

Sugar Substitutes: Mechanism, Availability, Current Use and Safety Concerns-An Update

Megha Gupta*

Preventive Dental Sciences, Division: Pedodontics College of Dentistry, Jazan University, Jazan, Saudi Arabia

Abstract

Citation: Gupta M. Sugar Substitutes: Mechanism, Availability, Current Use and Safety Concerns-An Update. Open Access Maced J Med Sci. <https://doi.org/10.3889/oamjms.2018.336>

Keywords: Sugar substitutes; Dental caries; Artificial sweeteners; Xylitol; Cariogenicity

***Correspondence:** Megha Gupta. Preventive Dental Sciences, Division: Pedodontics College of Dentistry, Jazan University, Jazan, Saudi Arabia. E-mail: meghamcods@gmail.com

Received: 17-Aug-2018; **Revised:** 27-Sep-2018; **Accepted:** 02-Oct-2018; **Online first:** 19-Oct-2018

Copyright: © 2018 Megha Gupta. This is an open-access article distributed under the terms of the Creative Commons Attribution-NonCommercial 4.0 International License (CC BY-NC 4.0)

Funding: This research did not receive any financial support

Competing Interests: The authors have declared that no competing interests exist

BACKGROUND: Dental caries has continued to be the major oral disease in the past, as well as the present scenario. Cariogenic sugars in the presence of specific bacteria *Streptococcus mutans* over a period have been attributed as the major etiologic agent for dental caries. The association between sugar consumption and dental caries has been well documented.

AIM: Hence, the dental profession shares an interest in the search for safe, palatable sugar substitutes.

METHODS: Therefore, the use of a suitable sugar substitute can help in combating dental caries.

RESULTS: Out of the various sugar substitutes available, xylitol is the most widely used. It is available in various forms. It decreases the plaque formation, bacterial adherence and inhibits the growth of Mutans Streptococci.

CONCLUSION: This article provides a comprehensive review of the sugar substitutes, present-day availability, role in the prevention of dental caries and their safety concerns.

Introduction

Sweetness is the taste that is strongly identified with affection and reward. Indulgence in sweets has been described as a “universal human weakness.” Carious lesions were sparse in ancient times but increased dramatically in the industrialised world. Epidemiological studies in many parts of the world support the hypotheses that increase in dental caries was associated with dietary changes. The classical evidence from Vipeholm, Hopewood house and Turku sugar studies has shown clearly the importance of diet in the carious process [1].

Many oral bacteria utilise sucrose, glucose, fructose and other simple sugars to produce organic acids (lactic, acetic and propionic) in sufficient concentration to lower the pH of plaque to levels that may result in some demineralisation of enamel [2].

Sucrose – An arch-criminal

Sucrose refined from sugar canes or sugar beets is the most common dietary sugar. A large variety of other common food like most breakfast cereals, many milk products, some meat and fish products, etc. also contain sucrose. It is also naturally present in fruit [3].

Sucrose has been called the arch-criminal in dental caries (Newbrun, 1967) [1]. This is because it is only from sucrose, that most oral bacteria can synthesise both soluble and insoluble extra-cellular polymers which increase the bulk of plaque and facilitate the attachment of bacteria, especially *Streptococcus mutans*. Unlike other sugars, sucrose can serve directly as a glycosyl donor in the synthesis of extracellular polymers.

The dietary sugars all diffuse into the plaque rapidly and are fermented to lactic and other acids or can be stored as intracellular polysaccharide by the

bacteria. The high free energy of hydrolysis of sucrose permits this reaction to proceed without other sources of energy. Thus, sucrose favours colonisation by oral microorganisms and increases the stickiness of the plaque, allowing it to adhere in larger quantities to the teeth. This property along with the high specificity of the enzymes involved in the synthesis of the extracellular polymers has led some workers to regard sucrose as having a unique role in caries. Therefore, sucrose may be expected to be somewhat more cariogenic than other sugars [3].

The prevalence of dental caries in children is declining, but children at high risk of developing dental caries are still an important public health concern. Dental caries has an age-specific characteristic in that ageing populations are also at risk of root caries. The use of non-cariogenic sweets can be recommended by professionals in these clinical settings as an important adjunct in reducing dental caries risk in these individuals. Many medicines have been found to have the side effect of producing a dry mouth (xerostomia), and prolonged use of such drugs contributes to an increased risk of dental caries, using non-cariogenic chewing gum to promote salivation would be beneficial in these cases.

