# Sugar Substitute: The Safety and Function of Artificial and Natural Sweeteners

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**Abstract.** As the global prevalence of obesity, diabetes, and other non-communicable diseases continues to rise, there is growing attention to the importance of a proper diet and managing energy intake. There is a growing desire for sugar alternatives as the harmful consequences of excessive sugar consumption on human health become more and more obvious. This article aims to consolidate current knowledge and research findings on sugar substitutes, with a focus on their digestive processes, taste characteristics, and potential health risks within the human body. The paper provides an examination of various sugar substitutes, including four artificial sweeteners which is aspartame, saccharin, Ace-K, and sucralose, as well as natural sweeteners like stevia and erythritol. Each category is assessed for its suitability in different food applications and associated toxicity studies, drawing comparisons to sucrose. The regulatory framework and safety assessment surrounding sugar substitutes are also discussed, underscoring the importance of understanding their potential health effects. Furthermore, this study explored the benefits of sugar substitutes in terms of calorie control and their potential to improve dietary choices for specific patient groups. The potential impact of sugar substitutes on environmental pollution, gut microbiota, and metabolic syndrome is also examined, highlighting areas that warrant further research. The conflicting results from some studies on the toxicity of sugar substitutes are also addressed, contributing to solve the ongoing controversy surrounding their use.

**Keywords:** Sugar substitutes; artificial sweeteners; natural sweeteners.

## 1. Introduction

People are becoming more aware of their sugar consumption as the incidence of diabetes and obesity around the world continues to grow. This is because excessive intake of sugar can induce or worsen diseases like obesity, type 2 diabetes, hyperlipidaemia, etc. [1]. Controlling the diet is also one of the must-do tasks for such patients. Sugar substitutes are very common food additives to provide sweetness to food products and drinks. Most of them have a similar taste to sucrose, but without calories, and also they have lower cost, resulting in widely used and affecting the nutrition intake and diet choice of people. As a result, low or even no-calorie sugar substitutes are becoming more and more popular, but with this comes a different discourse on the effects of sugar substitutes. A growing number of studies suggest that sugar substitutes may have metabolic, gut microbiota and neurological effects on the brain. This article interprets sugar substitutes in terms of both artificial sweeteners and natural sugar substitutes, analyses the digestive and metabolic processes of six typical sugar substitutes and summarised their health effects and potential risks. This paper may help to identify the progress and deficiencies of current research and suggest the way forward for future research.

## 2. Sugar Substitutes

As the name implies, artificial sweeteners are synthetic additions with a strong sweet flavour. In contrast to sugar, which has 4 calories per gram, most artificial sweeteners have no or few calories. Furthermore, most artificial sweeteners have a well-established manufacturing chain and can be produced in big quantities, resulting in a substantially lower cost. As a result, a huge number of producers utilise artificial sweeteners in the production of various products and are marketed as low

or zero-calorie to appeal to the purchasing public. Almost in the last few decades, the United States alone has produced almost 6,000 new food products containing artificial sweeteners [2]. People are paying more attention to the nutrient content and total energy on food labels as society advances and people become more health conscious in order to limit their dietary consumption. While artificial sweeteners are thought to lower energy and boost palatability, they are also thought to have possible safety and health risks.

In contrast to artificial sweeteners, natural sweeteners are derived from plants, animals, or microorganisms. They are generally viewed as a healthier alternative to sucrose because they naturally occur. Natural sweepers can be divided into two categories: nutritional sweepers and non-nutritional sweepers. Nutritional sweeteners include honey, maple syrup, and agave produced from specific plants, as well as polyols, whereas non-calorie sweeteners include steviol glycosides and rebaudiosides extracted from stevia, luo han guo extracted from a kind of monk fruit, and thaumatin [2]. Nonetheless, natural does not imply fully safe, and they can be potentially hazardous, as proven by extensive and diverse sample research.

