GRADUATION PROJECT

Degree in Dentistry

UPDATE ON NON-CARIOGENIC SWEETENERS

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Abstract

Introduction: Sugar consumption is a significant factor in the process of caries development. With 80% of the world being affected by dental caries, it makes it the most prominent non-communicable disease in the world. Artificial sweeteners may assist in the reduction of sugar consumption and therefore decrease the incidences of caries; **Objectives**: The main objective was to find which non-cariogenic sweeteners have shown the most beneficial results in caries prevention. The secondary objective was to find new and upcoming sweeteners which can be potentially used to prevent caries; **Materials and methods**: Searches on the databases PubMed, Google Scholar and Dentistry and Oral Sciences were conducted to specify articles associated with non-cariogenic sweeteners and their effectiveness in reducing incidences of caries; **Results and Discussion**: The majority of studies of xylitol have found an inhibition of growth of *S.mutans*, *S.sobrinus*, and *S.wiggsiae* when xylitol is consumed. Erythritol has shown more growth inhibition of *S.mutans* compared to other cariogenic pathogen. Stevia, at high concentrations inhibit the growth of *S.mutans*. Monk fruit extract and Synsepalum dulcificum have shown evidence of maintaining oral pH and inhibition of some cariogenic bacteria; **Conclusion**: The numerous and continuing studies of xylitol, indicate that it is still the most beneficial non-cariogenic sweetener in reducing cariogenic pathogens, however, some studies have shown a similar result when erythritol was used but there were more varying results with this sweetener as well as a lack of studies, more research needs to be done on erythritol's ability to inhibit cariogenic bacteria. Studies on monk fruit and Synsepalum dulcificum extract are lacking and more research needs to be done to establish the potential as non-cariogenic sweeteners.

Key words: 'Dentistry'; 'non-cariogenic sweetener'; 'artificial sweetener'; 'non-nutritive sweetener'; 'caries'.

Abbreviations: Streptococcus mutans (*S.mutans*), Streptococcus wiggsiae (*S.wiggsiae*), Streptococcus sobrinus (*S.sobrinus*), Lactobacillus salivarius (*L.salivarius*), Pseudomonas aeruginosa (*P.aeruginosa*), Escherichia coli (*E.coli*), Aggregatibacter actinomycetemcomitans (A. *actinomycetemcomitans*), Fusobacterium nucleatum (*F.nucleatum*)

Resumen

Introducción: El consumo de azúcar es un factor significativo en el proceso de desarrollo de caries. Con el 80% del mundo afectado por la caries dental, la convierte en la enfermedad no transmisible más prominente del mundo. Los edulcorantes artificiales pueden ayudar a reducir el consumo de azúcar y, por lo tanto, disminuir la incidencia de caries; **Objetivos**: El objetivo principal fue encontrar que edulcorantes no cariogénicos han mostrado los resultados más beneficiosos en la prevención de caries. El objetivo secundario era encontrar edulcorantes nuevos y futuros que puedan usarse potencialmente para prevenir la caries; **Materiales y métodos**: Se realizaron búsquedas en las bases de datos PubMed, Google Scholar y Dentistry and Oral Sciences para encontrar artículos asociados con edulcorantes no cariogénicos y su efectividad en la reducción de la incidencia de caries; **Resultados y discusión**: La mayoría de los estudios de xilitol han encontrado una inhibición del crecimiento de *S.mutans*, *S.sobrinus* y *S.wiggsiae* cuando este se consume. El eritritol ha mostrado más inhibición del crecimiento de *S.mutans* en comparación con otros patógenos cariogénicos. La stevia, en altas concentraciones inhibe el crecimiento de *S.mutans*. El extracto de fruta del monje y Synsepalum dulcificum han mostrado evidencia de mantener el pH oral e inhibir algunas bacterias cariogénicas; **Conclusión**: Los numerosos y continuos estudios de xilitol indican que sigue siendo el edulcorante no cariogénico más beneficioso para reducir los patógenos cariogénicos, sin embargo, algunos estudios han demostrado un resultado similar cuando se usó eritritol, pero hubo resultados más variables con este edulcorante, debido a la falta de estudios, se necesita más investigación sobre la capacidad del eritritol para inhibir las bacterias cariogénicas. Faltan estudios sobre la fruta del monje y el extracto de Synsepalum dulcificum y se necesita más investigación para establecer el potencial como edulcorantes no cariogénicos.

Palabras clave: 'Odontología', 'edulcorante no cariogénico', 'edulcorante artificial', 'edulcorante no nutritivo', 'caries'.

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1. INTRODUCTION

1.1. Caries etiology and causes

Dental caries is one of the most common prevalent oral diseases in people of all ages although it being more prevalent in children and adolescents. The cause of dental caries is multifactorial, those being diet, microbiota in the oral cavity, time given for the caries to develop and the tooth anatomy itself. The bacteria's primary energy source is the fermentable sugars being produced from our diet. The result is the production of acid by the bacteria, such as lactic acid and acetic acid, which leads to a reduction in the pH of the saliva which causes demineralisation of the hard tissue in the tooth. The combination of these factors can result in caries and looking specifically at the contribution of sugar in the development of caries and the fact that there is an increase in consumption of sugar rich foods and drink, alternatives have been introduced in an effort to reduce the average intake of sugar in the diet. Apart from an increase in consumption of a sugar rich diet, the frequency of consumption is also a major factor in caries development due to keeping the pH in the oral cavity low, leading to demineralisation and caries. (1)

This is demonstrated with the Stephan curve which describes the pH of the mouth in different phases which are divided into: the resting phase, which is the value of pH of plaque not exposed to sugars for at least 12 hours, the initial decline, decline of pH when exposed to sugar, the next phase is when the pH values fall under the 'critical pH', and the recovery phase where the pH returns to normal. The exact value of the critical pH has been debated where it can range from as low as 5.1 to 5.5 as the enamel generally begins to dissolve at 5.5 in saliva but may differ in plaque fluid. After a period of time the pH of the mouth returns to normal values, time varies with a number of factors such as salivary flow. The continued consumption of sugar will keep the pH reduced as long as there is availability of sugar and dental plaque is able to produce acid therefore keeping the pH at critical and increasing demineralisation of enamel. (2)

Although dental caries can occur anywhere on a tooth there are areas where the biofilm is allowed to accumulate and develop over a period of time, increasing the chances of developing caries. These areas protect the biofilm which allow it to develop, such areas include pits, fissures, and grooves on the occlusal surface of teeth. Also, the interproximal area of a tooth and along the gingival margin. There are other factors such as current fillings which have been inappropriately treated, leading to surfaces which favour biofilm accumulation, dentures and orthodontic appliances also provide a suitable environment for biofilm accumulation and therefore, caries development. (3)

The introduction of protective factors or pathological factors will shift between remineralisation and caries arrest or caries and progression of oral disease. The preventive factors include fluoride dental products such as toothpaste which remineralise the dental tissue while the pathological factors include diet (sugar). Some artificial sweeteners are seen as protective factors, most notably xylitol which is in various dental health products. (4)

Starches play a significant role in the diet, especially the Western diet, where the diet consists of 40-75% starch. These starches hydrolyse into multiple monosaccharides, such as glucose, providing substrates for oral bacteria. The clearance of sugars derived from starch in the mouth is longer in certain foods than others e.g. bread has a longer clearance time compared to rice and potatoes, indicating its retentive effect in the mouth. The combination of sugars and starch lead to the highest levels of lactobacillus and with the increasing frequency of consumption of foods containing these products has shown a rise in risk of developing caries. A diet consisting of starch with little to no sugar content, has been shown to decrease the risk of caries but this is not seen in the Western diet which contains more processed sugars and starch contents. This diet can cause abnormally high insulin secretion, which is associated with the disruption of the hormone, leptin. This hormone is responsible for the regulation of energy balance and hunger inhibition using signals to the brain when a sufficient consumption of food has been realized. The regular consumption of the Western diet can result in the disruption of the hormone which doesn't lead to the feeling of being full and causes a rise in snacking. The consumption of these retentive foods at regular meals as well as in

between meals for snacking, leads to the pH in the mouth staying under the critical pH of 5.5, promoting the development of caries. (5)

The control of sugar intake would greatly benefit oral health but also possible chronic diseases which would be prevented. The world health organisation (WHO) has recommended that the intake of free sugars for both adults and children be limited to under 10% of the total energy intake with a further 5% decrease being suggested to combat dental caries. As mentioned previously, the consumption of sugar has increased with a 15-21% of total energy intake being consumed by adults and 16-26% of total energy intake being consumed by children. (6)

1.2. Oral health diseases due to sugar consumption

Dental caries affects approximately 2.3 billion adults and 530 million children across the world. The consequences of caries can be minimal, or it could evolve into more serious problems such as infections, pain, abscesses which could lead to tooth loss and even sepsis. Due to the frequency of this and the possible consequences if not treated quickly, it can have a huge financial burden on the health care system. It has been estimated that dental caries accounts for approximately 5-10% of the total budget for health care in industrialised countries. (6)