Sugar substitutes

A sweetener is a food additive, which mimics the effect of sugar on taste. Therefore, they are called sugar substitutes [4].

To be an acceptable sweetener of commercial utility, a substance must:

1. Have sufficient sweetening power [1] [5].
2. Have no unpleasant aftertaste [1].
3. Be non-carcinogenic and non-mutagenic [1] [5].
4. Be reasonably inexpensive [1] [5].
5. Be thermostable (i.e. resist cooking temperatures) [1] [5].
6. Have little or no calories [5].

Classification of sweeteners

Sweeteners, which give food a sweet taste, are classified as carbohydrate sweeteners (caloric) and non-carbohydrate sweeteners (non-caloric). Caloric sweeteners are also called nutritive/bulk sweeteners and include sugar and sugar-alcohols.

Sugar alcohols are erythritol, sorbitol, mannitol, xylitol, maltitol, lactitol, and reducing starch syrup [6].

The noncaloric sweetening agents are also called nonnutritive sweetening agents that have no caloric value and are not fermented by microorganisms of the oral cavity. The noncaloric sweeteners are generally much sweeter than sucrose and can, therefore, be used in smaller amounts. The high-intensity sweeteners are non-caloric, non-acidogenic. E.g., Aspartame, Saccharin, Acesulfame. They are further divided into chemically synthesised sweeteners, including saccharin, aspartame and sucralose, and those obtained from plants, including stevioside, thaumatins, and monellin [7].

There is another way to classify the sweeteners, based on the time of origin. Saccharin, cyclamate and aspartame which were the earliest known sweeteners are called as "first generation sweeteners". The newer sweeteners such as acesulfame-K, sucralose, alitame and neotame are categorised as second generation sweeteners [8].

The sweeteners approved by the Food and Drug Administration (FDA) of the United States are aspartame, acesulfame potassium, saccharin, sucralose and neotame only [4] [6] [9]. Also, stevia, a natural sweetener made from extracts of a plant, has been approved for limited use [10].

Prevention of dental caries by sugar substitutes

When the general health is concerned, sugar substitutes are a useful aid to maintain reduced energy intake and body weight and decrease the risk of type-2 diabetes and cardiovascular diseases compared with sugars. Further, they also facilitate the maintenance of a nutritionally balanced diet by satisfying a diabetic person's desire for sweets and assisting in the control of caloric intake [4].

The dentist often has the opportunity to provide advice regarding the importance of diet and the role of sugars in caries formation. Reducing the amount of sugar in the diet of humans, especially children, is an important consideration in preventing caries. Non-cariogenic sweeteners offer an alternative to sugar if used in moderation. The identification of new, safe, palatable, heat stable, non or low-caloric sweetener substitutes for the more cariogenic sugars such as sucrose, glucose, fructose and maltose would be extremely helpful in combating dental caries.

The use of sucrose substitutes in sweets is believed to have contributed in part to the decline in the prevalence of dental caries in industrialised

countries.

The anticariogenic effects of sugar substitutes include:

A. Inhibition of insoluble glucan synthesis from sucrose by Mutans Streptococci (MS).

B. The decrease in MS numbers in whole saliva and plaque.

C. Increase in the buffering capacity and pH of dental plaque

D. Interference with enamel demineralisation and an increase in enamel remineralisation [11].

Sugar substitutes of clinical importance are being elaborated here.

Sugar alcohol (polyol)

Important benefits of sugar alcohols include their none or low fermentability in human dental plaque and their ability to promote remineralisation of demineralised enamel. However, except for erythritol, the general demerits of sugar alcohols are side effects such as abdominal discomfort, flatulence, softened stools, and diarrhoea when taken in excess. Hence, they are not recommended for children less than three years of age [12].

Sorbitol (D – glucitol)

It is moderately sweet (about half that of sucrose) and relatively inexpensive. Practically all strains isolated (96%) of caries-inducing mutans group of streptococci will ferment sorbitol (and mannitol) in vitro to give a final pH of below 5. The failure of sorbitol to appreciably lower pH of plaque can be explained by the fact that, although Streptococcus mutans ferment sorbitol, the rate of acid production is much slower compared to other fermentable hexoses and disaccharides. This permits salivary buffers to neutralise acid and end products as they are formed [5] [6]. Candies and chewing gum sweetened with sorbitol are available commercially. Sorbitol-sweetened gums reported having low cariogenicity when they were chewed three times a day [12].

