# Artificial Sweeteners: Efficacy, safety, and physiological effects in humans: Review

# لمحليات الصناعية: الفعالية والسلامة والتأثيرات الفسيولوجية على البشر: مراجعة

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**Abstract**

With the increased demand for better health among many individual, the turning to sweeteners has been rampant as most of them contain low calories. As such, many companies have turned to the production and purchase of artificial sweeteners due to their less usage, lowering the production cost, while also improving users' calories level of consumption. The U.S. Food and Drug Administration recognize various artificial sweeteners including acesulfame-K, aspartame, saccharin, and sucralose, among others, where it also defines the acceptable daily intake value (ADI). However, despite the immense use and benefits, there are many concerns, particularly the health concerns over increased use of artificial sweeteners, where some people perceive that they promote cancer, gastrointestinal issues, and brain damage, among other issues. Hence, this review discussed artificial sweeteners, types, and their metabolic and health effects, and their usage.

**Key words**: Low-calorie; non- nutritious sweeteners; Acceptable daily intake; risk.

**المستخلص**

مع زيادة الطلب على صحة أفضل بين العديد من الأفراد ، انتشر التحول إلى المحليات لأن معظمها يحتوي على سعرات حرارية منخفضة. على هذا النحو ، تحولت العديد من الشركات إلى إنتاج وشراء المحليات الاصناعية نظرًا لاستخدامها الوتسع ، انخفاض سعراتها الحراية وخفض تكلفة الإنتاج ، مع تحسين مستوى استهلاك السعرات الحرارية للمستهلكين. تعترف إدارة الغذاء والدواء الأمريكية بالعديد من المحليات الصناعية بما في ذلك acesulfame-K ، والأسبارتام ، والسكرين ، والسكرالوز ، ومن بين الامور أخرى المهمة ، هو حيث تحديد قيمة المدخول اليومي المقبول (ADI). ومع ذلك ، على الرغم من الاستخدام والفوائد الهائلة ، هناك العديد من المخاوف ، لا سيما المخاوف الصحية بشأن زيادة استخدام المحليات الصناعية ، حيث يرى بعض الناس أنها قد تحفز الاصابة بامراض السرطان ، ومشاكل الجهاز الهضمي ، وتلف الدماغ، وامراض اخرى. ومن ثم ، ناقشت هذه المراجعة المحليات الصناعية وأنواعها وآثارها الأيضية والصحية واستخداماتها.

**الكلمات المفتاحية**: منخفضة السعرات الحرارية؛ المُحليات غير المغذية ؛ المدخول اليومي المقبول؛ المخاطر.

## Introduction

Artificial sweeteners( ASs) are known as food additives that provide a sweet taste, and they are also called low-calorie, such as alcoholic or non-caloric sugars (e.g. Sucralose, Aspartame, Acesulfame K, and etc.) Sweeteners (Lohner *etal.*, 2017). It produces an intense sweet taste compared to the concentration of caloric sweeteners such as dextrose sucrose, and high-fructose corn syrup, in addition to that, non- nutritious artificial sweeteners (NNSs) have grown increasingly and are popular since their introduction into the food and beverage market, because of their low cost, low-or zero calorie count, and their role in Weight loss, control and normalization of blood sugar levels (Gardner *etal.*,2012;Mattes &Popkin 2009)

People have gained a lot of interest in their health over the recent past, employing every available means to ensure good health

(Drummond *et al.,* 2015). According to Mayo Clinic (2018), people aimed at reducing calories and sugar in their diet have adopted the nature of turning to sweeteners, among other sugar substitutes. In this case, chemical sweeteners refer to additives added to beverages and food to improve everyday products' taste. Some of this additives are naturally occurring, while the rest are artificially made (Strawbridge, 2018). The NNSs that are heavily promoted by the food industry are among the most controversial food additives due to suspicions about adverse health effects (Olivier *etal.*,2015). These claims include causing skin dermatological problems, headaches, mood swings, difficulty breathing, allergies and cancer. The artificially made have raised ample concerns over their probability of causing health issues, which is why they are a major concern. Despite that, their production and use has been on rise, in most beverages and foods. Therefore, to better understand ASs, the discussion will look at common sweeteners and their production, give an overview of the ASs, identify associated health effects, discuss their general use, their use in food use, and defines their permissible levels of use.