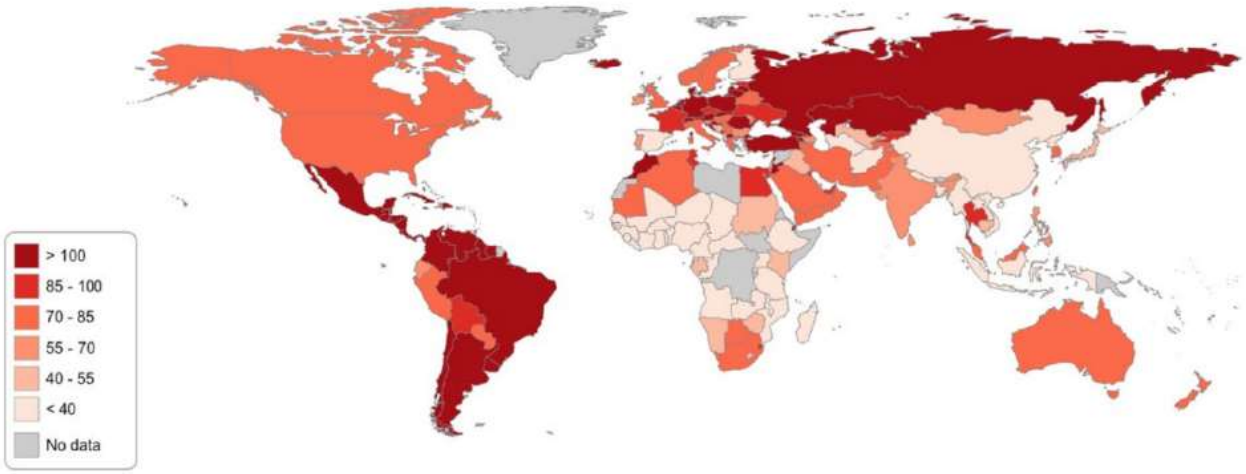

Figure 1. Oral health diseases related to sugar consumption. (7)

The map indicates the number of oral health diseases related to sugar consumption. The difference in prevalence in disease can be due to a number of factors such as improper education on the importance of oral hygiene and the facilities to be able to get such diseases treated. The consequences of sugar consumption can lead to multiple oral health diseases which include caries, periodontal disease, severe tooth loss and edentulism. In 2010, disability-adjusted life years (DALYs) of 4.1 million in dental diseases due to sugar with 1.9 million being caries, 1 million for periodontal disease, and 1.2 million for severe tooth loss/edentulous. The extent of these oral diseases due to sugar has resulted in an approximate 172 billion US dollars in financial burden worldwide. (7)

In the Global Burden of Disease Report in 2015, permanent tooth decay was listed as first, with caries being the most common non-communicable chronic disease. 80% of the world Is affected by caries with the main factor being the consumption of sugar. This is demonstrated in studies on restricting sugar in school children's diet had shown a positive effect on their oral health. Sugar has been linked to a number of diseases such as impaired cognition, obesity, diabetes mellitus, cardiovascular diseases, cancer, and dental caries. This demonstrates the importance of regulating sugar consumption as well as having alternatives to sugar in an effort to reduce oral health diseases which is both beneficial to the individual's health as well as the health services. (8)

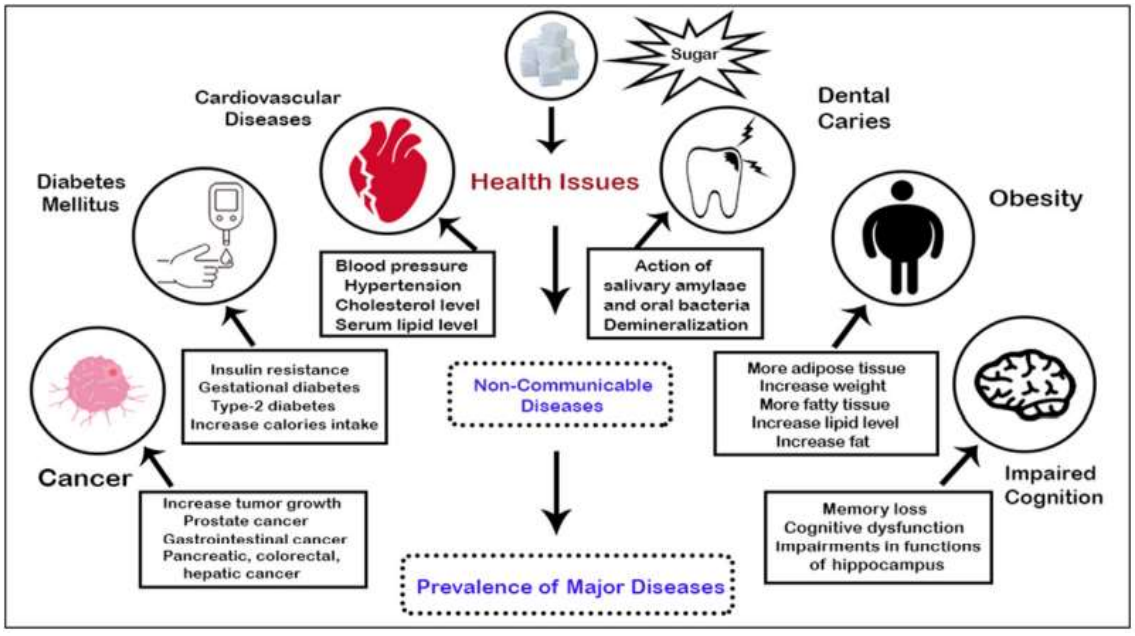

Figure 2. The different health issues associated with excess sugar consumption. (8)

1.3. Sugar consumption in different countries

Country	n	Total Sugar Intake														
		g/Day					%TE					%CHO				
		Mean	SD	P25	P50 [2]	P75	Mean	SD	P25	P50 [2]	P75	Mean	SD	P25	P50 [2]	P75
Argentina	1266	115.2	53.2	75.5	107.5 [a]	145.0	21.1	7.1	16.2	20.8 [a]	25.5	40.3	10.8	33.3	40.6 [a]	47.9
Brazil	2000	86.2	39.3	58.5	80.9 [b]	107.4	19.1	6.5	14.8	19.0 [b,c]	23.3	37.0	10.5	30.2	37.4 [b]	44.1
Chile	879	84.9	33.9	60.5	80.0 [b]	104.8	19.8	5.6	16.0	19.7 [b]	23.3	36.3	8.5	30.9	36.6 [b,c]	41.6
Colombia	1230	109.8	34.4	85.7	105.6 [a]	128.8	20.9	4.8	17.6	20.7 [a]	23.8	38.4	7.1	33.6	38.5 [d,e]	43.1
Costa Rica	798	95.8	39.1	68.3	91.5 [c]	116.1	20.7	6.1	16.6	20.6 [a]	24.4	35.5	9.1	29.7	35.4 [c]	41.6
Ecuador	800	102.4	35.1	78.4	98.1 [d]	120.4	18.7	4.6	15.4	18.6 [c]	21.7	33.8	7.1	29.1	34.0 [f]	38.5
Peru	1113	106.4	34.8	82.2	101.8 [a]	126.1	20.4	4.8	16.9	20.3 [a]	23.5	31.1	7.0	26.3	31.1 [g]	36.1
Venezuela	1132	98.8	39.1	70.7	93.0 [c,d]	122.0	20.7	5.9	16.8	20.8 [a]	24.5	38.6	8.9	32.8	38.9 [e]	45.0
All	**9218**	**99.4**	**41.0**	**70.9**	**94.6**	**121.0**	**20.1**	**5.9**	**16.2**	**20.0**	**23.8**	**36.7**	**9.4**	**30.5**	**36.8**	**42.8**

Table 1. Total sugar intake in Latin American countries. (9)

Country	n	Added Sugar Intake (from Total Sugar)														
		g/Day					%TE					%CHO				
		Mean	SD	P25	P50 [2]	P75	Mean	SD	P25	P50 [2]	P75	Mean	SD	P25	P50 [2]	P75
Argentina	1266	91.4	55.2	51.2	82.4 [a]	122.9	16.4	7.5	11.1	15.7 [a]	21.2	31.0	12.2	22.3	31.3 [a]	39.7
Brazil	2000	57.6	34.1	32.4	52.4 [b]	76.3	12.6	6.0	8.0	12.2 [b]	16.4	24.3	10.2	16.9	24.2 [b]	31.3
Chile	879	52.3	28.4	31.4	47.9 [c]	68.5	12.0	5.2	8.3	11.8 [b,c]	15.6	22.0	8.7	16.0	21.9 [c]	28.2
Colombia	1230	59.5	24.1	42.7	56.6 [d]	73.5	11.4	4.0	8.7	11.2 [c]	13.8	20.9	6.7	16.4	20.6 [c,d]	25.2
Costa Rica	798	68.5	33.6	45.1	64.6 [e]	85.7	14.7	5.6	10.8	14.3 [d]	18.2	25.2	8.8	18.5	25.2 [a,e]	31.3
Ecuador	800	56.2	23.7	39.2	53.0 [b,d]	68.9	10.3	3.8	7.6	10.0 [e]	12.2	18.6	6.1	14.4	18.2 [f]	22.5
Peru	1113	70.4	29.9	49.9	66.5 [e]	87.6	13.4	4.5	10.3	13.2 [f]	16.3	20.5	6.7	15.8	20.1 [d]	24.9
Venezuela	1132	67.0	30.6	44.3	61.7 [e]	84.9	14.0	5.1	10.5	13.8 [d,f]	17.2	26.2	8.5	20.2	26.0 [e]	32.1
All	**9218**	**65.5**	**36.5**	**41.1**	**59.4**	**82.5**	**13.2**	**5.8**	**9.2**	**12.6**	**16.5**	**23.9**	**9.7**	**17.1**	**23.1**	**30.0**

Table 2. Added sugar intake in Latin American countries. (9)

