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# Artificial Sweeteners and Sugar Substitutes -Some Properties and Potential Health Benefits and Risks.

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**ABSTRACT**

Sugar is one of the most widely consumed sweetening agents. Unfortunately, its use has been linked to various disease states, such as obesity and diabetes mellitus (DM). This has led to the search for alternative sources of sweetness that are devoid of the health hazards of sugar. Sugar substitutes are food additives that provide a sweet taste more or less similar to that of sugar. Sugar substitutes can either be natural or synthetic. Natural sugar substitutes are those that occur naturally in certain fruits and vegetables. Sugar alcohols, such as xylitol and erythritol, and novel sweeteners, such as tagatose and trehalose, are examples of sugar substitutes of natural origin. Artificial sweeteners are sugar substitutes that are chemically synthesized. Examples of artificial sweeteners are saccharin, aspartame, sucralose and acesulfame potassium. This review summarizes some information on properties and possible health benefits and hazards of natural sugar substitutes and artificial sweeteners.

**Keywords:** sugar, artificial sweeteners, sugar substitutes

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## INTRODUCTION

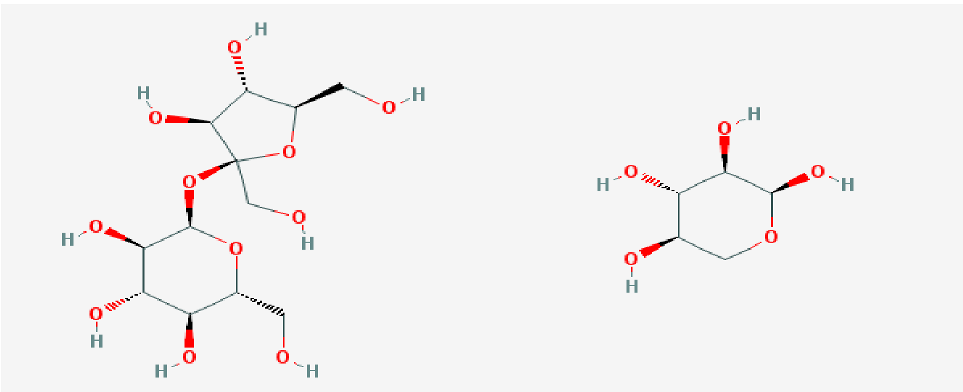
Sucrose, commonly known as table sugar, is the most widely used compound to provide sweet taste. Although the exact time and place where it was first discovered and consumed is not completely agreed upon between historians, it is known that sugar had not become widely available for consumers until the 18$^{th}$ century. Until then, sugar was a luxury only the wealthy could afford. Since then, the use of sugar has expanded gradually to a state of being a necessity and a basic commodity [1]. It is important to note that only in 1747 AndraeasMarggraf found out that beet and cane sugar are identical [1]. Nowadays, the widespread consumption of sugar is a cause of concern due to increasing evidence linking its use to a variety of health problems, such as obesity, diabetes and tooth decay[2]. This has driven the search for alternative sources of sweetness, including sugar substitutes and artificial sweeteners. This report will discuss the main compounds used as sugar substitutes and artificial sweeteners, their potential health benefits and dangers, and reflect on issues of concern regarding their consumption by general population.

## SUCROSE

Sucrose, or table sugar, is a naturally occurring carbohydrate found in all fruits and vegetables. In fact, it is the major product of photosynthesis. Sucrose found in different plants is identical, yet it is produced in very large amounts by sugar beets and sugar cane. Sugar beets and sugar cane contain about 16% and 14% sucrose, respectively, and are thus used for commercial extraction and production of sugar[1].