## 3. Artificial Sweeteners

### 3.1. Aspartame

Aspartame is an important and typical artificial sweetener, which is widely used. It was discovered by accident in 1965 when a chemist accidentally ingested aspartame, an intermediate of a drug used to treat gastric ulcers, and found it sweet [3]. Aspartame, whose full name is N-L-alpha-aspartyl-L-phenylalanine1-methyl ester, provides 4 kcal per gram. However, because its sweetness is around 200 times that of sucrose, it is frequently used after being entirely diluted, and the number of calories consumed each time can be minimal [4]. Aspartame is thermally unstable and therefore cannot be used in baking and cooking and is often used in low-calorie products or reputed sugar-free products, such as chewing gum, beverages, yoghurt, etc [5]. Aspartame also has a slightly bitter taste, food manufacturers always add other sweeteners for better taste and flavour, such as saccharin and Ace-K [4].

Aspartic acid, methanol and phenylalanine will be produced in the intestine due to the hydrolysis of aspartame, which flows into the bloodstream and is metabolised one by one [5]. However, in conditions with a pH greater than 6, aspartame is metabolised in some tissues to produce formaldehyde, formic acid, and maybe even diketopiperazine, a carcinogen [5]. In an animal study to assess the effects of aspartame toxicity during pregnancy, 14 adult female rats were used to compare the effects of aspartame at a dose of 14 mg/kg on their placental development. According to the fact that the weight and thickness of the placenta of rats in the group interfered by Aspartame decreased significantly, it is speculated that this is related to the accumulation of formaldehyde and other derived substances and may affect the function and structure of the placenta [6].

For some specific groups of people, such as those with hereditary phenylketonuria (PKU), aspartame produces a range of adverse effects when ingested [7]. This is a rare group of genetic disorders that prevent them from metabolising phenylalanine properly [7]. There are also studies that suggest aspartame has a positive impact on intestinal microbiota and glucose metabolism. For example, a randomised double-blind crossover clinical trial by Samar et al. involved 17 subjects whose blood and stool samples were collected during a prescribed 12-week dietary regimen to inspect the impact of glucose metabolism level of the subjects under the intervention of aspartame and sucralose [8]. This study found that the two artificial sweeteners did not have a substantial effect on the gut microbiota in the short term (14 days), but this result conflicts with the findings of some animal studies [8]. Human experiments on aspartame and gut microbes are still scarce, and the results of animal studies do not directly reflect those in humans, more experiments are needed to support the results of this study.

### 3.2. Saccharin

Fig. 1 showed that saccharin was the first artificial sweetener to be discovered, resulting from experiments carried out in 1878 on a toluene derivative [5]. Saccharin is an organic acid that exists as acid saccharin, sodium saccharin, and calcium saccharin. Its chemical structure is shown in Fig. 1, which is $C_7H_5NO_3S$. Its most popular form is sodium salt [2]. Saccharin is used frequently to enhance flavour in toothpaste, food, beverages, medicinal formulations, and even tobacco products [9]. It is 300–500 times sweeter than sucrose and is easily soluble in water. However, saccharin is not suitable for use at high concentrations because it has organoleptic properties not found in sucrose, and the bitterness of saccharin is proportional to its sweetness [9]. To resolve this situation, sweeteners are often used to slow down the bitterness and increase the sweetness of saccharin. After ingestion of saccharin, the intestine does not digest and metabolise it but excretes it through the kidneys [9]. The safety of saccharin has been the subject of much research. For instance, one mice study found that saccharin had no impact on the pharmacokinetics of bupropion, indicating that the substance was safe and the chance of interaction with the medication was very low [10]. This conclusion may provide some safety for those taking medication for diabetes and cancer.

But likewise, saccharin is controversial. Many studies on saccharin and gut microbes have come to different conclusions. Some studies indicate no significant effect between the two, while others indicate that the proportions of some microorganisms are altered [11]. Alterations in the microbiota are influenced by many factors, with most experiments utilising different assays and most being animal studies, which need to be validated by more ethical human clinical trials. There is also an animal study published in 2019 that showed that prolonged saccharin intake can cause liver and kidney damage in rats, as well as an increased risk of obesity and diabetes [12]. As shown in Fig. 2, three groups of male rats were subjected to three doses of saccharin (2.5, 5 and 10 mg/kg) for 120 days in a control group, and blood samples, urine, liver and brain tissue were examined and found to increase creatinine concentrations, uric acid and isoprostane [12]. This also reflects an increase in liver oxidation and weight gain in rats after the ingestion of saccharin, which could elevate the risks of obesity and diabetes.

