to be in a high quantity to exert its preventive effect on dental caries in children. According to the authors, there is an evident dose-response relationship, and a high amount of xylitol is needed to affect the interdental plaque-pH in habitual xylitol consumers. Moreover, 2 articles demonstrated another limitation of xylitol which is its necessity to be combined with other substances to be powerful enough to show its carioprotective effect (10,11).

Discussion

This systematic review provides information based on the results of the preventive effect of xylitol on dental caries in children. The aim was to identify caries prevention factors of xylitol in pediatric patients; to determine secondarily caries prevention practices related to xylitol, as well as the limitations of the preventive effect of xylitol.

Caries prevention factors of xylitol in pediatric patients:

The results revealed that xylitol has a protective effect against dental caries in children. This conclusion agrees with other systematic reviews that have also examined the effect of xylitol on oral health (15,16). The studies reviewed showed that xylitol can reduce the concentration of *Streptococcus Mutans* (SM) in saliva and dental plaque (7,8,10,12). These results can be explained by the fact that xylitol stabilizes calcium phosphate solutions, stimulates salivation, and simultaneously operates in salivary and microbiological effects such as the reduction of SM counts in both saliva and dental plaque. It also reduces the adhesion of microorganisms to the surface of teeth and reduces their acid production potential (17). However, one study had different results regarding the magnitude of SM counts in saliva compared to other studies (8). We suspect that there is some missing information or some mistakes in the methodology or conditions of the experiment. According to Mäkinen et al. (11), there is a significant decrease in the crude caries rate after using xylitol sticks or pellets. In the study made by Milgrom et al. (14), topical oral syrup containing xylitol was also found to have a preventive effect on caries. Other interventions such as candies, chewing gums, and wipes applied by mothers on their babies were associated with a reduced onset of dental caries in children and babies. Regarding dental plaque, in the study of Holgerson et al. (8), the amount of visible dental plaque was significantly reduced in both groups after using xylitol-containing chewing gum, regardless of whether the children had dental caries or not. This suggests that xylitol can reduce dental plaque irrespective of caries experience. One study (9) examined the interdental plaque pH and found that a high single dose of xylitol had a short and limited beneficial effect on the interdental plaque pH. Another study (18) supported these findings, indicating that interdental plaque pH is related to the incidence of dental caries. Overall, the various factors examined in the systematic review, including SM counts, incidence of dental caries, visible dental plaque amount, and interdental plaque pH, are all interconnected and contribute to the preventive effect of xylitol on dental caries in children.

Caries prevention practices related to xylitol:

This systematic review focused on three forms of xylitol: chewing gums (7–11), mouthwashes (12,13), and topical oral syrup (14). Chewing gums were found to be the most used form due to their ease of use, especially for children. Other forms of xylitol consumption include toothpaste (19–24), topical wipes (25), gummies/candies (22,24,26), and even lollipops (27–29). The availability of various forms makes xylitol suitable for different age groups. When considering chewing gums, lollipops, gummies, and candies, these methods provide an easy and enjoyable way for children to take care of their oral health. Children may not realize they are consuming a product that has beneficial effects on their oral health and helps prevent caries. The convenience of consuming xylitol may explain the low dropout rates observed in the selected studies. Toothpastes and mouthwashes are also suitable for children to use xylitol (19–24). Several studies have demonstrated the efficacy of xylitol when combined with other substances such as fluoride (20,30–32), chlorhexidine (33,34), or Stevia (35). These substances are well-established in the field of oral hygiene and combining them with xylitol enhances their preventive effects. Overall, the use of different forms of xylitol provides options for individuals to incorporate it into their oral hygiene routine, particularly for children. Combining xylitol with other established oral hygiene products can further enhance its preventive effects.

Limitations of the preventive effect of xylitol:

Xylitol is often used in combination with traditional substances like chlorhexidine (33,34,36), or fluoride (20,30–32), known for their effectiveness in preventing dental caries. This combination aims to enhance the properties of both substances because xylitol alone may not be potent enough to produce a significant protective effect against dental caries in children. Some studies have found that xylitol alone had limited or insignificant effects on dental caries prevention (8,9,37). However, xylitol does have side effects, with digestive issues being the most common. Allergic reactions and blood sugar fluctuations can occur in individuals, especially if they consume more than 10g of xylitol. The threshold dose for blood sugar fluctuations in children varies depending on factors like age, weight, and individual tolerance. These side effects, especially for children who are more susceptible to high doses, can limit its use. Another limitation of xylitol is its cost compared to established products. However, it is worth exploring xylitol as an alternative to refined sugars, considering the high sugar consumption among children. More studies on xylitol can help increase its accessibility and usage. While it may not be the most powerful product in terms of anticaries effects, xylitol shows promise for the future.