Xylitol

The sugar corresponding to xylitol is xylose. It is a non-fermentable, pleasant tasting, non-cariogenic polyol. It has sweetness similar to that of sucrose and has a cooling effect on the mouth. It is primarily used in chewing gum. Regular use of xylitol-containing chewing gum reduces the amount of dental plaque as well as increases the salivary flow [11].

Dental benefits of xylitol were first recognised

in Finland. The first chewing gum developed with the aim of reducing caries and improving oral health was released in Finland in 1975 and the United States shortly after. The first xylitol studies in humans known as the Turku Sugar studies demonstrated the relationship between dental plaque and xylitol as well as the safety of xylitol for human consumption [1] [3].

Xylitol reduces plaque formation and bacterial adherence (i.e., it is antimicrobial), inhibits enamel demineralisation (i.e. reduces acid production) and has a direct inhibitory effect on Mutans Streptococci. The continuous-culture biofilm model showed that within a young biofilm, sucrose significantly promotes whereas xylitol reduces bacterial colonisation and proliferation. The results indicate that xylitol affects the ability of certain S. mutans strains to adhere to the hydroxyapatite [13].

Prolonged use of xylitol appears to select for a “xylitol resistant” mutant of the MS cells [14]. These mutants appear to shed more easily into saliva than the parent strains, resulting in a reduction of MS in plaque. Xylitol has been credited in reducing the transmission of cariogenic bacteria from mother to infant and has been shown to have bactericidal qualities [12] [15]. A recent Cochrane review concluded that Xylitol also increases the production of saliva and reduces the growth of acidogenic bacteria in the oral cavity [16].

Xylitol currently is available in many forms (e.g. gums, mints, chewable tablets, lozenges, toothpaste, mouthwashes, cough mixtures). Xylitol is approved for food, cosmetics, and pharmaceuticals in about 40 countries. It is used as a sweetener mainly in noncariogenic confectionery (chewing gum, candies, gumdrops, in pharmaceutical products (tablets, throat lozenges, vitamin tablets, cough syrup), and occasionally in dentifrices. A significant deterrent to the widespread use of xylitol as a sweetener is its cost, currently ten times that of sucrose [2].

Long lasting effects have been demonstrated up to years after years of using xylitol chewing gums [17].

Alanzi et al., [18] conducted a study to measure the xylitol content in the sugar-free chewing gums available in the market of the Gulf Cooperation Council (GCC) countries in the Middle East. The mean measured xylitol content/piece was 0.33 ± 0.21 g. Xylitol content was < 0.3 g/piece in 9 products, 0.3 g in 7 and > 0.5 g in 5 products. They stated that majority of xylitol chewing gums sold on the GCC market do not provide the consumers with the recommended daily dose of xylitol for caries prevention. They also recommended that clear, accurate labelling for xylitol chewing gums.

AAPD Recommendations (2014-15) for the use of xylitol in caries prevention [17]:

1. It supports the use of xylitol in caries

prevention. Clinicians may recommend its use in moderate to high-risk caries patients.

2. Dosing frequency should be a minimum of two times a day, not to exceed 8 grams/day.

3. Chewing gums, mints and hard candies have been the predominant modality for xylitol delivery. In children, less than four years, xylitol syrup 3 to 8 gms/day in divided doses should be given. In children above four years of age, the same dosage in an age-appropriate product such as chewing gums, mint or lozenges can be given.

A recent meta-analysis proved xylitol to be an effective self-applied caries preventive agent [19].

Lactitol

Lactitol is disaccharide alcohol of galactose and sorbitol obtained by the dehydrogenation of lactose. It has a sweetness that is 30-40% of sucrose, and its quality and taste resemble that of sucrose. It is not easily metabolised by acidogenic and polysaccharide forming oral microorganisms [1] [5].