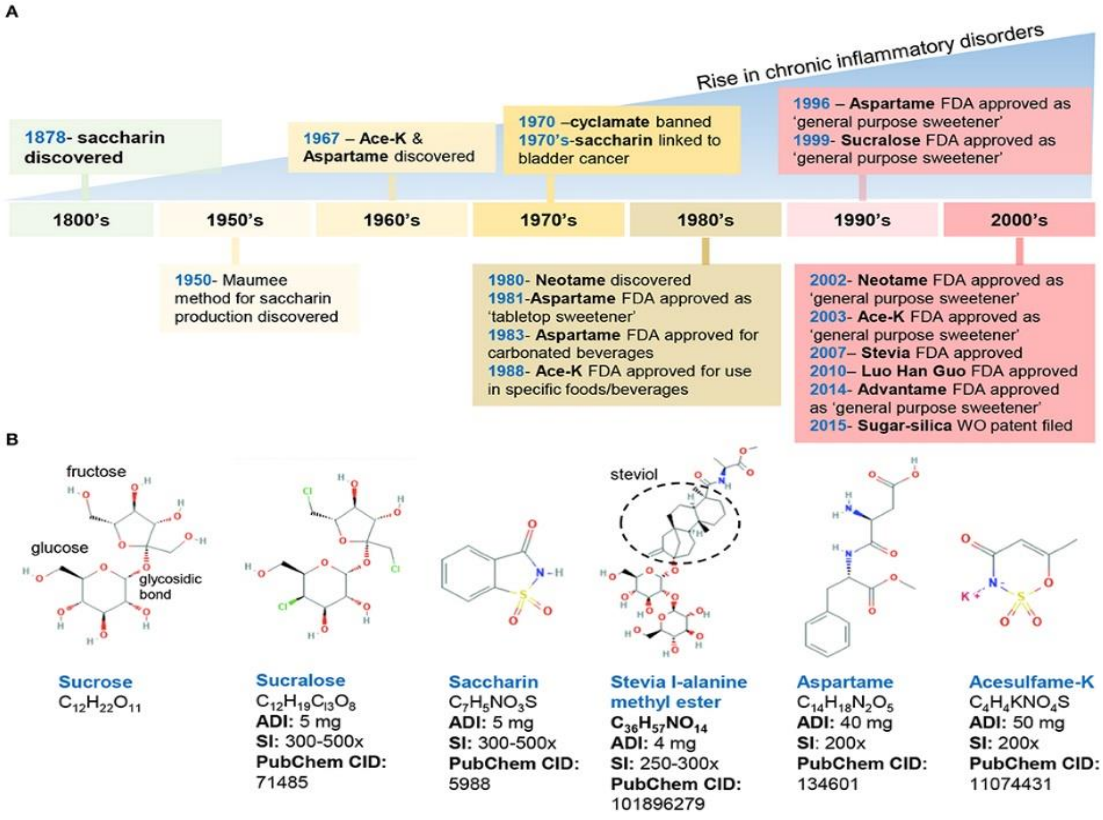


**Fig 1.** The timeline and chemical structure of several sweeteners [5].

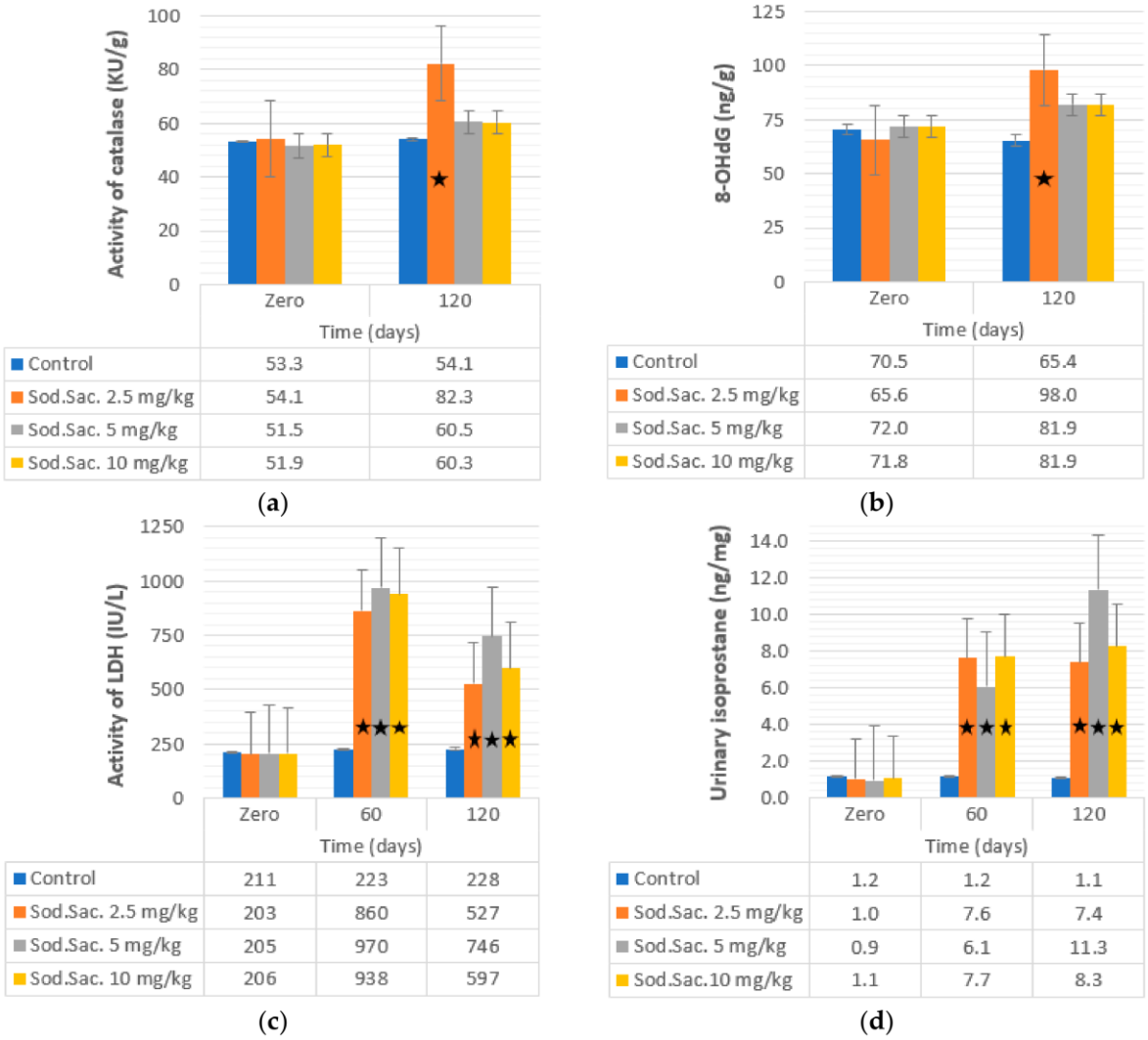


**Fig 2.** Effects of Saccharin Sodium on four indexes of 10 rats(n=10) at doses of 2.5, 5, and 10 mg/kg.b.w. at 0 time, and after 60 and 120 days [12].

### 3.3. Sucralose

Sucralose is a disaccharide produced by selectively chlorinating the three main hydroxyl groups of sucrose molecule, as shown in Fig. 1, its chemical formula is $C_{12}H_{19}C_{13}O_8$ [11]. Sucralose is structurally similar to sucrose and therefore has a similar flavour to sucrose, but it is 600 times sweeter [4]. Sucralose is not digested or absorbed in the body and therefore provides no calories, most of which are excreted directly in the faeces, with a small proportion entering the kidneys and being excreted in the urine [2]. Sucralose is thought to affect the microbiota in the gut and for this reason, many studies have been conducted to find a link between these factors. However, the way in which the experiments were conducted, the doses of sugar substitutes, the subjects and the emphasis placed on the target have led to contradictory results in some studies. Sucralose has been discovered to change the composition and quantity of different microbes in the gut in many animal studies. For example, a study in 2020 showed the influence on the gut microbiota in the presence of several sweeteners and varying levels of dietary fat [13]. Where rats fed a calorie-free sweetener had less gut microbial diversity than those fed a calorie sweetener, and sucralose altered the Bacteroidetes/Firmicutes ratio and reduced the abundance of intestinal occludin in a high-fat diet [13]. In past short-term human experiments using amounts below the sucralose ADI have generally not found sucralose to alter intestinal microbes [11]. For example, a randomised double-blind study of 780 subjects was studied by Thomson et al, 17 of whom received 17 days of sucralose capsules (7 mg/day), and no significant changes in microbiota were found after sequencing by 7S rRNA [14].