**Fig 1 Chemical formulas of sugars, artificial sweeteners and sugar replacements (source PubChem). (A) Sucrose, (B) xylose, (C) xylitol, (D) erythritol, (E) tagatose, (F) aspartame, (G) acesulfame potassium, and (H) saccharin.**

A B



Sucrose is a crystalline white powder with a chemical formula of$C_{12}H_{22}O_{11}$.It is a disaccharide that consists of an α-glucose and a fructose, joined by a glycosidic bond between carbon atom 1 of the glucose unit and carbon atom 2 of the fructose unit(Fig. 1A) [3].Despite its profound nutritional value as an energy supply for the body, extensive sugar consumption is linked to various ailments including dental caries, obesity, and certain degenerative diseases. The growing health awareness, increasing public interest in fitness and figure, and the rising imbalance between calorie consumption and expansion are all factors that led to the demand of food products that support better health. The use of sugar substitutes is one way to overcome disadvantages of sugar consumption[2].

## SUGAR SUBSTITUTES

Sugar substitutes are food additives that are used to mimic the sweet taste of sugar. Reasons to substitute sugar may vary from availability, cost, product formulation and health or dietary concerns. Sugar substitutes can either be intense or bulk sweeteners.Intense or non-nutritive sweeteners are sugar substitutes that are usually many times sweeter than sucrose[4]. Their sweetness may overcome sweetness of glucoseup to 8000 times[2], thus a much less amount of sweetener is used and only a minute fraction of the caloric content of sucrose is consumed.However, these sweeteners lack the bulk properties provided by sucrose that are needed to give a product a certain texture or mouthfeel. This is why a bulking agent might be added to products formulated with intense sweeteners. Bulk sweeteners, on the other hand, are not non-nutritive in the sense that they do contain some calories and are sometimes less sweet than sucrose. Nevertheless, they are used in some products for financial reasons as well as some product formulation needs [4]. Sugar substitutes are mainly categorized into natural and synthetic sugar substitutes; the latter are generally referred to as artificial sweeteners [2].

## SUGAR SUBSTITUTES OF NATURAL ORIGIN

Natural sugar substitutes are those that are found naturally in certain fruits and vegetable, yet they may not be found in adequate amounts suitable for major extraction and consumption. This necessitates their chemical synthesis[5].Natural sugar substitutes are of varying sweetening potency [2].For example, surculin is 550 time sweeter than sucrose, brazzein is 800 times sweeter and other naturals substance monellin is even 3000 sweeter than sucrose (by weight) [2].

Sugar substitutes of natural origin can be further categorized into several groups.

## SUGAR ALCOHOLS

Sugar alcohols, also known as polyols, are carbohydrates in which the carbonyl group is hydrogenated to form a hydroxyl group(see Fig. 1B,C). An example is the conversion of xylose (Fig. 1B) to xylitol (Fig.1 C).

Sugar alcohols can be naturally found in many fruits and vegetables, butthey can also be manufactured. They are not considered nonnutritive sweeteners, because they contain calories. There caloric content, however, is less than that of sucrose. This property of sugar alcohols along with the fact that many of them are of nearly the same molecular weight of sucrose made them an appealing alternative that can be used in many food products as a low energy bulk sweetener, replacing sugar on an equal basis.Nonetheless, food items sweetened with sugar alcohols and labeled “sugar free” may sometimes be misleading to consumers, as the term does not imply, but maybe interpreted as calorie free [3].

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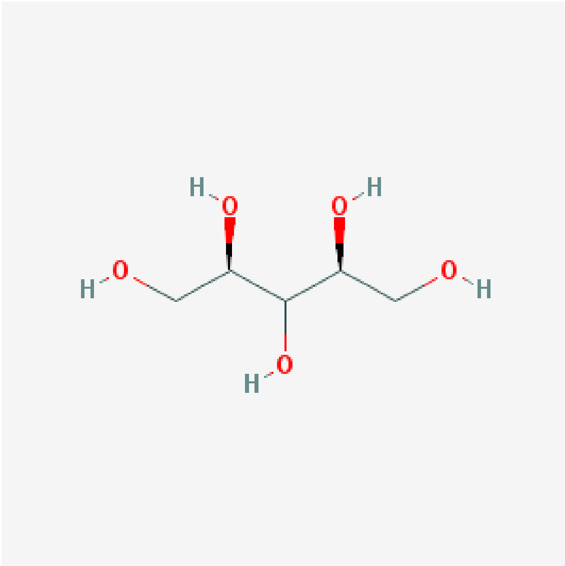