**Overview of Artificial Sweeteners**

Artificial sweeteners refer to synthetic sugar substitutes found in most beverages and foods. Most artificial sweeteners are available in large amounts in most beverages and foods marketed as "free sugar," including baked goods and drinks (Strawbridge, 2018). Due to the need for individuals to understand artificial sweeteners' health benefits, there have been many rising questions. Most importantly, some people argue about these compounds' name as they feel some of them are derived from natural sweeteners. In contrast, others think that they have more negative implications than the benefits associated with them. As such, one can vividly see that

sweeteners' health effects are a controversial subject, which is sometimes hyped by media or supported by inadequate evidence. Nevertheless, being cheap due to the small amount used, they have helped lower the cost of production, while also helping individuals reduce calories consumption.

**Common Sweeteners and Their Production**

Classification of Sweeteners

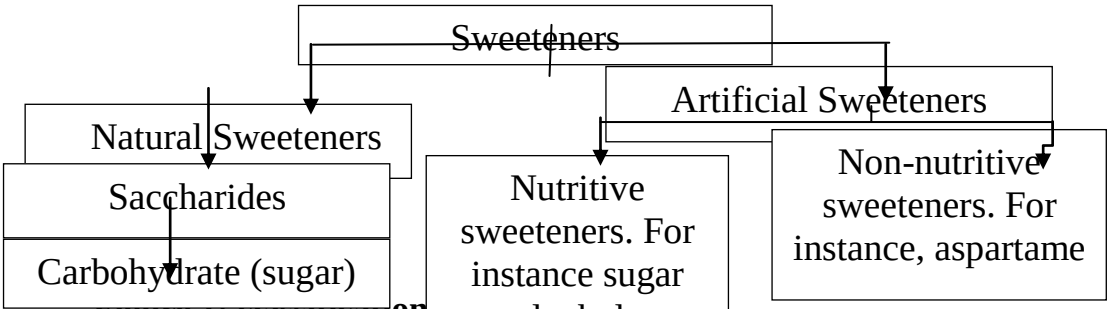


**Figure 1: classification**

As aforementioned, s of sugar substitute, among many others that exist. In this case, Tandel (2011) defines a sugar substitute refer to a food additive that elevates the effects that sugar gives in the taste of a specified food product, typically encompassing less food energy. Some of the sweeteners are natural, commonly referred to as natural sweeteners, while others are made artificially, widely referred to as artificial sweeteners. As is notable, the ASs further divides into nutritive and non-nutritive sweeteners. Nutritive are the caloric group, while non-nutritive are those without calories. Examples of nutritive include Monosaccharide polyols and Sorbitol. ScienceDirect Topics stated that the essential class of sugar substitutes is the high-intensity sweeteners, which are compounds that bring from sweetness that is often that of ordinary sugar. As such, according to Arbeláez et al. (2015), high-intensity sweeteners are way less cost-effective, as only a little amount of them is needed to bring