Country & year of survey	Adults						Children					
	Total sugar intake (g/day)-mean ± SD			Total sugar contribution to daily energy intake (%)- mean ± SD#			Total sugar intake (g/day)-mean ± SD			Total sugar contribution to daily energy intake (%)- mean ± SD#		
	Female	Male	Both	Female	Male	Both	Girls	Boys	Both	Girls	Boys	Both
Belgium, 2004	97.1*	132.5*	115.3*	20.9 ± 6.2	19.1 ± 5.4	19.9 ± 5.8	121.5*	180.1*	150.3*	23.9 ± 5.7	25 ± 7.3	24.5 ± 6.6
France, 2007	84.8 ± 31.2	97.9 ± 46.1	91.1 ± 38.5	17.6.0 ± 4.9	15.0 ± 5.6	16.41 ± 5.4	87.2 ± 29.2	99.7 ± 34.9	93.6 ± 32.6	20.8 ± 4.7	20.6 ± 5.0	20.7 ± 4.8
Ireland, 1997–99	Not available		108.3 ± 44.8	Not available		16.8 ± 4.8	Not available		108.5 ± 43.0	Not available		20.4 ± 5.0
Italy, 2005–06.	79.5 ± 33.4	86.0 ± 37.7	82.5**	15.4 ± 5.1	13.5 ± 4.7	14.5**	88.4 ± 35.6	107.6 ± 53.7	96.8**	15.8 ± 5.2	15.4 ± 4.7	15.6**
The Netherlands, 2007–10	108.3 ± 47.4	125.5 ± 60.5	116.9 ± 55.4	21.3 ± 6.8	19.7 ± 7.3	20.5 ± 7.1	133.9 ± 23.5	151.9 ± 28.3	143.1 ± 26.5	25.9 ± 3.5	25.8 ± 3.6	25.8 ± 3.5
Spain, 2013	72.4*	78.6*	75.8*	17.3	16	16.7	87.5*	89.7*	89.3*	19.2	16.9	17.7
United Kingdom, 2008–12	84.6 ± 39.4	105.6 ± 48.3	93.4**	20.5 ± 6.8	19.8 ± 6.6	20.2**	92.3 ± 34.6	108.8 ± 42.4	100.7**	22.6 ± 6.3	22.7 ± 6.2	22.7**

Table 3. Total sugar intake in European countries. (10)

Country	Adults						Children					
	Added or NME sugar intake (g/day)-mean ± SD			Added sugar contribution to daily energy intake (%)-mean ± SD			Added or NME sugar intake (g/day)-mean ± SD			Added sugar contribution to daily energy intake (%)-mean ± SD		
Adults	Female	Male	Both	Female	Male	Both	Girls	Boys	Both	Girls	Boys	Both
Denmark	43.0 ± 30.2	56.0 ± 44.6	49.0 ± 38.4	8 ± 5.0	8 ± 5.4	8 ± 5.2	53 ± 34.4	67 ± 34.3	60 ± 35.1	11.0 ± 5.0	11.0 ± 5.0	11.0 ± 5.0
France	41.6 ± 25.6	49.6 ± 38.5	45.4 ± 31.7	8.5 ± 4.5	7.5 ± 5.1	8.0 ± 4.8	50.3 ± 21.8	62.6 ± 29.3	57.1 ± 26.2	12.2 ± 4.12	12.9 ± 4.7	12.5 ± 4.4
Hungary	44.0 ± 26.2	50.2 ± 35.3	46.1 ± 30.7	8.2 ± 4.3	7.0 ± 4.4	7.6 ± 4.4	Not available					
Ireland	Not available		61,9 ± 3 7,7	Not available		9,4 ± 4,3	Not available		65,7 ± 31,6	Not available		12,4 ± 4,9
Norway	36 ± 30	48 ± 43	42 ± 38	7,4 ± 5,2	7,2 ± 5,7	7,3 ± 5,4	Not available					
The Netherlands	68.2 ± 44.3	83. 9 ± 55.9	76 ± 51.3	11.1 ± 6.4	11.3 ± 6.4	11.2 ± 6.6	98.2 ± 21.3	113.7 ± 26.8	106 ± 24.7	17.1 ± 3.5	16.5 ± 3.3	16.8 ± 3.4
United Kingdom	41.6 ± 35.0	62.2 ± 41.8	50.2*	11.1 ± 6.3	11.9 ± 6.0	11.4*	61.5 ± 30.4	74.6 ± 38.6	68.1*	14.8 ± 5.8	15.4 ± 6.1	15.1*

Table 4. Added sugar intake in European countries. (10)

Previously mentioned, the WHO recommended the intake of sugar to be 10% of the total energy intake per day to reduce the risk of developing a non-communicable disease, decreasing this to 5% total intake in preventing caries (5). The information gathered on sugar consumption in both Latin American countries and European countries, indicate that regardless of location, both the total sugar intake and the added sugar intake is beyond the recommended threshold for both reducing the risk of non-communicable diseases and caries prevention. Table 1 shows the mean total intake of sugar per day of Latin American countries to be 99.4 grams which contributed to 20.1% of the total daily energy intake which is double the threshold suggested to reduce non-communicable disease risk and four times more than the suggested intake to reduce caries development. Similarly, the European countries studied had shown an overall mean of 97.6 grams of sugar consumed per day which contributed to 17.8% of the total energy intake which is still 7.8% over the threshold to reduce non-communicable disease risk and over three times the recommended intake for caries prevention. Although, there are some value differences depending on the individual country, all values were above the recommended threshold for both non-communicable disease risk reduction and caries prevention. (10)

In the 1990s, sugar substitutes were not normalised and many medications, especially for paediatric patients, contained sugar to give a pleasant taste and make the intake of medicine more palatable. In this period, over the counter medicine for children in New

Zealand contained sugar, in the north-east of England 59% of long-term use liquid oral medications contained sugar and there is an association of these medicines in chronically ill children and an increase in prevalence of dental caries with the primary sugar used being sucrose. The use of sucrose in these medicines are due to ease of processing and cost effective which is a big factor that as impeded the development of sugar-free alternatives. There have been calls for sugar-free alternatives, especially from parents and there are a higher number of medicines which incorporate this with common sweeteners used such as xylitol, sorbitol, mannitol, and aspartame. (11)

In these medicines, it is common to find sucrose in the form of lozenges, antibiotic syrups, vitamin preparations and cough drops. There are differences in the amount of sugar depending on the daily intake of the medication, for e.g. if a medication is needed 3-4 times a day, the sugar content is lower in these medications than in medications which only require one daily dose. Apart from sugar, acids such as citric acid are also added to improve taste which can lead to dental erosion. (12)

The issue with certain treatments is patient compliance which is particularly a concern in paediatric patients and can lead to consequences in effectiveness of a treatment. If the medication contains sucrose, it is important to maintain a good oral hygiene to minimize the negative impacts, although there is still an increased risk of caries development, especially in longer term treatments. The use of sugar these medicines can also be a problem in children with diabetes as it has the potential of raising plasma glucose levels. Despite there being more availability of sugar alternatives in medicine, the market continues to offer sugar sweetened medicine due to cost and ease of processing. The methods of consumption of medicine in children can help palatability, such as modified feeding bottles with the medicine submerged in a reservoir. Such methods and movement towards alternative sweeteners will allow more options in finding treatments, tailor-made for each child. (13)

The introduction of artificial sweeteners has been very common in beverages. Soft drinks contain a high amount of sugar and in a bid to reduce sugar intake, diet drinks were created with reduced or no sugar at all. With the lack of sugar, it is seen as likely to be beneficial to the oral cavity as sugar is a huge cariogenic factor. However, these sugar free drinks use food acids to enhance and give different flavours into these drinks

which could be calcium-chelating. Citrate is a component which causes dental erosion, lowering the pH to approximately 3, surpassing the critical pH for demineralisation of the enamel. Individuals with poor quality saliva or salivary flow problems are more prone to dental erosion. The erosion of the tooth increases the chance of developing dental caries, suggesting these sugar alternative drinks can be misleading in terms of benefitting the oral health and perhaps a misuse of their potential purpose. (14)

1.4. Sweeteners classification

Sweeteners are classified based on their sweetening power, nutritive value and place of origin. They are classes into nutritive and intense groups (most commonly used), and synthetic and natural. (15)

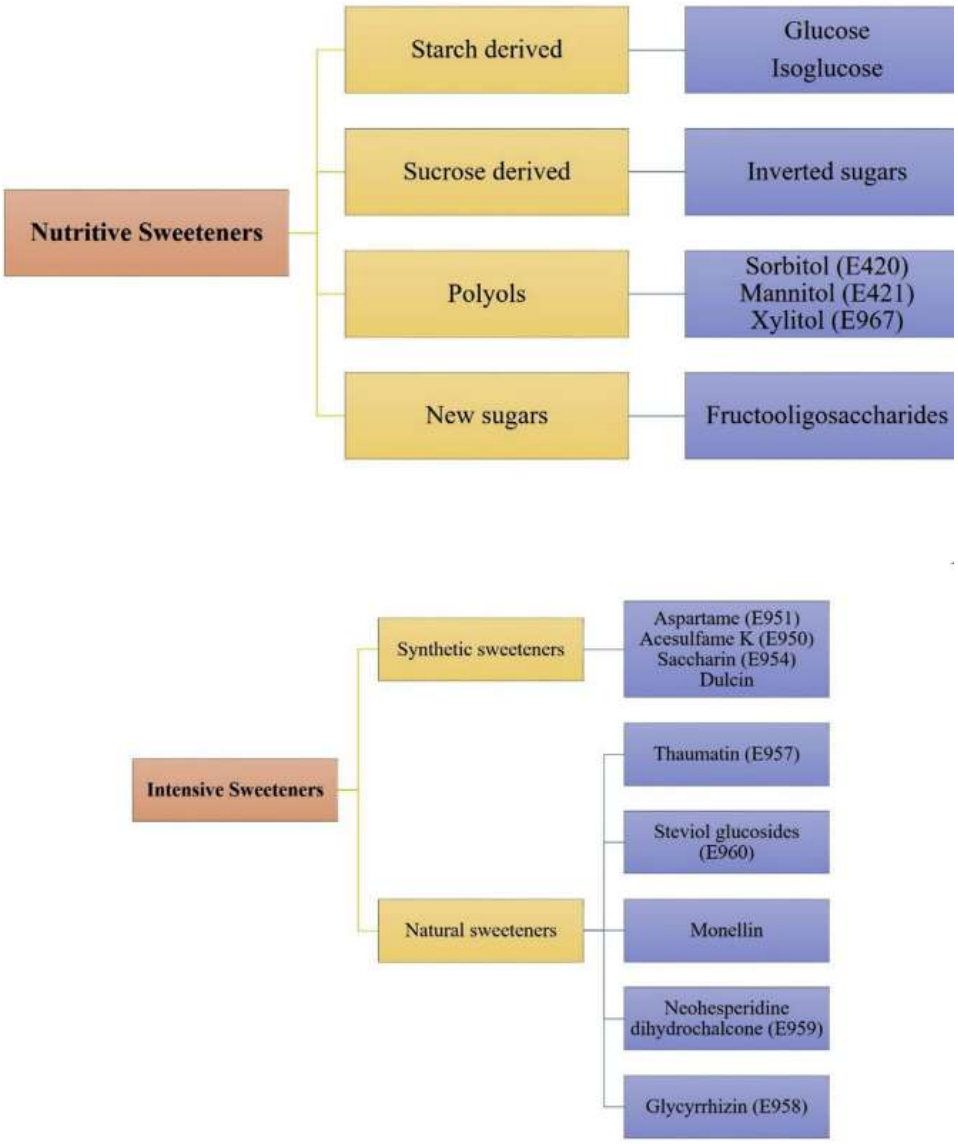

Figure 3. Classifications of sweeteners. (15)