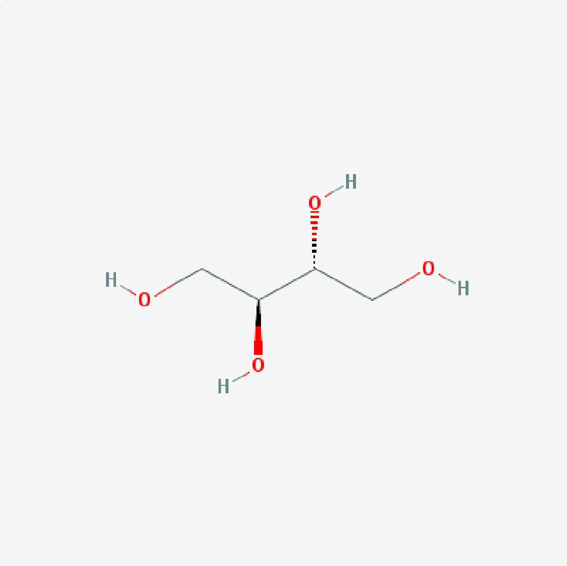

Sugar alcohols may also be added to processed foods to protect them from browning upon heating. This is because sugar alcohols are non-reducing sugars, thus do not caramelize nor do they participate in the Maillard reaction.For this reason they are used as food additives to protect the color of some processed foods[3,6].

Another remarkable feature of sugar alcohols is their ability to produce a perceptible cooling sensation in the mouth when dissolving from the crystalline state.This cooling sensation is due to the characteristic endothermic dissolution of sugar alcohols, making them ideal sweeteners for sugar free menthol and peppermint flavored candies and chewing gums[7].

One of the most noticeable findings about sugar alcohols is that theirabsorption from gastrointestinal tract is slow and incomplete. This contributes to some of their benefits for human, such as their low glycemic index[8]. Sugar alcohols are used to replace sucrose in many sweets, chocolates, and baked goods that can be consumed by diabetics as their consumption results in a slower and smaller increase in blood sugar compared to products with sucrose.This leads to a decrease of the glycemic load of a person and a diet where sucrose is replaced by sugar alcohols presumably reduces the risk of obesity, type 2 diabetes and cardiovascular diseases [9].Furthermore, the incomplete absorption of sugar alcohols results in their incomplete metabolism. Consequently,theircaloric content (between 1 to 3 kcal/g)[3] and energy yield is less than that of sucrose and other carbohydrates (4 kcal/g)[8], making them a suitable option for those wanting to lose weight [10].

Another benefit of sugar alcohols is that they are noncariogenic, i.e. they do not result in tooth decay. This is because oral bacteria do not ferment them as readily as sucrose. Therefore, they are extensively used in products that are intended to be kept in the mouth for a long while, such as chewing gums and breath mints [11].

On the other hand, sugar alcohols are widely known to produce various undesirable gastrointestinal side effects, including diarrhea, bloating, and flatulence due to their incomplete digestion [10] and some, such as sorbitol, are medically used as hyperosmotic laxatives[10].

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## NOVEL SWEETENERS

These novel sugar substitutes have a relative recent history of consumption. Because of their variable chemical structures, novel sweeteners are extracted from varying sources and used for different purposes according to their individual chemical functionalities. In addition to their natural sources, some of them can also be partially or completely manufactured. Their uses vary from stabilizers and binders for meat and poultry products, to flavor enhancers in dried fruits, soups, and many types of baked goods[12].