However, a recent study of a controlled trial (40 subjects) lasting 10 weeks found that sucralose could alter the gut microbiota to affect glucose and insulin levels. When comparing pre- and post-study, volunteers who took sucralose for 10 weeks had a significant increase in AUCG of 8 ± 1.7% ($p = 0.02$) and their gut microbiota was also altered, with a significant 0.6-fold decrease in the relative abundance of *Lactobacillus acidophilus* ($p = 0.03$) and an induced increase in *Blautia coccoides* abundance [15].

### 3.4. Acesulfame Potassium (Ace-K)

Ace-K is an oxamide dioxide chemical that may be added to soft drinks, which has a high water solubility [2]. Ace-K is 200 times sweeter than sucrose, and, like saccharin, its concentration is proportional to bitterness. Ace-K can also be used with other sweeteners—but not saccharin—to lessen flavours [4]. Ace-K is similar to saccharin in that it is excreted mainly in the urine after ingestion, except that the process is more rapid and less likely to affect gut microbes [2]. Ace-K is also widely added to animal feeds because of its ability to improve the taste of feed and make animals eat more [16]. Since Ace-K is excreted intact in urine and is chemically stable and not easily removed, the question of whether it is environmentally contaminated is of particular importance. The study by Li and Gao, who collected data by culturing strains and then adding Ace-K to mediate, found that when environmental concentrations of Ace-K ranged from 0.1005 mg/L to 2.01 mg/L, it can significantly increase antibiotic resistance by culturing strains and then adding Ace-K mediated data collection, but it does not occur when the concentration is too high [16]. This indicates that there may also be other potential hazards to the environment [16] in the current study, the environmental concentrations of Ace-K today do not meet the toxicity criteria for aquatic plants and animals, and therefore do not have a considerable effect on the aquatic environment [17]. In general, both the degradation and treatment of Ace-K in wastewater need to be taken into account to exclude its environmental impact. In addition to environmental impacts, studies have also explored the possibility of finding out whether Ace-K as a sweetener is a safety concern for humans. Although not as many toxicity studies have been reported as with other sweeteners, it has been mentioned that male mice gained weight in the presence of Ace-K within a week as a result of the influence of Ace-K on the gut microbiota of CD-4 mice [18].

## 4. Natural Sweeteners

### 4.1. Stevia

Stevia, the chemical formula is $C_{38}H_{60}O_{18}$, which is a glycoside extracted from the leaves of *Stevia rebaudiana*, which is from Paraguay [2]. RebA and sterol glycoside are the main two glycosides extracted from it, with a sweetness 300 times that of sucrose [2]. Since the body cannot metabolise these sweet glycosides, it is not possible to obtain calories from stevia [2]. Stevia glycosides have different properties from artificial sweeteners in that they are highly heat stable, making them resistant to breakdown even during cooking and baking [2].

Sensually, high-purity stevia has some bitter and astringent flavours. Reb A and steviol glycosides have different organoleptic characteristics, compared to Reb A, which has a better flavour, less pronounced bitterness and higher sweetness than steviol glycosides [4].

According to recent studies, stevia is often safe for human consumption. Casas-Grajales et al. (2019) found that stevioside can promote the antioxidant activity of Nrf2 to prevent liver damage [19]. An additional recent study has shown that stevia does not significantly affect blood glucose levels in people with type 2 diabetes, meaning that stevia can be used in place of sucrose in diabetic patients [20]. The study also compared stevia with sucralose, and from the fluctuations in PPG in the line graph in Fig. 3, it can be seen that the effects of the two were similar, but the PPG affected by stevia was lower [20]. Although there have been no significant and immediate negative effects found from long-term usage of stevia, it cannot be guaranteed to be totally non-toxic and some delayed effects cannot be ruled out.