Maltitol

Maltitol also termed reducing maltose, is disaccharide alcohol of glucose and sorbitol obtained by the hydrogenation of maltose. The sweetness of maltitol is 75-80% that of sucrose, and its quality of taste resembles that of sucrose [11]. In-vivo studies have shown that maltitol does not lower plaque pH [20]. A recent study showed that maltitol in chewing gums significantly reduced the concentration of cariogenic bacterial species (*S. mutans*, *S. sobrinus*, *A. viscosus* and *Lactobacillus*) in dental plaque compared to gum base [21].

Aspartame

Aspartame sold under the brand names of Nutrasweet and Equal, is a dipeptide methyl ester discovered in 1965 by James Schalter. It is an artificial, non-saccharide sweetener [4]. Aspartame was accidentally discovered to have a pronounced sweet taste, is about 180 times sweeter than sucrose in aqueous solution [1].

Aspartame was the first sweetener to be approved by the FDA in 1981. It is the most commonly used non-cariogenic artificial sweetener. Its primary use is in diet soft drinks, yoghurt, puddings, gelatin and snack foods [5].

The manufacturers are required to label aspartame and to indicate that it contains phenylalanine, and its intake is restricted for individuals with phenylketonuria.

Based on government research reviews and

recommendations from advisory bodies such as the European Commissions Scientific Committee, aspartame has been found to be safe for human consumption by more than ninety countries worldwide [22]. Despite, of some unscientific assumptions, there is no evidence that aspartame is carcinogenic [23].

Saccharin

Saccharin was discovered accidentally by Remsen and Fahlberg in 1879. Saccharin was the first artificial sweetener discovered and was well accepted during the World Wars I and II because of its low production cost and shortcoming of regular sugar [24]. It is 200 to 500 times sweeter than sucrose [1] [2]. It is an aromatic organic compound used mainly in the form of its sodium salt. Most commonly it has been used as tablets containing 15, 30, or 60 mg of sodium saccharin. Saccharin is pharmacologically inert and untoward effects are very rare [1].

There have been bladder cancer-inducing effects of saccharin from animal studies in the rat; however epidemiological studies in human did not find such effects [23].

Acesulfame – K

Acesulfame-K is 130 times as sweet as sucrose. It is stable in the temperature, pH and storage range that is likely to be encountered in foods and beverages. Safety studies have found no evidence of carcinogenicity, mutagenicity, cytotoxicity or teratogenicity [1].

In 1988, the FDA approved acesulfame-K for use in dry food products, including chewing gum, dry mixes for beverages, instant coffee, instant tea, gelatins, puddings, and non-dairy creamers. Acesulfame-K has been approved in twenty other countries, where it is also used in soft drinks, candies, toothpaste, mouthwashes and pharmaceutical preparations [1] [2].

Stevioside

Stevioside is an intensely sweet, naturally occurring compound found in the leaves of a small shrub, *Stevia rebaudiana* Bertoni, also called *yerba dulce*. It is 150-300 times sweeter than sucrose. It is a steroid glycoside.

Stevia is calorie-free, non-cariogenic sweetener. Stevioside is heat stable, resistant to acid hydrolysis and non-fermentable that makes them advantageous over the non-caloric sweeteners [25]. In 1995, the FDA approved the import and use of stevia as a dietary supplement, but not as a sweetener. Steviol glycoside has been extensively

tested to demonstrate safety for use for humans [26]. A recent study showed that the inhibitory effect of *Stevia rebaudiana* extract against *Streptococcus mutans* was superior when compared with chlorhexidine [27]. Brambilla et al., [28] evaluated the effects of *S. rebaudiana* extracts on in vitro *S. mutans* biofilm formation and in vivo pH of plaque. Higher in vitro *S. mutans* biofilm formation was observed with sucrose solution. Also, in-vivo sucrose rinse produced a statistically significant lower pH value compared to *S. rebaudiana* extracts.

Neotame

Neotame is a derivative of a dipeptide compound of the amino acids aspartic acid and phenylalanine. It is 7000 to 13,000 times and about 30 to 60 times sweeter than sugar and aspartame, respectively. It was approved by the US FDA as a general purpose sweetener in July 2002 [29].

Alitame

Alitame is an intense sweetener with sweetness potency 200 times greater than that of sucrose. It is a dipeptide of L-aspartic acid and D-alanine with a terminal N-substituted methylthietanyl-amine moiety [4].