the desired effect on the taste of the targeted product. However, despite their uniqueness, they give a flavor that is way different from the regular sugar and hence is used in complex mixtures to ascertain a natural sweet sensation (Arbeláez et al., 2015). Their usage occurs commonly in soft drinks labeled as "light" or "diet," typically containing artificial sweeteners with varying mouth feel. The United States, through the U.S. Food and Drug Administration, recognizes six intensely-sweet sugar, which they indicated safe for use (Gupta, 2018). Such include acesulfame potassium, Aspartame, stevia saccharin, Sucralose, and Neotame. It is worth saying that most of these are ASs. However, as Grembecka (2015) indicated, some recognized natural bulk sugar substitutes, such as xylitol and sorbitol, are commonly found in vegetables, berries, mushrooms, and fruits. Besides, there are also other common sweeteners, referred to as polyols or "sweet alcohols." The "sweet alcohols," unlike the aforementioned intensely-sweet sugar, have a less sweet taste than the ordinary sugar but are characterized by almost if not similar bulk properties, making them useful in a wide range of products (Grembecka, 2015). It is worth noting that their taste is adjusted by mixing them high-intensity sweeteners, giving them a delicate mouth feel in the products they are used. However, it is worth noting that studies indicate that the most commonly used artificial sweeteners are Sucralose, which is usually a chlorinated sugar, about 600 times as sweet as regular sugar (Yang, 2010). The production of various sweeteners and their sources vary significantly. The production and sources of various common sweeteners is shown in table 1 below.

**Table 1: source and production of common sweeteners**

| Common sweetener Name | Production method | General use | Effectiveness compared to table sugar |
|---|---|---|---|

| | | | |
|---|---|---|---|
| Acesulfame potassium $C_4H_4KNO_4S$ | According to *Food Insight*, the output of Acesulfame potassium occurs through the process that incorporates the transformation of an organic intermediary, acetoacetic acid, which is then combined with naturally occurring mineral, potassium. | Stable under the heat and in moderate basic or acidic conditions, hence enabling its use in baking products. | 200 time sweeter than sucrose and has a slightly bitter aftertaste |
| Aspartame $C_{14}H_{18}N_2O_5$ | Aspartame sweetener is a white, odorless, crystalline powder discovered in 1965. According to Madehow.com, compound production occurs through the combination of microbial fermentation and synthesis. | Aspartame naturally breaks down into its integral amino acids under high temperatures, rendering it unsuitable as a baking sweetener. stable in some acidic conditions, hence suitable for soft drinks | 200 times sweeter than sucrose. |
| Stevia | International | suitable for soft | About 200 times |

| | | | |
|---|---|---|---|
| $C_{38}H_{60}O_{18}$ | Food Information Council (2018) indicated that the stevia sweetener is derived from the leaves of the Stevia rebaudiana plant, one of the most known native shrubs in South Africa. The compound production occurs by extracting steviol glycosides from stevia plant leaves before its purification to eliminate some of the crude extract's bitter attributes. | drinks | sweeter than table sugar |
| Sucralose $C_{12}H_{19}Cl_3O_8$ | Sucralose is produced through the chlorination of sucrose. | Used in frozen desserts, beverages, chewing gum, various foods, and baked goods. More stable under heat, making it | About 320 - 1,000 times sweeter than sugar. According to Tate & Lyle (n.d), it is 3 times sweeter than Aspartame and acesulfame |

| | | | |
|---|---|---|---|
| | | suitable for fried and baked products. | potassium, and 2 times sweeter than sodium saccharin. |
| Neotame $C_{20}H_{30}N_2O_5$ | A derivative of a dipeptide compound of the amino acids phenylalanine and aspartic acid, which is obtained by N-alkylating Aspartame. Its manufacturing occurs through a single process, with no isolated intermediates. | Commonly used in both baking and cooking uses due to its ability to withstand high temperatures. It is used in baked products, candies, beverages, chewing gum, frozen desserts, dairy products, puddings, and yogurts. | According to the suggestion of *Sciencedirect.com*, Neotame is about 8,000 times sweeter than sucrose. |
| Saccharin $C_7H_5NO_3S$ | According to *Healthline*, Saccharin, a white, crystalline powder, is one of the artificially made sweeteners that do not contain calories, explaining its use as a sugar substitute. The compound production occurs in the laboratory | Commonly used to improve the taste of dietary foods, kinds of toothpaste, and beverages. | The compound is 300-400 times sweet than sucrose |

| | | | |
|---|---|---|---|
| | through the oxidation of chemicals phthalic anhydride or o-toluene sulfonamide. | | |