Polyols

Polyols sweeteners classification are among the most consumed sweeteners on the market. These sweeteners are produced by hydrogenation of reducing sugars, replacing a carboxyl group with an alcohol group. They are very commonly used because they do not interfere with Maillard reactions which give food its distinct flavours and are stable at high temperatures. These sweeteners can be found naturally in fruits and vegetables and have been around in the market since the 1920s. These sweeteners are not recommended for children under the age of one as they can cause diarrhoea. (15)

Sorbitol has a sweetening power of 60-70% that of sucrose and is the most frequently added polyol to foods. Although it is considered non-cariogenic, during its metabolism bacterial plaque may be able to produce acid in the mouth but this process is very slow. This polyol has been associated with gastrointestinal issues which include malabsorption and diarrhoea. Mannitol has a sweetening power of 50-70% that of sucrose. If the intake of mannitol is over 20g, it is known to have a laxative effect on some individuals. It is most commonly used in the form of chewable tablets in medications due its sweetness, negative heat of solution, and mouth feel. (13)

Xylitol is one of the most used sweeteners in dentistry. It was first produced in 1891 and it has a very high sweetening power to that of sucrose with 95%, out of all the polyols, it is the sweetest and due to its beneficial properties for dental hygiene, it has a market of approximately 670 million dollars across the world and has been increasing 6% every year. (15)

Erythritol, a four-carbon polyol, has only been more recently studied on its oral health benefits, with the studies being after the year 2000. It does not have laxative effects unlike some other sweeteners which makes it more viable as a sugar alternative. Erythritol has been suggested to have even greater beneficial effects on preventing caries than that of xylitol. (16)

Intense sweeteners

Intense sweeteners, as the name suggests have an intense sweetening power, higher than that of sucrose, needing little quantity to achieve the sweetening effect and offer little to no energy. They do not act as an energy source for bacterial plaque and so are not cariogenic. They can be split by synthetic and natural classifications. (13)

Synthetic

The more commonly used sweeteners include aspartame, acesulfame K, saccharin, cyclamates, and sucralose. Aspartame was first discovered in 1965, it has little solubility in water and its pH is unstable and so is unable to be used in already acidic drinks. It has a sweetening power of 180-200 times more than sucrose and does not present a sour

or metallic taste. It does contain phenylalanine and so is not recommended for individuals with phenylketonuria and has a admissible daily intake of 40mg/kg. (15)

Acesulfame K, discovered in 1967, has a sweetening power of over 200 times more than sucrose and does not have residual flavour, making it the more common of the synthetic sweeteners used nowadays. Its admissible daily intake is 15mg/kg due to its metabolization in the body and has synergistic effects with other sweeteners to further add sweetness and flavour to foods. (15)

Aspartame, the ADI is 40mg/kg a day. With a sweetening power of approximately 200-fold that of sucrose, it makes it an attractive alternative to sugar. The composition of aspartame consists of L-phenylalanine and L-aspartic acid and through digestion releases 10% methanol, 40% aspartic acid and 50% phenylalanine. This release of phenylalanine makes this sweetener unsuitable for individuals with the genetic disorder phenylketonuria, leading aspartame to be clearly labelled as containing phenylalanine by the FDA. (17)

Saccharin, has a sweetening power of 200-500 times than sucrose, is generally used in hypocaloric food products, and it is also non-cariogenic. Although there is no evidence of carcinogenicity in humans, there have been reports of its carcinogenic potential in animal studies. It has also been linked to cross-sensitivity reactions in individuals that have a sulfonamide allergy. (13)

Sucralose is approximately 600 times sweeter than sucrose and it is produced via chemical synthesis with a reaction of thionyl chloride and sucrose, and like these other classifications of sweeteners, it contains no calories, no nutritional value, and it is non-cariogenic. (13)

<u>Natural</u>

The most common of the natural sweeteners' classification is steviol glycosides, thaumatin, and neohesperidine dihydrochalcone. Steviol glycosides are derived from the plant Stevia rebaudiana Bertoni, the leaves themselves aren't allowed within the EU but purified into steviol glycosides contain a high concentration of steviosides which are

permitted and are used as a sweetener. Steviol glycosides are a combination of mainly steviosides and rebaudiosides, with type A being the sweetest compound. This results in a sweetening power 300 times that of sucrose and has an admissible daily intake of 4mg/kg. It has little to no calories and has anti-inflammatory and diuretic effects. It works from pH 2-10 and is relatively heat stable. (15)

One of the main concerns of artificial sweeteners is their side effects. Some are well documented and mild while others have been linked to more severe adverse effects with more studies needed for confirmation which could inhibit the progression of the use of sweeteners in a day-to-day diet. In general, polyol sweeteners contain known side effects when there is overconsumption but are not associated with significant symptoms in the digestive system. The overconsumption adverse effects include gastrointestinal symptoms, abdominal pain, diarrhoea, bloating and can act as a laxative. (18)

1.5. Aspartame

Although little evidence in humans, aspartame has been studied in rats and how it affected their offspring. The results in the study had displayed a more negative effect in the male offspring, presenting higher levels of obesity, a negative effect on glucose and insulin tolerance, as well as a deviation in gene expression in a dopaminergic pathway reward system. These offspring when matured into adults had shown an increase in weight, higher plasma glucose levels, and an increase in LDL and cholesterol in general compared to rats whose mother had not consumed aspartame. These effects have linked aspartame with other diseases such as type 2 diabetes, cardiovascular diseases, some hormone related cancers, and non-alcoholic fatty liver disease. (17)

Aspartame has also been linked with behavioural and neurological disorders e.g. headaches, seizures and depression. The increased consumption of aspartame elevates plasma phenylalanine levels, competitively inhibiting tyrosine hydroxylase and tryptophan hydroxylase which is the rate-limiting enzyme for the neurotransmitters serotonin and dopamine synthesis. The reduction in the level of these neurotransmitters

leads to neurological disorders such as depression. Despite this link, there has been a lack of evidence of the negative effects of aspartame. (17)

This particular sweetener has been linked various types of cancer. Multiple studies have been done to study the possible carcinogenicity with none conclusively confirming its carcinogenic characteristics in humans. In fact, there are a considerable amount of studies which are in support of its safe use in foods and beverages. The mutagenicity potential of aspartame has been studied on various strains of Salmonella typhimurium with metabolic activation and without, with results presenting negative. Positive results were seen when nitrosation of aspartame was done but due to this not having physiological relevance, it is not able to be translated into genotoxic potential in humans. There was also no sister chromatid exchanges observed in both in vivo and in vitro studies. There is some evidence of chromosomal alterations in vitro and statistically significant chromosomal alterations when lymphocytes, which were cultured from humans were exposed to different concentrations of aspartame in 24 hours but this was seen as an indirect cytotoxic effect due to the introduction of very high doses. (19)

DNA damage was also studied using the comet assay to identify any damage. An experiment with rats being administered 75 or 1550mg/kg of aspartame for 4 weeks had seen a positive result in the heart, kidney, and liver tissue. Another saw a positive result was seen in the bone marrow with a single low dose of 35mg/kg after 18 hours. However, these experiments were not seen to follow the relevant guidelines set by the Organisation for Economic Co-operation and Development, especially with the single dose results as at least two doses or two different time points need to me measured. (19)

A longer study on mice was performed in 2010 where rats were exposed to aspartame from the 12^{th} day of gestation until death with different daily doses of aspartame being administered. The animals remaining at the age of 130 weeks were euthanised and their organs and tissues e.g., heart, brain, liver, lung, kidney, etc. were harvested and evaluated to identify any pathological changes. This study did not observe any significant differences in tumour incidences between the control groups and the aspartame exposed groups. There had been a difference in hepatocellular carcinomas in the male

mice depending on the dose given with 15.6% diagnosed at 16,000ppm and 18.1% at 32,000ppm, compared with the control group at 5.1%. However, in this study, these values were in the control range. Similar results were found in hepatocellular adenomas and alveolar/bronchiolar carcinomas observed with dose-related incidences, but these values were also in the control range in the study. Thus far, there are no studies which conclusively prove aspartame can cause genotoxicity in humans, especially at the ADI as these studies use doses far above what is advised per day. (20)