Novel sweeteners such as tagatose, inulin, and fructose oligosaccharides are not completely digested by the human. This, along with their selective support of the growth of beneficial colonic bacteria,makesthemprebiotics.Prebiotic sweeteners are used in foods because their indigestibility renders them less caloric. More importantly, these novel sweeteners were proven to support the growth of *bifidobacteria* and *lactobacilli* in the intestinal tract at the expense of pathogenic *clostridia,coliform*and other types of bacteria. The composition of the colonic microbial community has been strongly linked to various disease states. A healthy composition is one that is high in *bifidobacteria* and *lactobacilli* and low in *clostridium* and *coliform*bacteria. Furthermore, it was found that low populations of *bifidobacteria* induce a state of chronic inflammation in genetically susceptible individuals. This state of chronic inflammation with elevated levels of circulating inflammatory markers, i.e. C-reactive protein, is associated with a number of diseases, such as ulcerative colitis, obesity, diabetes, hyperlipidemia and cardiovascular diseases [13]. This led to the assumption that restoring *bifidobacteria* populations in patients with these diseasesmay be of clinical benefit. Later, a clinical intervention study in patients suffering from ulcerative colitis was performed. Patients' diet was supplemented byoligofructose-enriched inulin together with a probiotic (*Bifidobacteriumlongum*) diet for one month. This resulted in a 42-fold increase in *bifidobacteria* numbers in mucosal biopsies. It also resulted in an improvement of the clinical appearance of chronic inflammation. [14].

Novel sweetener were approved for consumption only recently but are regarded as safe. They are not genotoxic, teratogenic and no long-term toxic effects was related to their use.Additionally, the novel sweetenerstrehalose, tagatose,andfructo-oligosaccharideswere granted a GRAS (generally recognized as safe) status by the FDA for use in foods and beverages [15,16].

## ARTIFICIAL SWEETENERS

Artificial sweeteners are synthetic sugar substitutes that can either be completely synthesized or chemically derived from naturally occurring substances.They are considered intense sweeteners and are thus used to replace sucrose in many foods for health and dietary reasons [5]. Their sweetnessoften requires them to be mixed with other sweeteners to dilute their intensity, mimic the sweetness of sugar and cover any aftertaste caused by the particular intense sweetener. The used amount of sweetener needed to produce a sweet taste is very minute compared to sucroseand they should be mixed with bulk sweeteners in order for them to be sold to consumers as tabletop sweeteners. Artificial sweeteners are also mixed with bulk sweeteners when used in baked goods and confectionaries, because they lack the bulk properties needed in these types of foods[17].These statements may be supported by the fact that acesulfame, alitame, aspartame, glucin and saccharing are all 160-300 times sweeter compared to glucose [2].

There are several possible health benefits in human supporting the use of artificial sweeteners.Artificial sweeteners are extensively publicized for being non-cariogenic. Thus they substitute sucrose in numerous products such as toothpastes, chewing gums and many medications, especially those intended for the pediatric population. Unlike, sucrose, artificial sweeteners are not fermented by the oral microflora. Hence, they do not produce the acidic waste responsible for the fall in oral pH - the primary cause of tooth decay [2].

As was mentioned earlier in this research, artificial sweeteners are nonnutritive sweeteners, meaning that their caloric content is negligible compared to that of sucrose (4kcal/g). This is why they are often an attractive option for those wanting to loose or control weight[5].
Artificial sweeteners may also be of possible benefit for diabetics, as they are not metabolized in the body into glucose. Thus, they do not cause a rise in blood sugar nor do they cause reactive hypoglycemia associated with high GI foods. This allows diabetics to satisfy their sugar cravings while still managing their blood glucose[2].

**POSSIBLE HEALTH HAZARDS OF ARTIFICAL SWEETENERS**

The safety of artificial sweeteners has been widely debated and has been a controversial issue for a long time. This is because of various studies that suggested they may cause a number of diseases, including cancer, metabolic syndrome, obesity, and others. That said, the FDA regulates artificial sweeteners as food additives in the USA. Food additives must gain approval by the FDA before they are marketed and are available for sale. To date, the FDA has not been presented with any sound scientific evidence to disapprove any of the five artificial sweeteners approved by the FDA, namely saccharin, aspartame, sucralose, neotame, and acesulfame potassium. This decision has been based on a large body of toxicological and clinical studies [18].