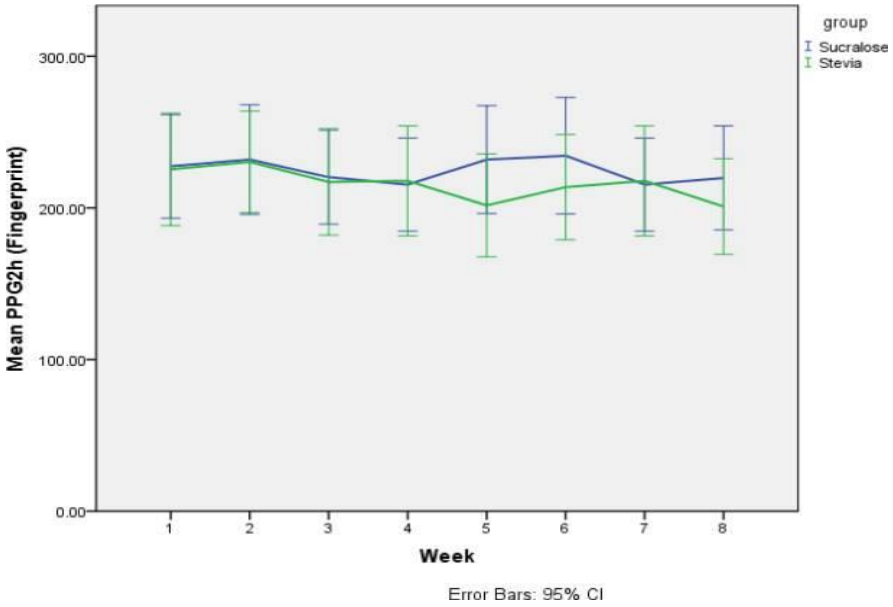


**Fig 3.** Comparison between stevia and sucralose on the mean PPG2h of type 2 diabetic patients [20].

### 4.2. Erythritol

Erythritol ((2R,3S)-Butan-1,2,3,4-tetrol), a polyol that can be found in vegetables and fruits as well as in foods such as mushrooms, is formed by hydrolysing the aldehyde or ketone groups in various carbohydrates [21]. It is only about 70% as sweet as sucrose, but it can mask some of the bad aftertaste, such as Ace-K and aspartame would need its addition for a better taste [4]. Like most sugar substitutes, erythritol is not easily digestible, is excreted mainly in the urine, and blood glucose levels are not affected by it [21]. Erythritol is most commonly added to a wide range of products such as chewing gums, drinks and kinds of toothpaste to add flavour and, depending on its properties, can also be added to specific foods for obese and diabetic people to reduce calories [21]. Despite this, studies have found that erythritol has a risk for cardiovascular disease [22]. In a recently published cohort study involving nearly 3,000 trial participants, this association was found, with erythritol having a role in stimulating thrombosis in vivo and promoting platelet reactivity in vitro [22]. Similar results were also obtained in a prospective pilot intervention study [22].

## 5. Conclusion

Firstly, after extensive research into sugar substitutes to rule out their harmful effects, some of them have been deemed safe for consumption by the FDA. However, other sugar substitutes, such as aspartame and Ace-K, are still the subject of debate. The results from these studies need to be further examined and validated. Secondly, despite the advantages and disadvantages of both artificial and natural sweeteners, it is possible to find that the findings of side effects of natural sweeteners have been found to be much less than those of artificial sweeteners in recent studies, such as stevia and luo han guo. However, due to the lack of long-term studies with numerous subjects, the potential impact of some sugar substitutes cannot be ruled out, so this view is questionable. In conclusion, sugar replacements can aid in sugar consumption control, which is beneficial for those who need to restrict their sugar intake, such as those on a diet or those with diabetes. Further research is required in light of the rising popularity of sugar replacements in order to prevent any negative effects from prolonged use. To limit excessive sugar consumption and ensure proper and safe use, future governments should think about promoting the use of sugar replacements as a public health policy. Additionally, particular guidelines for their release could be established. It should be noted that sugar substitutes have the potential to create environmental damage. Additionally, healthcare providers should educate patients on the various sugar replacements that are readily available as well as how to utilize them correctly.

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