Study limitations:

This systematic review had several limitations. One major limitation was the small sample sizes of participants in the included studies (10–13). Many studies acknowledged that the number of participants was too small to provide significant results, particularly in studies focusing on children. Challenges in recruiting participants, obtaining parental consent, and going through institutions further complicated the issue. Another challenge was the inconsistency in units or measurement tools used across studies, making it difficult to compare and calculate averages. For example, different studies evaluated the incidence of dental caries (11,14) but used different units of measurement, such as CCR or percentage of surfaces with dental decay. The short follow-up duration of some studies (9,11,13,14) was also a limitation, ranging from 2 weeks to a year. Some authors (38,39) expressed skepticism regarding the actual effectiveness of xylitol in protecting children from dental caries, emphasizing the need for combining xylitol with other substances to achieve significant effects. Furthermore, the limited number of studies available on xylitol, particularly in relation to children, posed challenges in drawing definitive conclusions. The novelty of xylitol as a dental product made it difficult to assess the results objectively, and different studies produced varying outcomes, which raised concerns about the reliability of the findings. Overall, xylitol shows anticaries properties for children but more studies are needed to address these limitations and provide a clearer understanding of the effectiveness of xylitol in preventing dental caries in children.

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Table 1: General characteristics of the included studies

Title	Author and Year	Number of paediatric participants	Type of study	Type of intervention	Patient follow-up time	Analysed
Antimicrobial efficacy of Xylitol, Probiotic and Chlorhexidine mouth rinses among children and elderly population at high risk for dental caries (73)	(Krupa et al., 2022	30	Randomized clinical trial	Mouthwash	2 weeks	Count of Streptococcus mutans levels in dental plaque
Comparative evaluation of efficacy of "Green Tea" and "Green Tea with Xylitol" mouthwashes on the salivary streptococcus mutans and lactobacillus colony count in children (74)	Hajiahmadi et al., 2019	64	Randomized Clinical Trial	Mouthwash	2 weeks	Count of Streptococcus mutans and Lactobacillus colonies in saliva
Effect of chewing xylitol containing and herbal chewing gums on salivary Mutans Streptococcus count among school children (68)	Chavan et al., 2015	72	Randomized, clinical, follow-up study	Chewing gum	21 days	Count of Streptococcus mutans colonies in saliva
Dental plaque formation and salivary mutans streptococci in schoolchildren after use of xylitol-containing chewing gum (69)	Lif Holgerson et al., 2007	128	Double-blind randomized controlled trial	Chewing gum	4 weeks	Count of Streptococcus mutans levels in saliva Visible dental plaque amount

Effect of xylitol-containing chewing gums on interdental plaque-pH in habitual xylitol consumers (70)	Lif Holgerson et al., 2005	11	Single-blind crossover (clinical trial)	Chewing gum	4 weeks	pH of interdental plaque Count of Streptococcus mutans levels in saliva
A Comparative Evaluation of Xylitol Chewing Gum and a Combination of IgY + Xylitol Chewable Tablet on Salivary Streptococcus mutans Count in Children (71)	Jain et al. 2022	120	Double-blind Randomized Controlled Trial	Chewing gum	3 months	Count of Streptococcus mutans levels in saliva
Xylitol Pediatric Topical Oral Syrup to Prevent Dental Caries A Double-blind Randomized Clinical Trial of Efficacy (75)	Milgrom et al., 2009	94	Double-blind randomized controlled trial	Topical oral syrup	12 months	Incidence of dental caries
Polyol chewing gums and caries rates in primary dentition: A 24-month cohort study (72)	Mäkinen et al., 1996	510	Double-blind cohort study	Chewing gum	24 months	Incidence of dental caries