The alleged health benefits of artificial sweeteners regarding weight loss and diabetes control have also been lately subject to clinical controversy.Despite the fact that artificial sweeteners were originally devised to reduce weight and aid diabetics in controlling blood sugar, epidemiological data suggest the contrary. Though both forward and reverse causalities have been proposed,it is apparent that the rise in the percent of the American population who are obese correlates with the increase in the widespread consumption of food products sweetened with non-caloric artificial sweeteners[19].This study [19] also reports on a number of large-scale prospective cohort studies that have found a positive correlation between artificial sweetener use and weight gain. Moreover, several interventional studies proposed that it is unsuccessful to use artificial sweeteners alone as a method to reduce weight and that weight loss seen in multidisciplinary programs that included artificial sweeteners is attributed to vigilant monitoring, caloric restriction, as well as physical exercise [19].

Artificial sweeteners are also being investigated for their possible association with increased risk of metabolic syndrome and type-2 diabetes. The association between diet soda intake and the risk of incident metabolic syndrome and type-2 diabetes was assessed in the multi-ethnic study of atherosclerosis. Although the study could not demonstrate definite causality, consumption of diet soda at least daily was associated with a 67% greater relative risk of incident type-2 diabetes and 36% greater relative risk of incident metabolic syndrome.However, it was shown that diet soda consumption is not actually associated with the totality of metabolic syndrome but that the observed association is rather mediated by changes in adiposity, fasting glucose, pre-diabetic and diabetic conditions in response to diet soda consumption[20].

## REPRESENTATIVE EXAMPLES OF SUGAR SUBSTITUTES

### XYLITOL

Xylitol(Fig. 1C) is a 5-carbon sugar alcohol. It is found in many fruits and vegetables, the richest sources being plums, strawberries, raspberries and cauliflower. Commercially, it is produced by hydrogenation of D-xylose obtained by prehydrolysis of xylan-containing materials, such as birchwood, coconut shells, and cottonseed hulls. Xylitol is an odorless white crystalline powder that has a sweetness profile similar to that of sucrose, yet with only two thirds of the caloric value (2.4 vs. 4.0 Cal/g). Other than being a sugar substitute, xylitol is increasingly being used for its various health benefits. When ingested, xylitol is phosphorylated to xylitol-5-phosphate that is then accumulatedintracellularly, since bacterial species such as *Streptococcus pneumonia* and *Streptococcus mutans* do not possess metabolizing enzymes. Because of this, xylitol-5-phosphate is toxic for this microorganisms and inhibitsbacterial growth. Consequently, the anti-cariogenicity of xylitol is one of its most important properties. Besides inhibition of *streptococcus mutans*, as a result of its pleasant taste, xylitol was found to increase salivation without increasing acid production in dental plaque. When saliva increases, so does calcium and phosphate ions, which promote remineralization of the teeth. Increased saliva also increases the pH of the plaque. This neutralizes other acids formed from other fermentable carbohydrates that were ingested. Consequently, the levels of other enzymes that enhance the buffering capacity and the bacteriostatic activity of the salivaincrease[21].

### ERYTHRITOL

Erythritol is a 4-carbon sugar alcohol that occurs naturally in many foods as well as a variety of microorganisms, plants and animal (Fig. 1D). Erythritol is commercially produced by fermentation of glucose obtained from hydrolysis of raw materials such as starch or sugar. The procedure is performed using organisms that have a high yield of erythritol in theirfermentation products, such as the fungus *Aureobasidium,* or the yeast*Moniliella*[22].