**Overall Description of Artificial Sweeteners**

According to Chattopadhyay *et al.* (2014), ASs refers to sweeteners derived from the chemical synthesis of organic compounds that may not be found in nature. As Lange *et al*. (2012) indicated, ASs, are still new in the food industry, meaning that there is a lot of ongoing research to ensure their safety and improve their everyday effects. Notably, there are many controversies concerning the health implications of artificial sweeteners, where some individuals perceive that they might breakdown into harmful chemical sub compounds. Nevertheless, as a way to reduce the cost of production, and due to their low prices, many people are still coming up with more and more artificial sweeteners, giving them a higher probability of becoming the primary sweeteners in the world (Tighrine *et al.*, 2019). ASs work in a unique way to give the desired mouth feel. Notably, the human tongue is made in a manner covered by numerous taste buds, each with varying taste receptors, hence enabling the detection of varying flavors (Woertz *et al.*, 2011). As such, when an individual eats food, the taste receptors come upon the food molecules, and if perfect fit, they send impulses to the brain, enabling the identification of the molecule's taste. The food sweeteners are made so that they are an ideal fit with the sweetness receptors, allowing the sending of impulses to the brain for identification. Like sugar sweeteners, the artificial sweeteners also have the same effects and enable the sending of impulses to the brain for identification. However, when it comes

to breakdown, ASs are way different from sugar sweeteners in that they lack calories, as suggested by Steinert *et al.* (2011). There are various types of ASs allowed for use in the U.S. States and the European Union, as *Healthline* indicated. Such include Aspartame. Zafar *et al.* (2017) suggested that the compound is sold under NutraSweet's brand name and is about 200 times sweeter than sucrose. Another notable artificial sweetener is the Acesulfame potassium, which other people refer to as acesulfame K. The sweetener, just like Aspartame, is 200 times sweeter than ordinary sugar (Shankar et al., 2013). The fact that Acesulfame potassium is stable under high heating, it is suitable for cooking and baking. Commonly the compound sells under the brand names Sweet One or Sun net. Also, Advantame is another common ASs, which is about 20,000 times sweeter than sucrose (Sclafani & Ackroff, 2015). The compound is stable under high temperature and is therefore suited for baking and cooking. Another is Aspartame-acesulfame salt, which is commonly sold under the name Twinsweet. The complex is about 350 times sweeter than ordinary sugar (Nikoleli & Nikolelis, 2012). Though banned in the United States since 1970, Cyclamate is another notable ASs (von Schwerin, 2019). The complex is about 50 times sweeter than sucrose, which was stable under high temperatures, and therefore was suitable for baking and cooking purposes. Others include Neotame, which is 13,000 times sweeter than sugar, Neohesperidin, 340 times sweeter than sucrose, and Saccharin, which is 700 times sweeter than sucrose. Also, there is Sucralose, which is 600 times sweeter than ordinary sugar. The varieties prove the increased production of ASs worldwide (Brown et al., 2010). The permissible intake of various sweeteners on daily basis is shown below in table 2:

**Table 2: permissible sweeteners intake per day by an individual (*SHP*, 2020).**

| Sweetener | Molecular Formulae | Permissible levels intake by an individual per day |
|---|---|---|
| • **Saccharin** | $C_7H_5NO_3S$ | 5 milligrams per kilogram of body weight. |
| • **Aspartame** | $C_{14}H_{18}N_2O_5$ | 50 milligrams for each kilogram of body weight. |
| • **Sucralose** | $C_{12}H_{19}Cl_3O_8$ | 5 milligrams for each kilogram of body weight |
| • **Acesulfame potassium** | $C_4H_4KNO_4S$ | 15 mg per kilogram of body weight |
| • **Neotame** | $C_{20}H_{30}N_2O_5$ | 0.3 mg per kg of bodyweight |