Although not extensively studied, there has been links of artificial sweeteners and negative effects on foetuses and early childhood via second hand intake, i.e., the mother consuming artificially sweetened products during pregnancy. In Canada a study had observed that 30% of pregnant women had consumed artificial sweeteners during their pregnancy with those who consumed them daily had 2x risk of the child being overweight by the age of 1. Another study in Denmark had seen 50% of mothers consuming artificial sweeteners, with 9% of those consuming them daily. The results showed that they had a higher risk of having children who were considered large for gestational at birth and presented an increased risk of overweight or obesity by the age of 7. Despite these results, there are limited studies surrounding this topic which need to be investigated further as other factors may be involved in producing these negative consequences. There has also been links of increased risk of preterm delivery with sweeteners but again with limited studies and also links between this and sugar, more studies need to be conducted to confirm these links. Although alternative sweeteners have been considered in patients who present obesity or diabetes, the taking of these sweeteners by the mother during pregnancy may actually negatively impact the very diseases these sweeteners were considered to be used for. These studies were observational and so the cause of these changes cannot be conclusively deduced without further investigations. (21)

1.6. Artificial sweeteners and diabetes

The replacement of sugar with artificial sweeteners may be beneficial for patients with diabetes due to the negative effects of sugar as they are seen as metabolically inert so in theory can be effective in diabetic patients. However, there are suggestions that the increased consumption of artificial sweeteners result in glucose intolerance and alteration of the gut microflora. Currently in adults it is recommended by dieticians and clinicians, when it comes to children, they seem to take a more cautious approach, indicating that not enough information on artificial sweeteners is available to completely confirm their lack of negative impacts. This could be because the effects of sweeteners are observational as well as many randomised controlled trials obtaining conflicting results. There are suggestions that the effects of non-nutritive sweeteners on the gut microflora can vary depending on the individual which could lead to these conflicting results. (22)

Sucralose is one of the more studied sweeteners on their effects on glycaemic response and plasma insulin levels. Using the glucose tolerance test at week 4 and then 8, the results did not show any effect on plasma insulin or glycaemic response in healthy mice, humans, and individuals with diabetes and even some cases of improving glucose tolerance mice on a high fat diet. However, in obese individuals which do not consume artificial sweeteners, an acute dose of sucralose had shown an elevation in peak plasma glucose as well as insulin concentration. There has been varying results in regard to liver toxicity in mice with some studies observing hepatocyte degeneration, although this occurred with a much higher dose than the recommended ADI and this was not seen in mice which consumed close to the ADI. It is thought that sucralose begins to interact in the intestine and communicates with pancreatic beta cells which stimulates insulin secretion. (23)

A study on saccharin and sucralose was done to investigate its influence on glucose tolerance recorded using a glucose tolerance test. With a control group using glucose, it was seen that the glycaemic response of both saccharin and sucralose was significantly higher than that of the glucose group in the exposure period. The doses of saccharin and sucralose were lower than the advisable daily intake and the results indicate that they can have an impact on the glycaemic response in healthy individuals. The same tests were done with aspartame and stevia which did not display significant effects on

glycaemic response. It is hypothesized the intestinal microflora could be a factor in this glycaemic response, with sucralose having the greatest impact on glycaemic response and its poor absorption, suggesting there is more interaction with the intestinal flora. There was microbiome interactions found in sucralose, saccharin, stevia, and aspartame. Non-nutritive sweeteners may inhibit the growth of microbes, seen in faecal matter in animals exposed to sucralose or saccharin which presented a reduction in bacteria. It is known how non-nutritive sweeteners target the bacteria but there are suggestions that they can affect membrane permeability, increase the frequency of mutations, and inhibition of transport of glucose/sucrose to the bacterial cell. These results indicate that non-nutritive sweeteners may not be entirely metabolically inert, and more research needs to be done on their interactions with bacteria and its use for disease prevention or control with diseases such as diabetes. (12)

1.7. Xylitol

Xylitol has been linked to a reduction of S. Mutans and/or lactobacilli due to its anti-cariogenic properties and it is not fermented by the majority of cariogenic bacteria. The recommended dose of xylitol for the cariogenic preventative effect is 6-10g/day and it is being used in gum, dental products such as toothpaste and mouthwash. (23)

To obtain the beneficial effects of xylitol such as remineralisation, the use of the compound is needed frequently which may be an issue in regard to patient cooperation. It has therefore been included into varnishes so there is a steady release of xylitol being increased the saliva which does not need patient cooperation. The adhesion of the varnish to the enamel surface is long-term and so allows the time for xylitol to remineralise enamel and prevent caries. This allows another option for caries prevention on high-risk patients, including patients with orthodontic brackets which have a higher risk of white lesions forming due to aggregation of bacteria. (24)

This type of varnish may be especially beneficial in children as immature teeth which have recently been erupted are more at risk of caries development than permanent dentition. In the post-eruptive maturation phase of the teeth, chemical changes such as

fluoride are integrated into the enamel as well as other ions which decrease enamel solubility. Due to the greater susceptibility of both remineralization and demineralization in post-eruptive teeth, xylitol varnish is an alternative which can greatly reduce the susceptibility of caries development in children. (25)

The use of xylitol in different forms such as, mouth rinses, candies, gum etc vary in their effectiveness in caries prevention. Some studies have shown that xylitol in mouth rinses have not had the same effect as in chewing gum and wipes on reducing S. Mutans and so the form in which xylitol is administered is important in effective caries prevention. (16)

Chewing gum containing xylitol seems to be the most effective way of utilizing the anti-cariogenic effects of xylitol due to it remaining in the mouth for longer periods of time as well as ease of use which is particularly useful in children and disabled patients. It has also been linked to preventing periodontal disease as well as caries with the suggestion that short-term use of xylitol may reduce the pro-inflammatory cytokines which are involved in the development of periodontal disease. (26)

However, there are conflicting evidence when it comes to quantity and frequency to gain their anti-cariogenic properties. In many studies measuring the effectiveness of xylitol, the amount of xylitol used varied from as low as 200mg per day to 8g a day and so showed different results in terms of the compound's effectiveness. There seems to be a threshold of 5-6g per day which is divided by three or more doses in a day with anything below this dosage showing a minimal effect on reducing S. Mutans and therefore, caries. (27)

The effectiveness of xylitol in chewing gum in caries prevention has been studied more extensively than that of mouth rinses. Chlorhexidine mouthwash has been seen as very effective in reduction of cariogenic bacteria in the mouth but with possible side effects such as staining teeth and burning sensation, it results in less patient cooperation. Alternatives to this are being studied which include xylitol rinses and also probiotic rinses. Although a study comparing the three rinses had shown chlorhexidine being the most effective and xylitol being the least effective, it can be argued that since they all reduce S. Mutans in the mouth by a significant amount, the use of any of these rinses

are better than none at all, allowing alternatives to chlorhexidine and its undesirable side effects. (28)

Multiple studies of the preventative fraction of xylitol on caries prevention yield various percentages in terms of effectiveness although the majority show a reduction in developing caries. The cause of these variations are thought to be because of the method of xylitol intake, depending on the method on intake, there may be additive factors which contribute to caries prevention, for e.g., using sugar free gum with xylitol can stimulate saliva secretion which doesn't occur in some other forms of xylitol intake. (29)

Certain polyols such as xylitol could also be beneficial for prevention of dental fluorosis. With extensive studies on fluoride showing its effectiveness in reducing caries probability, dental products containing fluoride are essential for prevention. Regarding dental fluorosis, one way of preventing this is reducing the ppm of fluoride used, however, this would increase caries risk. The addition of other caries preventing compounds have been considered and are being implemented in fluoride containing products to reduce both caries and the risk of dental fluorosis. (30)

Xylitol has been shown in past and recent studies to be the sweetener of choice in caries prevention due to its ability to not only prevent caries development, but also to remineralize enamel. It is one of the most studied non-cariogenic sweetener and continuous studies are being done to determine what roles it can play in various dental and consumer products. However more recent studies on erythritol have shown evidence of remineralization as well as more significant caries prevention characteristics than some other sweeteners which are used in products to reduce caries. A quality of erythritol which is attractive and not seen in many other sweeteners includes not inducing diarrhoea and bloating due to only a small portion being passed through the small bowel. (31)

1.8. Erythritol

Erythritol demonstrates a high ability of minimizing the adherence of *S.mutans*, which has been shown to be more effective than xylitol in this regard. This would make it a useful product to add in dental products and to increase the caries preventive effects of low fluoride toothpastes. Aside from the added protection to caries with addition of these polyols, it will also prevent dental fluorosis which can be a significant risk in children that are not supervised when brushing, reducing the chronic toxicity of the compound on the tooth. (30)

Studies also compared the specific polyols, erythritol and xylitol, on their individual effects on cariogenic bacteria in the mouth as well as possible synergistic effects of these polyols and whether a combination of the two would be more beneficial for the oral cavity or the use of the polyols individually would yield better results. Erythritol had shown a superior inhibitory effect on the adherence of *S.mutans*, while xylitol was more effective in inhibiting the growth of *S.sobrinus* and *S.wiggsiae*. The effectiveness of caries prevention may then be dependent on the individual, as the profile of pathogens found in the oral cavity are different and therefore, some may benefit from one polyol than another. (32)

There is a concern for the appropriate use of artificial sweeteners to maximize the preventive effects against caries. A study was performed to observe the inhibitory effects of different concentrations of xylitol and sorbitol on S. mutans and C. albicans single species biofilm formation. Xylitol and sorbitol did not present any synergistic effects but individually did reduce S. mutans biofilm formation. They did not affect C. albicans single species but did reduce it when in the presence of sucrose. However, the inhibitory effects of xylitol and sorbitol where reduced when in the presence of sucrose as it presented higher accumulation of S. mutans and an increased production of glucans. This study suggests that regardless of the use of non-cariogenic sweeteners for improving oral hygiene, if the individual does not decrease sugar consumption, especially at the times the sweeteners are consumed, the inhibitory effects for S. mutans may not be adequate to prevent caries. (33)