In terms of sweetness, erythritol is a bulk sweetener that is 60-70% as sweet as sucrose. Thus, it is not extensively used to provide intense sweetness, but is rather combined with other sweeteners to improve the mouthfeel and mask any unwanted aftertastes. Unlike other bulk sweeteners, erythritol is the only sugar alcohol that is not metabolized in the body and is non-caloric. Erythritol shares the noncariogenic and diet friendly properties of other sugar alcohols, yet it has an additional advantage of being highly bioavailable.This limits the flatulence and laxation typically observed with other sugar alcohols due to their poor absorption.Becausepolyols contain many hydroxyl groups, they are all known to be excellent scavengers of hydroxyl radicals. These antioxidant properties, however, are of low utility in most polyols due to their limited absorption. Erythritol, in contrast, is an exception as it exhibits excellent absorption and no metabolism, thus it circulates throughout the body toscavengehydroxyl radicals.Erythritolis being studied as a potential endothelialprotectingagent; especially in diabetes associated vascular diseases, including atherosclerosis. These diseases are thought to be mediated byhigh glucose-induced endothelial cell apoptosis,triggered by reactive oxygen species[22,23].

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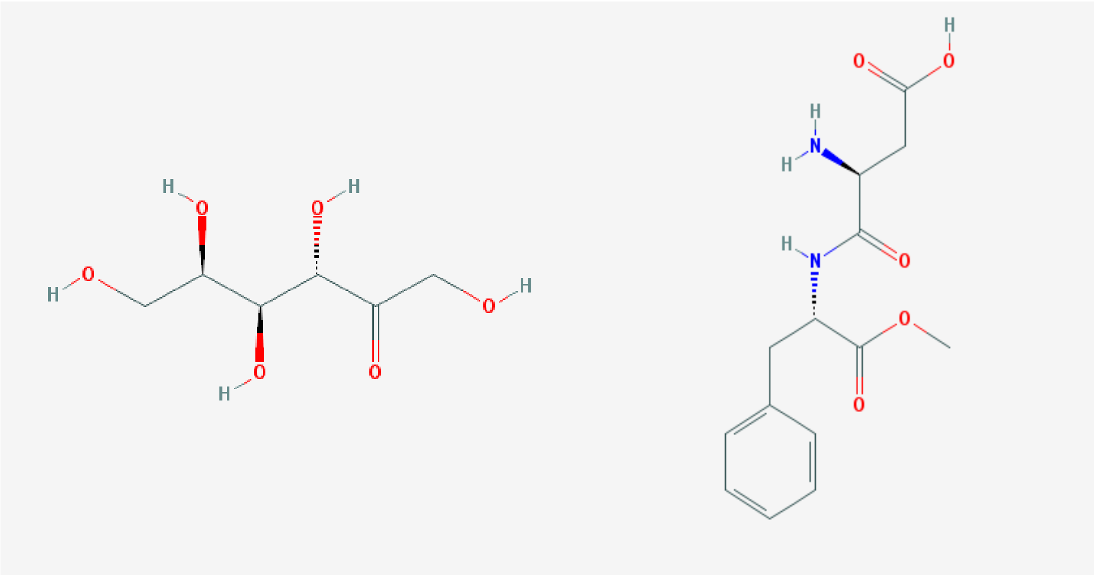
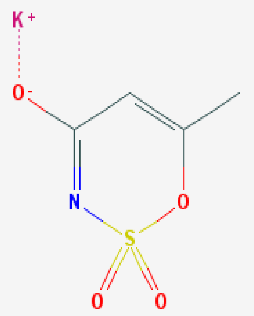


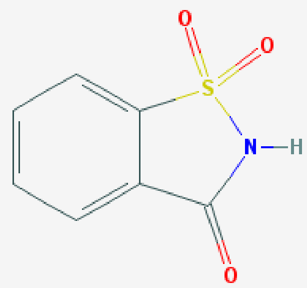
**TAGATOSE**

D-Tagatose is a novel sweetener found in dairy products and some fruits, such as apples, pineapples and oranges. Commercially, it is produced by hydrolyzing lactose into glucose and galactose. Galactose is then isomerized to D-tagatose. Tagatoseis a ketohexose with a chemical structure very similar to that of D-fructose (Fig1E)[24].