Palatinose

Palatinose is a disaccharide of glucose and fructose. The sweetness of palatinose is forty-two per cent that of sucrose and quality of taste resembles sucrose, but the sweet taste disappears faster. It is considered an excellent sweetener for sweets and drinks for infants, children and diabetic patients [11].

Little or no acid production activity by some serotypes of *mutans streptococci* and other oral *streptococci* has been demonstrated following fermentation of palatinose, and acid production by dental plaque suspensions was noticeably lower in the presence of palatinose compared with sucrose. It has also been found that the plaque suspensions produce little or no lactate following fermentation of palatinose [7]. Candy and dairy product drinks containing palatinose are being marketed today.

Sucralose

Sucralose is a non-nutritive, non-caloric trichlorinated derivative of sucrose. It is chemically synthesised from sucrose. Sucralose is 600 times sweeter than sucrose and has been approved for use in some products. Results from various studies have shown it to be non-cariogenic [5] [11].

Sucralose is widely used throughout the world

in many food products such as tea and coffee sweetener, carbonated and non-carbonated beverages, baked goods, chewing gum and frozen desserts. No health concerns have been reported with sucralose [5].

3, 6-Anhydro-l-galactose (AHG)

3, 6-anhydro-l-galactose (AHG) is a rare sugar obtained from red macroalgae. The inhibitory effects of AHG and xylitol were evaluated on *S. mutans*. In the presence of 5g/l of AHG, the growth of *S. mutans* was retarded. At a concentration of 10g/l of AHG, the growth and acid production by *S. mutans* were completely inhibited; whereas, 40gm/l of xylitol still showed the growth of *S. mutans*. These results suggest that AHG can be used as a new anticariogenic sugar substitute for preventing dental caries [30].

Safety aspects of the use of sugar substitutes

Extensive scientific research has demonstrated the safety of the six low-calorie sweeteners, ie. *Stevia*, acesulfame –K, aspartame, neotame, saccharin and sucralose currently approved for use in the US and Europe; if taken in acceptable quantities daily [31]. According to the current literature, the possible risk of artificial sweeteners to induce cancer seems to be negligible [23]. In studies done on the pediatric population, using aspartame and placebo, no differences in blood pressure, glucose, or lipid profiles between the two groups were observed [32]. In another study, on teenage girls using sugar-sweetened or artificially sweetened soda no differences between groups in blood pressure, waist circumference or lipid profile was seen [33]. Hence, it can be concluded that sugar substitutes have no untoward effect on the general health and metabolism of an individual.

For each sweetener, the FDA establishes an Acceptable Daily Intake, (ADI) [34] in mg per kg body weight, which is the amount of sweetener thought to be safe to consume every day for a lifetime. The ADI is typically 100 times lower than the dose of the sweetener that caused toxicity in animal studies. The acceptable daily intake ADI for sucralose in the US is 5mg/kg body weight/day. The ADI for neotame in the US is 18mg/person/day [35].

Aspartame, saccharin, sucralose and neotame are classified as food additives by the FDA, while *stevia* is classified as Generally Recognized as Safe (GRAS), meaning that similar data consistent with its safety exist as for food additives [36].

Recent scientific evidence indicates that routine and long-term consumption of beverages with non-nutritive sweeteners are associated with an increase in risks for type 2 diabetes, cardiovascular disease, hypertension and stroke [37]. However, for its anticariogenic properties, sugar substitutes are used for a comparatively shorter duration of time; hence these side effects would not be seen.

In conclusion, dental caries is a matter of concern worldwide, and so effective measures must be taken at grass root level to prevent it. Considering diet as a factor, sugar substitutes can be used as an effective measure to control caries, especially with the sugar-free chewing gums as they have a dual role. Sugar substitutes can play an important role in shifting the caries process in favour of maintaining dental health, and they should be recommended as part of overall preventive treatment for patients at high risk of developing caries. Although sugar substitutes have anticarcinogenic properties, there is not sufficient evidence to recommend them as a first-line anticaries strategy in light of the large body of evidence on the effectiveness of topical fluorides and dental sealants. However, they should be recommended as an adjunct to other preventive intervention strategies.