**Health Effects of Artificial Sweeteners**

The consumption of ASs should be reduced within the permissible limits and for short periods. It was noted that the highest intake of Aspartame [2.5(1.4-3.7) mg/kg per consumer], followed by Sodium Cyclamate[1.6(1.3-2.6)mg/kg per consumer], and Steviol glycosides[1.2(0.2-2.1)mg/kg per consumer]. beverages were the highest food group that contributed to the increase in the intake of ASs. In the case of using ASs for long periods, consumers must undergo medical examinations to ensure the biological processes inside the body within the normal range. Extensive studies are needed to assess the role of ASs (Khamise et al., 2020). Each ASs has its own chemical structure that may affect the metabolic processes and

other downstream effects, and more studies are needed to clarify this (Hunter etal., 2019). According to Sharma *et al.* (2019), though still under investigation, there has been developing and constant concern over artificial sweeteners' health implications. Some people suggest that ASs cause several chronic diseases and conditions. Examples of health concerns are discussed below.

**Cancer**

Among the notable concerns is the possibility of ASs to cause cancer. Various investigations have been undertaken to confirm the claim's truth, such as the study carried in 1981, linking the Aspartame to increasing brain cancer incidents (Mishra et al., 2015). The study claimed that the high intake of aspartame sweetener increased hematopoietic cancer risk (Mishra et al., 2015). Also, there has been another claim that saccharin promotes bladder cancer. However, some researchers have proved the suggestions wrong with time, at which point more investigation the sweeteners were approved safe for use. Nevertheless, people are still concerned about artificial sweeteners' potential to cause various types of cancers.

**Obesity**

Another health concern that Marinovich *et al.* (2018) raises about ASs is their linkage with the causing of obesity. In the article Added Sugars, the American Heart Association indicated that citizens in the U.S. Take about 22 teaspoons of sugar daily, accounting for about 355 calories, which is way high to the recommended 100 calories for women and 150 calories for men. As such, the number of obese individuals in America is way high, leading to concerns over the possibility of causing obesity. The problem arises from the decrease in white sugar use, with the increasing use of HFCS over the recent past. According to Melanson *et al.* (2008), the high intake of HFCS, the level of insulin or leptin reduce, and due to their primary function as crucial signals to CNS in energy regulation and suppression of

appetite, increased intake elevated the desire to take caloric food, hence overall leading to weight gain. As such, this makes individuals feel that ASs contribute to obesity.

**Gastrointestinal Tract Issues**

Another primary concern over the intake of artificial sweeteners has been issues related to the gastrointestinal tract. *Michigan Medicine* shows that some people feel that increased intake lead to irregular bowel movements and bloating, hence distracting an individual's comfort ability. Gerasimidis *et al.* (2019) argue that the implications that ASs have on the gastrointestinal tract are commonly associated with their interaction with the microbial flora found in the human gastrointestinal tract. Thursby & Juge (2017) indicates that the human intestine is a home for about 100 trillion micro-organisms of not less than 1000 different species. Xylitol and Sucralose have been demonstrated to cause a decrease in beneficial micro-organisms (Godswill, 2017). As such, there is still further research that is ongoing to address this concern. Increasing consumption of ASs can increase the spread of Non-alcoholic fatty liver disease (NAFLD). However, more human studies are needed to definitively determine this relationship (Emamat *etal.*, 2020).

**General Uses of Various Sweeteners**

Sugar is a standard or generic way of referring to sweet-tasting or carbohydrates that are soluble, mainly used in foods. Sugar can be granulated, regular sugar, table sugar, or simple sugar such as glucose, galactose, or fructose. In previous centuries sugar was natural. Fisberg *et al.* (2018) indicated it was a commodity currency and a wealth representative; hence, there was sugar in high amounts. Later along came the ASs such as Aspartame, saccharin, Neotame, acesulfame potassium, and stevia extracted from plants as indicated by Gupta *et al.* (2018).