Tagatose has a texture very similar to that of sucrose and is almost 92% as sweet, but with only 1.5kcal/g. This is why it is considered a low calorie bulk sweetener and is extensively used as a flavor enhancer.It is mixed with other sweeteners, i.e. acesulfame K or aspartame, to improve the flavor profile and the mouth-feel. Tagatose is also added to cereals, granola bars and yogurts for its prebiotic effects. Tagatose is a reducing sugar. This makes it suitable to produce sugar free caramel that has a soft and smooth consistency. The low GI of tagatose (GI=3) renders it a suitable sugar alternative for diabetics as well as those wanting to lose weight [24].
Moreover, apart from tagatose having a low GI, it is currently being studied as a potential anti-diabetic medication. Preliminary studies in humans show that tagatose significantly lowers postprandial blood glucose. This effect can be attributed to its inhibition of intestinal glucose and disaccharide transport, which in turn interferes with carbohydrate absorption. Tagatose may also reduce blood sugar by hepatic inhibition of glycogenolysis[25].

G H




**ASPARTAME**

Aspartame (Fig. 1F) is anon-nutritive artificial sweetener that was first discovered in 1965. Since then, it has gained vast popularity and is widely used and publicized by the food industry as a healthier substitute for sugar. Even thoughaspartame contains the same 4 kcal/g as sucrose, it is up to 200 times more sweet.Hence, the amount used is so little that its caloric contribution is negligible [7].

Aspartame is composed of constituents that are common to many foods, namely phenylalanine, aspartic acid, and a methyl group (Fig. 1F). In the body, aspartame is enzymatically broken into those three constituents and the amino acids are then absorbed similarly to those obtained from other proteins. The methyl group, on the other hand, is metabolized to methanol, which in turn, is rapidly oxidized to form formaldehyde. Ultimately, formaldehyde is broken down into carbon dioxide. Although, formaldehyde and methanol are known to be toxic, aspartame is still approved for human consumption, since the amounts produced from aspartame metabolism are below the threshold at which they may cause harm [26]. That said,some studies have attributed side effects, such as headache, mood swings, dizziness, nausea, and even cancer among aspartame consumers to one or more of its breakdown products[7]. These studies, though, are widely controversial and were contradicted by other studies of conflicting evidence. The only scientifically valid concerns regarding aspartame are in those suffering from epilepsy and phenylketonuria (PKU). Aspartame has demonstrated a decreasing effect on the threshold of seizures in epileptic patients, when consumed in excessive amounts. This effect, though, was not significant when the intake level did not exceed the recommended amount[25].What is unquestionable about aspartame is that it is contraindicated among patients with PKU due to the phenylalanine component. In fact, food products containing aspartame must bear a warning label indicating that the product contains phenylalanine[25,26]. Aspartame for table use should also carry a statement indicating that it is not to be used for cooking or baking, since it may breakdown to its constituents and loose its taste in elevated temperatures. High pH also affects stabilityofaspartame, rendering it useless in products that require a high pH for a long shelf life [27].

## ACESULFAME POTASSIMU (ACESULFAME K)

Acesulfame K (Fig. 1G), a non-caloric artificial sweetener, was first discovered in 1967.Like aspartame, it is 200 times as sweet as sucrose, only with a slight bitter aftertaste. For this reason it is often blended with other sweeteners, such as sucralose or aspartame, to mask the bitterness and produce a synergistic taste enhancement that is of greater resemblance to sucrose. Unlike aspartame, acesulfame K exhibits marked stability under a wide range of temperatures and pH levels. This makes it suitable for a wide range of applications, since its shelf life seems to be unlimited at room temperature and thermal decomposition is only seen at temperatures well above 200°C. Hence, it is a suitable sugar substitute for baking and for products that require a long shelf life. Acesulfame K is also used to sweeten many drinks, including soft drinks due to its stability at low pH levels often detected in such beverages [28].