References

- Newbrun E, Cariology, 3rd edition, Quintessence Publication, 1989.
- Nikiforuk G. Understanding dental caries, Etiology and mechanisms. Basic and Clinical Aspects. Karger Publication, 1985.
- Thylstrup A, Fejerskov O. Textbook of Clinical Cariology. 2nd edition, Munksgaard, Copenhagen, 1994.
- Chattopadhyay S, Raychaudhuri U, Chakraborty R. Artificial sweeteners – a review. J Food Sci Technol. 2014; 51(4):611-621. <https://doi.org/10.1007/s13197-011-0571-1> PMID:24741154 PMID:PMC3982014
- Roberts MW and Wright JT. Food sugar substitutes: a brief review for dental clinicians. J Clin Pediatr Dent. 2002; 27(1):1-5. <https://doi.org/10.17796/jcpd.27.1.bl98u70371655hp8> PMID:12413163
- Zero DT. Are sugar substitutes also cariogenic? J Am Dent Assoc. 2008; 139:5S–10S. <https://doi.org/10.14219/jada.archive.2008.0349>
- Takazoe I. New trends on sweeteners in Japan. Int Dent J. 1985; 35:58-65. PMID:3158612
- Lindley MG. New developments in low-calorie sweeteners. World Rev Nutr Diet. 1999; 85:44–51. <https://doi.org/10.1159/000059701> PMID:10647334
- Artificial sweeteners: no calories... sweet! FDA Consum. 2006; 40(4):27–28.
- Gardana C, Scaglianti M, Simonetti P. Evaluation of steviol and its glycosides in Stevia rebaudiana leaves and commercial sweetener by ultra-high-performance liquid chromatography-mass spectrometry. J Chromatogr A. 2010; 1217(9):1463–1470. <https://doi.org/10.1016/j.chroma.2009.12.036> PMID:20102764
- Matsukubo T, Takazoe I. Sucrose substitutes and their role in caries prevention. Int Dent J. 2006; 56(3):119-130. <https://doi.org/10.1111/j.1875-595X.2006.tb00083.x> PMID:16826877
- Burt BA. The use of sorbitol and xylitol sweetened chewing gum in caries control. J Am Dent Assoc. 2006; 137(2):190-6. <https://doi.org/10.14219/jada.archive.2006.0144> PMID:16521385
- Salli KM, Forssten SD, Lahtinen SJ, Ouweland AC. Influence of sucrose and xylitol on an early Streptococcus mutans biofilm in a dental simulator. Arch Oral Biol. 2016; 70:39-46. <https://doi.org/10.1016/j.archoralbio.2016.05.020> PMID:27318453
- Trahan L, Bareil M, Gauthier L. Transport and phosphorylation of xylitol by a fructose phosphotransferase system in Streptococcus mutans. Caries Res. 1985; 19:53-63. <https://doi.org/10.1159/000260829> PMID:3856485
- Makinen KK. The rocky road of xylitol to its clinical application. J Dent Res. 2000; 79:1352-1355. <https://doi.org/10.1177/00220345000790060101> PMID:10890712
- Riley P, Moore D, Ahmed F, Sharif MO, Worthington HV. Xylitol-containing products for preventing dental caries in children and adults (Review). Cochrane Database Syst Rev. 2015; 26(3):CD010743. <https://doi.org/10.1002/14651858.CD010743.pub2>
- American Academy of Pediatric Dentistry: Policy on the use of Xylitol. Reference manual. 2014-15; 37(6):45-47.
- Alanzi A, Soderling E, Varghese A, Honkala E. Xylitol Chewing Gums on the Market: Do They Prevent Caries? Oral Health Prev Dent. 2016; 14(5):459-466. PMID:27175449
- Janakiram C, Deepan Kumar CV, Joseph J. Xylitol in preventing dental caries: A systematic review and meta-analyses. J Nat Sci Biol Med. 2017; 8(1):16-21. <https://doi.org/10.4103/0976-9668.198344> PMID:28250669 PMID:PMC5320817
- Marsh PD. Dental plaque as a microbial biofilm. Caries Res. 2004; 38:204-11. <https://doi.org/10.1159/000077756> PMID:15153690
- Thabuis C, Cheng CY, Wang X, Pochat M, et al. Effects of maltitol and xylitol chewing-gums on parameters involved in dental caries development. Eur J Paediatr Dent. 2013; 14(4):303-8. PMID:24313583
- Magnuson BA, Burdock GA, Doull J. Aspartame: a safety evaluation based on current use levels, regulations, and toxicological and epidemiological studies. Crit Rev Toxicol. 2007; 37:629-727. <https://doi.org/10.1080/10408440701516184> PMID:17828671
- Weihrauch MR and Diehl V. Artificial sweeteners – do they bear a carcinogenic risk? Ann Oncol. 2004; 15(10):1460-5. <https://doi.org/10.1093/annonc/mdh256> PMID:15367404
- Bright G. Low calorie sweeteners - from molecules to mass markets. World Rev Nutr Diet. 1999; 85: 3-9. <https://doi.org/10.1159/000059697> PMID:10647330
- Giongo FC, Mua B, Parolo CC, Carlén A, Maltz M. Effects of lactose-containing stevioside sweeteners on dental biofilm acidogenicity. Braz Oral Res. 2014; 28:S1806–S8324. <https://doi.org/10.1590/1807-3107BOR-2014.vol28.0026> PMID:25098824
- Ferrazzano GF, Cantile T, Alcidi B, Coda M, Ingenito A, Zarelli A et al. Is Stevia rebaudiana Bertoni a Non Cariogenic Sweetener? A Review. Molecules. 2015; 21(1):E38. <https://doi.org/10.3390/molecules21010038> PMID:26712732
- Ajagannanavar SL, Shamarao S, Battur H, Tikare S, Al-Kheraif AA, Al Sayed MS. Effect of aqueous and alcoholic Stevia extracts against Streptococcus mutans and Lactobacillus acidophilus in comparison to chlorhexidine: An in vitro study. J Int Soc Prev Community Dent. 2014; 4:S116-21. <https://doi.org/10.4103/2231-0762.146215> PMID:25558451 PMID:PMC4278103
- Brambilla E, Cagetti MG, Ionescu A, Campus G, Lingström P. An in vitro and in vivo comparison of the effect of Stevia rebaudiana extracts on different caries-related variables: a