The main reason for sugar use is for its sweet taste. Sugar, however, has been used for many other functions in food technology. Some of the essential functions of sugar include preservation, fermentation, texture modifier, sweetener, as a colouring agent, for flavour modification, as an agent of bulking or reducing spoilage and balancing acidity. Ardalan *et al.* (2017) indicate that ASs are a class of food additives that provide a sweet taste without increasing calorie intake. Periyasamy (2019) suggested that the sweetness of natural sugar without the calories is possible by the ASs and produces a low glycaemic response. The sweetener is replacement sucrose or table sugar to sweeten beverages and foods. Recently, food producers, consumers, and manufacturers have a high demand to replace sucrose in foods and drinks with ASs. However, natural sweeteners include Agave, a sweetener extracted from the cactus plant, barley malt from barley, which is roasted and cooked into syrup. Cane sugar from sugar cane is removed mechanically; coconut sugar from coconut flower buds are dried and date sugar from date fruits and honey. Ali *et al.* (2017) noted that sweeteners had replaced natural sugar in the food and beverage industry for various reasons, including hyperglycaemia and cost. Other reasons for the use of sweeteners are that they are healthier, for diabetic patients are a safer choice since they do not raise blood sugar levels and control overweight. However, Hutchings *et al.* (2019) noted a need to address public health concerns regarding the amount of added sugars in foods and the merits of different techniques available for sugar content reduction. Especially with the use of sugar substitutes like non-nutritive sweeteners, fibres, and sugar alcohols. Non-nutritive artificial sweeteners (NNSs) that may have the ability to alter the gut microbiota, and thus can alter glucose metabolism (Ahmad *etal.*,2020).

**Artificial Sweeteners in Food**

Saccharin, a type of sweetener, is used as a table top sweetener in baked foods, chewing gums, and it is also used in making cosmetic products and vitamins. Saccharin is famous as a sweet-low sugar; it contains low calories and does not raise blood sugar levels. It sweeter than sucrose by about 200 to 700 times, and aftertaste bitterness characterizes it. Sucralose, which is among the newest sweetener in the market and claims to be made from sugar, is 600 times sweeter than table sugar. It is fully absorbed and contains no calories. It is commonly used in baking and cooking foods, making it one of the most popular and highly consumed foods. Neotame, another ASs that is 7000 to 13000 times sweeter than sucrose, is used and promoted as a flavour modifier or enhancer to upgrade the foods flavours. Carniel Beltrami *et al* (2018) noted that the sweeteners enhance sweet taste in the food industry through food science and technology. For example, as Li *et al*. (2020) indicated, they are used in alcoholic drinks using direct analysis in the real-time QTRAP mass spectrometry. It is said to friendly use to people of all ages, even children, pregnant and breastfeeding mothers. It is used in cooking. ASs are used to control weight gain; according to Periyasamy (2019), the theory is that our bodies sense the sweetness of the food and expect the calories, hence the need for the sweeteners since they contain low or no calories. Bian *et al.* (2017) indicated that ASs had been used in the modern diet to control excessive weight gain. Rogers et al. (2018) further noted that sweeteners prevent and manage overweight and obesity.

**Conclusion**

The essay showed that there is increased need for people to maintain good health, which has significantly promoted the increased use of sweeteners in food and beverages. Particularly, there is an observable increase in production and use of ASs

including acesulfame-K, aspartame, saccharin, and sucralose, among others. However, with their increased, intake, there has been more concern as some people argue that increased intake of the ASs promotes cancer, obesity, and brain damage, among other health implications. However, with the increased research by the FDA, there is significant showing that most of the artificial sweeteners do not pose increased threat to human health, which has significantly contributed to their increased use. Sweeteners have more effects on taste numerous times than the common sugar, making them efficient for use. Most of them are used for baking and coking purposes, particularly those that can withstand high temperatures. Other is used in beverages. Nevertheless, as more production and use increases, there is a need to carry further research to ensure human safety.

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