## SACCHARIN

Accidently discovered in 1878, saccharin (Fig. 1H) is the firstartificial sweetener to be used and one of the best known. It is thought to be approximately 300 times as sweet as sucrose, only with the limitation of having a bitter aftertaste. Likeacesulfame K, it is often combined with other sweeteners to mask the bitterness.Saccharin is a very stable sweetener at all the pH and temperature conditions to which it may be exposed to in food or beverage applications. Saccharin, however, is poorly solublein water forming acidic solutions; thus its highly soluble calcium or sodium salts are often commercially used instead[29].

In past, saccharin was regarded to be a potential carcinogen, based on a study reporting an increased incidence of bladder cancer in rats fed very high amounts of saccharin. The amount of saccharin fed to the rats was around 5% to 7.5% of their diet, the human equivalent of drinking at least 800 diet sodas a day [30]. Later it was shown that the carcinogenicity of saccharin was specific to rats [31].Human epidemiological studies have shown no consistent evidence that saccharin is associated with increased bladder cancer incidence [32].

## NOTES ON IMPORTANCE OF SUGAR SUBSTITUTES FOR PEOPLE'S BENEFITS

The increased prevalence of diabetes and obesity, and the rising interest in figure and shape has led to the search for alternative less caloric sources of pleasurable food. In developed countries, sugar substitutes are widely consumed, be it as tabletop sweeteners, or in diet sodas, sugar free chewing gums, candies, and confectionaries. Though sugar substitutes may have short-term beneficial effects in terms of weight reduction and diabetes management, the long-term benefits are widely controversial. Continued consumption of these substances without optimizing other factors contributing to disease occurrence, such as exercise and other dietary measures may result in undesirable outcomes.

With all sugar substitutes, moderation is key to achieving the desired outcomes. Thus it is important that general populationis educated in order to empower them to make informed choices regarding a healthy balanced diet. The main purpose of using sugar substitutes is to optimize weight and diabetes control. In both situations, consumers must be aware it is not only sugar restriction that counts; what matters is the total amount of calories consumed and the amount of energy expenditure through exercise and daily activities. A common misconception among consumers is that “Sugar Free” products are healthier and need not to be limited in consumption; this is not entirely true, as these products may contain other sources of calories that can affect bothweightandblood sugar. It is also important to know that a balanced healthy diet is one that contains adequate amounts of nutrients and minerals. Unfortunately, most sugar containing foods as well as their sugar free counterparts contribute little or no nutrition and take up the place of more nutritious food in usersdiet. Therefore, consumers must avoid excessive intake of empty calories from sugar substitute containing foods, often processed foods, and consume foods with nutritional sources of energy, such as fruits and vegetables[5].

## CONCLUSION

Presently, the two main categories of sugar substitutes, natural and artificial sweeteners, are continuously being studied for their potential health benefits and hazards. Most natural sweeteners are caloric bulk sweeteners that are rarely sweeter than sucrose, but exhibit a sweetness profile that is relatively similar to that of sucrose in terms of taste, texture, and mouthfeel. Artificial sweeteners are mostly non-caloric intense sweeteners that are usually many times as sweet as sucrose, but aregenerallycharacterized by an unnatural sweet taste and lack the bulk characteristics of sugar. Natural sweeteners, such as xylitol and trehalose, and artificial sweeteners, such as aspartame and saccharin, are used to substitute sugar as tabletop sweeteners, in baking, or in diet soft drinks, and confectionaries. Studies have demonstrated that sugar substitutes may aid in weight loss and diabetes management, but only when used along with other methods of caloric restriction and exercise. On the other hand, the use of artificial sweeteners may be their use may contribute to the increased of obesity and diabetes when used not correctly.Thus moderation is essential. In view of the available evidence, it is vital that the general population be educated to make informed decisions regarding the amount and type of sugar substitutes to use.

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