1.9. Stevia

Other sweeteners being marketed and are becoming popular include Stevia, normally being used in South America, has made its way in Europe, and is becoming increasingly common. Concerns for not only stevia but other non-cariogenic sweeteners consists of their purest form not being sold but rather, a commercial version which has other additives incorporated in the product which stops it from being non-cariogenic. (34)

In a study comparing chlorhexidine and stevioside mouthwashes displayed an inhibitory effect against S. mutans in both groups, however the inhibitory effects were stronger in the chlorohexidine group. Also, both presented antimicrobial properties in the mouth but again, stevioside had less effect compared to chlorhexidine. Despite it having a lesser inhibitory effect against cariogenic bacteria, it is a promising look at Stevia's potential as a non-cariogenic sweetener in the market, already steadily becoming more popular in the market. Its bacteriostatic properties decrease the risk of plaque build-up and gingivitis, increasing its viability as a replacement for sucrose. (35)

A study on Stevia by Giacaman R et al. had also seen a decrease in the amount of *S. mutans* in the oral cavity but there was no complete eradication of the bacteria. Stevia had shown a bacteriostatic effect on S. mutans but not a bactericidal quality in this study. The addition of stevia has also shown an increase in the pH of the mouth, leading to a protective factor against caries development. It has shown to have the greatest inhibitory effect on Lactobacillus bacterial strains and a to a lesser extent, *S.sobrinus* and *S.mutans*. More in vivo studies need to be done on stevia to determine the extent of effectiveness it has against caries development and overall benefit to the oral cavity. (36)

The usual glycosides used are stevioside and rebaudioside A. Stevioside is about 200-300 times sweeter than sucrose, while rebaudioside A is about 250-450 times sweeter than sucrose. It's an attractive substitute to sucrose with its various benefits such as its antihypertensive, anti-hyperglycemic, anti-diarrheal, diuretic, anti-inflammatory, and immunomodulatory properties. (37)

1.10. Synsepalum dulcificum

Potential on possible future sweeteners include Synsepalum dulcificum. It is commonly known as 'miracle fruit' due to its ability of making our taste perceptions change from a sour taste to a sweet taste when the fruit is eaten. It has very limited studies on its use in oral health but a study by Ibrahim et al, 2020 have specifically looked at its effects on S. mutans and *S.sobrinus*, which are the most cariogenic bacteria found in the mouth, as well as *L.salivarius* which is a probiotic, protecting the oral cavity from Streptococci bacteria and Candida. Synsepalum dulcificum has also been shown to have anti-oxidant, anti-mutagenic, anti-microbial and anti-diabetic properties, displaying its potential for various products, including oral healthcare. (38)

1.11. Monk fruit

Siraitia grosvenorii, also known as monk fruit, has a sweetening power of 100-250 times that of sucrose. Studies on this fruit have identified various health benefits such as antibacterial, anti-inflammatory, anti-diabetic, and anti-hyperglycaemic properties. The main extract of this fruit is mogroside V which has also shown antioxidant and anticarcinogenic properties. However, despite these health benefits, there have been limited studies on their effect on oral health. A study on oral pH levels in children with caries and caries free children had shown that the oral pH results were very similar with erythritol, xylitol and mogroside, keeping the pH between approximately 7-7.5. In the case of sucrose, the pH went to as low as 6 in 30 mins, demonstrating mogroside as a possible alternative to sugar. (39)

Monk fruit extract had been shown by Gong et al to have a significant inhibitory effect of the bacteria, *S. mutans*, *P. aeruginosa* and *E.coli*. Further in vitro studies on monk fruit extract had also shown antimicrobial activity on more oral bacteria such as *A.actinomycetemcomitans*, *F.nucleatum* and had even exhibited an inhibitory effect on Candida development. These properties demonstrate the potential of monk fruit extract use in medicines and oral health care products, replacing sucrose. (40)

1.12. Public perception on non-nutritive sweeteners

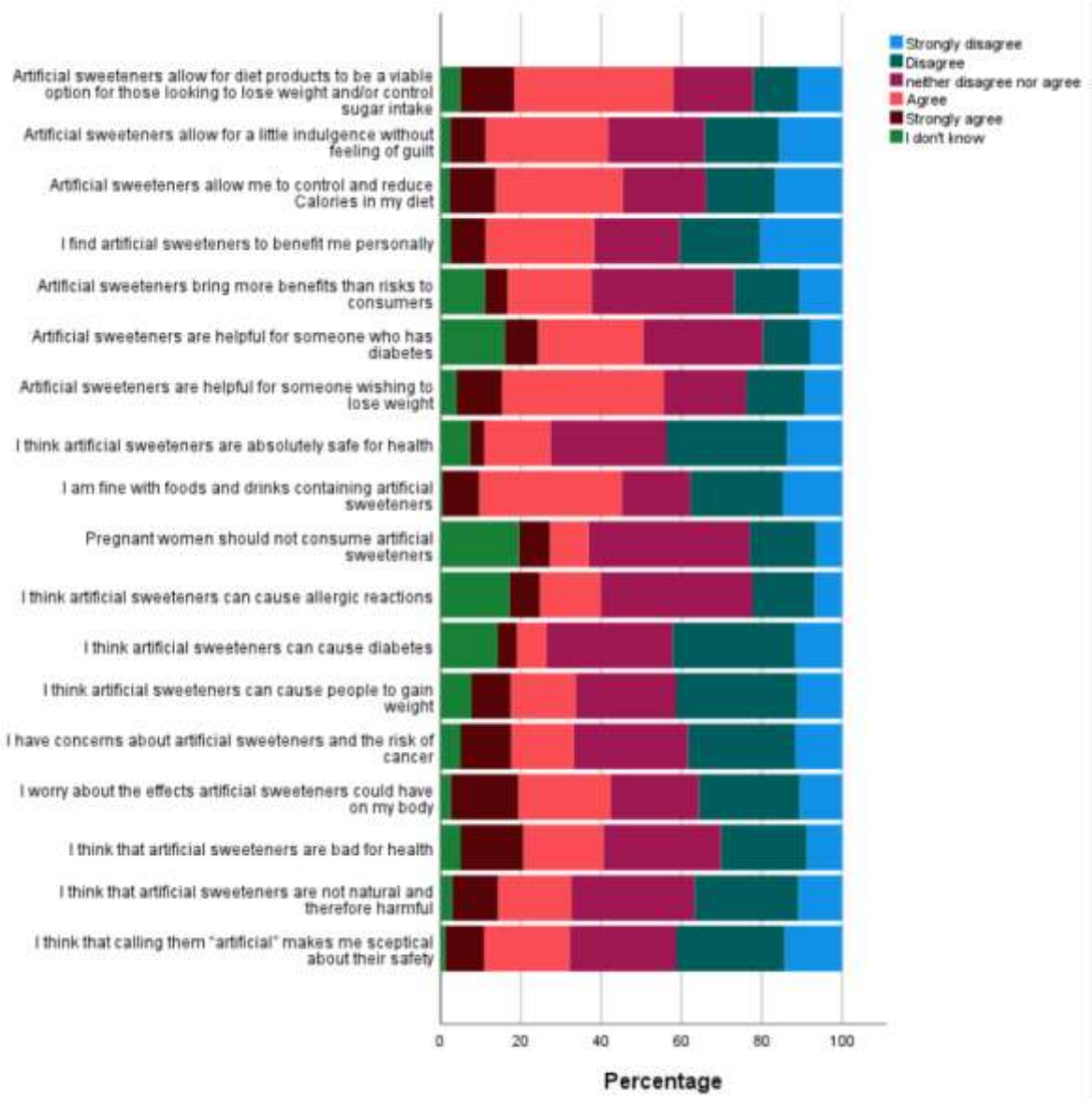

Figure 4. People's perceptions on the benefits and safety of non-nutritive sweeteners. (41)

In a survey asking people about their perceptions of artificial sweeteners, there were generally mixed reactions on safety, benefits and potential uses which had shown a correlation of people who were unsure of the safety of non-nutritive sweeteners leading to a reduction of their intake. A significant amount of participants had answered with a

'neither agree or disagree' response on perceived benefits and safety, seen in figure 4 The volume of this specific response has been reported to signify a lack of knowledge, uncertainty on their opinion or simply rejecting the statements. With the addition of the 'I don't know' response, it is seen that there isn't enough knowledge on the subject and further education is needed for the public to acquire all the necessary information to make an informed decision on such products. (41)

There is a perception of 'natural' being healthy while artificial is seen as harmful or less healthy than the 'natural' alternatives. This resulted in Stevia being seen as the safest sweetener, mainly due to it being natural. It is, therefore, important to educate the public and dissociate the term artificial from reduced safety as this is not the case. Alternatively, focussed improvements on natural sweeteners may be the way forward in public acceptance, although there is an obstacle in regard to taste of sweeteners with only 26.1% of participants enjoying the taste of sweeteners and so more development in improving taste by food manufacturers is needed to increase public acceptance. (41)

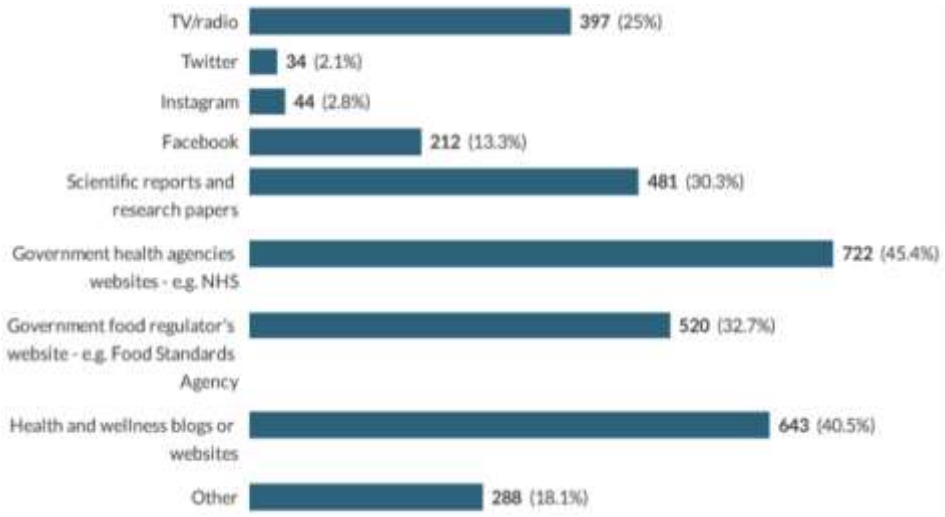

Figure 5. Sources in which the participants knowledge on non-nutritive sweeteners are derived from. (41)