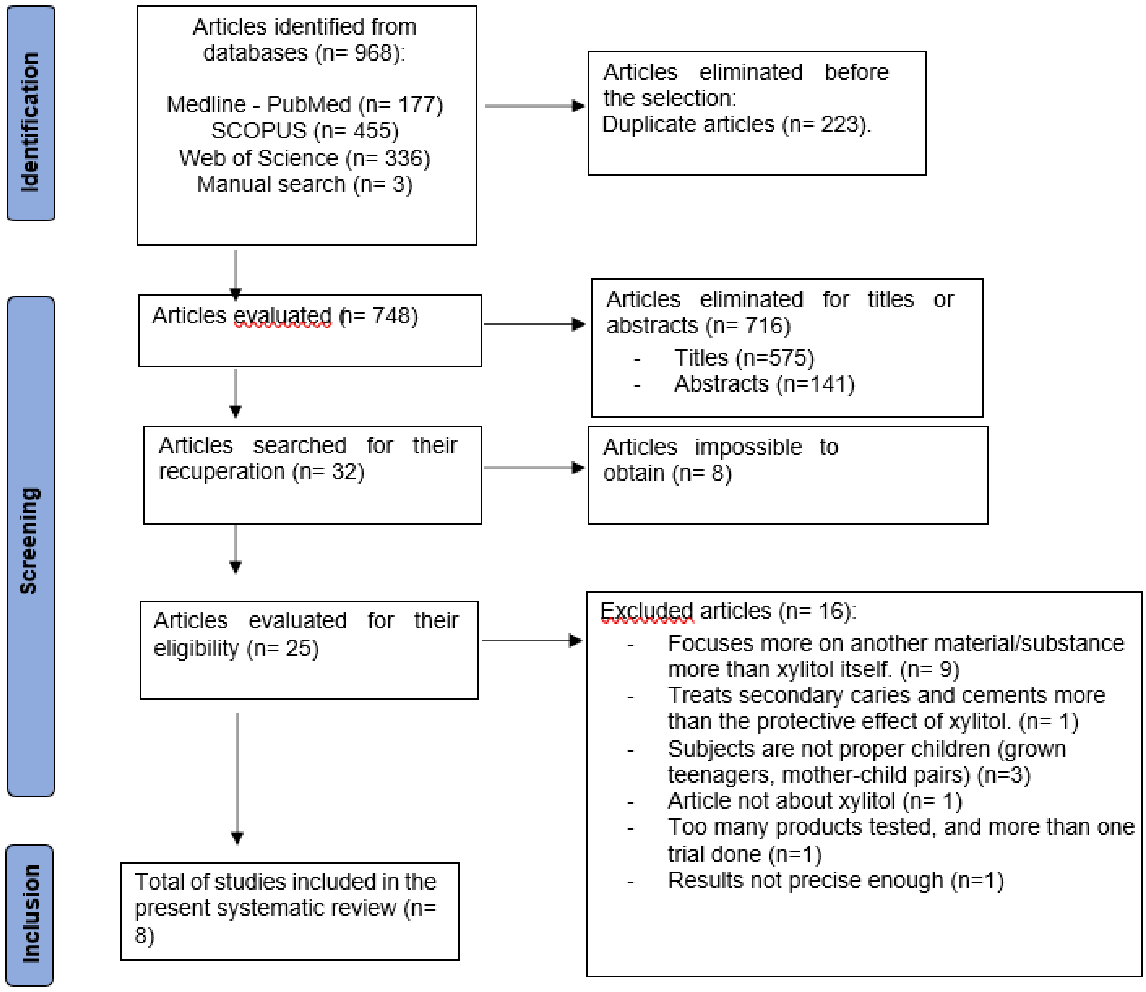

Figure 1: PRISMA flowchart of searching and selection process of titles during systematic review

	Generate randomized sequence (selection bias)	Allocation concealment (selection bias)	Blinding outcome assessment (detection bias)	Follow-up and exclusions (attrition bias)	Selective description (reporting bias)	Other biases
Krupal et al. 2022 (12)	−	−	+	+	+	+
Hajiahmadi et al., 2019 (13)	+	+	+	?	+	+
Chavan et al., 2015 (7)	+	+	−	−	+	+
Lif Holgerson et al., 2007 (8)	+	+	+	?	+	+
Lif Holgerson et al., 2005 (9)	+	+	+	+	+	?
Jain et al. 2022 (10)	+	+	+	−	+	+
Milgrom et al., 2009 (14)	+	+	+	−	−	?

Figure 2: Measurement of the risk of bias of the randomized studies according to the Cochrane guidelines.

	Definition of the cases	Representativeness	Selection of controls	Definition of controls	Comparability (most important factor)	Comparability (any other variable)	Exposure check	Same method for both groups	Dropout rate	Total
Mäkinen et al.,1996 (11)	☆	☆	☆	☆	☆	-	☆	☆	-	7

Figure 3: Measurement of the risk of bias of non-randomized observational studies with the Newcastle-Ottawa scale - observational cohort studies, no control group.