- randomized controlled trial pilot study. *Caries Res.* 2014; 48(1):19-23. <https://doi.org/10.1159/000351650> PMID:24216624
29. Prakash I, Corliss G, Ponakala R, Ishikawa G. Neotame: the next-generation sweetener. *Food Technol.* 2002; 56:36-40.
30. Yun E, Lee AR, Kim JH, Cho KM, Kim KH. 2,3,6-Anhydro-D-galactose, a rare sugar from agar, a new anticariogenic sugar to replace xylitol. *Food Chem.* 2017; 221:976-983. <https://doi.org/10.1016/j.foodchem.2016.11.066> PMID:27979302
31. Qurrat-ul-Ain, Khan SA. Artificial sweeteners: safe or unsafe? *J Pak Med Assoc.* 2015; 65(2):225-7. PMID:25842566
32. Knopp RH, Brandt K, Arky RA. Effects of aspartame in young persons during weight reduction. *J Toxicol Environ Health.* 1976; 2(2):417-28. <https://doi.org/10.1080/15287397609529443> PMID:796476
33. Williams CL, Strobino BA, Brotanek J. Weight control among obese adolescents: A pilot study. *Int J Food Sci Nutr.* 2007; 58(3):217-30. <https://doi.org/10.1080/09637480701198083> PMID:17514539
34. Services DoHaH. editor. Administration USFaD. Guidance for Industry and Other Stakeholders Toxicological Principles for the Safety Assessment of Food Ingredients, 2000.
35. [USFDA] US Food and Drug Administration. Food additives permitted for direct addition to food for human consumption: Sucralose. *Fed Reg.* 1999; 64:43908-43909.
36. Sylvetsky A, Rother KI, Brown R. Artificial sweeteners use among children: epidemiology, recommendations, metabolic outcomes, and future directions. *Pediatr Clin North Am.* 2011; 58(6):1467-1480. <https://doi.org/10.1016/j.pcl.2011.09.007> PMID:22093863 PMID:PMC3220878
37. Swithers SE. Not-so-healthy sugar substitutes? *Curr Opin Behav Sci.* 2016; 9:106-110. <https://doi.org/10.1016/j.cobeha.2016.03.003> PMID:27135048 PMID:PMC4846275