Figure 5 shows the sources of the participant's information on the benefits and safety of non-nutritive sweeteners. The main source of this information has been shown to be government health agency websites and trust towards this method has not changed perception. This gives an opportunity for government health agencies to provide effective communication methods to the public to educate about safety and benefits on

non-nutritive sweeteners. However, health professionals themselves need to be aware on the current research on these sweeteners as in this survey, not all were convinced by their safety. This is especially important for dentists in preventing caries, educating themselves and then educating their patients can lead to a higher acceptance of non-nutritive sweeteners being used in their diets. Despite the research indicating the safety of non-nutritive sweeteners, there needs to be more research on their effects on microbiota, pregnancy, and any other possible adverse effects as more results in favour of their safety will lead to a more positive perception on these sweeteners by health professionals and the public. (41)

2. OBJECTIVES

The first objective was to analyse which non-cariogenic sweeteners are most beneficial for caries prevention.

The secondary objective was to analyse any upcoming sweeteners which may be beneficial for caries prevention in the future.

3. MATERIALS AND METHODS

In this literature review the information needed to accomplish this topic 'Updates on non-cariogenic sweeteners', the following databases were used: PubMed, Dental and Oral Health, Google Scholar.

Inclusion Criteria	Exclusion criteria
Articles published within the last 10 years	Articles published over 10 years ago
Articles published in English	Other languages
Articles which allowed full text access	Articles with only the Abstract available

Non-cariogenic sweeteners	Sweeteners which may contribute to caries development

Table 5. Inclusion and Exclusion criteria of database searches.

PubMed

1st search	(((non-nutritive sweetener) OR (artificial sweetener)) OR (non-cariogenic sweetener)) AND (caries)	133 results
2nd search	((sugar) AND (caries)) OR (demineralization)	211 results
3rd search	(((artificial sweetener) OR (non-nutritive sweetener)) OR (non-cariogenic sweetener)) AND (glucose) OR (diabetes)	164 results
4th search	(((xylitol) AND (caries)) OR (demineralization)) AND (remineralization)	148 results

Table 6. Searches done via PubMed.

Dentistry & Oral Sciences

1st search	(((((sugar) AND (medicine)) OR (medication)) AND (artificial sweetener)) OR (non-nutritive sweetener))	175 results

	OR (non-cariogenic sweetener)	

Table 7. Searches done via Dentistry & Oral Sciences

Google scholar

1st search	(Synsepalum dulcificum and caries)	114 results
2nd search	(Mogroside and caries)	89 results

Table 8. Searches done via Google Scholar

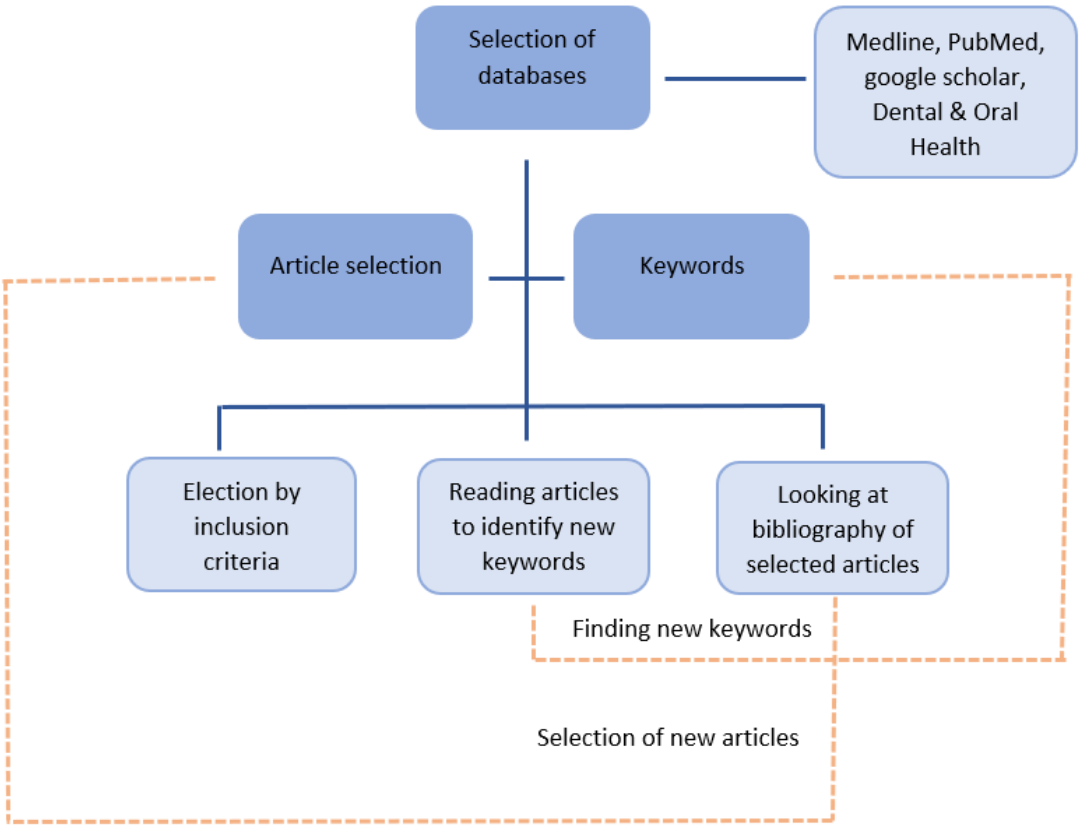

Figure 6. Systematic search for bibliography.

4. RESULTS

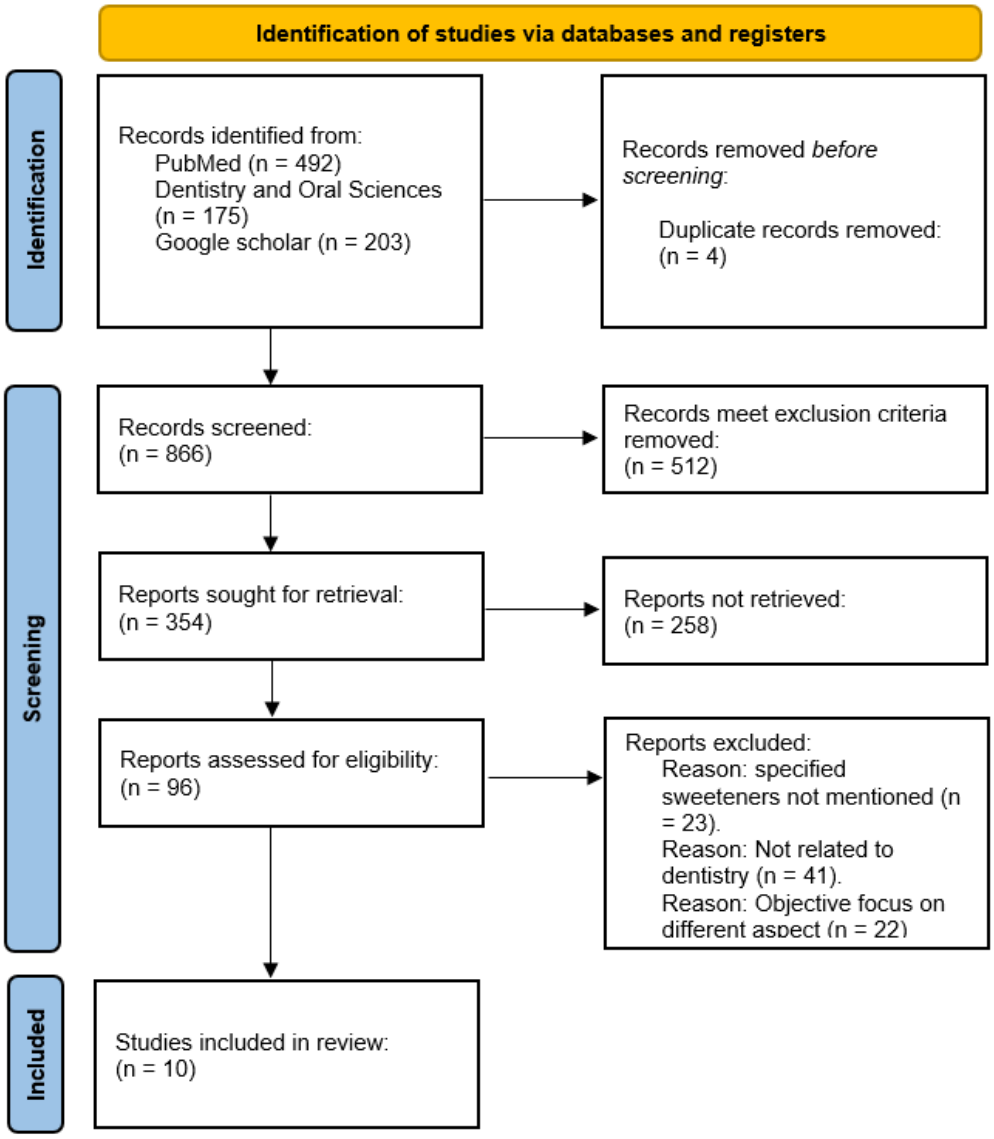

Figure 7. PRISMA 2020 flow diagram for systematic reviews which included the search of databases.

Association of sugar and caries

Article title	Authors	Publication Date	DOI	Results and conclusion
Association of sugar-sweetened drinks with caries in 10-and 15-year-olds. (1)	Pitchika V, Standl M, Harris C, Thiering E, Hickel R, Heinrich J, Kühnisch J.	December 2020	10.1186/s12903-020-01068-9.	Caries is multifactorial with sugar consumption being one of the most prominent factors for increased caries risk. Increased consumption of sugar sweetened drinks resulted in a higher incidence of caries.
The Stephan curve revisited. (2)	Bowen WH.	January 2013	10.1007/s10266-012-0092-z.	When plaque was exposed to sugar, pH decreased, to and below the critical pH due to acid production from the plaque resulting in an increased risk of caries development.
Oral health concerns with sweetened medicaments: P ediatricians' acuity (12)	S.V.S.G. Nirmala, Vimala Devi Popuri, Sandeep Chilamakuri, Sivakumar Nuvvula, Sindhuri Veluru, M.S. Minor Babu	January 2015	10.4103/2231-0762.151973	Intake of medications with sugar contributed to higher caries risk, especially in children with chronic conditions and an increased frequency in intake.

Dietary intake and meal patterns among young adults with high caries activity: a cross-sectional study. (6)	Guo A, Wide U, Arvidsson L, Eiben G, Hakeberg M.	December 2022	10.1186/s12903-022-02227-w.	Increased consumption of processed foods which contained sugar and starch was associated with higher incidence of caries in children and adolescents.

Table 9. Results of articles associating sugar to caries

Artificial sweeteners and caries prevention

Article title	Authors	Publication Date	DOI	Results and conclusion
Exploration of singular and synergistic effect of xylitol and erythritol on causative agents of dental caries (32)	Kõljalg S, Smidt I, Chakrabarti A, Bosscher D, Mändar R.	April 2020	10.1038/s41598-020-63153-x	Both individually and in combination, xylitol and erythritol inhibited the biofilm of S. sobrinus, S. mutans and S. wiggsiae.
Effects of xylitol and erythritol consumption on mutans streptococci and the oral microbiota: a systematic review (16)	Söderling E, Pienihäkkinen K.	November 2020	10.1080/00016357.2020.1788721	Majority of studies have found a reduction in S. Mutans when xylitol is consumed. In vitro studies on erythritol had been shown to reduce S. Mutans, however an in vivo study showed reduction of S. Mutans only after the third year.

In situ evaluation of 200 ppm fluoride toothpaste content trimetaphosphate, xylitol and erythritol on enamel demineralization and dental biofilm (30)	Marcato RA, Garbelini CC, Danelon M, Pessan JP, Emerenciano NG, de Souza Ishikawa A, Cannon ML, Delbem AC.	August 2021	10.1016/j.dent.2021.103724	The addition of xylitol and erythritol to low concentration fluoride toothpaste (200ppm) produced an increased protective effect when compared to a 1,100-ppm fluoride concentration toothpaste without the addition of artificial sweeteners.
Growth and viability of Streptococcus mutans in sucrose with different concentrations of Stevia rebaudiana Bertoni (36)	Escobar E, Piedrahita M, Gregory RL.	September 2020	10.1007/s00784-020-03197-5	This in vitro study showed the reduction of S. Mutans growth and biofilm formation as the concentration of Stevia increased. It has also shown to reduce the metabolic activity of S. Mutans at higher concentrations.
Mogroside, palatinose, erythritol, and xylitol differentially affect dental plaque pH in cariesactive and caries-free children: An in vitro study (39)	Nagsuwanchart P, Nakornchai S, Thaweboon S, Surarit R.	December 2021	10.1016/j.pdj.2021.08.004	An in vitro study had shown the addition of mogroside, erythritol and xylitol did not decrease the pH of both the caries-free group and caries-active group compared to the reduction of pH in both groups when sucrose was added and to a lesser extent palatinose.

Antibacterial Property of Synsepalum dulcificum Leaves Aqueous Extract against Oral Pathogens and its Chemical Compounds. (38)	Ibrahim HA, Kassim NK, Che Soh NA, Othman Z, Tuan Ismail TN.	June 2020	10.21315/aos2020.20.15.1.427	An in vitro study on the antibacterial effects of Synsepalum dulcificum had shown an inhibitory effect on S. mutans and S. sobrinus as the concentration increased with those pathogens being inhibited by 16mg/mL but an inhibitory effect was not seen on L. salivarius.

Table 10. Articles comparing results from various non-cariogenic sweeteners and their effects on cariogenic bacteria.

5. DISCUSSION

There has been plenty of studies linking caries development with an increase consumption of sugar. Pitchika et al, 2020, in a 10 year follow up had observed a higher consumption of sugar sweetened drinks had resulted in higher incidences of caries. The regular consumption of sugar as explained by Bowen 2013, decreases the pH beyond the critical pH by providing nutrients for the oral bacteria to produce acids such as lactic and acetic acid which results in the dissolving of the tooth enamel, leading to caries development.

Through a cross-sectional study done by Guo et al, 2022, it was a discovered that there was a possible association between an increase in caries incidence and an increase in snack frequency. These studies and numerous others have found a positive association of sugar intake and caries development and is well known today, although multifactorial, starches and sugars, especially foods with retention, increase the risk of caries development.

In a systematic review done by Soderling and Pienihakkinen, 2020, using their inclusion criteria, 21 studies on xylitol were looked at and 1 on erythritol. The majority of studies on xylitol had shown a reduction in S. mutans with no change on other bacteria in the

oral microbiota while the erythritol study did not show any initial changes on the level of S. mutans, only a reduction was seen at a 3-year follow-up.

The effects of erythritol on S. mutans, S. sobrinus, S. wiggsiae Koljalg et al, 2020, showed a more immediate effect than shown on the review by Soderling and Pienihakkinen, 2020, in its inhibitory effects, reducing growth and biofilm inhibition. Individually, xylitol and erythritol had shown a reduction of these caries causative agents with a combination of the two also being effective but not more than individually. There was evidence that, specifically, S. mutans growth inhibition was more effective with a higher concentration of erythritol while a higher growth inhibition was seen with S. sobrinus and S. wiggsiae when a higher concentration of xylitol was introduced.

These various studies showing the effectiveness of xylitol on causative agents of dental caries and the potential of erythritol to rival xylitol has led to the addition of these polyols to dental products to make them more effective as a preventative measure. This is seen in a study by Marcato et al, 2021, showing that lower concentration of the fluoride, combined with xylitol and erythritol are as effective as high concentration fluoride toothpaste, this may be useful in reducing incidences of fluorosis as well as keeping the same effectiveness in caries prevention.

Although xylitol has been extensively studied and more studies on erythritol are emerging, there is a lack of studies on new and upcoming sweeteners, however, the studies already published, do show potential of these sweeteners. Escobar et al, 2020, used an in vitro study to observe the effects of Stevia on S. mutans. In this study, there is an indication of Stevia inhibiting the total growth and biofilm formation of S. Mutans but did not exhibit a bactericidal effect. The minimum inhibitory concentration was shown to be 25mg/ml, while the minimum biofilm inhibitory concentration had a value of 6.25mg/ml.

More recently, Mogroside from monk fruit has been studied and compared alongside xylitol and erythritol in its ability on affecting pH in the mouth. Nagsuwanchart et al, 2021, observed that Mogroside, xylitol and erythritol did not create an acid environment and did not lower pH, compared to sucrose which significantly decreased

pH. This suggests the possibility that monk fruit extract be used as a non-cariogenic sweetener, although, despite this, there are no current studies on its effects on cariogenic bacteria.

Synsepalum dulcificum also known as 'miracle fruit' due to its ability to make sour and acidic foods taste sweet, giving potential for artificial sweeteners as taste has been a complaint which limits their acceptance. Ibrahim et al, 2020, studied the antibacterial properties of Synsepalum dulcificum extract on oral pathogens with a comparison to chlorohexidine. The bacteria tested were *S. mutans, S. sobrinus, L. salivarius*. It was shown that with 16mg/ml of Synsepalum dulcificum, inhibited both *S. mutans* and *S. sobrinus* but no concentrations tested inhibited *L. salivarius*.

6. CONCLUSION

In the present, the various years of study, support the use of xylitol in caries prevention as the primary non-nutritive sweetener of choice. Erythritol has been studied more recently alongside xylitol and has shown promising results and there was even some suggestions that it's even more effective than xylitol in inhibiting certain cariogenic pathogens. The ongoing studies on xylitol continue to support its use in dental care products and as an adequate substitute for sugar, preventing caries development. Regarding erythritol, positive results have been obtained and could be another prominent sweetener used in preventive dentistry, however, there are a lack of studies on erythritol's effects on cariogenic pathogens, especially in patients and so more research on the sweetener needs to be done to be affirm its possible use in dental products.

The most popular recent sweetener of choice is Stevia which has shown positive results in its bacteriostatic effects on S. mutans. Its limitations are similar to erythritol, in which there aren't a sufficient number and types of studies which confirm its effectiveness against cariogenic bacteria. Monk fruit extract, Mogroside, has exhibited no change in pH in the oral cavity oral pH, showing similar effects to erythritol and xylitol. The potential of mogroside as a beneficial sweetener for teeth is present but there has been

very limited studies on this topic and its effects on cariogenic bacteria. Synsepalum dulcificum or ‘miracle fruit’ is an interesting prospect for sweeteners as it changes the taste of food from sour and acidic to sweet, making it very appealing as a major setback for sweeteners is the taste. It has shown at higher concentrations that it prevents growth of S. mutans and S. sobrinus but due to the inadequate number and types of studies, in this moment can only be seen as a potential solution for improving taste of sweeteners while protecting the oral cavity from caries.

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